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MATERNAL-FETAL MEDICINE

Delayed interval delivery in multiple gestations: the Munich experience

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Abstract

Objective To evaluate delayed interval deliveries in multiple gestations in regard of delayed interval and neonatal survival and to provide a protocol.

Methods Data of multiple pregnancies with delayed interval delivery at a tertiary maternity unit between 2002 and 2017 were collected. Contraindications for evaluation of a delay of the delivery of the remaining child were: severe maternal blood loss, poor maternal general condition, preeclampsia, placental abruption, fetal distress, serious congenital malformations of the remaining child, chorioamnionitis, and premature rupture of membranes of the second fetus. A total of 14 cases was included in this retrospective monocentric analysis.

Results The cohort comprised nine twin and five triplet pregnancies. Mean gestational age at delivery of the first fetus was 21 + 6 and 26 + 0 of the retained fetus, respectively. The earliest delivery of the first fetus was at 15 + 2 weeks. The mean interval of the delay was 29.3 days (2–82 days). Mortality of the first fetuses was 53.3%, while it was 17.6% for the retained fetuses. Maternal outcome was good in general: two cases of major blood loss occurred with the necessity of a blood transfusion.

Conclusion Delayed interval delivery is a reasonable approach in cases of an imminent preterm birth in multiple gestations which can be performed with a good fetal outcome and limited maternal risks. The situation when this procedure may be an option always comes unexpected. Therefore, the team of perinatologists should keep it in mind as one potential therapeutic approach. In addition, a standard protocol for the procedure should be established in the perinatal center.

Keywords Delayed interval delivery · Multiple gestations · Twins · Triplets · Preterm birth

Introduction

The frequency of multiple pregnancies has increased over the last decades. This is attributed to advanced childbearing age and the more frequent use of assisted reproductive technologies [1]. Multiple pregnancies are at significantly higher risk of preterm birth due to preterm labour, premature rupture of membranes, or cervical insufficiency. Prematurity is associated with higher mortality and morbidity accompanied by unfavourable long-term development. Therefore, prolongation of the pregnancy of the second twin after delivery of the leading twin is a promising option in the management once the delivery of the leading fetus becomes inevitable.

The procedure of delaying delivery of the remaining child after birth of the first one has become more commonly used in the last years.

Aside from several case reports or smaller case series [2–4], focusing on this topic also some larger monocentric reports with cases from 9 to 50 pregnancies can be found in the literature [5–9]. The perinatal care and treatment has been improved over time, including several options of tocolytics, antibiotics, and the performance of a cerclage. However, the treatment protocols described in many reports vary widely and no consensus is available concerning the management of these cases which is also the conclusion of a very current review [10].

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Since international guidelines for the procedure of delayed interval deliveries are still lacking and prospective randomized trials are unlikely and difficult to be performed, the aim of this study was to add experiences from a large delivery unit to facilitate the decision and treatment process in delayed interval deliveries.

Methods

This study was designed as a retrospective and monocentric analysis. Data of twin and triplet pregnancies with delayed interval delivery at a tertiary care center between 2002 and 2017 were collected. The study was considered exempt from approval by the Institutional Review Board of the Ludwig-Maximilians-University, Munich, since all patient data were collected retrospectively and anonymized. According to the current definition of delayed interval delivery, the minimum time of prolongation was set as 24 h. Contraindications for evaluation of a delay of the delivery of the remaining child were: severe maternal blood loss, poor maternal general condition, preeclampsia, placental abruption, fetal distress, serious congenital malformations of the remaining child, chorioamnionitis, and premature rupture of membranes of the second fetus.

If possible antenatal corticosteroid prophylaxis with betamethasone (4 doses of 6 mg every 12 h) was started at 23 + 5 weeks of gestation.

Except one delivery which was done by cesarean section, all other births of the first fetus were performed vaginally. After delivery of the first child intravenous (i.v.)-tocolysis (fenoterol (1–3 µg/min, changed to bolus tocolysis when stable) or atosiban (6.75 mg initial bolus, followed by 18 mg/h over 3 h, then 6 mg/h over 45 h) was initiated. A high cervical microbiological swab was taken. After desinfection of the vagina with a bacteriostatic liquid (povidone iodine), high ligation of the umbilical cord was performed. All patients received prophylactic antibiotic treatment with broadspectrum antibiotics intravenously according to the standard protocol of the department at the given time of treatment [amoxicillin and clavulanic acid (2.2 g 3x/d) or ampicillin (2 g 3x/d), combined with clarithromycin orally (250 mg 1x/d) for atypic bacteria (mycoplasma, ureaplasma, and chlamydia)] after reception of the sensitivity testing the antibiotic agents were adjusted accordingly. Rhesus-negative women received one dose of intramuscular anti-D-globulin (300 µg) after birth of the first child in case of impossible blood group typing due to low gestational age or fetal Rhesus-positivity and after blood typing of the second or third child, respectively.

Infection parameters were tested daily for the first days if stable the control intervals were prolonged. Cervical cultures were not taken routinely. Cervical cerclages were not performed after delivery of the first child.

The fetal status was monitored by cardiotocography, ultrasound scans including fetal biometry and Doppler flow examinations in regular intervals (Table 1). The patients remained hospitalized until the delivery of the remaining child or children (13/14 patients), while one was monitored on an outpatient base.

Prolongation of the pregnancies was stopped in case of any signs of deterioration of fetal or maternal status, amnion infection or if the delivery of the remaining twin/triplet could not be prevented anymore.

All placentas were sent for histological examination.

Fetal (week of gestation and birth weight) and maternal outcomes are provided.

Table 1 Munich treatment algorithm for delayed interval deliveries

Before delivery
Antenatal corticosteroid prophylaxis with betamethasone (4 doses of 6 mg every 12 h) from 23 + 5 weeks of gestation.
First delivery
After delivery intravenous (i.v.) tocolysis (fenoterol (1–3 µg/min, changed to bolus tocolysis when stable) or atosiban (6.75 mg initial bolus, followed by 18 mg/h over 3 h, then 6 mg/h over 45 h)
High cervical microbiological swab
High ligation of the umbilical cord
Washing of the vagina with a bacteriostatic liquid (povidone iodine)
Prophylactic antibiotic treatment intravenously (ampicillin (i.v. 2 g 3x/d), combined with clarithromycin (p.o. 250 mg 1x/d) adjusted after reception of the sensitivity testing
Intramuscular anti-D-globulin (300 ug) for Rhesus-negative women after birth of the first child in case of impossible blood group typing due to low gestational age or fetal Rhesus-positivity and after blood typing of the second or third child, respectively
Delayed interval
Daily monitoring of infection parameters, prolongation of intervals, if stable
Monitoring of fetal status was by cardiotocography, ultrasound scans including fetal biometry and Doppler flow examinations in regular intervals

Statistical analysis

All analyses were carried out with Microsoft Office Excel 2012.

Results

A total of 14 cases of multiple gestations were included in our analysis: nine twin pregnancies (eight dichorionic and two monochorionic diamniotic) and five triplet pregnancies (three trichorionic and two dichorionic triamniotic) comprising 33 children. One fetus was excluded from the analysis (patient number 2): the fetus could not be examined due to fetocide below the 14th week of gestation.

Artificial reproductive technologies were performed in 28.6% of cases (4/14) (Table 2). Cerclages for cervical incompetency were performed in 28.6% (4/14) prior to the first delivery, while no emergency cerclage was performed afterwards.

Preterm labour associated with suspected intraamniotic infection was the main reason for the birth of the first fetus (71.4%; 10/14). The delayed deliveries were also mainly due to intraamniotic infection (42.9%; 6/14), and one case was due to placental abruption (Table 2).

The mode of delivery for the first fetus was vaginally in 92.9% (13/14), and once a cesarean section was performed. The completed births were six vaginal births vs. eight cesarean sections (42.9% vs. 57.1%) (Table 2).

The mean gestational age of delivery of the first fetus was 21 + 6 (15 + 2–25 + 4), and 26 + 0 (20 + 1–32 + 0) weeks and days of the retained fetus, respectively. The mean interval of the delay was 29.3 days (2–82 days) (Fig. 1). Mean weight at first birth was 461 g (80–860 g), while it was 884 g (350–1680 g) at completed birth (Table 3).

The mortality of the first fetuses was 53.3% (6 silent birth + 2 deaths post partum: 8/15), while it was 17.6% (1 silent birth + 2 deaths post partum: 3/17) for the retained fetuses (Table 4). Regarding the triplet pregnancies, in three of the four cases, one fetus was delivered first with two fetuses remaining, while only in one case, delivery of two triplets took place in the first place with one remaining fetus.

Maternal outcome was good in general: only two cases of major blood loss due to a retained placenta occurred with the necessity of transfusion of one red blood cell concentrate. Histopathology of the placenta revealed chorioamnionitis

Table 2 Patient characteristics, indication, and mode of delayed interval deliveries

Patient no.	Age	Gravida/para	Conception	Chorionicity	Indication for first delivery	Indication for completed delivery	Mode of first delivery	Mode of completed delivery
1	31	3/2	Spontaneous	MC/DA	TTTS abnormal Doppler (donor)	Intraamniotic infection	CS	VB
2	29	1/1	ART	DC/DA	Preterm labour intraamniotic infection	IUGR abnormal fetal heart tracing	VB	CS
3	32	2/1	ART	TC/TA	Preterm labour intraamniotic infection	Non-reassuring fetal heart tracing, intraamniotic infection	VB	VB
4	35	4/2	Spontaneous	DC/DA	Preterm labour	Cervical dilation and effacement over time	VB	VB
5	30	1/1	ART	DC/DA	Preterm labour intraamniotic infection	Preterm labour intraamniotic infection	VB	CS
6	37	1/1	ART	DC/TA	Preterm labour	Maternal exhaustion	VB	CS
7	23	1/1	ART	DC/DA	Preterm labour intraamniotic infection	Placental abruption	VB	VB
8	32	1/1	Spontaneous	MC/DA	TTTS preterm labour PROM	Abnormal fetal heart tracing, intraamniotic infection	VB	CS
9	30	4/1	ART	DC/DA	Preterm labour	Vaginal bleeding	VB	CS
10	36	3/1	Spontaneous	DC/DA	Preterm labour intraamniotic infection	PROM	VB	VB
11	39	3/2	ART	DC/DA	PROM	PROM	VB	CS
12	34	2/1	ART	DC/TA	PROM	Intraamniotic infection	VB	VB
13	31	2/2	ART	TC/TA	Preterm labour	Preterm labour	VB	CS
14	29	1/1	ART	DC/DA	Preterm labour	Intraamniotic infection	VB	CS

ART artificial reproductive technologies, *MC* monochorionic, *DC* dichorionic, *TC* trichorionic, *DA* diamniotic, *TA* triamniotic, *TTTS* twin twin transfusion syndrome, *PROM* premature rupture of membranes, *CS* cesarean section, *VB* vaginal birth

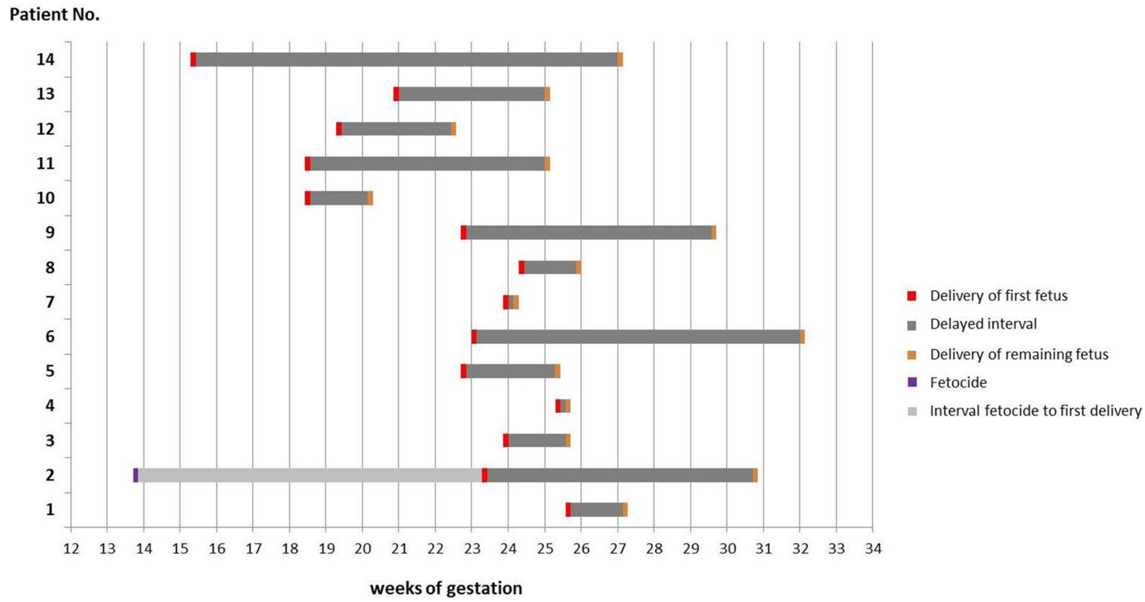

Fig. 1 Interval of delayed deliveries in multiple gestations

in 42.9% (6/14) of placentas at the completed delivery. No endomyometritis or sepsis occurred.

Discussion

This analysis could demonstrate delayed interval delivery being a reasonable approach in cases of imminent preterm birth in multiple gestations with good fetal outcome and limited maternal risks. Several case reports or smaller case series are available focusing on this topic [2–4]. Two multicenter studies reported larger numbers ($n=35$ and $n=200$) [11, 12]; however, they lacked reliable information on maternal and neonatal morbidity or specific treatment procedures. Only few monocentric analyses providing a uniform treatment algorithm can be found in the literature [5–9]. This study evaluated the data of 14 cases of delayed interval deliveries treated uniformly which makes it one of the largest ones. Thus, it provides additional information and a suitable treatment algorithm in regard to neonatal and maternal outcome.

In this analysis, the mean delayed interval of the delivery of the retained fetuses was 29.3 days, similar to the one reported by Farkouh (36 days) [6]. However, it was relevantly longer than reported elsewhere [8]. Even a delay of only 48 h seems reasonable beyond 24 weeks of gestation to administer a complete course of antenatal corticosteroid therapy. Delayed delivery could also be successfully performed far before extrauterine fetal viability at 15 + 2 weeks with the retained fetus reaching the 28th week. This was even earlier than two other cases described previously with delivery of the first fetus in the 17th week [13, 14]. Farkouh et al. offered the procedure to women between 16 + 0 through 29 + 0 weeks of gestation. They summarized that ideal candidates for delayed interval delivery were those in whom delivery of the first fetus occurs at an early gestational age (< 24 weeks) [6].

The outcome regarding neonatal mortality was very positive. The survival rate of the first born fetuses was 46.7%, while it reached 82.4% in the group of retained fetuses. This was accompanied by an almost doubled mean birth weight (first fetus: 461 g vs. retained fetus: 884 g). With respect to the first born fetuses born at a viable age of gestation (> 23 weeks), the outcome was even better (survival 83.3%, survival of the remaining fetuses beyond 23rd week: 93.3%). The observed outcome is strikingly better than described before [6–8, 11, 15, 16]. The time gained in utero by delaying delivery leads to a higher birth weight and consecutively to higher maturity of the newborns, which explains the better outcome.

Another very important aspect of this analysis was that this procedure could also be performed before extrauterine fetal viability in order to give the remaining fetus a relevant chance for survival. Prolonging the delayed delivery beyond 32 weeks seems not to be warranted, because the neonatal outcome is excellent when treated in the neonatal intensive care unit.

In total, the maternal complications were minimal which was in accordance with a very recent review [10]. Histopathology reports revealed 43% of chorioamnionitis at completed delivery similar to another analysis [12]; however, none resulted in severe further maternal

Table 3 Fetal outcome in delayed interval deliveries

Patient no.	Gestational age at delivery (weeks + days)	Weight (g)	Survival	Delayed interval (days)
1	25 + 4	670	+	11
	27 + 1	1170	+	
2	13 + 5	Unknown	− (fetocide)	52
	23 + 2	560	+ (died pp)	
	30 + 5	1040	+	
3	23 + 6	570	+	12
	25 + 4	650	+	
		700	+	
4	25 + 2	860	+	2
	25 + 4	875	+	
5	22 + 5	530	+	18
	25 + 2	720	+	
6	23 + 0	508	+ (died pp)	63
	32 + 0	1680	+	
		1560	+	
7	23 + 6	650	+	2
	24 + 1	440	+ (died pp)	
8	24 + 2	600	+	11
	25 + 6	940	+	
9	22 + 5	530	+	48
	29 + 4	1370	+	
10	18 + 3	250	−	12
	20 + 1	350	+ (died pp)	
11	18 + 3	251	− (fetocide)	46
	25 + 0	590	+	
12	19 + 2	235	−	22
	22 + 3	170	−	
		415	−	
13	20 + 6	450	−	29
	25 + 0	680	+	
		760	+	
14	15 + 2	80	−	82
	27 + 0	1080	+	
Mean	21 + 6 (15 + 2–25 + 4)	461 (80–860)		29.3 (2–82)
	26 + 0 (20 + 1–32 + 0)	884 (350–1680)		

+: alive, −: dead, *pp* post partum

Table 4 Survival of fetuses

Survivors/total fetuses (perinatal survival rate)	First born	Second born	Total
≤ 23rd week	2/9 (22.2)	0/2 (0.0)	2/11 (18.2)
> 23rd week	5/6 (83.3)	14/15 (93.3)	19/21 (90.5)
Total	7/15 (46.7)	14/17 (82.4)	21/32 (65.6)

infections like sepsis which was pointed out by Zhang (up to 5%) [12]. Only two cases of major blood loss were reported but no other complications. An incidence of serious maternal morbidity (postpartal hemorrhage requiring blood transfusion and hysterectomy, sepsis) related to the procedure of up to 32% was described before [8].

In contrast to Porreco et al., monochorionicity was no exclusion criteria in our analysis [7]. Both fetuses from the two cases which were included survived the procedure.

Outpatient treatment, reported before [6, 17], which was possible due to a very stable situation after first delivery at 16 weeks, will be reserved to a minority of cases, since intravenous medication and bed rest is often necessary or advised.

This analysis is limited by its retrospective design. However, it comprises one of the larger cohorts reported so far. Furthermore, we are aware of a potential selection bias resulting from the experience of the perinatal team available at the time of patient presentation. Nevertheless, delayed interval delivery represents a reasonable approach for suitable cases in the hand of an experienced team of perinatologists.

The following summary is meant to help to perform delayed interval deliveries successfully: (1) the situation when this procedure may be an option almost always comes unexpected and occurs at a very critical time for the unborn children. (2) Therefore, most importantly, the team of perinatologists has to keep delayed interval delivery in mind as one potential therapeutic approach in case of an imminent preterm birth in multiple gestations. (3) A standard treatment protocol should be established in the perinatal center.

Considering the lack of guidelines for delayed interval deliveries, this analysis provides a protocol and meaningful evidence that this approach is reasonable in selected cases. Neonatal morbidity and mortality can be relevantly reduced with risks of poor maternal outcome appearing minimal. Close fetal and maternal monitoring in an interdisciplinary setting at an expert perinatal center is required.

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Compliance with ethical standards

Conflict of interest S Mahner has received research support, advisory board fees, honoraria, and travel support from AstraZeneca, Bayer, Boehringer Ingelheim, Jenapharm, GSK, JanssenCilag, Medac, MSD, Pharmamar, Roche, Tesaro, and Teva. All other authors declare no conflict of interest.

Research involving human participants and informed consent For this type of study, formal consent is not required.

References

1. Pison G, D'Addato AV (2006) Frequency of twin births in developed countries. Twin Res Hum Genet 9(2):250–259. https://doi.org/10.1375/183242706776382338
2. Poeschmann PP, van Oppen CA, Bruinse HW (1992) Delayed interval delivery in multiple pregnancies: report of three cases and review of the literature. Obstet Gynecol Surv 47(3):139–147
3. Sakala EP, Branson BC (1987) Prolonged delivery-abortion interval in twin and triplet pregnancies. A report of two cases. J Reprod Med 32(1):79–81
4. Ziegler WF, Welgoss J (1996) Delayed delivery of a triplet pregnancy without surgical intervention: a case report. Am J Perinatol 13(3):191–193. https://doi.org/10.1055/s-2007-994323
5. Arabin B, van Eyck J (2009) Delayed-interval delivery in twin and triplet pregnancies: 17 years of experience in 1 perinatal center. Am J Obstet Gynecol 200(2):154.e1–154.e8. https://doi.org/10.1016/j.ajog.2008.08.046
6. Farkouh LJ, Sabin ED, Heyborne KD, Lindsay LG, Porreco RP (2000) Delayed-interval delivery: extended series from a single maternal-fetal medicine practice. Am J Obstet Gynecol 183(6):1499–1503. https://doi.org/10.1067/mob.2000.107319
7. Porreco RP, Sabin ED, Heyborne KD, Lindsay LG (1998) Delayed-interval delivery in multifetal pregnancy. Am J Obstet Gynecol 178(1 Pt 1):20–23
8. Roman AS, Fishman S, Fox N, Klauser C, Saltzman D, Rebarber A (2011) Maternal and neonatal outcomes after delayed-interval delivery of multifetal pregnancies. Am J Perinatol 28(2):91–96. https://doi.org/10.1055/s-0030-1262513
9. van Doorn HC, van Wezel-Meijler G, van Geijn HP, Dekker GA (1999) Delayed interval delivery in multiple pregnancies. Is optimism justified? Acta Obstet Gynecol Scand 78(8):710–715
10. Feys S, Jacquemyn Y (2016) Delayed-interval delivery can save the second twin: evidence from a systematic review. Facts Views Vis ObGyn 8(4):223–231
11. Fayad S, Bongain A, Holhfeld P, Janky E, Durand-Reville M, Ejnes L, Schaaps JP, Gillet JY (2003) Delayed delivery of second twin: a multicentre study of 35 cases. Eur J Obstet Gynecol Reprod Biol 109(1):16–20
12. Zhang J, Hamilton B, Martin J, Trumble A (2004) Delayed interval delivery and infant survival: a population-based study. Am J Obstet Gynecol 191(2):470–476. https://doi.org/10.1016/j.ajog.2004.03.002
13. Berghella V, Davis GH, Macones GA, Wapner RJ (1996) Prolongation of pregnancy and survival of remaining fetuses after operative evacuation of one triplet at 18 weeks' gestation. Obstet Gynecol 88(4 Pt 2):665–666
14. Nagy S, Ducz R (2002) Delayed interval delivery in multiple pregnancy: case report and review of the literature. Orv Hetil 143(38):2193–2198
15. Reinhard J, Reichenbach L, Ernst T, Reitter A, Antwerpen I, Herrmann E, Schlosser R, Louwen F (2012) Delayed interval delivery in twin and triplet pregnancies: 6 years of experience in one perinatal center. J Perinat Med 40(5):551–555. https://doi.org/10.1515/jpm-2011-0267
16. Rosbergen M, Vogt HP, Baerts W, van Eyck J, Arabin B, van Nimwegen-Hamberg JM, van Lingen RA (2005) Long-term and short-term outcome after delayed-interval delivery in multi-fetal pregnancies. Eur J Obstet Gynecol Reprod Biol 122(1):66–72. https://doi.org/10.1016/j.ejogrb.2004.11.036
17. Omsjo IH, Alsos R (1984) Twin pregnancy: report of a case with 35 days between deliveries. Eur J Obstet Gynecol Reprod Biol 17(6):413–415