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Does induction of labor at term increase the risk of cesarean section in advanced maternal age? A Systematic Review and Meta-Analysis

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Abstract

Background: Women of advanced maternal age, defined as ≥ 35 years at delivery, are at increased risk of multiple complications during pregnancy, with perinatal death being one of the most feared. For instance, the risk of stillbirth at term in this subgroup of women is higher than in younger women, and particularly high beyond 39 weeks of gestation. Induction of labor at 39-40 weeks might help prevent some cases of perinatal death, however, the fact that induction of labor has been historically associated with an increased risk of cesarean delivery and the knowledge that advanced maternal age is an independent risk factor for cesarean delivery are some of the major reasons why clinicians are reluctant to offer elective induction of labor in this particular group.

Objective: The aim of the study was to assess if induction of labor in advanced maternal age was associated with increased rates of cesarean delivery when compared to expectant management.

Material and Methods: We performed an electronic search limited to published articles available between January 2000 and March 2020. Randomized clinical trials and retrospective studies with large cohorts comparing induction of labor with expectant management in singleton pregnancies at term, of women aged ≥ 35 years were included. The primary outcome was the rate of cesarean delivery in induction of labor versus expectant management, and secondary outcomes were the occurrence of assisted vaginal delivery and postpartum hemorrhage.

Results: Eight studies, including 81151 pregnancies (26631 in the induction group and 54520 expectantly managed), were included in the analysis. Six of the included studies were randomized clinical trials with the remaining two being observational and retrospective cohort studies. Induction of labor was not associated with a significant increased risk of cesarean delivery (OR 0.97, 95% CI 0.86-1.1), assisted vaginal delivery (OR 1.12, 95% CI 0.96-1.32) or postpartum hemorrhage (OR 1.11, 95% CI 0.88-1.41).

Discussion: The belief that induction of labor is associated with an increased risk of cesarean delivery is based on the results of retrospective studies comparing induction with spontaneous labor at the same gestational age. However, at any point in a pregnancy, the comparison should be between induction of labor and expectant management, with the latter contributing to a pregnancy of greater gestation age and not always leading to spontaneous labor. When comparing induction to expectant management, our study shows no significant increase of cesarean section, assisted vaginal delivery or postpartum hemorrhage. Our study was not powered to assess neonatal outcomes, and additional research is needed to confirm whether induction of labor might have a positive effect in preventing stillbirth.

Conclusion: Induction of labor at term in advanced maternal age has no significant impact on cesarean delivery rates, assisted vaginal delivery or postpartum hemorrhage, giving additional reassurance to obstetricians who would consider this intervention in this particular subgroup.

Keywords: Cesarean delivery, Advanced Maternal age, Induction of labor, Meta-Analysis, Expectant management

Introduction

In the past decades, particularly in industrialized countries, there has been a steadily increase in the average age of women at childbirth.[1] Many factors play an important role in the decision-making of postponing childbearing, including advances in assisted reproductive techniques and women's career and financial goals.[2] Even though there is rising controversy concerning the definition of advanced maternal age (AMA), the most accepted definition is maternal age of 35 years or older at time of birth.[3]

The association between AMA and adverse maternal and neonatal outcomes has been shown in recent studies, with increased risk of hypertensive disorders, gestational diabetes mellitus, preterm labor, placenta previa and placental abruption. [1,2,4,5,6] Adding to the previous risk factors, one of the major concerns surrounding AMA is the fact that pregnant women aged 35 years or older are at increased risk of antepartum and intrapartum stillbirths and neonatal deaths.[7]

There is growing evidence that women of AMA achieve at 39 weeks of gestation the same risk of younger women at 41 weeks (gestational age at which induction of labor is commonly offered).[8] Additionally, in women aged ≥ 35 years, risk of stillbirth doubles between 39th and 40th weeks of gestation (from 5/10,000 to 10/10,000).[9]

Given these data, it does not come as a surprise that, worldwide, the rate of elective induction of labor at 39-40 weeks of gestation is higher among women of AMA due to the concerns for stillbirth.[9] However, this approach is not yet supported by most obstetric societies, in part due to the fact that induction of labor itself carries important risks, such as cord prolapse and uterine hyperstimulation and also because it has been historically associated with an increased risk of cesarean section, particularly in nulliparous women. In addition, its benefits may be offset by long term adverse outcomes in children because of delivery at early term gestation (37 – 38 weeks of gestation). [7]

The common knowledge that induction of labor for nonmedically indicated reasons (elective induction) is associated with increased risk of cesarean section, is supported by several observational studies that compared rates of cesarean section in induced versus spontaneous labor. However, spontaneous labor may not be the ideal comparison and is certainly not an alternative to labor induction.[10]

In fact, most of the observational studies that used the clinically relevant comparator of expectant management versus induction of labor, have not shown higher risk of adverse outcomes with induction, with some of them showing a decreased risk of cesarean delivery in the induction group.[11,12,13] This data has been supported by two recent randomized trials, 35/39 and ARRIVE trial, supporting the evidence that induction of labor for nonmedical indications at 39 weeks does not increase or may even lower the rates of cesarean section. [10,14]

The aim of our study, using meta-analysis techniques, was to estimate if induction of labor in pregnant women of AMA at term increases the rates of cesarean delivery and other maternal adverse outcomes, comparing to expectant management.

Methods

Information sources, search strategy and eligibility criteria

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

The research was performed using PubMed/MEDLINE and the Cochrane Database of Systematic Reviews. We limited our search to published articles available between January 2000 and March 2020 in English, Portuguese, Spanish and

French. Other foreign language articles were not included as translation services were unavailable. References from included original papers and recent reviews were hand-searched for additional relevant publications.

The search terms were "induction of labor" and "advanced maternal age", "induction of labor versus expectant management", "elderly women" and "induction of labor".

Data extraction

Randomized Clinical Trials (RCT) and retrospective studies with a large cohort comparing induction of labor versus expectant management of pregnancy at term in women aged ≥ 35 years which reported one or more of the study outcomes were included in the analysis.

The primary outcome of this meta-analysis was the incidence of cesarean delivery. Secondary outcomes were the occurrence of assisted vaginal delivery (AVD) and postpartum hemorrhage (PH). PH was defined as estimated blood loss greater than 500mL for vaginal delivery and greater than 1000mL for cesarean delivery.

Specific and prospectively defined inclusion criteria were used to determine which studies were suitable for inclusion in the meta-analysis. Studies concerning term singleton pregnancies of women aged ≥ 35 years, with intact membranes and cephalic presentation who were offered either expectant management or elective induction of labor were included.

In studies comparing induction of labor versus expectant management at term which included stratified analysis by gestational age (39 to 41 weeks), only the subgroup of women at 39 weeks was selected for subsequent analysis.

Walker KF et al, conducted a recent meta-analysis, with individual patient data, comparing induction of labor with expectant management at term by subgroups of maternal age. [7] Authors from previously published randomized clinical trials (RCT) comparing expectant management and induction of labor, who did not present data stratified by age, where contacted and five agreed to share anonymized datasets. Walker KF et al, sorted the data according to maternal age, and presented new results stratified by age, including women at AMA. Four of the five studies were included in our study.

Duplicated studies were removed, and papers were excluded if they were case reports, were restricted to multiple pregnancies / did not separate data from multiple pregnancies and singletons or included women of all ages and did not stratify results by age group.

The initial search was conducted by one investigator (MF) and validated by a secondary conductor (FS) to ensure accuracy of search and application of exclusion criteria. Citations were first screened at the title/abstract level by two independent reviewers and complete manuscripts were retrieved if potentially pertinent. Disputes regarding inclusion criteria were resolved by consensus. Studies comparing the two strategies that did not report clinical outcomes were excluded. (Figure 1).

Data synthesis

Meta-analysis was conducted using STATA (Version 13, StataCorp, Texas,USA).
Homogeneity among the studies was evaluated using Cochran's Q test and the I^2 statistic (the values of 0.25, 0.50, and 0.75 indicated low, moderate, and high degrees of heterogeneity, respectively).
Continuous variables are expressed as means ± standard deviations or median (with interquartile range) values, and categorical variables are described as numbers and percentages. To calculate the pooled effect estimates, we used the inverse variance assuming a fixed-effects model and the DerSimonian-Laird method assuming a random-effects model.[15] Publication bias were evaluated using the funnel plot. We performed a sensitivity analysis to show the impact of each study on the results. MetaXL 2.0 (EpiGear International Pty Ltd, Wilston, Queensland, Australia) was used to calculate the pooled risk difference effect sizes (difference in occurrence risk between induction of labor and expectant management).

Results

Study identification

Database searches initially retrieved 853 citations. 10 articles were duplicated after review of the title and therefore excluded. We excluded 798 articles after careful review of the title and abstract. After thorough assessment according to the selection criteria, we further excluded 37 studies. A final total of eight studies were included in the analysis. These eight studies included 81151 participants which met the inclusion criteria for this meta-analysis: 26631 in the induction group, and 54520 in the expectant management group.

Characteristics of included studies

From the eight included studies, six were randomized clinical trials (RCT) and two were non-randomized, observational and retrospective in design. The characteristics of the eight included studies are summarized in Table 1.
All studies enrolled full-term gestations with intact membranes with cephalic presentation. Four studies included complicated pregnancies, two of those with suspected intra-uterine growth restriction, one with suspected macrosomia and another one with pregnancy induced hypertension.

Quantitative synthesis of outcomes

Cesarean Section

Cesarean Section was reported in eight studies, which we considered for pooled analysis, for a total of 81178 patients. The forest plot (Figure 2) describes the weighted meta-analysis for Cesarean section: pooled analysis showed moderate heterogeneity among the studies (I2 = 75%; $p < 0.01$) and there was no significant difference between induction of labor and expectant management with a pooled Odds Ratio [OR] of 0.97 (95% CI = 0.79–1.19). The exclusion of any single study did not alter the overall combined result.

The forest plot (Figure 3) describes the weighted meta-analysis for cesarean section when including only randomized controlled trials: pooled analysis showed low heterogeneity among the studies (I2 = 7%; p = 0.37) and there was no significant difference between induction of labor and expectant management with a pooled Odds Ratio [OR] of 0.97 (95% CI = 0.86–1.1). The exclusion of any single study did not alter the overall combined result

Assisted vaginal delivery

AVD was reported in three studies, which we considered for pooled analysis, for a total of 80561 patients. The forest plot (Figure 4) describes the weighted meta-analysis for AVD: pooled analysis showed high heterogeneity among the studies (I2 = 84%; $p < 0.01$) and there was no significant difference between induction of labor and expectant management with a pooled Odds Ratio [OR] of 1.12 (95% CI = 0.96–1.32). The exclusion of any single study did not alter the overall combined result.

Postpartum Hemorrhage

PH was reported in two studies, which we considered for pooled analysis, for a total of 3234 patients. The forest plot (Figure 5) describes the weighted meta-analysis for PH: pooled analysis showed negligible heterogeneity among the studies (I2 = 0%; p = 0.6) and there was no significant difference between induction of labor and expectant management with a pooled Odds Ratio [OR] of 1.11 (95% CI = 0.88–1.41).

Study Bias

Visual inspection of the funnel plot for the C-Section did not reveal any asymmetry among the studies (Figure 6). Further, the Begg rank correlation test was not statistically significant.

Discussion

The increasing prevalence of AMA during the past decades has brought several concerns to the obstetrical community, due to maternal and fetal adverse outcomes associated with this condition.

AMA poses a challenge not only in the management of pregnancy and the known complications that might arise, but also at term, in the decision of when to terminate the pregnancy.

AMA is a known and well stablished independent risk factor for stillbirth, with women aged 35 years or over having a 65% increase in the odds of stillbirth.[22] This risk is even greater in nulliparous women, with placental aging and insufficiency being believed to play an important role in this association.[23,24]

Nowadays, in most industrialized countries, induction of labor is offered to all women at 41-42 weeks of gestation, when the risk of stillbirth is 2 to 3 per 1000 deliveries.[25] Women at AMA achieve the same stillbirth risk earlier in pregnancy, around 38th-39th week of gestation, with the lowest cumulative risk of perinatal death in this age group being achieved at 38 weeks of gestation.[23]

When considering elective induction of labor in older women, at the due date, Walker KF et al. found that one third of obstetricians are reluctant to offer induction because they are concerned about increasing the rates of cesarean delivery, even though they believe induction would improve perinatal outcomes.[26]

This belief was based on the results of several observational studies comparing women who were induced versus women with spontaneous labor, which demonstrated an increased risk of cesarean section associated with induction of labor.[27,28,29] However, at any point in a pregnancy, the decision is not between induction of labor or spontaneous labor, but between induction and expectant management, with the latter contributing to a pregnancy of greater gestational age and not always leading to spontaneous labor.
In the past decades, instead of comparing induction to spontaneous labor, several authors have conducted studies evaluating the maternal and neonatal outcomes of induction of labor versus expectant management at term. Saccone et al. showed, in a recent meta-analysis including 7 randomized clinical trials (including 7598 women), that induction of labor at full-term in women with uncomplicated singleton pregnancies was not associated with increased risk of cesarean delivery.[30]

Additionally, a recent RCT, the ARRIVE (A randomized trial of induction versus expectant management) trial, concluded that elective induction of labor at 39 weeks in low-risk nulliparous women of any age resulted in lower frequency of cesarean delivery. [10]

Even though recent studies suggest that induction of labor at 39-40 weeks of gestational do not increase or might even lower cesarean deliveries, there has been uncertainty on whether these results apply to women at AMA, particularly due to the fact that AMA is an independent risk factor for failure of labor induction.[31,32]

In 2016, the 35/39 trial, including 619 singleton pregnancies of women aged 35 years or older, concluded that elective induction of labor does not increase the rate of cesarean section in this particular subgroup of women of AMA.[14]
Our meta-analysis is consistent with these recent findings, showing no statistical difference in the rates of cesarean section in AMA between the induction and expectant management group, with some tendency towards lower rates of cesarean section in the induction group. According to our findings, women in the induction group have higher rates of AVD and PH, although the difference was not statistically significant.

Adding to the growing evidence that elective induction of labor at 39-40 weeks does not alter the delivery mode, Hersh et al, conducted a cost effectiveness analysis on expectant management versus induction of labor at 39 weeks of gestation, and concluded that inducting of labor may be a cost-effective solution when maternal and neonatal outcomes are considered.[33]

The desire to minimize the occurrence of stillbirth of women of AMA is one of the main reasons why obstetricians would consider elective induction of labor. Even though women of AMA are at increased risk of stillbirth, it is still a rare event in any pregnancy, which explains the fact that five of the included studies did not report any case of stillbirth. From the remaining studies, the ARRIVE trial had five cases of stillbirth (two in the induction group and three in expectant management) but did not stratify the occurrence of stillbirth by maternal age.[10] Despite having a large cohort, the retrospective study conducted by Kawakita et al was not powered to assess the rate of stillbirth.[21] Knight et al found that induction of labor at 39 weeks in AMA was associated with a third of the risk of stillbirth compared with expectant management.[20]

Strengths and limitations

This meta-analysis includes data from a large number of pregnancies and is, to our knowledge, the largest systematic review of the effects of induction of labor at term on rates of cesarean delivery in AMA. To our knowledge, this is the first meta-analysis comparing the rates of cesarean section between induction of labor and expectant management in women of AMA which includes data from the two most recent RCT's on the topic.

The conclusions drawn from this meta-analysis are subject to the limitations and differences of the original studies included in the analysis. Additionally, the presence of clinical trials with small sample sizes and the inclusion of retrospective studies in the analysis constitute a limitation to our study.

We were able to retrieve data on the primary outcome in every included study, however, when considering secondary outcomes, only three of the papers included retrievable data on AVD and two on PH.

Considering that one of the major concerns on inducing labor at full term or having an expectant attitude until 41-42 weeks of gestation, in this particular age group, is not only but mostly driven by the fear of stillbirth, one of the major limitations of this study is the inability to evaluate the impact of induction of labor in the rates of stillbirth in AMA, mostly due to the rarity of the event.

This meta-analysis identified significant heterogeneity between different studies when both observational studies and RCT's were included in the analysis of cesarean section (I^2 75%) and AVD (I^2 84%), which might reflect the very large number of women included in the analysis and difficulty to control for confounding factors, particularly in cohort studies. When observational studies are excluded from the analysis of the primary outcome, heterogeneity between studies is low (I^2 7%), adding consistency to our results.

Conclusion

Our study suggests that induction of labor at term in a subgroup of women of AMA does not significantly alter the risk of cesarean section, AVD or PH, when comparing to expectant management.

Although the decision between elective induction of labor at 39-40 weeks of gestation or expectant management until 41 weeks of gestation should be individualized and ultimately discussed with women, these findings could help the decision making of those clinicians who, despite considering that induction of labor could prevent fetal and neonatal severe complications, do not consider elective induction of labor due to its potential risk of cesarean section.
In this subgroup of women with increased risk of one of the most feared pregnancy complications such as stillbirth, this evidence supports the theory that induction of labor at 39-40 weeks does not increase some of the most feared adverse maternal outcomes related to time of delivery. Additional research is needed to confirm whether this intervention might have a positive impact in preventing stillbirth, without increasing neonatal risks associated with induction of labor.

Disclosure of Interests
None to declare.

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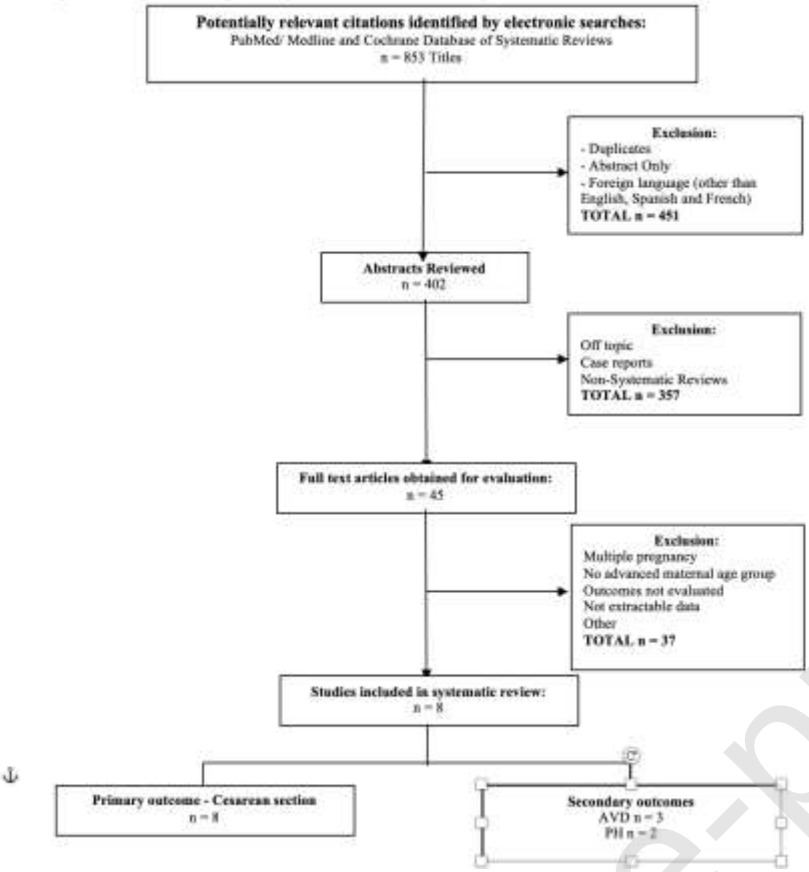
Table 1. Characterization of the studies included in the meta-analysis

Author	**Year**	**Study design**	**Sample size, n (induction/expectant management)**	**Inclusion criteria**	**Gestational age at induction**	**Induction method**	**Cesarean Delivery**	**AVD**	**PH**
Van den Hove et al[16]	2006	RCT	3 (2/1)	Suspected IUGR	≥ 37 weeks	PGE/AROM/oxytocin	OR 0.067 (95% CI 0.00081-5.5)	Not reported	Not reported
Koopmans et al[17]	2009	RCT	132 (67/65)	Mild PIH	37^{+0}– 41^{+6} weeks	PGE/Foley catheter/Oxytocin	OR 1.2 (95% CI 0.5 – 2.8)	Not reported	Not reported
Boers et al[18]	2010	RCT	72 (41/31)	Suspected IUGR	36^{+0} – 41^{+6} weeks	PGE/Foley catheter/Oxytocin	OR 3 (95% CI 0.57 – 16)	Not reported	Not reported
Boulvain et al[19]	2012	RCT	133 (63/70)	EFW>95 %	37^{+0} – 38^{+6} weeks	Not provided	OR 1.2 (95% CI 0.58 – 2.7)	Not reported	Not reported
Walker et al[14]	2016	RCT	618 (304/314)	Nulliparous women ≥ 35 years on the expected due date. Singleton live fetus in cephalic	39^{+0} – 39^{+6} weeks	AROM/ PGE/ Oxytocin	OR 0.99 (95% CI 0.87 – 1.14)	OR 1.3 (95% CI 0.96 – 1.77)	OR 1.09 (95% CI 0.85 – 1.4)

				presentation.					
Knight et al[20]	2017	Retrospective cohort study	77327 (25583/51744)	Non complicated, singleton, pregnancies of healthy women aged ≥ 35 years	≥39 weeks	AROM/ PGE/ Oxytocin	RR 1.19 (95% CI 0.14 – 0.25)	RR 1.12 (95% CI 1.06 – 1.19)	Not reported
Kawakita et al[21]	2019	Retrospective cohort study	2616 (457/2159)	Nulliparous women aged ≥ 35 years with singleton gestations with cephalic presentation	39^{+0} – 39^{+6} weeks	Not provided	OR 0.69 (95% CI 0.53 – 0.91)	OR 0.91 (95% CI 0.61 – 1.35)	OR 1.33 (95% CI 0.66 - 2.66)
Grobman et al[10]	2018	RCT	250 (114/136)	Singleton, uncomplicated, nulliparous women	39^{+0} - 39^{+6} weeks	PGE/ Foley catheter/ Oxytocin	OR 0.78 (95% CI 0.56 – 1.1)	Not reported	Not reported

RCT, randomized clinical trial; IUGR, intrauterine growth restriction; EFW, estimated fetal weight; PIH, pregnancy induced hypertension, PGE, prostaglandin E; AROM, artificial rupture of membranes; AVD, assisted vaginal delivery; PH, postpartum hemorrhage

Figure 1. PRISMA flow diagram of systematic review search strategies



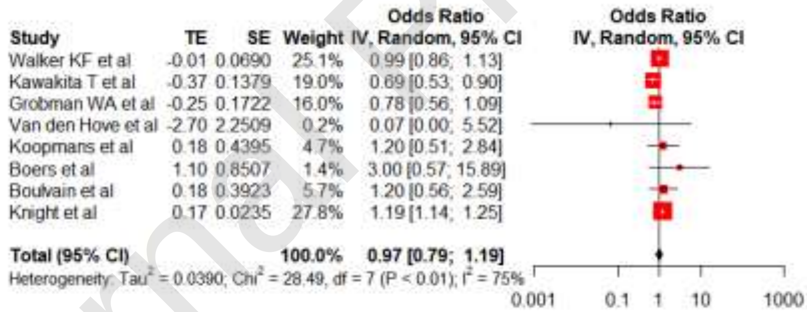


Figure 2, Forest plot of the pooled odds ratio for the outcome Cesarean Section. Size of data markers indicates the weight of the study. CI indicates confidence interval.

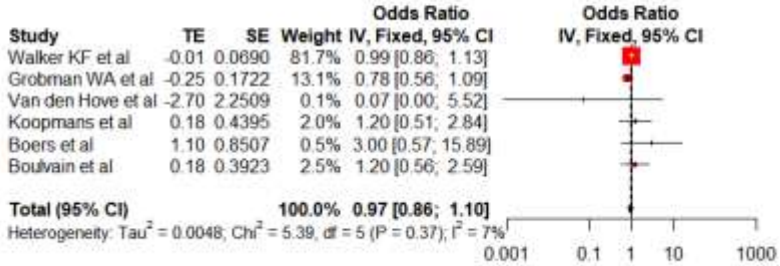


Figure 3, Forest plot of the pooled odds ratio for the outcome Cesarean Section (only randomized studies). Size of data markers indicates the weight of the study. CI indicates confidence interval.

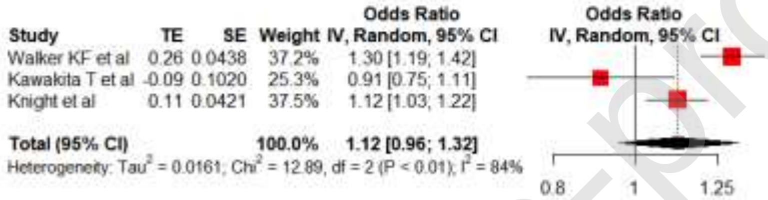


Figure 4, Forest plot of the pooled odds ratio for the outcome AVD. Size of data markers indicates the weight of the study. CI indicates confidence interval.

Figure 5, Forest plot of the pooled odds ratio for the outcome PH. Size of data markers indicates the weight of the study. CI indicates confidence interval.

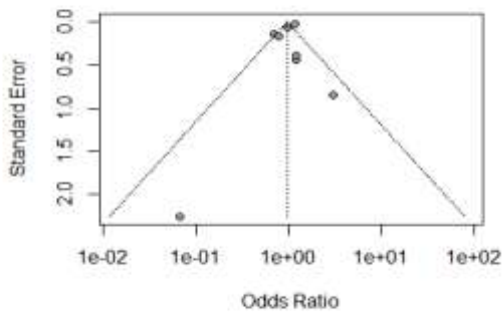


Figure 6. Publication bias for C-Section. Circles represent individual studies of the meta-analysis and the vertical line the pooled estimate of the OR for C-Section