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Meta-Analysis

Efficacy and safety of prostaglandins vs double balloon catheter in inducing labor: a meta-analysis

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ABSTRACT

Background: To compare the efficacy and safety of double-balloon catheter with prostaglandin E2 (PGE2) in induction of labor.
Methods: We searched electronic sources from Medline, Scopus, PubMed, Science Direct and Cochrane Library Database of Systematic Reviews. Only randomized controlled trials and observational studies comparing the PGE2 agents with double-balloon catheter for cervical ripening and labour induction in women with unfavorable cervix were included in the analysis. The main outcomes included vaginal delivery rate within 24 hours and cesarean delivery rates. We calculated relative risks and mean differences using fixed effects and random-effects models.
Results: Prostaglandin was more favourable for vaginal delivery within 24 hours compared to double balloon catheter, but was not statistically significant (RR 1.17: 95% CI 0.96-1.42 p =0.12). The induction to delivery time yielded a non-significant result that again favors prostaglandin (SMD 0.02 CI:0.18,0.22, p = 0.86). There was no significant difference in the cesarean delivery rates between the two groups (RR 1.02: 95% CI 0.92-1.14, p = 0.68). Uterine hyperstimulation and Neonatal Intensive Care Unit (NICU) admissions were significantly higher with prostaglandin. (RR 0.09: CI 0.04, 0.22 p<0.00001 and RR 0.75 CI: 0.62,0.90 p=003).
Conclusions: There is no significant difference in the success of induction of labour between use of PGE2 and double balloon catheter. Uterine hyperstimulation and NICU admissions were significantly higher in Prostaglandin group.

Keywords: Prostaglandin, Double-balloon catheter, Efficacy, Full term pregnancy, Induction of labor, Singleton

INTRODUCTION

Induction of labour is defined as artificial ripening of the cervix by either using pharmacological or mechanical methods to stimulate uterine contractions before labour begins in order to achieve a successful vaginal delivery.[1] It is carried out if the continuation of the pregnancy is harmful to the mother or the fetus. Common indications for induction of labour include post-dated pregnancy, premature rupture of membranes, medical disorders like pre-eclampsia, gestational diabetes and intrauterine growth restriction. It is contraindicated in complete placenta previa and fetal malpresentation.[2]

Various methods have been used in the past, which includes breast stimulation, purgatives like castor oil and laxatives. Prostaglandins have been in use since the 1980's.[3] Foley catheter has been a good alternative to prostaglandins in view of cost and low incidence of fetal distress.[4] A variant of the Foley, the double balloon catheter (DBC) was thought to be superior to the Foley by virtue of improved anchorage.[5]

The two main types of prostaglandins used are misoprostol (PGE1) and dinoprostone (PGE2). It is applied vaginally or intra-cervically nowadays because intramuscular or oral routes have more side effects.

Preparations of Dinoprostone include prostin, prepedil and cervidil.[6] The advantage of Misoprostol is that it can be administered by many routes, including oral, vaginal, sublingual and rectal.[6] However, it has an increased incidence of uterine tachysystole, uterine hyperstimulation, and changes in the fetal heart rate compared to dinoprostone.[7]

Mechanical methods include use of Dilapan and Foley catheters. Of these, the latter has become a popular choice. Both single and double-balloon catheters are available. The principle behind the use of double-balloon catheter is that it has two balloons, an intrauterine balloon above the internal cervical os, while the other balloon is situated below the external os of the cervix intravaginally. The aim is to apply pressure from above and below the cervix when the balloons are filled up with saline. This increases endogenous release of prostaglandins.[8]

The primary aim of this systematic review is to compare the efficacy of prostaglandins (PGE2) and double-balloon catheter in inducing labour in indicated cases.

METHODS

Data sources and search strategy

This review adopted the Preferred Reporting Items in Systematic Review and Meta-analysis (PRISMA) 2015.[9] The review protocol was registered on PROSPERO (CRD42018110421). The research questions were formulated using PICO. The population is pregnant women with gestational age between 36-42 weeks, double balloon catheter is the intervention, prostaglandin E analogue is the control and outcomes are (i) 24 hours vaginal delivery rate, (ii) cesarean delivery rates, (iii) induction to delivery time, (iv) uterine hyperstimulation, and (v) neonatal intensive care unit (NICU) admissions. MEDLINE, SCOPUS, PubMed, Science Direct and Cochrane were systematically searched from its inception to January 2019 using Boolean logic. The MeSH terms used in the search were induction of labor, prostaglandin analogues, double balloon catheter and dinoprostone. We also hand-searched for additional papers based on the bibliographies of included articles and relevant review papers. Experts and authors were contacted at least twice for further studies or missing data.

Selection of outcomes

In this review, we aim to study the efficacy and safety of both induction methods. The outcomes were selected before we retrieved individual studies. Main outcomes for our study were vaginal delivery within 24 hours after the initiation of ripening and rate of cesarean deliveries. We also included secondary outcomes regarding the efficacy of induction methods, such as induction-to-delivery time; safety outcomes i.e. the incidence of uterine hyperstimulation and rate of NICU admissions.

Study selection and data extraction

Only randomized controlled trials and observational studies published in English Language and only comparing locally applied PGE2 against double-balloon catheter, with or without intravenous oxytocin for induction of labour in women with unfavorable cervix were included in this review.

Inclusion criteria for the review were women aged 18 and above, with healthy, live and single fetus in a cephalic presentation, gestational age between 37+0 to 42+0 weeks, Bishop score (BS) less than 6/10.

Exclusion criteria included pregnant women with preterm pregnancy (gestational age<36 weeks), multiple pregnancy, intrauterine growth restriction (IUGR), acute fetal distress, placenta previa, fetal malpresentation (breech position), latex allergy, fetal demise, premature rupture of membrane, studies comparing double-balloon catheter with pharmacological agents other than prostaglandins. Studies in which double-balloon catheter has been used simultaneously or sequentially with prostaglandins, articles which includes only the abstract or the full text is unavailable even after two attempts at contacting the author, studies in which the full article was published in a foreign language were also excluded.

From our preliminary screening, we realized that oxytocin is commonly used if the investigated labor methods (PGE2 and double-balloon catheter) were unsuccessful. Both induction agents are known to be effective in priming the cervix to become 'ripe' and oxytocin is used to complete the delivery process. Therefore, we did not exclude studies in which oxytocin was given after removal of double-balloon catheter or last dose of PGE2. For studies comparing PGE2, double-balloon catheter and other induction methods, we only extracted data comparing both double-balloon catheter and PGE2.

Titles and abstracts were screened independently against eligibility criteria by three authors (JS, AY, CY). We excluded a study if the title or abstract was unsuitable. Any disagreements at this stage were resolved by consulting the fourth author (S). Selection of the final included articles was based on a consensus between all the reviewers. We then independently reviewed full articles for final selection against the inclusion and exclusion criteria.

A standardized data extraction sheet was developed and refined by the reviewers. The following data were extracted from the full text: Study characteristics (authors, publication year, study designs, total number of patients, country), Patient characteristics (gestational age, maternal age, Bishop score, presentation), Induction methods (type of PGE2 and dosage, volume of double-balloon catheter), Measure of outcome

When the values were reported as median (IQR), they were changed to mean (SD).[10] Any discrepancies or disagreements at any stage were resolved by consulting the fourth author (S). All the included RCTs were assessed for risk of bias by two authors (JS and AY) independently using the Cochrane Collaboration Risk of Bias Assessment Tool.[11] For cohort studies, risk of bias was assessed using Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) as illustrated in Table 3.[12]

The GRADE assessments of the evidence and summary of findings were independently performed by two authors (JS and CY) using the GRADE pro/GDT software.[13] Based on the Cochrane Handbook, we downgraded a starting rating of 'high quality' evidence of RCT based on the five criteria by one level for serious concern or by two levels for very serious concerns.[14]

Statistical analysis

Statistical analyses were undertaken using Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Findings were reported as relative risks (RR) or mean difference (MD) with 95% CI. If no substantial heterogeneity was noted, a fixed-effect model analysis was used. If substantial heterogeneity (I^2>60%) was noted, a random-effects model analysis was used. The I^2 test was used to assess the heterogeneity of studies; values of less than 40%, 40–60% and more than 60% were used to determine low, moderate and substantial heterogeneity respectively.15 A two-sided $p<0.05$ or an I^2>50% was considered statistically significant for heterogeneity.

Forest plot was generated to illustrate the heterogeneity of studies and subgroup analysis was done to investigate potential sources of heterogeneity. In addition, a sensitivity analysis was performed by analysing studies with low risk of bias only. Each study was sequentially removed, and the remaining dataset was re-analysed to assess the influence of each study on the estimates. Though funnel plot analysis is not recommended if there are less than 10 studies for each measured outcome to assess the risk of publication bias, we planned to proceed with this analysis. Only eight studies were included in this review, and thus, the evaluation of publication bias was suboptimal.[16]

Trial sequential analysis was performed by using the trial sequential analysis viewer version 0.9.5.5 Beta (Copenhagen Trial Unit, 2016) on the outcomes to prevent the risk of random error and multiplicity phenomenon secondary to repeated significance testing in meta-analyses.[17] The required information size and adjusted significance thresholds were calculated based on two-sided sequential analysis-adjusted random effects model with 5% risk of type-1 error and a type II error of 20% (power of 80%).

RESULTS

Search results

From our extensive literature search, a total of 141 potential research articles were obtained. After removing duplicate articles, screening them based on the inclusion-exclusion criteria and going through a full text screening, only nine articles were finally selected. A total of 3197 cases were analyzed out of which 1598 (50%) received double balloon catheter and 1599 (50%) received PGE2.

Study characteristics and quality assessment

The study characteristics are summarized in Table 1. The inclusion criteria across all nine studies varied, as some included only nulliparous women (Suffecool et al.) while others included nulliparous, primiparous or multiparous, (Du et al.) or only primiparous (Wang et al).[18-20] Gestational age was similar across most studies (more than or equal to 37 weeks) except in Cromi et al. which included a total of 208 patients out of which 17 of them were <37 weeks ,but it does not influence our study.[21] The BS was similar across most studies with it being less than or equal to 6 except in Brown et al. the Bishop score (BS) included was less than 7.[22] The study sample selected for studies Wang and Shechter et al included only patients with oligohydramnios with an AFI less than or equal to 5 cm while other studies did not. [20,23] The indications for induction of labor were similar and most of the studies included women with a singleton pregnancy, vertex presentation and with intact membranes. Women with contraindications for vaginal delivery, preeclampsia, placenta previa, premature rupture of membranes and abnormal fetal heart rate tracing were excluded in most studies. The sample size of the selected studies ranged from 52 to 854. The volume of double-balloon catheter and prostaglandin dosage was not standardized across all studies. The volume ranged from 50 ml to 80 ml and the dosage for PGE2 (Dinoprostone) ranged from 1-12 mg.

Risk of bias within studies

Five of the studies was judged as having an overall low risk of bias and one, high risk of bias. Lokkegaard et al was judged as being at high risk due to the limitation of study design.[24] A common limitation of all studies in this meta-analysis is the lack of blinding of participants, healthcare personnel and outcome assessment. The reviewers agreed that blinding was unlikely to affect the outcome, and thus, these domains were rated as low risk of bias for all studies. For observational studies, Brown et al was judged as having an overall serious risk of bias due to lack of information from a few domains.[22] If a major proportion of studies have an overall low risk of bias, it reflects a relatively high quality of reporting (Table 2).

Table 1: Study characteristics.

Studies	Design	Country	Characteristics	n	PGE dosing	Volume of catheter	Vaginal delivery within 24 hour, h (n, %)	Induction - Delivery time, h (Mean, Standard Deviation)	C-section rate (n, %)	Uterine Hyperstimulation (n, %)	Neonatal Intesive Care Unit Admission (n, %)	Overall risk of bias
Beckmann. M	Randomized Control Trial (RCT)	Australia	Inclusion Criteria: Singleton pregnancies, cephalic presentation, ≥37+0 weeks, undergoing IOL for low-risk indications including post-term, socia' or elective' reasons, and advanced maternal age (≥40 years) Exclusion Criteria: major congenital abnormality, clinical suspicion or ultrasound diagnosis of small for gestational	N=312 DB = 157 PGE2= 155	Dinoprostone, either 2mg gel (Prostin) or 10mg controlled-release tape (Cervidil)	80/80	Not reported	Not reported	DB: 70 (32.6) PGE2: 60 (25.8) P= 0.240	DB: 0 (0.0) PGE2: 5 (3.0) P=0.029	DB: 27 (12.6) PGE2: 36 (15.5) P= 0.379	Low
Brown. J	Matched retrospective cohort study	Australia	Inclusion Criteria: Pregnant women at term with singleton cephalic pregnancies. (modified bishop score<7) Exclusion Criteria: multiple pregnancies, previous CS, fetal anomalies, fetal demise	n=854 DB= 427 PGE2 =427	PGE2 vaginal gel primiparous-2mg, multiparous-1mg	80/80	DB: 144 (33.7) PGE2: 110 (25.8) P= 0.011	DB: 23.3 ± 6.6 PGE2: 24.2 ± 9.9 P = 0.102	DB: 120 (28.1) PGE2: 132 (30.9) P= 0.368	Not reported	DB: 37 (8.7) PGE2: 54 (12.7) P= 0.059	Serious**

Continued.

Studies	Design	Country	Characteristics	n	PGE dosing	Volume of catheter	Vaginal delivery within 24 hour, h (n, %)	Induction - Delivery time, h (Mean, Standard Deviation)	C-section rate (n, %)	Uterine Hyperstimulation (n, %)	Neonatal Intesive Care Unit Admission (n, %)	Overall risk of bias
Cromi A	Randomized Control Trial (RCT)	Italy	Inclusion Criteria: Pregnant women with gestational age ≥ 34 weeks,singleton pregnancy with a vertex presentation (bishop score ≤ 6) Exclusion Criteria: Premature rupture of membranes, favourable cervix, known colonozation with GBS, intrauterine fetal death, non-reasuring fetal heart rate on admission antepartum bleeding, intrauterine fetal death, prior uterine scars, positive vaginal or rectal group B streptococcus screening cultures, placenta previa, or any other contraindication to vaginal delivery	n=208, DB=105 PGE2= 103	10-mg controlled-release dinoprostone vaginal insert	50/50	DB: 72 (68.6) PGE2: 51 (49.5) p=0.007	DB: 18.8±5.4 PGE2: 19.9±9.6 P=0.86	DB: 25 (23.8) PGE2: 27 (26.2) p=0.75	DB: 0 (0. 0) PGE2: 10 (9.7) p=0.002	DB: 8 (7.6) PGE2: 5 (4.8) p=0.57	Low
Du C	Prospective Study	China	Inclusion criteria: Pregnant women with gestation age of ≥ 37 weeks, singleton gestation, vertex presentation, intact membranes, and a normal pre-induction fetal heart rate tracing.(Bishop score≤6) Exclusion criteria: Woman with any contraindication for vaginal delivery, previous uterine or cervical surgery including the loop electrosurgical excision procedure (LEEP), intrauterine fetal death, antepartum bleeding, any active infection of the lower vaginal tract, and eclampsia	n=155, DB: 76 PGE2: 79	10 mg-controlled release dinoprostone vaginal insert	80/80	DB: 38 (50.0) PGE2: 42 (53.2) p=0.694	DB: 18.44 ± 6.3 PGE2: 12.96±13.8 p=0.022*	DB: 30 (39.5) PGE2: 25 (31.6) p=0.185	DB: 0 (0.0) PGE2: 8 (10.1) p=0.007	DB: 9 (11.8) PGE2: 11 (13.9) p=0.699	Moderate **

Continued.

Studies	Design	Country	Characteristics	n	PGE dosing	Volume of catheter	Vaginal delivery within 24 hour, h (n, %)	Induction - Delivery time, h (Mean, Standard Deviation)	C-section rate (n, %)	Uterine Hyperstimulation (n, %)	Neonatal Intesive Care Unit Admission (n, %)	Overall risk of bias
Løkkegaard E	Randomized Control Trial (RCT)	Denmark	Inclusion Criteria: Pregnant women with intact foetal membranes, cephalic position and unfavourable cervix (Bishop score ≤6), together with the usual indications for induction of labour, such as prolonged pregnancy (≥ 42 weeks' gestation), preeclampsia/hypertension, placental insufficiency, gestational diabetes mellitus and twins. Previous caesarean sections. Exclusion criteria: Spontaneous labour, rupture of membranes, placenta previa, acute foetal distress, specific vaginal/cervical infections (e.g. group-B Streptococcus, Condyloma and acute herpes), asthma, glaucoma and latex allergy.	n = 825 DB = 412 PGE2= 413	Vaginal tablet PGE2 dinoprostone (3 mg of Minprostin) 3 -12mg	80/80	Not reported	DB 21.5 (2.5-79)* PGE 19.6 (4.3-83.1)* no p value	DB: 114 (27.7) PGE2: 107 (25.9) P= 0.568	Not reported	DB: 56 (13.6) PGE2: 73 (17.6) p=0.108	High
Pennell. CE	Randomized Control Trial (RCT)	Australia	Inclusion Criteria: Nulliparous pregnant women > 36 weeks' gestation, with a singleton fetus in cephalic presentation and intact membranes. (modified Bishop score of 0–4) Exclusion Criteria: Women <16 years, previous uterine sur- gery, low-lying placenta, any active or purulent infection of the lower vaginal tract, or an abnormal pre-induction fetal heart rate (FHR) tracing."	n= 220 DB = 107 PGE2= 113	Prostaglandin gel 2mg Prostin E2; Pfizer Australia, West Ryde, NSW, Australia	80/80	DB: 40 (37) PGE2: 49 (43) p=0.27	DB: 24.5 (23.7–30.6)* PGE2: 23.8 (21.7–26.8)* p=0.043	DB: 46 (43) PGE2: 42 (37) p=0.567	DB: 0 (0.0) PGE2: 16 (14)	DB: 21 (20) PGE2: 33 (29) p=0.245	Low

Continued.

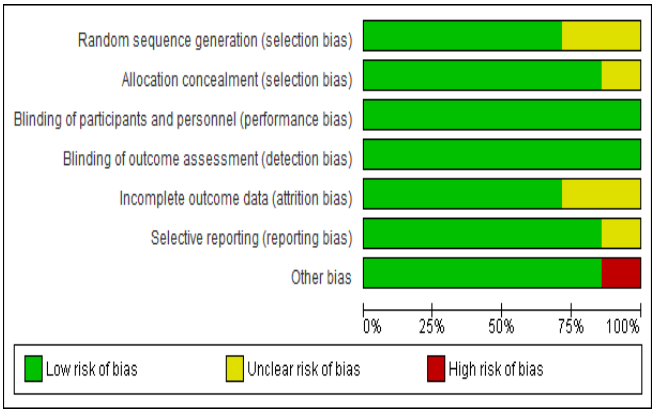
Studies	Design	Country	Characteristics	n	PGE dosing	Volume of catheter	Vaginal delivery within 24 hour, h (n, %)	Induction - Delivery time, h (Mean, Standard Deviation)	C-section rate (n, %)	Uterine Hypersti mulation (n, %)	Neonatal Intesive Care Unit Admission (n, %)	Overall risk of bias
Suffecool. K	Randomized Control Trial (RCT)	USA	Inclusion Criteria: Nulliparous pregnant women ≥18-year-old with term (≥ 37 completed weeks) singleton gestations in vertex presentation and intact membranes. (Bishop score < 6) Exclusion Criteria: Women with contraindications for a vaginal delivery (place nta previa, nonve rtex presentation), pr esence of ruptured membranes, severe preeclampsia, sus pected fetal growth restriction with ab normal Doppler stud- ies, presence of a uterine scar, and a nonreassuring fetal heart tracing requiring immediate interven tion.	n = 62 DB: 31 PGE2: 31	10-mg controlled-release dinoprostone vaginal insert	80/80	DB: 27 (87.1) PGE2: 15 (48.4) p=0.002	DB: 17.9 ± 5.8 PGE2: 26.3 ± 9.7 p=0.0001	DB: 17 (54.8) PGE2: 16 (51.6) p=0.9	DB: 0 (0.0) PGE2: 8 (25.8)	DB: 0 (0.0) PGE2: 0 (0.0)	Low
Shechter-Maor. G	Randomized Control Trial (RCT)	Israel	Inclusion Criteria: Pregnant women with term gestation (≥37 weeks), a singleton, cephalic presentation, intact membranes, oligohydramnios, defined as AFI ≤ 5 cm. (Bishop score ≤ 6) Exclusion Criteria: Women with a multifetal gestation, fetal malpresentation, spontaneous labor, contraindication to prostaglandins or a vaginal delivery (e.g., placenta previa), non-reassuring fetal heart rate tracing, a fetus with major anomalies or previous cesarean delivery.	n = 52, DB = 26 PGE2 = 26	10-mg controlled-release dinoprostone vaginal insert	Atad double-balloon catheter (Cook Cervical Ripening Balloon; Cook Incorporated, IN, USA) volume not mentioned	Not reported	DB: 20.5 (5–55)* PGE2:16 (5–47)* p=0.045	DB: 2 (7.7) PGE2: 4 (15.4) p=0.668	DB: 0 (0.0) PGE2: 2(7.7) p=0.49	Not reported	Low

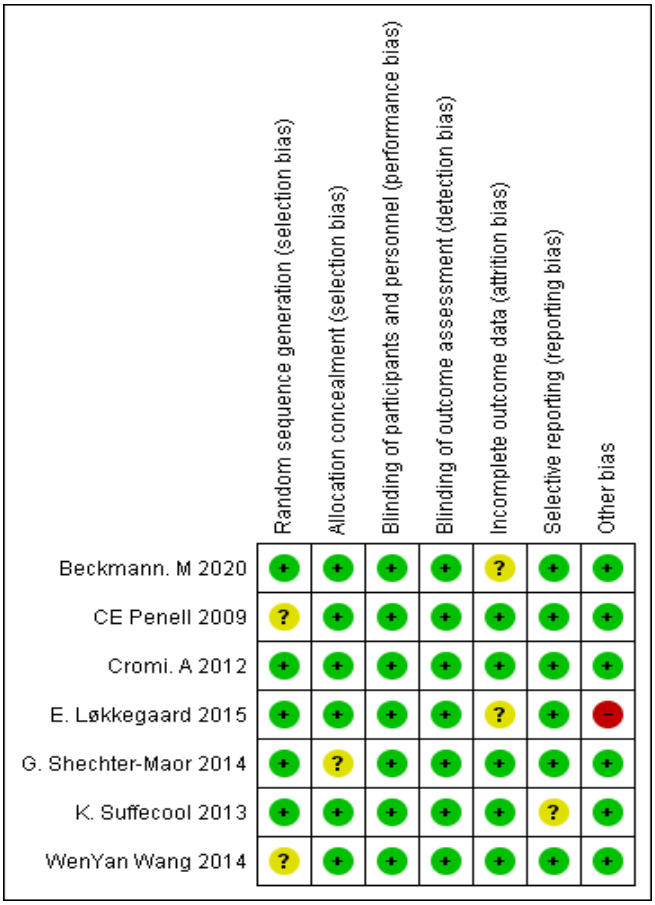
Continued.

Studies	Design	Country	Characteristics	n	PGE dosing	Volume of catheter	Vaginal delivery within 24 hour, h (n, %)	Induction - Delivery time, h (Mean, Standard Deviation)	C-section rate (n, %)	Uterine Hypersti mulation (n, %)	Neonatal Intesive Care Unit Admission (n, %)	Overall risk of bias
Wang. W	Randomized Control Trial (RCT)	China	Inclusion Criteria: Primiparous women with gestational age > 37 0/7 weeks' singleton pregnancy, vertex presentation, oligohydraminos (defined as AFI ≤ 5 cm), intact membranes, the absence of documented uterine contractions, the absence of prior C-section delivery history, and reassuring antenatal fetal testing (non-stress test, NST) active, and oxytocin challenge test (OCT) negative. (Bishop Score < 6) Exclusion Criteria: Women with antepartum bleeding, chorioamnionitis, placenta previa, or any other contraindication to vaginal delivery were excluded. Patients with a documented prostaglandin allergy, maternal asthma history, vaginitis or cervicitis at presentation, and/or glaucoma history were not eligible for the pharmacological treatment arm.	n = 126, DB = 67 (Analysed), PGE2 = 59	10-mg controlled -release dinoprostone vaginal insert	80/80	DB: 40 (59.7) PGE2: 36 (61.0) p=0.88	DB: 1170±32 PGE2: 1122±53 p=0.54	DB: 11 (16.4) PGE2: 13 (22.0) p=0.42	DB: 3 (4.5) PGE2: 10 (16.9) p=0.04	DB: 0 (0.0) PGE2: 2 (3.4) p= 0.22	Low

Study Characteristics Table: DB= Double Balloon, PGE2= Prostaglandin E2, * = reported in median and range. **= Grade based on ROBINS-I

Table 2: Risk of bias of studies.





Primary outcome

Vaginal delivery within 24 hours

Out of the 9 articles analyzed, only 6 articles reported data for vaginal delivery within 24 hours. Studies (12, 19& 27) had no data for this outcome. Near forty five percent, 361(44.4%) of patients from the double balloon catheter group and 303 (37.3%) patients from the prostaglandin E2 group achieved vaginal delivery within 24 hours. According to the forest plot, double balloon catheter group is 17%) (0.17) times more likely to achieve a vaginal delivery within 24 hours compared to the prostaglandin group. But this result is statistically insignificant., (RR 1.17 :95%CI 0.96-1.42, P=0.12) (Figure 2). Due to the high heterogeneity across the studies (I^2= 66%) a random effect model was used and subgroup analysis was done.

Subgroup analysis

Studies by Shechter et al, Lokkegaard et al and Beckmann M et al were removed as these three studies did not report on this outcome.[23,24,27] The subgroups were dinoprostone preparation(vaginal gel, vaginal insert, vaginal tablet), dinoprostone dosage (3mg, 10mg), sample size (<500,>500) and volume of double-balloon catheter were (50ml, 80ml). The vaginal tablet was reported only in Lokkegaard et al. study and no results were obtained as this study was not included.[24] Volume of double-balloon catheter (50 ml) was reported only in one study and therefore I^2 is not significant.

After removing these studies, the heterogeneity of subgroups (dinoprostone preparation, dinoprostone dosage and sample size) was I^2= 75% and volume of DB catheter was I^2=70%. According to Table 4, the test for subgroup differences showed that there was no heterogeneity between(dinoprostone preparation, dinoprostone dosage and sample size) subgroups as I^2=0% with P>0.05, except in volume of double-balloon catheter subgroup where there was heterogeneity between the two subgroups (50ml vs 80ml) I^2= 70.6% with P=0.06 but this is not significant as I^2 cannot be measured in 50 ml DB catheter as only one study was included. Therefore, none of the subgroups measured had a significant effect on vaginal delivery within 24 hours.

Secondary outcomes

Caesarean delivery rate

All nine articles analyzed measured the cesarean delivery rate. 435 (30.8%) patients from the double balloon catheter group and 426 (30.3%) patients from the prostaglandin E2 group underwent cesarean delivery. There was no significant difference in cesarean delivery rate among the patients who were induced using either Double balloon catheter or PGE2 (dinoprostone). (RR 1.02: 95% CI 0.92-1.14. p=0.68). Due to low heterogeneity across the studies, a fixed effect model was used, (I^2=0%).

Induction to delivery time

Only eight studies reported Induction-Delivery Time (I-D time). I-D time was shorter in the prostaglandin group as SMD>0 (0.02 CI: -0.18,0.22, p=0.86), with moderate quality of evidence, but it is statistically not significant as p=0.86. Due to the high heterogeneity across the studies, a random effect model was used. (I^2=80%). A subgroup analysis was done based on the high heterogeneity.

Table 3: Risk of bias of studies based on ROBINS-I.

Studies	Domain 1: con founding	Domain 2: selection of participants	Domain 3: classification of intervention	Domain 4: deviation from interventions	Domain 5: missing data	Domain 6: measurement of outcomes	Domain 7: selection of reported result	ROBINS-I overall
Brown. J (2017)	2	0	2	2	0	2	0	3
Du.C (2014)	2	1	**2-3**	2	1	2	0	2

Risk of bias assessment: 0 No information; 1 Low; 2 Moderate; 3 Serious; 4 Critical
Bold figures indicate disagreement of two or more levels of bias across assessments between assessors

Table 4: Subgroup analysis of 24hr vaginal delivery.

	N	Odds ratio, 95% CI, h	P	I^2, %
Dinoprostone preparation type	6			
Vaginal gel	2	1.27[0.98,1.64]	0.07	75
Vaginal insert	4	1.53[1.09,2.14]	0.01	75
Vaginal tablet	-			
Dinoprostone dosage	6			
<3mg	2	1.27[0.98,1.64]	0.07	75
10mg	4	1.53[1.09,2.14]	0.01	75
Sample size	6			
>500	1	1.26[0.95,1.68]	0.01	
<500	5	1.47[1.09,1.97]	0.11	75
Volume of balloon catheter	6			
50/50	1	2.22[1.26,3.91]	0.006	
80/80	5	1.26[1.01,1.57]	0.04	70

Table 5: Subgroup analysis for induction to time delivery.

	N	MD (95% CI), h	P	I^2,%
Dinoprostone preparation type	8			
Vaginal gel	2	-0.08 [-0.20,0.04]	0.21	0
Vaginal insert	5	-0.0 1[-0.46,0.43]	0.95	85
Vaginal tablet	1	0.15 [0.01,0.28]	0.04	
Dinoprostone dosage	7			
<3 mg	2	-0.08 [-0.20,0.04]	0.21	0
10 mg	5	-0.01 [-0.46,0.43]	0.95	85
Sample size	8			
>500	2	0.02 [-0.23,0.27]	0.88	85
<500	6	0.00 [-0.34,0.34]	0.99	82
Volume of balloon catheter	7			
50/50	1	-0.14 [-0.41,0.13]	0.31	
80/80	6	0.00 [-0.24,0.24]	0.98	84

Subgroup analysis

Subgroup analysis was conducted by stratifying the pooled data according to dinoprostone preparation (vaginal gel, vaginal insert, vaginal tablet) dinoprostone dosage (<3mg, 10mg) sample size (<500, >500) and double-balloon catheter volume (50ml, 80ml). All 8 studies were included in dinoprostone preparation and sample size. We excluded studies by Lakeward, Shechter and Beckmann for double-balloon catheter volume.[12,19,27]

None of the subgroups measured had a significant effect on the induction to delivery time between the two groups (p>0.05) For the two parameters, vaginal tablet and volume of double-balloon catheter (50ml) I^2 was not significant as both included only one study. The overall test for subgroup differences for all parameters excluding the dinoprostone preparation was not statistically significant (p>0.05) and there was no heterogeneity between the subgroups as I^2=0%. For the dinoprostone preparation parameter though it was statistically not significant (p=0.06) there is moderate heterogeneity between the different preparation methods used as I^2= 65.5%

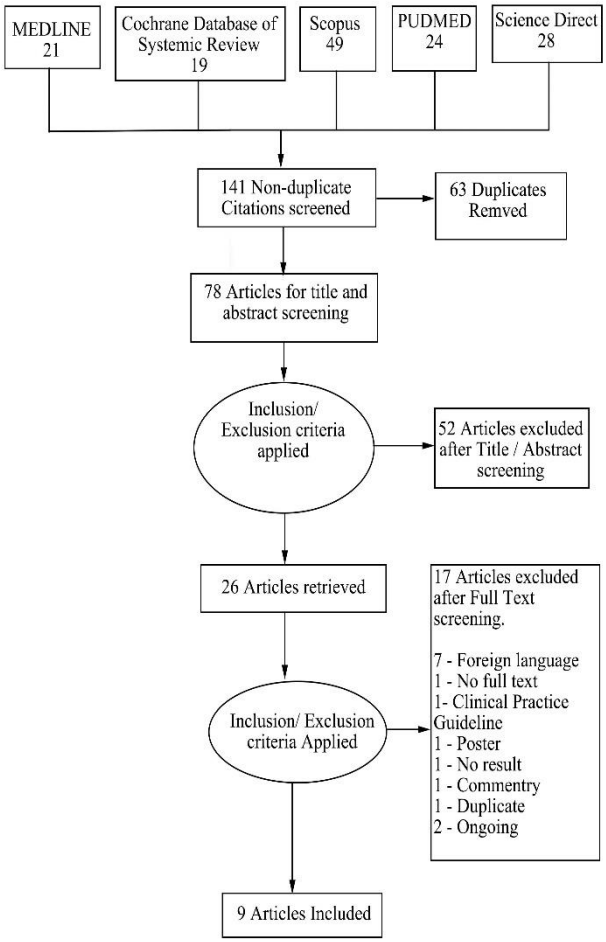


Figure 1: PRISMA flow chart.

Maternal outcomes

Out of the 9 studies only 7 reported on adverse maternal outcomes. According to the forest plot it shows that women induced with double balloon catheter is 9%, (0.09) times less likely to have adverse maternal outcomes compared to the prostaglandin group. This is statistically significant as p<0.00001(RR 0.09: CI 0.04, 0.22). As there is no heterogeneity across the studies a fixed effect model was used. I^2=0%

Neonatal outcome

Only 8 articles reported on neonatal outcomes (NICU admission). The forest plot depicts that inducing with a double balloon catheter is 0.75 times less likely to result in adverse neonatal outcome (NICU admission) compared to prostaglandin group and is statistically significant. (RR 0.75 CI: 0.62,0.90 p=0.003). There was no heterogeneity across the studies and a fixed effect model was used, I^2 =0%.

Publication bias

The funnel plot for cesarean delivery rates is symmetrical with equal distribution of studies on either side. Out of the nine studies, eight of them are with a moderate to low Standard error (SE). One study showed a high SE, but the RR=1, therefore this shows that inducing with dinoprostone or double-balloon catheter has an equal effect on the cesarean delivery rates. The was no major publication bias (but we cannot conclude for certain, as the number of studies included is less than 10)

The funnel plots for maternal outcome and neonatal outcome are symmetrical with all six studies falling under the graph with confidence intervals (CI:0.04, 0.22) and (CI:0.62,0.90) respectively. For the maternal outcome, there is only one study that shows a low SE while the rest have high SE (smaller sample size). The RR=0.09; as it is less than 1, it shows that uterine hyperstimulation is less likely to occur in double-balloon catheter group. For the neonatal outcome, only one study showed a high SE, while the rest of the studies have a low SE, RR=0, depicting neonatal outcomes are less likely to occur in double-balloon catheter group. With respect to maternal and neonatal outcome, there is no major publication bias, but we cannot decipher for certain as the number of studies included is less than 10.

Overall quality of evidence

Sensitivity analyses were performed on vaginal delivery within 24 hours and induction-to-delivery-time, which had substantial heterogeneity, I^2 greater than 50%. Estimate results for both outcomes remained the same for both random effects and fixed effect models. By sequentially removing the most recent trials and re-analysing the remaining dataset, it did not change the results for the outcomes. Sensitivity analyses carried out with only studies with low risk of bias also reveals no changes to the outcomes.

The overall quality of the evidence was assessed according to the type of studies (RCTs and observational). In this review, all outcomes, except uterine hyperstimulation were downgraded by one level for imprecision, as the optimal information size criterion is not met and the 95% CIs of their pooled effect sizes included the unit. Several outcomes were further downgraded by one level for serious risk of bias due to

lack of information on the selection of participants, missing data, and selection of reported result. For RCTs, the overall quality was moderate for vaginal delivery within 24 hours, cesarean delivery rate, induction-to-delivery time, and NICU admissions, and high for uterine hyperstimulation. For observational studies, the overall quality is low for vaginal delivery within 24 hours, cesarean delivery rate, induction-to-delivery time, and NICU admissions, and moderate for uterine hyperstimulation. Since the effect estimates remained the same when sensitivity analysis was conducted with only studies of low risk of bias, the overall quality of evidence combining both types of studies is moderate for vaginal delivery within 24 hours cesarean delivery rates, induction-to-delivery time, and NICU admission, and high for uterine hyperstimulation.

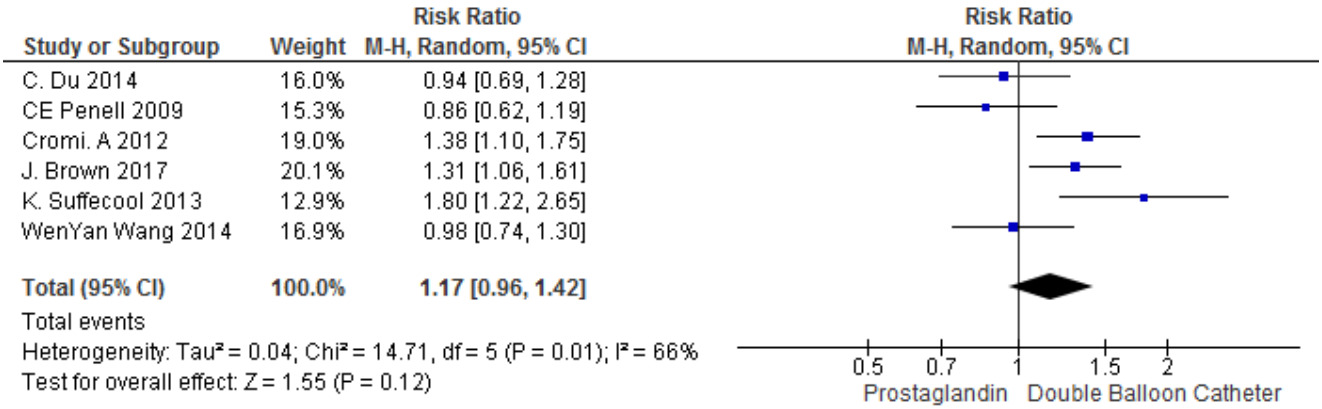


Figure 2: Forest plot of comparison: double balloon catheter VS PGE2, outcome: vaginal dselivery within 24 hr.

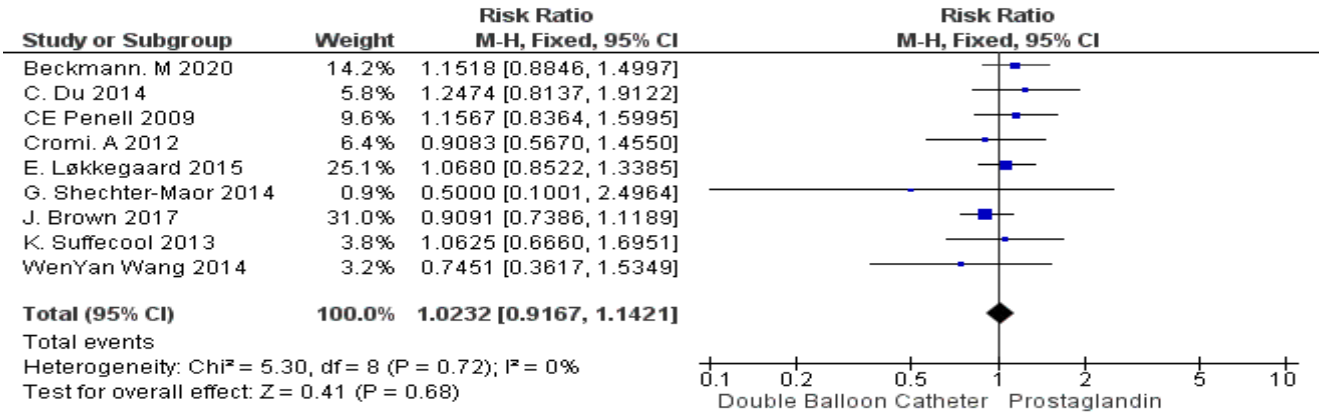


Figure 3: Forest plot of comparison: double balloon catheter VS Prostaglandin, outcome: C-section rate.

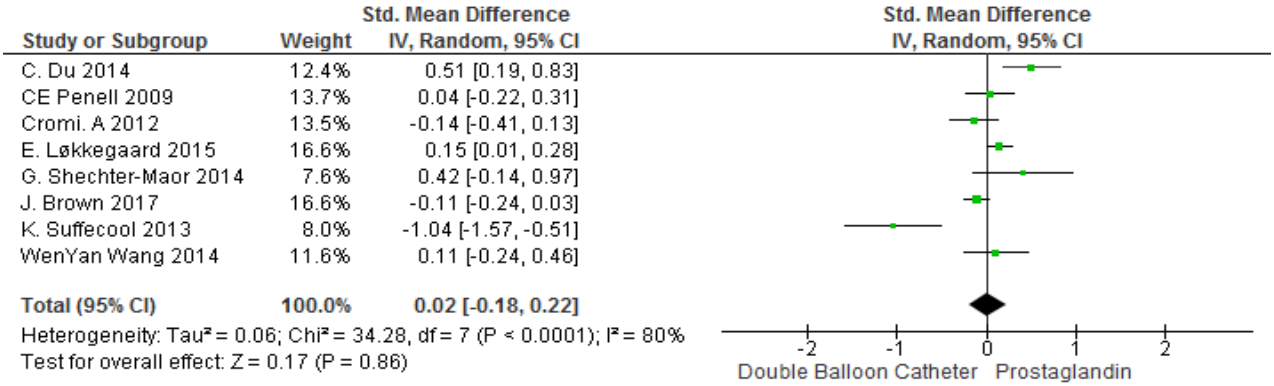


Figure 4: Forest plot of comparison: double balloon catheter VS PGE2, outcome: induction to delivery time.

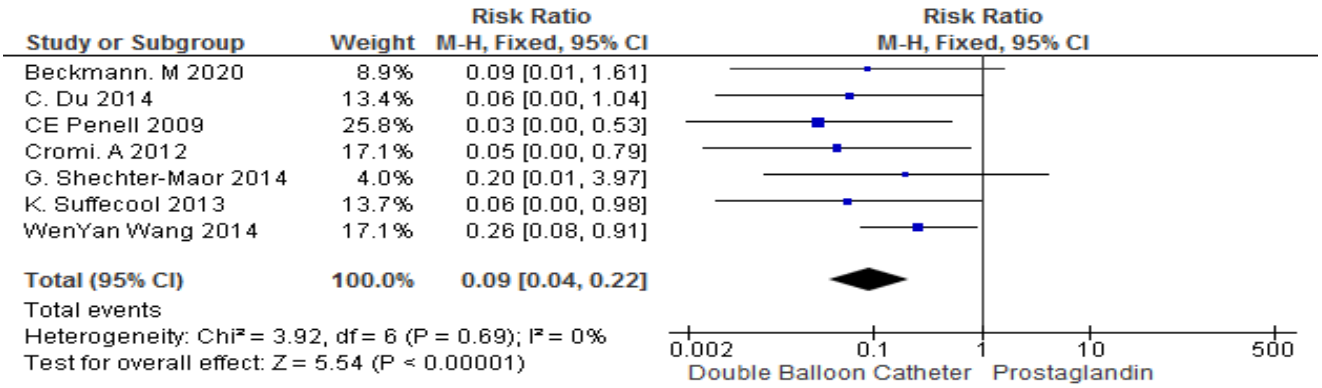


Figure 5: Maternal outcome - uterine hyperstimulation.

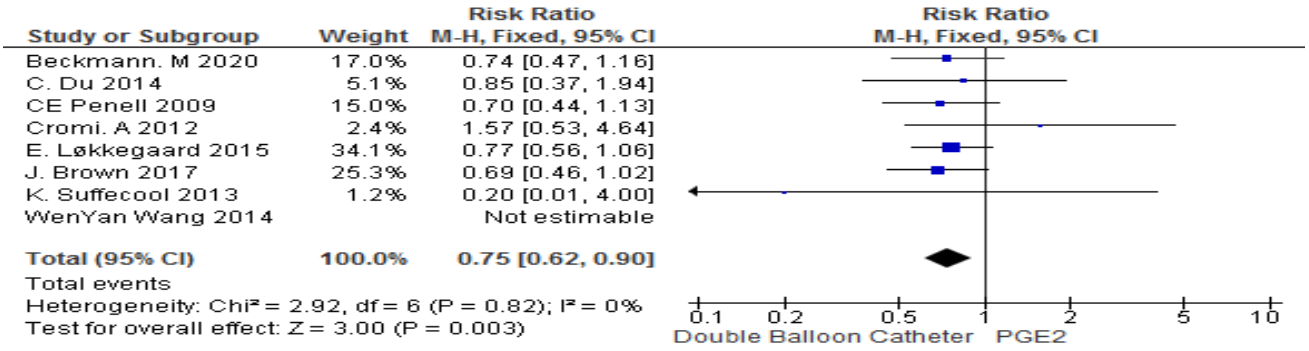


Figure 6: Neonatal outcome - NICU Admission.

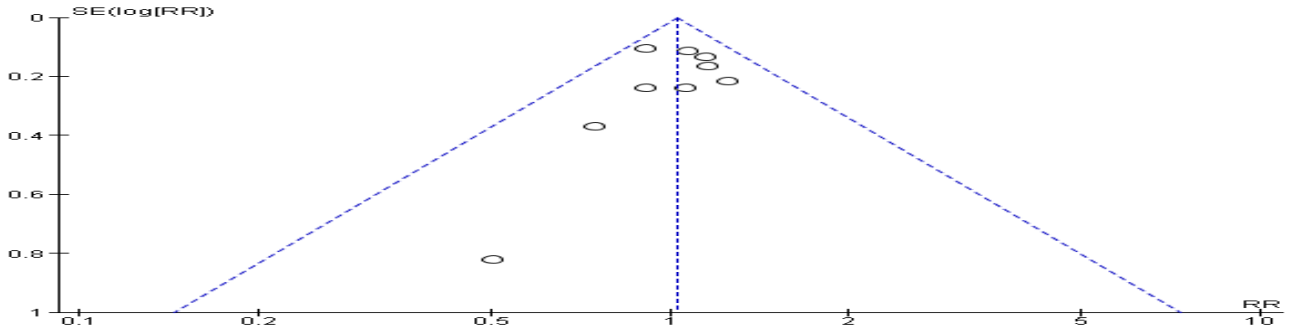


Figure 7: Funnel plot-caesarean delivery rate.

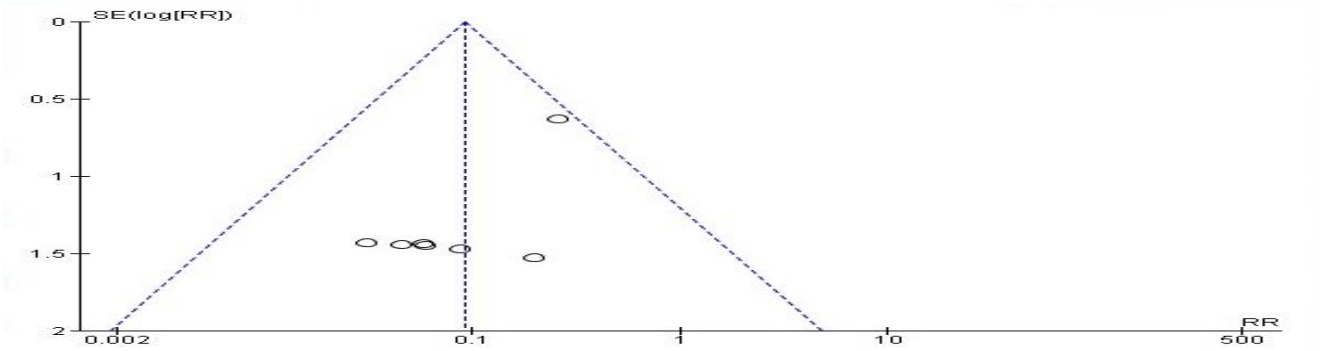


Figure 8: Funnel plot - maternal outcome: uterine hyperstimulation.

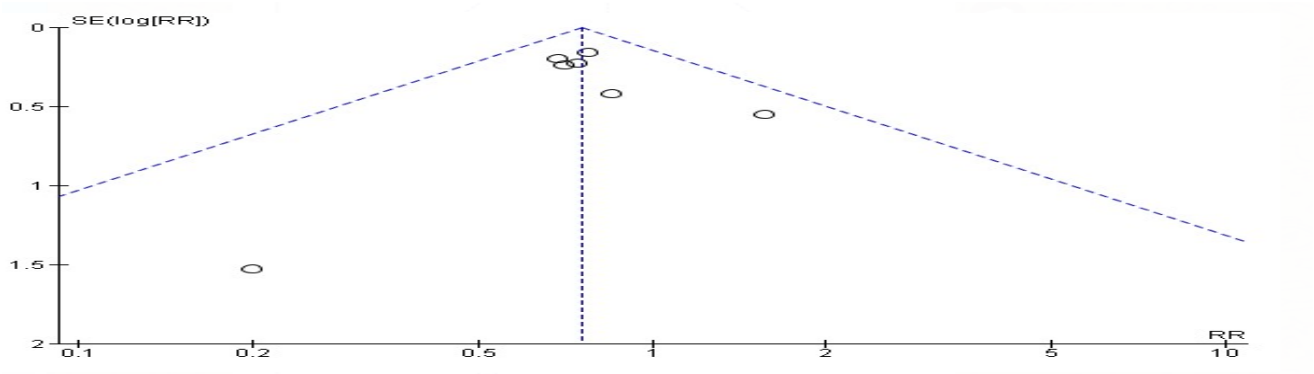


Figure 9: Funnel plot for neonatal outcome-NICU admission.

DISCUSSION

This meta-analysis provided an extensive comparison between PGE2 (vaginal insert, tablet, and gel) and double-balloon catheter in inducing labor in women with unfavorable cervix and it has demonstrated that both interventions were similar with respect to vaginal delivery within 24 hours, cesarean delivery rates, and induction-to-delivery interval. Meanwhile, PGE2 has a higher risk of uterine hyperactivity and neonatal outcome of intensive care unit admission.

Comparison with similar systematic reviews

Currently, there are only two systematic reviews on this topic by Du et al and Liu et al.[25,26]

By comparing our result with their systematic reviews, we are able to infer that double-balloon catheter and prostaglandin E2 have comparable efficacy in induction of labor. Du et al included seven studies whereby two of them were published before the year 2000 that yielded a non-significant result that favored PGE2 as compared to double-balloon catheter with regard to 24-hour vaginal delivery.[25] Liu et al also reached the same conclusion for this outcome.[26]

Besides that, Du et al also reported no difference in the cesarean delivery rates between PGE2 and double-balloon catheter, which again showed the same findings as our analysis.[25] Liu et al noted a lesser number of women who required cesarean delivery in double-balloon catheter arm as compared with the dinoprostone arm, but it was not statistically significant.[26] In terms of induction-to-delivery time, both Du et al and Liu et al have a comparable results whereby it revealed no significance between double-balloon and prostaglandin, which corresponds to our findings.[25,26]

In addition, Du et al and Liu et al showed that PGE2 has a higher rate of uterine hyperactivity as compared to double-balloon catheter, which is statistically significant.[25,26] For NICU admissions rate, Du et al showed that it is high in prostaglandin group while Liu et al showed no differences.[25,26] Our analysis indicates that both maternal and neonatal outcomes have a higher incidence rate in prostaglandins arm compared to double-balloon catheter. The disparity between the reported findings in neonatal outcome could be explained by the relatively small sample size in the meta-analysis done by Liu et al.[26]

Although our review does not focus on patient satisfaction, it is an important factor that should be considered when inducing patients and would be beneficial if more research is done on this topic.

Limitations

One of the limitations in this review is the study characteristics and the method used which are not homogenous across all studies. To name a few, the indication for removal of double-balloon catheter and dinoprostone, the time allowed for intervention, preparations of dinoprostone, oxytocin administration and the definition of the measurements and outcomes e.g. the dosage of oxytocin administered varied from 2-30 mIU/min across the studies. Another limitation is the inability to blind the participants and healthcare personnel and outcome assessment. Therefore, bias may arise in these areas.

The research for our meta-analysis included articles published only in the English Language. Though we did search for the translation of the foreign articles when carrying out full text screening before excluding them, other relevant articles that may have helped with our findings would have been excluded.

Strengths

Compared to other similar reviews on the same topic, we have included Trial Sequential Analysis (TSA), which is a statistical test that determines how conclusive our review is, and GRADE assessment which assess the risk of bias across the studies for each outcome.

In conclusion, there is no difference in the efficacy of double-balloon catheter and prostaglandins in the induction of labor. However, our results showed that, in

terms of maternal and neonatal outcomes, double-balloon catheter was safer than the prostaglandin group to induce labor.

CONCLUSION

There is no difference in the efficacy of double balloon catheter and prostaglandins in the induction of labour. However, results showed that in terms of maternal and neonatal outcomes the double balloon catheter was safer than prostaglandins to induce labor.

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