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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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1 **Condensation page**

2 **Condensation**

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

5

6 **Short title**

7 Timing of birth in cases of antenatally diagnosed vasa previa

8

9 **AJOG at a glance**

10 A. Why was this study conducted?

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

14

15 B. What are the key findings?

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

18

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

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

23 **Abstract**

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

28

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

31

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

38

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

42

43 **Results:** The search identified 3,435 studies, of which 1,264 were duplicates. After screening
44 2,171 titles and abstracts, 140 studies proceeded to the full text screen. 37 studies were included
45 for analysis, 14 of which were included in a quantitative synthesis. Among 490 neonates, there
46 were two perinatal deaths (0.4%), both of which were neonatal deaths below 32 weeks. In
47 general, the rate of neonatal complications decreased steadily from <32 weeks (4.6% rate of

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

53

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

56

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

59

60 Introduction

61 Vasa previa is an uncommon condition of pregnancy, affecting between 1 in 2,000 and 1 in
62 5,000 pregnancies,¹⁻⁹ although the true incidence is difficult to estimate as there are scarce
63 reports in the literature. The most common risk factors for vasa previa include low-lying
64 placenta (seen in 61.5% of diagnosed cases of vasa previa), pregnancies conceived via assisted
65 reproduction techniques (28.2% of diagnosed cases) and multiple gestation (8.9% of diagnosed
66 cases).^{3,9} Vasa previa can be caused by velamentous cord insertions, coursing of vessels
67 between a bilobed placenta or succenturiate lobe,¹ or when fetal vessels follow a ‘boomerang’
68 orbit.¹⁰

69
70 Pregnancies affected by vasa previa present a significant threat to the fetus. As the fetal blood
71 vessels are embedded within the fetal membranes, rupture of the amniotic sac during (or prior
72 to) labor can lead to fetal hemorrhage, exsanguination, and death.^{1,4} Additionally, as the fetus
73 descends into the pelvis, the pressure on the unsupported vessels can cause fetal asphyxia.¹¹ To
74 reduce these complications, it is vital to make a diagnosis in the antenatal period. Oyelese *et*
75 *al.* showed that the survival rate in cases of diagnosed vasa previa is approximately 97%,
76 whereas in undiagnosed cases the survival rate is approximately 40%.¹² As such, some studies
77 have recommended routine sonographic screening for vasa previa, especially in pregnancies
78 with risk factors, such as low-lying placenta,¹³⁻¹⁵ allowing for close monitoring and scheduling
79 of an elective cesarean birth prior to membrane rupture.¹⁶

80
81 Whilst delivering the fetus before membrane rupture is key to the management of vasa previa,
82 it is also important to consider that neonates delivered at earlier gestations are more likely to
83 be affected by complications of prematurity. The safest time to deliver should hence be
84 considered the gestation that most appropriately balances the risks of prematurity with the risks

85 associated with the onset of labor. The ideal window of delivery remains unclear, and
86 recommendations differ. Some observational studies have suggested delivery as early as 33
87 weeks,¹⁷ whilst others have proposed that birth can potentially wait until 37 weeks.¹⁸⁻²⁰
88 Additionally, a purely theoretical decision-tree analysis advocated that scheduled delivery at
89 34-35 weeks would result in the highest quality-adjusted life-years.²¹ Guidelines from leading
90 institutions are largely based upon experts' opinion and similarly do not have consistent
91 recommendations; they also generally suggest delivery within a broad window of 2-3
92 weeks.^{11,16,22} This breadth allows ample room for interpretation, and could result in delivery at
93 either late-preterm or early-term gestations, each of which carries a unique set of risks. This
94 highlights the need for a more specific, evidence-based recommendation for timing of delivery
95 in pregnancies diagnosed with vasa previa.

96

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

100

101 **Methods**

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

106

107 **Eligibility criteria, information sources and search strategy**

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

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

116

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

122

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

129

130 **Study Selection**

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

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

139

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

146

147 **Data Extraction**

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

156

157 **Assessment of Risk of Bias**

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

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

164

165 **Outcomes of Interest and Data Synthesis**

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

180

181 **Results**

182 **Study Selection**

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

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

190

191 Three studies were excluded from the quantitative synthesis as they had a study sample less
192 than five.²⁷⁻²⁹ Of the remaining 34 studies, four presented a data breakdown by gestational
193 age.^{1,18,19,30} The remaining 30 studies only reported the total incidence of complications across
194 all deliveries, and did not specify the gestational age that they occurred at.^{2,4,7,12-14,17,20,31-52}
195 Authors of these papers were contacted to request the breakdown of complications by
196 gestational age. Nineteen authors either could not be contacted, did not respond, or did not have
197 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
198 corresponding author of one study³⁹ reported that their data was included in another, larger
199 study,³¹ so this was treated as a duplicate and was removed from the quantitative synthesis. Ten
200 sets of raw, stratified data were obtained from corresponding authors.^{17,20,31,36-38,40,41,43,47}
201 Hence, 14 studies were included in the quantitative synthesis.^{1,17-20,30,31,36-38,40,41,43,47}

202

203 **Risk of bias**

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

206

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

210 series were rated as ‘good,’ and six were rated as ‘fair.’ All three case reports were rated as
211 ‘fair’.

212

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

219

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

223

224 **Qualitative synthesis**

225 The most commonly reported outcomes included perinatal mortality,^{4,7,12–14,18,19,27–43,45–52}
226 respiratory distress syndrome (RDS) requiring intubation,^{12,14,27,30,33,34,36–38,40,41,46} 5-minute
227 Apgar scores <7,^{1,2,12,14,18,19,27–29,31–43,45–48,50} requirement of blood transfusion to the
228 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
229 birthweight.^{1,2,14,18–20,27–29,32,33,37,38,40,41,43,45–49,51}

230

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

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

241

242 Other complications of prematurity were also included in a small number of studies. Six studies
243 reported on IVH (0 – 16.7%),^{1,17,34,38,41,46} two studies reported on cases of bronchopulmonary
244 dysplasia (0.02 – 8.7%),^{38,48} and five studies reported cases of necrotizing enterocolitis (0 –
245 8.7%).^{1,17,38,41,48} However, there was not enough data available to perform a quantitative
246 analysis on these neonatal outcomes.

247

248 Of the 37 included studies, 14 provided recommendations on the timing of delivery, which
249 ranged from 33 to 37 weeks. The most common recommendations were 34 to 35 weeks^{30,33,42}
250 and 35 weeks.^{7,12,29} Only one study suggested delivery earlier than this at 33 to 34 weeks.¹⁷
251 Broader recommendations included 34 to 36 weeks,⁴⁶ 34 to 37 weeks,²⁰ and 35 to 37 weeks.^{18,19}
252 35 to 36 weeks^{14,40} and 36 weeks³² were also proposed by some other studies.

253

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

259

260 **Quantitative synthesis**

261 A total of 490 neonates were included across the 14 studies for analysis. This included 44
262 (9.0%) neonates born at less than 32 weeks, 20 (4.1%) at 32 weeks, 34 (6.9%) at 33 weeks, 122
263 (24.9%) at 34 weeks, 145 (29.6%) at 35 weeks, 80 (16.3%) at 36 weeks, 33 (6.7%) at 37 weeks
264 and 12 (2.4%) at 38 weeks or later. Figure 2 demonstrates the unweighted pooled rates of
265 perinatal complications, whilst Supplementary Table 3 summarizes the rates (numerically) of
266 different perinatal complications. Supplementary Figure 1(A–E) presents the forest plots of the
267 inverse-variance weighted proportions of morbidity outcomes overall, and Supplementary
268 Figure 2(A–E) by gestational age at birth. Meta-analyses were not possible for the outcome of
269 perinatal mortality given the low number of events.

270

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

279

280 Perinatal mortality

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

285

286 Respiratory Distress Syndrome requiring intubation

287 The highest rate of RDS was unsurprisingly amongst neonates born <32 weeks of gestation,
288 with an incidence of 91.2%. RDS affected 47.1% of neonates born at 32 weeks, 44.0% at 33
289 weeks, 27.5% at 34 weeks and 21.1% at 35 weeks. This further decreased to 5.3% at 36 weeks
290 (5.7%), rose to 16.7% at 37 weeks and then decreased again to 0.0% at 38 weeks or later.

291

292 Apgar <7 at five minutes

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

297

298 NICU Admission

299 All neonates born before or at 32 weeks required an admission to NICU. The lowest rate of
300 NICU admission was 0.0% at 38 weeks or later, followed by 29.2% at 36 weeks. Other rates
301 of NICU admission included 94.1% at 33 weeks, 86.9% at 34 weeks, 64.7% at 35 weeks and
302 31.8% at 37 weeks.

303

304 Low birthweight

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

308

309 Neonatal blood transfusion

310 The highest incidence of transfusions occurred at <32 weeks (23.3%). Neonatal blood
311 transfusion at other gestations was relatively uncommon, with incidence of 0.0% at 32 weeks,
312 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
313 and a slight rise to 8.3% at 38 weeks or later.

314

315 **Comment**

316 **Principal findings**

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

323

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

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

340

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

346

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

358

359 **Comparison with existing literature**

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

364

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

373

374 Another important resource to compare these findings to are current guidelines. The American
375 College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal
376 Medicine (SMFM) both recommend birth at 34 to 37 weeks, and the Royal College of
377 Obstetricians and Gynaecologists (UK) and the Royal Australian and New Zealand College of
378 Obstetricians and Gynaecologists (RANZCOG) recommend delivery at 34 to 36 weeks.^{11,16,22}
379 Given the lack of large studies to base these recommendations upon, most guidelines rely on
380 experts' consensus of a gestational age period at which the rates of adverse neonatal outcomes
381 are usually low in high-resource settings. Our finding of relatively low complication rates at
382 36 weeks supports these guidelines and could also add greater specificity.

383

384 **Strengths and limitations**

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

390

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

398

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

409

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

422

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

431

432 **Conclusions**

433 In otherwise uncomplicated cases of prenatally diagnosed vasa previa, perinatal mortality is
434 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.