ELECTIVE DELIVERY VERSUS EXPECTANT MANAGEMENT FOR GASTROSCHISIS: A SYSTEMIC REVIEW AND META-ANALYSIS

Short title: Time of elective delivery for gastroschisis

Abbreviations: GA, Gestational age; LOS, length of stay; TPN, total parenteral nutrition; CI, confidence interval; OR, odds ratio; OCS, observational clinical studies; RCT, randomized controlled trial

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What is Known:

- Premature delivery of neonates with gastroschisis is associated with complications such as acute respiratory distress and sepsis.
- Prolonged exposure of intestines to amniotic fluid in utero leads to complications associated to bowel mortality such as bowel atresia and perforation.

What is New:

- Moderate preterm and near-term elective delivery were compared separately to the respective control of expectant management to find the optimal time to deliver a fetal gastroschisis.

- There was no benefit of early elective delivery at GA 34-35 weeks identified
- Electively delivery at GA 36-37 weeks was associated with improves outcome of gastroschisis (less bowel morbidity and shorter TPN days).

INTRODUCTION

Gastroschisis is a paraumbilical abdominal wall defect with an incidence of 3.1-4.3 per 10,000 pregnancies, making it the most common abdominal wall defect alongside omphalocele [1, 2]. Although the aetiology is unclear, the development of gastroschisis is known to start at gestation age of 3-5 weeks when the foetal abdominal wall fails to close and the bowel is unable to return to the abdominal cavity [3]. Prolonged exposure of the intestines to amniotic fluid can lead to inflammation and matting of the intestines. In addition, non-rotation of the bowel increases the risk of intrauterine bowel atresia, perforation, and volvulus due to narrowing of the mesenteric pedicle. Hence, early elective delivery has been advocated by some studies to prevent intestinal damage and its associated complications [4, 5]. However, early delivery is associated with morbidities of prematurity such as hyperbilirubinemia (59%), acute respiratory distress (28%), hypoglycaemia (16%), and bacterial infections (15%), as reported in a Swedish population-based study of 6674 preterm infants with a GA between 30 and 34 weeks [6]. Therefore, most of centres only electively deliver infants with gastroschisis after 34 weeks of gestation. There is still no consensus on the optimal time of elective delivery for gastroschisis. Some reports suggests that preterm delivery of gastroschisis is associated with significantly worse outcomes compared to those delivered at term [7, 8]. While another study has found that elective premature delivery shortens the time to full feeding and hospital stay [9].

The inconsistent results is potentially attributable to the heterogeneity in delivery modes (such as elective versus spontaneous delivery) and time of premature delivery among the different studies. In this study, we performed a systematic review and meta-analysis on elective delivery for gastroschisis at 2 time points: moderate preterm (34-35 weeks of gestation) and at near-

term (36-37 weeks of gestation), to determine the optimal time to electively deliver a neonate with gastroschisis.

METHODS

This systematic review was performed following PRISMA guideline and registered in Prospero CRD42021272531

Search Strategy

Electronic searches were conducted and updated on June 28, 2021, from MEDLINE, Embase and Cochrane databases using the following search terms: [('gastroschisis'/exp OR gastroschisis) AND (deliver* OR labo*) AND (elective*OR earl* OR prematu* OR preterm)]. No language restrictions were applied. The reference lists of relevant articles were analysed to identify any potentially eligible studies that were not found during the electronic search. Titles and abstracts were screened by two investigators (CY and ZJ), who independently assessed study eligibility according to predetermined inclusion and exclusion criteria. Potentially relevant full-text articles were then read by both authors to determine eligibility, and studies that did not meet inclusion criteria were excluded. Disagreements were addressed through discussions and resolved by consensus agreement.

Study Selection/Eligibility criteria

Randomized control trials, retrospective and prospective cohort studies, cross-sectional studies and case-control studies were included if they compared one or both of the following:

- Group 1: Elective delivery at gestational age of 34 to 35 weeks versus the control of expectant management and delivery after gestational age of 34-45 weeks for the infants with antenatally detected gastroschisis.
- Group 2: Elective delivery at gestational age of 36 to 37 weeks versus the control of expectant management and delivery after gestational age of 36-37 weeks for the infants with antenatally detected gastroschisis.

Exclusion Criteria

Case reports, case series, descriptive surveys, reviews, conference abstracts, book chapters, and editorials were excluded. In addition, studies without clear timing of delivery, data overlapping with previous publications, and lack of comparable results were excluded. Most importantly, studies that compared preterm birth to term birth but did not specify whether preterm birth was elective or spontaneous were excluded.

Data Extraction

Two authors (YC and ZJ) independently extracted relevant results. When there was disagreement, consensus was reached through discussion amongst all authors. Data related to study design, study year, level of evidence, number of patients, patient characteristics, criteria for pre-term delivery, gestational age and outcomes were identified and extracted using an appropriate spreadsheet. Primary outcomes were: (i) length of stay and (ii) mortality. Secondary outcomes were sepsis, duration of TPN, time to full feeding, bowel morbidity (including bowel atresia/stenosis, perforation, necrosis, and volvulus), short gut syndrome and respirator days. Data recording was conducting using an excel spreadsheet, and missing data was noted in the analysis. If the primary outcome is not available, then the study was excluded.

If one or more of the secondary outcomes are not available, then the study was included but only analysed for the outcomes presented in that study.

Risk for Bias

We used the Risk of Bias 2 (RoB2) tool for assessing risk of bias in randomized control trials for the randomized control trials in this review and the Risk of Bias in Non-Randomized Studies-of Interventions (ROBINS-I) for the non-randomized studies. Each criterion was assessed as high, moderate, low, or unclear risk of bias. For each domain, judgement of categorization were made by the two authors (YC and ZJ) who selected the studies, and disagreements were resolved through discussion and consensus agreement. The results were then tabulated using the RobVis software[10].

Statistical Analysis and Assessment of Heterogeneity

The data from the RCTs, prospective and retrospective cohort studies was analysed for the same outcomes according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and using Review Manager 5.4 (Cochrane Collaboration). The primary outcomes of length of hospital stay and mortality were required information for inclusion from the studies analysed. Secondary outcomes as mentioned above were also extracted.

Continuous data presented with various forms (median, interquartile range, 95% CI, standard error), were converted to the estimated mean and standard deviation (SD) using the following formula to facilitate meta-analysis.

- Mean = Median
- SD = Range/4 =Interquartile range/1.35

The studies were then compared using forest plot analysis, and a weighted mean difference and/or odds ratio analysis, with a 95% confidence interval and a p-value of 0.05 considered to be significant. Heterogeneity of data was assessed using I^2. A fixed effect model was used if I_2 is less than 25% and a random effect model will be used if I^2 is equal to or greater than 25%.

RESULTS

A total of 524 titles were obtained through our search (Figure 1). Titles/abstracts were screened, resulting in 33 articles which met inclusion criteria and these full texts were read by two investigators. 18 studies were excluded for only comparing pre-term versus term delivery without specifying whether the intervention was elective, two were excluded for not having comparable outcomes and three were excluded due to an unclear time of delivery. Two RCTs and eight observational cohort studies were included in the meta-analysis. All studies were published in English. Six of the included studies compared elective delivery at gestational age of 34 to 35 weeks for the infants with antenatally detected gastroschisis versus the control of expectant management, and four studies compared elective delivery at gestational age of 36 to 37 weeks versus the control of expectant management and delivery after gestational age of 36-37 for gastroschisis.

Population and interventions

There was a total of 629 participants in the included studies (Table 1), of which 216 infants were in group 1: moderate preterm elective delivery (N=109) *versus* expectant treatment (N=107). Overall delivery time in the preterm delivery group was 2.37 weeks earlier than control. (MD=-2.37; CI -3.15, -1.59; $p<0.0001$; $I^2=54\%$; 4 studies, 149 infants) (Supplementary Figure 1). 413 infants were included in group 2, near-term elective delivery

(N=161) *versus* control of expectant treatment (N=252). The overall delivery time in near-term elective delivery group was 1.15 weeks earlier than the control group (MD=-1.15; CI -1.53, - 0.78; p<0.0001; I^2=74%; 4 studies, 357 infants) (Supplementary Figure 2).

Most of the elective delivery in the study were performed via Caesarean section as highlighted in our meta-analysis in which the elective moderately preterm group are 19.06 times as likely to be delivered by Caesarean section (RR=19.06; CI 1.25, 290.77; p=0.03; I^2=71%; 4 studies, 120 infants) (Supplementary Figure 3), while the near-term group are 4.34 times as likely to be delivered by Caesarean section compared to control (RR=4.34; CI 0.49, 38.69; p=0.88; I^2=72%; 3 studies, 270 infants) (Supplementary Figure 4). However, the difference was only significant in the elective moderate preterm group and not the near-term group.

Quality of the Evidence

The overall quality of the included non-RCTs (Table 2) was judged as moderate for most of the studies with exception of the Sakala 1993 study was deemed to have a serious risk of bias due to inadequate identification and elimination of confounders when examining neonatal outcome with mode of delivery instead of timing of delivery.

The risk of bias of the two RCTs (Table 3) identified that the risk of bias in both studies was low. In both studies, although the gynaecologist and patients were not blinded to the treatment, the neonatologist and paediatric surgeons were blinded to the time and mode of delivery. Furthermore, the outcomes measurement was objective, and unlikely to be affected by a lack of blinding. The rest of the bias domains used to judge the quality of studies were deemed as low risk.

Primary Outcomes

Length of stay (LOS)

Group 1: There is no significant difference in the overall LOS between elective delivery at GA of 34-35 weeks and control of expectant management (MD=-1.40; CI -20.15, 17.34; p=0.88; I^2=72%; 5 studies, 147 infants) (Supplementary Figure 5).

Group 2: The mean LOS appears shorter after elective delivery at GA 36-37 weeks (39.2 days) compared to expectant management (48.7 days) but did not reach statistical significance (MD=-13.80; CI -28.12, 0.52; p=0.06, I^2=46%; 3 studies, 272 infants) (Supplementary Figure 6).

Mortality

Group 1: Data was not sufficient for meta-analysis as only one study (Tosello 2017) presented date showing 0 death in elective delivery group and 2 (5.1%) deaths in control.

Group 2: There is no significant difference in the incidence of mortality between elective delivery at 36-37 weeks and control (RR=0.95; CI 0.31, 2.91; p=0.93; I^2=12%; 3 studies, 392 infants) (Supplementary Figure 7).

Secondary Outcomes

Bowel morbidity

Group 1: There is no significant difference in the incidence of bowel morbidity between elective delivery at 34-35 weeks and control (RR=0.93; CI 0.34, 2.53; p=0.88; I^2=0%; 3 studies, 113 infants) (Figure 2).

Group 2: Elective delivery at gestational age of 36-37 weeks significantly reduced bowel morbidity (7.4%) compared to infants that underwent expectant management (15.4%) (RR=0.39; CI 0.20, 0.78; p=0.008; I^2=0%; 4 studies, 414 infants).

Duration of total parenteral nutrition (TPN)

Group 1: There is no significant difference in the duration of total parenteral nutrition between elective delivery at 34-35 weeks and control (MD=-6.69; CI -18.1, 4.73; p=0.25; I^2=70%; 4 studies, 147 infants) (Figure 3).

Group 2: Elective delivery at gestational age 36-37 weeks significantly reduced the duration of TPN by 13.44 days (MD=-13.44; CI -26.68, -0.20; p=0.05; I^2=45%; 3 studies, 272 infants).

Sepsis

Group 1: There is no significant difference in the incidence of sepsis between elective delivery at GA of 34-35 weeks and control (RR=0.71; CI 0.36, 1.42; p=0.33; I^2=27%; 4 studies, 159 infants) (Supplementary Figure 8).

Group 2: There is no significant difference in the incidence of sepsis between elective delivery at GA of 36-37 weeks and control (RR=0.62; CI 0.24, 1.61; p=0.33; I^2=62%; 3 studies, 372 infants) (Supplementary Figure 9).

Time to first feeding

Group 1: Only Serra 2008 presented with data showing a significant reduction in time to first feeding for infants electively delivered at 34-35 weeks compared to expectant management of 8.10 days. (MD=-8.10; CI -12.10, -4.10; 1 study, 23 infants) As such, we do not have sufficient data to conduct a meta-analysis with only one study.

Group 2: There is no significant difference in the time to first feeding between elective delivery at GA of 36-37 weeks and control. (MD=-14.92; CI -36.88, 7.03; p=0.18; I^2=84%; 2 studies, 230 infants) (Supplementary Figure 10).

Short gut syndrome

Group 1: There is no significant difference in the incidence of short gut syndrome between elective delivery at GA of 34-35 weeks and the control group. (RR=1.83; CI 0.22, 14.97; p=0.57; I^2=0%; 2 studies, 67 infants) (Supplementary Figure 11).

Group 2: There is no significant difference in the incidence of short gut syndrome between elective delivery at GA of 36-37 weeks and the control group. (RR=0.77; CI 0.01, 42.46; p=0.90; I^2=77%; 2 studies, 164 infants) (Supplementary Figure 12).

Respirator days

Group 1: There is no significant difference in the number of respirator days between the elective delivery at GA of 34-35 weeks and the control group (MD=-0.52; CI -1.18, 0.14; p=0.13; I^2=36%; 6 studies, 216 infants) (Supplementary Figure 13).

Group 2: Only Logghe's RCT presented data showing no difference in time under respirator for infants electively delivered at 36-37 weeks (2.9±2.3 days) compared to expectant management (2.3±1.7days).

DISCUSSION

The incidence of gastroschisis has increased 2-10 folds over the last 3 decades [11-13]. As such, many research studies have been performed to identify and reduce the complications associated with gastroschisis. Evidence from both animal and clinical studies suggest that the severity of intestinal injury has been linked to prolonged exposure of bowel to amniotic fluid [14] . Therefore, some authors advocate early elective delivery.

There are conflicting recommendations on the effect and timing of early delivery amongst different studies. Many studies comparing early and late delivery are based on gestation age and usually lead to a conclusion that early delivery is associated with a worse outcome, such as a longer length of stay and higher bowel morbidity [15, 16]. However, these studies generally contain a mixed population of both elective and spontaneous delivery. As early spontaneous deliveries are usually secondary to foetal distress and are hence associated with worse outcome, mixing spontaneous with elective delivery may mask the benefit of early elective delivery for gastroschisis. As such, Landisch performed a meta-analysis based on 6 studies to separately compare elective premature delivery against expectant management in 2017. He found that elective premature delivery had fewer days to full feeds, less days on TPN and fewer sepsis cases compared to expectant management. However, the timing of elective premature delivery varied from GA 34 to 37 weeks in the included studies. It is thus still unclear what is the optimal timing for electively delivery of infants with gastroschisis.

In this study, we performed an updated literature research and a meta-analysis to compare either moderate premature (GA 34-35 weeks) or near-term delivery (GA 36-37 weeks) against their respective control of expectant management. We found that elective delivery at a gestational age of 34 to 35 weeks does not improve the outcome. While elective delivery at near-term is associated with significant less bowel morbidity and shorter TPN day duration compared to expectant management. The length of stay in the near-term electively delivery group is also shorter by 13.80 days compared to control, however, the difference did not reach statistical significance (p=0.06).

The average GA in the near-term elective delivery group is 36.29 weeks, which is only 1.15 weeks younger than the control. Such a slight yet early delivery significantly reduced the incidence of bowel mortality by 50% and TPN duration by 13 days. This data supports a previous study that showed that bowel injury in gastroschisis is usually developed near-term [17]. A slightly earlier delivery at near-term can be sufficient to preventing bowel damage and improving post-natal outcome.

Elective delivery before 36 weeks of GA did not demonstrate a significant benefit. Compared with the control group, GA was 2.26 weeks earlier in the moderately preterm group (mean GA 34.69 weeks), and such a large GA gap may predispose infants to higher rates of preterm birth-related morbidity. These findings are in line with the RCT (Shamshirsaz 2019) included in this meta-analysis. Shamshirsaz found that elective delivery at 34 weeks of GA did not improve outcomes and instead increased the risk of sepsis, which could be detrimental to babies with gastroschisis.

Our results suggest that the benefit of early delivery must be balanced against the morbidity that is associated with prematurity. The optimal time for delivery of pregnancy with gastroschisis based on our analysis is in the near-term period at 36-37 weeks of gestation.

Limitations

The applicability of these results should be interpreted with caution as the studies included have a few limitations. One of them would be the lack of an important outcome of stillborn/intrauterine foetal demise (IUFD). Gastroschisis is associated with the increased risk of IUFD with an adjusted odds ratio of 7.06 (95% CI: 3.33-14.96) compared to those without gastroschisis[18]. After 32 weeks, risk of IUFD/ongoing pregnancy was greater at each week of gestation in foetuses with gastroschisis. However, it is impossible to analyse this outcome, as most of studies only report the outcome for postnatal infants.

Another limitation is lack of RCTs (only having 2 RCTs) in the meta-analysis which predispose the study to multiple biases and confounders such as type of delivery and severity of gastroschisis as discussed below.

Simple vs complex gastroschisis

It is well known that complex gastroschisis is associated with a worsening of other outcomes such as TPN and LOS [19]. Gastroschisis in infants can be categorized as simple or complex based on the absence or presence of intestinal atresia, stenosis, perforation, necrosis, malrotation, or volvulus, and hence can be measured as an outcome (bowel morbidity in our study). But distinguishing between the two groups is challenging prenatally [20], as such most of the included studies failed to include the percentage of complicated gastroschises in the study arms. Our data did find that near term delivery (GA 36-37) reduced the incidence of

bowel morbidity/complex gastroschisis. Thus, this may have partially contributed to the improvement of other outcomes such as lesser TPN and LOS in near term delivery. More RCT studies are needed to control for these confounders.

Type of delivery

In the present study, there was a mismatch in delivery type between study groups. In our current data, caesarean section was more commonly chosen for elective delivery than expectant management (94% vs 37% in group 1 (GA 34-35 weeks) and 30% vs 11% in group 2 (GA 3637 weeks). However, from a recent meta-analysis, caesarean delivery did not improve outcomes for gastroschisis [21, 22]. From our current data, both Group 1 and Group 2 have a higher likelihood of being delivered via caesarean section, which does not correlate with the other outcomes of the study of near-term delivery being favourable and vice versa, which further supports the current literature. Therefore, the benefit of near-term elective delivery is unlikely to be affected by the caesarean sections.

CONCLUSION

In conclusion, compared to expectant delivery, there was no significant benefit in early elective delivery at gestational age 34-35 weeks for pregnancies with gastroschisis. However, elective delivery at GA 36-37 weeks did improve outcomes of gastroschisis (less bowel morbidity, shorter TPN days and LOS). The overall quality of evidence in support of these findings was moderate but limited to a small number of included studies. Additional multi-centred randomized control trails with large cohorts are needed to better validate these findings.

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FIGURE CAPTIONS

Figure 1: PRISMA flow diagram for selection of articles

Figure 2: Forest plot showing analyses of bowel morbidity, comparing elective delivery and control in group 1 (A) and group 2 (B).

Figure 3: Forest plot showing analyses of TPN duration, comparing elective delivery and control in group 1 (A) and group 2 (B).

Table 1: Characteristics and outcome of studies included in the meta-analysis

Table 2: ROBINS-1 risk of bias table for the eight non-RCTs, with the ones in blue being for the elective delivery at gestational age of 34 to 35 weeks studies and the ones in red being the elective delivery at gestational age of 36 to 37 weeks.

Table 3: RoB 2 risk of bias table for the two RCTs, with the ones in Logghe 2005 being for the elective delivery at gestational age of 34 to 35 weeks studies and the Shamsishirsac 2019 being the elective delivery at gestational age of 36 to 37 weeks.

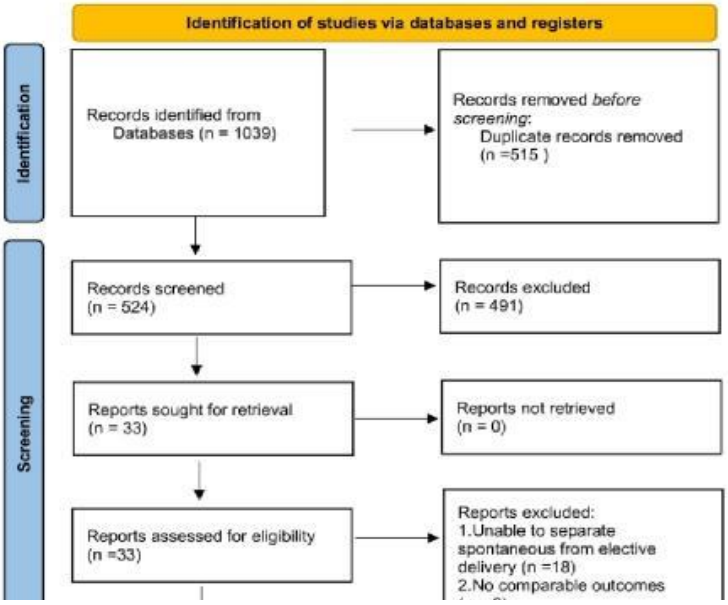

Figure 1: PRISMA flow diagram for selection of articles

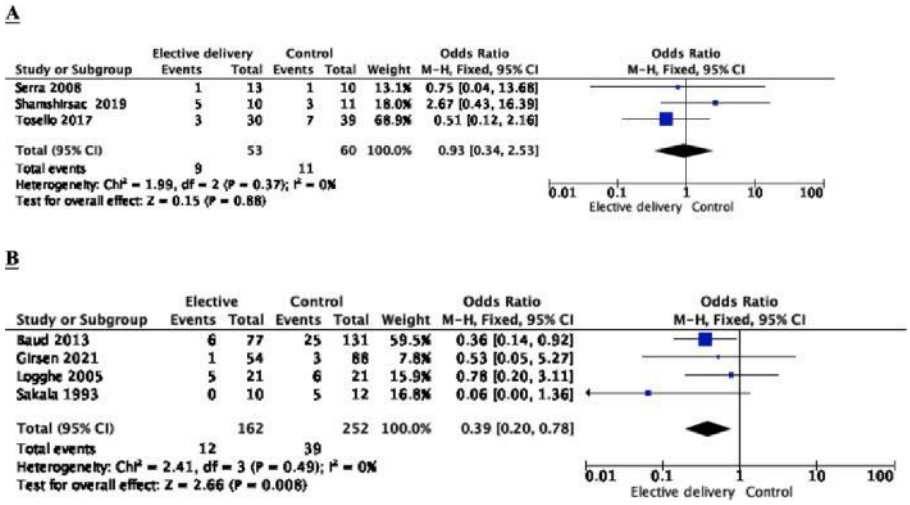

Figure 2: Forest plot showing analyses of bowel morbidity, comparing elective delivery and control in group 1 (A) and group 2 (B).

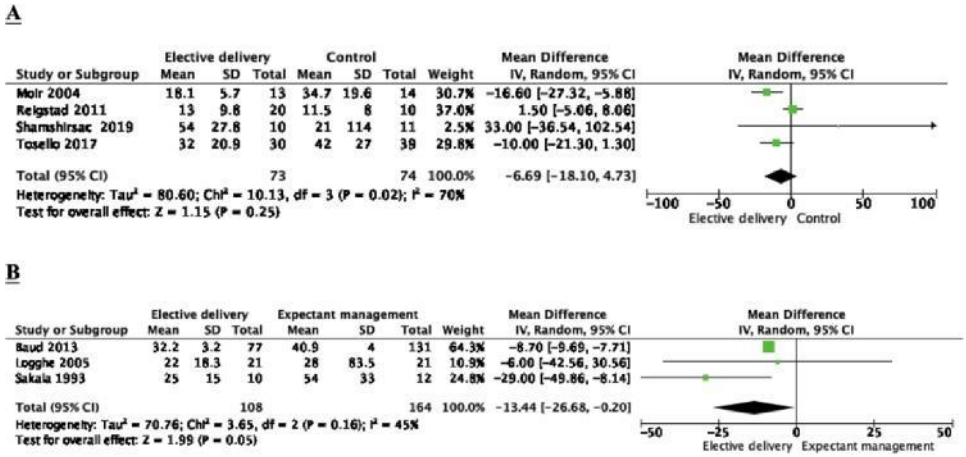

Figure 3: Forest plot showing analyses of TPN duration, comparing elective delivery and control in group 1 (A) and group 2 (B).

Study (Author, Year)	Study type	Groups & No of cases	Cesarean N (%)	Gestational age (weeks)	Time to start feeding (days)	Time to full feeding (days)	Duration of TPN (Days)	Motality N(%)	Sepsis N(%)	Bowel morbidity N(%)	Short bowel syndrome N (%)	Hospital stay (days)	Repirator Days
Hadidi 2008 [11]	OCS	Ele (GA<36): 23 Con (GA≧36):23	23 (100%) 0 (0%)		9.1 14			2(8.7%) 1(4.4%)	6 (26.1%) 9 (39.1%)		1 (4.3%) 0(0%)	51.6±31.0 61.8±33.1	3.8±3.39 4.6±4.24
Moir 2004 [4]	Prospective	Ele(GA=34):13 Con (Term): 14		34.2±2.4 37.7±1.8		19.1±5.6 35.1±9.8	18.1±5.7 34.7±19.6					22.7±5.8 35.6±21.2	1.3±0.9 1.4±1.1
Reigstad 2011 [12]	OCS	Ele (GA 35-37):20 Con(GA>37):10	20 (100%) 7 (70%)	35(34-37) 36.5(34-40)			13(7-46) 11.5(7-39)					22.5(13-195) 17.5(12-36)	1(1-7) 2(1-5)
Serra 2008 [13]	OCS	Ele (GA= 34):13 Con (GA>34):10	13 (100%) 9 (90%)	34.7±1.2 37.0±1.7	4.6±2.7 12.7±6.0				1(7.7%) 2(20%)	1 (7.7%) 1(10%)		30.7±20.6 83.6±108.9	2.7±1.4 4.3±1.7
Shamshirsaz 2019 [14]	RCT	Ele (GA=34) :10 Con (GA>34):11	6 (60%) 4 (36.4%)				54 (17-128) 21(9-465)		4 (40%) 0(0%)	5 (50%) 3 (27.3%)	1 (10%) 1 (9.1%)	70.5 (22-137) 31.0(19-186)	4 (1-24) 3 (1-13)
Tosello 2017 [15]	RCS	Ele (GA=35):30 Con (Near term):39		34.3±1.3 37.0±2.1			32(23.8-52)* 42(28-64.5)*	0 (0%) 2(5.1%)	8 (26.6%) 17(44%)	3(10%) 7(17.9%)			4(3-5)* 3.5(2-7.3)*
Baud 2013 [16]	OCS	Ele (GA=37):77 Con (GA >37):131	15 (19.5%) 9(11.8%)	36.6±0.1 37.6±0.4	23.8±2.9 29.2±2.6		32.2±3.2 40.9±4.0	2 (2.6%) 7(5%)	19(24.7%) 54(41.3%)	6(7.8%) 25(19.1)		38.8±4.4 47.4±3.6	
Girsen 2021 [5]	OCS	Ele (GA<37):54 Con (GA≧37):88	NA 21(23%)	35.9±0.9 37.4±0.67		25(18-38)* 23(17-30)*		1 (2%) 1 (1%)	15 (28%) 21 (24%)	1 (2%) 3 (3%)	3(6%) 1 (1%).		
Logghe 2005 [17]	RCT	Ele (GA=36): 20 Con (GA>36):20	7 (35%) 9(45%)	35.8±0.7 36.7±1.5		30.5(18-96) 37.5(15-358)	22(14-87) 28(12-346)	2 (10%) 0 (0%)		5 (25%) 6 (30%)		47.5(23-126) 53 (22-399)	2.9±2.3 2.3±1.7
Sakala 1993 [18]	OCS	Ele (GA=37):10 Con (GA>37):12	10 (100%) 0(0%)	37.0±2.1 37.8±2.0	13±9 42±30		25±15 54±33		0(0%) 4(33%)	0(0%) 5(42%)	0(0%) 4(33%)	25±15 55±35	

RCT: randomized controlled trials; OCS: observational clinical studies; Ele: elective delivery ; Con: control ;
Data was presented as Mean±SD or Median (range) except for * Median (interquartile range)

Table 1: Characteristics and outcome of studies included in the meta-analysis

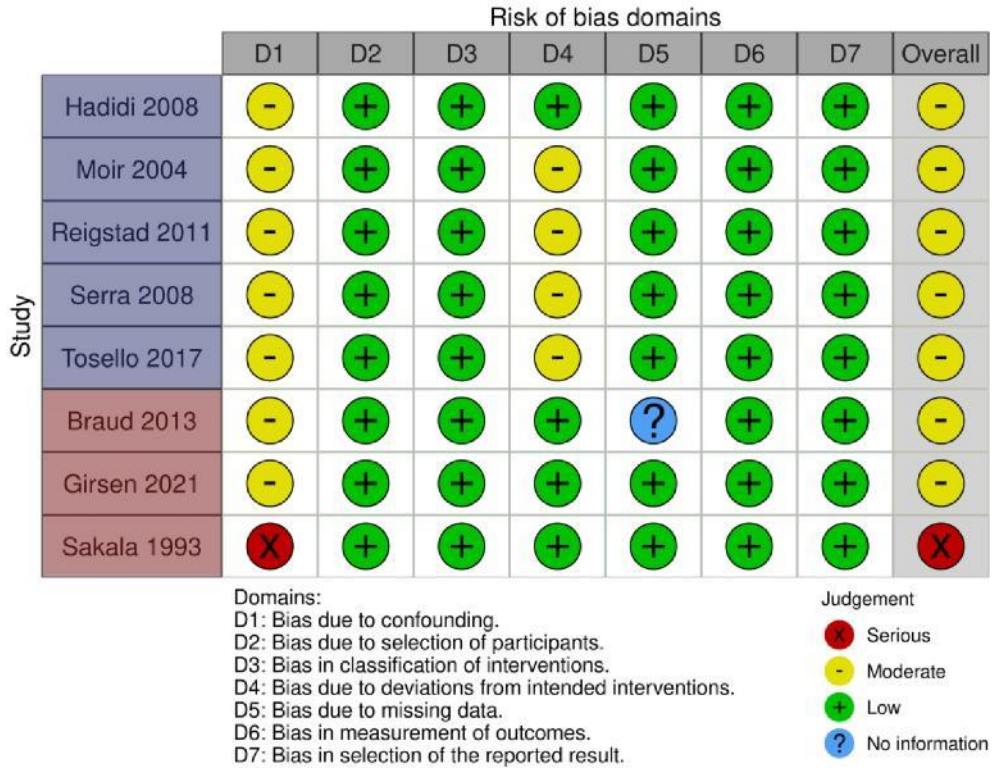

Table 2: ROBINS-1 risk of bias table for the eight non-RCTs, with the ones in blue being for the elective delivery at gestational age of 34 to 35 weeks studies and the ones in red being the elective delivery at gestational age of 36 to 37 weeks.

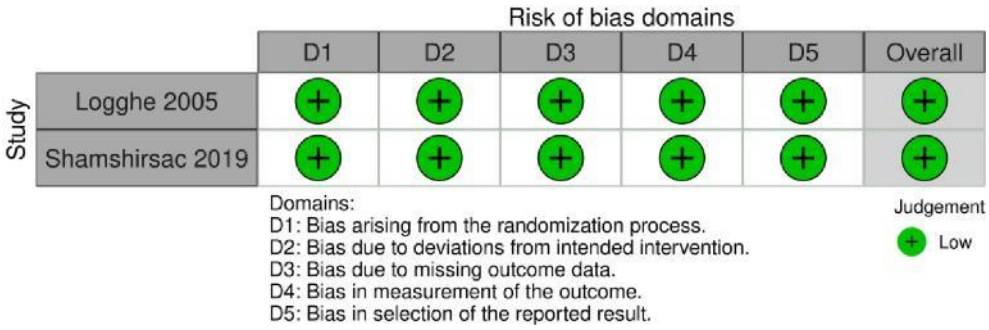

Table 3: RoB 2 risk of bias table for the two RCTs, with the ones in Logghe 2005 being for the elective delivery at gestational age of 34 to 35 weeks studies and the Shamsishirsac 2019 being the elective delivery at gestational age of 36 to 37 weeks.