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Effect of mode of delivery on perinatal outcome in severe preterm birth: systematic review and meta-analysis

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KEYWORDS: breech; cephalic; Cesarean section; grade; meta-analysis; mode of delivery; neonatal death; perinatal death; preterm birth; survival; vaginal delivery

CONTRIBUTION

What are the novel findings of this work?
Vaginal delivery may increase the odds of neonatal death and decrease the odds of survival to discharge in breech fetuses born before 28 weeks' gestation. It may also increase the odds of perinatal death (intrapartum and neonatal) of breech fetuses born between 28 and 32 weeks. We did not observe a significant effect of mode of delivery on the mortality of cephalic fetuses.

What are the clinical implications of this work?
Evidence, albeit of low quality, indicates that Cesarean section may be the preferred mode of delivery in severe preterm birth with breech presentation, while evidence for non-breech fetuses is inconclusive.

ABSTRACT

Objective *To review the evidence on the effect of mode of delivery on perinatal outcome of fetuses born before 32 weeks' gestation.*

Methods *MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), the ClinicalTrials.gov registry and gray literature sources were searched, starting from the year 2000 to reflect contemporary practice in perinatal care. Non-randomized or randomized studies that included singleton fetuses without chromosomal abnormality or major congenital defect delivered vaginally or via Cesarean section were eligible for inclusion in the analysis. Primary outcomes were neonatal death, defined as death in the first 28 days of age, and survival to discharge. Secondary outcomes were other adverse perinatal events. The ROBINS-I tool was used to assess the risk of bias. The overall quality of evidence for the outcomes was assessed according to GRADE. Summary odds ratios (ORs) with 95% CIs were calculated, and random-effects models were used for data synthesis. Subgroup analysis was performed for delivery before 28 weeks, delivery between 28 and 32 weeks and according to fetal presentation at delivery.*

Results *A total of 27 retrospective studies (22 887 neonates) were included in the systematic review and meta-analysis, all of which reported on singleton pregnancies. Among cases born before 28 weeks, vaginal delivery significantly increased the risk of neonatal death of fetuses with any type of presentation* ($n = 1496$) *(OR 1.87 (95% CI, 1.05–3.35);* $I^2 = 65\%$*, very low quality of evidence) and of fetuses with breech presentation* ($n = 733$) *(OR 3.55 (95% CI, 2.42–5.21);* $I^2 = 21\%$*, moderate quality of evidence). The odds of survival to discharge were significantly decreased among fetuses with breech presentation delivered before 28 weeks* ($n = 646$) *(OR 0.36 (95% CI, 0.24–0.54);* $I^2 = 21\%$*, low quality of evidence). Among breech fetuses born between 28 and 32 weeks, vaginal delivery increased the odds of perinatal death (intrapartum and neonatal)* ($n = 1581$) *(OR 3.06 (95% CI, 1.47–6.35);* $I^2 = 0\%$*, high quality of evidence). In non-cephalic fetuses born between 24 and 32 weeks, vaginal delivery decreased the odds of survival to discharge* ($n = 1030$) *(OR 0.28 (95% CI, 0.19–0.40);* $I^2 = 0\%$*, moderate quality of evidence). No significant*

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effect on mortality of mode of delivery was observed in cephalic fetuses at any gestational age.

Conclusions *This systematic review and meta-analysis suggests that vaginal delivery in severe preterm birth is associated with an increased risk of neonatal and perinatal death in breech fetuses, while no significant association was observed for cephalic fetuses. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Severe preterm birth is an uncommon event in singleton pregnancies, as only 1.5% of live births occur before 32 weeks[1], and only 5% of all preterm births occur before 28 weeks[2]. Yet, it accounts for a significant proportion of admissions to the neonatal intensive care unit and is associated with significant short- and long-term morbidity of the offspring.

The effect of mode of delivery in the severely preterm period on perinatal outcome is not clear. Retrospective studies have reported heterogeneous results for outcomes such as neonatal death[3–8] and composite adverse outcome[5–9]. Cesarean section may improve outcomes in severely preterm fetuses with breech presentation according to some studies[5,10,11], but it may also increase the risk of maternal peripartum complications[12]. The uncertainty of the evidence base is also reflected in the current guidelines, some of which recommend Cesarean delivery for extremely preterm fetuses or preterm fetuses with breech presentation, whereas others do not provide specific recommendations[13–15]. However, all guidelines are consistent in that the evidence on the choice of mode of delivery is suboptimal.

As survival and intact survival of very preterm fetuses has improved in recent years[16], the potential effect of mode of delivery (vaginal delivery *vs* Cesarean section) on perinatal outcome has become more relevant, especially for births before 28 weeks. Therefore, the aim of this systematic review and meta-analysis was to assess critically and synthesize the available evidence regarding the effect of mode of delivery on perinatal outcome in severe preterm birth, with subgroup analyses to improve the homogeneity of the current evidence.

METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for meta-analyses and is registered with PROSPERO (CRD42022361076).

Search strategy

We searched the literature for studies that included data on the mode of delivery and compared vaginal with Cesarean delivery in women with preterm birth before 32 weeks. MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), the ClinicalTrials.gov registry and gray literature sources were searched using combinations of the following terms: 'preterm birth', 'very preterm', 'extreme preterm', 'delivery', 'mode of delivery', 'vaginal delivery', 'Cesarean delivery'. This search was complemented by perusal of the references of the retrieved articles and additional automated search using the 'search for related articles' function in PubMed. All studies were carefully compared to avoid inclusion of duplicates or overlapping samples. In case of overlap, the study with the largest number of cases was included.

Study selection

Eligible were randomized or non-randomized (prospective or retrospective cohorts or case–control) studies, published from the year 2000 to reflect contemporary practice in perinatal care, written in any European language and reporting on singleton fetuses without chromosomal abnormality or major congenital defect with spontaneous or iatrogenic preterm birth at or before 32 weeks' gestation via vaginal or Cesarean delivery (all types).

Exclusion criteria were multiple pregnancy (unless they could be separated from the total sample or represented $< 15\%$ of it), fetal chromosomal or structural anomaly, and emergency delivery for maternal or fetal reasons that would exclude the option of vaginal delivery (unless they could be separated from the total sample or represented $< 10\%$ of it).

Outcomes

The main outcomes were neonatal death, defined as death in the first 28 days postpartum, and survival to discharge. Secondary outcomes were neonatal complication, as defined by the authors, including severe intraventricular hemorrhage (IVH) (Grade III and IV), periventricular leukomalacia (PVL), severe respiratory distress syndrome (RDS), need for mechanical ventilation, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity, cerebral palsy (CP) and neonatal sepsis (both early- and late-onset); composite adverse outcome, as defined by the authors of the primary studies but including at least two of the abovementioned outcomes; composite adverse outcome in later life; intact survival at 2 years; moderate or severe neurodevelopmental impairment, defined as the presence of any of the following: cognitive impairment, defined based on Bayley Scale scores ≤ 85 as moderate and ≤ 70 as severe, CP according to the Gross Motor Function Classification System, severe bilateral hearing loss or severe visual impairment at the age of 18 to 36 months.

Data extraction

Data extraction and assessment of study quality were performed independently by two authors (E.D. and C.C.).

The characteristics of each included study were assessed according to a predefined data extraction form. Extracted information included: study setting, study population, participant demographic and baseline characteristics, definition of prematurity, details on delivery (including the cause of prematurity (spontaneous *vs* indicated)), pregnancy complication (e.g. preterm prelabor rupture of membranes (PPROM)) and onset of labor (spontaneous *vs* induction), details on mode of delivery, study methodology, potential confounders (antenatal corticosteroids and administration of magnesium sulfate), outcomes and timing of outcome assessment and information for the assessment of the risk of bias.

In case of disagreement, a consensus was reached after a discussion between the two authors. If outcomes were reported for both actual and intended mode of delivery, the latter was chosen.

Assessment of risk of bias of individual studies

Two review authors (E.D. and C.C.) independently assessed the risk of bias in the included studies. We planned to use the Cochrane risk of bias tool-2 (RoB-2) for randomized controlled trials (RCTs)[17] and the Cochrane ROBINS-I tool[18] for non-randomized studies.

As only non-randomized studies were included, the following seven risk of bias domains per ROBINS-I were assessed: confounding, selection of participants into the study, classification of interventions, deviation from intended intervention, missing data, measurement of outcomes and selection of the reported results. Studies were subsequently classified as having an overall low risk of bias if all domains were rated as low risk, moderate risk of bias if all domains were at low or moderate risk, serious risk of bias if at least one domain was at serious risk but not at critical risk and critical risk of bias if at least one domain was at critical risk.

Overall quality of evidence

The overall quality of evidence for each outcome was assessed according to grading of recommendations assessment, development and evaluation (GRADE)[19,20] using the GRADEpro GD tool. Briefly, GRADE is a system for rating the quality of evidence in systematic reviews and guidelines using a scoring system across five fields: risk of bias, inconsistency, indirectness, imprecision and publication bias. GRADE specifies four categories for the quality of a body of evidence. This reflects the degree of confidence regarding how close an estimate of the effect lies to the true effect. High quality means that there is a high degree of confidence that the true effect lies close to the estimate of the effect calculated by the meta-analysis. The level of confidence decreases with decreasing quality (from high to moderate to low to very low), and very low quality means that the true effect is likely to be substantially different from that estimated in the review[20].

Summary measures and synthesis of results

For dichotomous data, we calculated summary odds ratios (ORs) with 95% CIs. The mean difference was calculated for continuous outcomes if they were measured in the same way between studies. Both fixed and random effects were calculated; however, as heterogeneity was expected among the studies, the random-effects model was used for data synthesis and interpretation of the results. Between-study statistical heterogeneity was assessed using the I^2 statistic, which is the ratio of between-study variance to the sum of the within- and between-study variances and reflects the percentage of the true effect variation that is due to heterogeneity rather than chance (range, 0–100%). I^2 values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively[21]. The unit of analysis was the neonate/offspring for perinatal outcomes. Statistical analysis was carried out in R version 4.2.1 (Open-source software, Vienna, Austria).

Subgroup and sensitivity analysis

All outcomes were analyzed for two subgroups according to gestational age at delivery: (1) before 28 weeks and (2) between 28 and 32 weeks. Studies reporting on outcomes for fetuses delivered between 24 and 32 weeks were analyzed separately. Further subgroup analyses were planned for presentation (cephalic or breech) and intact or ruptured membranes (PPROM). A sensitivity analysis excluding studies with iatrogenic indication for preterm birth was performed for the main outcomes.

RESULTS

Study selection

The electronic search yielded 3266 potential studies, of which 3171 were excluded based on their title and abstract, because they were duplicates or because the full text was not retrievable. The reasons for exclusion were irrelevant pathology, irrelevant gestational period, lack of information on mode of delivery and irrelevant outcomes (Figure 1).

The full text of 95 studies was reviewed. After the full manuscript was reviewed and further exclusion criteria were applied (Table S1), 37 studies[3–11,22–49] were considered. Of those, 27 studies (22 887 neonates)[3–11,32–49] reported quantitative data and were eventually included in the systematic review and meta-analysis.

Study characteristics

The characteristics of the included studies are shown in Table 1. All of them were observational retrospective studies, and all reported results on singleton pregnancies. Nine studies provided data on cephalic fetuses, of which three[36,38,49] included only fetuses with cephalic presentation, and six[10,11,33,35,44,48] had extractable data for this presentation. Data on breech fetuses could be extracted from 14 studies[3–5,9,10,11,33,34,39,42,44–47], while data for cases with unspecified presentation were provided in nine studies[6–8,32,35,37,40,41,43]. Sixteen[3–11,33,40,42–45,47] studies reported on delivery before 28 weeks and four[6,9,42,44] on delivery between 28 and 32 weeks. Fifteen[6,9,32,34–39,41,42,44,46,48,49] studies reported on delivery between 24 and 32 weeks.

Risk of bias

The risk of bias of included studies is presented in Table 2. No studies were classified as having a low risk of bias. Twenty-one[3,4,6–11,32,35–37,39–41,44–49] studies were classified as having a moderate risk of bias, mainly owing to moderate risk of bias in reported results and classification of interventions. Six[5,33,34,38,42,43] studies were classified as having a serious risk of bias owing to serious risk of bias in either confounding or selection of participants. There were no studies with a critical risk of bias.

Quantitative synthesis

Delivery before 28 weeks

Among all studies reporting on delivery before 28 weeks, seven studies[3–8,33] (1496 neonates) reported results on neonatal death. Vaginal delivery was associated with increased odds of neonatal death (OR 1.87 (95% CI, 1.05–3.35); $I^2 = 65\%$, very low quality of evidence), while no association with survival to discharge was observed (four studies[5,10,11,47], $n = 1355$; OR 0.58 (95% CI, 0.32–1.05); $I^2 = 79\%$, very low quality of evidence) (Table 3, Figure 2). Vaginal delivery was associated with increased odds of perinatal death (intrapartum and neonatal death) (six studies[5,7,9,33,42,44], $n = 2670$; OR 2.22 (95% CI, 1.23–4.00); $I^2 = 84\%$, low quality of evidence) (Figure S1), decreased need for mechanical ventilation (two studies[7,44], $n = 1373$; OR 0.76 (95% CI, 0.59–0.99); $I^2 = 0\%$, moderate quality of evidence) (Figure S6) and decreased odds of BPD (three studies[7,40,47], $n = 1143$; OR 0.61 (95% CI, 0.45–0.83); $I^2 = 0\%$, moderate quality of evidence) (Figure S7). There

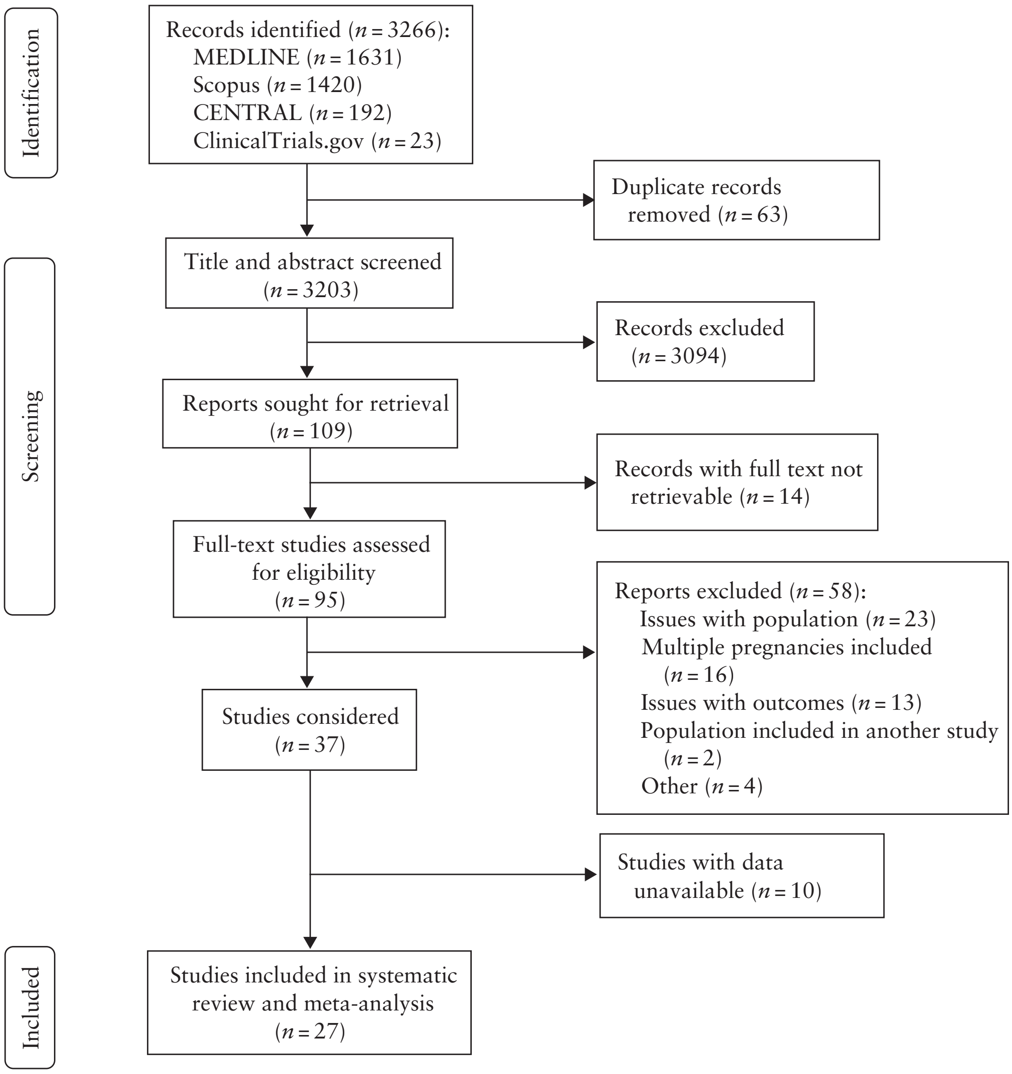

Figure 1 Flowchart of selection process of included studies.

Table 1 Characteristics of the 27 studies included in systematic review

Study	*Country*	*Study design*	*Study period*	*Study population*	*GA (weeks)*	*Fetal presentation*	*Method of reporting results*	*Evaluated subgroups (n)*	*Outcomes of interest*	*ANS*	*$MgSO_4$*
Bergenhene-gouwen (2015)[9]	Netherlands	Retro registry	2000–2011	8356	26 + 0 to 36 + 6	Breech	Intended and actual mode	26 + 0 to 27 + 6w (395); 28 + 0 to 31 + 6w (1096)	PNM, composite mortality and morbidity	Yes	No
Blue (2015)[32]	USA	Retro	1996–2014	652	24 + 0 to 30 + 6	NS	Intended and actual mode	—	Death before discharge, RDS, neonatal intubation, sepsis, IVH III/IV	Yes	Yes
Boyd (2019)[33]	Australia	Retro	1998–2017	688	22 + 0 to 25 + 6	Cephalic or breech	Actual mode	Cephalic (415); breech (273)	NND, PNM	Probably yes	NS
Bruey (2015)[4]	France	Retro	2008–2012	145	25 + 0 to 34 + 6	Breech	Intended mode	25 + 0 to 27 + 6w (17)	NND, IVH	Yes	Yes
Demirci (2012)[34]	Turkey	Retro	2000–2006	1537	> 24	Breech	Actual mode	<1000 g (mean GA < 32w) (51); 1000–1500 g (mean GA < 32w) (80)	NND, IVH, RDS, NEC	NS	NS
Effer (2002)[10]	Canada	Retro	1991–1996	860	24 + 0 to 25 + 6	Cephalic or breech	Actual mode	Cephalic (426); breech (305)	Survival to discharge	Yes	NS
Ehrhardt (2022)[35]	EU	Secondary analysis of prosp multicenter study (EPICE)	2011–2012	2748	24 + 0 to 31 + 6	Cephalic or NS	Actual mode	Any presentation (including cephalic) (2748); cephalic (1910)	Death in hospital, moderate/severe BPD, composite (death/BPD)*	Yes	Yes
Gaudineau (2020)[36]	France	Secondary analysis of prosp multicenter (EPIPAGE-2) (part of EPICE)	2011	1008	24 + 0 to 31 + 6	Cephalic	Intended mode	—	NEC, ROP, death before discharge, BPD, composite (IVH/PVL)†	Yes	Yes
Ghi (2010)[37]	Italy	Retro	1990–2007	109	25 + 0 to 32 + 6	NS	Actual mode	—	NND, IVH, PVL	Yes	NS
Gluck (2021)[6]	Israel	Retro	2009–2017	475	24 + 1 to 34 + 0	NS	Actual mode	24 + 1 to 28 + 0w (110); 28 + 1 to 32 + 0w (225)	NND, RDS, sepsis, IVH, NEC, composite (≥2 adverse outcomes)	Yes	NS
Herbst (2007)[3]	Sweden	Retro registry	1990–2002	2674	25–36	Breech	Actual mode	25 + 0 to 27 + 6w (387)	NND, RDS, IVH	Yes	NS
Hills (2018)[5]	Australia	Retro	2005–2014	150	23 + 0 to 27 + 6	Breech	Actual mode	—	NND, PNM, survival to discharge, composite (RDS/IVH/PVL/MAS/seizures)	Yes	Yes
Hübner (2016)[38]	Argentina, Brazil, Chile, Paraguay, Peru and Uruguay	Retro registry	2001–2011	4386	24–30	Cephalic	Actual mode	—	Death before discharge, sepsis (EOS), IVH III/IV	Yes	NS
Kayem (2015)[39]	France	Retro	1999–2010	303	26 + 0 to 29 + 6	Breech	Intended mode	—	NND, sepsis, BPD, IVH III/IV, PVL, NEC	Yes	NS
Lodha (2020)[40]	Canada	Retro	1995–2010	881	23–29	NS	Intended mode	—	RDS, sepsis (LOS), IVH III/IV, PVL, ROP, BPD, NEC, CP, mortality at 36 months, NDI at 36 months, composite at 36 months (death/NDI with WPPSI III/IV)	Yes	NS
Minguez-Milio (2011)[41]	Spain	Retro	1994–1998	138	Mean, 28 (< 32)	NS	Actual mode	—	Death before discharge, RDS, IVH, PVL, ROP, NEC, BPD, mechanical ventilation, sepsis	Yes	NS

Continued over.

Table 1 *Continued*

Study	*Country*	*Study design*	*Study period*	*Study population*	*GA (weeks)*	*Fetal presentation*	*Method of reporting results*	*Evaluated subgroups (n)*	*Outcomes of interest*	*ANS*	*MgSO₄*
O'Reilly (2018)[42]	Ireland	Retro	2001–2011	1000	< 37	Breech	Actual mode	24 + 0 to 27 + 6w (64); 28 + 0 to 31 + 6w (105)	PNM	Probably yes	NS
Običan (2015)[43]	USA	Secondary analysis of RCT (BEAM)	1997–2004	158	23 + 4 to 25 + 6	NS	Actual mode	—	Bayley II at 2 years (NDI moderate/severe), sepsis	Yes	Yes
Pierre (2021)[45]	France	Retro	1997–2015	193	25 + 0 to 27 + 6	Breech	Intended mode	—	IVH III/IV	Yes	NS
Reddy (2012)[44]	USA	Retro	2002–2008	2906	24 + 0 to 31 + 6	Cephalic or breech	Intended mode	Cephalic 24 + 0 to 27 + 6w (714); cephalic 28 + 0 to 31 + 6w (1424); breech 24 + 0 to 27 + 6w (388); breech 28 + 0 to 31 + 6w (380)	PNM, RDS, IVH, NEC, sepsis, mechanical ventilation	Yes	NS
Schmidt (2019)[46]	EU	Secondary analysis of prosp multicenter study (EPICE)	2011–2012	572	24 + 0 to 31 + 6	Breech	Actual mode	—	Death before discharge, composite (mortality/IVH/PVL)	Yes	Yes
Stohl (2011)[47]	USA	Retro	2000–2008	65	24 + 0 to 26 + 6	Breech	Actual mode	—	Death before discharge, IVH III/IV, PVL, BPD, NEC	Yes	Yes
Thomas (2016)[11]	Australia	Retro	1998–2009	451	23 + 0 to 26 + 6	Cephalic, breech or non-cephalic	Actual mode	Cephalic (239); breech (126); non-cephalic (44)	Survival to discharge	Yes	NS
Wolf (2021)[49]	EU	Secondary analysis of prosp multicenter (EPICE)	2011–2012	1966	24 + 0 to 31 + 6	Cephalic	Actual mode	—	Composite (death/PVL/IVH), long-term composite (neurosensory, gross motor and developmental impairment at 2 years), death before discharge‡	Yes	Yes
Wood (2018)[48]	USA	Secondary analysis of RCT (BEAM)	1997–2004	1943	24–31	Cephalic or non-cephalic	Actual mode	Cephalic (1485); non-cephalic (458)	NICU death, IVH III/IV, PVL, sepsis, NEC, ROP, RDS, mechanical ventilation, BPD, any CP at 2 years, moderate/severe CP (NDI moderate/severe), composite (death/moderate/severe CP)	Yes	Yes
Yamamoto (2022)[8]	Japan	Retro	2010–2014	80	23 + 0 to 25 + 6	NS	Intended mode	—	NND, composite at neonatal period (death/IVH/PVL/NEC or FIP/sepsis), IVH III/IV, PVL, sepsis, composite at 36 months (death/CP/severe NDI), CP, severe NDI	Yes	Yes
Zahedi-Spung (2022)[7]	USA	Retro	2010–2015	271	22 + 0 to 29 + 0	NS	Actual mode	—	NND, composite neonatal morbidity, mechanical ventilation, IVH, NEC, BPD, PNM	Yes	Yes

Only first author is given for each study. Perinatal mortality (PNM) was defined as intrapartum or neonatal (NND) death. In studies reporting on death before discharge, survival to discharge was calculated. *Survival to discharge was evaluated only in cephalic cases owing to non-cephalic population overlapping with Schmidt *et al.*[46]. Composite outcome of death and bronchopulmonary dysplasia (BPD) was excluded owing to overlap with Wolf *et al.*[49]. BPD was evaluated in cases with any presentation. †Survival to discharge and BPD were not evaluated owing to overlapping population with Ehrhardt *et al.*[35]. Composite outcome of severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was not evaluated owing to overlap with Wolf *et al.*[49]. ‡Survival to discharge was not evaluated owing to overlapping population with Ehrhardt *et al.*[35]. ANS, antenatal steroids; Bayley II, Bayley Scales of Infant Development version II; CP, cerebral palsy; EOS, early-stage sepsis; EU, 11 European countries; FIP, focal intestinal perforation; GA, gestational age at delivery; LOS, late-stage sepsis; MAS, meconium aspiration syndrome; $MgSO_4$,magnesium sulfate; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NS, not specified; RCT, randomized controlled trial; RDS, respiratory distress syndrome; Retro, retrospective; ROP, retinopathy of prematurity; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

was no significant effect of mode of delivery on the risk of severe IVH, PVL, RDS, NEC, sepsis or neonatal composite adverse outcome. There was insufficient evidence for the rest of the outcomes (Figures S2–S5 and S8–S13).

Among studies reporting on delivery before 28 weeks with unspecified fetal presentation, the risk of neonatal death did not differ according to mode of delivery (three studies[6–8], $n = 461$; OR 0.81 (95% CI, 0.33–2.02); $I^2 = 0\%$, low quality of evidence) (Table 3, Figure 2a). There were no studies reporting on the primary outcome of survival to discharge. Vaginal delivery was associated with decreased odds of BPD (two studies[7,40], $n = 1078$; OR 0.63 (95% CI, 0.47–0.86); $I^2 = 0\%$, moderate quality of evidence) (Figure S7) and increased odds of NEC (three studies[6,7,40], $n = 1262$; OR 1.73 (95% CI, 1.14–2.64); $I^2 = 0\%$, moderate quality of evidence) (Figure S8). There was no significant effect of mode of delivery on the odds of IVH, RDS, CP, sepsis, neonatal composite adverse outcome, neurodevelopmental impairment or composite adverse outcome in later life. There was insufficient evidence for the rest of the outcomes (Figures S1–S6 and S9–S13).

Among studies reporting on delivery before 28 weeks with cephalic presentation, there were insufficient data for the primary outcome of neonatal death, whereas

Table 2 Risk of bias assessment using ROBINS-I tool[18]

Study	*Confounding*	*Selection of participants*	*Classification of intervention*	*Deviation from intended intervention**	*Missing data*	*Measurement of outcome*	*Reported results*	*Overall risk*
Bergenhenegouwen (2015)[9]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Blue (2015)[32]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Boyd (2019)[33]	Serious	Low	Moderate	NA	Low	Low	Moderate	Serious
Bruey (2015)[4]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Demirci (2012)[34]	Serious	Low	Moderate	NA	Low	Low	Moderate	Serious
Effer (2002)[10]	Moderate	Low	Moderate	NA	Low	Low	Moderate	Moderate
Ehrhardt (2022)[35]	Low	Low	Low (as secondary analysis)	NA	Low	Low	Moderate	Moderate
Gaudineau (2020)[36]	Low	Low	Low (as secondary analysis)	Low	Low	Low	Moderate	Moderate
Ghi (2010)[37]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate
Gluck (2021)[6]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate
Herbst (2007)[3]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate
Hills (2018)[5]	Serious	Low	Moderate	NA	Low	Low	Moderate	Serious
Hübner (2016)[38]	Serious	Low	Moderate	NA	Low	Low	Moderate	Serious
Kayem (2015)[39]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Lodha (2020)[40]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Minguez-Milio (2011)[41]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate
O'Reilly (2018)[42]	Serious	Low	Moderate	NA	Low	Low	Moderate	Serious
Občan (2015)[43]	Low	Serious (only survivors)	Moderate	NA	Low	Low	Moderate	Serious
Pierre (2021)[45]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Reddy (2012)[44]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Schmidt (2019)[46]	Low	Low	Low (as secondary analysis)	NA	Low	Low	Moderate	Moderate
Stohl (2011)[47]	Moderate	Low	Moderate	NA	Low	Low	Moderate	Moderate
Thomas (2016)[11]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate
Wolf (2021)[49]	Low	Low	Low (as secondary analysis)	NA	Low	Low	Moderate	Moderate
Wood (2018)[48]	Low	Low	Low (as secondary analysis)	NA	Low	Low	Moderate	Moderate
Yamamoto (2022)[8]	Low	Low	Moderate	Low	Low	Low	Moderate	Moderate
Zahedi-Spung (2022)[7]	Low	Low	Moderate	NA	Low	Low	Moderate	Moderate

Only first author is given for each study. *Actual mode instead of intended mode of delivery was defined as deviation from intended intervention. Risk was deemed to be low if intended mode of delivery analysis was conducted or not applicable (NA) if only actual mode of delivery analysis was presented.

there was no significant effect of mode of delivery on survival to discharge (two studies[10,11], $n=665$; OR 1.40 (95% CI, 0.92–2.12); $I^2=0\%$, low quality of evidence) (Table 3, Figure 2b). There was no significant effect of mode of delivery on perinatal mortality and insufficient evidence to assess the effect on the other secondary outcomes.

Among studies reporting on delivery before 28 weeks with breech presentation, vaginal delivery was associated with increased odds of neonatal death (four studies[3–5,33], $n=733$; OR 3.55 (95% CI, 2.42–5.21); $I^2=21\%$, moderate quality of evidence) (Table 3, Figure 2a) and decreased odds of survival to discharge (four studies[5,10,11,47], $n=646$; OR 0.36 (95% CI, 0.24–0.54); $I^2=21\%$, low quality of evidence) (Figure 2b). Moreover, vaginal delivery was associated with increased odds of perinatal mortality (five studies[5,9,33,42,44], $n=1270$; OR 2.88 (95% CI, 1.15–7.21); $I^2=88\%$, very low quality of evidence) (Figure S1). There was no significant effect of mode of delivery on the odds of IVH, RDS, NEC or neonatal composite adverse outcome. There was insufficient evidence for other outcomes (Figures S2–S13).

Delivery between 28 and 32 weeks

Among all studies reporting on delivery between 28 and 32 weeks, there was insufficient evidence on the outcomes of neonatal death and survival to discharge. There was no significant effect of mode of delivery on perinatal mortality, severe IVH, RDS, need for mechanical ventilation, NEC, sepsis or neonatal composite adverse outcome. There was insufficient evidence for the rest of the outcomes (Table 4, Figure 3, Figures S14–S20).

Among studies reporting on delivery between 28 and 32 weeks with breech presentation, vaginal delivery

Table 3 Odds ratios (OR) for different adverse outcomes in fetuses born before 28 weeks following vaginal delivery (*vs* Cesarean delivery), overall and according to presentation at birth

	Not specified		*Cephalic*		*Breech*		*Non-cephalic*		*All*
Outcome	*Studies (n^ref)*	*OR (95% CI)*	*Studies (n^ref)*	*OR (95% CI)*	*Studies (n^ref)*	*OR (95% CI)*	*Studies (n^ref)*	*OR (95% CI)*	*OR (95% CI)*
NND ($n=1496$)	3[6–8]	0.81 (0.33–2.02)	1[33]	1.25 (0.76–2.07)	4[3–5,33]	3.55 (2.42–5.21)	NA	NA	1.87 (1.05–3.35)
Survival to discharge ($n=1355$)	NA	NA	2[10,11]	1.40 (0.92–2.12)	4[5,10,11,47]	0.36 (0.24–0.54)	1[11]	0.38 (0.09–1.60)	0.58 (0.32–1.05)
PNM ($n=2670$)	1[7]	1.49 (0.65–3.41)	2[33,44]	1.57 (0.87–2.81)	5[5,9,33,42,44]	2.88 (1.15–7.21)	NA	NA	2.22 (1.23–4.00)
Neonatal composite adverse outcome ($n=998$)	3[6–8]	1.28 (0.79–2.08)	NA	NA	2[5,9]	0.42 (0.06–3.12)	NA	NA	0.91 (0.44–1.88)
IVH ($n=3085$)	4[6–8,40]	1.33 (0.94–1.87)	1[44]	0.98 (0.65–1.47)	5[3,4,44,45,47]	1.09 (0.70–1.70)	NA	NA	1.14 (0.92–1.41)
PVL ($n=817$)	2[8,40]	7.42 (1.77–31.15)	NA	NA	1[47]	0.12 (0.01–2.24)	NA	NA	1.15 (0.02–66.12)
RDS ($n=1142$)	2[6,40]	1.84 (0.81–4.21)	1[44]	0.77 (0.49–1.21)	2[3,44]	0.80 (0.48–1.33)	NA	NA	1.08 (0.65–1.80)
Need for mechanical ventilation ($n=1373$)	1[7]	0.95 (0.53–1.71)	1[44]	0.83 (0.57–1.19)	1[44]	0.60 (0.38–0.93)	NA	NA	0.76 (0.59–0.99)
BPD ($n=1143$)	2[7,40]	0.63 (0.47–0.86)	NA	NA	1[47]	0.31 (0.08–1.20)	NA	NA	0.61 (0.45–0.83)
NEC ($n=2429$)	3[6,7,40]	1.73 (1.14–2.64)	1[44]	1.09 (0.60–1.99)	2[44,47]	0.80 (0.43–1.48)	NA	NA	1.28 (0.95–1.74)
ROP ($n=612$)	1[40]	1.65 (1.03–2.62)	NA	NA	NA	NA	NA	NA	NA
CP ($n=811$)	2[8,40]	0.88 (0.12–6.55)	NA	NA	NA	NA	NA	NA	NA
Sepsis ($n=2322$)	4[6,8,40,43]	1.31 (0.96–1.80)	1[44]	0.94 (0.66–1.34)	1[44]	0.57 (0.37–0.88)	NA	NA	0.98 (0.70–1.36)
Composite adverse outcome in later life ($n=839$)	2[8,40]	0.77 (0.19–3.11)	NA	NA	NA	NA	NA	NA	NA
NDI ($n=971$)	3[8,40,43]	1.46 (0.68–3.15)	NA	NA	NA	NA	NA	NA	NA

BPD, bronchopulmonary dysplasia; CP, cerebral palsy; IVH, severe intraventricular hemorrhage; NA, not available; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NND, neonatal death; PNM, perinatal mortality; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ref, reference; ROP, retinopathy of prematurity.

increased the odds of perinatal death (three studies[9,42,44], $n = 1581$; OR 3.06 (95% CI, 1.47–6.35); $I^2 = 0\%$, high quality of evidence) (Table 4, Figure 3). There was insufficient evidence for all other outcomes. There were insufficient data to analyze the outcomes in studies with unspecified fetal presentation and in those with cephalic presentation.

Delivery between 24 and 32 weeks

Among all studies reporting on delivery between 24 and 32 weeks, four studies[6,34,37,39] reported on neonatal death. Vaginal delivery was associated with increased odds of this outcome ($n = 878$; OR 2.47 (95% CI, 1.08–5.65); $I^2 = 61\%$, very low quality

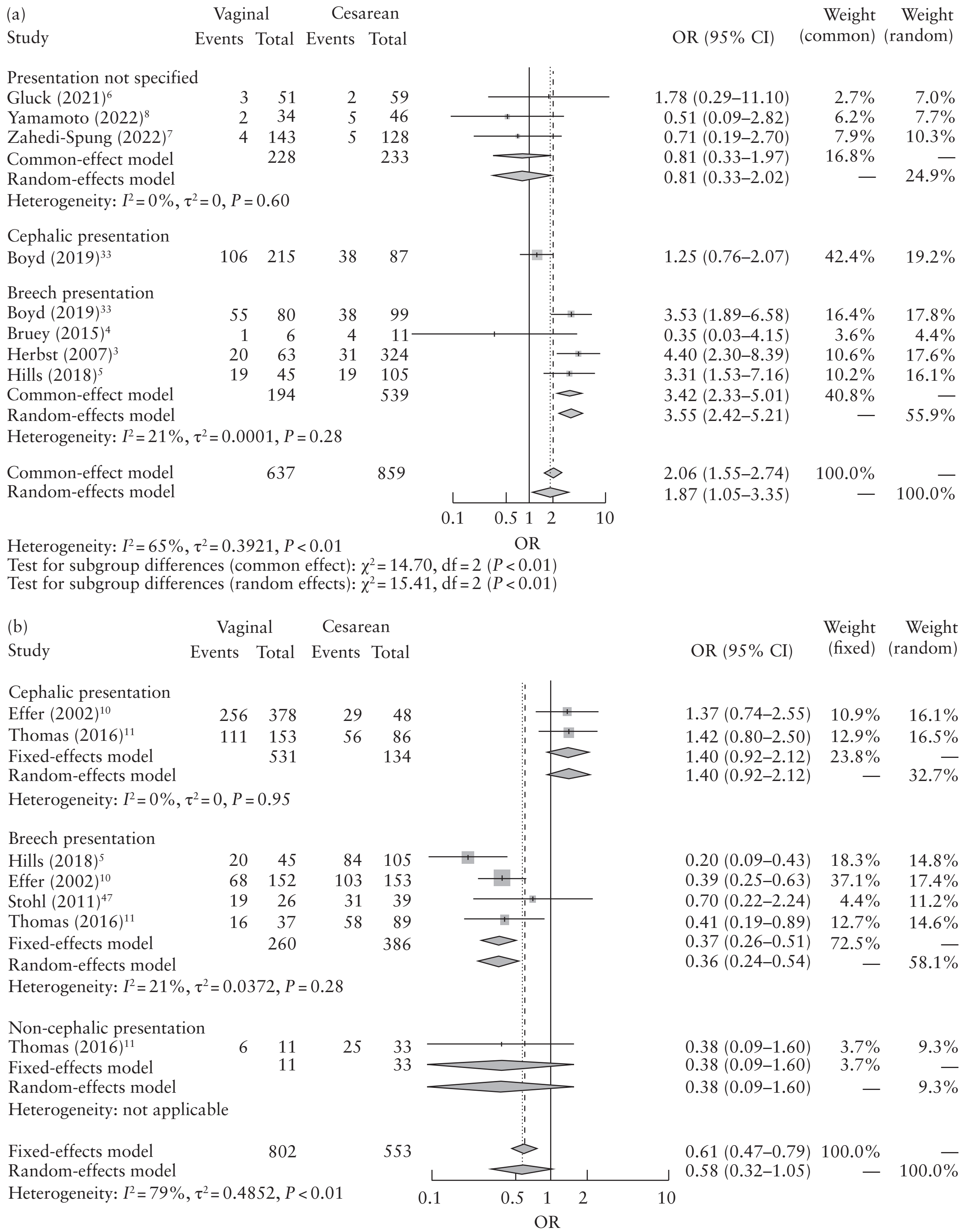

Figure 2 Forest plot showing odds ratios (OR) with 95% CIs for neonatal death (a) and survival to discharge (b) in fetuses born before 28 weeks following vaginal delivery (*vs* Cesarean delivery), according to presentation at birth. Only first author is given for each study.

of evidence) (Table 5, Figure 4a). There was no significant effect of mode of delivery on survival to discharge (six studies[32,35,38,41,46,48], $n = 9597$; OR 1.26 (95% CI, 0.40–4.01); $I^2 = 98\%$, very low quality of evidence) (Figure 4b). Vaginal delivery was associated with increased odds of severe IVH (nine studies[6,32,34,37–39,41,44,48], $n = 10\,899$; OR 1.29 (95% CI, 1.02–1.63); $I^2 = 45\%$, low quality of evidence) (Figure S23), while there was no significant effect on perinatal mortality, PVL, need for mechanical ventilation, BPD, NEC, retinopathy of prematurity, RDS, CP, sepsis, neonatal composite adverse outcome or neurodevelopmental impairment (Figures S21, S22 and S24–S33).

Among studies reporting on delivery between 24 and 32 weeks with unspecified presentation, there was no significant effect of mode of delivery on neonatal death (two studies[6,37], $n = 444$; OR 1.54 (95% CI, 0.57–4.19); $I^2 = 0\%$, low quality of evidence) (Table 5, Figure 4a) or survival to discharge (two studies[32,41], $n = 786$; OR 4.24 (95% CI, 0.14–131.73); $I^2 = 97\%$, very low quality of evidence) (Figure 4b). Vaginal delivery decreased the odds of RDS (three studies[6,32,41], $n = 1121$; OR 0.64

Table 4 Odds ratios (OR) for different adverse outcomes in fetuses born between 28 and 32 weeks following vaginal delivery (*vs* Cesarean delivery), overall and according to presentation at birth

	Not specified		*Cephalic*		*Breech*		*All*
Outcome	*Studies (n[ref])*	*OR (95% CI)*	*Studies (n[ref])*	*OR (95% CI)*	*Studies (n[ref])*	*OR (95% CI)*	*OR (95% CI)*
NND ($n = 225$)	1[6]	1.59 (0.1–25.8)	NA	NA	NA	NA	NA
PNM ($n = 3005$)	NA	NA	1[44]	0.69 (0.32–1.50)	3[9,42,44]	3.06 (1.47–6.35)	1.93 (0.72–5.17)
Neonatal composite adverse outcome ($n = 1321$)	1[6]	0.62 (0.33–1.15)	NA	NA	1[9]	1.79 (1.04–3.08)	1.06 (0.37–3.03)
IVH ($n = 2029$)	1[6]	1.28 (0.32–4.91)	1[44]	2.08 (1.31–3.31)	1[44]	0.56 (0.24–1.35)	1.20 (0.49–2.95)
RDS ($n = 2029$)	1[6]	0.68 (0.37–1.26)	1[44]	0.67 (0.52–0.87)	1[44]	1.23 (0.78–1.95)	0.82 (0.55–1.21)
Need for mechanical ventilation ($n = 1804$)	NA	NA	1[44]	0.68 (0.52–0.89)	1[44]	1.15 (0.74–1.77)	0.86 (0.51–1.43)
NEC ($n = 1804$)	NA	NA	1[44]	0.78 (0.41–1.49)	1[44]	1.32 (0.54–3.25)	0.94 (0.56–1.57)
Sepsis ($n = 2029$)	1[6]	0.44 (0.09–2.17)	1[44]	1.16 (0.87–1.55)	1[44]	0.70 (0.44–1.11)	0.88 (0.55–1.41)

No data were available for non-cephalic presentation and for survival to discharge, periventricular leukomalacia, bronchopulmonary dysplasia, retinopathy of prematurity, cerebral palsy, composite adverse outcome in later life and neurodevelopmental impairment. IVH, severe intraventricular hemorrhage; NA, not available; NEC, necrotizing enterocolitis; NND, neonatal death; PNM, perinatal mortality; RDS, respiratory distress syndrome; ref, reference.

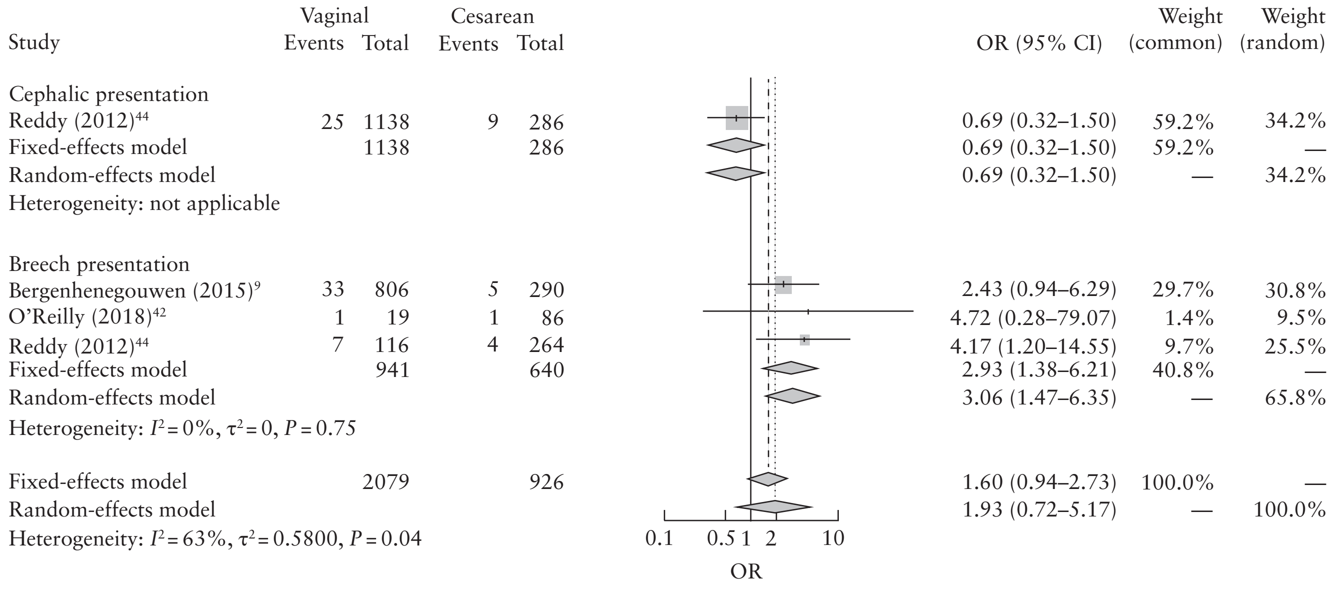

Figure 3 Forest plot showing odds ratios (OR) with 95% CIs for perinatal death in fetuses born between 28 and 32 weeks following vaginal delivery (*vs* Cesarean delivery), according to presentation at birth. Only first author is given for each study.

(95% CI, 0.43–0.95); $I^2 = 51\%$, low quality of evidence) (Figure S25), while there was no significant effect on the odds of IVH, PVL, need for mechanical ventilation, BPD, NEC or sepsis (Figures S21–S24, S26–S28, S31). There was insufficient evidence for the remaining outcomes.

Among studies reporting on delivery between 24 and 32 weeks with cephalic presentation, there were no data available to evaluate the outcome of neonatal death. There was no significant effect of mode of delivery on survival to discharge (three studies[35,38,48], $n = 7781$; OR 1.70 (95% CI, 0.69–4.22); $I^2 = 97\%$, very low quality of evidence) (Table 5, Figure 4b). Vaginal delivery was associated with increased odds of severe IVH (three studies[38,44,48], $n = 8009$; OR 1.44 (95% CI, 1.08–1.91); $I^2 = 58\%$, very low quality of evidence) (Figure S23), decreased odds of RDS (two studies[44,48], $n = 3623$; OR 0.67 (95% CI, 0.57–0.80); $I^2 = 0\%$, moderate quality of evidence) (Figure S25) and decreased need for mechanical ventilation (two studies[44,48], $n = 3623$; OR 0.59 (95% CI, 0.41–0.86); $I^2 = 79\%$, low quality of evidence) (Figure S26). There was no significant effect of mode of delivery on BPD, NEC, retinopathy of prematurity, sepsis, neonatal composite adverse outcome or neurodevelopmental impairment (Figures S21, S23–S25, S27–S33). There was insufficient evidence for the rest of the outcomes.

Among studies reporting on delivery between 24 and 32 weeks with non-cephalic presentation (including breech), there was no significant effect of mode of delivery on the outcome of neonatal death (two studies[34,39], $n = 434$; OR 3.27 (95% CI, 0.86–12.43); $I^2 = 83\%$, very low quality of evidence) (Table 5, Figure 4a), whereas vaginal delivery was associated with decreased survival to discharge (two studies[46,48], $n = 1030$; OR 0.28 (95% CI, 0.19–0.40); $I^2 = 0\%$, moderate quality of evidence) (Figure 4b). Vaginal delivery was associated with increased perinatal mortality (three studies[9,42,44], $n = 2428$; OR 2.00 (95% CI, 1.14–3.53); $I^2 = 52\%$, very low quality of evidence) (Figure S21) and neonatal composite adverse outcome (three studies[9,46,48],

Table 5 Odds ratios (OR) for different adverse outcomes in fetuses born between 24 and 32 weeks following vaginal delivery (*vs* Cesarean delivery), overall and according to presentation at birth

	Not specified		*Cephalic*		*Breech*		*Non-cephalic*		*All*
Outcome	*Studies (n^{ref})*	*OR (95% CI)*	*Studies (n^{ref})*	*OR (95% CI)*	*Studies (n^{ref})*	*OR (95% CI)*	*Studies (n^{ref})*	*OR (95% CI)*	*OR (95% CI)*
NND ($n = 878$)	2[6,37]	1.54 (0.57–4.19)	NA	NA	2[34,39]	3.27 (0.86–12.43)	NA	NA	2.47 (1.08–5.65)
Survival to discharge ($n = 9597$)	2[32,41]	4.24 (0.14–131.73)	3[35,38,48]	1.70 (0.69–4.22)	NA	NA	2[46,48]	0.28 (0.19–0.40)	1.26 (0.40–4.01)
PNM ($n = 4566$)	NA	NA	1[44]	0.93 (0.62–1.41)	3[9,42,44]	2.00 (1.14–3.53)	NA	NA	1.60 (0.91–2.81)
Neonatal composite adverse outcome ($n = 6301$)	1[6]	0.84 (0.52–1.35)	2[48,49]	0.97 (0.68–1.38)	NA	NA*	3[9,46,48]	2.44 (1.52–3.91)	1.47 (0.90–2.41)
IVH ($n = 10\,899$)	4[6,32,37,41]	1.39 (0.89–2.16)	3[38,44,48]	1.44 (1.08–1.91)	NA	NA*	4[34,39,44,48]	0.92 (0.63–1.34)	1.29 (1.02–1.63)
PVL ($n = 2493$)	2[37,41]	0.37 (0.03–5.27)	1[48]	0.54 (0.24–1.19)	NA	NA*	2[39,48]	1.70 (0.60–4.85)	0.77 (0.33–1.79)
RDS ($n = 6101$)	3[6,32,41]	0.64 (0.43–0.95)	2[44,48]	0.67 (0.57–0.80)	NA	NA*	3[34,44,48]	1.73 (0.64–4.66)	0.92 (0.57–1.50)
Need for mechanical ventilation ($n = 5634$)	2[32,41]	0.98 (0.21–4.59)	2[44,48]	0.59 (0.41–0.86)	NA	NA*	2[44,48]	0.94 (0.65–1.37)	0.75 (0.55–1.04)
BPD ($n = 4763$)	2[35,41]	1.31 (0.78–2.19)	1[48]	0.77 (0.57–1.17)	NA	NA*	2[39,48]	1.06 (0.70–1.60)	1.09 (0.80–1.48)
NEC ($n = 6643$)	2[6,41]	(1.10 (0.66–1.83)	3[36,44,48]	0.98 (0.72–1.34)	NA	NA*	4[34,39,44,48]	1.13 (0.58–2.17)	1.06 (0.85–1.32)
ROP ($n = 3088$)	1[41]	0.09 (0.01–0.70)	2[36,48]	0.89 (0.64–1.23)	NA	NA	1[48]	1.16 (0.60–2.25)	0.87 (0.46–1.65)
CP ($n = 1943$)	NA	NA	1[48]	0.73 (0.38–1.42)	NA	NA	1[48]	1.75 (0.58–5.31)	1.01 (0.44–2.28)
Sepsis ($n = 10\,659$)	3[6,32,41]	1.01 (0.48–2.14)	3[38,44,48]	1.08 (0.76–1.53)	NA	NA*	3[39,44,48]	1.39 (0.59–3.27)	1.12 (0.80–1.55)
Composite adverse outcome in later life ($n = 1965$)	NA	NA	1[49]	1.10 (0.79–1.53)	NA	NA	NA	NA	NA
NDI ($n = 3908$)	NA	NA	2[48,49]	0.74 (0.30–1.82)	NA	NA	1[48]	5.11 (1.23–21.22)	1.13 (0.43–3.00)

*Not available (NA), as breech cases were combined with non-cephalic ones to enhance results. BPD, bronchopulmonary dysplasia; CP, cerebral palsy; IVH, severe intraventricular hemorrhage; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NND, neonatal death; PNM, perinatal mortality; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ref, reference; ROP, retinopathy of prematurity.

$n = 2516$; OR 2.44 (95% CI, 1.52–3.91); $I^2 = 68\%$, low quality of evidence) (Figure S22), while there was no significant effect on the odds of IVH, RDS, PVL, need for mechanical ventilation, BPD, NEC and sepsis (Figures S23–S33).

Sensitivity analysis

A *post-hoc* sensitivity analysis was performed on studies reporting explicitly that cases with iatrogenic indication, such as placental abruption, HELLP, intrauterine growth restriction and cord prolapse, were excluded. Three studies[7,9,44] reported on perinatal mortality, and three[35,46,48] reported on survival to discharge, for delivery before 32 weeks. Neither analysis demonstrated any effect of mode of delivery (Figures S34 and S35), similar to the findings of the main analysis for this gestational-age group. Further analysis considering earlier gestational age or presentation was not feasible owing to the small number of studies.

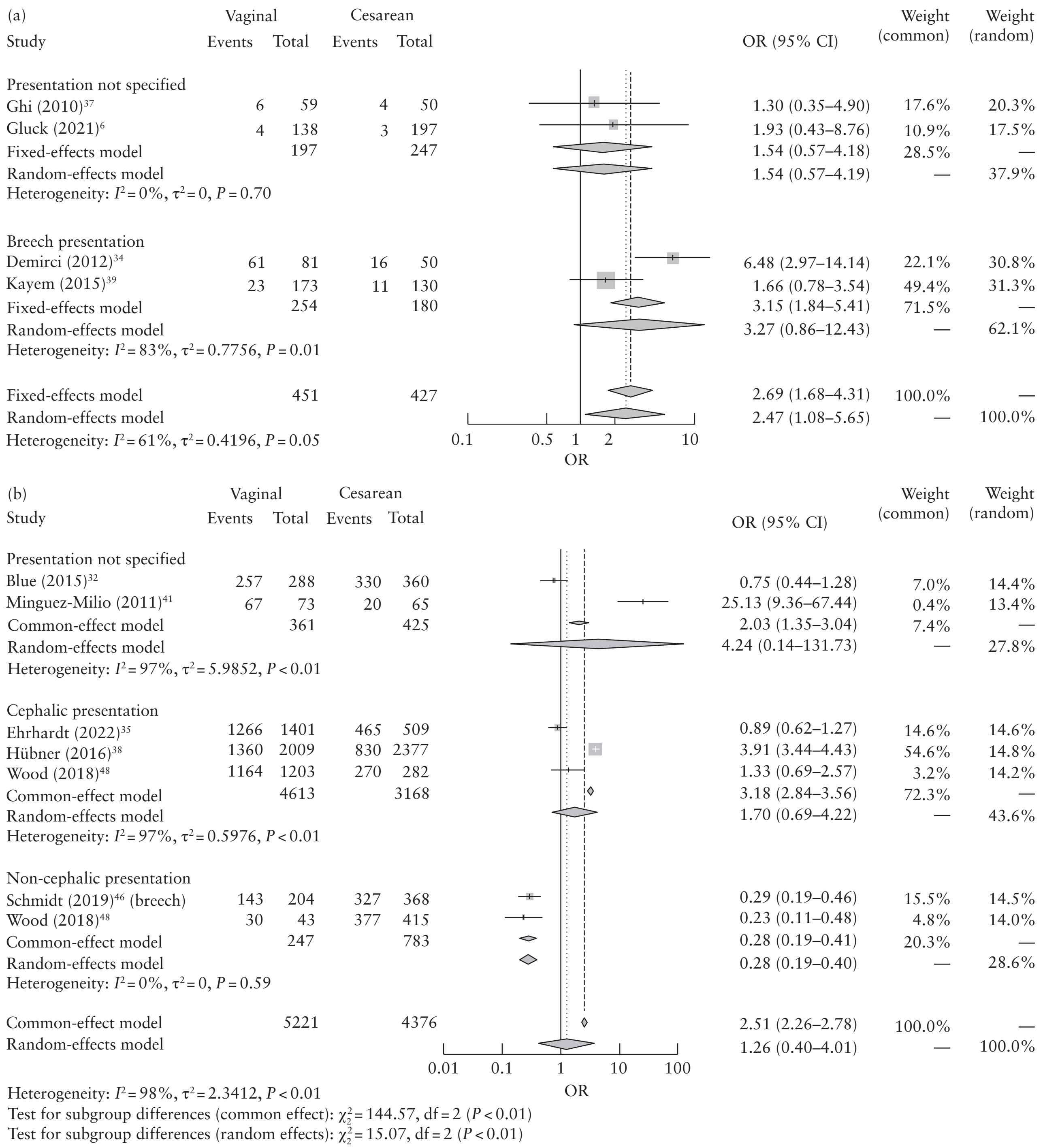

Figure 4 Forest plot showing odds ratios (OR) with 95% CIs for neonatal death (a) and survival to discharge (b) in fetuses born between 24 and 32 weeks following vaginal delivery (*vs* Cesarean delivery), according to presentation at birth. Only first author is given for each study.

Overall quality of evidence

The quality of evidence was assessed per GRADE (Table S2). None of the included studies was considered to be at low risk of bias. The quality of evidence for each outcome was downgraded by one level if at least one study was at moderate risk of bias or two levels if at least one study was at serious risk of bias. The quality of evidence for some outcomes was downgraded by one level for inconsistency if the heterogeneity between the studies was high. Imprecision was found in the outcomes of neonatal death and survival to discharge in fetuses delivered before 28 weeks; subsequently, these outcomes were downgraded by one level for imprecision. None of the included studies showed evidence of publication bias. A strong association was found, owing to a large effect, in the outcomes of neonatal death in breech fetuses delivered before 28 weeks and perinatal death in breech fetuses delivered between 28 and 32 weeks.

DISCUSSION

Summary of evidence

Our meta-analysis shows that, in fetuses born before 28 weeks, vaginal delivery increases the risk of neonatal death. This result is mainly driven by the subgroup of breech fetuses, while we did not observe a significant effect for fetuses with cephalic presentation. Furthermore, vaginal delivery may increase the risk of NEC but may reduce the risk of BPD and the need for mechanical ventilation in the overall extremely preterm population. For moderately severe preterm births (28–32 weeks), vaginal delivery similarly increases the risk of perinatal mortality in breech fetuses. There was no available evidence to allow for subgroup analysis according to history of PPROM and for iatrogenic *vs* spontaneous onset of birth. There was limited evidence on the effect of mode of delivery on long-term neurodevelopmental outcome and for the subgroup with delivery between 28 and 32 weeks.

Limitations of evidence

The published evidence presents multiple limitations, which are also reflected by the GRADE assessment. The major limitation refers to the non-randomized design of the studies, which increases the risk for several forms of bias, notably selection bias. It is hard to predict how selection bias may affect the direction of effect, as more severe cases may be channeled to undergo either Cesarean (emergency) or vaginal delivery (many clinicians may opt to spare mothers a Cesarean section in the case of a critically ill fetus). Moreover, the scarcity of data prevented us from performing our planned analyses for potential confounders, including obstetric history and cause of prematurity (iatrogenic or spontaneous) for all the subgroups and presentations. Additionally, while six studies[4,8,39,40,44,45] reported their outcomes per intention to treat (ITT), and two studies[9,32] reported both ITT and as treated results, the data were too sparse and scattered across the outcomes to allow for a meaningful sensitivity analysis. For similar reasons, we had to deviate from the PROSPERO registered protocol for the outcome of perinatal mortality, which we reported *a posteriori*, and that of intact survival to discharge, as there were limited data to assess it.

Implications

Early preterm Cesarean section entails considerable technical difficulties, including challenging extraction of the fetus and need for non-isthmic incision[50], and it significantly increases the risk of maternal complications, especially hemorrhage and infection[12]. Therefore, vaginal delivery would be the logical option for spontaneous delivery before 28 weeks, unless there is evidence for fetal harm. Our meta-analysis shows that, particularly for breech presentation, vaginal delivery increases the risk of neonatal death and reduces the chance of survival to discharge from the hospital. Head entrapment can be a concern in such cases; the ratio of head circumference to abdominal circumference is increased in less advanced pregnancy[51], and it may be even more increased in fetuses with underlying pathology[52], which is prevalent in preterm births[53]. However, it is unlikely that head entrapment alone can explain the increased risk associated with vaginal delivery in breech fetuses[39].

There was insufficient evidence to assess the effect of the mode of delivery on neonatal mortality in non-breech fetuses. However, vaginal delivery may be associated with an increased risk of severe IVH in these fetuses. The reason for this is also not clear, but it could be associated with the fragility of brain perfusion[54] and partial ossification of the skull bones[55] in preterm fetuses, together with the rapid decompression of the head during vaginal delivery. Similarly, inadequate intrapartum fetal monitoring and reluctance to perform operative vaginal delivery in cases of second-stage fetal heart rate abnormalities may have a contributing role in hypoxic brain injury[54,56,57]. On the other hand, there is some evidence that the process of vaginal delivery facilitates neonatal respiratory transition[58,59], which is compatible with the observation of this meta-analysis that vaginal delivery may be associated with a reduced risk of RDS and need for mechanical ventilation.

In terms of clinical decision, the most informative outcomes are neonatal mortality or its inverse (i.e. survival) and long-term morbidity. Current data provide weak evidence that neonatal mortality/survival may be improved by Cesarean section in breech fetuses. However, we could not demonstrate an effect for cephalic fetuses and there was little evidence on long-term outcomes, with a single study indicating an adverse effect of vaginal delivery on neurodevelopmental outcome in preterm non-cephalic fetuses[48].

Comparison with previous studies

There are two previous meta-analyses and one Cochrane review on the topic. Jarde *et al.*[60] included only cephalic fetuses born before 28 weeks. However, inclusion of cases with congenital anomaly and the use of birth certificate data, which may be subject to low reliability and validity, potential systematic errors and uncontrollable missing information[61], constituted major limitations of the study. Grabovac *et al.*[62] included only breech fetuses born before 28 weeks and reported similar results on neonatal death to the ones reported in our study. However, their meta-analysis included only studies whose authors responded to communication by the authors of the meta-analysis and confirmed active resuscitation, which could have introduced selection bias. Finally, a Cochrane review by Alfirevic *et al.*[63] included only RCTs; however, all five RCTs were stopped before completion, were very old, having been conducted before administration of antenatal steroids became standard practice, had unclear or high risk of bias, included cases with congenital anomaly and included small populations, which prevented definitive conclusions from being drawn.

Strengths and limitations

Our review was limited to 27 studies whose data were available at the time of the search. Our attempts to contact the authors of another 10 studies, reporting potentially eligible data, were unsuccessful. Nevertheless, to our knowledge, this is the first meta-analysis to include fetuses born between 28 and 32 weeks, which represent 10% of all preterm births[2]. Furthermore, our analysis is the most comprehensive to date, examining overall births before 32 weeks and analyzing them according to the major cut-off of 28 weeks and according to fetal presentation at delivery. Given the retrospective design of the studies, we took all efforts to apply uniform inclusion criteria and address potential confounders. In this context, we critically assessed the results on the main outcomes using GRADE in order to provide realistic estimates of their certainty.

Conclusions

Cesarean delivery in breech fetuses before 32 weeks appears to reduce neonatal and perinatal mortality (very low to moderate quality of evidence), while in cephalic fetuses we could not demonstrate any effect on perinatal mortality.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Tables S1 and S2, and Figures S1–S35.