Effect of delayed interval delivery of remaining fetus(es) in multiple pregnancies on survival

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Title page

Title: Effect of delayed interval delivery of remaining fetus(es) in multiple pregnancies on survival: a systematic review and meta-analysis

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33 **Condensation, Short Title, AJOG at a Glance, and Keywords**

34 **Condensation:**

35 Compared with immediate delivery, delayed interval delivery improves the survival of

36 remaining fetus(es) in multiple pregnancy.

37

38 **Short Title:**

39 Delayed interval delivery in multiple pregnancy

40

41 **AJOG at a Glance:**

42 Why was this study conducted?

43 A. Multiple pregnancy increases the risk of periviable preterm birth which is

44 associated with significant neonatal morbidity and mortality.

45 B. This systematic review and meta-analysis evaluated whether delayed interval

46 delivery improves the survival of the remaining fetus(es) in multiple pregnancy.

47

48 Key Findings

49 A. Delayed interval delivery is an effective management option to increase the

50 perinatal survival of the remaining fetus(es), but about 39% of women may

51 experience serious morbidity including local infection/sepsis, chorioamnionitis,

hemorrhage, placental abruption and hysterectomy.

What does this add to what is known?

A. Obstetricians should be aware that delayed interval delivery is an effective management option to improve survival of remaining fetus(es) for women with multiple pregnancy who deliver the first fetus between 13 to 31 weeks of gestation.

Keywords

Antibiotics; cerclage; dichorionic; monochorionic; preterm birth; preterm delivery; triplet; twin

Abstract:

Background

The management of the pregnancy after delivery of the first fetus during second trimester miscarriage or very early preterm birth has not been well defined.

Objective

To evaluate whether delayed interval delivery of the remaining fetus(es) in twins/triplets is associated with improved survival, when compared with immediate delivery, after miscarriage or very preterm birth of the first fetus in multiple pregnancy.

Data sources

PubMed, MEDLINE and Cochrane Library were systematically searched through January 2019.

Study eligibility criteria (study design, populations, and interventions)

The following eligibility criteria applied: full-text original article; included at least five cases of delayed interval delivery for remaining fetus(es); reported the survival rate of the first born and the remaining fetus(es).

Study appraisal and synthesis methods

K.W.C. and W.W. searched, screened and reviewed the articles. The quality of the studies was assessed according to the 'Strengthening the Reporting of Observational studies in Epidemiology' checklist. If possible data were stratified for assigned chorionicity. Effect sizes were pooled through meta-analysis.

Results

A total of 2295 published article and abstracts were identified. Only 16 studies met inclusion criteria. Meta-analysis of 492 pregnancies (432 twins (88%), 56 triplets (11%), 3 quadruplets and 1 quintuplets) showed delayed interval delivery significantly improved the perinatal survival of remaining fetus(es) compared to the first born (OR 5.22, 95% CI 2.95-9.25, I^2 = 53%), before 20+0 weeks (OR 6.32, 95% CI 1.99-20.13, I^2 = 0%), between 20+0 and 23+6 weeks (OR 3.31, 95% CI 1.95-5.63, I^2 = 0%), and after 24+0 weeks (OR 1.92, 95% CI 1.21-3.05, I^2 = 0%), in dichorionic twin pregnancy (OR 14.89, 95% CI 6.19, 35.84, I^2 = 0%) and unselected triplet pregnancy (OR 2.33, 95% CI 1.02-5.32, I^2 = 0%.). Among the survivors, there were no significant differences in the short-term and long-term neonatal morbidities between the first born and the remaining fetus(es) . Serious maternal morbidity was reported in 39%

(71/183) of pregnancy after delayed interval delivery. In addition, two cases were managed by post-partum hysterectomy and one reported post-operative uterovaginal fistula. There were no recorded cases of maternal mortality.

Conclusions

Delayed interval delivery when a fetus has delivered in a multiple pregnancy is an effective management option to increase the survival rate of the remaining fetus(es). About 39% of women may experience morbidity following this management option.

111 **Introduction**

112 Multiple pregnancy is associated with an increased risk of miscarriage; premature,
113 preterm rupture of membranes and preterm birth. Data from the United States
114 National Vital Statistics revealed the rate of preterm birth was 8.1% in singleton
115 pregnancy and 59.4% in twin pregnancy.(1) 36% of twin and 28% of triplet pregnancy
116 could be complicated by preterm, premature rupture of membranes before 28 weeks
117 of gestations.(2) Approximately 20% of twin and 68% of triplet pregnancy delivered
118 before 34 weeks of gestation.(1) The risk of perinatal morbidity and mortality was
119 inversely correlated to the gestational age of preterm birth.(3) The overall outcome
120 for the fetuses is also very dependent upon assigned chorionicity but these data are
121 rarely defined prospectively.(4) These preterm neonates are at risk of respiratory
122 distress syndrome, chronic lung disease of prematurity, retinopathy of prematurity,
123 necrotizing enterocolitis, significant intraventricular hemorrhage, sepsis, cerebral
124 palsy, motor and sensory impairment, learning difficulties, and increased risks of
125 chronic diseases.(5) It is estimated that the societal cost of preterm birth was $26
126 billion annually in the U.S.A. alone.(6)

127

128 The management of the pregnancy after delivery of the first fetus during second
129 trimester miscarriage or very early preterm birth has not been well defined.

Depending on the gestational age, termination of pregnancy before 24 weeks of gestation (if the law allows it) or immediate medical induction is an option due to the grave fetal prognosis and an anticipated risk of ascending infection to the remaining fetus(es) following cervical dilatation. However, this approach may potentially reduce the survival of the remaining fetus(es) and be associated with significant perinatal morbidity and mortality with early preterm birth.

Delayed interval delivery (DID) of a second fetus in a twin pregnancy in an anatomically normal uterus was first reported in 1957.(7) This management option was then adopted in individual cases with the aim to improve the survival of the remaining fetus(es) by prolonging the gestational age. A number of case reports and small retrospective case series were published and described the fetal and maternal outcomes.(8-23) In these studies, the outcome of the first born, in term of morbidity and mortality, was used as a surrogate control as the outcome of the remaining fetus(es), with the assumption that their outcomes would be the same if they were born at the same time. There are no randomized control trials on DID, as it would be difficult to conduct. A systematic review of 13 articles with 128 cases of twin pregnancy was published and concluded that DID of the second fetus was associated with a lower perinatal mortality rate compared to the first born fetus (relative risk

149 0.44, 95% confidence interval 0.34-0.57).(24) However, only dichorionic diamniotic
150 twin pregnancies were reported and included (as DID was considered
151 contraindicated in monochorionic twins due to placental conjoining of the fetal
152 circulations) and several large studies were excluded due to inclusion of
153 monochorionic or triplet/ higher order pregnancy. The objective of this systematic
154 review and meta-analysis of maternal and perinatal outcomes was to evaluate
155 whether DID of the remaining fetus(es) improves perinatal survival, when compared
156 with the first born, after a preterm birth in multiple pregnancy. We also evaluate the
157 maternal morbidity/mortality, short-term and long-term neonatal morbidity among
158 survivors after DID.
159

160 **Methods**

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

162 A systematic review and meta-analysis was performed according to a priori protocol.
163 This study was performed in keeping the PRISMA guideline.(25) PubMed, MEDLINE
164 and Cochrane Library were searched electronically, with no start date to 01.01.2019,
165 utilizing a combination of the keywords and word variants for “delayed
166 delivery”, ”interval delivery”, “delay delivery”, “twin” and “multiple pregnancy". We
167 also hand searched journals and discussed this with the Tommy's Centre for

168 miscarriage research in Birmingham, United Kingdom. There was no restriction of
169 language. Studies must have included: 1) at least five cases of multiple pregnancies
170 with a DID for the remaining fetus(es) after the delivery of first fetus, including cases
171 of higher order multiple pregnancy and 2) record the survival rate of the first born
172 and the remaining fetus(es). We excluded pregnancy with monochorionic
173 monoamniotic pairs and studies with duplicated data.

174

175 **Study selection, data extraction and assessment of risk of bias**

176 The title and the abstract were screened for articles fulfilling the criteria. Full text
177 review of these articles was performed. Reference lists of relevant articles were
178 searched manually for additional reports. Two reviewers (K.W.C. and W.W.)
179 performed the selection of articles and extracted the data independently, any
180 inconsistencies were resolved by a third reviewer (E.H.Y.N.). The quality of the studies
181 was assessed according to the 'Strengthening the Reporting of Observational studies
182 in Epidemiology' (STROBE) checklist. (26)

183

184 Assessment of heterogeneity and publication bias

185 Heterogeneity was assessed by I^2, an I^2 over 50% is regarded as high risk of
186 heterogeneity. Publication bias was assessed visually by funnel plots when over 10

187 studies were included. Studies with larger sample sizes appeared in the top of the
188 plot, while those with smaller samples were showed in the bottom. If studies in the
189 bottom were asymmetric in one side of the mean, publication bias was indicated.
190
191 **Data synthesis**
192 Intervention used to delay the delivery of remaining fetus(es), gestational age of
193 delivery of first fetus, duration of delayed interval and mode of delivery of remaining
194 fetus(es) were collected.
195 The outcomes were defined a priori as:
196 - Perinatal survival of the remaining fetus(es) compared to the survival of the first
197 fetus
198 ✓ Subgroup analysis was performed to evaluate the survival of these fetuses:
199 • First fetus delivered before 19+6 week of gestation
200 • First fetus delivered between 20+0 to 23+6 weeks of gestation
201 • First fetus delivered between 24+0 to 31+6 weeks of gestation
202 • Monochorionic and dichorionic twin pregnancy
203 • Triplet pregnancy – include trichorionic triamniotic and dichorionic
204 triamniotic pregnancy
205 • None, selective or routine insertion of cerclage

- Perinatal survival of the remaining fetus(es) with or without insertion of cerclage after delivery of first fetus
- Maternal morbidity was defined as per study, which included clinical infection/ sepsis, placental abruption, hemorrhage, hysterectomy (and indications) and maternal mortality.
- Short-term neonatal outcomes among survivors were defined as per study, which included infection, retinopathy of prematurity, patency of the ductus arteriosus, necrotizing enterocolitis, significant intraventricular hemorrhage and bronchopulmonary dysplasia
- Long-term neonatal outcomes among survivors were defined as per study, which included neurodevelopmental outcome and infants without major morbidity.

Statistical analysis

The meta-analysis was conducted following general meta-analysis methods. Data analysis was performed by Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. Odds ratio (OR) with random effect was calculated by using Mantel-Haenzel method to evaluate the effect of DID on the survival rate among the first fetus and the remaining fetus(es). ORs

225 with random effect were also calculated to explore the impact of DID on subgroups
226 including 1) first fetus delivered at different gestational age; 2) dichorionic diamniotic
227 twin pregnancies; 3) triplet pregnancies; 4) short-term neonatal morbidity; 5)
228 Long-term neonatal morbidity. OR was calculated to evaluate the impact of cervical
229 cerclage on the survival rate of the remaining fetus(es). Subgroups analysis was
230 performed when high risk of heterogeneity was identified.
231

232 **Result**

233 **Study selection and characteristics**

234 The search identified 2295 articles of which 2270 were excluded on the title or
235 abstract. Twenty-five full text articles were assessed and 16 were finally eligible for
236 inclusion (Figure 1). The characteristics of the included studies were shown in
237 supplementary table 1. There were 14 retrospective and two prospective cohort
238 studies, including 492 pregnancies (432 twins – 153 dichorionic diamniotic, 6
239 monochorionic diamniotic, 273 not specified; 56 triplets – 40 trichorionic triamniotic,
240 3 dichorionic triamniotic, 13 not specified; 3 quadrachorionic quadramniotic
241 quadruplets and 1 quintochorionic quintoamniotic quintuplet) and 1049 fetuses, of
242 which 556 fetuses had DID (one triplet only had one remaining fetus for DID as first
243 and second triplets delivered at the same time)(11). Figure 2 showed the quality of

the included studies. All of them had reported their study designs and survival of the first born and remaining fetus(es). Most of the studies were retrospective and of small sample size (12 studies with sample size ≤ 20, 3 studies with sample size between 20 and 50, one population cohort with 258 subjects). There was no randomized controlled trial. No study addressed potential source of bias and sample size calculation. Oyelese et al. published the largest cohort study using the data between 1995 to 1998 in the USA from ‘‘matched multiple birth’’ file of the Centers for Disease Control and Prevention’s National Center for Health Statistics. The gestational age of delivery was recorded in completed gestational weeks. Exact duration of DID could be inaccurate (ie. delaying delivery from 23+6 weeks to 24 weeks may be misinterpreted as delaying for a week; delaying delivery from 23+0 weeks to 23+6 weeks may be interpreted as no delay). The data could also overlap with other studies carried out within the same period in the USA.(9, 11, 13, 15, 19). Exact gestational age of delivery of fetus(es) was recorded in eleven studies. (9, 10, 12, 13, 16, 18-23)

Synthesis of results

The delivery of the first fetus had a mean gestational age of 21.6 weeks (n = 127 pregnancies, ranging from 13 to 31 weeks of gestation). Mean delayed interval was

263 29.0 days (n = 127 pregnancies, ranging from 1 to 153 days). Five studies had a
264 standard or uniform protocol for DID.(9, 11, 13, 18, 23) Of 170 pregnancies with
265 details of DID, antibiotic, tocolysis and cerclage were used in 100% (170/170), 99.4%
266 (168/170) and 47% (80/170) respectively. The number of pregnancies and fetus(es)
267 available for subgroup analysis was showed in supplementary table 2. Publication
268 bias was assessed by funnel plots (supplementary figure 1-6).
269
270 The rate of perinatal survival is higher for remaining fetus(es) after DID, compared
271 with the first born (OR 5.22, 95% CI 2.95-9.25, I^2 = 53%, 16 studies, 492 pregnancies)
272 (Figure 3). Perinatal survival benefit in remaining fetus(es) was observed in all groups
273 where the first fetus was born before 20+0 weeks of gestation (OR 6.32, 95% CI
274 1.99-20.13, I^2 = 0%. 11 studies, 43 pregnancies), between 20+0 and 23+6 weeks (OR
275 3.31, 95% CI 1.95-5.63, I^2 = 0%. 12 studies, 154 pregnancies) and after 24+0 weeks
276 (OR 1.92, 95% CI 1.21-3.05, I^2 = 0%. 12 studies, 182 pregnancies) (Figure 4a-c).
277 Publication bias was noted in funnel plots (Supplementary figure 2b and 2c).
278
279 In view of the significant heterogeneity, we did a sensitivity analysis with exclusion of
280 study of Oyelese et al.. The result then became homogenous and no publication bias
281 was noted at the funnel plots (Supplementary figure 3, 4a-c). Perinatal survival

282 benefit in the remaining fetus(es) was observed in all groups where the first fetus
283 was born between 13-31 weeks (OR 5.59, 95% CI 3.55-8.80, I^2 = 5%. 15 studies, 234
284 pregnancies), before 20+0 weeks of gestation (OR 6.32, 95% CI 1.99-20.13, I^2 = 0%.
285 11 studies, 43 pregnancies), between 20+0 and 23+6 weeks (OR 7.65, 95% CI
286 2.74-21.30, I^2 = 0%. 11 studies, 40 pregnancies) and after 24+0 weeks (OR 4.75, 95%
287 CI 1.49-15.15, I^2 = 0%. 11 studies, 38 pregnancies) (Figure 5, 6a-c). We also
288 performed a sensitivity analysis excluding studies with higher order pregnancy. The
289 beneficial effect of DID on survival of remaining fetus(es) was still significant (Figure
290 7).
291
292 We evaluated the perinatal survival rate of first and remaining fetus(es) with respect
293 to the gestational age of delivery of the first born. The perinatal survival rate of first
294 born and remaining fetus were 0% (0/43) and 29.0% (18/62) before 20+0 weeks,
295 16.2% (25/154) and 41.8% (69/165) between 20+0 to 23+6 weeks, and 59.6%
296 (109/183) and 72.9% (140/192) after 24+0 weeks. The perinatal survival rates of first
297 and remaining fetus(es) with respect to their actual gestational age of delivery were
298 shown in Table 1. The survival rate of remaining fetuses was 0% (0/23) before 21+0
299 weeks, 17-33% between 21+0 and 24+6 weeks, 21% to 78% between 25+0 and 27+6
300 weeks, and 100% after 28+0 weeks.

301

302 In dichorionic diamniotic twin pregnancy, DID significantly improved the perinatal
303 survival rate of remaining twin (OR 14.89, 95% CI 6.19, 35.84, I^2 = 0%. 10 studies, 87
304 pregnancies) (Figure 8a). Only one cohort provided individual data on monochorionic
305 diamniotic twin pregnancy with 100% survival of first and remaining fetuses (two
306 cases).(23) In unselected triplet pregnancy, DID also significantly increased the rate
307 of perinatal survival of remaining fetus(es) (OR 2.33, 95% CI 1.02-5.32, I^2 = 0%. 11
308 studies, 46 pregnancies) (Figure 8b).

309

310 A trend towards better perinatal survival of the remaining fetus(es) after cervical
311 cerclage was observed (OR 3.96, 95% CI 0.86-18.25, I^2 = 0%, 3 studies, 30
312 pregnancies), compared with those without cerclage (Figure 9). The survival of the
313 remaining fetus(es) was higher than the first born in studies with no cerclage for DID
314 (OR 3.36 95% CI 1.43-7.90, I^2 = 17%, 3 studies 70 pregnancies), with selective
315 approach (OR 7.44 95% CI 1.57-35.19, I^2 = 0%, 3 studies 40 pregnancies) and with
316 universal cerclage for DID (OR 8.85 95% CI 3.69-21.26, I^2 = 0%, 6 studies 60
317 pregnancies) (10a-c).

318

319 There were no significant differences in the short-term (infection, retinopathy of

prematurity, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage and bronchopulmonary dysplasia) and long-term (neurodevelopmental outcome and infants without major morbidity) neonatal morbidities among survivors between the remaining fetus(es) and the first born, but the numbers were small. (Figure 11a-f and 12).

Maternal morbidity was described in 12 studies.(8-12, 15, 16, 18, 19, 21-23) The risk of maternal complications was 38.8% after DID (71/183, 12 studies) and variable in severity and type. More than one complication occurred in 7 pregnancies. There were 56 local infection and/or sepsis, 12 postpartum hemorrhages, 8 placental abruptions, 2 postpartum hysterectomies (one for sepsis and one for hemorrhage) and 1 uterovaginal fistula. Cesarean section was required for delivery of remaining fetus(es) in 31.8% of pregnancy (41/129, 10 studies). There were no recorded cases of maternal mortality.

Comments

Main findings

Our results demonstrated that DID, when the first fetus has delivered in multiple pregnancy between 13+0 to 31+6 weeks of gestation, is an effective management

339 option to increase the survival of the remaining fetus(es). Among those surviving, the
340 first born and remaining fetus(es) do not have evidence of significant difference in
341 perinatal and long-term morbidity. 38.8% of pregnancies would have associated
342 adverse maternal complications from DID, and these may be potentially serious.
343
344 **Strengths and limitations**
345 This study was performed using a structured search strategy and predefined (á priori)
346 eligibility criteria. We excluded case report of less than five cases to avoid publication
347 bias. Compared to the previous systematic review,(24) we included a larger cohort,
348 examined the effectiveness of DID in triplet pregnancy and at various gestational
349 periods. We therefore provide a more robust and comprehensive analysis.
350
351 Our performed meta-analysis had several limitations. Firstly, we could not determine
352 the optimal management algorithm of DID. In most studies, the treatment of a DID
353 involved cleansing the vagina and cervical canal using antiseptic solution, leaving the
354 placenta of the first born in-situ with high ligation of umbilical cord using absorbable
355 suture, administering prophylactic board spectrum antibiotics and then adjusting the
356 optimal antibiotic regimen according to the vaginal/ cervical culture results.(8-12, 16,
357 18, 21-23) The use of tocolysis and cervical cerclage is however controversial.

358 Routine use of tocolysis after delivery of the first born was employed in some
359 studies,(75%, 12/16 studies) (8-13, 15, 18, 20-23) while others may choose to
360 observe and use tocolysis only if contraction persisted.(16, 19) The decision to use
361 cervical cerclage also differed. Our result suggested additional cerclage may increase
362 the benefit of DID, however the number was small and highly self-selective.
363 Comparison among studies with different approach could induce bias due to
364 different management among centers in different studied period, and should be
365 interpreted with caution. The individualized management of DID may introduce
366 selection bias. For example, women with minimal uterine activity and spontaneous
367 closure of cervix after delivery of first born were offered DID with tocolysis and
368 cerclage while other women with persistent contraction and open cervix may be
369 advised for immediate delivery. There was also no consensus on the mode and
370 frequency of monitoring for the remaining fetus(es) after DID. Only two studies were
371 prospective and had a standardized protocol for DID.(18, 19) Therefore, our result
372 should be used to pursuit a further evaluation of DID and invite a worldwide
373 collaboration among perinatal centers for a randomized controlled trial to assess the
374 optimal management of DID. Figure 13 presented a possible management algorithm
375 of DID. Secondly, most studies did not provide both detailed short-term and
376 long-term neonatal outcomes. The early and late neurodevelopment assessment

377 should be part of the outcome evaluation of remaining fetus(es) from DID.(27) In our
378 analysis, the insignificant differences in the risk of short- and long-term neonatal
379 complications between the first born and remaining fetus(es) could be related to the
380 small number of cases available for analysis. Thirdly, we cannot identify the best
381 candidate and the gestational age limits for DID. Some older studies were included in
382 our analysis. The advancement of neonatal management over time would eventually
383 improve the survival rate of both the first born and remaining fetus(es). For instance,
384 the upper gestational limit for DID in the literature was around 28-31 weeks of
385 gestation, at which the extension of in-utero life of remaining fetus(es) beyond this
386 period may pose extra risk to the pregnant women without significant reduction of
387 neonatal mortality and morbidity. At a later gestation, the level of neonatal support
388 available would alter the decision between DID or immediate delivery, especially
389 after 28 weeks of gestation, and a multidisciplinary discussion of management
390 option with the neonatologist should be considered. In low resource countries,
391 prolonging the gestational age at delivery from 28 weeks onwards could still
392 decrease neonatal mortality and morbidity.(28) The benefits of DID and the
393 amelioration of the adverse effects of prematurity have to be balanced against the
394 maternal and fetal risks of conservative management.
395

Interpretation and implication

Multiple pregnancy is particularly at risk of periviable delivery (20+0 to 25+6 weeks) and early preterm delivery; among twins, 2.5% of births occurred at periviable gestation and 10% delivered before 28 weeks of gestation.(2, 31) Induction to deliver the remaining fetus immediately after the first born would result in miscarriage at previable gestation and death or survival with a high chance of serious morbidity at periviable gestation. The perinatal survival of preterm birth greatly depends on the gestational age at delivery, which increases gradually from 7% at 22 weeks, 32% at 23 weeks, 62% at 24 weeks, 77% at 25 weeks, 85% at 26 weeks and plateaus at around 90% at 27-28 weeks of gestation.(3) This improvement of perinatal survival with advancing gestational age forms the rationale for DID of multiple pregnancy, especially in women with early periviable preterm birth where significant survival gain could be achieved by prolonging the pregnancy by few days to weeks.

Our data is therefore important to both the obstetricians and the women. DID might be underutilized. It should be discussed with women who suffered from second trimester miscarriage or early preterm delivery. Obstetricians who are not aware of this management option and its benefit may deliver the remaining fetus following the first born. Obstetricians should be prepared to offer this treatment option as an

415 alternative to immediate delivery. Obstetrician also needs to familiar with the
416 common selection criteria for this option: 1) the first born should be vaginally
417 delivered, 2) the women should not have excessive bleeding or maternal indication
418 for immediate delivery, and 3) the remaining fetus(es)' amniotic membranes should
419 be intact with normal fetal well-being and no lethal anomaly. Although there was
420 case report of favorable outcome of remaining twin after chorioamnionitis,(32) it
421 was generally considered as a contraindication to DID in view of potential risk of
422 maternal sepsis. Monochorionic pregnancy may also be eligible for DID but more
423 data is needed on its effectiveness for perinatal survival improvement and potential
424 neurological effect of the remaining twin in view of the theoretical risk of transient
425 acute transfusion during delivery of first born. On the other hand, even for
426 pregnancy considered suitable to DID, 32.4% may fail the attempt and result in
427 immediate delivery.(18) Secondly, women should be given a realistic expectation of
428 potential perinatal survival gain from DID. The survival rate of remaining fetus
429 remains very poor at 29% when DID is performed before 20 weeks of gestation. The
430 reported mean duration of DID ranges from 12 days to 42 days which means most of
431 these pregnancies may not be prolonged long enough to reach the periviable or early
432 preterm gestation. Nonetheless, in view of no chance of survival with immediate
433 delivery before 20 weeks, DID should still be an alternative and not be precluded by

434 this extreme gestational age. Hamersley et al. reported the longest delayed interval
435 of 153 days, in which the first and the remaining twin were delivered at 15+3 weeks
436 and 37+2 weeks respectively.(13) Petousis et al. reported a remaining twin survivor
437 born at 37+2 weeks, after a delivery interval of 141 days from delivery of the first
438 born at 17+2 weeks.(20) Arabin et al. reported another case of two survivors at 36+
439 weeks of gestation from a triplet pregnancy after 118 days DID from the first born at
440 19+ weeks of gestation.(18)
441
442 In fact, the survival rate of remaining fetus(es) may not depend on the delayed
443 interval but their actual gestational age of delivery. Around 28%, 58% and 100%
444 perinatal survival rate may be observed if the remaining fetus delivered between
445 22+0-24+6 weeks, 25+0-27+6 and after 28+0 weeks' gestation. These gestational
446 landmarks could be used to guide prognosis during parental counseling.
447
448 The potential improvement in perinatal survival rate should be balanced with the risk
449 of maternal morbidity and transforming a perinatal demise to serious neonatal
450 morbidity by delivery at periviable gestation. The risk of infection was around 31%
451 and hysterectomy was performed in 1%. The risk of infective complications was
452 difficult to predict. Negative amniocentesis for infective markers of the remaining

453 fetus did not guarantee a low risk of maternal infective complication. Roman et al.
454 reported 21% sepsis rate (4/19) and one women required hysterectomy for
455 postpartum hemorrhage, despite a negative amniocentesis for infection in most of
456 these women.(19) Women should be counseled and given the options of both DID
457 and immediate delivery.

458

459 **Conclusion**

460 Delayed interval delivery is an effective management option to improve the perinatal
461 survival rate of the remaining fetus(es) for women with multiple pregnancy who
462 deliver the first fetus between 13 to 31 weeks of gestation. About 39% of women
463 may experience serious morbidity including local infection/sepsis, chorioamnionitis,
464 hemorrhage, placental abruption and hysterectomy.

465

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Table 1. Survival rate of first and remaining fetus(es) with respect to their actual gestational age of delivery		
Gestational weeks at delivery	Survival rate of the first fetus	Survival rate of remaining fetus(es)
13 - 20+6	0% (0/42)	0% (0/23)
21 - 21+6	0% (0/11)	16.7% (1/6)
22 - 22+6	27.3% (3/11)	23.5% (4/17)
23 - 23+6	18.2% (2/12)	28.6% (2/7)
24 - 24+6	46.7% (7/15)	33.3% (3/9)
25 - 25+6	33.3% (2/6)	77.8% (14/18)
26 - 26+6	33.3% (2/6)	21.4% (3/14)
27 - 27+6	Not available	75% (9/12)
28 - 28+6	100% (1/1)	100% (7/7)
29 - 29+6	Not available	100% (5/5)
> 30+	100% (2/2)	100% (23/23)

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Figure legends

Figure 1. Systematic literature search for delayed interval delivery.

Figure 2. Quality assessment of included studies according to 'Strengthening The Reporting of Observational studies in Epidemiology' (STROBE) checklist (27).

Figure 3. Forest plot of meta-analysis compared the survival rate between the first born and the remaining fetus(es) and in all pregnancies.

Figure 4. Forest plots of meta-analyses compared the survival rate between the first born and the remaining fetus(es) a) before 20+0 weeks of gestation, b) between 20+0 and 23+6 weeks gestation, c) after 24+0 weeks of gestation.

Figure 5. Forest plot of meta-analysis compared the survival rate between the first born and the remaining fetus(es) in all pregnancies after exclusion of the study of Oyelese et al. (2005)

Figure 6. Forest plots of meta-analyses compared the survival rate between the first born and the remaining fetus(es) after exclusion of the study of Oyelese et al. (2005) a) before 20+0 weeks of gestation, b) between 20+0 and 23+6 weeks gestation, c) after 24+0 weeks of gestation.

Figure 7. Forest plot of meta-analysis compared the survival rate between the first born and the remaining fetus(es) in twin and triplet pregnancies. (Studies with higher order pregnancies were excluded)

Figure 8. Forest plots of meta-analyses compared the survival rate between the first born and the remaining fetus(es) in a) DCDA twin and, b) triplet pregnancy.

Figure 9. Forest plot of meta-analysis compared the survival rate of remaining fetus(es) with or without cervical cerclage insertion

Figure 10. Forest plots of meta-analyses compared the survival rate between the first born and the remaining fetus(es) in a) no cerclage, b) selective cerclage and, c) all cerclage

Figure 11. Forest plots of meta-analyses compared the short term neonatal

morbidities between the first born and the remaining fetus(es) in a) infection, b) retinopathy of prematurity, c) patent ductus arteriosus, d) necrotizing enterocolitis, e) intraventricular hemorrhage, f) bronchopulmonary dysplasia

Figure 12. Forest plots of meta-analysis compared the long-term survival without morbidity between the first born and the remaining fetus(es)

Figure 13. Suggested management algorithm for delayed interval delivery