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Delayed-Interval Delivery in Multifetal Pregnancy: A Review and Guidelines for Management

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Abstract

The objective of the study was to review the literature concerning delayed deliveries in multiple pregnancies and to highlight the existing guidelines for a better management of asynchronous births.

A literature-search was done using Medline and ScienceDirect. All articles reporting at least 4 cases of delayed delivery were included, if they provided full information on gestational age and outcome of each offspring. The main outcome was the survival rate of the second twin or other higher-order multiples, stratified for gestational age of the first born (before or after 24 weeks of gestation). Secondary outcomes were: management strategies, interval between deliveries, neonatal and maternal complications.

Among 18 relevant cohort studies, 391 twin and 34 triplet pregnancies could be analysed. In case of delayed delivery, the survival rate of the second twin or higher-order multiple was respectively 44.8% and 82.7% when the first twin was born before or after 24 weeks of gestation The later was the delivery of the first twin, the higher was the second twin's survival rate, but the shorter was the interval between births (14 vs. 26 days). Conservative measures included: high ligature of umbilical cord, tocolysis, corticoids, antibiotic therapy and cerclage. Main neonatal complications were septicemia (42%), retinopathy (62%) and intraventricular hemorrhage (37%), and the most frequent maternal complication was chorioamniotitis (30%).

In spite of higher rates of chorioamniotitis, there was a clear advantage in delaying delivery of remaining multiples, as this improved the outcome of preterm birth.

The possible strategies and their grades of recommendation for the management of asynchronous deliveries are summarized.

Keywords: Delayed delivery; Interval delivery; Multiple pregnancy; Multifetal pregnancy; Twin pregnancy; Asynchronous birth; Guidelines

Introduction

The objective of this study was to review the literature concerning delayed deliveries in multiple pregnancies and to reinforce the existing guidelines for a better management of asynchronous births.

Indeed, since the introduction of assisted reproductive technology, the incidence of multifetal pregnancies has increased considerably. Concomitantly, the incidence of severe complications, such as threatened preterm labor and premature rupture of membranes has also risen, soon followed by the premature delivery of all multiple fetuses. This condition is often related to severe adverse outcomes for the offspring, with both increased mortality and morbidity.

However, in some cases, contractions cease after the delivery of the first fetus and the first report of delayed delivery among twins by 44 days was described in 1880 [1]. Since then, medical teams across the word have understood the considerable interest in delaying delivery of the remaining multiples after immature delivery. Countless case reports have been published, describing the feasibility of delaying the delivery of twins, triplets or higher-order multiples, the longest delay ever reached being 154 days [2].

In our hospital (University Hospital of St Pierre, Reunion Island), we have faced this type of situation in three twin pregnancies for whom we have tried to delay the delivery, without success We managed to delay the delivery of the second fetus during 3 to 25 days, but none of them remained alive. Two deliveries were complicated by postpartum hemorrhage.

Based on this experience, we reviewed the literature and noted that, despite some attempts to establish guidelines [3-5], neither validated protocol nor clear recommendation are available. Moreover, factors influencing the effectiveness of delayed delivery are not exhaustively elucidated by the above studies.

The present investigation was carried out in order to address the following questions on asynchronous delivery in multiple pregnancies:

1) Indications and contraindications;

2) Choice of management strategies;

3) Benefits and risks for both mother and subsequent infants;

4) Factors associated with effectiveness of delayed delivery.

Finally, in the light of our findings, we aimed to highlight the existing guidelines, for a better management of asynchronous births, in order to help obstetricians to overcome this gap of knowledge, to

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adopt optimal decisions and to give the most appropriate parental information.

Material and Methods

Search strategy

Computerized medical literature search was performed back to 1994, up to July 2015, using Medline and ScienceDirect databases with the following terms: (all fields) 'delayed delivery' OR 'interval delivery' OR 'multiple pregnancy 'OR' multifetal pregnancy' OR 'twin pregnancy' OR 'asynchronous birth'.

We restricted language keywords to English.

Trial selection and patient population

Articles were included in the analysis only if they provided full information on gestational age at delivery and clinical outcomes for each newborn. Cases reports with less than 5 cases were excluded, as this kind of reports are often criticized for their selectivity, publications bias, and lack of an adequate comparison group [6]. If multiple publications of the same patient groups were retrieved, only the one giving more detail on delivery and infant survival was included. Pregnancies with more than three fetuses were excluded from the analysis.

Explored outcomes and clinical variables

The primary outcome measure was the "success rate", defined as the survival rate of the second twin or higher-order multiple, not only at birth but also the survival before discharge from neonatal intensive care unit (NICU). Secondary outcomes were: interval between deliveries (days), rate of neonatal complications, length of hospital stay for born alive infants (days), rate of maternal complications.

The following clinical variables were also investigated: indications and contraindications to delayed delivery, management strategy, factors influencing the success of delayed delivery.

Analyses

All the data detailed in each study were reported in one single table Microsoft Excel Worksheet, enabling us to carry out the analyses.

For the analysis of the main outcome and also of the neonatal outcomes, gestational age of the first born was categorized as < or ≥ at 24 weeks of gestation.

Data were presented as numbers and percentages for categorical variables and as mean and standard deviation for continuous ones, unless specified elsehow.

Results

We identified more than 80 original case reports or case series of delayed delivery published within the past 20 years. Among them, 18 cohort studies met our criteria and were retained for the analysis: two reviews [7,8], one prospective study [9], one case-control study [6] and 14 retrospective studies [3,10-22]. Two studies [6, 20] used the same dataset, therefore only the one giving more detail on delivery and infants survival [6] was taken into account for the analysis.

A total of 391 twin and 34 triplet pregnancies were analyzed, that is to say: 425 multiple pregnancies

Although most authors excluded monochorionic pregnancies, 7 cases of monochorionic diamniotic pregnancies and 9 cases of dichorionic triamniotic pregancies were reported.

Indications and contraindications

When the first infant was born vaginally between 16 and 31 weeks, delayed delivery for subsequent fetuses was considered in case of: preterm labor, premature rupture of membranes or intrauterine demise of the presenting fetus, incompetent cervix, or intra-amniotic infection of the presenting fetus without signs of maternal systemic infection.

Most frequently encountered contraindications were the following: severe preeclampsia, abruptio placentae, placenta praevia, C-section required for the first delivery, fetal distress (abnormality in the ultrasound or the tococardiography), congenital abnormalities, premature rupture of membranes of the remaining fetus, intra-amniotic infection of the non-presenting fetus. In Porreco's team [14], an amniocentesis was performed on retained siblings to analyze amniotic fluid for evidence of subclinical intra-amniotic infection.

Management measures

Conservative measures included: high ligature of umbilical cord with absorbable suture, hospitalization with bed rest and preventive anticoagulation therapy, tocolysis (94%), antenatal glucocorticoids (33% of all cases, 96% after 24 weeks), antibiotic prophylaxis (98%), and cerclage (61%) (Table 1). Concerning tocolysis and antibiotherapy, a variety of drugs for variable treatment periods was administered. Nevertheless, tocolysis was started after the delivery of the first fetus, even when the latter was born before 24 weeks. The following drugs

	Gestation age of first twin at birth	<24GW			≥24GW		
		T1	T2	T3	T1	T2	T3
	number of cases	257	257	15	168	168	19
	gestational age (weeks)	21.1 ± 1.2	24.8 ± 3.8	23.3 ± 3.7	25.9 ± 1.5	27.9 ± 2.2	27.2 ± 2.1
	Survival (%)	7.8%	44.8%	26.6%	50.6%	82.7%	52.6%
	weight (g)	453 ± 95	817 ± 482	699 ± 225	727 ± 167	1022 ± 284	866 ± 259
	Delay between T1 and T2/T3 (days [minimum-maximum])	26 [1-143]			14 [1-92]		
Therapies	Antibiotic therapy [7, 13]	98%			95%		
	Tocolysis [7, 13, 19]	94%			70%		
	Corticoids [7]	26%			96%		
	Cerclage [7, 10, 19]	59%			62%		
GW: Gestational week; T1: First Born of the Multiple Pregnancy; T2: Second born; T3: Third born							

Table 1: Results of reviewed delayed interval deliveries and therapeutic interventions, grouped according to gestational week (GW).

were used either alone or in association: Progesterone (500mg intra muscular), Magnesium Sulfate, beta-2-agonists, or calcium inhibitors. It seemed like broad-spectrum antibiotherapy such as Amoxycillin-clavulanic acid, or Ceftriaxon in association with Metronidazole did help in the prevention of chorioamniotitis. Zhang [21] reviewed 7 case series with 70 individuals to assess the impact of cerclage on inter-delivery interval and infectious complications and reported that when cerclage was infrequently used, the inter-delivery interval was shorter compared to studies where cerclage was systematically used (9 versus 26 days, p<0.001), without significantly increasing the risk of intrauterine infection (relative risk = 1.1 [confidence interval 95%: 0.4-3.4). Moreover, Farkhoukh [10] reported that, among 24 patients, those with a previous cerclage at the beginning of the pregnancy, had significantly shorter latency intervals than those without previous cerclage (11 vs. 40 days, p=0.004). Thus, both authors concluded that cerclage should be placed after the delivery of the first neonate.

Infants characteristics and outcome

Among the 425 exploitable cases, the first fetus was born before 24 weeks in 257 cases, and in the remaining 168, the first fetus was born at 24 weeks or after (Table 1).

When the first twin (T1) was born before 24 weeks, his mean gestational age was 21.1 ± 1.2 weeks, whereas the second twin (T2)'s mean gestational age was 24.8 ± 3.8 weeks, the latency interval between them being around 26 days (1-143). There was only 7.8% of survival among first fetuses whereas 44.8% of later born survived. The median weight of T1 was 453 g and 817 g for T2.

When T1 was born at 24 weeks or after, T1's mean gestational age was 25.9 ± 1.5 weeks, and T2's was 27.9 ± 2.2 weeks, meaning a delay interval of 14 days (1-92). Survival was 50.6% for first born and 82.7% for second twins, and mean weight was 727 g for T1 and 1022 g for T2.

In a case control study, Zhang [6] highlighted that in case of delayed delivery, second twin's survival rate and birth weight were significantly higher than for the non delayed control cases (p=0.01).

Only 8 studies reported results on third multiple born and data are disappointing. Even though the survival rate and the weight of the third born were slightly higher than those of the first born, they were not as good as those of the second born.

All articles reported neonatal survival, but only 6 gave detail with regards to neonatal complications. Over the 97 patients who were followed up on a long-term period, the most frequent neonatal complications were: retinopathy (62%), septicemia (42%), patent ductus arteriosus (39%), intraventricular hemorrhage (37%) and membrane hyaline disease (26%) (Table 2). Unfortunately, none of the studies detailed which infant was affected by a complication, nor indicated his/her gestational age. Thus, we could not conclude whether the first or the later born was more susceptible to have a complication, nor on the relationship between the degree of prematurity and the prevalence of neonatal complications. Nevertheless, Uhm [23] stated that composite comorbidities (including: respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia, necrotizing enterocolitis and intraventricular hemorrhage) affected 100% of the first-born neonate, and 57.6% of the second born neonates (p=0.009). Moreover, Kalchbrenner [10] reported that for the first delivered neonates, the hospital stay was longer than for the latter-born ones (p<0.05), the duration of ventilatory support was longer (p<0.05), and the number of surgical procedures was five times greater (p<0.05). He also noticed that the average hospital cost was higher for the first born, theory also supported by Porreco [14].

Maternal complications

Maternal complications and perinatal outcomes after delayed delivery were poorly described. Chorioamniotitis was reported in 30% of the patients, and in case of histologically confirmed chorioamniotitis, the survival of T2 was reduced to 47% [6]. Other maternal complications after delayed delivery included: 1 septicemia [7], 1 post-partum hemorrhage [16], 4 abruptio placentae [11,14,17], 7 endometritis [10], 1 septic pelvic thrombophlebitis [10].

Rate of success and factors associated with effectiveness of delayed delivery

Arabin [9] described in his prospective study a procedure of delayed delivery that could be performed in only 41% of twin and 35% of triplet pregnancies admitted with threatened early delivery.

None of the maternal characteristics such as age, parity, gravidity, previous miscarriages and method of conception of the present pregnancy, nor the fetal characteristics such as chorionicity or fetal sex, were associated with the success of a delayed delivery, although emergency cervical cerclage may be effective in order to achieve delayed-interval delivery in dichorionic twins [12].

Discussion

Threatened preterm labor and premature rupture of membranes are frequent complications of multiple pregnancies. Before thinking about delaying deliveries, management measures to prevent these should be studied. Arabin [9] recommends routine transvaginal sonography in all multiple pregnancies from 15 weeks onwards and the treatment of patients with a short cervix (<15 mm) or funneling. However, these recommendations should be moderated, since there are no general consensus concerning the follow-up of multiple pregnancies, whether we are referring to the European or American College of Obstetricians and Gynecologists [24,25].

In case of premature delivery in a multiple pregnancy, a delayed delivery on remaining multiples is possible, provided that contractions cease after the first delivery and that contraindications to prolong pregnancy (placenta praevia, abrutio placentae, pre-eclampsia and fetal pathology or distress) are excluded.

Most studies agree on the following conservative measures to attempt to defer the delivery: high ligature of umbilical cord with absorbable suture, hospitalization with bed rest, to colysis, antenatal glucocorticoids, antibiotic prophylaxis, and cerclage, especially when set up after the birth of the first neonate. Publications have recently risen concerning the use of cervical pessaries as an alternative for cerclage in multiple pregnancy. Liem et al. shows a reduction of neonatal morbidity in the sub-group with a cervical length <38 mm

Complications		% of cases
Neurological	periventricular leukomalacia [13,16]	12
	intraventricular hemorrhage [11,13,16,17]	37
	psychomotor retardation [13,15]	11
Respiratory	membrane hyaline disease [7,13,16,17]	26
	bronchopulmonary dysplasia [7]	5
Other	necrotizing enterocolitis [7,11,16]	7
	nephrocalcinosis [7]	3
	septicemia [13,16,17]	42
	patent ductus arteriosus [11,13]	39
	retinopathy [11,17]	62

Table 2: Neonatal outcome.

who used a pessary (RR 0.42 [0.19-0.91]) [26,27]. However, more hindsight is needed before using these devices in this indication.

It should be noted that in the latest recommendations [24], routine hospitalization and bed rest has not been proved to decrease neonatal morbidity or mortality and therefore should no longer be used in women with multifetal gestations.

When the first neonate was delivered before 24 weeks, he had very poor chances to survive, whereas second twins had a better survival rate. When the first neonate was delivered after 24 weeks, the second twin's survival was much improved.

Thus, our literature review points the fact that the higher was T1's gestational age, the better was T2's survival, with an almost 100% survival rate when the delivery of the first twin happened after 26 weeks. No matter before or after 24 weeks, T2 is heavier than T1.

On the other hand, the sooner was T1's delivery, the longer was the delay before the delivery of T2. This tendency would be consistent with the hypothesis that myometrial oxytocin receptors increase gradually throughout the pregnancy, in parallel with increased uterine oxytocin sensitivity. Therefore, when the first delivery occurs later, the uterus is more likely to pursue contractions that will deliver the second twin within a short time period [4].

Neonatal complications do not differ from complications already described in preterm delivery. We may be tempted to say that since delaying the delivery of second twins may prolong their gestational age, it may reduce the rate of prematurity and thus reduce the rate of complications. Unfortunately, the delayed neonate hardly reaches more than 37 weeks.

What can be pointed out, though, is that when the first twin is delivered after 24 weeks, the benefice of delaying the delivery of the second twin seems an evidence, since each day passing is a won battle in order to reduce the morbidity and mortality linked with prematurity. Nevertheless, when the first twin is delivered before 24 weeks, before tempting to delay the delivery of the second twin, the discussion between obstetricians and parents should include the neonatal complications cited above, and maternal consent should be looked for, since the risk of delaying delivery is small but potentially life-threatening [5].

This review helps to understand the interest of delaying delivery in multiple pregnancy. Indeed, if the birth of the second twin is concomitant to that of the first twin, his mortality rate may approach 100%, especially before 24 weeks of gestation; on the contrary, the delayed delivery gives him a second chance to rise his survival rate, to prolong his gestation in utero and to pass the threshold of extreme prematurity, thus diminishing his morbidity. Notwithstanding the fetal benefit, we may underline a higher maternal morbidity, especially a rate of chorioamniotitis reaching 30% whereas this occurs in 0.5 to 10% in general pregnancies [28]. There is nonetheless no consequence on the length of hospitalization nor on the rate of NICU admission.

To our knowledge, this is the first study to summarize the results of such a big population, with 425 multiple pregnancies reported, although we were limited by the fact that the studies included were very heterogeneous : they were interested in different outcomes, inclusion and exclusion population criteria were different, management protocols differed according to the medical teams, most studies were lacking of consistency concerning neonatal and maternal outcome, and the follow-up was rather short. It was thus difficult to make any hasty conclusions and we remain humble about the scope of our results.

Some guidelines concerning the management of delayed deliveries have already been proposed [3,5]. However, according to the aforementioned results, our review put together all the data available in the literature, and offer possible strategies with a grade of recommendation in (Figure 1), to help obstetricians and parents in the management of asynchronous deliveries. Although some patients have been sent home a few days after the first birth, we vividly recommend hospitalization for better medical supervision. Besides we noticed that delayed delivery has been tried with success in monochorial pregnancies, thus this is not an absolute contraindication for future attempts.

Conclusion

To conclude, delaying the delivery of second twins increases their survival rate and their birth weight compared to their first delivered sibling, and also compared to control cases. The later was the delivery of the first twin, the better was the second twin's survival rate, but the shorter was the interval delay. It seems like delaying the delivery comes up with interesting results, whether the birth of the first fetus comes up before 24 weeks or after.

Maternal complications included chorioamniotitis, and fetal complications incorporated all the complications of prematurity especially retinopathy, septicemia and intraventricular hemorrhage, though these complications may be reduced for second twins.

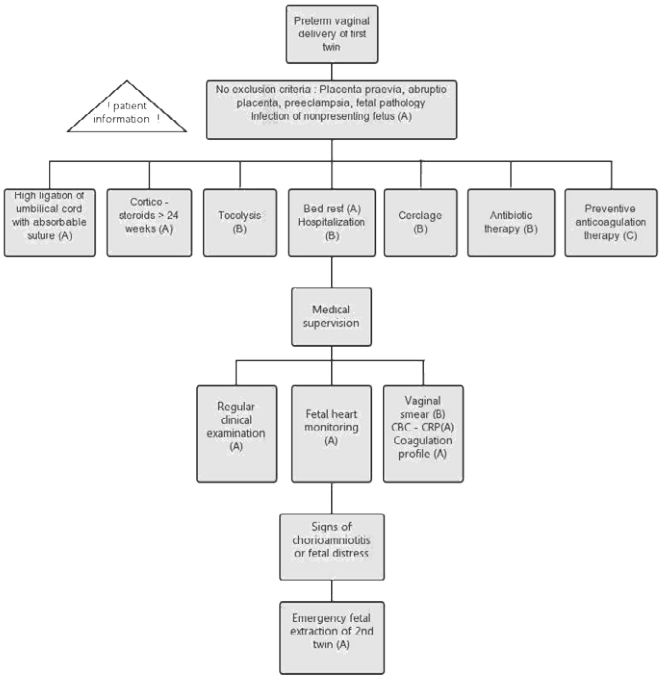

Figure 1: Decisional tree for the management of delayed delivery in multiple pregnancies.
(A) = grade of recommendation A, based on level 1 evidence (from meta-analysis of randomized controlled trials or from at least one randomized controlled trial)
(B) = grade of recommendation B, based on level 2 evidence (from at least one controlled study without randomization) or extrapolated recommendations from level 1 evidence
(C) = grade of recommendation C, based on level 3 evidence (from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies), or extrapolated recommendations from level 1 and 2 evidence
CBC = complete blood count
CRP = C-reactive protein

Nevertheless the improvements in neonatal reanimation give room for hope for a better future in these children.

The events that were associated with a successful management were: the delivery of the first twin after 24 weeks, tocolysis, corticoids after 24 weeks, antibiotic therapy and cerclage.

All situations requiring a delayed delivery should be discussed in a multidisciplinary approach with the rest of the medical team, and also with parents after clear and loyal information, with regard to the rate of success (35-41%), the benefit and the risks of such procedure. However, since the prevalence is rare, the medical team may have no experience in this process.

We established a summary of the strategies to adopt in this kind of emergency management of delayed delivery based on a serious review of the literature. However, more prospective studies are needed to evaluate the neurological development and the evolution of these delayed infants, especially when born extremely premature.

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