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

Condensation:

Compared with immediate delivery, delayed interval delivery improves the survival of remaining fetus(es) in multiple pregnancy.

Short Title:

Delayed interval delivery in multiple pregnancy

AJOG at a Glance:

Why was this study conducted?

A. Multiple pregnancy increases the risk of periviable preterm birth which is associated with significant neonatal morbidity and mortality.

B. This systematic review and meta-analysis evaluated whether delayed interval delivery improves the survival of the remaining fetus(es) in multiple pregnancy.

Key Findings

A. Delayed interval delivery is an effective management option to increase the perinatal survival of the remaining fetus(es), but about 39% of women may 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.

Introduction

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

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.

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

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

Study selection, data extraction and assessment of risk of bias

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

Assessment of heterogeneity and publication bias

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

studies were included. Studies with larger sample sizes appeared in the top of the plot, while those with smaller samples were showed in the bottom. If studies in the bottom were asymmetric in one side of the mean, publication bias was indicated.

Data synthesis

Intervention used to delay the delivery of remaining fetus(es), gestational age of delivery of first fetus, duration of delayed interval and mode of delivery of remaining fetus(es) were collected.

The outcomes were defined a priori as:

- Perinatal survival of the remaining fetus(es) compared to the survival of the first fetus
    - ✓ Subgroup analysis was performed to evaluate the survival of these fetuses:
        - First fetus delivered before 19+6 week of gestation
        - First fetus delivered between 20+0 to 23+6 weeks of gestation
        - First fetus delivered between 24+0 to 31+6 weeks of gestation
        - Monochorionic and dichorionic twin pregnancy
        - Triplet pregnancy – include trichorionic triamniotic and dichorionic triamniotic pregnancy
        - 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

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

Result

Study selection and characteristics

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

benefit in the remaining fetus(es) was observed in all groups where the first fetus was born between 13-31 weeks (OR 5.59, 95% CI 3.55-8.80, I^2 = 5%. 15 studies, 234 pregnancies), before 20+0 weeks of gestation (OR 6.32, 95% CI 1.99-20.13, I^2 = 0%. 11 studies, 43 pregnancies), between 20+0 and 23+6 weeks (OR 7.65, 95% CI 2.74-21.30, I^2 = 0%. 11 studies, 40 pregnancies) and after 24+0 weeks (OR 4.75, 95% CI 1.49-15.15, I^2 = 0%. 11 studies, 38 pregnancies) (Figure 5, 6a-c). We also performed a sensitivity analysis excluding studies with higher order pregnancy. The beneficial effect of DID on survival of remaining fetus(es) was still significant (Figure 7).

We evaluated the perinatal survival rate of first and remaining fetus(es) with respect to the gestational age of delivery of the first born. The perinatal survival rate of first born and remaining fetus were 0% (0/43) and 29.0% (18/62) before 20+0 weeks, 16.2% (25/154) and 41.8% (69/165) between 20+0 to 23+6 weeks, and 59.6% (109/183) and 72.9% (140/192) after 24+0 weeks. The perinatal survival rates of first and remaining fetus(es) with respect to their actual gestational age of delivery were shown in Table 1. The survival rate of remaining fetuses was 0% (0/23) before 21+0 weeks, 17-33% between 21+0 and 24+6 weeks, 21% to 78% between 25+0 and 27+6 weeks, and 100% after 28+0 weeks.

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

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

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

option to increase the survival of the remaining fetus(es). Among those surviving, the first born and remaining fetus(es) do not have evidence of significant difference in perinatal and long-term morbidity. 38.8% of pregnancies would have associated adverse maternal complications from DID, and these may be potentially serious.

Strengths and limitations

This study was performed using a structured search strategy and predefined (á priori) eligibility criteria. We excluded case report of less than five cases to avoid publication bias. Compared to the previous systematic review,(24) we included a larger cohort, examined the effectiveness of DID in triplet pregnancy and at various gestational periods. We therefore provide a more robust and comprehensive analysis.

Our performed meta-analysis had several limitations. Firstly, we could not determine the optimal management algorithm of DID. In most studies, the treatment of a DID involved cleansing the vagina and cervical canal using antiseptic solution, leaving the placenta of the first born in-situ with high ligation of umbilical cord using absorbable suture, administering prophylactic board spectrum antibiotics and then adjusting the optimal antibiotic regimen according to the vaginal/ cervical culture results.(8-12, 16, 18, 21-23) The use of tocolysis and cervical cerclage is however controversial.

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

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

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

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

this extreme gestational age. Hamersley et al. reported the longest delayed interval of 153 days, in which the first and the remaining twin were delivered at 15+3 weeks and 37+2 weeks respectively.(13) Petousis et al. reported a remaining twin survivor born at 37+2 weeks, after a delivery interval of 141 days from delivery of the first born at 17+2 weeks.(20) Arabin et al. reported another case of two survivors at 36+ weeks of gestation from a triplet pregnancy after 118 days DID from the first born at 19+ weeks of gestation.(18)

In fact, the survival rate of remaining fetus(es) may not depend on the delayed interval but their actual gestational age of delivery. Around 28%, 58% and 100% perinatal survival rate may be observed if the remaining fetus delivered between 22+0-24+6 weeks, 25+0-27+6 and after 28+0 weeks' gestation. These gestational landmarks could be used to guide prognosis during parental counseling.

The potential improvement in perinatal survival rate should be balanced with the risk of maternal morbidity and transforming a perinatal demise to serious neonatal morbidity by delivery at periviable gestation. The risk of infection was around 31% and hysterectomy was performed in 1%. The risk of infective complications was difficult to predict. Negative amniocentesis for infective markers of the remaining

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

Conclusion

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

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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