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Timing of birth and adverse pregnancy outcomes in cases of prenatally diagnosed Vasa Previa: A systematic review and meta-analysis

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Condensation page

Condensation

This systematic review examines the risks of prematurity and of pregnancy prolongation in prenatally diagnosed vasa previa across deliveries at various gestational ages.

Short title

Timing of birth in cases of antenatally diagnosed vasa previa

AJOG at a glance

A. Why was this study conducted?

- The optimum time of delivery in pregnancies diagnosed with vasa previa is unclear
- Recommendations from individual studies differ, and guidelines suggest delivery within broad periods of 2-3 weeks

B. What are the key findings?

- The overall rate of complications in cases of prenatally diagnosed vasa previa decreased until 36 weeks and remained generally low thereafter.

C. What does this study add to what is already known?

- This is the only study that has analyzed the complications of vasa previa by each discrete gestational week at birth
- The findings of this study could add greater specificity to existing guidelines

Abstract

Objective: The ideal time of birth in pregnancies diagnosed with vasa previa remains unclear. We conducted a systematic review aiming to identify the gestational age of delivery that best balances the risks of prematurity and of pregnancy prolongation in cases of prenatally diagnosed vasa previa.

Data sources: Ovid MEDLINE, PubMed, CINAHL, EMBASE, SCOPUS and Web of Science were searched from inception to January 2022.

Study eligibility criteria (study design, populations, and interventions): The intervention analyzed was delivery at various gestational ages in pregnancies prenatally diagnosed with vasa previa. Cohort studies, case series and case reports were included in the qualitative synthesis. Where summary figures could not be obtained directly from the studies for the quantitative synthesis, authors were contacted and asked to provide a breakdown of perinatal outcomes by gestational age at birth.

Study appraisal and synthesis methods: Study appraisal was completed using the NIH quality assessment tool for respective studies. Statistical analysis was performed using random-effects meta-analysis of proportions.

Results: The search identified 3,435 studies, of which 1,264 were duplicates. After screening 2,171 titles and abstracts, 140 studies proceeded to the full text screen. 37 studies were included for analysis, 14 of which were included in a quantitative synthesis. Among 490 neonates, there were two perinatal deaths (0.4%), both of which were neonatal deaths below 32 weeks. In general, the rate of neonatal complications decreased steadily from <32 weeks (4.6% rate of

perinatal death, 91.2% respiratory distress, 11.4% 5-minute Apgar score <7, 23.3% neonatal blood transfusion, 100% neonatal intensive care unit (NICU) admission, 100% low birthweight) until 36 weeks (0% perinatal death, 5.3% respiratory distress, 0% 5-minue Apgar score <7, 2.9% neonatal blood transfusion, 29.2% NICU admission, 30.9% low birthweight). Complications then increased slightly at 37 weeks before decreasing again at 38 weeks.

Conclusions: Prolonging pregnancies until 36 weeks appears to be safe and beneficial in otherwise uncomplicated pregnancies with antenatally diagnosed vasa previa.

Key words: Vasa previa, fetal hemorrhage, cesarean, stillbirth, perinatal death, blood transfusion, prematurity, neonatal outcomes

Introduction

Vasa previa is an uncommon condition of pregnancy, affecting between 1 in 2,000 and 1 in 5,000 pregnancies,[1–9] although the true incidence is difficult to estimate as there are scarce reports in the literature. The most common risk factors for vasa previa include low-lying placenta (seen in 61.5% of diagnosed cases of vasa previa), pregnancies conceived via assisted reproduction techniques (28.2% of diagnosed cases) and multiple gestation (8.9% of diagnosed cases).[3,9] Vasa previa can be caused by velamentous cord insertions, coursing of vessels between a bilobed placenta or succenturiate lobe,[1] or when fetal vessels follow a 'boomerang' orbit.[10]

Pregnancies affected by vasa previa present a significant threat to the fetus. As the fetal blood vessels are embedded within the fetal membranes, rupture of the amniotic sac during (or prior to) labor can lead to fetal hemorrhage, exsanguination, and death.[1,4] Additionally, as the fetus descends into the pelvis, the pressure on the unsupported vessels can cause fetal asphyxia.[11] To reduce these complications, it is vital to make a diagnosis in the antenatal period. Oyelese *et al.* showed that the survival rate in cases of diagnosed vasa previa is approximately 97%, whereas in undiagnosed cases the survival rate is approximately 40%.[12] As such, some studies have recommended routine sonographic screening for vasa previa, especially in pregnancies with risk factors, such as low-lying placenta,[13–15] allowing for close monitoring and scheduling of an elective cesarean birth prior to membrane rupture.[16]

Whilst delivering the fetus before membrane rupture is key to the management of vasa previa, it is also important to consider that neonates delivered at earlier gestations are more likely to be affected by complications of prematurity. The safest time to deliver should hence be considered the gestation that most appropriately balances the risks of prematurity with the risks

associated with the onset of labor. The ideal window of delivery remains unclear, and recommendations differ. Some observational studies have suggested delivery as early as 33 weeks,[17] whilst others have proposed that birth can potentially wait until 37 weeks.[18–20] Additionally, a purely theoretical decision-tree analysis advocated that scheduled delivery at 34-35 weeks would result in the highest quality-adjusted life-years.[21] Guidelines from leading institutions are largely based upon experts' opinion and similarly do not have consistent recommendations; they also generally suggest delivery within a broad window of 2-3 weeks.[11,16,22] This breadth allows ample room for interpretation, and could result in delivery at either late-preterm or early-term gestations, each of which carries a unique set of risks. This highlights the need for a more specific, evidence-based recommendation for timing of delivery in pregnancies diagnosed with vasa previa.

In this systematic review, we aimed to identify the gestational age at which the rate of perinatal complications was the lowest, which is likely to represent the safest time to deliver in pregnancies affected by vasa previa.

Methods

We conducted a systematic review of studies with prenatally diagnosed vasa previa. The protocol of this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42020186416) and the results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[23]

Eligibility criteria, information sources and search strategy

Given the rarity of vasa previa, study included in this review were cohort studies, case series and case reports. Due to the limited literature on neonatal outcomes from pregnancies affected

by vasa previa, conference abstracts were not strictly excluded from eligibility criteria; however, they were excluded if they were too brief to draw relevant conclusions from or did not contain enough data on outcomes of interest. Studies were only included if they were available in English and if they were human studies. Studies only proceeded to the quantitative synthesis if they had more than five cases and a detailed breakdown of complications by gestational age was available.

A systematic search of Ovid MEDLINE, PubMed, CINAHL, EMBASE, SCOPUS and Web of Science databases from inception to January 2022 was performed to identify studies that analyzed prenatally diagnosed cases of vasa previa and neonatal outcomes. Reference lists of relevant studies were also searched to identify any additional studies that may not have been captured in the initial searches.

A combination of medical subject headings (MeSH) terms and key terms and variants of prenatally diagnosed, vasa previa, delivery, cesarean and outcomes were searched in the aforementioned databases. Variations of search teams were combined with the Boolean operator 'OR', and the different elements of the PICO (Population, Intervention, Comparator and Outcome) framework were combined with the Boolean operator 'AND'. The complete search strategy is included in Appendix A.

Study Selection

The study selection process was performed using Covidence systematic review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). After duplicates were removed, two independent reviewers (GN and SM) screened the title and abstract of each study for eligibility; studies that were mutually considered relevant, as well as

any conflicts, proceeded to the next stage of screening. Full texts of these papers were then assessed for eligibility by the same two independent reviewers, with strict adherence to the pre-defined inclusion and exclusion criteria. Disagreements were discussed, and any persistent conflicts were resolved through discussion with a third reviewer (DLR).

Papers from the qualitative synthesis were excluded from the quantitative synthesis if they had a sample size less than five, as the presence of outcomes in studies with smaller sample sizes were likely to cause overly significant shifts in proportions.[24] Where data breakdown by gestational age was not reported, authors were contacted, and further data was requested. As per the eligibility criteria, if sufficient data could not be obtained, the paper was excluded from the quantitative analysis.

Data Extraction

Two authors (GN and SM) independently extracted author names, year of publication, study design, sample sizes and outcomes directly from papers. Additionally, for the quantitative synthesis, the counts of relevant outcomes at each gestational age were also extracted, either directly from the paper or from a raw data set requested from authors. Gestational ages were grouped as: <32 weeks, 32 weeks (i.e., 32+0 to 32+6), 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, and 38 weeks or later. Once the extraction was complete, the spreadsheets were then directly cross-checked between the two authors to identify any discrepancies; these were resolved through consensus among the authors.

Assessment of Risk of Bias

The quality assessment was completed using the NIH Study Quality Assessment Tools, as recommended by Ma *et al.* for non-randomized studies.[25] The tool for observational cohort and

cross-sectional studies was used for cohort studies, and the tool for case series was used for both case series and case reports. These checklists were completed by two independent reviewers (GN and SM) and compared. Discrepancies were again resolved through discussion. Study quality was globally rated as poor, fair, or good.

Outcomes of Interest and Data Synthesis

Data extracted from each study for the quantitative analysis included the total number of neonates delivered at each gestational age and the number of neonates with the outcomes of interest These included perinatal mortality, respiratory distress syndrome (RDS) requiring intubation, Apgar scores <7 at five minutes, neonatal intensive care unit (NICU) admission, low birthweight (<2500 grams), and neonatal blood transfusions. We then analyzed the aggregate rates of each outcome of interest overall and per gestational age. Pooled proportions of different adverse pregnancy outcomes, overall and stratified by gestational age, were calculated with random-effects models using inverse-variance weights and the arcsine transformation to achieve stabilization of the variances. Publication bias was investigated by inspection of funnel plots and the Egger's test for outcomes reported by ten studies or more. Finally, we performed sensitivity analysis of the aggregate rates of adverse pregnancy outcomes including only studies considered of good quality, to investigate the impact of studies at high risk of bias on the results. Analyses were conducted with the package metafor in the statistical software R.[26]

Results

Study Selection

A total of 3,435 studies were identified through the search, of which 1,264 were duplicates. After screening 2,171 titles and abstracts, 140 studies were deemed potentially relevant and

were included in the full text screen, although nine reports could not be retrieved. A further 94 were then excluded due to inconsistency with the pre-defined eligibility criteria or irrelevance. This left 37 studies to be included in the systematic review. The study selection process is presented in Figure 1, and the characteristics of included studies are included in Supplementary Table 1.

Three studies were excluded from the quantitative synthesis as they had a study sample less than five.[27–29] Of the remaining 34 studies, four presented a data breakdown by gestational age.[1,18,19,30] The remaining 30 studies only reported the total incidence of complications across all deliveries, and did not specify the gestational age that they occurred at.[2,4,7,12–14,17,20,31–52] Authors of these papers were contacted to request the breakdown of complications by gestational age. Nineteen authors either could not be contacted, did not respond, or did not have the data that we requested available.[2,4,7,12,13,14,32–35,42,44–46,48–52] 11/03/2022 22:35:00 The corresponding author of one study[39] reported that their data was included in another, larger study,[31] so this was treated as a duplicate and was removed from the quantitative synthesis. Ten sets of raw, stratified data were obtained from corresponding authors.[17,20,31,36–38,40,41,43,47] Hence, 14 studies were included in the quantitative synthesis.[1,17–20,30,31,36–38,40,41,43,47]

Risk of bias

In total, there were three case reports, 21 case series and 13 cohort studies. The scoring and overall rating of the studies is shown in Supplementary Tables 2A and 2B.

In terms of case series and case reports, the criterion that was consistently poor was the use of statistical analysis; however, reviewers believed that this was not necessary in most cases, given the small sample sizes and the descriptive nature of the series. Fifteen of the 21 case

series were rated as 'good,' and six were rated as 'fair.' All three case reports were rated as 'fair'.

There were some criteria that were consistently not applicable to cohort studies. These included variation in amount or level as an exposure (as one can only have vasa previa or not), whether outcome assessors were blinded (as most studies were retrospective) and whether there was a sample size justification (this was considered unnecessary as most studies included all consecutive cases within a reasonable period). Overall, six cohort studies were rated as 'good', and seven were rated as 'fair'.

There was difficulty in assessing the overall quality of conference abstracts, due to the lack of essential information for this. For this reason, it was difficult for the global assessments of conference abstracts to exceed 'fair.'

Qualitative synthesis

The most commonly reported outcomes included perinatal mortality,[4,7,12–14,18,19,27–43,45–52] respiratory distress syndrome (RDS) requiring intubation,[12,14,27,30,33,34,36–38,40,41,46] 5-minute Apgar scores <7,[1,2,12,14,18,19,27–29,31–43,45–48,50] requirement of blood transfusion to the neonate,[4,7,12,14,19,31–34,36–38,40,41,43–45,48,50] NICU admission,[4,7,14,19,28,29,31,32,36–41,43,45–49] and low birthweight.[1,2,14,18–20,27–29,32,33,37,38,40,41,43,45–49,51]

The number of cases of vasa previa in the included studies ranged from two to 586 with a mean of 63.7 and a median of 23. Three of the 37 studies were prospective, of which two were case series and one was a cohort study.[1,13,32] Broadly, cohort studies that compared outcomes of prenatally diagnosed vasa previa with vasa previa undiagnosed prenatally reported a reduced

risk of neonatal mortality among diagnosed cases.[12,20,35,46] Studies comparing women without vasa previa to women with vasa previa demonstrated an increased risk of neonatal mortality, RDS requiring intubation and need for neonatal blood transfusions. Perinatal mortality ranged from 0% to 16.6% in the studies analyzing prenatally diagnosed vasa previa. NICU admission was a common event for neonates delivered from pregnancies affected by vasa previa, with the rates ranging from 53.5% to 100%.

Other complications of prematurity were also included in a small number of studies. Six studies reported on IVH (0 – 16.7%),[1,17,34,38,41,46] two studies reported on cases of bronchopulmonary dysplasia (0.02 – 8.7%),[38,48] and five studies reported cases of necrotizing enterocolitis (0 – 8.7%).[1,17,38,41,48] However, there was not enough data available to perform a quantitative analysis on these neonatal outcomes.

Of the 37 included studies, 14 provided recommendations on the timing of delivery, which ranged from 33 to 37 weeks. The most common recommendations were 34 to 35 weeks [30,33,42] and 35 weeks.[7,12,29] Only one study suggested delivery earlier than this at 33 to 34 weeks.[17] Broader recommendations included 34 to 36 weeks,[46] 34 to 37 weeks,[20] and 35 to 37 weeks.[18,19] 35 to 36 weeks[14,40] and 36 weeks[32] were also proposed by some other studies.

To note, while all studies largely defined vasa previa as fetal vessels running unprotected over or close to the internal cervical os, four studies defined the distance of the fetal vessels to the internal cervical os explicitly.[13,14,33,36,45–47] Six studies defined vasa previa as fetal vessels within 2 cm of the cervical os, and the last defined close proximity as within a distance of 4 cm.

Quantitative synthesis

A total of 490 neonates were included across the 14 studies for analysis. This included 44 (9.0%) neonates born at less than 32 weeks, 20 (4.1%) at 32 weeks, 34 (6.9%) at 33 weeks, 122 (24.9%) at 34 weeks, 145 (29.6%) at 35 weeks, 80 (16.3%) at 36 weeks, 33 (6.7%) at 37 weeks and 12 (2.4%) at 38 weeks or later. Figure 2 demonstrates the unweighted pooled rates of perinatal complications, whilst Supplementary Table 3 summarizes the rates (numerically) of different perinatal complications. Supplementary Figure 1(A–E) presents the forest plots of the inverse-variance weighted proportions of morbidity outcomes overall, and Supplementary Figure 2(A–E) by gestational age at birth. Meta-analyses were not possible for the outcome of perinatal mortality given the low number of events.

There was no evidence of publication bias for the outcomes of respiratory distress requiring intubation, Apgar < 7 at five minutes, low birthweight, and blood transfusion (Egger's test p-values 0.196, 0.833, 0.132 and 0.817, and Supplementary Figures 3A, 3B, 3D and 3E, respectively). There was some evidence of small study effects for the outcome of NICU admission, with a tendency towards smaller studies reporting lower rates of NICU admission (Egger's test p-value 0.033, Supplementary Figure 3C). A sensitivity analysis restricted to good quality studies showed similar trends to those of the main analysis (Supplementary Table 4 and Supplementary Figure 4).

<u>Perinatal mortality</u>

There were two cases of perinatal mortality, both of which occurred below 32 weeks of gestation due to complications of prematurity (4.6% of births in this age bracket). The cumulative incidence of perinatal death after the diagnosis of vasa previa was 4.1 in 1,000 (95% confidence interval [CI] 0.5 to 14.7 in 1,000).

Respiratory Distress Syndrome requiring intubation

The highest rate of RDS was unsurprisingly amongst neonates born <32 weeks of gestation, with an incidence of 91.2%. RDS affected 47.1% of neonates born at 32 weeks, 44.0% at 33 weeks, 27.5% at 34 weeks and 21.1% at 35 weeks. This further decreased to 5.3% at 36 weeks (5.7%), rose to 16.7% at 37 weeks and then decreased again to 0.0% at 38 weeks or later.

Apgar <7 at five minutes

The highest rate of Apgar scores <7 at five minutes occurred at 33 weeks of gestation (14.7%). In contrast, the lowest rate was at 36 weeks and 38 weeks or later (both 0%). The incidence of five-minute Apgar scores <7 at other gestations was 11.4% at less than 32 weeks, 10.0% at 32 weeks, 4.2% at 34 weeks, 4.2% at 35 weeks, and 9.1% at 37 weeks.

NICU Admission

All neonates born before or at 32 weeks required an admission to NICU. The lowest rate of NICU admission was 0.0% at 38 weeks or later, followed by 29.2% at 36 weeks. Other rates of NICU admission included 94.1% at 33 weeks, 86.9% at 34 weeks, 64.7% at 35 weeks and 31.8% at 37 weeks.

Low birthweight

All neonates delivered at <32 weeks and at 32 weeks were of low birthweight. This steadily declined at each subsequent gestational week to 90.5% at 33 weeks, 84.1% at 34 weeks, 48.3% at 35 weeks, 30.9% at 36 weeks, 16.7% at 37 weeks and 0.0% at 38 weeks.

Neonatal blood transfusion

The highest incidence of transfusions occurred at <32 weeks (23.3%). Neonatal blood transfusion at other gestations was relatively uncommon, with incidence of 0.0% at 32 weeks, 5.9% at 33 weeks, 0.9% at 34 weeks, 2.2% at 35 weeks, 2.9% at 36 weeks, 3.6 % at 37 weeks and a slight rise to 8.3% at 38 weeks or later.

Comment

Principal findings

In this systematic review, we analyzed 37 studies. The qualitative synthesis identified relevant neonatal outcomes relating to vasa previa, including perinatal mortality, RDS, five-minute Apgar scores <7, NICU admissions, low birthweight, and requirement of neonatal blood transfusion; other complications of prematurity (including IVH, BPD and NEC) were less commonly reported neonatal outcomes. Moreover, the qualitative synthesis reiterated the importance of a prenatal diagnosis of vasa previa.

Fourteen studies were included in the quantitative synthesis to investigate the gestational age with the lowest rate of complications. This analysis found a downward trend in the rate of complications until 36 weeks; this gestational age saw no perinatal deaths or 5-minute Apgar scores <7, low rates of RDS (5.3%) and blood transfusion (2.9%), and relatively low rates of NICU admission (29.2%) and low birthweight (30.9%). At 37 weeks, the rates of most complications slightly increased again (RDS, 5-minute Apgar <7, blood transfusions, and NICU admission), but remained generally low. The lowest absolute risk of complications appeared to be at 38 weeks or later, where the rate of all complications was 0.0%, except for neonatal blood transfusion (8.3%). However, it must be considered that there was only a small number of neonates born after 38 weeks (n = 12), which was likely due to guidelines suggesting delivery prior to this time. The small sample size at 38 weeks and later significantly limits the

reliability of conclusions about the rates of adverse outcomes at these gestational ages; hence, it cannot be confidently stated that delivery at this time is safe. Given the decrease in complications until 36 weeks and small increase in complications at 37 weeks, this may suggest that waiting until late preterm may be the best time to deliver in otherwise uncomplicated pregnancies with prenatally diagnosed vasa previa.

In total, there were two neonatal deaths (0.4% of all neonates in this study), both of which were due to complications of prematurity. Since we only included cases of vasa previa with prenatal diagnosis, the low rate of perinatal mortality is in line with previous studies demonstrating much lower death rates in cases diagnosed prenatally as compared to those without prenatal diagnosis.[12]

When examining the 'safest' time to deliver in cases of prenatally diagnosed vasa previa, it is also important to consider the individual patient. For example, some women may be at higher risk of preterm premature rupture of membranes (PPROM) than others; a relevant predictor of PPROM is short cervical length, which can be assessed using transvaginal ultrasound.[53] Hence, this relatively simple assessment could provide valuable patient-specific information on the risk of fetal vessel rupture at earlier gestational ages, and subsequently guide timing of delivery.[54] Recent literature has also suggested elective hospitalization of women in the weeks prior to planned delivery, which would allow for closer monitoring for signs of preterm labor and timely access to emergency cesarean if indicated.[55] However, data to endorse this as standard practice is lacking, and the cost-effectiveness of this strategy has not been adequately explored.[11]

Comparison with existing literature

There have been some recent systematic reviews on vasa previa which have explored risk factors and neonatal outcomes in cases of vasa previa.[3,56,57] This review differs from these as we examined a broader range of outcomes and included both a qualitative and quantitative synthesis.

We found 14 studies that provided recommendations on timing of delivery in cases of vasa previa. Suggestions ranged from as early as 33 to 34 weeks,[17] up until 37 weeks.[18–20] Half of the 14 studies recommended delivery at 35 weeks or earlier.[7,12,17,29,30,33,42] One study recommended 36 weeks.[32] The remaining studies proposed a window of time that extended to at least 36 weeks, but also included gestations at 35 weeks or prior.[14,18–20,40,46] Our data suggests that it is generally safe and beneficial to prolong otherwise uncomplicated pregnancies with a diagnosis of vasa previa to at least 36 weeks, slightly more than most recommendations made by previous studies.

Another important resource to compare these findings to are current guidelines. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) both recommend birth at 34 to 37 weeks, and the Royal College of Obstetricians and Gynaecologists (UK) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommend delivery at 34 to 36 weeks.[11,16,22] Given the lack of large studies to base these recommendations upon, most guidelines rely on experts' consensus of a gestational age period at which the rates of adverse neonatal outcomes are usually low in high-resource settings. Our finding of relatively low complication rates at 36 weeks supports these guidelines and could also add greater specificity.

Strengths and limitations

Existing literature on this topic commonly analyzed the cohort as a whole and reported mean event rates. This study was unique as it analyzed the rate of complications at each discrete gestational age, as well as the trends in these adverse outcomes. To the best of our knowledge, no study has stratified neonatal outcomes in cases of vasa previa by gestational age in order to find the age with the lowest rate of complications.

There were also weaknesses to this study. As the incidence of vasa previa is low, there is only limited literature available. Although this study combined results of many previous studies, the stratified data from some of the largest studies could not be obtained. This left us with a relatively small sample (490 cases) to obtain reliable estimates, and potentially introduced some bias into our results. Future studies should hence focus on prospective data collection through multicenter collaborations to increase confidence, with clear and uniform criteria for vasa previa diagnosis.

When interpreting these results, it is important to consider that not all outcomes are equal in severity, and that individual patients would likely have differing opinions on which risks (prematurity or vasa previa) they are most accepting of. However, the rates of all complications seem to be well balanced at 36–36+6 weeks, minimizing the need for subjective data interpretation. Moreover, long-term outcomes were not reported, and hence could not be accounted for in this study. For example, neonates born with RDS are at risk of developing bronchopulmonary dysplasia.[16] Prolonged fetal anemia, which could be secondary to preterm delivery or fetal hemorrhage, can lead to ischemic brain lesions and, consequently, neurodevelopmental delay or other forms of disability.[58] These could form further important considerations women and clinicians may have in the decision-making for timing of birth.

As the data that we received from authors was aggregate patient data, we were unable to obtain the indications for delivery, including whether the delivery was planned or emergent. This is a limitation to our study, as emergent or medical indications for earlier delivery may bias the data towards more complications. Subgroup analysis examining emergent delivery, and the specific indications, prior to planned deliveries would have been valuable but was not possible in this review. Formal meta-analysis techniques were used to consider clustering, as well as intra- and between-study variability in the calculation of weights and in the assessment of statistical heterogeneity. Further adjustments for clustering are only possible in individual participant data meta-analyses, which was outside the scope of this study. It was also unclear which particular management protocols were being followed in most studies. We acknowledge that the comparison of management protocols could also have been of great interest, but we lacked the data to do so.

This study only analyzed pregnancies that had been diagnosed prenatally. One of the most significant prognostic markers for poor neonatal outcomes in pregnancies affected by vasa previa is the lack of a prenatal diagnosis; these pregnancies are likely to be prolonged until the labor occurs spontaneously, or birth is indicated for other reasons, which places the fetus at high risk of exsanguination. Unfortunately, the benefits of screening the general population remain unclear and routine antenatal screening is currently not performed in many settings.[16] However, with advances in ultrasound technology and guidelines for more thorough evaluation of high-risk pregnancies, many cases are still able to be identified.[16,58]

Conclusions

In otherwise uncomplicated cases of prenatally diagnosed vasa previa, perinatal mortality is low, and it seems safe and beneficial to prolong pregnancy until 36 weeks. Given the possible

435 small increase in complications at term, 36–36+6 weeks may represent the gestational age that
436 best balances the risks of complications from vasa previa and prematurity.

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Figure legends

Figure 1: PRISMA flow diagram

Figure 2: Pooled rates of respiratory distress syndrome requiring intubation, Apgar score <7 at five minutes, NICU admission, low birthweight, blood transfusion and perinatal death (Numbers and percentages provided in Supplementary Table 3)

Appendix A: Search strategy

Supplementary Table 1. Table of Included Studies

Supplementary Table 2. NIH Study Quality Assessments. A. Cohort studies; B. Case series and case reports

Supplementary Table 3. Rates of perinatal morbidity and mortality according to gestational age at birth in cases of prenatally diagnosed vasa previa

Supplementary Table 4. Rates of perinatal morbidity and mortality according to gestational age at birth in cases of prenatally diagnosed vasa previa. Sensitivity analysis restricted to studies considered of good quality / low risk of bias.

Supplementary Figure 1. Forest plots presenting meta-analyses of the overall proportions with random effects models and including studies with at least five cases of prenatally diagnosed vasa previa. A: Respiratory distress syndrome requiring intubation at birth; B: Apgar scores <7 at five minutes; C: Neonatal intensive care unit (NICU) admission; D: Low birthweight; E: Neonatal blood transfusion.

Supplementary Figure 2. Forest plots presenting meta-analyses of proportions with random effects models and including studies with at least five cases of prenatally diagnosed vasa previa. A: Respiratory distress syndrome requiring intubation at birth; B: Apgar scores <7 at five

minutes; C: Neonatal intensive care unit (NICU) admission; D: Low birthweight; E: Neonatal blood transfusion.

Supplementary Figure 3. Funnel plots of different adverse perinatal outcomes. A: Respiratory distress syndrome requiring intubation at birth (Egger's test p-value 0.196); B: Apgar scores <7 at five minutes (p-value 0.833); C: Neonatal intensive care unit (NICU) admission (p-value 0.033); D: Low birthweight (p-value 0.132); E: Neonatal blood transfusion (p-value 0.817).

Supplementary Figure 4. Pooled rates of respiratory distress syndrome requiring intubation, Apgar score <7 at five minutes, NICU admission, low birthweight, blood transfusion and perinatal death. Sensitivity analysis restricted to studies considered of good quality / low risk of bias.