Delayed-Interval Delivery of Twins in 13 Pregnancies

Margaux Louchet, Chloé Dussaux, Dominique Luton, François Goffinet, Stéphane Bounan, Laurent Mandelbrot

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Margaux Louchet [1,2,3], Chloé Dussaux [1,2,3], Dominique Luton [2,3,4], François Goffinet [3,5,6], Stéphane Bounan [7], Laurent Mandelbrot[1,2,3,8]

[1] Assistance Publique-Hôpitaux de Paris, Hôpital Louis Mourier, Department of Obstetrics and Gynecology, Colombes, France

[2] Université de Paris, Paris, France

[3] DHU Risques et Grossesse, Paris, France

[4] Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Department of Obstetrics and Gynecology, Paris, France

[5] Assistance Publique-Hôpitaux de Paris, Hôpital Cochin-Port Royal, Department of Obstetrics and Gynecology, Paris, France

[6] Inserm U1153 Epopé, Paris, France

[7] Department of Obstetrics and Gynecology, Hôpital Delafontaine, Saint-Denis, France

[8] Inserm IAME U1137, F-75018 Paris, France

Corresponding author:

Prof Laurent Mandelbrot, MD

Service de Gynécologie-Obstétrique, Hôpital Louis Mourier, Université Paris-Diderot

178 rue des Renouillers

92700 Colombes, France

+33147606339

laurent.mandelbrot@aphp.fr

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Abstract

Background :

Delayed interval delivery is a rare practice aiming at prolonging gestation for the second twin in case of pre-viable birth of twin one. Our objective was to identify factors related to successful delayed delivery of the second twin, among cases in which the interval after delivery of the first twin was above 24 hours.

Method :

A descriptive, retrospective and multicenter study of all delayed interval deliveries in dichorionic twins in 4 perinatal centers in Paris over a 14-year period**.**

Results :

In 13 cases of delayed interval delivery, delivery of twin 1 was at a median of 18 weeks' gestation (range 14WG+2days to 24WG), and none survived. Delivery of the second twin occurred at a median of 25 weeks' gestation +3 days, 51 days after twin 1 (range 13 to 138 days). Seven of the 13 second twins (54%) survived. There were 5 cases of chorioamnionitis and 1 case of maternal disseminated intravascular coagulation. Poor outcome was not significantly associated with the gestational age, presentation for PPROM or inflammatory markers (C-reactive protein and white blood cell count) at the time of delivery of twin 1.

Conclusion :

Delayed-interval delivery of the second twin may prolong pregnancy and lead the second twin child to a viable term of birth; but carries a risk of maternal complications.

Key words : Delayed interval delivery; twins ; preterm delivery; asynchronous birth

INTRODUCTION

Delayed delivery of the second twin is a little-known practice, aimed at prolonging the gestation until viability in case of very premature delivery of the first fetus. The first case, with a delay of 44 days until delivery of the second twin was reported by L. Carson in 1880[1]. This rare practice is mostly the topic of case reports and few retrospective cohorts. Obstetricians may be confronted with this situation when the second twin is not born spontaneously after the birth of twin one. However, there is a lack of data to inform patients and to anticipate whether it is reasonable or not to consider delayed second twin delivery [2].

The purpose of our study was to identify factors related to favorable outcomes in delayed delivery of the second twin, among cases in which the interval after delivery of the first twin was above 24 hours.

METHODS

We carried out a retrospective, multicenter study in 4 tertiary care maternity hospitals in the Paris region, from January 2005 to August 2018. We included cases of delayed delivery for which the 1st twin was born after 14 weeks' gestation (WG), thus excluding first-trimester miscarriages, and for which the second twin was not born within 24 hours of twins 1. We set no gestational age limit for delivery of twin 2. We excluded cases of delayed delivery after selective termination of pregnancy or known malformation of one or both fetuses.

The case search was conducted using the obstetrical databases in each center for the ICD-10-CM Diagnosis Codes O31.10X0 "Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester, not applicable or unspecified" and Z37.3 "Twins, one liveborn and one stillborn".

Data were extracted and anonymized from the patients' computer files (DiammG, Micro6, Nancy, France) and archived paper records. The variables of interest at baseline were maternal history and the course of pregnancy. The delivery data were for twin 1 and twin 2: reason for presentation, gestational age, clinical examination, ultrasound, and biological findings (including markers of inflammation or infection). We examined the events of the surveillance period between the two births (clinical examination, biology, ultrasound and management), postpartum events and perinatal outcomes. We reported outcomes as defined in the EPIPAGE 2 study (Etude épidémiologique sur les Petits Ages Gestationnels 2, a national prospective population-based cohort study in France). Severe maternal morbidity and

mortality was defined as the occurrence of at least 1 of the following complications: severe postpartum hemorrhage defined by the use of a blood transfusion, intensive care unit admission, or death[3]. Neuromotor and sensory disabilities in infants is defined as levels 2-5 of the Gross Motor Function Classification System for cerebral palsy with or without unilateral or bilateral blindness or deafness)[4]. We also collected the placental pathology findings, and post-mortem examinations when available.

This study was approved by the French National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n° 1755849). Under French law, retrospective observational studies using anonymized data from medical records are exempt from IRB review. All women were informed that their hospital records can be used for the evaluation of medical practices and provided the option to opt out of these studies.

RESULTS

We collected data from 13 biamniotic bichorionic twin pregnancies (Table 1). Twelve pregnancies were obtained by in vitro fertilization and one was spontaneous (case 13). There was no triplet or higher-order pregnancy. The median maternal age was 34 years (range 28 to 36 years old), median gravidity was 2.7 (range 1 to 7). Uterine malformations were suspected or confirmed for 3 patients.

Seven patients initially consulted for preterm premature rupture of the membranes (PPROM) at a median gestational age of 16 WG + 6 days [16+3 ; 21+3] (Table 2). In utero demise of twin 1 was diagnosed at admission in 4 cases. At admission, no patient had fever but there was an inflammatory syndrome with a C-reactive protein (CRP) above 10 in five cases. The median CRP at admission was 16 mg / L [5 ; 32] and median white blood cell count was 11G / L [10 ; 13]. Vaginal swab samples were positive in 4 patients and all urine cultures were negative. 9 patients were treated with amoxicillin and 1 patient did not receive antibiotics (3 missing data).

All 13 patients had spontaneous vaginal delivery of twin 1. Only one patient (case 12) was febrile at the time of delivery. The median gestational age for delivery of twin 1 was 18 WG [16+3 ; 21+6] from 14+2 to 24 WG. No first twin survived. There was no case of spontaneous delivery of the first placenta.

After delivery of the first fetus, intravenous prophylactic antibiotics were used for 10 patients (Table 1). Cervical cerclage was performed in 2 cases, 10 and 14 days, respectively, following

delivery of twin 1. On the blood test after delivery (one or two days later), the results were stable with a median CRP of 10 mg / L [4 ; 19] and leukocytosis of 11G / L [9 ; 13]. Subsequently, 5 patients remained hospitalized and 8 were monitored in home hospitalization. Home hospitalization was as for premature rupture of the membranes: monitoring of inflammatory syndrome, vaginal swab samples and daily cardiotocograms beyond 24 WG. Corticosteroid maturation with betamethasone was administered in 7 patients (cases n° 1, 2, 5, 7, 8, 10 and 12) among the 9 who delivered after 24WG. Corticosteroid maturation was administered at a median of 24WG + 4 days [23+5 ; 25+3] from 23 to 29 WG + 5 days. For case n°11, corticosteroids were not administered because there were no contractions during the expectative period and for case n°13, it was decided with the neonatologist to withhold the injection because of chorioamnionitis and active labor. Tocolysis was used for three patients: with intravaginal progesterone in one case, with intramuscular progesterone in one case and with intravenous nicardipine in one case (during transfer to a tertiary level center).

The median gestational age for delivery of twin 2 was 25 WG + 3days [22+5; 31+2] from 18+2 to 36+6 WG. The median delay after delivery of twin one was 51 days (range 13 to 138 days). Magnesium sulfate for neuroprotection of the neonate was administered for 3 patients (cases n° 1, 7 and 12) (3 among the 5 patients who delivered between 23 and 32WG). The delivery of twin 2 occurred after spontaneous labor for 10 patients and after induction for 3 patients. Biological inflammatory markers were a median CRP of 14 mg/L [5 ; 32] and white blood cell count (WBC) of 11.5 G/L [10.7 ; 12.6].

Neonatal outcomes for twin 2 were 7 liveborn and 6 stillbirths or neonatal deaths. The characteristics for the 2 groups are summarized in Table 3. There was no significant difference in perinatal outcome according to the gestational age at the time of delivery of twin 1 (17+5 WG vs 18WG). Although the proportion of PPROM was higher in the group with poor outcome, the difference was not statistically significant. Nor was the difference in inflammatory markers, CRP and WBC counts at the time of delivery of twin 2.

Among the liveborn children, 3 were admitted into neonatal intensive care (cases 1, 7 and 9). None of the three children had any neuromotor nor sensory disabilities (as defined in EPIPAGE 2 study). Twin 2 from case n°1, born at 28WG, has severe asthma but normal neurobehavioral development at 14 months. The child from case n°7, born at 25WG+6 days, has normal neurobehavioral development at 3 years of age. The child from case n°9, born at 25WG+3

days, has persistence of the arterial canal but normal neurobehavioral development at 14 months.

The four others (cases 8, 10, 11 and 12) were live born at favorable gestational ages, 36WG+6days, 31WG+5 days, 35WG+2 days, and 31WG+2 days. They are healthy at the moment of the maternal post-natal visit (two to three months post partum). We have no long-term follow-up for case n°10.

Regarding maternal outcomes, 3 women had no postpartum complication (cases n°2, 6, 13). There were 5 cases of chorioamnionitis at delivery of twin 2 (diagnosed with fever, abdominal pain and biological inflammatory syndrome). 3 mothers (23%) had severe maternal morbidity. 2 patients (cases 5 and 9) had severe postpartum hemorrhage requiring sulprostone and blood transfusion. In case 5, the patient had DIC beginning prior to delivery, in a context of fetal growth restriction and oligohydramnios. One patient (case 4) was admitted to the intensive care unit for septic shock in the immediate postpartum period, which was treated with ephedrine, tazocilline and amikacine. Patient n°7 had a postpartum endometritis.

Bacteriological examination of the stillborn infants was not contributive. Histopathological examination of the placenta showed signs of hypoxia or villous infarction for twin 1 in 2 cases.

DISCUSSION

This study is the second-largest French retrospective cohort to date, reflecting the fact that this approach is uncommon, since the cases of was identified over a 14-year period in four centers which totalize over 15000 deliveries of more per year. Since Carlson's 1880 pioneering case report, there have been only two prospective studies of delayed-interval twin delivery. Arias[5] reported 8 cases managed with cerclage, tocolysis and antibiotics, with a mean interval to the second birth of 48 days. Arabin et al.[6] reported 50 cases, 38 twins and 12 triplets, with a mean interval of 19 days between twins and 18 days for triplets. Most publications are case reports or retrospective cohort studies. We have summarized the studies reporting four or more cases in Table 4.

In our series, the rate of favorable outcomes for the second twin, without neuromotor nor sensory disabilities and survival through discharge from neonatal care, was over one half. Since all of the first twins were pre-viable and died, presumably the second twins would not

have survived with conventional management. The success rate is consistent with previous reports.

In our cohort, the median gestational age at delivery of twin 1 was 18 WG, which is earlier than in the literature, since we excluded those beyond 24 WG. The delivery of twin 1 was subsequent to in utero fetal demise in nearly one third of our cases, and 25% in the literature[8]. Gestational age at birth was the major prognostic factor for survival of twin 2. However the gestational age at delivery of twin 1 was not related to the outcome for twin 2 in our cohort. In the literature, when delivery of twin 1 occurred before 24-25 WG, studies showed that interval delivery increased survival of twin 2, compared to twin 1 : 33% vs 13% for Zhang[7] (p=0.01), 50% vs 0% for Arabin[6](p<0.001) and 44.8% vs 7.8% for Tran[9]. The advantage was less clear when delivery of twin 1 was after 24-25 WG, where some studies showed a significant improvement in survival for twin 2[7, 9, 10] whereas others found that twin 1 and twin 2 had the same survival rate [11]. The median latency period between the deliveries of the two twins was 51 days in our cohort, which is longer than in the largest retrospective studies, where it ranged from 6 days[7] to 49 days[5]. The gestational age at the first delivery did not seem to affect the latency period[12]

Regarding neonatal morbidities, the rate of infectious complications for the second twin was high, with a 42% incidence of sepsis[9]. Other complications were mostly related to prematurity. Additionally, the proportion of SGA (small for gestational age) increased with the interval between the two deliveries[11].

Regarding the mothers, the risks were mainly chorioamnionitis in 22%[6] and endometritis in 29%[12] of cases reported. Several cases of septic shock have been described[13], [14] and one patient even required an emergency hysterectomy[2].

We failed to identify prognostic factors at presentation, since the association with a context of premature rupture of the membranes or elevated inflammatory markers did not reach statistical significance.

There remains a lack of evidence on which to base management. The initial presentation was PPROM in 67 to 86% of cases[2], leading rapidly to spontaneous labor in over one half of cases, as found in our study and others. The indications for antibiotics at diagnostic of PPROM are similar to those in twin pregnancies[16]. In most cases, the first placenta was not delivered spontaneously, and was left in place without any attempt at manual removal. A resorbable

ligature should be placed as high as possible without exerting cord traction. Vaginal cleansing with antiseptics was usually performed.

Antibiotics are indicated as prophylaxis, and in previous studies were continued in 42.8% of cases[12] ; they might be adapted to vaginal or urinary microbiological results. After delivery of twin 1, repeated testing for infection was performed including WBC counts, CRP and vaginal microbiology.

Tocolysis was used liberally in the literature, in 94% of the cases after of twin 1 at gestational ages before 24 WG. Although there is concern about the risk of infection, a short course of tocolysis may reduce severe neurological outcome[17] and allow for fetal lung maturation with betamethasone[18], which was prescribed for delayed deliveries in 96% of patients after 24 WG[9]. Cervical cerclage was performed sparingly in our experience, in patients who were not in labor after delivering twin 1. There is no consensus on the literature. In the review by Zhang et al. [19], cerclage was associated with a longer interval to the birth of the second twin, 25 days, versus 8 days in patients without cerclage. A shorter intertwin interval was also found in two additional retrospective studies[20], [21]. There is concern that cerclage may increase the risk of infection, although this was not the case in the review by Zhang et al [19]. Thus, some authors propose cerclage only in case of persistent cervical dilation[21]. The presence of uterine malformations, which are more frequent in infertile patients[22, 23], may be an additional reason to consider cerclage.

Some other aspects of clinical care have received little attention. Outpatient management may be considered in the absence of any signs of infection or contractions. Ultrasound surveillance should be repeated because of the risk of SGA. There is no mention in the literature of the role of psychological support, which should be encouraged in this stressful context.

For the delivery of twin 2, labor was usually spontaneous, with vaginal delivery in 76% of cases[6], [12]. The indications for labor induction or cesarean section are not specific to this situation, mainly abnormal fetal heart rate tracings, symptoms or signs of infection, DIC, pre-eclampsia.

In our study, as in most previous reports, the number of cases was small, leading to lack of power to study prognostic factors; furthermore, data was lacking on long-term follow-up. The main limitation to all retrospective studies is the lack of information on intention to treat.

Cases for which the obstetrician attempted a delayed delivery, but the second twin was born within 24 hours after the first, were not identified in our study, nor in the literature. After delivery of the first twin, it has been estimated that contraindications to continuing the pregnancy, such as intrauterine infection with fever or hemorrhage, are present in more than one half of very preterm twin deliveries [6]. In the absence of obvious contra-indications, it is likely that even if there is an attempt to delay delivery, uterine contractions will continue or reappear, leading to delivery of the second twin. Thus, defining delayed-interval delivery as more than 24 hours after the first twin, as is usual in the literature, excludes cases for which expectant management was attempted but failed. It is important to point out that no survival rates nor prognostic factors may be advanced before 24 hours of successful expectant management.

There are several unresolved issues for clinical practice, in addition to the original decision to attempt delayed second twin delivery: how to manage the placenta, how to prevent infection, whether to use tocolysis, whether to perform cerclage, the place of outpatient management and when to induce the delivery of twin 2.

Delayed triplet deliveries, which were not observed in our experience, have been reported in in the literature[24, 25,26, 27, 28]. With a mean of 18 days between the 1st and 3rd triplet deliveries; the delivery of the 2nd and 3rd occurring on the same day for 10 cases/12 for Arabin[6]. Exceptional cases have been described of delayed birth in case of quadruplet pregnancy[29, 30, 28, 25, 31]; or even quintuplets[32].

Delayed 2nd-twin delivery raises several ethical issues. Pre-viable delivery of the first twin is a dramatic and often unpredictable event. The perspective of successful delayed delivery can only be estimated after 24 hours, but the initial decision must be made on an emergency basis on whether to expedite delivery of the second twin or to attempt expectant management. Furthermore, there is a conflict of interest between the potential benefit for the fetus and the potential risk for the mother. This type of conflict of interest is similar to the one more commonly addressed in cases of preterm premature rupture of membranes before 24 weeks. Thus, couples should receive complete information as early as possible, at the beginning of labor or PROM. They should be informed that the most likely outcome in case of delivery of twin 1 will be the rapid delivery of twin 2, even in case of expectant management, that delayed delivery may be considered in some cases, and that if delivery is delayed more than 24 hours,

the chance of survival of twin 2 with in most cases severe prematurity will be on the order of one half. They must also be advised that delayed-interval deliveries carry a risk of maternal complications such infections and hemorrhage. The original decision to perform expectant management may be reversed secondarily.

CONCLUSION

In this study, we confirm that delayed delivery after very premature delivery of the 1st twin can in some cases improve the survival rate of the 2nd twin. The benefits are clearest for pre-viable deliveries of the first twin and less so at more advanced gestational ages. If delivery of the first child occurs before the limit of viability and if the second child is not born spontaneously, expectant management may be considered. However, this must remain an exceptional practice in view of the maternal risks and lack of long-term follow-up of the babies. It is necessary to obtain informed consent, which should preferably be discussed prior to the delivery of twin 1, and closely monitor these very high-risk pregnancies.

Table 1. Description of 13 cases of delayed-interval delivery of the second twin

	Delivery of first twin				Delivery of second twin				
Case	Presentation	Gestational age (WG)	Management After delivery	Discharge to home hospitalization	Presentation	Mode of delivery	Gestational age (WG)	Time from 1st delivery (days)	Outcome of twin 2
1	IUFD of T1	18	0	yes	Spontaneous labor	CS	28	70	Alive
2	IUFD of T1	17+3	0	yes	Chorioamnionitis Spontaneous labor	VB	21+6	31	Stillborn
3	Spontaneous labor	14+2	Vaginal PG	yes	Spontaneous labor	VB	18+2	28	Stillborn
4	Spontaneous labor	19+3	IM PG	no	Chorioamnionitis	VB	22+5	23	Neonatal death at 150min
5	Spontaneous labor	18	0	yes	DIC, induction	VB	25+2	51	Intra partum demise
6	IUFD of T1	17+3	0	no	Chorioamnionitis, Spontaneous labor	VB	19+2	13	Stillborn
7	Spontaneous labor	24	0	no	Chorioamnionitis, Spontaneous labor	CS	25+6	13	Alive
8	Chorioamnionitis	22+3	0	yes	Spontaneous labor	VB	36+6	101	Alive
9	Spontaneous labor	16+3	0	yes	Spontaneous labor	CS	25+3	63	Alive
10	Spontaneous labor	16+1	cerclage	no	Spontaneous labor	VB	31+5	109	Alive
11	Spontaneous labor	15+4)	cerclage	yes	Spontaneous labor	VB	35+2	138	Alive
12	Influenza, IUFD	21+6	0	yes	Spontaneous labor	VB	31+2	66	Alive
13	Chorioamnionitis	21+6	0	no	Chorioamnionitis, induction	VB	24+2	17	Intra partum demise

CS : cesarean section, DIC : disseminated intravascular coagulation, IM: intramuscular; IUFD: intra utero fetal death, min: minute; NA : not available,, PG: progesterone; VB : vaginal birth, WG: week of gestation

Table 2. Markers of infection and antibiotic therapy in 13 cases of delayed-interval delivery of the second twin

	Delivery of 1st twin				Interval period		Delivery of 2nd twin			
Case	**CRP**	**WBCs**	**ABX**	**Vaginal pathogens on admission**	**Change of ABX**	**Vaginal pathogens**	**CRP**	**WBCs**	**Vaginal pathogens in labor**	**ABX Post-partum**
1	3	10	amox	0	CF3-MTZ	E. faecalis	5	13	0	0
2	8	10	amox	0	CF3	BV, P. bivia	81	13	BV	0
3	2	16	NA	C.Koseri, E.Coli	amox	BV	2	11	0	0
4	7	9	amox	E. Coli	CF3	E. Coli	28	13	E. Coli	CF3, tazocilline
5	NA	NA	NA	NA	UD	NA	3	13	E. Coli	amox
6	16	15	amox	C. Albicans, E. ColiK1	amox-genta	NA	24	11	NA	amox-clav
7	35	12	amox	E. Coli	CF3	0	51	12	E. Coli (CF3-R)	tazocilline
8	35	13	amox	C Albicans	amox-genta	BV	11	12	NA	0
9	4	7	0	0	NA	BV	5	7	BV	amox-MTZ
10	5	7	amox	0	amox	E. Coli	5	7	NA	0
11	NA	NA	NA	NA	NA	NA	14	9	NA	0
12	32	11	amox	G. vaginalis, GBS	CF3-genta	NA	32	11	GBS	amox
13	32	NA	amox	0	amox	C. Freundii, S.Aureus, K. Pneumoniae	74	16	NA	CF3-genta-MTZ

ABX: antibiotics, amox : amoxicillin, clav : clavulanic acid; bacterial vaginosis; CF3: 3rd generation cephalosporin, CRP : C-reactive protein, GBS : group B streptococcus, genta : gentamycin, MTZ: metronidazole, NA : not available, WBCs: white blood cells

Table 3. Characteristics at baseline and at the time of the second delivery, according to the outcome for the 2nd twin

	Stillborn* (n=6)	Liveborn** (n=7)
Baseline, twin 1 delivery		
Following PPROM	4/6 (66%)	4/7 (57%)
Following IUFD	2/6 (33%)	1/7 (12.5%)
Gestational age (WG)* **	17+5 [17+3; 19+1]	18 [16+2; 22+1]
CRP (mg/L)* **	13 [6; 22]	5 [4; 34]
WBCs (G/L)* **	10 [10; 13]	11 [9; 12]
Twin 2 delivery		
Gestational age (WG)*	22+2 [19+6; 23+6]	31+2 [26+6; 33+4]
Birthweight (grams)* **	520 [480; 540]	1330 [1030; 2033]
CRP (mg/L)* **	26 [8; 63]	11 [5; 23]
WBCs (G/L)* **	13 [12; 13]	11 [8; 12]

* Stillborn: cases 2, 3, 4, 5, 6, 13

** Liveborn: cases 1, 7, 8, 9, 10, 11, 12

***median [range]

CRP : C-reactive protein; IUFD: intra utero fetal death ; PPROM: preterm premature rupture of membranes; WBCs: white blood cells; WG: week of gestation

Table 4. Literature Review of delayed-interval twin deliveries (from 1994 to 2009)

Study	Number of cases	Twin 1 survival rate (mean gestational age)	Twin 2 survival rate (mean gestational age)	Management	Maternal complications
Arias F, 1994[5]	n=4	NA (19.6WG)	NA (26.7WG)	Tocolysis+CC+ATB	
Kalchbrenner DO.1998[33]	n=5	57% (22.6WG)	78% (27.4WG)		Chorioamnionitis 43%
Farkouch L. 2000[8]*	n=24 T1<24WG, n=16 T1>24WG, n=9	16% (22.7WG) 0% 44%	63% (27.9WG) 44% 100%	Tocolysis+CC (100%) Excludes: chorioamnionitis of T2	Endometritis 29% 1 Pelvic thrombophlebitis
Fayad S. 2002[12]	n=28	7.4% (20.8WG)	79% (27.9WG)	Tocolysis (82%), ATB (100%), CC (32%)	Chorioamnionitis 28.5%
Hamersley SL. 2002[34]	n=6 T1<24WG, n=6	NA	83%	Tocolysis+CC+ATB	
Zhang J. 2004[7]	n=200 T1<23WG, n=130 T1>24WG, n=70	18% (23WG) 13% (21.5WG) 61% (25.4WG)	50% 33% (23WG) 82% (27.1WG)		
Livingston JC, 2004 [2]	n=14	7% (21WG)	37% (21.2WG)	Tocolysis+ATB (100%)	1 Septic Shock
Oyelese Y. 2005[11]	n=258 T1<24WG, n=114 T1>24WG, n=144	18% 63%	44% 74%		
Rosbergen M. 2005[35]	n=23	35% (24.2WG)	70% (27.1WG)	Tocolysis+ATB (100%)	
Arabin B. 2009[6]	n=38 T1<25WG, n=18 T1>25WG, n=20	34% 0% 65%	74% 50% 95%	Tocolysis+ATB (100%)	Chorioamnionitis 22% Retained placenta 10%
Roman AS.2011[36]	n=19	15.6% (20.2WG)	53.8% (25.2WG)		1 hysterectomy for hemorrhage
Reinhard J.2012[37]	n=5	20% (23.2 WG)	60% (25WG)		

Doger E.[3]2014[3]	n=10	0% (17+4 WG)	30% (23+2WG)	Tocolysis +/-CC+ATB	
Kolben T. 2019[39]	n=14 T1<23 WG, n=9 T1>23WG, n=6	46.7% (15.2 WG) 22.2% 83.3%	82.4% (26WG) 0% 93%	Tocolysis+CC+ATB	

** Analyse includes triplets*
CC: cervical cerclage, T1: twin 1, WG: week of gestation, NA : not available

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Delayed-Interval Delivery of Twins in 13 Pregnancies

Margaux Louchet [1,2,3], Chloé Dussaux [1,2,3], Dominique Luton [2,3,4], François Goffinet [3,5,6], Stéphane Bounan [7], Laurent Mandelbrot[1,2,3,8]

[1] Assistance Publique-Hôpitaux de Paris, Hôpital Louis Mourier, Department of Obstetrics and Gynecology, Colombes, France

[2] Université de Paris, Paris, France

[3] DHU Risques et Grossesse, Paris, France

[4] Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Department of Obstetrics and Gynecology, Paris, France

[5] Assistance Publique-Hôpitaux de Paris, Hôpital Cochin-Port Royal, Department of Obstetrics and Gynecology, Paris, France

[6] Inserm U1153 Epopé, Paris, France

[7] Department of Obstetrics and Gynecology, Hôpital Delafontaine, Saint-Denis, France

[8] Inserm IAME U1137, F-75018 Paris, France

Corresponding author:

Prof Laurent Mandelbrot, MD

Service de Gynécologie-Obstétrique, Hôpital Louis Mourier, Université Paris-Diderot

178 rue des Renouillers

92700 Colombes, France

+33147606339

laurent.mandelbrot@aphp.fr

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Abstract

Background :

Delayed interval delivery is a rare practice aiming at prolonging gestation for the second twin in case of pre-viable birth of twin one. Our objective was to identify factors related to successful delayed delivery of the second twin, among cases in which the interval after delivery of the first twin was above 24 hours.

Method :

A descriptive, retrospective and multicenter study of all delayed interval deliveries in dichorionic twins in 4 perinatal centers in Paris over a 14-year period.

Results :

In 13 cases of delayed interval delivery, delivery of twin 1 was at a median of 18 weeks' gestation (range 14WG+2days to 24WG), and none survived. Delivery of the second twin occurred at a median of 25 weeks' gestation +3 days, 51 days after twin 1 (range 13 to 138 days). Seven of the 13 second twins (54%) survived. There were 5 cases of chorioamnionitis and 1 case of maternal disseminated intravascular coagulation. Poor outcome was not significantly associated with the gestational age, presentation for PPROM or inflammatory markers (C-reactive protein and white blood cell count) at the time of delivery of twin 1.

Conclusion :

Delayed-interval delivery of the second twin may prolong pregnancy and lead the second twin child to a viable term of birth; but carries a risk of maternal complications.

Key words : Delayed interval delivery; twins ; preterm delivery; asynchronous birth

INTRODUCTION

Delayed delivery of the second twin is a little-known practice, aimed at prolonging the gestation until viability in case of very premature delivery of the first fetus. The first case, with a delay of 44 days until delivery of the second twin was reported by L. Carson in 1880[1]. This rare practice is mostly the topic of case reports and few retrospective cohorts. Obstetricians may be confronted with this situation when the second twin is not born spontaneously after the birth of twin one. ~~The practice cannot be recommended on a large scale but might be considered in some very favorable cases.~~ However, there is a lack of data to inform patients and to anticipate ~~after the birth of the first twin~~ whether it is reasonable or not to consider delayed second twin delivery ~~and inform patients~~ [2].

The purpose of our study was to identify factors related to favorable outcomes in delayed delivery of the second twin, among cases in which the interval after delivery of the first twin was above 24 hours.

METHODS

We carried out a retrospective, multicenter study in 4 tertiary care maternity hospitals in the Paris region, from January 2005 to August 2018. We included cases of delayed delivery for which the 1st twin was born after 14 weeks' gestation (WG), thus excluding first-trimester miscarriages, and for which the second twin was not born within 24 hours of twins 1. We set no gestational age limit for delivery of twin 2. We excluded cases of delayed delivery after selective termination of pregnancy or known malformation of one or both fetuses.

The case search was conducted using the obstetrical databases in each center for the ICD-10-CM Diagnosis Codes O31.10X0 "Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester, not applicable or unspecified" and Z37.3 "Twins, one liveborn and one stillborn".

Data were extracted and anonymized from the patients' computer files (DiammG, Micro6, Nancy, France) and archived paper records. The variables of interest at baseline were maternal history and the course of pregnancy. The delivery data were for twin 1 and twin 2: reason for presentation, gestational age, clinical examination, ultrasound, and biological findings (including markers of inflammation or infection). We examined the events of the surveillance period between the two births (clinical examination, biology, ultrasound and management), postpartum events and perinatal outcomes. We reported outcomes as defined

in the EPIPAGE 2 study (Etude épidémiologique sur les Petits Ages Gestationnels 2, a national prospective population-based cohort study in France). Severe maternal morbidity and mortality was defined as the occurrence of at least 1 of the following complications: severe postpartum hemorrhage defined by the use of a blood transfusion, intensive care unit admission, or death[3]. Neuromotor and sensory disabilities in infants is defined as levels 2-5 of the Gross Motor Function Classification System for cerebral palsy with or without unilateral or bilateral blindness or deafness)[4]. We also collected the placental pathology findings, and post-mortem examinations when available.

This study was approved by the French National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n° 1755849). Under French law, retrospective observational studies using anonymized data from medical records are exempt from IRB review. All women were informed that their hospital records can be used for the evaluation of medical practices and provided the option to opt out of these studies.

RESULTS

We collected data from 13 biamniotic bichorionic twin pregnancies (Table 1). Twelve pregnancies were obtained by in vitro fertilization and one was spontaneous (case 13). There was no triplet or higher-order pregnancy. The median maternal age was 34 years (range 28 to 36 years old), median gravidity was 2.7 (range 1 to 7). Uterine malformations were suspected or confirmed for 3 patients.

Seven patients initially consulted for preterm premature rupture of the membranes (PPROM) at a median gestational age of 16 WG + 6 days [16+3 ; 21+3] (Table 2). In utero demise of twin 1 was diagnosed at admission in 4 cases. At admission, no patient had fever but there was an inflammatory syndrome with a C-reactive protein (CRP) above 10 in five cases. The median CRP at admission was 16 mg / L [5 ; 32] and median white blood cell count was 11G / L [10 ; 13]. Vaginal swab samples were positive in 4 patients and all urine cultures were negative. 9 patients were treated with amoxicillin and 1 patient did not receive antibiotics (3 missing data).

All 13 patients had spontaneous vaginal delivery of twin 1. Only one patient (case 12) was febrile at the time of delivery. The median gestational age for delivery of twin 1 was 18 WG [16+3 ; 21+6] from 14+2 to 24 WG. No first twin survived. There was no case of spontaneous delivery of the first placenta.

After delivery of the first fetus, intravenous prophylactic antibiotics were used for 10 patients (Table 1). Cervical cerclage was performed in 2 cases, 10 and 14 days, respectively, following delivery of twin 1. On the blood test after delivery (one or two days later), the results were stable with a median CRP of 10 mg / L [4 ; 19] and leukocytosis of 11G / L [9 ; 13]. Subsequently, 5 patients remained hospitalized and 8 were monitored in home hospitalization. Home hospitalization was as for premature rupture of the membranes: monitoring of inflammatory syndrome, vaginal swab samples and daily cardiotocograms beyond 24 WG. Corticosteroid maturation with betamethasone was administered in 7 patients (cases n° 1, 2, 5, 7, 8, 10 and 12) among the 9 who delivered after 24WG. Corticosteroid maturation was administered at a median of 24WG + 4 days [23+5 ; 25+3] from 23 to 29 WG + 5 days. For case n°11, corticosteroids were not administered because there were no contractions during the expectative period and for case n°13, it was decided with the neonatologist to withhold the injection because of chorioamnionitis and active labor. Tocolysis was used for three patients: with intravaginal progesterone in one case, with intramuscular progesterone in one case and with intravenous nicardipine in one case (during transfer to a tertiary level center).

The median gestational age for delivery of twin 2 was 25 WG + 3days [22+5; 31+2] from 18+2 to 36+6 WG. The median delay after delivery of twin one was 51 days (range 13 to 138 days). Magnesium sulfate for neuroprotection of the neonate was administered for 3 patients (cases n° 1, 7 and 12) (3 among the 5 patients who delivered between 23 and 32WG). The delivery of twin 2 occurred after spontaneous labor for 10 patients and after induction for 3 patients. Biological inflammatory markers were a median CRP of 14 mg/L [5 ; 32] and white blood cell count (WBC) of 11.5 G/L [10.7 ; 12.6].

Neonatal outcomes for twin 2 were 7 liveborn and 6 stillbirths or neonatal deaths. The characteristics for the 2 groups are summarized in Table 3. There was no significant difference in perinatal outcome according to the gestational age at the time of delivery of twin 1 (17+5 WG vs 18WG). Although the proportion of PPROM was higher in the group with poor outcome, the difference was not statistically significant. Nor was the difference in inflammatory markers, CRP and WBC counts at the time of delivery of twin 2.

Among the liveborn children, 3 were admitted into neonatal intensive care (cases 1, 7 and 9). None of the three children had any neuromotor nor sensory disabilities (as defined in EPIPAGE 2 study). Twin 2 from case n°1, born at 28WG, has severe asthma but normal neurobehavioral development at 14 months. The child from case n°7, born at 25WG+6 days, has normal

neurobehavioral development at 3 years of age. The child from case n°9, born at 25WG+3 days, has persistence of the arterial canal but normal neurobehavioral development at 14 months.

The four others (cases 8, 10, 11 and 12) were live born at favorable gestational ages, 36WG+6days, 31WG+5 days, 35WG+2 days, and 31WG+2 days. They are healthy at the moment of the maternal post-natal visit (two to three months post partum). We have no long-term follow-up for case n°10.

Regarding maternal outcomes, 3 women had no postpartum complication (cases n°2, 6, 13). There were 5 cases of chorioamnionitis at delivery of twin 2 (diagnosed with fever, abdominal pain and biological inflammatory syndrome). 3 mothers (23%) had severe maternal morbidity. 2 patients (cases 5 and 9) had severe postpartum hemorrhage requiring sulprostone and blood transfusion. In case 5, the patient had DIC beginning prior to delivery, in a context of fetal growth restriction and oligohydramnios. One patient (case 4) was admitted to the intensive care unit for septic shock in the immediate postpartum period, which was treated with ephedrine, tazocilline and amikacine. Patient n°7 had a postpartum endometritis.

Bacteriological examination of the stillborn infants was not contributive. Histopathological examination of the placenta showed signs of hypoxia or villous infarction for twin 1 in 2 cases.

DISCUSSION

This study is the second-largest French retrospective cohort to date, reflecting the fact that this approach is uncommon, since the cases of was identified over a 14-year period in four centers which totalize over 15000 deliveries of more per year. Since Carlson's 1880 pioneering case report, there have been only two prospective studies of delayed-interval twin delivery. Arias[5] reported 8 cases managed with cerclage, tocolysis and antibiotics, with a mean interval to the second birth of 48 days. Arabin et al.[6] reported 50 cases, 38 twins and 12 triplets, with a mean interval of 19 days between twins and 18 days for triplets. Most publications are case reports or retrospective cohort studies. We have summarized the studies reporting four or more cases in Table 4.

In our series, the rate of favorable outcomes for the second twin, without neuromotor nor sensory disabilities and survival through discharge from neonatal care, was over one half. Since all of the first twins were pre-viable and died, presumably the second twins would not

have survived with conventional management. The success rate is consistent with previous reports.

In our cohort, the median gestational age at delivery of twin 1 was 18 WG, which is earlier than in the literature, since we excluded those beyond 24 WG. The delivery of twin 1 was subsequent to in utero fetal demise in nearly one third of our cases, and 25% in the literature[8]. Gestational age at birth was the major prognostic factor for survival of twin 2. However, the gestational age at delivery of twin 1 was not related to the outcome for twin 2 in our cohort. In the literature, when delivery of twin 1 occurred before 24-25 WG, studies showed that interval delivery increased survival of twin 2, compared to twin 1 : 33% vs 13% for Zhang[7] (p=0.01), 50% vs 0% for Arabin[6](p<0.001) and 44.8% vs 7.8% for Tran[9]. The advantage was less clear when delivery of twin 1 was after 24-25 WG, where some studies showed a significant improvement in survival for twin 2[7, 9, 10] whereas others found that twin 1 and twin 2 had the same survival rate [11]. The median latency period between the deliveries of the two twins was 51 days in our cohort, which is longer than in the largest retrospective studies, where it ranged from 6 days[7] to 49 days[5]. The gestational age at the first delivery did not seem to affect the latency period[12]

Regarding neonatal morbidities, the rate of infectious complications for the second twin was high, with a 42% incidence of sepsis[9]. Other complications were mostly related to prematurity. Additionally, the proportion of SGA (small for gestational age) increased with the interval between the two deliveries[11].

Regarding the mothers, the risks were mainly chorioamnionitis in 22%[6] and endometritis in 29%[12] of cases reported. Several cases of septic shock have been described[13], [14] and one patient even required an emergency hysterectomy[2].

We failed to identify prognostic factors at presentation, since the association with a context of premature rupture of the membranes or elevated inflammatory markers did not reach statistical significance.

There remains a lack of evidence on which to base management. The initial presentation was PPROM in 67 to 86% of cases[2], leading rapidly to spontaneous labor in over one half of cases, as found in our study and others. The indications for antibiotics at diagnostic of PPROM are similar to those in twin pregnancies[16]. In most cases, the first placenta was not delivered spontaneously, and was left in place without any attempt at manual removal. A resorbable

ligature should be placed as high as possible without exerting cord traction. Vaginal cleansing with antiseptics was usually performed.

Antibiotics are indicated as prophylaxis, and in previous studies were continued in 42.8% of cases[12] ; they might be adapted to vaginal or urinary microbiological results. After delivery of twin 1, repeated testing for infection was performed including WBC counts, CRP and vaginal microbiology.

Tocolysis was used liberally in the literature, in 94% of the cases after of twin 1 at gestational ages before 24 WG. Although there is concern about the risk of infection, a short course of tocolysis may reduce severe neurological outcome[17] and allow for fetal lung maturation with betamethasone[18], which was prescribed for delayed deliveries in 96% of patients after 24 WG[9]. Cervical cerclage was performed sparingly in our experience, in patients who were not in labor after delivering twin 1. There is no consensus on the literature. In the review by Zhang et al. [19], cerclage was associated with a longer interval to the birth of the second twin, 25 days, versus 8 days in patients without cerclage. A shorter intertwin interval was also found in two additional retrospective studies[20], [21]. ~~However, T~~there is concern that ~~it~~ cerclage may increase the risk of infection, although this was not the case in the review by Zhang et al [19]. Thus, some authors propose cerclage only in case of persistent cervical dilation[21]. The presence of uterine malformations, which are more frequent in infertile patients[22, 23], may be an additional reason to consider cerclage.

Some other aspects of clinical care have ~~not~~ received little attention. Outpatient management may be considered in the absence of any signs of infection or contractions. Ultrasound surveillance should be repeated because of the risk of SGA. There is no mention in the literature of the role of psychological support, which should be encouraged in this stressful context.

For the delivery of twin 2, labor was usually spontaneous, with vaginal delivery in 76% of cases[6], [12]. The indications for labor induction or cesarean section are not specific to this situation, mainly abnormal fetal heart rate tracings, symptoms or signs of infection, DIC, pre-eclampsia.

In our study, as in most previous reports, the number of cases was small, leading to lack of power to study prognostic factors ~~a~~; furthermore, ~~nd~~ data was lacking on long-term follow-up. The main limitation to all retrospective studies is the lack of information on intention to

treat. Cases for which the obstetrician attempted a delayed delivery, but the second twin was born within 24 hours after the first, were not identified in our study, nor in the literature. After delivery of the first twin, it has been estimated that contraindications to continuing the pregnancy, such as intrauterine infection with fever or hemorrhage, are present in more than one half of very preterm twin ~~pregnancies~~deliveries ~~and two thirds of triplet pregnancies~~[6]. In the absence of obvious contra-indications, it is likely that even if there is an attempt to delay delivery, uterine contractions will continue or reappear, leading to delivery of the second twin. Thus, defining delayed-interval delivery as more than 24 hours after the first twin, as is usual in the literature, excludes cases for which expectant management was attempted but failed. It is important to point out that no survival rates nor prognostic factors may be advanced before 24 hours of successful expectant management.

~~Thus, there is little data to study prognostic factors for successful delayed delivery. Also, there may be a publication biases in the literature in favor of cases with survival of the second twin. After delivery of the first twin, it has been estimated that contraindications to continuing the pregnancy are present in more than one half of twin pregnancies and two thirds of triplet pregnancies[6]. In our study, as in most previous reports, the number of cases was small, leading to lack of power and data was lacking on long-term follow-up.~~

There are several unresolved issues for clinical practice, in addition to the original decision to attempt delayed second twin delivery: how to manage the placenta, how to prevent infection, whether to use tocolysis, whether to perform cerclage, the place of outpatient management and when to induce~~d~~ the delivery of twin 2.

Delayed triplet deliveries, which were not observed in our experience, have been reported in in the literature[24, 25,26, 27, 28]. With a mean of 18 days between the 1st and 3rd triplet deliveries; the delivery of the 2nd and 3rd occurring on the same day for 10 cases/12 for Arabin[6]. Exceptional cases have been described of delayed birth in case of quadruplet pregnancy[29, 30, 28, 25, 31]; or even quintuplets[32].

Delayed 2nd-twin delivery raises several ethical issues. Pre-viable delivery of the first twin is a dramatic and often unpredictable event. The perspective of successful delayed delivery can only be estimated after 24 hours, but the initial decision must be made on an emergency basis on whether to expedite delivery of the second twin or to attempt expectant management. Furthermore, there is a conflict of interest between the potential benefit for the fetus and the

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potential risk for the mother. This type of conflict of interest is similar to the one more commonly addressed in cases of preterm premature rupture of membranes before 24 weeks. Thus, couples should receive complete information as early as possible, at the beginning of labor or PROM. They should be informed that the most likely outcome in case of delivery of twin 1 will be the rapid delivery of twin 2, even in case of expectant management, that delayed delivery may be considered in some cases, and that if delivery is delayed more than 24 hours, the chance of survival of twin 2 with in most cases severe prematurity will be on the order of one half. They must also be advised that delayed-interval deliveries carry a risk of maternal complications such infections and hemorrhage. The original decision to perform expectant management may be reversed secondarily.

CONCLUSION

In this study, we confirm that delayed delivery ~~may prolong pregnancy~~ after very premature delivery of the 1st twin can in some cases ~~,~~ improv~~e~~~~ing~~ the survival rate of the 2nd twin. The benefits are clearest for pre-viable deliveries of the first twin and less so at more advanced gestational ages. If delivery of the first child occurs before the limit of viability and if the second child is not born spontaneously, expectant management may be considered. However, this must remain an exceptional practice in view of the maternal risks and lack of long-term follow-up of the babies. It is necessary to obtain informed consent, which should preferably be discussed prior to the delivery of twin 1, and closely monitor these very high-risk pregnancies.

Table 1. Description of 13 cases of delayed-interval delivery of the second twin

	Delivery of first twin				Delivery of second twin				
Case	Presentation	Gestational age (WG)	Management After delivery	Discharge to home hospitalization	Presentation	Mode of delivery	Gestational age (WG)	Time from 1st delivery (days)	Outcome of twin 2
1	IUFD of T1	18	0	yes	Spontaneous labor	CS	28	70	Alive
2	IUFD of T1	17+3	0	yes	Chorioamnionitis Spontaneous labor	VB	21+6	31	Stillborn
3	Spontaneous labor	14+2	Vaginal PG	yes	Spontaneous labor	VB	18+2	28	Stillborn
4	Spontaneous labor	19+3	IM PG	no	Chorioamnionitis	VB	22+5	23	Neonatal death at 150min
5	Spontaneous labor	18	0	yes	DIC, induction	VB	25+2	51	Intra partum demise
6	IUFD of T1	17+3	0	no	Chorioamnionitis, Spontaneous labor	VB	19+2	13	Stillborn
7	Spontaneous labor	24	0	no	Chorioamnionitis, Spontaneous labor	CS	25+6	13	Alive
8	Chorioamnionitis	22+3	0	yes	Spontaneous labor	VB	36+6	101	Alive
9	Spontaneous labor	16+3	0	yes	Spontaneous labor	CS	25+3	63	Alive
10	Spontaneous labor	16+1	cerclage	no	Spontaneous labor	VB	31+5	109	Alive
11	Spontaneous labor	15+4)	cerclage	yes	Spontaneous labor	VB	35+2	138	Alive
12	Influenza, IUFD	21+6	0	yes	Spontaneous labor	VB	31+2	66	Alive
13	Chorioamnionitis	21+6	0	no	Chorioamnionitis, induction	VB	24+2	17	Intra partum demise

CS : cesarean section, DIC : disseminated intravascular coagulation, IM: intramuscular; IUFD: intra utero fetal death, min: minute; NA : not available,, PG: progesterone; VB : vaginal birth, WG: week of gestation

Table 2. Markers of infection and antibiotic therapy in 13 cases of delayed-interval delivery of the second twin

	Delivery of 1st twin				Interval period		Delivery of 2nd twin			
Case	**CRP**	**WBCs**	**ABX**	**Vaginal pathogens on admission**	**Change of ABX**	**Vaginal pathogens**	**CRP**	**WBCs**	**Vaginal pathogens in labor**	**ABX Post-partum**
1	3	10	amox	0	CF3-MTZ	E. faecalis	5	13	0	0
2	8	10	amox	0	CF3	BV, P. bivia	81	13	BV	0
3	2	16	NA	C.Koseri, E.Coli	amox	BV	2	11	0	0
4	7	9	amox	E. Coli	CF3	E. Coli	28	13	E. Coli	CF3, tazocilline
5	NA	NA	NA	NA	UD	NA	3	13	E. Coli	amox
6	16	15	amox	C. Albicans, E. ColiK1	amox-genta	NA	24	11	NA	amox-clav
7	35	12	amox	E. Coli	CF3	0	51	12	E. Coli (CF3-R)	tazocilline
8	35	13	amox	C Albicans	amox-genta	BV	11	12	NA	0
9	4	7	0	0	NA	BV	5	7	BV	amox-MTZ
10	5	7	amox	0	amox	E. Coli	5	7	NA	0
11	NA	NA	NA	NA	NA	NA	14	9	NA	0
12	32	11	amox	G. vaginalis, GBS	CF3-genta	NA	32	11	GBS	amox
13	32	NA	amox	0	amox	C. Freundii, S.Aureus, K. Pneumoniae	74	16	NA	CF3-genta-MTZ

ABX: antibiotics, amox : amoxicillin, clav : clavulanic acid; bacterial vaginosis; CF3: 3rd generation cephalosporin, CRP : C-reactive protein, GBS : group B streptococcus, genta : gentamycin, MTZ: metronidazole, NA : not available, WBCs: white blood cells

Table 3. Characteristics at baseline and at the time of the second delivery, according to the outcome for the 2nd twin

	Stillborn* (n=6)	Liveborn** (n=7)
Baseline, twin 1 delivery		
Following PPROM	4/6 (66%)	4/7 (57%)
Following IUFD	2/6 (33%)	1/7 (12.5%)
Gestational age (WG)* **	17+5 [17+3; 19+1]	18 [16+2; 22+1]
CRP (mg/L)* **	13 [6; 22]	5 [4; 34]
WBCs (G/L)* **	10 [10; 13]	11 [9; 12]
Twin 2 delivery		
Gestational age (WG)*	22+2 [19+6; 23+6]	31+2 [26+6; 33+4]
Birthweight (grams)* **	520 [480; 540]	1330 [1030; 2033]
CRP (mg/L)* **	26 [8; 63]	11 [5; 23]
WBCs (G/L)* **	13 [12; 13]	11 [8; 12]

* Stillborn: cases 2, 3, 4, 5, 6, 13
** Liveborn: cases 1, 7, 8, 9, 10, 11, 12
***median [range]

CRP : C-reactive protein; IUFD: intra utero fetal death ; PPROM: preterm premature rupture of membranes; WBCs: white blood cells; WG: week of gestation

Table 4. Literature Review of delayed-interval twin deliveries (from 1994 to 2009)

Study	Number of cases	Twin 1 survival rate (mean gestational age)	Twin 2 survival rate (mean gestational age)	Management	Maternal complications
Arias F, 1994[5]	n=4	NA (19.6WG)	NA (26.7WG)	Tocolysis+CC+ATB	
Kalchbrenner DO.1998[33]	n=5	57% (22.6WG)	78% (27.4WG)		Chorioamnionitis 43%
Farkouch L. 2000[8]*	n=24 T1<24WG, n=16 T1>24WG, n=9	16% (22.7WG) 0%(NA) 44%(NA)	63% (27.9WG) 44%(NA) 100%(NA)	Tocolysis+CC (100%) Excludes: chorioamnionitis of T2	Endometritis 29% 1 Pelvic thrombophlebitis
Fayad S. 2002[12]	n=28	7.4% (20.8WG)	79% (27.9WG)	Tocolysis (82%), ATB (100%), CC (32%)	Chorioamnionitis 28.5%
Hamersley SL. 2002[34]	n=6 T1<24WG, n=6	NA	83% (NA)	Tocolysis+CC+ATB	
Zhang J. 2004[7]	n=200 T1<23WG, n=130 T1>24WG, n=70	18% (23WG) 13% (21.5GWG) 61% (25.4WG)	50% (NA) 33% (23WG) 82% (27.1WG)		
Livingston JC, 2004 [2]	n=14	7% (21WG)	37% (21.2WG)	Tocolysis+ATB (100%)	1 Septic Shock
Oyelese Y. 2005[11]	n=258 T1<24WG, n=114 T1>24WG, n=144	18% (NA) 63% (NA)	44% (NA) 74% (NA)		
Rosbergen M. 2005[35]	n=23	35% (24.+2WG)	70% (27.+1WG)	Tocolysis+ATB (100%)	
Arabin B. 2009[6]	n=38 T1<25WG, n=18 T1>25WG, n=20	34%(NA) T1<25WG, 0% (NA) T1>25WG, 65%(NA)	74%, (NA) T1>25WG, 50%, (NA) T1>25WG, 95%, (NA)	Tocolysis+ATB (100%)	Chorioamnionitis 22% Retained placenta 10%
Roman AS.2011[36]	n=19	15.6% (20.+2WG)	53.8% (25.+2WG)		1 hysterectomy for hemorrhage
Reinhard J.2012[37]	n=5	20% (23.+2 WG)	60% (25WG)		

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Doger E.[3]2014[3]	n=10	0% (17+4 WG)	30% (23+2WG)	Tocolysis +/-CC+ATB	
Kolben T. 2019[39]	n=14 T1<23 WG, n=9 T1>23WG, n=6	46.7% (15.+2 WG) 22.2% ~~(NA)~~ 83.3% ~~(NA)~~	82.4% (26WG) 0% ~~(NA)~~ 93% ~~(NA)~~	Tocolysis+CC+ATB	

** Analyse includes triplets*
CC: cervical cerclage, T1: twin 1, WG: week of gestation, NA : not available

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