Placental implantation abnormalities and risk of preterm delivery: a systematic review and metaanalysis

Sevan A. Vahanian, MD; Jessica A. Lavery, MS; Cande V. Ananth, PhD, MPH; Anthony Vintzileos, MD

We sought to evaluate the extent of the association between placental implantation abnormalities (PIA) and preterm delivery in singleton gestations. We conducted a systematic review of English-language articles published from 1980 onward using PubMed, MEDLINE, EMBASE, CINAHL, LILACS, and Google Scholar, and by identifying studies cited in the references of published articles. Search terms were PIA defined as ≥1 of the following: placenta previa, placenta accreta, vasa previa, and velamentous cord insertion. Observational and experimental studies were included for review if data were available regarding any of the aforementioned PIA and regarding gestational age at delivery or preterm delivery. Case reports and case series were excluded. Studies were reviewed and data extracted. The primary outcome was gestational age at delivery or preterm delivery <37 weeks' gestation. Secondary outcomes included birthweight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, neonatal and perinatal death, and small for gestational age. Of the 1421 studies identified, 79 met the defined criteria; 56 studies were descriptive and 23 were comparative. Based on the descriptive studies, the preterm delivery rates for low-lying/marginal placenta, placenta previa, placenta accreta, vasa previa, and velamentous cord insertion were 26.9%, 43.5%, 57.7%, 81.9%, and 37.5%, respectively. Based on the comparative studies using controls, there was decreased pregnancy duration for every PIA; more specifically, there was an increased risk for preterm delivery in patients with placenta previa (risk ratio [RR], 5.32; 95% confidence interval [CI], 4.39–6.45), vasa previa (RR, 3.36; 95% CI, 2.76–4.09), and velamentous cord insertion (RR, 1.95; 95% CI, 1.67–2.28). Risks of NICU admissions (RR, 4.09; 95% CI, 2.80–5.97), neonatal death (RR, 5.44; 95% CI, 3.03–9.78), and perinatal death (RR, 3.01; 95% CI, 1.41–6.43) were higher with placenta previa. Perinatal risks were also higher in patients with vasa previa (perinatal death rate RR, 4.52; 95% CI, 2.77–7.39) and velamentous cord insertion (NICU admissions [RR, 1.76; 95% CI, 1.68–1.84], small for gestational age [RR, 1.69; 95% CI, 1.56–1.82], and perinatal death [RR, 2.15; 95% CI, 1.84–2.52]). In singleton gestations, there is a strong association between PIA and preterm delivery resulting in significant perinatal morbidity and mortality.

Key words: cesarean delivery, metaanalysis, neonatal death, neonatal morbidity, placenta accreta, placenta previa, prematurity, preterm birth, preterm delivery, vasa previa, velamentous cord insertion

One of the consequences of increasing cesarean delivery rates over the last 2 decades is an increase in placental implantation abnormalities (PIAs) including placenta previa, placenta accreta, vasa previa, and velamentous cord insertion.[1-9] Since PIAs can have catastrophic complications for both the mother and fetus, efforts have been focused on reducing maternal and fetal risk by not allowing the pregnancy to advance to term, thus resulting in preterm delivery. As a matter of fact, following ischemic placental disease, PIAs are the second most common cause for indicated preterm delivery, accounting for 5.6-8.7% of indicated preterm deliveries at <35 weeks' gestation.[10]

Given the increasing cesarean delivery rate, we undertook a systematic review and metaanalysis of PIAs in relation to preterm delivery and other adverse perinatal outcomes. The goal was to alert the clinician regarding the significance and extent of the association between PIAs and preterm delivery with its consequences.

Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines for undertaking the systematic review and metaanalysis.[11]

Literature review

This was a metaanalysis of studies published on singleton gestations with PIA including placenta previa, placenta accreta, vasa previa, and velamentous cord insertion. Studies chosen for review were selected on the basis of a comprehensive literature search with the use of PubMed, MEDLINE, EMBASE, LILACS, CINAHL, and Google Scholar, and by identifying studies cited in the references of published articles. Key words that were used in the search included the following exposures: "placenta pr(a)evia," "placenta accreta," "placenta increta," "placenta percreta," "morbidity adherent placenta," "c(a)esarean scar pregnancy," "low-lying placenta," "marginal placenta," "vasa pr(a)evia," "velamentous cord insertion," "accessory

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lobe," "succenturiate lobe," "bilobed placenta," and the following outcomes: "gestational age at birth," "preterm birth," "preterm delivery," "prematurity," and "premature birth." English-language restrictions were imposed on the search to minimize heterogeneity due to differences in practice patterns, resource utilization, and scrutiny of peer review process among non-English-language studies. Articles were included from January 1980 through April 2015.

Eligibility criteria

Observational and experimental studies were included for review if data were available regarding any of the aforementioned PIA and regarding gestational age at delivery or preterm delivery. Case reports and case series were excluded from review. Abstracts and poster presentations were included for review if they fulfilled the above criteria. Multiple articles resulting from the same data source were included only once. However, if 2 studies came from the same data source but spanned nonoverlapping time periods of data accrual, or studied different PIA, they were both included in the metaanalysis. Searches were updated on a regular basis from November 2014 through April 2015.

In addition to placenta previa, our analysis also included instances of low-lying/marginal placenta previa by defining them as cases with internal os to placental edge distance <1 cm. The placenta accreta group included placenta increta, placenta percreta, and cesarean scar implantations as the latter have been known to be a precursor to placenta accreta.[9] In addition to searching for vasa previa, we searched for other placental abnormalities (succenturiate lobe, bilobed placenta) to capture as many cases of vasa previa as possible. We also included velamentous cord insertions because of their association with vasa previa and suspected contribution to our primary and secondary outcomes.

Study selection

Two authors (S.A.V. and J.A.L.) were involved in retrieving studies for eligibility. We identified a total of 1421 English-language studies fulfilling our search terms that were published since 1980. Titles and abstracts were screened to determine potential inclusion of the articles. Many of these studies were excluded on the basis of lacking clinical outcome data (ie, ultrasound studies, basic science research, or animal models) or clearly stating that they were case reports or case series. This left us with 90 remaining studies that fit our inclusion criteria. These were individually reviewed and from these, information regarding PIA and their association with preterm delivery was available in only 79 studies.[2,8,12-89] These studies were critically reviewed and data were extracted by 1 author. In case of discrepancies or when the data presented in a study were unclear, a second reviewer (C.V.A. or A.V.) was consulted.

Data collection process

Information regarding the type of PIA, type of study (descriptive vs comparative, ie, cohort or case-control), country of origin, total number of pregnancies and pregnancies complicated by PIA, and years' duration of the study were ascertained.

Primary and secondary outcomes

The primary outcome in this metaanalysis was preterm delivery <37 weeks' gestation, which we chose because of its consistency throughout the reviewed studies. Secondary outcomes, if available, included birthweight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, neonatal death, perinatal death, and small for gestational age. Studies that did not provide data for a comparison group (ie, outcomes of patients without the PIA) were included as descriptive studies.

Summary measures

Statistical analysis for the metaanalysis was implemented at the biostatistics coordinating center in the Department of Obstetrics and Gynecology at Columbia University, New York, NY, through software (Review Manager, version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). In an initial analysis, we observed substantial heterogeneity in the risk of the primary outcome (preterm delivery) and most of the secondary outcomes. Heterogeneity was assessed based on both the Cochran Q statistic[90] and the Higgins I^2 statistic.[91] To account for the between-study heterogeneity, we performed the metaanalysis through random effects models,[92] with the study constituting the unit of analyses. The summary measure of effect was the random effects pooled risk ratio (RR) with 95% confidence interval (CI) for binary outcomes and the random effects pooled risk difference with 95% CI for continuous outcomes. Finally, we plotted the effect measure against the logarithm of the SE of the effect measure (RR or risk difference) to assess the potential for publication bias.

Results

Study selection and characteristics

In all, 79 studies were reviewed that met the above-mentioned inclusion criteria and for which information on the incidence of PIA and its association with gestational age at birth or preterm delivery were available (Figure 1). In all, 56 studies[8,12-66] were descriptive and did not have a comparison group. These studies instead compared different variables within the same PIA, for example: previa with hemorrhage compared to previa without hemorrhage. A total of 23 studies[2,67-89] had comparison or control groups. The characteristics of the comparative studies are outlined in Table 1.

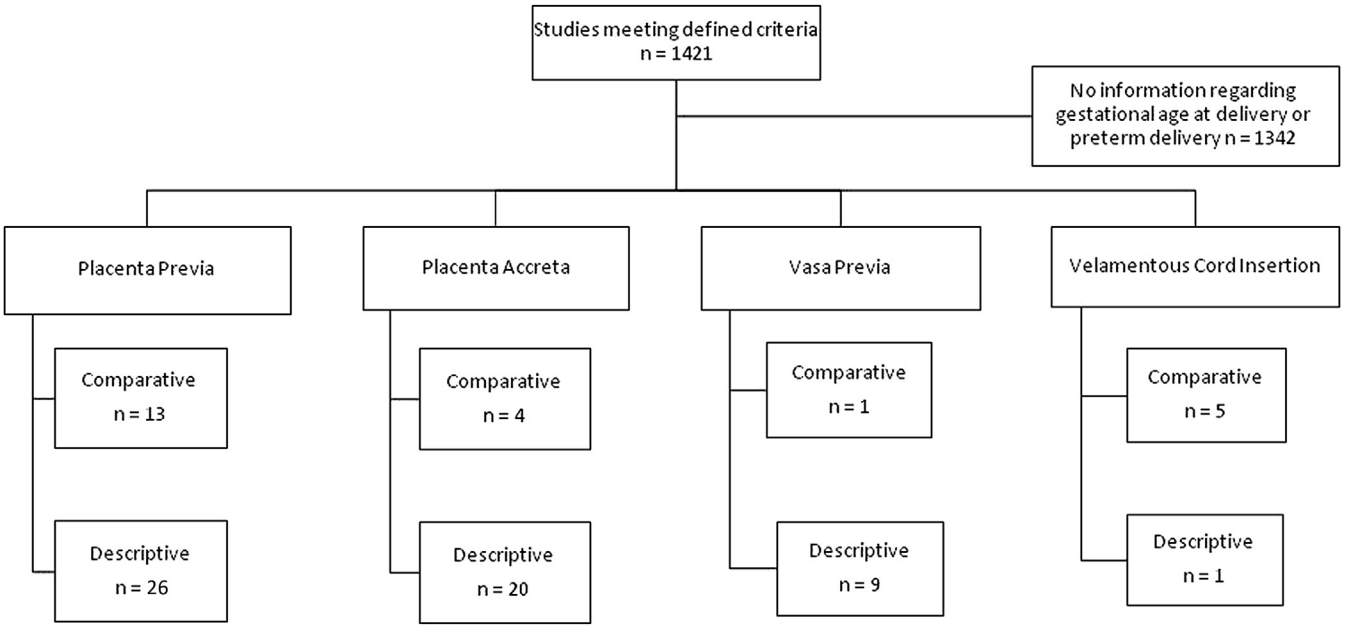
Risk of bias within studies

We evaluated each included study for bias based on several characteristics. These included representativeness of the population, ascertainment of the exposure (PIA), assessment of the outcomes, blinding of the investigators to the exposure (PIA), incomplete outcome data (loss to follow-up), and control for confounders. Each of these categories were assessed on 3 levels: green (indicating that the criteria was met), red (indicating that the criteria was not met), and orange (indicating an uncertain status).

Results of individual studies

Incidence of PIA among the studies ranged from 0.14–29.8 per 1000 live births for placenta previa, 3.0–9.0 per 1000 live births for placenta accreta,

FIGURE 1
Flow diagram of study inclusion and exclusion criteria



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0.2—1.9 per 1000 live births for vasa previa, and 4.8—24.0 per 1000 live births for velamentous cord insertion. The wide range of incidences may be related to natural variations in the different populations or differences in the accuracy or timing of diagnosis (ie, prenatal vs postnatal) of the PIA.

The findings of the descriptive studies are summarized in Table 2. The preterm delivery rates for low-lying/marginal placenta, placenta previa, placenta accreta, vasa previa, and velamentous cord insertion were 26.9%, 43.5%, 57.7%, 81.9%, and 37.5%, respectively. The mean (or median) gestational age was <37 weeks in all PIAs except in cases of low-lying/marginal placenta previa.

Synthesis of results

In the comparative studies, placenta previa was significantly associated with preterm delivery (RR, 5.32; 95% CI, 4.39—6.45) and low 1- and 5-minute Apgar scores, NICU admissions, and neonatal and perinatal death (Figure 2, A, and Table 3). There were only 3 placenta accreta comparative studies where placenta accreta was clinically or histologically diagnosed[2,24,25]; in all 3 studies the only available information with respect to outcomes of interest were the average gestational ages and birthweights. Placenta accreta cases had a significantly shorter duration of pregnancy by 1.50 weeks and decreased birthweight by approximately 240 g (Figure 2, B). The mean gestational ages at delivery for placenta accreta were higher, as compared to those of the descriptive studies; this could be the result of higher percentage of prenatally undiagnosed cases in the comparative studies. One comparative study did not report average gestational ages but rather a significant preterm delivery adjusted odds ratio of 16.9 (95% CI, 7.5—38.1).[81]

Only 1 comparative study pertaining to vasa previa was identified[82]; In this study, preterm delivery occurred in 29.5% of vasa previa cases compared to 8.8% in patients without vasa previa (RR, 3.36; 95% CI, 2.76—4.09). Velamentous cord insertion was significantly associated with preterm delivery (RR, 1.95; 95% CI, 1.67—2.28) and also low 1- and 5-minute Apgar scores, NICU admissions, perinatal death, and small-for-gestational-age neonates (Figure 2, C, and Table 3).

Risk of bias across studies

We tabulated every study based on bias characteristics (Figure 3). Of the 23 studies included in the metaanalysis, 39% (9 of 23) were population-based (representative of the population), only 26% (6 of 23) reported the criteria for the diagnosis of PIAs, and 39% (9 of 23) reported information as to how the outcomes were determined. In addition, 57% (13 of 23) studies evaluated the associations after adjusting for confounding factors. We generated funnel plots for each of the PIA category and the outcomes evaluated in this metaanalysis. We did not identify any potential for publication bias (data not shown, but funnel plots available upon request).

Additional analysis

Our initial goal was to identify sources of heterogeneity in the pooled effect measures across studies. We had hoped to accomplish this by performing a series of sensitivity analyses, including by year when studies were published (before or after 1990), country (North America vs other countries), and study design (retrospective, including case-control designs vs prospective cohort studies).

TABLE 1
Characteristics of comparative studies

Type of PIA	Study	Country	Duration	Design	Total no. of subjects	Cases of interest	Outcomes
Placenta previa	Ananth et al[89] 2001	United States	1989 through 1993	Retrospective cohort	544,734	2744	Preterm delivery, birthweight
	Ananth et al[67] 2003	United States	1989 through 1997	Retrospective cohort	22,368,235	61,711	Preterm delivery, birthweight, LBW, Apgar, neonatal mortality
	Crane et al[68] 1999	Canada	1988 through 1995	Retrospective cohort	92,983	305	Preterm delivery, birthweight, Apgar, NICU admission, RDS, IVH, NEC, perinatal mortality
	Erez et al[69] 2012	Israel	1988 through 2010	Retrospective cohort	9983	297	Preterm delivery
	Lal and Hibbard[76] 2015	United States	2002 through 2008	Retrospective cohort	19,069	452	Preterm delivery, birthweight, Apgar, umbilical artery pH, NICU admission, RDS, IVH, NEC, neonatal mortality
	Nørgaard et al[70] 2012	Denmark	2001 through 2006	Retrospective cohort	318,704	1721	Preterm delivery, birthweight, LBW, Apgar, NICU admission, perinatal mortality
	Olive et al[72] 2005	Australia	1998 through 2002	Retrospective cohort	375,790	1612	Preterm delivery, birthweight, NICU, neonatal mortality
	Rosenberg et al[77] 2011	Israel	1988 through 2009	Retrospective cohort	185,476	771	Preterm delivery, LBW, Apgar, neonatal mortality, perinatal mortality
	Tsuda et al[78] 2014	Japan	2009 through 2012	Retrospective cohort	186	35	Preterm delivery, birthweight, Apgar, umbilical artery pH, RDS
	Yeniel et al[74] 2012	Turkey	2004 through 2010	Retrospective cohort	12,034	123	Preterm delivery, birthweight, IUFD
	Zlatnik et al[75] 2007	United States	1976 through 2011	Retrospective cohort	38,540	230	Preterm delivery, birthweight, Apgar, umbilical artery pH, NICU admission, RDS
	Ofori et al[71] 2008	Canada	1997 through 2003	Retrospective case-control	70,207	616	Preterm delivery
	Tuzovic et al[73] 2003	Croatia	1992 through 2001	Retrospective case-control	53,042	202	Preterm delivery
Placenta accreta	Eshkoli et al[2] 2013	Israel	1988 through 2011	Retrospective cohort	34,869	139	Preterm delivery, LBW, Apgar, perinatal mortality
	Hung et al[80] 1999	Taiwan	1994 through 1997	Retrospective cohort	9349	28	Preterm delivery, birthweight
	Fitzpatrick et al[81] 2012	United Kingdom	2010 through 2011	Retrospective case-control	798,634	134	Preterm delivery
	Gielchinsky et al[79] 2004	Israel	1990 through 2000	Retrospective case-control	34,450	310	Preterm delivery, birthweight, perinatal mortality

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TABLE 1
Characteristics of comparative studies *(continued)*

Type of PIA	Study	Country	Duration	Design	Total no. of subjects	Cases of interest	Outcomes
Vasa previa	Weintraub et al[82] 2012	Israel	Not stated	Retrospective case-control	246,525	237	Preterm delivery, birthweight, Apgar, perinatal mortality
Velamentous cord insertion	Eddleman et al[84] 1992	United States	1985 through 1989	Retrospective cohort	16,210	77	Preterm delivery, birthweight, LBW, Apgar
	Esakoff et al[85] 2015	United States	2006	Retrospective cohort	482,812	2327	Preterm delivery, birthweight, IUFD
	Heinonen et al[86] 1996	Finland	1989 through 1993	Retrospective cohort	12,750	216	Preterm delivery, LBW, Apgar, umbilical artery pH, NICU admission, perinatal mortality
	Ebbing et al[83] 2013	Norway	1999 through 2009	Population-based registry	623,478	9500	Preterm delivery, birthweight, Apgar, NICU admission, perinatal mortality
	Räisänen et al[87] 2012	Finland	2000 through 2011	Retrospective hospital-based registry	26,849	633	Preterm delivery, birthweight, LBW, Apgar, umbilical artery pH, NICU admission, IUFD

IUFD, intrauterine fetal demise; *IVH*, intraventricular hemorrhage; *LBW*, low birthweight; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *PIA*, placental implantation abnormalities; *RDS*, respiratory distress syndrome.

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There were not enough studies within the subsets of each of the factors to permit meaningful secondary analyses. However, in evaluating the studies included in our metaanalysis, it appeared that the assigned study weights for individual studies were roughly evenly distributed. This suggests that even the planned subgroup analyses may not have provided meaningful insights to uncover the sources of heterogeneity.

Comment

Preterm delivery remains a major contributor to short- and long-term morbidity and mortality both to the mother and her newborn.[93] In the United States, approximately 60% of preterm deliveries are spontaneous and 40% are indicated.[94,95] We have previously identified that 5.6% of indicated preterm births at <35 weeks' gestation were related to placenta previa and an additional 3.1% were related to "unexplained bleeding."[10] Since placental abruption was a separate category in that data set, it is very likely that unexplained bleeding may have included many PIA cases. Therefore, the contribution of PIAs to the indicated preterm deliveries at <35 weeks' gestation could be as high as 8.7%.[10]

The main finding of our study is that there is a significant association between PIAs and preterm delivery as well as NICU admissions and mortality. Patients with placenta previa have a 5-fold increase in prematurity, NICU admission, and perinatal/neonatal death compared to patients without placenta previa. In our descriptive analysis, we found that the degree of preterm delivery is greater for placenta accreta and vasa previa as compared to placenta previa. This can be attributed to increased vigilance in patients with suspected placenta accreta and vasa previa and efforts to deliver prior to the development of catastrophic complications or labor. We found high preterm delivery rates of 26.9%, 43.5%, 57.7%, 81.9%, and 37.5% for low-lying/marginal placenta, placenta previa, placenta accreta, vasa previa, and velamentous cord insertion, respectively. These rates were based on descriptive studies published as early as

1980 most likely including many patients without prenatal diagnosis and thus allowed to go to term. However, in modern practice the prenatal diagnosis of PIAs is possible in most cases due to widespread use of ultrasound. It is therefore reasonable to assume that the preterm delivery rates in today's practice may even be higher than the aforementioned rates since delivery before term is recommended even in asymptomatic patients.[96,97]

The strengths of this metaanalysis are the size of the study and combined number of subjects analyzed for our primary and secondary outcomes. Limitations include the interstudy heterogeneity, which we tried to account for during the analysis by utilizing random effects models. The included studies were both prenatally diagnosed PIAs and those diagnosed at the time of delivery or by pathology/histology. In addition, since we included studies published from 1980 onward, some data may have been collected prior to 1980. Since there have been changes in the prenatal diagnosis of PIA over the past 35 years, those data may not be representative of current practices. Our reasoning for excluding studies prior to 1980 was to reflect current practices of using ultrasound for prenatal diagnosis. After 1980, there was an increase in the use of ultrasound and therefore an increase in antenatal diagnosis of PIA. Prior to 1980, there was scarce use of ultrasound so that the assigned gestational age was in error in a significant number of cases. Since gestational age at birth was our primary outcome, this would have interfered with our results. Furthermore, there was a paucity of comparative studies analyzing our primary outcomes in clearly stated groups (those with PIAs and those without), specifically in regard to placenta accreta and vasa previa. The majority of studies screened for inclusion were comprised of case reports, case series, or had small sample sizes. Within the group of studies that met our inclusion criteria, the majority of those were descriptive studies detailing outcomes of PIAs not compared to control groups without PIAs. Another potential limitation in any metaanalysis is the potential for publication and study selection biases. However, we did not detect any publication bias in our metaanalysis for all the PIA groups and outcomes.

TABLE 2
Summary of descriptive studies

Outcome	No. of study groups	No. of subjects	Risk, % or mean (95% CI)
Placenta previa			
Preterm delivery	7[19-23,66]	1110	43.5 (40.6–46.4)
Neonatal death	4[19,24]	563	0.51 (0.0–1.1)
NICU admissions	10[19,21,23-27]	1139	24.4 (21.9–26.9)
1-min Apgar score <7	5[19,20,22,26]	499	31.1 (27.0–35.1)
5-min Apgar score <7	5[19,20,22,66]	717	5.9 (4.1–7.6)
Gestational age, wk	16[12-14,16,18,23-27,29,30,32,34]	5555	35.3 (35.3–35.3)[a]
Birthweight, g	13[17-19,23-27,34]	1585	2704 (2692–2715)[a]
Low-lying placenta/marginal placenta previa			
Preterm delivery	2[20,22]	227	26.9 (21.1–32.7)
NICU admissions	2[35]	43	23.1 (10.5–35.7)
1-min Apgar score <7	2[20,22]	227	21.6 (16.2–26.9)
5-min Apgar score <7	4[20,22,35]	270	3.3 (1.2–5.5)
Gestational age, wk	2[36,37]	106	37.4 (37.3–37.4)[a]
Placenta accreta			
Preterm delivery	7[23,39,48,49,51]	259	57.7 (51.7–63.7)
NICU admissions	9[23,43,45,49,51,53]	333	54.9 (49.6–60.2)
Perinatal death	3[23,51]	123	8.0 (3.2–12.8)
1-min Apgar score <7	2[45,48]	98	16.0 (8.8–23.3)
5-min Apgar score <7	5[45,49,51]	185	13.6 (8.6–18.5)
Gestational age, wk	16[8,18,23,40,44-48,50,53-55]	584	34.8 (34.7–34.8)[a]
Birthweight, g	13[18,23,40,43,45,48,50,51,53-55]	522	2590 (2572–2607)[a]
Vasa previa			
Preterm delivery	2[59,60]	28	81.9 (67.7–96.2)
Gestational age, wk	4[60-63]	201	36.5 (36.4–36.6)[a]
Birthweight, g	4[59-62]	55	2613 (2540–2686)[a]
Velamentous cord insertion			
Preterm delivery	1[56]	8	37.5
Gestational age, wk	1[56]	8	36.5 (35–39)[b]

CI, confidence interval; *NICU*, neonatal intensive care unit.

[a] Mean (95% CI); [b] Median (range).

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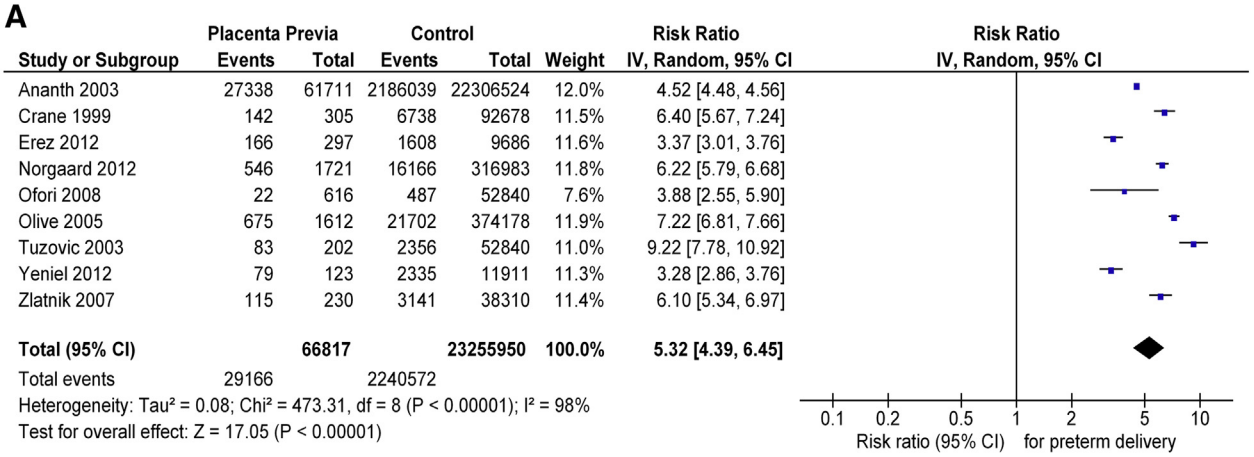
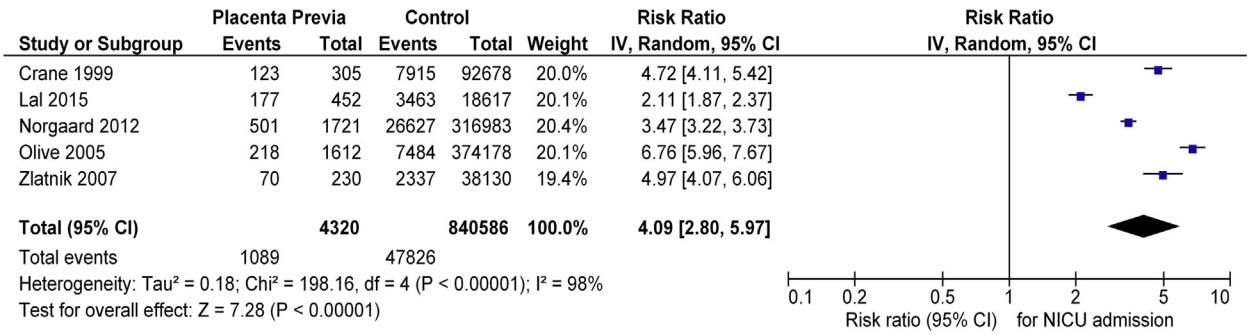
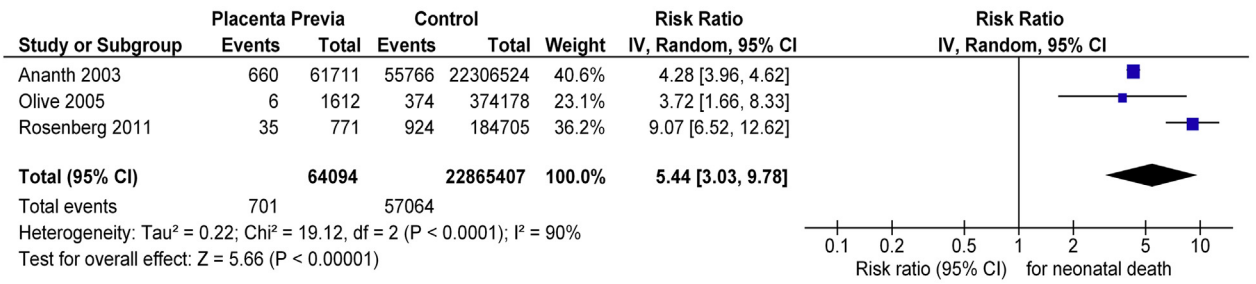
The importance of these findings is 2-fold. We first wish to alert the clinician of the contribution of PIA to the indicated preterm delivery rate. Current guidelines and recommendations for delivery even in asymptomatic patients are as follows: 36-37 weeks for placenta

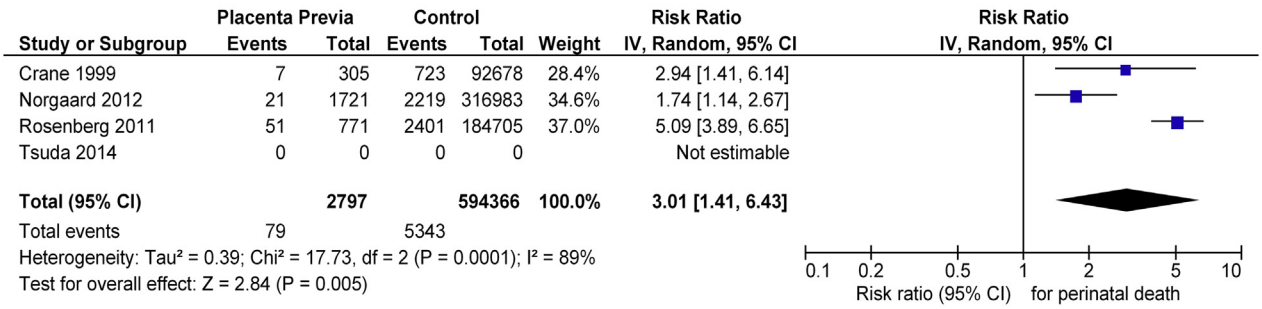
FIGURE 2
Metaanalysis and forest plot of comparative studies

A









A, Placenta previa with respect to preterm delivery (<37 weeks), neonatal intensive care unit (NICU) admission, and neonatal and perinatal mortality; **B**, placenta accreta with respect to gestational age and birthweight; **C**, velamentous cord insertion with respect to preterm delivery (<37 weeks), NICU admission, and perinatal mortality.

CI, confidence interval; *velamentous CI*, velamentous cord insertion.

Ananth et al[67]; Crane et al[68]; Erez et al[69]; Norgaard et al[70]; Ofori et al[71]; Olive et al[72]; Tuzovic et al[73]; Yeniel et al[74]; Zlatnik et al[75]; Lal and Hibbard[76]; Rosenberg et al[77]; Tsuda et al.[78]

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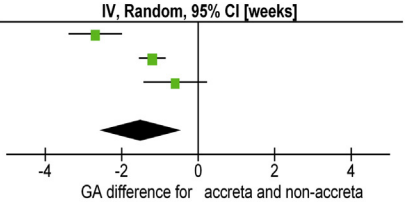
FIGURE 2
Metaanalysis and forest plot of comparative studies (*continued*)

B

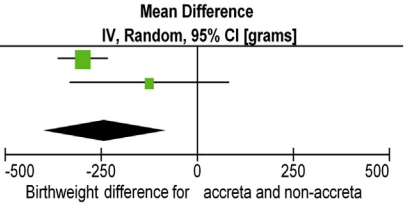
Study or Subgroup	Accreta Mean [weeks]	Accreta SD [weeks]	Accreta Total	Control Mean [weeks]	Control SD [weeks]	Control Total	Weight	Mean Difference IV, Random, 95% CI [weeks]
Eshkoli 2013	35.32	4.1	139	38.01	2.9	34730	32.7%	-2.69 [-3.37, -2.01]
Gielchinsky 2004	39.3	3	310	40.5	1	34140	36.5%	-1.20 [-1.53, -0.87]
Hung 1999	38.1	2.2	28	38.7	1.8	9321	30.9%	-0.60 [-1.42, 0.22]
Total (95% CI)			**477**			**78191**	**100.0%**	**-1.50 [-2.56, -0.45]**

Heterogeneity: Tau² = 0.77; Chi² = 18.79, df = 2 (P < 0.0001); I² = 89%
Test for overall effect: Z = 2.79 (P = 0.005)



Study or Subgroup	Accreta Mean [grams]	Accreta SD [grams]	Accreta Total	Control Mean [grams]	Control SD [grams]	Control Total	Weight	Mean Difference IV, Random, 95% CI [grams]
Gielchinsky 2004	3,110	572	310	3,408	415	34140	66.7%	-298.00 [-361.83, -234.17]
Hung 1999	3,109	556	28	3,234	466	9321	33.3%	-125.00 [-331.16, 81.16]
Total (95% CI)			**338**			**43461**	**100.0%**	**-240.41 [-400.20, -80.62]**

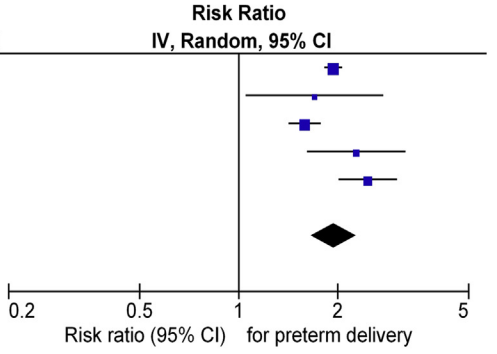
Heterogeneity: Tau² = 8902.33; Chi² = 2.47, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 2.95 (P = 0.003)



C

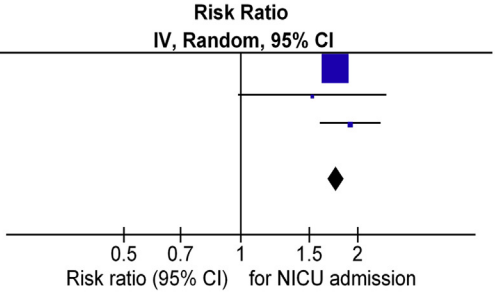
Study or Subgroup	Velamentous CI Events	Velamentous CI Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ebbing 2013	1101	9500	36716	613978	30.5%	1.94 [1.83, 2.05]
Eddleman 1992	14	77	1726	16133	8.1%	1.70 [1.06, 2.74]
Esakoff 2015	291	2015	43724	480485	27.7%	1.59 [1.43, 1.77]
Heinonen 1996	30	216	765	12534	12.8%	2.28 [1.62, 3.19]
Raisanen 2012	89	633	1494	26216	21.0%	2.47 [2.02, 3.01]
Total (95% CI)		**12441**		**1149346**	**100.0%**	**1.95 [1.67, 2.28]**
Total events	1525		84425			

Heterogeneity: Tau² = 0.02; Chi² = 19.32, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 8.33 (P < 0.00001)



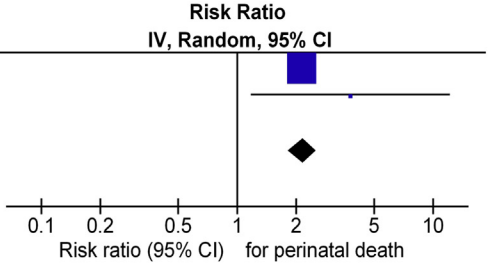
Study or Subgroup	Velamentous CI Events	Velamentous CI Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ebbing 2013	1359	9500	50223	613978	91.4%	1.75 [1.66, 1.84]
Heinonen 1996	19	216	722	12534	1.2%	1.53 [0.99, 2.36]
Raisanen 2012	109	633	2359	26216	7.4%	1.91 [1.61, 2.28]
Total (95% CI)		**10349**		**652728**	**100.0%**	**1.76 [1.68, 1.84]**
Total events	1487		53304			

Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 23.16 (P < 0.00001)



Study or Subgroup	Velamentous CI Events	Velamentous CI Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ebbing 2013	156	9500	4728	613978	98.2%	2.13 [1.82, 2.50]
Heinonen 1996	3	216	46	12534	1.8%	3.78 [1.19, 12.07]
Total (95% CI)		**9716**		**626512**	**100.0%**	**2.15 [1.84, 2.52]**
Total events	159		4774			

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 9.60 (P < 0.00001)



Eskoli et al[2]; Gielchinsky et al[79]; Hung et al[80]; Ebbing et al[83]; Eddleman et al[84]; Esakoff et al[85]; Heinonen et al[86]; Raisanen et al.[87]
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TABLE 3
Summary of comparative metaanalysis analyses

Outcome	No. of studies	No. of subjects	Risk of outcome		Summary measure
Placenta previa			**Risk in previa, %**	**Risk in nonprevia, %**	**Risk ratio (95% CI)**
Preterm delivery	9[67-75]	23,322,767	43.7	9.6	5.32 (4.39–6.45)
Neonatal death	3[67,72,77]	2,292,501	1.1	0.2	5.44 (3.03–9.78)
NICU admissions	5[68,70,72,75,76]	844,906	25.2	5.7	4.09 (2.80–5.97)
SGA	5[72,74,76,77,89]	1,137,103	8.6	8.7	1.01 (0.62–1.65)
Perinatal death	3[68,70,77]	597,163	2.8	0.9	3.01 (1.41–6.43)
1-min Apgar score <7	2[68-77]	278,459	24.4	7.2	3.14 (1.69–5.85)
5-min Apgar score <7	3[68,70,77]	635,703	4.9	1.8	2.73 (2.25–3.29)
Placenta accreta			**Mean (SD) in accreta**	**Mean (SD) in nonaccreta**	**Mean difference (95% CI)**
Gestational age, wk	3[2,79,80]	78,668	38.1 (1.8)	39.2 (1.2)	−1.5 (−2.6 to −0.5)
Birthweight, g	2[79,80]	43,799	3110 (0.3)	3371 (71)	−240 (−400 to −81)
VP			**Risk in VP, %**	**Risk in non-VP, %**	**Risk ratio (95% CI)**
Preterm delivery	1[82]	246,525	29.5	8.8	3.36 (2.76–4.09)
SGA	1[82]	246,525	8.4	2.1	4.02 (2.64–6.12)
Perinatal death	1[82]	246,525	6.3	1.4	4.52 (2.77–7.39)
5-min Apgar score <7	1[82]	246,525	6.8	3.1	2.18 (1.36–3.50)
VCI			**Risk in VCI, %**	**Risk in non-VCI, %**	
Preterm delivery	5[83-87]	1,161,787	12.3	7.3	1.95 (1.67–2.28)
Neonatal death	0				
NICU admissions	3[8,86,87]	663,077	14.4	8.2	1.76 (1.68–1.84)
SGA	4[83,85-87]	1,145,889	14.6	8.9	1.69 (1.56–1.82)
Perinatal death	2[83,86]	636,228	1.6	0.8	2.15 (1.84–2.52)
1-min Apgar score <7	3[84,86,87]	55,809	8.1	4.1	1.66 (1.31–2.09)
5-min Apgar score <7	4[83,84,86,87]	679,287	3.2	1.7	1.96 (1.71–2.25)

CI, confidence interval; *NICU*, neonatal intensive care unit; *SGA*, small for gestational age; *VCI*, velamentous cord insertion; *VP*, vasa previa.

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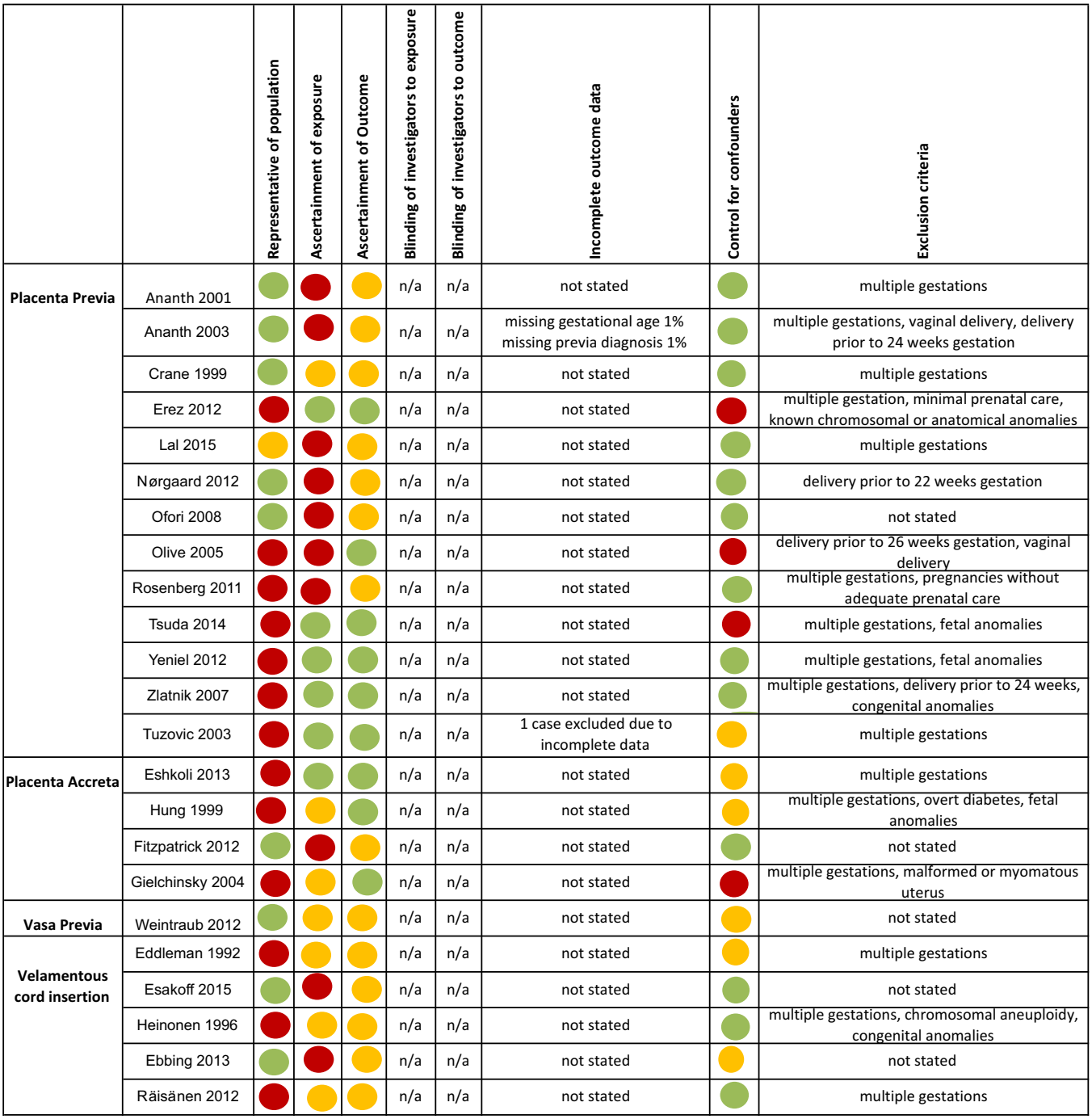
previa,[96] 34-35 weeks for placenta accreta,[96] and 34-36 weeks for vasa previa.[63,97] However, many of these cases can be individualized and management guided clinically to prolong pregnancy safely. For example, clinical clues such as vaginal bleeding or the use of ultrasound to evaluate the cervix and placenta might be able to predict these catastrophic complications. Secondly, as a public health concern, with the rising cesarean delivery rates there is also an increase in PIA. As we have previously stated, almost all cases of PIA are delivered prematurely to avoid complications. Therefore, the next step is not only to individualize management of PIA but to alert clinicians that decreasing the primary cesarean delivery rate will in turn decrease the overall contribution of PIA to preterm delivery. ■

FIGURE 3
Risk of bias across studies



		Representative of population	Ascertainment of exposure	Ascertainment of Outcome	Blinding of investigators to exposure	Blinding of investigators to outcome	Incomplete outcome data	Control for confounders	Exclusion criteria
Placenta Previa	Ananth 2001				n/a	n/a	not stated		multiple gestations
	Ananth 2003				n/a	n/a	missing gestational age 1% missing previa diagnosis 1%		multiple gestations, vaginal delivery, delivery prior to 24 weeks gestation
	Crane 1999				n/a	n/a	not stated		multiple gestations
	Erez 2012				n/a	n/a	not stated		multiple gestation, minimal prenatal care, known chromosomal or anatomical anomalies
	Lal 2015				n/a	n/a	not stated		multiple gestations
	Nørgaard 2012				n/a	n/a	not stated		delivery prior to 22 weeks gestation
	Ofori 2008				n/a	n/a	not stated		not stated
	Olive 2005				n/a	n/a	not stated		delivery prior to 26 weeks gestation, vaginal delivery
	Rosenberg 2011				n/a	n/a	not stated		multiple gestations, pregnancies without adequate prenatal care
	Tsuda 2014				n/a	n/a	not stated		multiple gestations, fetal anomalies
	Yeniel 2012				n/a	n/a	not stated		multiple gestations, fetal anomalies
	Zlatnik 2007				n/a	n/a	not stated		multiple gestations, delivery prior to 24 weeks, congenital anomalies
	Tuzovic 2003				n/a	n/a	1 case excluded due to incomplete data		multiple gestations
Placenta Accreta	Eshkoli 2013				n/a	n/a	not stated		multiple gestations
	Hung 1999				n/a	n/a	not stated		multiple gestations, overt diabetes, fetal anomalies
	Fitzpatrick 2012				n/a	n/a	not stated		not stated
	Gielchinsky 2004				n/a	n/a	not stated		multiple gestations, malformed or myomatous uterus
Vasa Previa	Weintraub 2012				n/a	n/a	not stated		not stated
Velamentous cord insertion	Eddleman 1992				n/a	n/a	not stated		multiple gestations
	Esakoff 2015				n/a	n/a	not stated		not stated
	Heinonen 1996				n/a	n/a	not stated		multiple gestations, chromosomal aneuploidy, congenital anomalies
	Ebbing 2013				n/a	n/a	not stated		not stated
	Räisänen 2012				n/a	n/a	not stated		multiple gestations

Legend: green = criteria met; red = criteria not met; orange = uncertain status

Ananth et al[67]; Ananth et al[89]; Crane et al[68]; Erez et al[69]; Norgaard et al[70]; Ofori et al[71]; Olive et al[72]; Tuzovic et al[73]; Yeniel et al[74]; Zlatnik et al[75]; Lal and Hibbard[76]; Rosenberg et al[77]; Tsuda et al[78]; Eshkoli et al[2]; Gielchinsky et al[79]; Hung et al[80]; Fitzpatrick et al[81]; Weintraub et al[82]; Ebbing et al[83]; Eddleman et al[84]; Esakoff et al[85]; Heinonen et al[86]; Raisanen et al.[87]

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