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Perinatal outcome of pregnancies with prenatal diagnosis of vasa previa: systematic review and meta-analysis

W. ZHANG[1], S. GERIS[1], N. AL-EMARA[1], G. RAMADAN[2], A. SOTIRIADIS[3] and R. AKOLEKAR[1,4,5]

[1]*Medway Fetal and Maternal Medicine Centre, Medway NHS Foundation Trust, Gillingham, UK;* [2]*Oliver Fisher Neonatal Unit, Medway NHS Foundation Trust, Gillingham, UK;* [3]*Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece;* [4]*Medway Innovation Institute, Gillingham, UK;* [5] *Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK*

KEYWORDS: perinatal survival; prenatal diagnosis; stillbirth; vasa previa

CONTRIBUTION

What are the novel findings of this work?
In pregnancies with vasa previa, prenatal diagnosis is associated with a high rate of perinatal survival, whereas in the absence of prenatal diagnosis, the risk of perinatal death and hypoxic morbidity in surviving neonates is increased 25- and 50-fold, respectively. This study highlights the importance of prenatal diagnosis in preventing stillbirth and neonatal death due to vasa previa.

What are the clinical implications of this work?
Prenatal diagnosis of vasa previa is essential for improving perinatal outcomes associated with this obstetric complication. Further research should be undertaken to investigate and incorporate screening for vasa previa into routine clinical practice.

ABSTRACT

Objectives *To derive accurate estimates of perinatal survival in pregnancies with and without a prenatal diagnosis of vasa previa based on a systematic review of the literature and meta-analysis.*

Methods *A search of MEDLINE, EMBASE and The Cochrane Library was performed to review relevant citations reporting on the perinatal outcomes of pregnancies with vasa previa. We included prospective and retrospective cohort and population studies that provided data on pregnancies with a prenatal diagnosis of vasa previa or cases diagnosed at birth or following postnatal placental examination. Meta-analysis using a random-effects model was performed to derive weighted pooled estimates of perinatal survival (excluding stillbirths and neonatal deaths) and intact perinatal survival (additionally excluding hypoxic morbidity). Incidence rate difference (IRD) meta-analysis was used to estimate the significance of differences in pooled proportions between cases of vasa previa with and those without a prenatal diagnosis. Heterogeneity between studies was estimated using Cochran's Q and the* I^2 *statistic.*

Results *We included 21 studies reporting on the perinatal outcomes of 683 pregnancies with a prenatal diagnosis of vasa previa. There were three stillbirths (1.01% (95% CI, 0.40–1.87%)), five neonatal deaths (1.19% (95% CI, 0.52–2.12%)) and 675 surviving neonates, resulting in a pooled estimate for perinatal survival of 98.6% (95% CI, 97.6–99.3%). Based on seven studies that included cases of vasa previa with and without a prenatal diagnosis, the pooled perinatal survival in pregnancies without a prenatal diagnosis (61/118) was 72.1% (95% CI, 50.6–89.4%)* vs *98.6% (95% CI, 96.7–99.7%) in cases with a prenatal diagnosis (224/226). Therefore, the risk of perinatal death was 25-fold higher when a diagnosis of vasa previa was not made antenatally, compared with when it was (odds ratio (OR), 25.39 (95% CI, 7.93–81.31);* $P < 0.0001$*). Similarly, the risk of hypoxic morbidity was increased 50-fold in cases with vasa previa without a prenatal diagnosis compared with those with a prenatal diagnosis (36/61* vs *5/224; OR, 50.09 (95% CI, 17.33–144.79)). The intact perinatal survival rate in cases of vasa previa without a prenatal diagnosis was significantly lower than in those with a prenatal diagnosis (28.1% (95% CI, 14.1–44.7%)* vs *96.7% (95% CI, 93.6–98.8%)) (IRD, 73.4% (95% CI, 53.9–92.7%);* $Z = -7.4066$*,* $P < 0.001$*).*

Correspondence to: Prof. R. Akolekar, Medway Fetal and Maternal Medicine Centre, Medway Maritime Hospital, Gillingham, Kent ME7 5NY, UK (e-mail: ranjit.akolekar@canterbury.ac.uk)

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Conclusions *Prenatal diagnosis of vasa previa is associated with a high rate of perinatal survival, whereas lack of an antenatal diagnosis significantly increases the risk of perinatal death and hypoxic morbidity. Further research should be undertaken to investigate strategies for incorporating prenatal screening for vasa previa into routine clinical practice.* © *2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Vasa previa is a condition in which arterial or venous fetal blood vessels traverse the amniotic membranes in the lower uterine segment in close proximity to the internal cervical os, unsupported by placental tissue or the umbilical cord[1–4]. Vasa previa can occur either with a velamentous cord insertion, when fetal vessels traverse the amniotic membranes from the cord insertion to the placental tissue, or with a bilobed or succenturiate placenta, when fetal vessels run freely in the membranes connecting the placental masses[3–5]. As these fetal vessels lie close to the internal cervical os and freely traverse the amniotic membranes, they can be damaged in the antenatal or intrapartum period following spontaneous or iatrogenic rupture of amniotic membranes, thus leading to severe hypovolemic shock and hemorrhagic fetal death[6–8].

Several studies have reported a high rate of live births in pregnancies with a prenatal diagnosis of vasa previa[9–12]. In contrast, there is a high risk of stillbirth, neonatal death and morbidity in pregnancies with vasa previa without an antenatal diagnosis[8,9,11]. A recent large prospective cohort study examining the effectiveness of a two-stage screening strategy for vasa previa reported that an accurate prenatal diagnosis of vasa previa is feasible in routine clinical practice and is associated with a high rate of live birth[13]. The findings of the study suggested that an effective strategy for the prenatal diagnosis of vasa previa could potentially contribute to prevention of up to 10% of all stillbirths[13].

The objective of this study was to undertake a systematic review of the literature and perform a meta-analysis to determine accurate estimates of perinatal survival in pregnancies with and without a prenatal diagnosis of vasa previa.

METHODS

Data sources and search strategy

This systematic review and meta-analysis was undertaken based on an *a-priori* designed study protocol recommended for systematic reviews and meta-analyses[14]. The study protocol of the systematic review was registered in advance with PROSPERO (registration number: CRD42020125495). An electronic search of MEDLINE, EMBASE and The Cochrane Library was carried out on 30 March 2020 utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'vasa previa', 'abnormal cord insertion', 'velamentous cord', 'marginal cord', 'bilobed placenta' and 'succenturiate lobe'. The search and selection criteria were restricted to studies in the English language. The citations retrieved following the electronic search were examined for relevance to this study based on their design, sample size, study period and whether they reported perinatal outcomes of pregnancies with and without a prenatal diagnosis of vasa previa.

Eligibility and selection criteria for studies

Eligible for inclusion in our study were prospective or retrospective cohort studies and population-based studies reporting on the outcomes of pregnancies with vasa previa that was diagnosed prenatally, at birth or following postnatal placental examination. Only studies that were published after the year 2000 were included to ensure that prenatal diagnosis and perinatal outcomes reflect current obstetric and neonatal care.

The citations were examined by two reviewers (W.Z. and S.G.) to produce a list of relevant studies after exclusion of duplicates, studies that did not fit the selection criteria after review of the title and abstract, case reports, letters to the editor, review articles and conference abstracts. These two authors independently assessed all the potential studies identified from the search strategy for inclusion or exclusion and extracted data using a prespecified template. The reference lists of relevant articles and reviews were searched manually for additional reports and any inconsistencies were discussed with a third reviewer (R.A.) to reach a consensus.

Data extraction and synthesis

For each study included in the systematic review, information about the following was extracted: authors, year of enrolment for cases and, if applicable, for controls, study design, whether the study was single- or multicenter, whether the study included cases of vasa previa with or without a prenatal diagnosis, sample size, rates of stillbirth, neonatal death and hypoxic neonatal morbidity, defined as 5- or 10-min Apgar score of < 7, arterial or venous cord pH of < 7 or a need for neonatal blood transfusion. The primary outcome measure was perinatal survival, defined as the total number of surviving neonates after excluding cases of stillbirth or neonatal death in the first 7 days after birth. The secondary outcome measure was intact perinatal survival, defined as the total number of surviving neonates after excluding stillbirths, neonatal deaths in the 7 days postpartum and cases with hypoxic neonatal morbidity. Data extracted for each study were inputted into contingency tables. Haldane correction was used to account for small event rates to allow for estimation of variance and pooled effects. The authors of primary studies were contacted if further details or clarifications were required.

Quality assessment

The methodological quality of studies included in the review was assessed using the Newcastle–Ottawa scale (NOS), which assesses the quality of non-randomized studies such as cohort studies with specific regard to three perspectives: selection of study groups, comparability of groups and ascertainment of outcome of interest[15]. Assessment of the domains is performed based on a standardized checklist and indicators of high quality are awarded a star. The number and combination of stars expresses the overall quality of a study compliant with the protocols of the Agency for Healthcare Research and Quality (good, fair or poor). The quality of this systematic review and meta-analysis was validated using PRISMA (preferred reporting items for systematic reviews and meta-analyses). The PRISMA statement for this study included a checklist and a flowchart to allow uniform and transparent reporting of the systematic review and meta-analysis[16].

Meta-analysis and estimation of pooled statistics

Data were extracted from each study to document study design, sample size and rates of stillbirth, neonatal death and hypoxic neonatal morbidity. Data were entered into contingency tables and perinatal survival and intact survival rates (with 95% CIs) were estimated for each study weighted by its sample size. Summary statistics for the outcomes (with 95% CIs) were derived for each study and were then combined to obtain a pooled estimate, which was calculated as a weighted average of the individual study estimates. The pooled summary statistics were estimated using a random-effects model (REM), which was chosen for two reasons: firstly, it allows for assessment of between-study variability in results by weighting studies using a combination of their own variance and between-study variance and, secondly, it provides a pragmatic conservative estimate of pooled statistics with wider CIs[17]. Forest plots of summary statistics for each study were constructed and final pooled estimates were calculated using data from the REMs. For studies that included both women with and those without a prenatal diagnosis of vasa previa, pooled odds ratios (OR) using REM were calculated for outcomes with available data. Incidence rate difference (IRD) meta-analysis using REM was used to estimate the significance of differences in pooled proportions between the two groups. The heterogeneity between studies was estimated using Cochran's Q heterogeneity statistic and the I^2 statistic. The statistical software package StatsDirect version 2.7.9 (StatsDirect Ltd, Cheshire, UK) and MedCalc Statistical Software version 16.4.3 (MedCalc Software, Ostend, Belgium) were used for data analysis.

RESULTS

Data search results

The electronic search of the databases yielded 1238 potential citations. Of these, we excluded 561 duplicates, 248 citations after review of the title and 384 citations after review of the abstract. Forty-five manuscripts were retrieved in full text for detailed assessment and a further 24 studies that did not meet the selection criteria were excluded; thus, 21[4,9–13,18–32] studies were included in the systematic review and meta-analysis. The study selection process is shown in Figure 1.

Characteristics of included studies

All 21 studies included in the systematic review reported on the perinatal outcome of pregnancies with vasa previa. Of these, 14[4,11,13,22–32] were case series or cohort studies that reported on perinatal outcome only in pregnancies with an antenatal diagnosis of vasa previa, while seven[9,10,12,18–21] reported on outcomes in women with a prenatal diagnosis and those that were diagnosed incidentally during labor or following postnatal placental examination. There were three multicenter studies[9,12,20] and 18 single-center studies[4,10,11,13,18,19,21–32].

Assessment of quality and heterogeneity of studies

The methodological quality of the studies included in this systematic review was assessed using the NOS. The rating of the studies based on selection and comparability of study groups and ascertainment of outcomes of interest is shown in Table S1. The PRISMA guidance was followed for reporting this meta-analysis (Table S2).

Stillbirths, neonatal deaths and perinatal survival in pregnancies with vasa previa

All 21 studies reported on the incidence of stillbirth and neonatal death in a total of 683 pregnancies

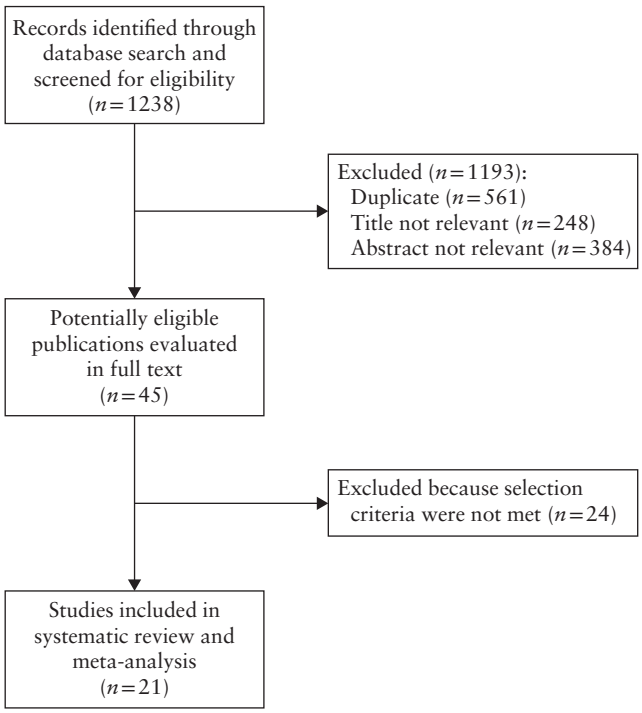

Figure 1 Flowchart showing selection of studies included in systematic review and meta-analysis.

with a prenatal diagnosis of vasa previa. There were three stillbirths (1.01% (95% CI, 0.40–1.87%)) and five neonatal deaths (1.19% (95% CI, 0.52–2.12%)), thus adding up to a total of eight perinatal deaths (1.41% (95% CI, 0.67–2.41%)). Therefore, 675 of the 683 pregnancies resulted in surviving neonates, with a weighted pooled perinatal survival rate of 98.6% (95% CI, 97.6–99.3%) ($I^2 = 0\%$ (95% CI, 0–41.5%)) (Table 1, Figure 2).

Seven studies[9,10,12,18–21] reported on the incidence of stillbirth and neonatal death in both pregnancies with ($n = 226$) and those without ($n = 118$) a prenatal diagnosis of vasa previa. Amongst the pregnancies with a prenatal diagnosis, there were two perinatal deaths (1.39% (95% CI, 0.29–3.29%)), including one stillbirth (1.11% (95% CI, 0.17–2.86%)) and one neonatal death (1.11% (95% CI, 0.17–2.86%)). In pregnancies without a prenatal diagnosis of vasa previa, the stillbirth rate (32/118; 27.4% (95% CI, 20.0–35.6%)) and neonatal death rate (25/118; 15.8% (95% CI, 6.98–27.27%)) were significantly higher than in pregnancies with a prenatal diagnosis (IRD, 24.5% (95% CI, 19.9–66.8%); $Z = 4.9853$, $P < 0.001$ and IRD, 28.6% (95% CI, 13.3–34.0%); $Z = 4.4821$, $P < 0.001$, respectively). The weighted pooled perinatal survival rate in pregnancies with a prenatal diagnosis of vasa previa (224/226), was significantly higher than in those without a prenatal diagnosis (61/118) (98.6% (95% CI, 96.7–99.7%) *vs* 72.1% (95% CI, 50.6–89.4%); IRD, 43.3% (95% CI, 19.9–66.8%); $Z = -3.6134$, $P < 0.001$) (Table 2, Figure 3). Therefore, the risk of perinatal death was 25-fold higher when a diagnosis of vasa previa was not made antenatally, compared with when it was (57/118 *vs* 2/226; pooled OR, 25.39 (95% CI, 7.93–81.31); $P < 0.0001$).

Neonatal morbidity and intact perinatal survival in pregnancies with vasa previa

Of 683 pregnancies with a prenatal diagnosis of vasa previa, there were 675 surviving neonates. Of these, 12 neonates (12/675; 1.78% (95% CI, 0.92–3.11%)) had features of hypoxic morbidity, thus leaving 663 neonates without any morbidity and resulting in an intact neonatal survival rate of 97.1% (95% CI, 95.2–98.4%); $I^2 = 32.1\%$ (95% CI, 0–59.2%) (Table 3, Figure 4). Similarly, in the seven studies[9,10,12,18–21] that evaluated perinatal outcomes in pregnancies with and those without a prenatal diagnosis of vasa previa, after exclusion of stillbirths and neonatal deaths, there were five neonates (5/224; 2.70% (95% CI, 1.01–5.17%)) with hypoxic morbidity in the prenatal diagnosis group compared with 36 neonates (36/61; 58.23% (95% CI, 37.15–77.84%)) in the group without a prenatal diagnosis (IRD, 57.9% (95% CI, 37.1–78.8%); $Z = 5.4474$, $P < 0.001$). The pooled weighted intact neonatal survival rate in pregnancies with a prenatal diagnosis was 96.7% (95% CI, 93.6–98.8%); $I^2 = 18.4\%$ (95% CI, 0–65.7%) compared with 28.1% (95% CI, 14.1–44.7%); $I^2 = 40.0\%$ (95% CI, 0–73.4%) in those without a prenatal diagnosis of vasa previa (IRD, 73.4% (95% CI, 53.9–92.7%); $Z = -7.4066$, $P < 0.001$) (Table 4, Figure 5). The risk of hypoxic perinatal morbidity in survivors was increased more than 50-fold if a prenatal diagnosis of vasa previa was not made compared to when it was (36/61 *vs* 5/224; pooled OR, 50.09 (95% CI, 17.33–144.79); $P < 0.0001$).

DISCUSSION

Principal findings

The findings of this systematic review and meta-analysis demonstrate that in pregnancies with a prenatal diagnosis of vasa previa, the total and intact perinatal survival rates were 99% and 97%, respectively. In contrast, in cases of vasa previa without a prenatal diagnosis, there was a significantly increased risk of hypoxic morbidity and mortality, with correspondingly reduced total and intact perinatal survival rates of 72% and 28%, respectively. The impact of prenatal diagnosis on the prevention of morbidity and mortality from vasa previa is profound, with a 50-fold increased risk of hypoxic morbidity and a 25-fold increased risk of perinatal death if a timely prenatal diagnosis of vasa previa is not made.

Strengths and limitations

The strength of our study is that it summarizes the results of all relevant contemporary studies published in the last two decades and provides accurate summary statistics of the live-birth rate, perinatal survival rate and intact survival rate in pregnancies with and without a prenatal diagnosis of vasa previa to highlight the importance of antenatal screening and prenatal diagnosis in preventing mortality and morbidity due to this obstetric complication. This systematic review and meta-analysis was conducted according to a standardized methodology, using an *a-priori* designed protocol, PROSPERO registration, a comprehensive search strategy, appropriate quality assessment of the included studies using the NOS and validation of the quality of the systematic review using PRISMA. The limitations of our study relate to standard biases associated with meta-analyses, such as inclusion of studies with different sample sizes, methodology and study design, which may introduce heterogeneity into the analysis. However, we tried to overcome these limitations, firstly, by using strict selection criteria, for example excluding case reports without supporting clinical information; secondly, by undertaking not only meta-analysis on all included studies but also nested analysis on selected studies that were similar in study design and methodology; and thirdly, by choosing to use a REM over a fixed-effects model to minimize the impact of heterogeneity between studies by taking into account between-study variance, weighting the studies based on sample size and providing estimates of summary

Table 1 Meta-analysis to derive aggregate summary statistics of perinatal survival rate from studies reporting on pregnancies with prenatal diagnosis of vasa previa

Study	*Total*	*Perinatal survival rate*	*Weight (%)*
Lee (2000)[22]	18	16 (88.9 (65.3–98.6))	2.70
Catanzarite (2001)[4]	10	10 (100.0 (69.2–100.0))	1.56
Francois (2003)[18]	8	8 (100.0 (63.1–100.0))	1.28
Oyelese (2004)[9]	61	59 (96.7 (88.7–99.6))	8.81
Baulies (2007)[23]	9	9 (100.0 (66.4–100.0))	1.42
Smorgick (2010)[19]	10	10 (100.0 (69.2–100.0))	1.56
Hagesawa (2010)[24]	10	10 (100.0 (69.2–100.0))	1.56
Kanda (2011)[10]	9	9 (100.0 (66.4–100.0))	1.42
Rebarber (2014)[25]	24	24 (100.0 (85.8–100.0))	3.55
Bronsteen (2013)[26]	56	53 (94.6 (85.1–98.9))	8.10
Golic (2013)[27]	18	18 (100.0 (81.5–100.0))	2.70
Hasegawa (2015)[28]	21	21 (100.0 (83.9–100.0))	3.13
Catanzarite (2016)[11]	96	96 (100.0 (96.2–100.0))	13.78
Swank (2016)[20]	47	47 (100.0 (92.5–100.0))	6.82
Kulkarni (2018)[21]	33	33 (100.0 (89.4–100.0))	4.83
Nohuz (2017)[29]	8	8 (100.0 (63.1–100.0))	1.28
Sullivan (2017)[12]	58	58 (100.0 (93.8–100.0))	8.38
Melcer (2018)[30]	38	38 (100.0 (90.7–100.0))	5.54
Fishel Bartal (2019)[31]	109	109 (100.0 (96.7–100.0))	15.63
Yerlikaya-Schatten (2019)[32]	19	19 (100.0 (82.4–100.0))	2.84
Zhang (2020)[13]	21	20 (95.2 (76.2–99.9))	3.13
Pooled analysis (random effects)	683	675 (98.6 (97.6–99.3))	100.0
Cochran's Q (*P*)	18.1513 (0.5774)		
I^2 statistic (% (95% CI))	0 (0–41.5)		
Bias (*P*)	−0.3070 (0.0792)		

Only first author is given for each study. Data given as *n* or *n* (% (95% CI)) unless indicated otherwise.

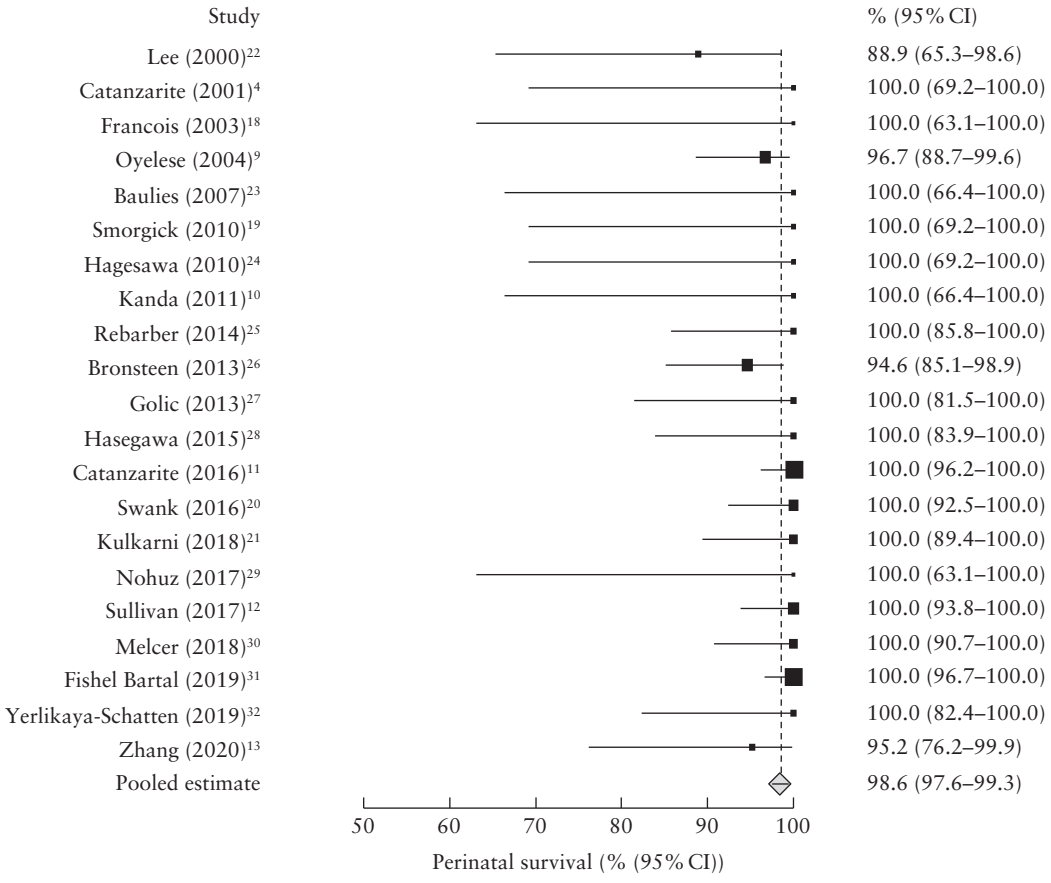

Figure 2 Forest plot showing summary statistics for incidence of perinatal survival derived using random-effects model in pregnancies with prenatal diagnosis of vasa previa. Only first author is given for each study.

Table 2 Meta-analysis to derive aggregate summary statistics for perinatal survival rate from studies reporting on cases of vasa previa with prenatal diagnosis and those without prenatal diagnosis of vasa previa

Study	*Total*	*Perinatal survival rate*	*Weight (%)*
Pregnancies with prenatal diagnosis			
Francois (2003)[18]	8	8 (100.0 (63.1–100.0))	3.86
Oyelese (2004)[9]	61	59 (96.7 (88.7–99.6))	26.61
Smorgick (2010)[19]	10	10 (100.0 (69.2–100.0))	4.72
Kanda (2011)[10]	9	9 (100.0 (66.4–100.0))	4.29
Swank (2016)[20]	47	47 (100.0 (92.5–100.0))	20.60
Kulkarni (2018)[21]	33	33 (100.0 (89.4–100.0))	14.59
Sullivan (2017)[12]	58	58 (100.0 (93.8–100.0))	25.32
Pooled analysis (random effects)	226	224 (98.6 (96.7–99.7))	100.0
Cochran's Q (P)	3.1335 (0.7919)		
I^2 statistic (% (95% CI))	0 (0–58.8)		
Bias (P)	−0.1133 (0.7595)		
Pregnancies without prenatal diagnosis			
Francois (2003)[18]	5	4 (80.0 (28.4–99.5))	14.5
Oyelese (2004)[9]	94	41 (43.6 (33.4–54.2))	25.7
Smorgick (2010)[19]	9	8 (88.9 (51.8–99.7))	17.8
Kanda (2011)[10]	1	1 (100.0 (2.5–100.0))	7.5
Swank (2016)[20]	2	2 (100.0 (15.8–100.0))	9.9
Kulkarni (2018)[21]	2	2 (100.0 (15.8–100.0))	9.9
Sullivan (2017)[12]	5	3 (60.0 (14.7–94.7))	14.5
Pooled analysis (random effects)	118	61 (72.1 (50.6–89.4))	100.0
Cochran's Q (*P*)	15.8588 (0.0145)		
I^2 statistic (% (95% CI))	62.2 (0–81.4)		
Bias (*P*)	1.8417 (0.0068)		

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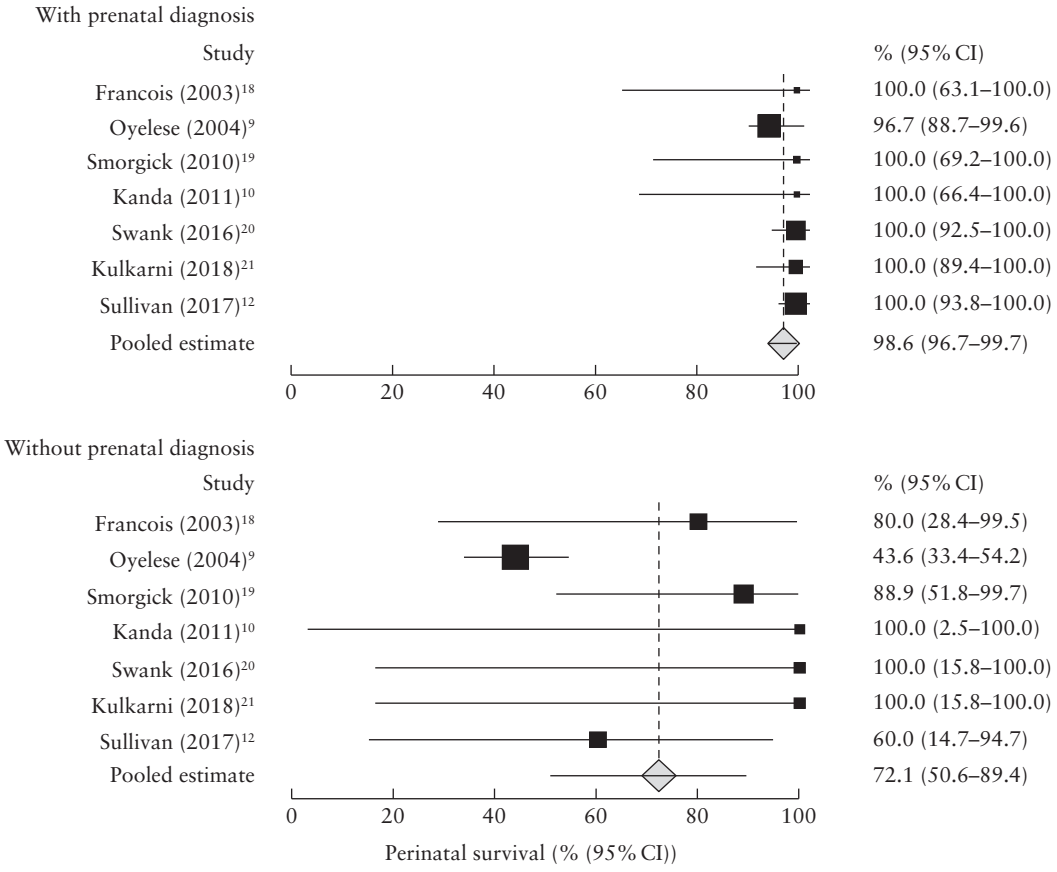

Figure 3 Forest plots showing summary statistics for incidence of perinatal survival derived using random-effects model in pregnancies with vasa previa diagnosed prenatally and those without prenatal diagnosis. Only first author is given for each study.

Table 3 Meta-analysis to derive aggregate summary statistics of intact perinatal survival rate from studies reporting on pregnancies with prenatal diagnosis of vasa previa

Study	*Total*	*Intact survival rate*	*Weight (%)*
Lee (2000)[22]	18	14 (77.8 (52.4–93.6))	3.61
Catanzarite (2001)[4]	10	10 (100.0 (69.2–100.0))	2.30
Francois (2003)[18]	8	8 (100.0 (63.1–100.0))	1.93
Oyelese (2004)[9]	61	57 (93.4 (84.1–98.2))	7.89
Baulies (2007)[23]	9	9 (100.0 (66.4–100.0))	2.12
Smorgick (2010)[19]	10	10 (100.0 (69.2–100.0))	2.30
Hagesawa (2010)[24]	10	10 (100.0 (69.2–100.0))	2.30
Kanda (2011)[10]	9	9 (100.0 (66.4–100.0))	2.12
Rebarber (2014)[25]	24	24 (100.0 (85.8–100.0))	4.44
Bronsteen (2013)[26]	56	53 (94.6 (85.1–98.9))	7.55
Golic (2013)[27]	18	18 (100.0 (81.5–100.0))	3.61
Hasegawa (2015)[28]	21	21 (100.0 (83.9–100.0))	4.04
Catanzarite (2016)[11]	96	96 (100.0 (96.2–100.0))	9.74
Swank (2016)[20]	47	47 (100.0 (92.5–100.0))	6.85
Kulkarni (2018)[21]	33	33 (100.0 (89.4–100.0))	5.51
Nohuz (2017)[29]	8	8 (100.0 (63.1–100.0))	1.93
Sullivan (2017)[12]	58	56 (96.6 (88.1–99.6))	7.69
Melcer (2018)[30]	38	38 (100.0 (90.7–100.0))	6.03
Fishel Bartal (2019)[31]	109	105 (96.3 (90.9–99.0))	10.24
Yerlikaya–Schatten (2019)[32]	19	19 (100.0 (82.4–100.0))	3.76
Zhang (2020)[13]	21	18 (85.7 (63.7–97.0))	4.04
Pooled analysis (random effects)	683	663 (97.1 (95.2–98.4))	100.0
Cochran's Q (*P*)		29.4583 (0.0791)	
I^2 statistic (% (95% CI))		32.1 (0–59.2)	
Bias (*P*)		−0.5253 (0.0838)	

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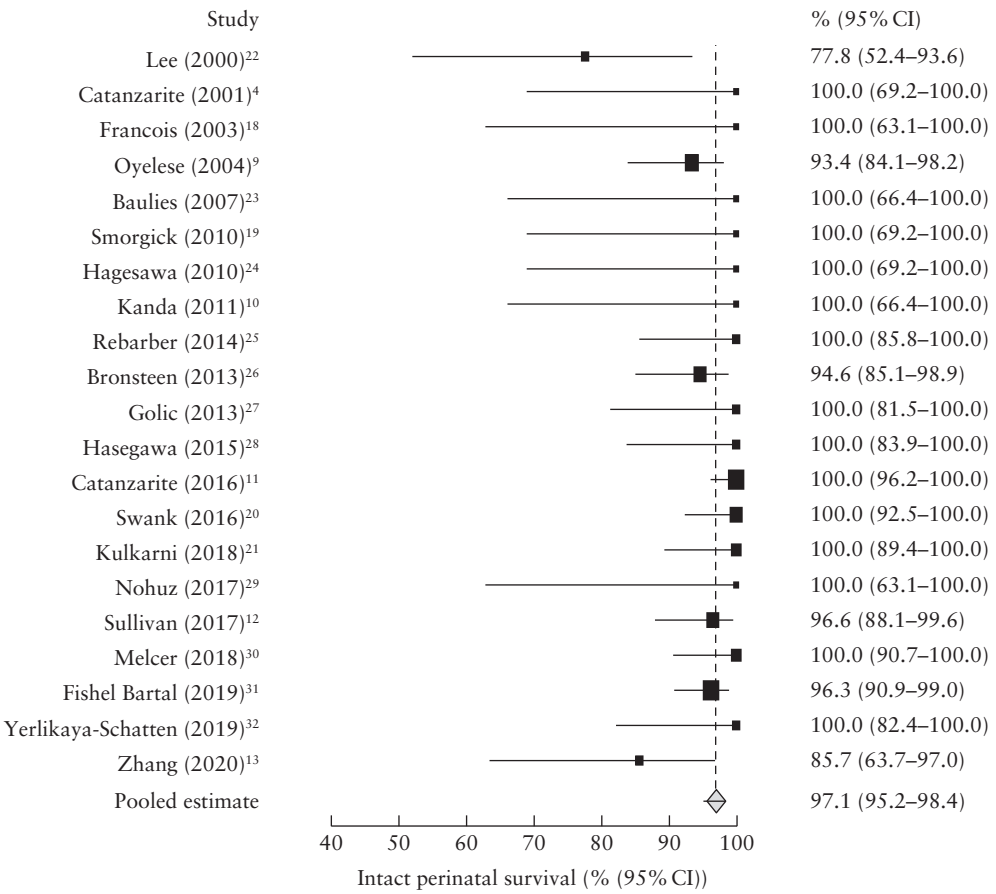

Figure 4 Forest plot showing summary statistics for incidence of intact perinatal survival derived using random-effects model in pregnancies with prenatal diagnosis of vasa previa. Only first author is given for each study.

Table 4 Meta-analysis to derive aggregate summary statistics for intact perinatal survival rate from studies reporting on cases of vasa previa with prenatal diagnosis and those without prenatal diagnosis

Study	*Total*	*Intact survival rate*	*Weight (%)*
Pregnancies with prenatal diagnosis			
Francois (2003)[18]	8	8 (100.0 (63.1–100.0))	4.8
Oyelese (2004)[9]	61	57 (93.4 (84.1–98.2))	24.4
Smorgick (2010)[19]	10	9 (90.0 (55.5–99.7))	5.8
Kanda (2011)[10]	9	9 (100.0 (66.4–100.0))	5.3
Swank (2016)[20]	47	47 (100.0 (92.5–100.0))	20.4
Kulkarni (2018)[21]	33	33 (100.0 (89.4–100.0))	15.6
Sullivan (2017)[12]	58	56 (96.6 (88.1–99.6))	23.6
Pooled analysis (random effects)	226	219 (96.7 (93.6–98.8))	100.0
Cochran's Q (*P*)		7.3527 (0.2895)	
I^2 statistic (% (95% CI))		18.4 (0–65.7)	
Bias (*P*)		−0.5944 (0.3766)	
Pregnancies without prenatal diagnosis			
Francois (2003)[18]	5	4 (80.0 (28.4–99.5))	12.9
Oyelese (2004)[9]	94	17 (18.1 (10.9–27.4))	35.7
Smorgick (2010)[19]	9	2 (22.2 (2.8–60.0))	17.7
Kanda (2011)[10]	1	0 (0.0 (0.0–97.5))	5.5
Swank (2016)[20]	2	1 (50.0 (1.3–98.7))	7.7
Kulkarni (2018)[21]	2	0 (0.0 (0.0–84.2))	7.7
Sullivan (2017)[12]	5	1 (20.0 (0.5–71.6))	12.9
Pooled analysis (random effects)	118	25 (28.1 (14.1–44.7))	100.0
Cochran's Q (*P*)		9.9960 (0.1248)	
I^2 statistic (% (95% CI))		40 (0–73.4)	
Bias (*P*)		0.6967 (0.4866)	

Only first author is given for each study. Data given as *n* or *n* (% (95% CI)) unless indicated otherwise.

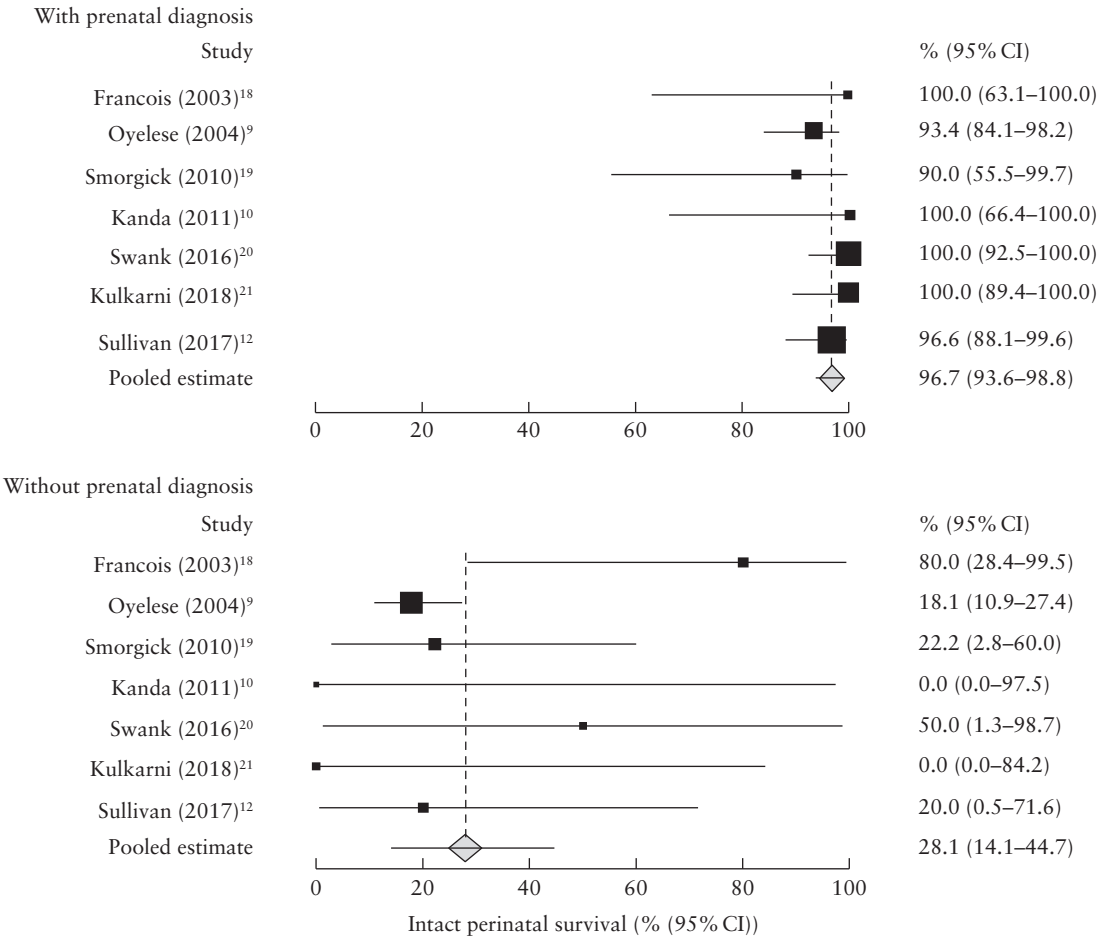

Figure 5 Forest plots showing summary statistics for incidence of intact perinatal survival derived using random-effects model in pregnancies with vasa previa diagnosed prenatally and those without prenatal diagnosis. Only first author is given for each study.

statistics with wider estimates of CIs that are more clinically generalizable. The adverse perinatal outcomes reported in the studies included in this systematic review could also potentially be secondary to causes other than vasa previa, such as fetal defects, but, given the low prevalence of these causes, it is unlikely that they affected the estimates of perinatal survival and 95% CIs reported in this study.

Implications for clinical practice

The results of our systematic review and meta-analysis provide unequivocal and clear evidence in favor of prenatal diagnosis for improving perinatal outcomes in pregnancies with vasa previa, and highlight and quantify the impact of a lack of prenatal diagnosis on stillbirths, hypoxic neonatal morbidity and mortality in these pregnancies. Our findings are consistent with those of previous studies that reported that prenatal diagnosis of vasa previa is associated with a high chance of a healthy perinatal outcome[9–12] compared with absence of antenatal diagnosis, which is associated with a high risk of stillbirth and neonatal death[8,9,11]. In addition to stillbirths and neonatal deaths, there is also evidence that a lack of prenatal diagnosis is associated with an increased risk of emergency Cesarean section as well as hypoxic morbidity in survivors, as evidenced by poor Apgar scores, low umbilical cord pH and a need for neonatal transfusion owing to anemia and hemorrhagic shock[9,12,21]. Therefore, failure to diagnose vasa previa prenatally is a considerable risk factor for perinatal morbidity and mortality.

The findings of this systematic review and meta-analysis provide a compelling argument in favor of prenatal diagnosis of vasa previa. It is imperative that further research be undertaken to investigate potential strategies to both classify pregnancies at high risk of vasa previa and identify cases with a confirmed prenatal diagnosis that could benefit from a structured plan for antenatal monitoring and delivery. A recent prospective study of more than 25 000 pregnancies examined the effectiveness of a two-stage screening program for vasa previa and reported that effective identification of pregnancies at high risk for vasa previa is feasible in a routine clinical setting and could lead to accurate prenatal diagnosis of the condition, which is associated with excellent perinatal outcomes[13]. Preventing perinatal death due to undiagnosed vasa previa in otherwise normal fetuses and neonates should be an important part of national and international strategies for the prevention of stillbirths and neonatal deaths.

Conclusions

Prenatal diagnosis of vasa previa is associated with a high rate of total and intact perinatal survival, whereas absence of antenatal diagnosis significantly increases the risk of perinatal death. Further research should be undertaken to investigate strategies for incorporating prenatal screening for vasa previa into routine clinical practice.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Methodological assessment of included studies based on Newcastle–Ottawa scale

Table S2 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist

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Resultado perinatal de los embarazos con diagnóstico prenatal de *vasa previa*: revisión sistemática y metaanálisis

RESUMEN

Objetivos Obtener estimaciones precisas de la supervivencia perinatal en los embarazos con y sin diagnóstico prenatal de vasa previa a partir de una revisión sistemática de la literatura y un metaanálisis.

Métodos Se realizó una búsqueda en MEDLINE, EMBASE y The Cochrane Library para revisar los estudios de las citas pertinentes que informasen sobre los resultados perinatales de embarazos con vasa previa. Se incluyeron estudios prospectivos y retrospectivos de cohortes y de poblaciones que proporcionaron datos sobre embarazos con un diagnóstico prenatal de vasa previa, o sobre casos diagnosticados en el momento del nacimiento o tras el examen postnatal de la placenta. Se realizó un metaanálisis utilizando un modelo de efectos aleatorios para obtener estimaciones combinadas ponderadas de la supervivencia perinatal (sin incluir el éxitus fetal y las muertes de recién nacidos) y de la supervivencia perinatal indemne (cuando se excluye además la morbilidad hipóxica). Se utilizó el metaanálisis de las diferencias en la tasa de incidencia (IRD, por sus siglas en inglés) para estimar la importancia de las diferencias en las proporciones combinadas entre los casos de vasa previa con y sin diagnóstico prenatal. La heterogeneidad entre estudios se estimó mediante la prueba Q de Cochran y la prueba estadística I2.

Resultados Se incluyeron 21 estudios que informaron sobre los resultados perinatales de 683 embarazos con un diagnóstico prenatal de vasa previa. Hubo tres casos de éxitus fetal (1,01% (IC 95%, 0,40–1,87%)), cinco muertes de recién nacidos (1,19% (IC 95%, 0,52–2,12%)) y 675 recién nacidos supervivientes, lo que dio lugar a una estimación combinada de la supervivencia perinatal del 98,6% (IC 95%, 97,6–99,3%). En función de los siete estudios que incluyeron casos de vasa previa con y sin un diagnóstico prenatal, la supervivencia perinatal combinada en los embarazos sin diagnóstico prenatal (61/118) fue del 72,1% (IC 95%, 50,6–89,4%), en comparación con el 98,6% (IC 95%, 96,7–99,7%) en los casos con diagnóstico prenatal (224/226). Por lo tanto, el riesgo de muerte perinatal fue 25 veces mayor cuando no se diagnosticó vasa previa prenatal, en comparación con cuando sí se hizo (razón de momios [RM], 25,39 (IC 95%, 7,93–81,31); $P < 0{,}0001$). De forma similar, el riesgo de morbilidad hipóxica se multiplicó por 50 en los casos con vasa previa sin diagnóstico prenatal, en comparación con los que sí que fue diagnosticado (36/61 frente a 5/224; RM, 50,09 (IC 95%, 17,33–144,79)). La tasa de supervivencia perinatal indemne en los casos de vasa previa sin un diagnóstico prenatal fue significativamente inferior a la de los casos con un diagnóstico prenatal (28,1% (IC 95%, 14,1–44,7%) frente a 96,7% (IC 95%, 93,6–98,8%)) (IRD, 73,4% (IC 95%, 53,9–92,7%); $Z = -7{,}4066$, $P < 0{,}001$).

Conclusiones El diagnóstico prenatal de vasa previa se asocia a una alta tasa de supervivencia perinatal, mientras que la falta de diagnóstico prenatal aumenta significativamente el riesgo de muerte perinatal y de morbilidad hipóxica. Se deben llevar a cabo más investigaciones para estudiar las estrategias para incorporar la detección prenatal de la vasa previa en la práctica clínica habitual.

妊娠期间被诊断为前置血管的围产期预后：系统评价和荟萃分析

摘要

<14>目的</14>基于文献和荟萃分析的系统评价，可以准确估算出有或没有产前诊断为前置血管的孕妇的围产期生存率。

<38>方法</38>对 MEDLINE，EMBASE 和 Cochrane 图书馆进行了检索，以审核有关妊娠期前置血管的围产期预后的相关引文报道。我们纳入了前瞻性和回顾性队列及人群研究，这些研究提供了有关妊娠期被诊断为前置血管或在出生时或出生后进行胎盘检查时确诊病例的数据。使用随机效应模型进行荟萃分析，以得出围产期存活率（不包括死产和新生儿死亡）和完整的围产期存活率（另外不包括低氧血症）的加权合并估计值。发病率差异（IRD）荟萃分析用于评估有或没有得到产前诊断的前置血管病例之间合并比例差异的重要性。研究之间的异质性是使用 Cochran 图书馆第一季度和第二季度统计数据估算的。

<140>结果</140>我们纳入了 21 项研究，报告了 683 例产前诊断为前置血管的围产期预后。有 3 例死产（1.01%（95%致信区间，0.40-1.87%）），5 例新生儿死亡（1.19%（95%置信区间，0.52-2.12%））和 675 例存活婴儿，因此，围产期存活率的综合估算为 98.6%（95%置信区间，97.6-99.3%）。基于七项研究，包括有或没有得到产前诊断的前置血管病例，未得到产前诊断的合并围产期存活率（61/118）为 72.1%（95%置信区间，50.6-89.4%）对比得到产前诊断的（224/226）病例（95%置信区间，96.7-99.7%）合并围产期存活率为 98.6%。因此，与产前确诊相比，那些产前未得到前置血管诊断的围产期死亡的风险要高 25 倍（优势比（OR），25.39（95%置信区间，7.93-81.31）；P <0.0001）。同样，与产前确诊的患者相比，未得到产前诊断的前置血管病例低氧血症的风险增加了 50 倍（36/61 对比 5/224；OR，50.09（95%置信区间，17.33-144.79））。未得到产前诊断的前置血管病例的完整围产期存活率显着低于那些有得到产前诊断的患者（28.1%（95%CI，14.1-44.7%）对比 96.7%（95%CI，93.6-98.8%））（IRD，73.4%（95%CI，53.9-92.7%）；Z = -7.4066，P <0.001）。

<290>结论</290>前置血管的产前诊断与围产期存活率高相关，而缺乏产前诊断会明显增加围产期死亡和低氧血症的风险。应该进行进一步的研究，以研究将前置血管的产前筛查纳入常规临床实践的策略。