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Intravaginal misoprostol versus Foley catheter balloon for induction of labor: A systematic literature review, meta-analysis, meta-regression, and trial sequential analysis

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Abstract
Induction of labor is a common procedure in obstetrics. Numerous methods (both mechanical and pharmacological) are used for induction, however, there is lack of consensus for a safe effective means.
Objective: The aim of this review was to compare intravaginal Misoprostol to Foley catheter balloon for induction of labor and cervical ripening in uncomplicated pregnancy, with regards to safety and effectiveness.
Method: We systematically searched MEDLINE and EMBASE for randomized controlled trials comparing both means. Included studies were assessed for risk of bias and certainty of evidence using GRADE methodology. Results were presented as forest plots of odds ratio or mean difference. Predefined subgroup analyses and meta regression were conducted to account for heterogeneity, and the conclusiveness of results was evaluated in a trial sequential analysis (TSA).
Results: 19 studies were identified, the primary outcome of caesarean section showed a 20% reduction in odd of CS with Misoprostol [OR = 0.8 (95% CI: 0.67 – 0.96; p = 0.02), secondary outcomes of NICU admission and APGAR score < 7 at 5 minutes were not different between both groups, while Misoprostol induced group had a lower intervention to delivery interval and a higher incidence of maternal tachysystole. Quality of evidence was downgraded low to Very low for the different outcomes, and results were deemed inconclusive by TSA.
Conclusion: Low quality inconclusive evidence suggest decreased likelihood of CS with intravaginal Misoprostol induction compared to Foley catheter balloon.

Keywords: Misoprostol, Foley catheter, induction, ripening

Introduction
Induction of labor (IOL) is the most common procedure in obstetrical practice, involving 20-30% of all deliveries with varying rates globally [1-3]. The aim of IOL is usually to attain vaginal delivery by stimulating uterine contraction earlier than it spontaneously onsets [4]. Diverse indications are recognized for IOL, common among which are post-term, hypertensive disorders, diabetes in pregnancy, macrosomia, intrauterine growth retardation, and elective reasons [5, 6].
IOL usually involves an unfavorable (unripe) cervix at the beginning of the procedure, prolonging induction to delivery time, increasing caesarean section (CS) rates, and raising risk of induction failure [7], unfavorable cervix may be tackled utilizing several pharmacological and mechanical agents, to hasten cervical ripening, plus their role in facilitating IOL [8].
Foley catheter balloon (FCB) is the most common mechanical method used for IOL [9]. It acts by applying local pressure to the cervix resulting in its dilatation, stimulating the release of endogenous prostaglandins locally, thus altering the cervical status [1], and a potential limited effect on uterine contraction [10].
The FCB method harbors several advantages including easiness, simplicity, low cost, and fewer baleful events (such as uterine tachysystole, fetal heart rate alteration, and operative vaginal deliveries). However, it is not without draw backs like the risk of infection, maternal discomfort, or contraindications such as low lying placenta [11, 12].

Prostaglandin derivatives have widely gained popularity, and are replacing mechanical methods as induction agents [5], particularly Misoprostol (PGE1 analogue) is an effective exogenous prostaglandin, initiates uterine contraction, and synergistically ripens the cervix [10, 13,14], in addition to being relatively cheaper compared to other prostaglandin preparations, stable at room temperature, and easy to store [13]. Although it has been argued that the widespread use of prostaglandins as induction agents was not based on sufficiently powered studies, nor with meticulous assessment of safety and effectiveness, particularly concerning the appropriate regimen of dosing [5].

Currently, a consensus regarding the optimal method of IOL is lacking [2, 3], especially with results of randomized controlled trials (RCT) showing supremacy of FCB over prostaglandins regarding safety [15, 16], while results of meta-analyses show comparable effectiveness [10].

This inconclusiveness is reflected in the recommendations of the major guidelines on IOL. The American College of Obstetricians and Gynecologists (ACOG) guidelines [17] state that prostaglandins E analogues are effective for cervical ripening and IOL, and Foley catheter is a reasonable alternative. Whereas the NICE guidelines on IOL [18] is much more conservative, stating that Misoprostol should not be used for IOL except in cases of intra-uterine fetal death (IUFD) or within the context of a clinical trial, and mechanical methods (including balloon catheter) should not be used routinely for IOL. In contradiction, the Canadian guideline [19] declares Misoprostol as a safe and effective agent of IOL, and FCB as an acceptable agent both in the settings of vaginal birth after CS and outpatient.

Objectives

The paucity of consensus about the preferable method of IOL is the purpose of this literature review to compare Misoprostol to FCB in terms of effectiveness and safety, both maternal and neonatal.

Method

We utilized the PRISMA checklist of minimum items to be reported in a review [20].

Studies selection *criteria*

We included only RCTs comparing vaginally inserted Misoprostol (in any dose, frequency, and maximum dose) to FCB (of any balloon filling volume and maximum allowed duration) whether or not IOL in either arms was augmented with oxytocin after completion of the induction protocol. However, studies administering oxytocin concomitantly with the induction agent were excluded. Included studies were published in English only, as of the year 2000. We excluded studies utilizing other forms of Prostaglandins, other routes or preparations of Misoprostol, other form of mechanical IOL, or comparing any of the two interventions of interest to placebo, or to a combination. If a study included a third arm, that arm was excluded, but the compared arms relevant to the review were sustained. We excluded other study designs, unpublished data, brief communications, letter to editors, and conference proceedings. Included studies must have reported at least one of our review's outcomes.

PICO framework

Population: Pregnant females admitted for IOL, regardless of the indication, gestational age, or associated medical conditions.

Interventions: One arm was subjected to intra-vaginally inserted Misoprostol as an induction and/or cervical ripening agent, oxytocin augmentation may be started after Misoprostol completion.

Control: Second arm was exposed to single FCB for induction and/or cervical ripening, oxytocin augmentation may be started after the maximum allowed duration.

Outcome: The primary outcome of this review was the rate of CS, secondary outcomes included: Maternal incidence of Tachysystole (definition in supplementary file), and intervention to delivery time (for successful inductions). Neonatal outcomes included: Rate of Neonatal Intensive Care Unit (NICU) admission, and rate of APGAR score < 7 at 5 minutes.

Identification of studies

We systematically searched MEDLINE and EMBASE databases for eligible studies using the terms "labor induction", "cervical ripening", 'Foley", and "Misoprostol" (detailed MEDLINE search strategy in supplementary file).

Data extraction

Two authors independently scrutinized each identified study to extract data on a pre-prepared data extraction sheet. Extracted data included: Last name of first author, year of publication, country, total sample size and number in each study arm, inclusion and exclusion criteria, protocol of Misoprostol administration, protocol of FCB insertion, and all reported outcomes. Authors reporting continuous outcomes as median and interquartile range (IQR) or range were contacted to provide mean and standard deviation (SD) summary, if we didn't receive a response we imputed data according to a mathematical method (details in supplementary file).

Assessment of risk of bias

Two authors independently assessed risk of bias for each study, deploying the modified version of the Cochrane Collaboration tool [21]. Regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias, reporting bias, and other sources of bias. Each domain of bias risk was graded as low, high, or unclear. Discrepancies between authors were resolved by a third author.

Certainty of evidence

Certainty of evidence was evaluated by first and last authors, and reviewed by all authors according to the GRADE approach [22], the GRADE system evaluates certainty of evidence aggregated as: high, moderate, low, or very low, for a particular outcome after consideration of five criteria (individual study risk of bias, directness, consistency, precision, and publication bias). Every criterion could be evaluated as: Not serious, serious, and very serious.

Statistical Method

In this review we presented outcomes as odds ratio (OR) for binary, and as mean difference (MD) for continuous outcomes, with corresponding 95% confidence interval (CI), both effect measures were results of fixed effect models (Mantel-Haenszel method), and were graphically presented as forest plots. We assessed heterogeneity using I^2 and chi^2 tests, considered significant for heterogeneity with chi^2 p value < 0.1, or $I^2 > 50\%$. When significant heterogeneity was detected the pooled effect

estimate was presented as random effects model (Der Simonian – Laird method) [23].

Investigation of heterogeneity and subgroup analysis

To investigate potential causes of heterogeneity we presented the random-effects model using inverse variance method (accounting for across studies variation) as measures of sensitivity analysis [21], we also conducted a meta-regression utilizing the continuous predictors of Misoprostol dose, maximum allowed dose, and maximum duration of Foley catheter, in addition to a combined logistic regression model of all three factors.

Furthermore, we set a priori the following sub-group analyses for the primary outcome, based on our expectations of variations in population and studies' criteria:

- Similar Misoprostol protocols.
- Similar Foley catheter protocols.
- Studies with low risk of bias.
- Term pregnancies.

Publication Bias Assessment

We graphically assessed publication bias using funnel plot, the significance of which was evaluated using Egger's test for the primary outcome (the null hypothesis of no effect of small studies could be rejected if $p<0.05$).

Data Management

Data that we couldn't obtain from authors were imputed mathematically. studies with no events in both arms (double zero studies) for an outcome were excluded from the analysis, whereas; studies with zero events in one arm only of an outcome (single zero studies) were retained in the analysis after zero-cell correction by adding 0.5 to all cells [21] using statistical software.

To account for studies with small sample size or rare events we conducted a trial sequential analysis (TSA) based on the assumption of 5% type I error and 90% power for a two sided test, represented as a cumulative Z-curve with futility, significance, and optimum information size (OIS) monitoring boundaries according to O'Brien - Fleming alpha and beta spending functions.

All statistical tests and graphs were generated using STATA 14 software (*Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP.). Review Manager (Rev Man) [Computer program]. Version 5.3.* And freely available TSA software [24].

Results

Our systematic MEDLINE search yielded 483 articles, 439 articles were excluded after review of title or abstract, 44 complete texts were reviewed resulting in exclusion of 27 articles that didn't meet our inclusion criteria (table S1supplementary file), and inclusion of 17 articles. EMBASE search resulted in inclusion of two more unique articles, bringing the total of included articles to 19 (Figure 1).

The included articles [25 – 43] recruited 2672 subjects, 1333 in the Misoprostol group, and 1339 in the FCB group. All studies were single centered except for one [33], the age of recruitment was specified to be at least 18 years in only two articles [33, 35], while the remaining studies did not define an age limit. The gestational age was mostly at least 37 weeks [25, 26, 33, 35, 36, 39, 43], two studies [29, 40] recruited patients of 28 weeks gestation, another [28] specified a minimum of 34 weeks, Gelisen *et al*. [31] and Kandil *et al*. [34] required completion of 41 weeks of gestation, while Sheikher *et al*. [41] specified a range of 37 to 42 weeks of gestation. The inclusion requirement was "term pregnancy" in four studies [30, 32, 38, 42], need of induction of labor in one study [27], and was not mentioned in one study [37]. All studies included singleton pregnancies, intact membranes, and vertex presentation (except for Prager *et al*. [38] which could recruit PROM), studies excluded patients with previous uterine scar, non-cephalic presentation or cephalo-pelvic disproportion, placenta previa, and antepartum hemorrhage. Misoprostol regimens varied from 25 micrograms every 6 hours for 3 doses [28], up to 50 micrograms every 6 hours for 4 doses [25]. FCB filling volume ranged between 30-60 ml, for 12-24 hours (Details of included studies in table S2 in supplementary file).

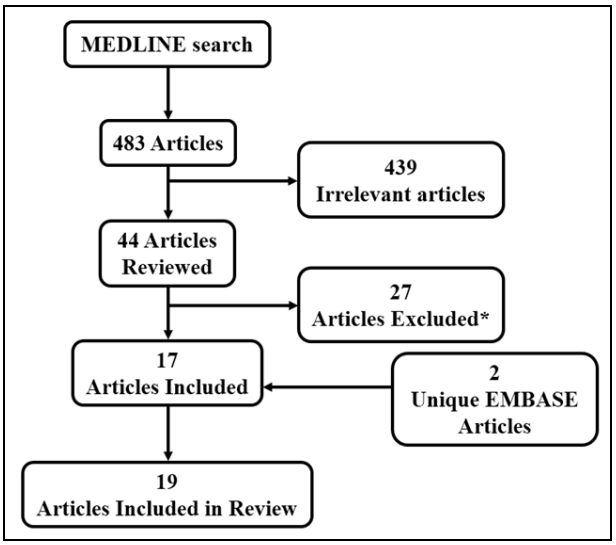

Fig 1: MEDLINE search and articles' inclusion

Risk of bias assessment

Generally, risk of bias was low (figure 2), all studies had low risk of attrition as well as blinding of participants and personnel bias, as all reported the numbers and reasons of excluded patients after randomization and were minimal in all studies. All studies were open label, however, this most probably had no effect on the outcomes as those were objectively measured. All studies reported either intention to treat or modified intention to treat analyses. All studies (but one [25]) had low risk of selective reporting bias, *Adeniji et al*. [25] reported outcomes in a manner different from what was described in the method. Risk of bias in random sequence generation was low in about 75%, one study [34] randomized patients based on odd and even days of admission, while three [36, 39, 41] didn't describe a method of randomization. Risk of allocation concealment bias was also low in about 75% of the studies, five studies [34, 35, 36, 39, 41] reported no method of allocation concealment. Risk of bias due to blinding of assessors was not clear in all studies except for *Levine et al*. [35] which clearly stated blinding of data assessors to group membership. Seven studies [34, 37, 39, 40, 41, 42, 43] might have had a selection bias due to lack of reporting on the number of screened patients, number and reasons of excluded patients. *Sciscione et al*. [40] might have had another source of selection bias since the study initially allowed recruitment of patients with history of CS, but later excluded them due to an adverse event. The issue of dividing tablets of Misoprostol to achieve the required dose was not considered as a bias risk since it was prepared by specialized pharmacists.

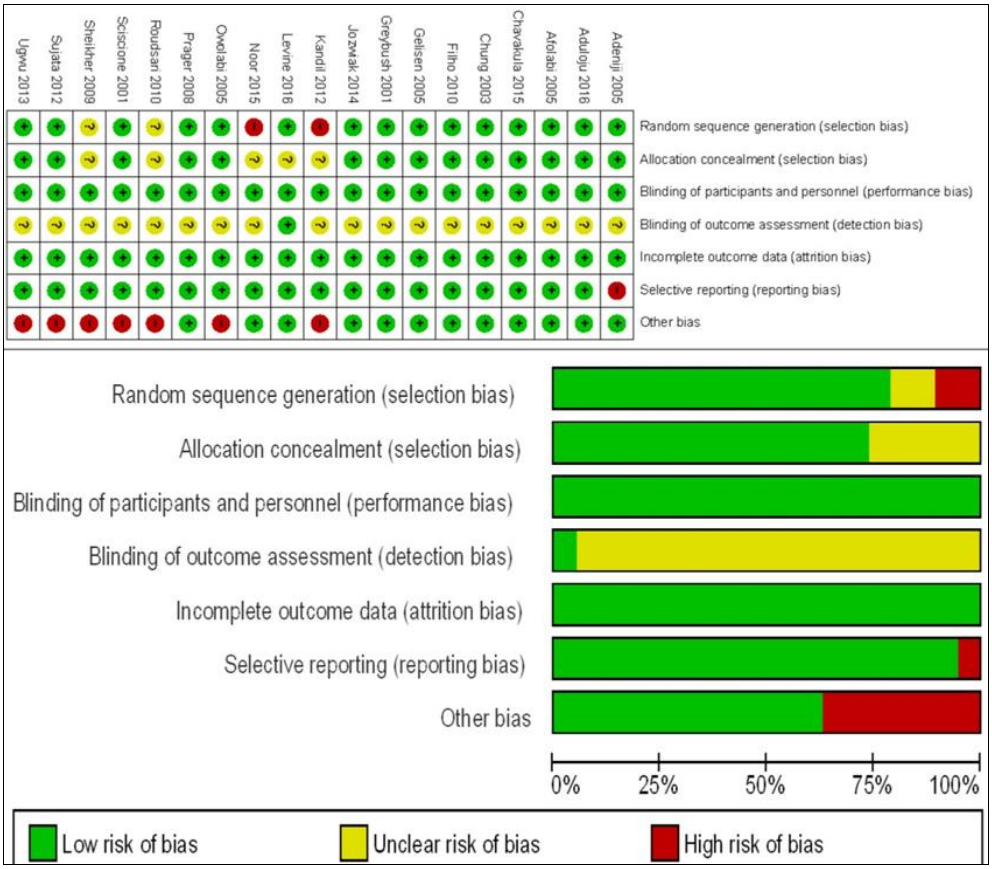

Fig 2: Risk of bias graph and summary

Primary outcome: Rate of CS

All 19 studies reported the rate of CS, 306 (23%) pregnant women required CS with Misoprostol, while 362 (27%) required CS with FCB, this result indicates a significant 20% lower odds of CS in the Misoprostol arm (OR 0.80; 95% CI: 0.67 – 0.96, p = 0.02) (figure 3).

Heterogeneity was not significant according to I^2 test (36%), however; chi^2 test yielded a p value of 0.06, so we performed a random effects model (figure S1) which had a significant result, with a wider CI as would be expected when there is no small study effects [44], the absence of small study effects is evident by Egger's test p value of 0.3, and a more or less symmetrical funnel plot (figure 4). In the random effects model OR of CS was 0.78 (95% CI: 0.61 – 0.98, p = 0.04) in favor of Misoprostol (figure S1).

As a sensitivity analysis to account for across studies heterogeneity the random effects inverse variance model was performed, and it showed exactly the same results as (Mantel – Haeszel) random effects model (figure S2).

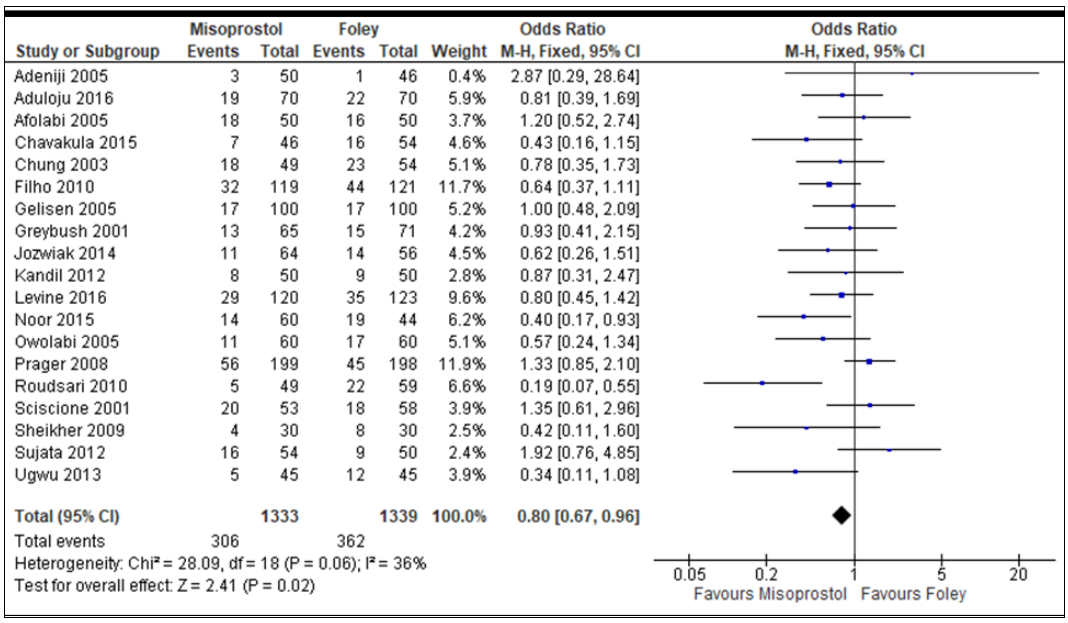

Fig 3: Forest plot of CS odds ratio, fixed effect model

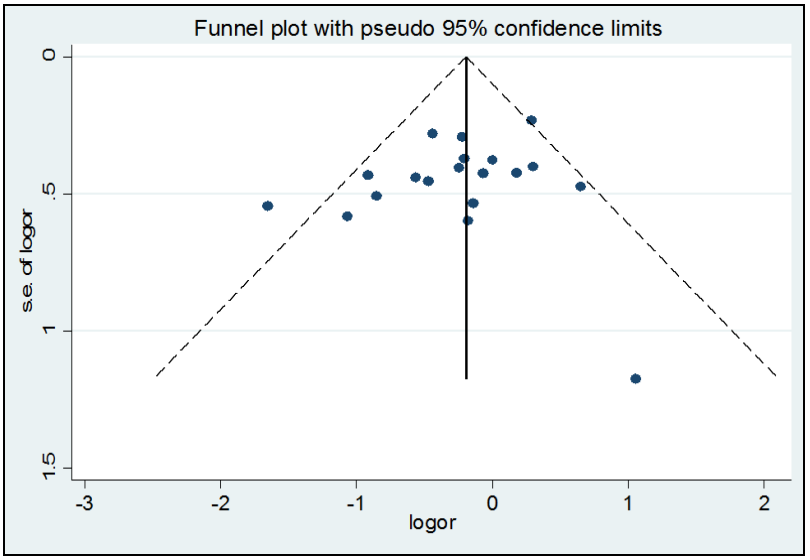

Fig 4: Funnel plot of primary outcome

Meta regression

None of the predefined variables included in the meta-regression was found to be significant, either when evaluated separately or when adjusted for other variables (table 1).

Table 1: Results of meta-regression

	Separately tested		Combined Model	
Variable	**95% CI**	**P value**	**95% CI**	**P value**
Misoprostol Dose	-0.004 to 0.014	0.3	-0.05 to 0.06	0.8
Maximum allowed Misoprostol dose	-0.0001 to 0.01	0.054	-0.014 to 0.02	0.7
Foley catheter size	-0.1 to 0.08	0.8	-0.2 to 0.3	0.7
Foley catheter filling volume	-0.02 to 0.02	0.9	-0.06 to 0.05	0.9
Allowed duration of Foley catheter	-0.03 to 0.04	0.6	-0.07 to 0.11	0.4

Fig S3 – S7: in supplementary file depict bubble plots of investigated variables. CI = confidence interval.

Subgroup analysis

None of the predefined subgroups' analyses showed statistical significance in favor of either intervention. Subgroup of the most common Misoprostol protocol of 25 micrograms every 4 hours included 9 studies [32-34, 36, 38, 39, 41-43], OR for CS was 0.71 (95% CI: 0.45 – 1.14; p = 0.16), there was high heterogeneity with I^2 = 61% and chi^2 p = 0.009 (figure S8 supplementary file).

The most common Foley catheter protocol was for a maximum duration of 24 hours with filling volume of 30 ml in 5 studies [25, 26, 27, 30, 43]. OR of CS was insignificant at 0.75 (95% CI: 0.5 – 1.14; p = 0.18) withlow heterogeneity (I^2 = 14%, chi^2 p = 0.32) (figure S9 supplementary file).

12 studies [25, 26, 30, 32, 33, 35, 36, 38, 39, 41, 42, 43] recruited term patients (at least 37 weeks of gestation), OR of CS was 0.83 and statistically insignificant (95% CI: 0.62 – 1.11; p = 0.2), heterogeneity was low (I^2 = 32%, chi^2 p = 0.14), figure S10 supplementary file.

The lowest heterogeneity was observed in the subgroup of studies with low risk of bias, I^2 = 0% and chi^2 p = 0.53, the subgroup included 11 studies [25-33, 35, 38] and also had an insignificant result (OR of CS = 0.89, 95% CI: 0.72 – 1.1; p = 0.27) (figure S11 supplementary file).

Secondary outcomes

Maternal incidence of tachysystole

Nine studies [25, 27-32, 39, 42] reported the incidence of tachysystole according to pre-specified definition (supplementary file). There was a significantly lower incidence of tachysystole in favor of FCB (OR = 4.1, 95% CI: 2.47 – 6.79; *p*<0.0001), there was no heterogeneity (I^2 = 0%, chi^2 p = 0.95). (figure S12 in supplementary file).

Intervention to delivery interval (for successful induction) showed a significant result in favor of Misoprostol with a reduction of about 2 hours between start of intervention and delivery (mean difference = -2.18, 95% CI: -3.85 to -0.5 hours, p = 0.01), heterogeneity was high (I^2 = 91%, chi^2 *p*<0.0001). This outcome was reported in 14 studies [26-30, 33-36, 38-42] (figure S13 supplementary file).

Rate of NICU admission was not statistically different between interventions (figure S14 supplementary file), OR was 1.11 (95% CI: 0.79 – 1.55; p = 0.56), there was no heterogeneity between studies (I^2 = 0%, chi^2 p = 0.77). NICU admission was reported in 13 studies [25, 26, 28, 29, 31-33, 35-38, 41, 43].

Rate of APGAR score < 7 at 5 minutes was not different between interventions. This outcome was reported in 6 studies [28-30, 33, 37, 41] with no heterogeneity between studies (I^2 = 0%, chi^2 p = 0.81). OR = 0.56 (95% CI: 0.27 – 1.19; p = 0.13) (figure S15 supplementary file).

Certainty of evidence assessment

The quality of evidence for the primary outcome was down-graded twice to low due to serious indirectness and imprecision, as was the case for the outcomes of NICU admission and Apgar score < 7 at 5 minutes. Whereas the quality of evidence for incidence of tachysystole and intervention to delivery interval were further down-graded to very low due to additional serious inconsistency (Table 2 and figure S16 supplementary file).

Table 2: Summary of findings and quality of evidence

Outcomes	Participants / Studies	Certainty of evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Foley Catheter	Risk difference with Misoprostol
CS Rate	2672 (19 RCTs)	⊕⊕⊖⊖ Low [a, b]	0.79 (0.63 – 1)	27 per 100	4 fewer / 100 (8 fewer – 0 fewer)
Tachysystole Rate	1187 (9 RCTs)	⊕⊕⊖⊖ Very Low [a, b, c]	3.98 (2.39 – 6.64)	5 per 100	12 more / 100 (6 more – 20 more)
Intervention delivery time	1987 (14 RCTs)	⊕⊖⊖⊖ Very Low [a, b, d]	----------	Mean time was 19.4 hours	MD 2.18 hours less (3.85 less – 0.5 less)
NICU Admission	1909 (13 RCTs)	⊕⊕⊖⊖ Low [a, b]	1.11 (0.78 – 1.57)	7 per 100	1 more / 100 (2 fewer – 1 more)
APGAR < 7 at 5 minutes	743 (6 RCTs)	⊕⊕⊖⊖ Low [a, b]	0.53 (0.24 – 1.17)	5 per 100	2 fewer / 100 (4 fewer – 1 more)

CS = caesarian section, NICU = Neonatal intensive care unit, RCT = randomized controlled trial, OR = odds ratio, MD = mean difference.

a. Studies had different populations in terms of gestational age, different Misoprostol protocols, and different maximum duration for Foley catheter.
b. OIS not met, confidence interval include null, considerable harm to benefit.
c. Wide variance of point estimates across studies.
d. Significant p value of heterogeneity.

Trial sequential analysis

The cumulative Z curve was drawn on the assumption of 5% type I error, 90% power and OIS of 3428 (assuming a risk of 27% CS incidence in FCB group, and 5% reduction in Misoprostol group). The curve didn't cross any of the significance, futility, or OIS boundaries, rendering results of the analysis inconclusive (figure 5).

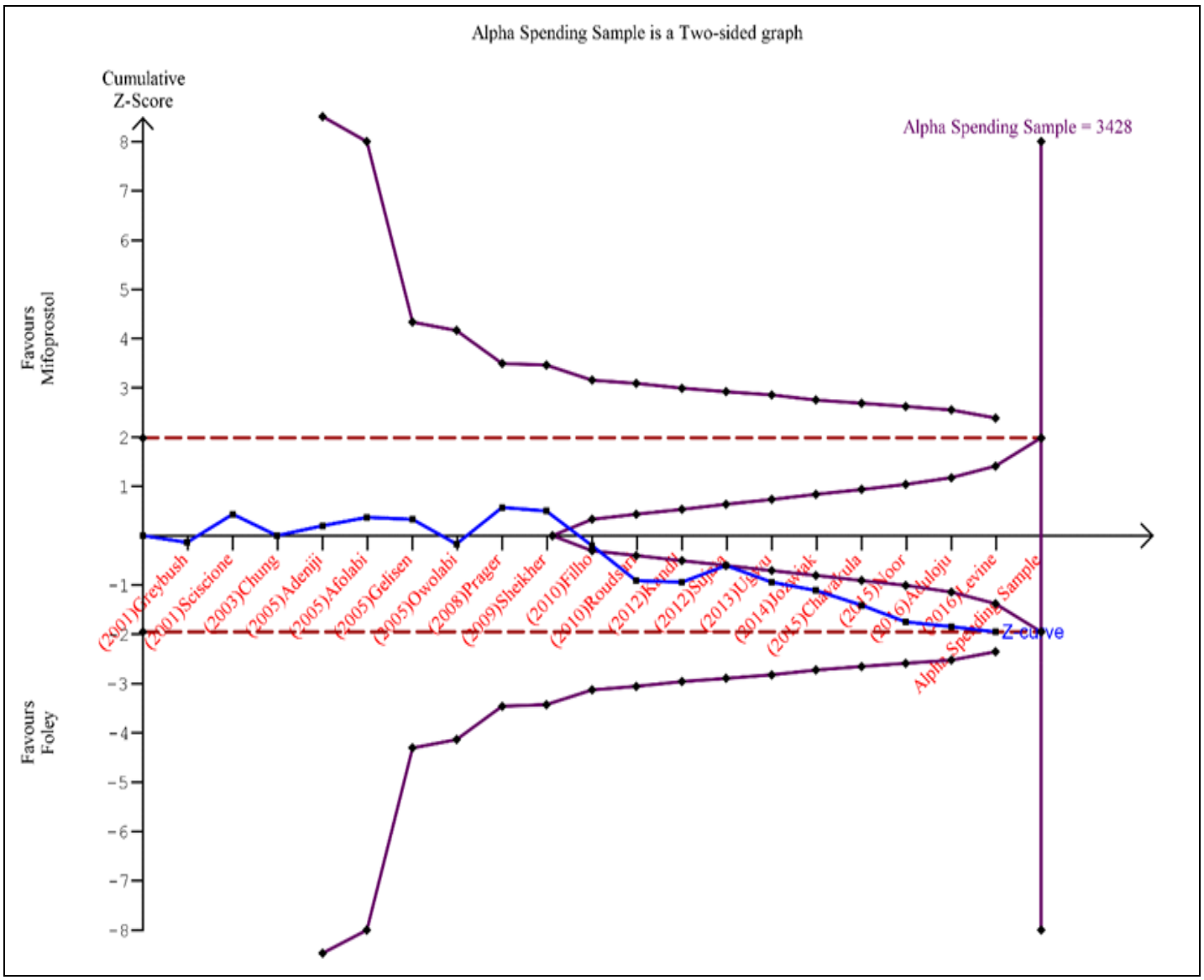

Fig 5: TSA and cumulative z-curve

Discussion

This review included 19 studies enrolling 2672 pregnant women, 1333 were induced with Misoprostol, and 1339 were induced using FCB. The primary outcome was the OR for CS, it was significantly lower for Misoprostol (OR = 0.8, 95% CI: 0.67 – 96; p = 0.02), however; this was the fixed effect model which yielded an insignificant value of 36% for I^2 test of heterogeneity, but a significant p value of 0.06 for chi^2 test of heterogeneity as per our statistical plan. Despite lower power and sensitivity of the chi^2 test [21] we proceeded for the random effects model which still produced a significant result with a wider CI (OR = 0.78, 95% CI: 0.61 – 0.98; p = 0.04), indicating 20% lower odds of CS with Misoprostol induction.

This result seems to contradict almost all previous reviews, however; the research question in many of the previous reviews was not as narrow as ours, and a different methodology may produce a different result. For example, the meta-analysis by *Fox et al*. [10] showed no difference of relative risk of CS between groups (RR = 0.99, 95% CI: 0.77 – 1.3), the included studies used other induction agents simultaneously with Misoprostol and / or FCB. A more recent review (45) also reported no difference between groups with regards to CS rate, in that review PGE1 analogues were only a subgroup of 486 patients with obvious lack of power, in addition to failure to search for all relevant RCTs for inclusion, as acknowledged by the authors. Another case of concomitant use of different induction agents along with FCB or Misoprostol is presented in the review by *Vankin et al*. [23] which also reports no difference in CS between groups. The review and RCT by *Jozwiak et al*. [33] compared 25 mics Misoprostol to FCB, and also reported insignificant difference of CS risk, the RCT was underpowered, while the meta-analysis despite reporting comparable CS rates, identifies that more CS were performed due to failure to progress in the FCB group.

The primary outcome of our review although uncommon is not unprecedented. *Boulvain et al*. [46] reports lower risk of CS with cervical or vaginal prostaglandins, although the comparisons were not strictly of intravaginal Misoprostol to FCB. In a safety review of medications used for IOL [47] Misoprostol was the most effective method of achieving vaginal delivery within 24 hours. In a RCT [48] 25 mics intravaginal Misoprostol/4 hours achieved a significantly lower rate of CS compared to FCB, the study was not included in our review since it is not indexed in Pubmed or EMBASE. Similar results were reported by 2 other RCTs [14, 49] with regards to CS rates or frequency of vaginal deliveries, however; both were excluded from our review due to concomitant use of is osorbide mononitrate with FCB and language restrictions respectively. In a network meta-analysis (50) vaginal Misoprostol ranked second to oral route on reduction of likelihood of CS, while FCB ranked fifth.

Having presented evidence both for and against our primary outcome result, we find it imperative to acknowledge that we don't see the protective effect of Misoprostol from CS in this review as solid evidence, for several reasons. First, the TSA concluded inconclusive evidence. Second, the result of the primary outcome was associated with considerable heterogeneity (p value of chi^2 test = 0.06), and we couldn't account for it by meta regression or subgroup analyses, we could only attribute the heterogeneity to clinical differences among included studies in several aspects such as inclusion/exclusion criteria, doses and frequencies of Misoprostol, and Foley catheter duration and balloon filling volumes. Third, application of GRADE methodology mandated downgrading of the quality of evidence twice to "low" in view of serious indirectness and imprecision. However, we didn't see fit to downgrade quality further for inconsistency, since the I^2 test was not significant. Last, among 19 included studies only two [36, 39] showed significantly lower odds of CS with Misoprostol, a fixed effect model excluding those two studies returns a comparable rate (figure S17 supplementary file). With that said, we must emphasis that the result of a lower odds of CS with Misoprostol induction should be valued, at least in terms of stimulating further studies and investigations.

Secondary outcomes were consistent with most published literature. Induction to delivery time interval was in favor of Misoprostol, showing a mean difference of about 2 hours (MD = -2.18, 95% CI: -3.85 to -0.5; p = 0.01). The same result was shown in several RCTs [14, 27, 30, 33, 36, 41], two reviews however, showed no difference [10, 23]. Tachysystole incidence was significantly lower in favor of FCB induction group, OR was 4.1 (95% CI: 2.47 – 6.79, $p<0.001$), most published reviews also report a protective effect of FCB induction against tachysystole (10, 23, 47, 49). Both neonatal safety outcomes were not different between groups, and in agreement with the majority of available literature [23, 33, 45, 47]. OR of NICU admission was 1.11 (95% CI: 0.79 – 1.55; p = 0.56) and of APGAR score < 7 at 5 minutes was 0.56 (95% CI: 0.27 – 1.19; p = 0.13). The quality of evidence for tachysystole incidence was downgraded thrice to "very low" as was the time to delivery outcome, downgrading was due to indirectness (differences in studied population and treatment protocols), imprecision (lack of power), and inconsistency (wide variations of point estimates across studies). Whereas, neonatal safety outcomes were only downgraded twice to "low" in view of differences in populations, and inclusion of the null value in the over-all effect estimate.

Conclusion

Low quality inconclusive evidence suggest lower likelihood of CS with intravaginal Misoprostol IOL over FCB, with shorter induction to delivery interval. However, it is associated with higher incidence of tachysystole. Neonatal safety outcomes are not different between both methods.

Limitations

Similar to all research, our study suffers several limitations. We didn't search for RCTs for inclusion in available sources of literature other than MEDLINE and EMBASE. Our inclusion criteria were quite strict, resulting in exclusion of many studies which might have produced different results should they have been included. We didn't consider several important outcomes when considering IOL such as instrumental deliveries, vaginal deliveries within a certain period of time, maternal complications, and outcomes related to infection. We also failed to differentiate between studies based on oxytocin augmentation, or the impact of augmentation.

Ethical Statement

In our institution IRB approval is not required for literature review. All authors confirm their active participation in the review and approval of the manuscript.

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Conflict of interest disclosure

All authors declare no conflict of interest.

Roles of investigators

First and last authors: literature search, GRADE methodology, and statistical analysis.

All authors: data extraction, risk of bias assessment, quality of evidence review and approval, review and approval of final manuscript.

First, second, and last authors: Drafting of final manuscript.

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Tachysystole

The accepted definition of Tachysystole in the included studies was at least five uterine contractions in 10 minutes, for two consecutive 10 minutes. This definition is a slight modification from that of the American College of Obstetricians and Gynecologists where Tachysystole is defined as: More than five contractions in ten minutes averaged over a 30-minute window [1].

1- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009; 114(1):192-202.

Detailed MEDLINE search strategy:

((("misoprostol"[MeSH Terms] OR "misoprostol"[All Fields]) OR Foley[All Fields]) AND ("labor, induced"[MeSH Terms] OR ("labor"[All Fields] AND "induced"[All Fields]) OR "induced labor"[All Fields] OR ("induction"[All Fields] AND "labor"[All Fields]) OR "induction of labor"[All Fields])) OR ("cervical ripening"[MeSH Terms] OR ("cervical"[All Fields]

AND "ripening"[All Fields]) OR "cervical ripening"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND ("2000/01/01"[PDAT] : "2019/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Date of search: February 11th, 2019.

Imputation of continuous variables

If we could not obtain the data as mean and SD through contacting the authors, we imputed the data according to the formulae described by Wan et al 2014 (1)

1- From median and interquartile range (IQR):
Mean = (Q1 + m + Q3) / 3
SD = (Q3 – Q1) / 1.35
2- From median and range:
Mean = (minimum + 2*median + maximum) / 4
SD = (Maximum – Minimum) / 4

Induction to delivery interval:

Data provided by authors:
Levine 2016:

	Misoprostol group (n = 120)	Foley group (n = 123)
Induction to delivery time (hours)	19.98681 (SD 10.46896)	18.85203 (SD 7.976209)

Imputed data:

Study		Reported data		Imputed data	
		Misoprostol	Foley	Misoprostol	Foley
Jozwiak 2014	Median (IQR)	25.4 (14 – 35)	36 (29 – 61)	24.8 ± 15.56	42 ± 23.7
Prager 2008	Median & Range	15 (2 – 51)	12 (4 -44)	20.75 ± 12.25	18 ± 10

1- Xiang Wan, WenqianWang, Jiming Liu, Tiejun Tong. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology. 2014, 14:135.

Table S1: Excluded Articles:

Study	Reason of Exclusion
Panelius 2012 [1]	Finnish, retrospective
Jalilian 2011 [2]	Letter to editor, Dinoprostone
Agboghoroma 2015 [3]	PGE2 vaginal suppository
Adeniji 2006 [4]	Brief Communication
Al-Taani 2004 [5]	Prostaglandin E2
Ande 2012 [6]	Intravaginal Misoprostol compared to Intravaginal Misoprostol and Foley Catheter together.
Barda 2018 [7]	Prostaglandin E2
Buccellato 2000 [8]	Extramniotic sodium chloride infusion
Barrilleaux 2002 [9]	Foley catheter and intravaginal dinoprostone gel compared to Foley catheter and 100 microg oral misoprostol, compared to serial 100-microg oral misoprostol.
Cromi 2011 [10]	PGE2 controlled release tablets
Edwards 2014 [11]	Dinoprost controlled release tablets.
Edwards 2015 [12]	PGE2 vaginal insert
El-Khayat 2015 [13]	Foley catheter plus vaginal isosorbide mononitrate
Gu 2015 [14]	4 arms of different protocols of Foley catheter, no comparator of Misoprostol
Hill 2009 [15]	Foley Plus Oral Misoprostol
Jozwiak 2013 [16]	PGE2 inserts
Kashanian 2006 [17]	Brief Communication
Lewis 2009 [18]	PGE2 pessaries
Mizrachi 2016 [19]	Case control, PGE2
Moini 2003 [20]	Brief communication, Dinoprost, extramniotic saline infusuion.
Niromanesh 2003 [21]	PGE2 tablets
Garba 2016 [22]	Foley catheter plus oxytocin
Oliveira 2010 [23]	Article in Portegese
Bani-Irshaid 2006 [24]	PGE2 vaginal tablets
Culver 2004 [25]	Oxytocin concomitant with Foley catheter
Rozenberg 2001 [26]	Intravaginal Misoprostol is compared to Dinoprostone.
Gemund 2004 [27]	Intravaginal Misoprostol is compared to Dinoprostone

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Table S2: Characteristics of included studies.

Study [ref]	Design/Country/Centers/Year	Total: Misoprostol Foley Catheter	Treatment: Misoprostol Foley Catheter	Main Inclusion Criteria	Main Exclusion Criteria	Outcomes of interest to review: Misoprostol : Foley
Adeniji [25]	Open label RCT, Nigeria, single center, 2005	96 / 50 / 46	M: 50 mic/6 hrs. Max 200 F: 30 ml, 16f, 24 hrs.	GA ≥ 37 wks. Single, cephalic, intact membranes, Bishop ≤ 5	Fetal weight > 4000 gm, placenta previa, vaginal bleeding, active genital infection, uterine scar, severe preeclampsia, eclampsia, suspected chorioamnionits, coexisting CVS or renal or hepatic disease, bleeding disorder.	CS: 3/50 : 1/46 Tachysystole: 1/50 : 0 /46 NICU: 4/50 : 3/46
Adolujo [26]	Open label RCT, Nigeria, single center, 2016	140/70/70	M: 25 mic/6 hrs. Max 100 F: 30 ml, 16f, 24 hrs.	GA ≥ 37 wks. Single, cephalic, intact membranes, Bishop < 6	IUFD, uterine scar, contraindicated vaginal delivery.	CS: 19/70 : 22/70 IDT: 9.96±2.11 : 11.79±2.43 NICU: 5/70 : 3/70
Afolabi [27]	Open label RCT, Nigeria, single center, 2005	100/50/50	M: 100 mic once F: 30 ml, 18f, 24 hrs.	Need IOL, single, cephalic, intact membranes, Bishop < 5	Not in labor, uterine scar, PG allergy.	CS: 18/50 : 16:50 Tachysystole: 4/50 : 0/50 IDT: 11.84±5.43 : 20.03±4.68
Chavakula [28]	Open label RCT, India, single center, 2015	100/46/54	M: 25 mic / 6 hrs. Max 75 F: 30 ml. 16f, 12 hrs.	GA > 34 wks. Single, cephalic, intact membranes,	Vaginal bleeding, uterine scar, severe IUGR	CS: 7/46 : 16/54 Tachysystole: 1/46 : 0/54 IDT: 13.5±111.5 : 13.9±124.6 NICU: 1/46 : 4/54 APGAR 0/46 : 1/54
Chung [29]	Open label RCT, USA, single center, 2005	103/49/53	M: 25 mic /3 hrs. Max 75 F: 30 ml, 16f, 12 hrs.	GA > 28 wks. Single, cephalic, intact membranes, Bishop ≤ 6	Antepartum bleeding, IUFD, uterine scar, PG allergy, suspected chorioamnionits	CS: 18/49 : 23/54 Tachysystole: 31/49 : 16/54 IDT: 17.5±9.3 : 19.5±9.4 NICU: 5/49 : 5/54 APGAR: 5/49 : 9/54
Filho [30]	Open label RCT, Brazil, single center, 2010	240/119/121	M: 25 mic / 6 hrs. Max 100 F: 30 ml, 14f, 24 hrs.	GA: at least term, single, cephalic, intact membranes, Bishop < 6	IUFD, placenta previa, antepartum bleeding, genital herpes, uterine scar, IOL attempt in same pregnancy.	CS: 32/119 : 44/121 Tachysystole: 2/119 : 2/121 IDT: 17±7.8 : 20.2±7.6 APGAR: 0/119 : 1/121
Gelisen [31]	Open label RCT, Turkey, single center, 2004	200/100/100	M: 50 mic /5 hrs. Max 200 F: 50 ml, 18f, max duration not defined.	GA ≥ 41 wks. Single, cephalic, intact membranes, Bishop < 5, amniotic fluid index ≥ 5 cm.	Fetal weight > 4500 gm, placental low lie, IOL attempt, diabetes, uterine scar, parity ≥ 5, PG allergy, BMI ≥ 30	CS: 17/100 : 17/100 Tachysystole: 5/100 : 1/100 NICU: 5/100 : 3/100
Greybush [32]	Open label RCT, USA, single center, 2001	136/65/71	M: 25 mic / 4 hrs. Max 150 F: 50 ml, 24f, 12 hrs.	GA: term, single, cephalic, Bishop ≤ 5	Active labor, uterine scar	CS: 13/65 : 15/71 Tachysystole: 25/65 : 9/71 NICU: 10/65 : 9/71
Jozwiak [33]	Open label RCT, Netherland, multi center, 2014	120/64/56	M: 25 mic / 4 hrs. Max 75 F: 30 ml, 16/18f, max duration not defined.	Age > 18, GA > 37 wks. Single, cephalic, intact membranes, Bishop < 6,	Uterine scar, PG hypersensitivity, lethal congenital anomalies.	CS: 11/64 : 14/56 IDT: 24.8±15.56 : 42±23.7 NICU: 1/64 : 2/56 APGAR: 2/64 : 0/56
Kandil [34]	Open label RCT, Egypt, single center, 2012	100/50/50	M: 25 mic / 4 hrs. Max not clear F: 30 ml, 18f, 12 hrs.	GA > 41 wks. Single, cephalic, intact membranes, Bishop < 4,	Antepartum bleeding, IUFD, vaginal infection, contraindicated vaginal labor, uterine scar,	CS: 8/50 : 9/50 IDT: 16.02±1.57 : 15±1.93
Levine [35]	Open label RCT with blinded assessors, USA, single center, 2016	243/120/123	M: 25 mic / hrs. max 150 F: 60 ml, 18f, 12 hrs.	Age ≥ 18, GA ≥ 37 wks. Single, cephalic, intact membranes, Bishop ≤ 6, cervix ≤ 2 cm,	HIV, HELLP, eclampsia, major fetal anomalies, non English speakers.	CS: 29/120 : 35/123 IDT: 19.99±10.47 : 18.85±7.98 NICU: 15/120 : 17/123
Noor [36]	Open label RCT, India, single center, 2015	104/60/44	M: 25 mic / 4 hrs. max 150 F: 50 ml, 18f, max duration not clear.	GA > 37 wks. Single, cephalic, intact membranes, Bishop ≤ 4	Contracted pelvis, antepartum bleeding, temperature > 38, cervix > 2.5 cm, chorioamnionits, uterine scar only for Misoprostol group	CS: 14/60 : 19/44 IDT: 14.03±7.61 : 18.4±8.02 NICU: 19/60 : 6/44
Owolabi [37]	Open label RCT, Nigeria, single center, 2009	120/60/60	M: 50 mic / 6 hrs. Max 100 F: 30 ml, 18f, 12 hrs.	Single, cephalic, intact membranes, Bishop ≤ 4,	Fetal weight > 4500 gm, placenta previa, unexplained bleeding, active genital herpes, PG contraindication, uterine scar, parity > 5,	CS: 11/60 : 17/60 NICU: 6/60 : 8/60 APGAR: 3/60 : 7/60
Prager [38]	Open label RCT, Sweden, single center, 2008	397/199/198	M: 25 mic / 4 hrs. max 150 F: 50 ml, brad, till expelled	GA: term, cephalic, Bishop ≤ 6, could be PROM,	Uterine scar, genital infection	CS: 56/199 : 45/198 IDT: 20.75±12.25 : 18±10
						NICU: 7/199 : 7/198
Roudsari [39]	Open label RCT, Iran, single center, 2011	108/49/59	M: 25 mic / 4 hrs. max 150 F: 50 ml, 18f, 12 hrs.	GA > 37 wks. Single, cephalic, intact membranes, Bishop < 7	Placenta previa, vaginal bleeding, fever > 38, macrosomy, polyhydramnios, chorioamnionits, uterine scar,	CS: 5/49 : 22/59 Tachysystole: 1/49 : 0/59 IDT: 11.08±5.6 : 13.6±16.9
Sciscione [40]	Open label RCT, USA, single center, 2001	111/53/58	M: 50 mic / 4 hrs. max 300 F: 30 ml, 16f, max duration not defined.	GA > 28 wks. Single, cephalic, intact membranes, Bishop < 6, may be diabetic, preeclamptic, May have a uterine scar	Antepartum bleeding, placenta previa, active genital herpes, previous IOL, PG hypersensitivity.	CS: 20/53 : 18/58 IDT: 16.3±7.2 : 19.1±10.1
Sheikher [41]	Open label RCT, India, single center, 2009	60/30/30	M: 25 mic / 4 hrs. max 125 F: 35 ml, 16/18f, 16 hrs.	GA 37-42 wks. Single, cephalic, Bishop < 5,	IUGR, fetal weight > 4 kg, malpresentation, cord prolapse, placenta previa, herpes infection, oligohydramnios, chorioamnionits, uterine scar	CS: 4/30 : 8/30 IDT: 10.35±13.8 : 22.14±29.5 NICU: 0/30 : 1/30 APGAR: 0/30 : 1/30
Sujata [42]	Open label RCT, India, single center, 2012	104/54/50	M: 25 mic / 4 hrs. max 200 F: 30 ml, 16f, till expelled or Bishop ≥ 6	Full term, single, cephalic, intact membranes, Bishop < 6,	Placenta previa, antepartum bleeding,	CS: 16/54 : 9/50 Tachysystole: 4/54 : 0/20 IDT: 21.04±2.32 : 19.18±2.12
Ugwu	Open label RCT, Nigeria, single center, 2013	90/45/45	M: 25 mic / 4 hrs. max 150 F: 30 ml, 16f, 24 hrs.	GA ≥ 37 wks. Single, cephalic, intact membranes, Bishop ≤ 5	Macrosomia, placenta previa, vaginal bleeding, active genital herpes, PG allergy, uterine scar, pre-existing CVS, renal, or hepatic disorders, grand multiparity.	CS: 5/45 : 12/45 NICU: 2/45 : 3/45

RCT = randomized controlled trial, M = Misoprostol, mic = micrograms, hrs. = hours, F = Foley catheter, f = French, GA = gestational age, wks. = weeks, gm = grams, CS = caesarean section, NICU = neonatal intensive care unit, CVS = cardiovascular, IDT = intervention to delivery time, IOL = induction of labor, IUFD = intra uterine fetal death, PG = prostaglandins, IUGR = intra uterine growth restriction, BMI = body mass index, HIV = human immunodeficiency virus, PROM = premature rupture of membranes.

All intervention to delivery times reported are in hours

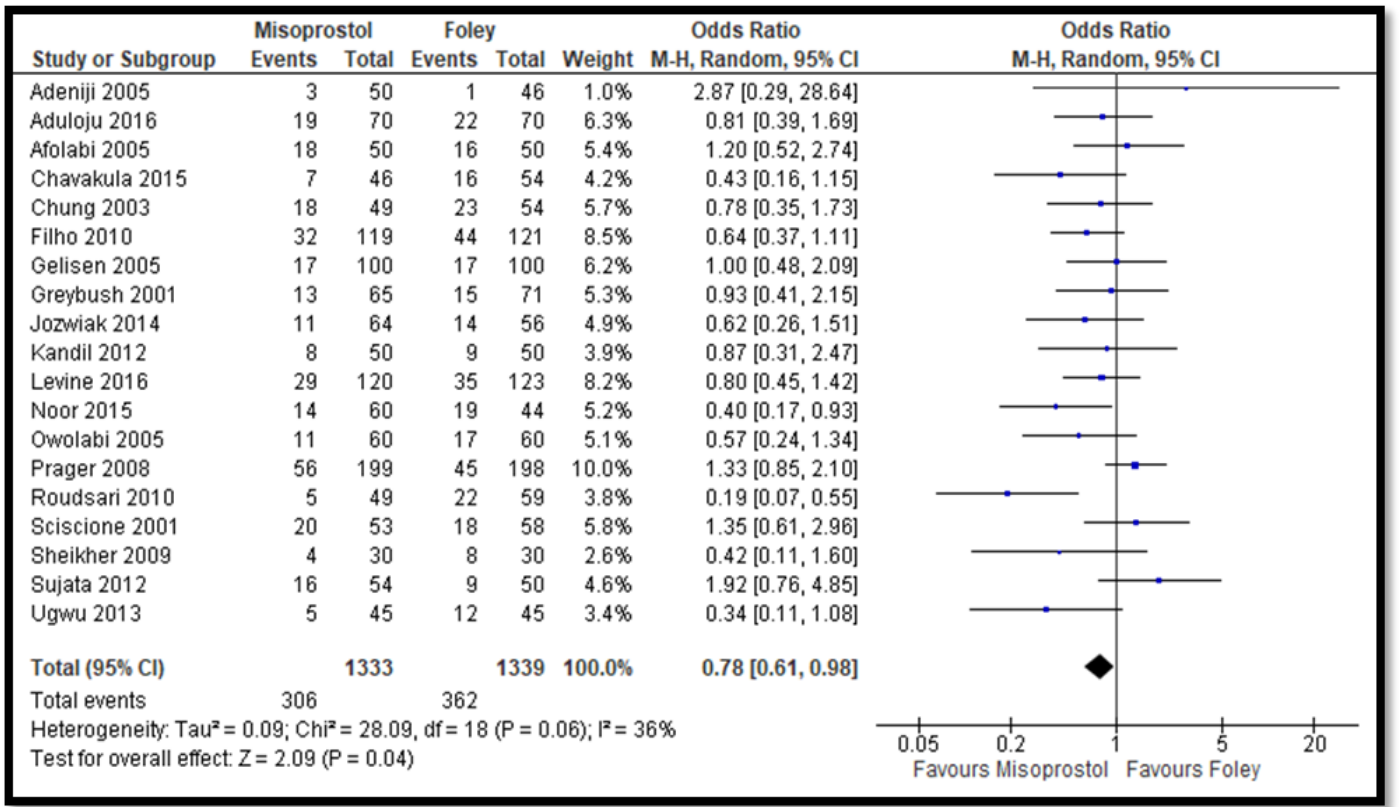

Fig S1: Random effects model (Mantel – Haenszel) of primary outcome:

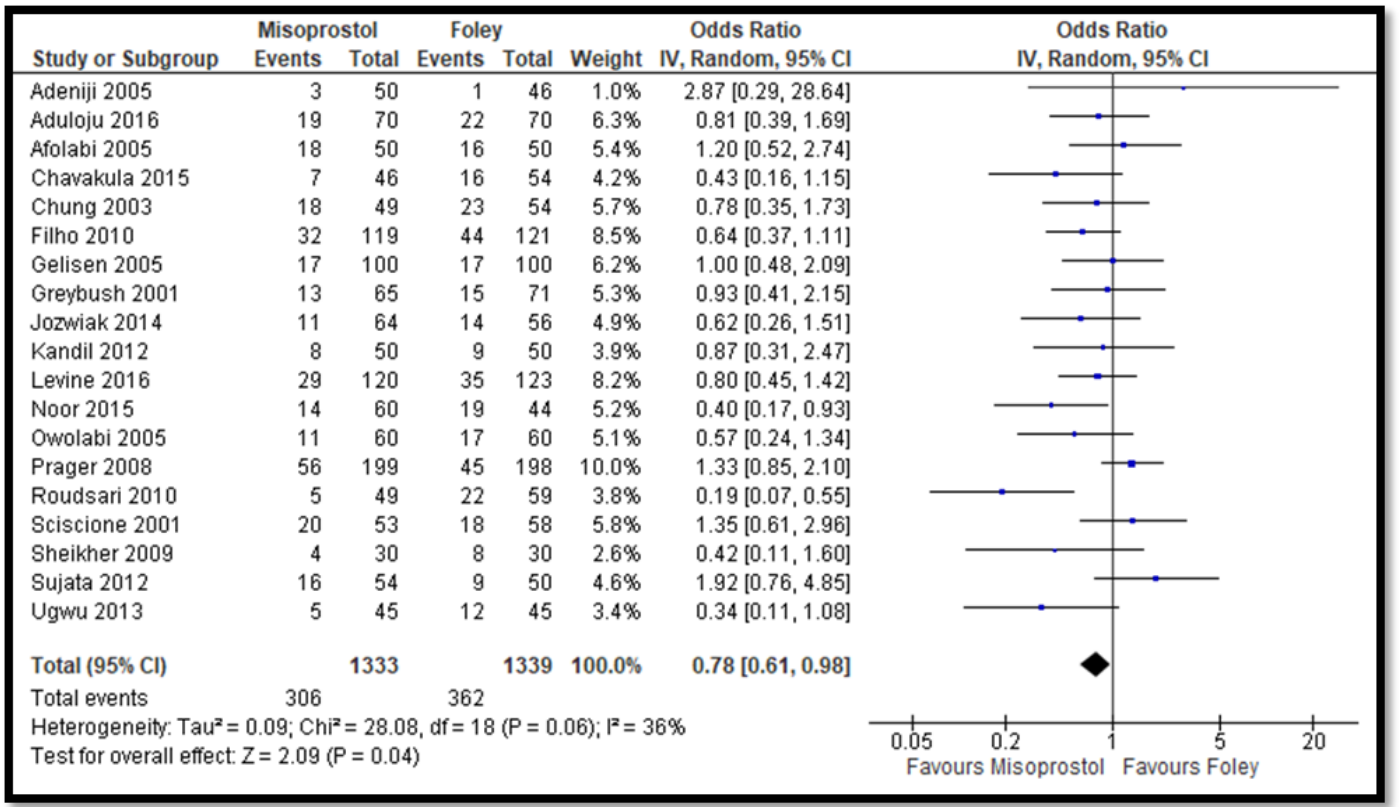

Fig S2: Random effects model (Inverse Variance) of primary outcome:

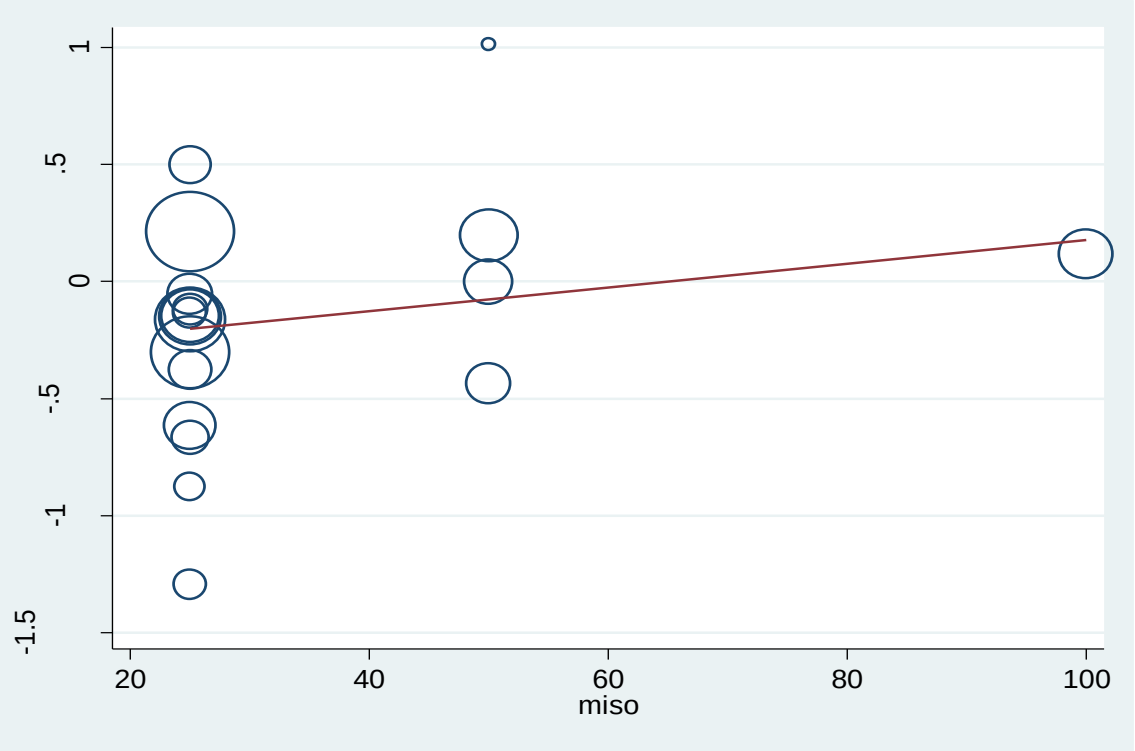

Fig S3: Meta regression: Single Misoprostol dose.

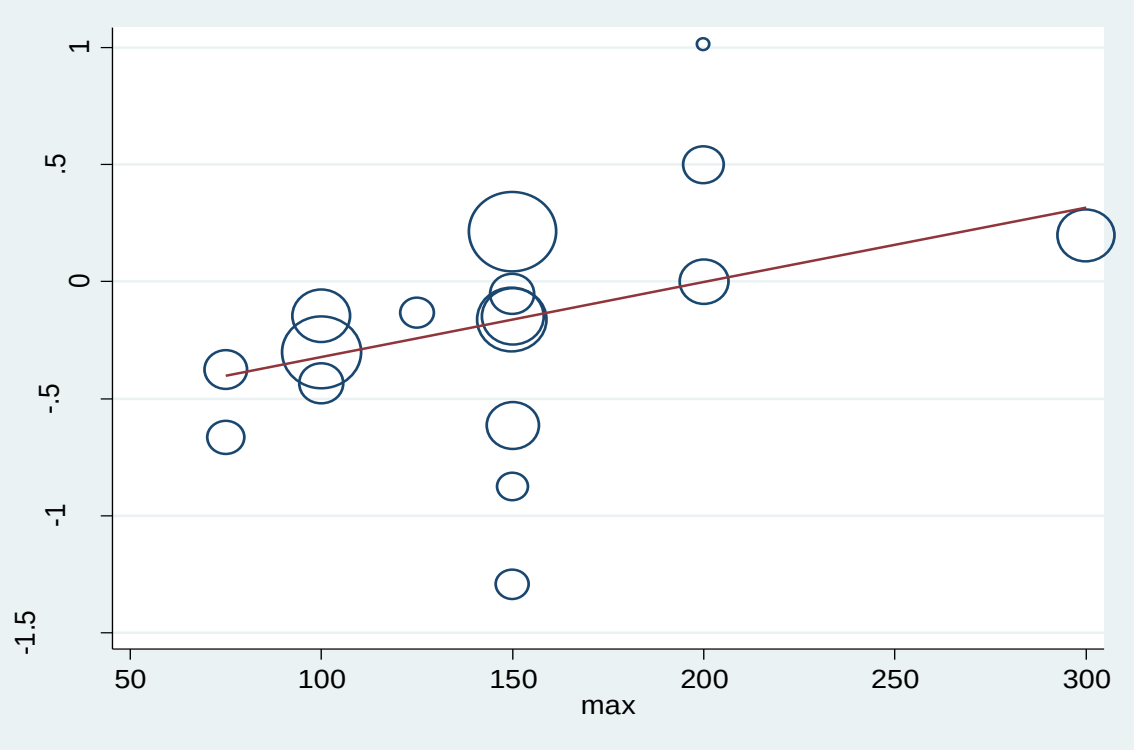

Fig S4: Meta regression: Maximum allowed Misoprostol dose.

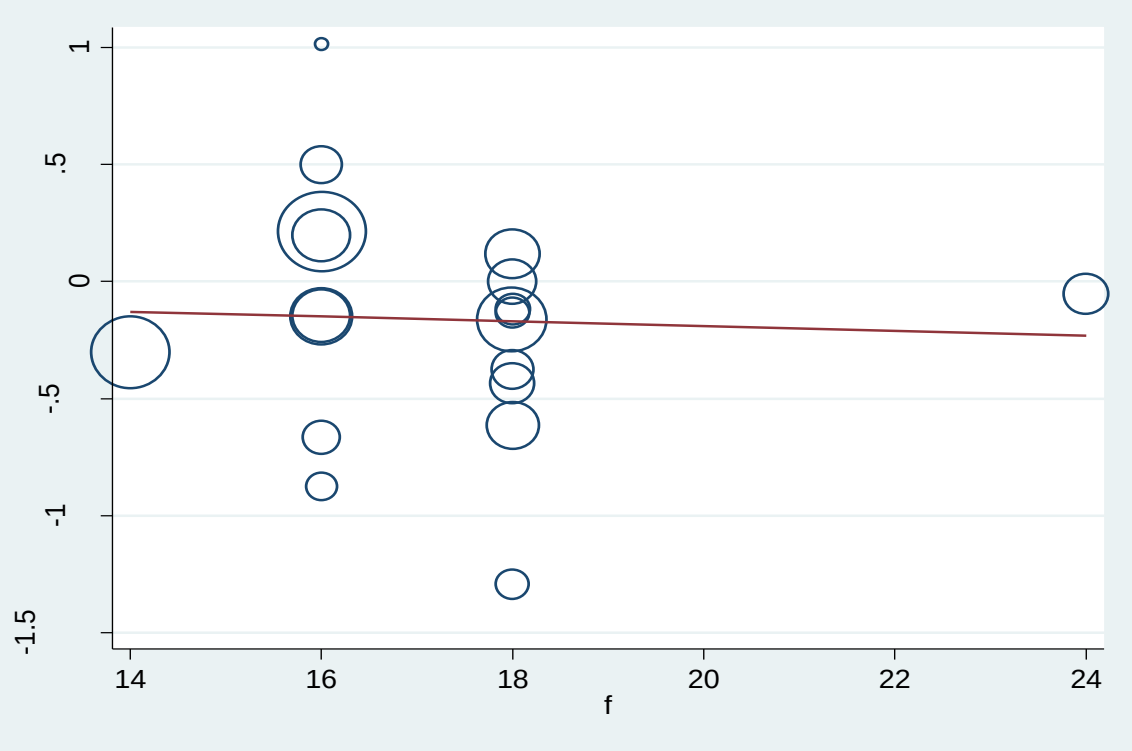

Fig S5: Meta regression: Foley catheter size.

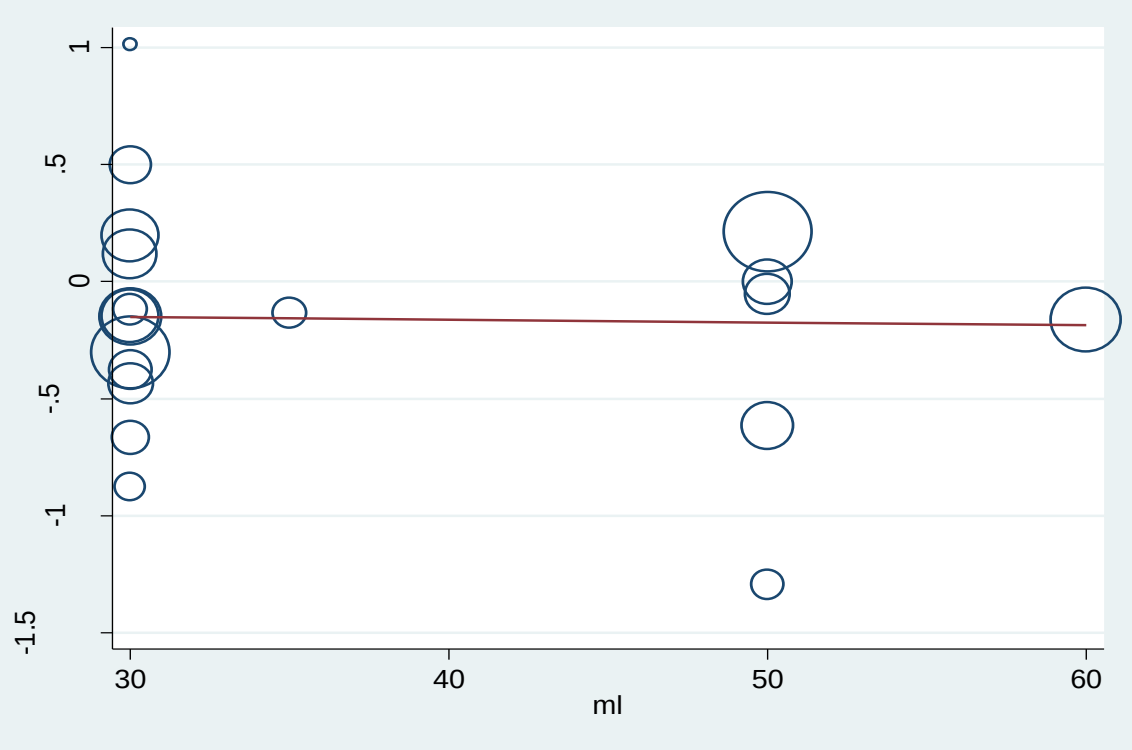

Fig S6: Meta regression: Foley catheter filling volume.

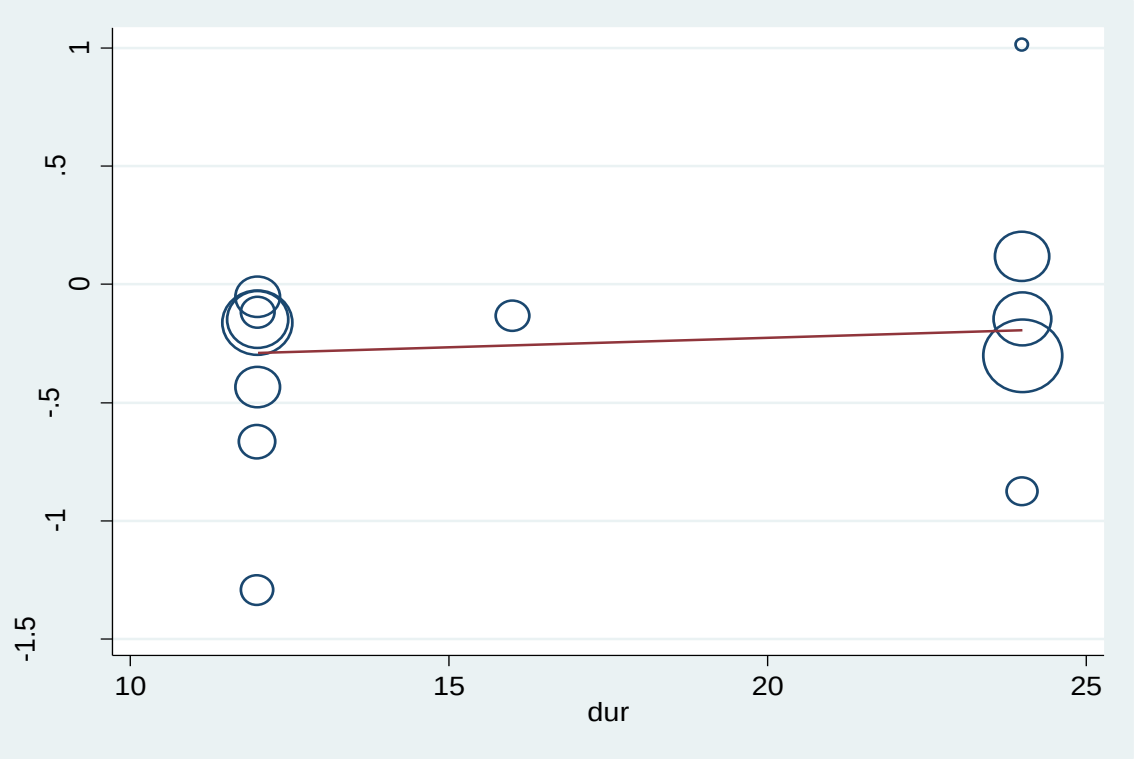

Fig S7: Meta regression: Foley catheter maximum allowed duration.

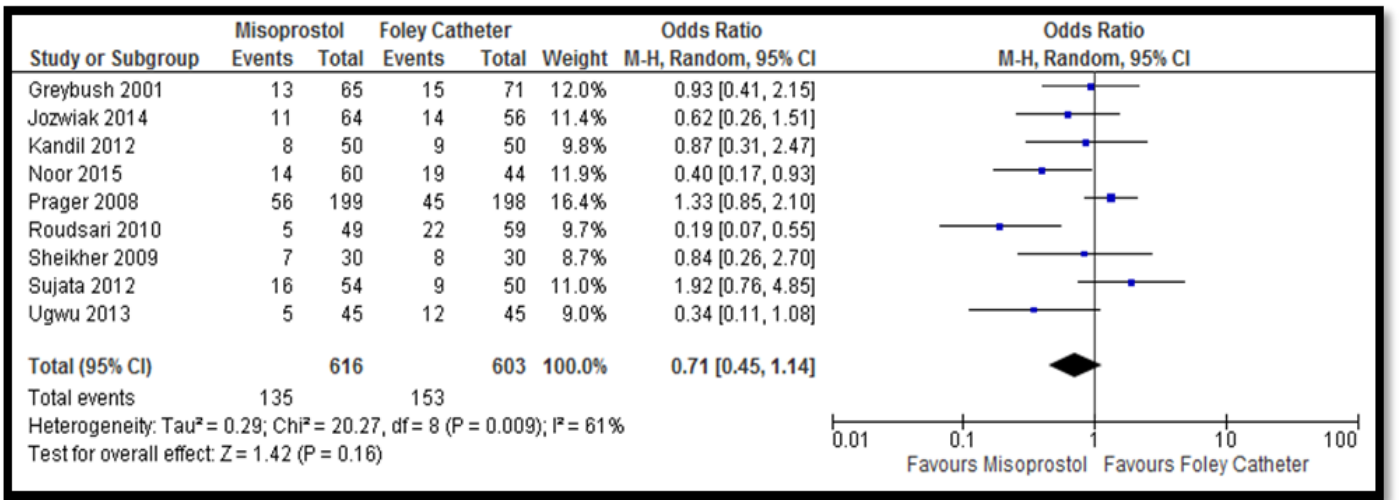

Fig S8: Forest plot of Subgroup of most common Misoprostol protocol:

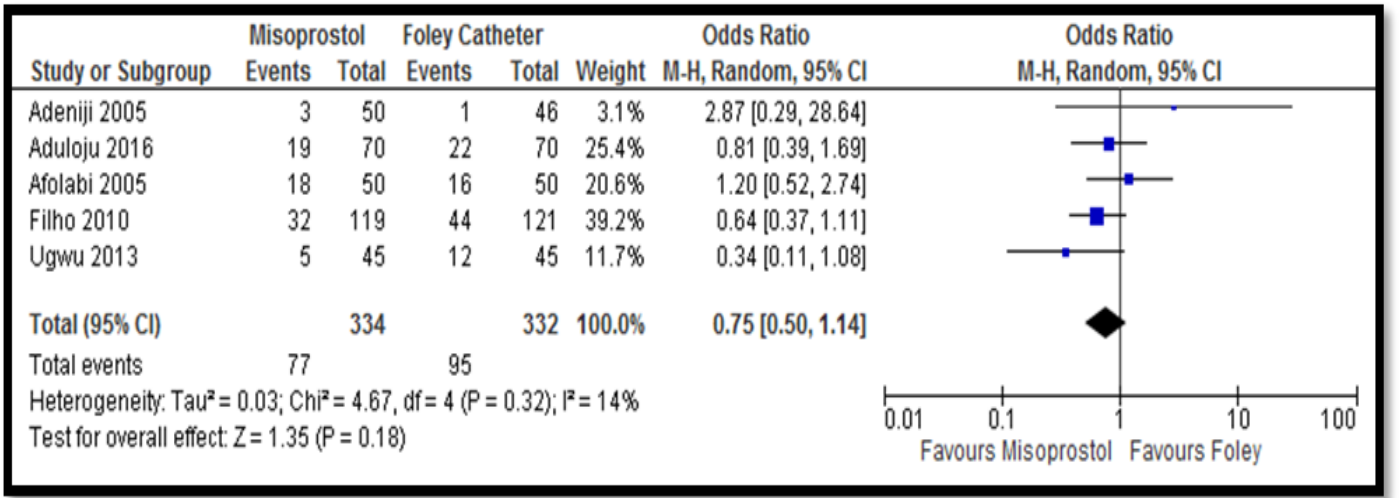

Fig S9: Forest plot of Subgroup of most common Foley catheter protocol:

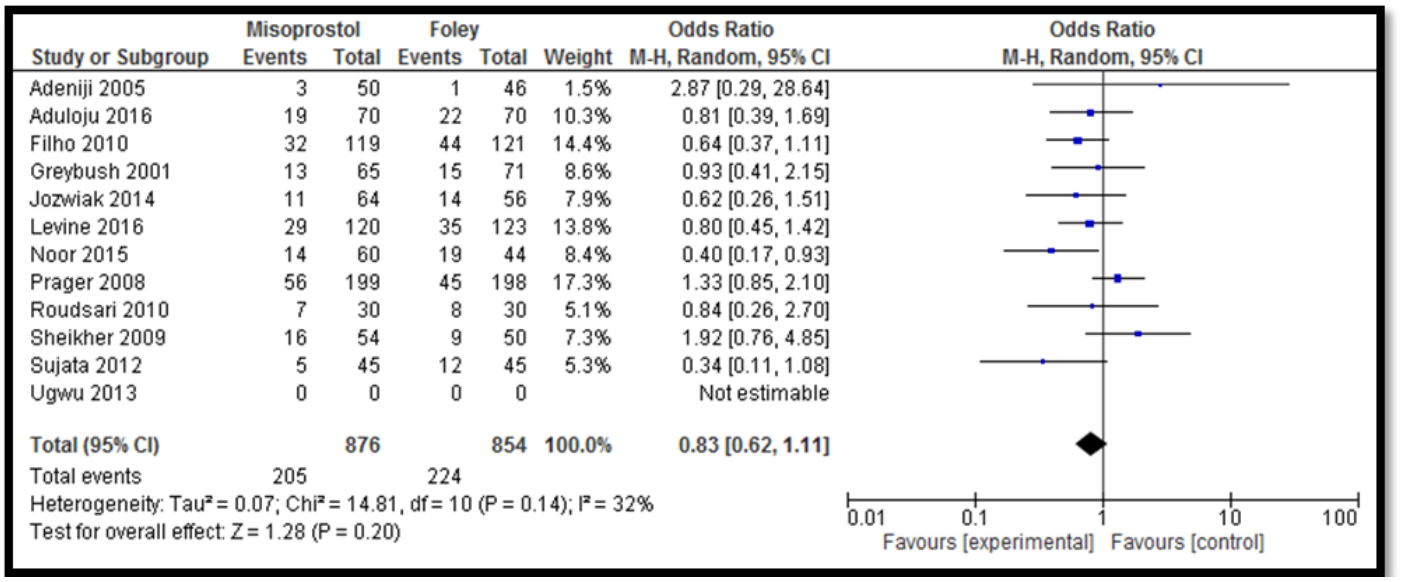

Fig S10: Forest plot of Subgroup of term (at least 37 weeks gestation) females:

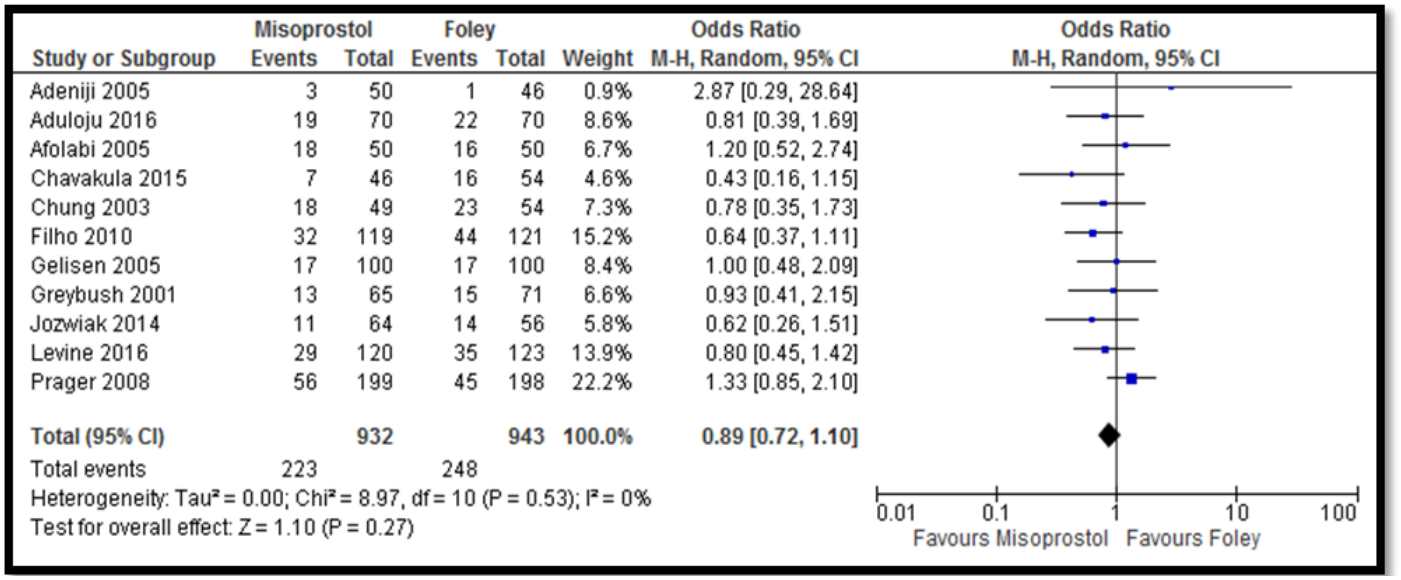

Fig S11: Forest plot of Subgroup of studies with low risk of bias:

Secondary outcomes

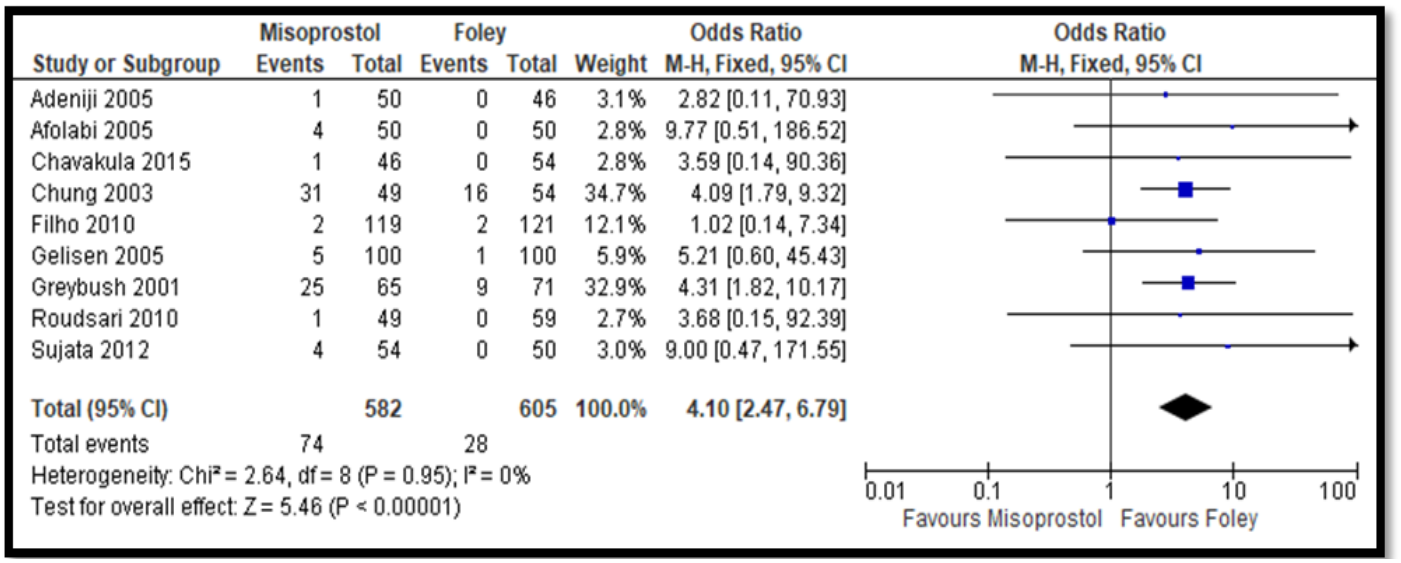

Fig S12: Forest plot of tachysystole incidence (fixed effect)

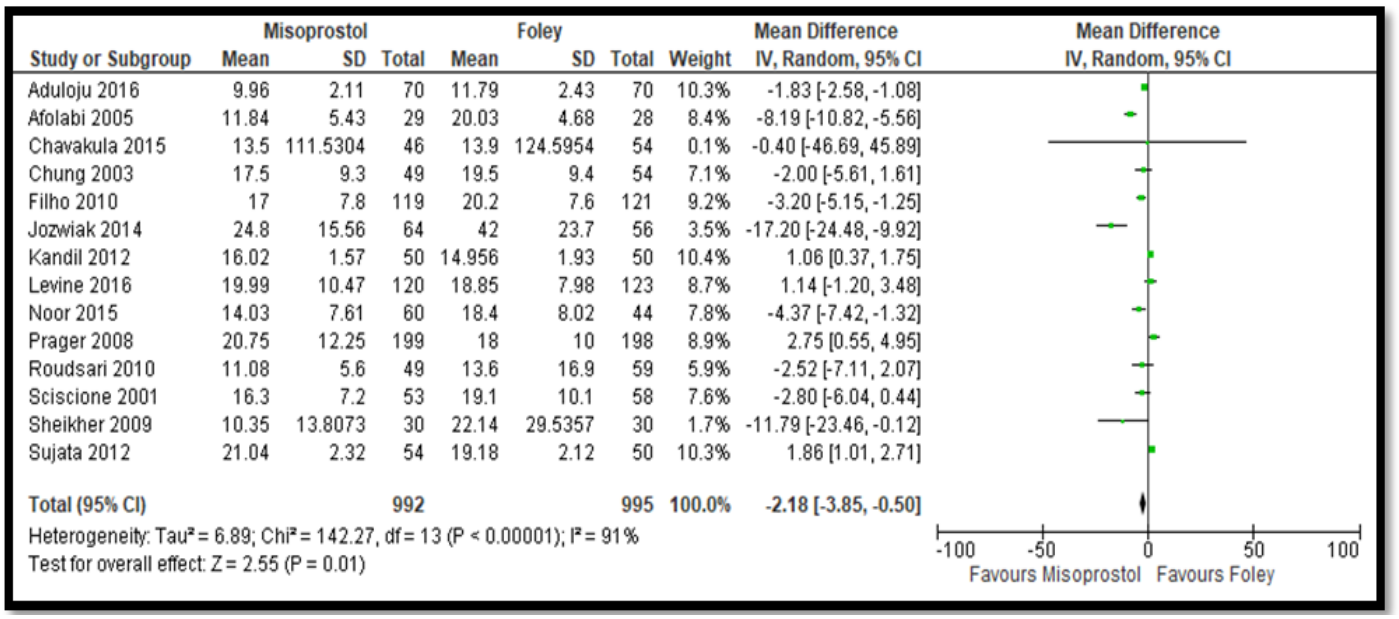

Fig S13: Forest plot for intervention to delivery interval (random effects):

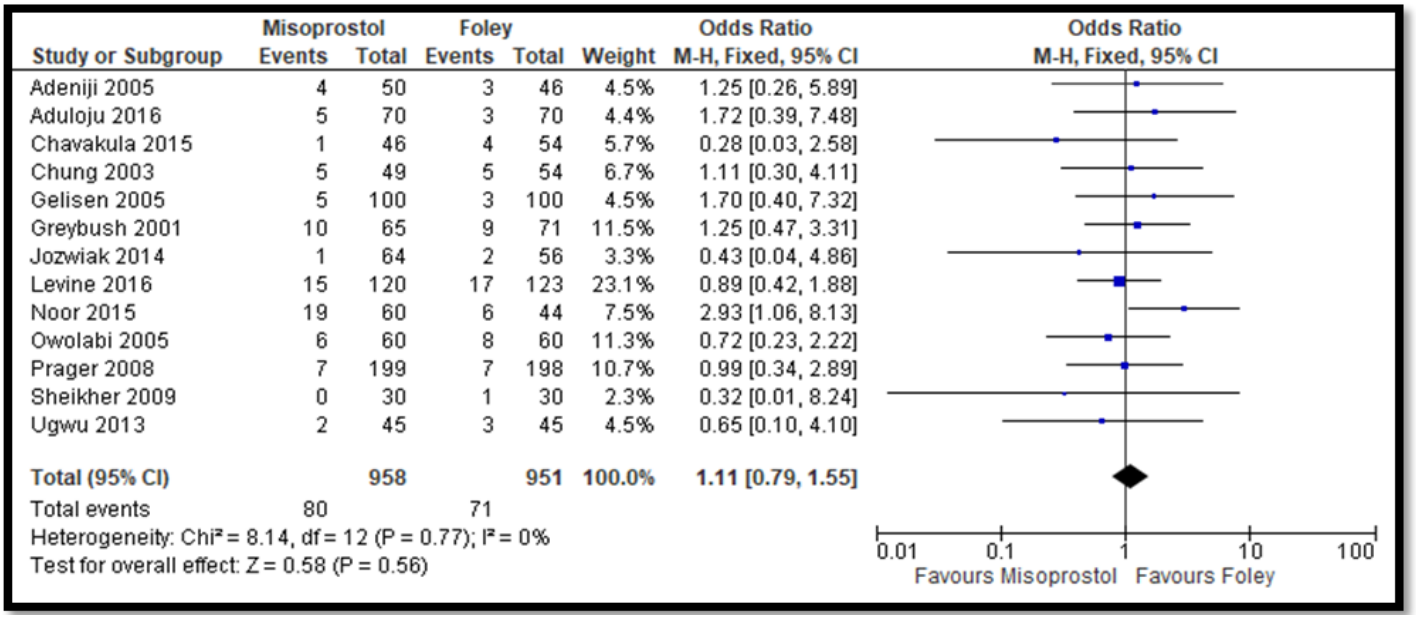

Fig S14: Forest plot for NICU admission (fixed effect):

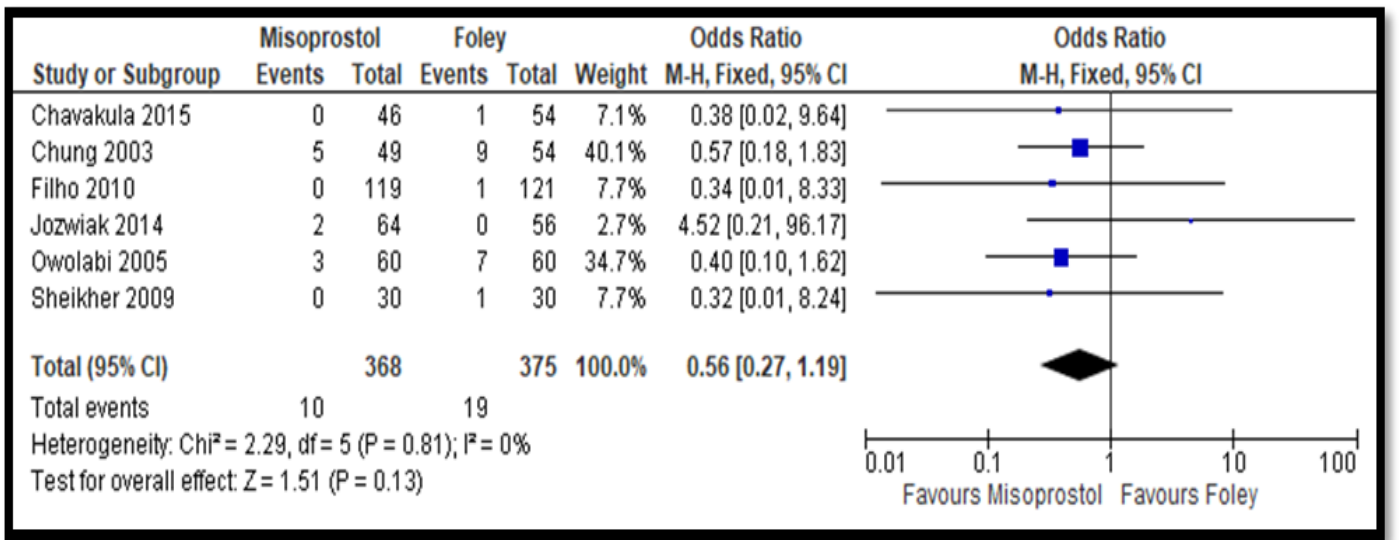

Fig S15: Forest plot of APGAR score < 7 at 5 minutes (fixed effect):

Outcomes	Absolute Effect: With Foley Catheter	Absolute Effect: With Misoprostol	Relative effect (95% CI)	Certainty of the evidence (GRADE)
Patients required CS	With Foley Catheter **27 out of 100** patients will develop an outcome and **73** would not.	With Misoprostol **23 out of 100** patients will develop an outcome and **77** would not.	OR 0.79 (0.63 to 1)	⨁⨁◯◯ LOW. Due to serious indirectness. Due to serious imprecision.
Incidence of Tachysystole	With Foley Catheter **5 out of 100** patients will develop an outcome and **95** would not.	With Misoprostol **17 out of 100** patients will develop an outcome and **83** would not.	OR 3.98 (2.39 to 6.64)	⨁◯◯◯ VERY LOW. Due to serious inconsistency. Due to serious indirectness. Due to serious imprecision.
Intervention to Delivery Time	With Foley Catheter, the intervention to delivery time would be **19.4** hours.	With Misoprostol, the intervention to delivery time would be **17.22** hours.		⨁◯◯◯ VERY LOW. Due to serious inconsistency. Due to serious indirectness. Due to serious imprecision.
NICU Admission	With Foley Catheter **7 out of 100** patients will develop an outcome and **93** would not.	With Misoprostol **8 out of 100** patients will develop an outcome and **92** would not.	OR 1.11 (0.78 to 1.57)	⨁⨁◯◯ LOW. Due to serious indirectness. Due to serious imprecision.
APGAR score < 7 at five minutes	With Foley Catheter **5 out of 100** patients will develop an outcome and **95** would not.	With Misoprostol **3 out of 100** patients will develop an outcome and **97** would not.	OR 0.53 (0.24 to 1.17)	⨁⨁◯◯ LOW. Due to serious indirectness. Due to serious imprecision.

Fig S16: Easily comprehendible summary of findings:

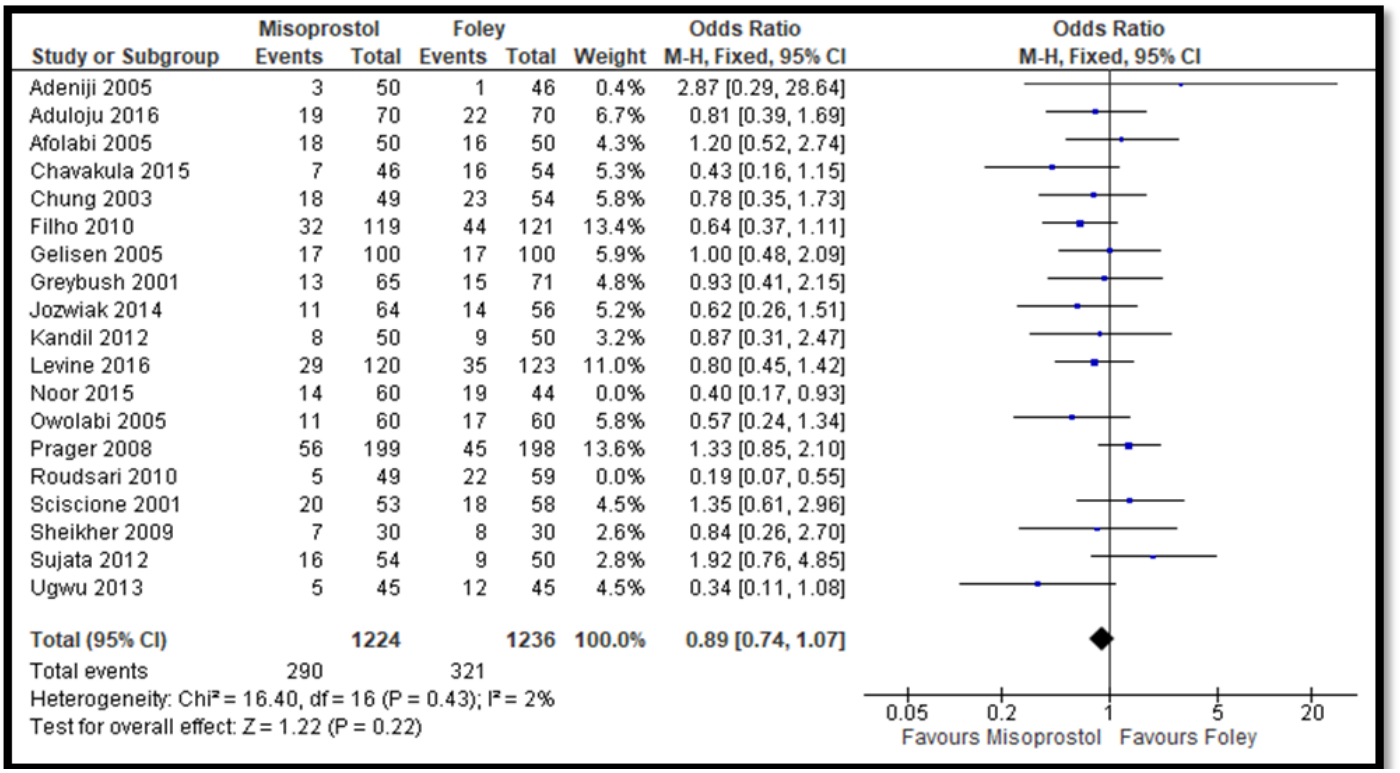

Fig S17: Forest plot for CS, Fixed effect model, excluding *Noor et al* and *Roudsari et al*