



# Delayed-Interval Delivery in Multiple Pregnancy: A Single-Center Experience of Five Cases

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AJP Rep 2024;14:e156–e161.

## Abstract

**Objectives** To describe the obstetric management and perinatal outcomes in multiple pregnancies with delayed-interval delivery (DID) of the cotwin in a tertiary hospital.

**Methods** This is a retrospective chart review of all cases of DID between December 2021 and 2022 at The Ottawa Hospital. Five cases of DID were identified and reviewed to obtain information on obstetric management and maternal–neonatal outcomes. We included eligible twins and triplets. No multiples were excluded. We obtained ethics approval for this case series.

**Results** Four sets of dichorionic diamniotic twins and one trichorionic triamniotic triplet were included. Our patients were admitted between 17<sup>3/7</sup> and 21<sup>5/7</sup> weeks of gestation. We achieved an interval delivery range between 1 and 36 days. Four out of six multiples did not survive in DID. The two surviving newborns were born at 23<sup>0/7</sup> and 23<sup>2/7</sup>, stayed in the neonatal intensive care unit (NICU) for 111 and 131 days, discharged with a weight of 3,594 and 2,743 g, respectively. All DID cases were delivered spontaneously except for two patients that required augmentation due to maternal sepsis.

**Conclusion** Despite the high risk of maternal, fetal, and neonatal morbidity and mortality, if delivery of the first twin occurs before 20 gestational weeks, DID could be considered in selected cases to improve outcomes for the cotwin.

## Keywords

- ▶ multiple
- ▶ preterm birth
- ▶ multiple pregnancy
- ▶ premature
- ▶ infant

The rate of multiple pregnancies has been rising recently due to increased use of assisted reproductive techniques and pregnancy in women of advanced maternal age.<sup>1</sup> Multiple pregnancies carry higher risks of maternal and fetal complications when compared with singleton pregnancies.<sup>1</sup> Maternal complications are many including hypertensive disorders, diabetes, and cervical incompetence. As for fetal complications, there is a higher prevalence of birth defects, premature rupture of membranes, and preterm birth leading to increased perinatal morbidity and mortality.<sup>2,3</sup>

Delayed-interval delivery (DID) is defined as the delivery of one fetus in a multiple gestation that is not followed immediately by birth of the remaining fetus or fetuses.<sup>4</sup> In the event of preterm delivery of one twin, especially at previable (less than 22 weeks' gestation) or periviable (between 22 and 24 weeks' gestation) gestational age, delaying delivery of the second twin has been described in the literature as a management option that can be considered when the aim is to carry the second twin to viable gestational age.<sup>5</sup>

received  
February 16, 2024  
accepted  
March 27, 2024

DOI <https://doi.org/10.1055/s-0044-1787112>.  
ISSN 2157-6998.

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DID of the second twin does not come without risks. Patients who decide on DID should be aware of the risks of infection of the retained placenta and chorionic membranes and cord (chorioamnionitis and funisitis, respectively) and/or endometrium (endometritis) that if not timely treated may culminate in maternal sepsis. Treatment consists of aggressive source control which clinically denotes broad-spectrum antibiotic therapy along with expediting delivery (regardless of the gestational age) and concurrent dilatation and curettage of remaining products of conception.

To date, the following contraindications to pursue DID for the cotwin are: monochorionicity of the fetus that has been delivered; premature rupture of membranes of the cotwin; gestational age more than 28 weeks; any evidence of fetal distress; major congenital anomalies of the remaining twin; and evidence of serious maternal complications that increase morbidity and mortality, such as maternal sepsis, antepartum hemorrhage (placental abruption), or severe preeclampsia.<sup>3</sup>

It is unknown whether the risk of infection outweighs the benefits of delivery of the second twin at a later viable gestational age, as treatment outcomes reported in the literature are inconsistent and guidelines are inexistent. Therefore, there is no consensus on whether or when DID may be safely offered as standard practice.<sup>6,7</sup>

We aim to share a single-center experience when managing DID and add our five cases to the global roster of reported cases of DID. Thus, our goal is to describe a case series of multiple pregnancies managed by DID in our tertiary hospital during 2022, analyzing maternal and neonatal outcomes in each scenario.

## Methods

We performed a retrospective observational study of all cases of DID at The Ottawa Hospital (TOH), a high-risk obstetric tertiary center in Eastern Ontario, Canada, from December 2021 to December 2022. Five cases of DID were identified upon review of all deliveries and information on obstetric management, and maternal–neonatal outcomes were obtained from detailed chart review. We included all eligible multiples. Data collected included maternal (age at delivery, parity, type of conception, antibiotics received), fetal (chorionicity, gestational age at delivery of the first twin and the reason for admission, mode of delivery, and gestational age of the cotwin), and neonatal variables (weight at birth, course of corticosteroids, Apgar scores, cord blood gases, sex, length of hospital stay, disposition). Neonatal data were limited to information included in TOH newborn charts. The description of cases and outcomes is summarized later. We obtained ethics approval (20230099-01H) for this case series.

## Results

A total of five cases (four sets of twins and one set of triplets) were identified for this review and are described in **Table 1**.

We reviewed the placenta pathology available for each case and results are summarized in **Table 2**.

### Case 1

A 30-year-old pregnant woman, G6T1A4L1, dichorionic diamniotic (DCDA) twins, conceived spontaneously with unremarkable medical history. Obstetric history was relevant for short cervix in a previous pregnancy and delivered at term. In the index pregnancy, patient presented to the hospital for the first time at 17<sup>5/7</sup> weeks of gestation and was diagnosed with preterm premature rupture of membranes (PPROM) of twin A confirmed by positive pooling of fluid in the posterior fornix of the vagina, positive nitrazine test, and anhydramnios upon ultrasound assessment. Cultures were obtained and workup was negative. Patient was admitted and started on empiric antibiotics for latency (cefazolin and erythromycin intravenous [IV]). The infectious disease team was involved in care and suggested therapy was broadened to cefotaxime and clindamycin IV. At 17<sup>6/7</sup> weeks, patient spontaneously vaginally delivered fetus A, with the placenta left in situ with no signs of separation. Contractions were resolved, and no signs of infection were identified.

Patient was counseled about the options of management (augmentation and delivery of the second twin or DID). As patient opted for DID, she was kept in hospital on IV antibiotic course. Patient was discharged after 9 days in stable condition on oral antibiotics (cefixime and clindamycin) for 3 weeks.

At 22<sup>2/7</sup> weeks, patient presented to triage complaining of foul-smelling vaginal discharge. She had no signs of labor. Cultures were obtained, and patient was started on metronidazole for 7 days for the presence of bacterial vaginosis on the vaginal sample. Three days later, patient has clinical findings ongoing with chorioamnionitis and suspicion of sepsis. Patient was started on IV clindamycin and gentamycin and extensively counseled regarding risks of maternal morbidity and mortality due to maternal sepsis; augmentation was recommended. Patient received two doses of betamethasone (completed at 22<sup>6/7</sup> weeks) and 24 hours of MgSO<sub>4</sub> before delivery. Augmentation was started at 23 weeks, patient progressed to spontaneous vaginal delivery of live male newborn, followed by vacuum aspiration of retained placenta. The newborn weighed 580 g, had Apgar 8/8 (1 and 5 minutes), and cord pH 7.37 developing interventricular hemorrhage, rickets of prematurity, right inguinal hernia, and retinopathy of prematurity during neonatal intensive care unit (NICU) stay. Newborn recovered and was discharged at 111 days of life (**Table 1**). Patient was kept on antibiotics (clindamycin and gentamycin for 4 days postpartum). She was discharged on day 4 postdelivery in stable condition on oral antibiotics (metronidazole and clindamycin for 7 days).

Placental pathology revealed stage 3/grade 2 chorioamnionitis of placenta for fetus B and stage 1/grade 1 chorioamnionitis for fetus A. Features of fetal vascular malperfusion noted for fetus B, with chorionic villitis. **Table 2**

**Table 1** Maternal and neonatal outcomes by case

Cases	Case 1	Case 2	Case 3	Case 4	Case 5
Parity	G6T1P0A4L1	G1	G4T1P2A0L1	G1	G2T0P0A1
Mode of conception	Spontaneous	Ovulation induction	Spontaneous	IUI	Ovulation induction
Chorionicity	DCDA	DCDA	DCDA	TCTA	DCDA
GA at admission	17 + 5	17 + 3	18 + 6	19 + 6	21 + 5
Reason for admission of twin A	PPROM	PPROM	PPROM	PTL and PPROM	PTL and PPROM
GA at birth of twin A	17 + 6	18	19	19 + 6	22 + 3
Weight at delivery (g)	153	163	220	271	501
Gender	Male	INA	Female	Male	Male
Umbilical cord	Clamped and tied	Clamped and tied	Clamped and tied	Clamped and tied	Clamped and tied
Cerclage	No	No	No	No	No
Steroids full course (wk)	Completed full course at 22 + 6	None	None	None	Completed full course at 22 + 6
MgSO <sub>4</sub> (h)	Infuse for 24 h before delivery	None	None	None	Infused for 11 h before delivery
GA at birth of twin B	23	18 + 1	21 + 2	Triplet (B and C) 20 + 2	23 + 2
Mode of delivery	SVD (viable)	E&C	SVD	SVD of second and third	Breech vaginal delivery (viable)
Weight at delivery (g)	580	NA	339	Twin (B) 286, (C) 243	610
Gender	Male	NA	Male	Male	Male
DID (d)	36	1	16	3	6

Abbreviations: DCDA, dichorionic diamniotic; DID, delayed-interval delivery; E&C, evacuation and curettage; GA, gestational age; INA, information not available; IUI, intrauterine insemination; NA, not applicable; PPROM, preterm premature rupture of membranes; PTL, preterm labor; SVD, spontaneous vaginal delivery; TCTA, trichorionic triamniotic.

**Table 2** Placenta histopathology report for each case

Placenta histopathology	Case 1	Case 2	Case 3	Case 4	Case 5
	Fetal inflammatory response (stage 3, grade 2) of placenta 2 with marginal insertion and three-vessel umbilical cord, eccentrically inserted on placenta 1, histologically within normal limits. Maternal inflammatory response with chorioamnionitis (stage 3, grade 2) of placenta 2 and maternal inflammatory response with chorioamnionitis (stage 1, grade 1) of placenta 1. Placental discs with second trimester villi with features of fetal vascular malperfusion (infarcts, hemorrhage, accelerated villous maturation, and decidual arteriopathy (placenta 2 only). Chorionic villitis. Histologic evidence of decidual arteriopathy (placenta 2 only)	Fetal inflammatory response (stage 1, grade 1) in placenta 2. Maternal inflammatory response with chorioamnionitis (stage 3, grade 2) in placenta 2 and chorionitis (stage 2, grade 1) in placenta 1. Three-vessel umbilical cords with peripheral funisitis in placenta 2. Placental discs with second trimester villi with acute villitis and intervillitis in placenta 2, and focal cistern formation and trophoblastic proliferation in placenta 1.	Placenta 1, acute chorioamnionitis with a maternal inflammatory response (stage 3/3, grade 2/2). Acute deciduitis. Placenta 2, acute chorioamnionitis with maternal inflammatory response equivalent to stage 2/3 and grade 1/2, fetal inflammatory response equivalent to stage 2/3 and grade 1/2, immature villi in keeping with gestational age, acute deciduitis, focal villous edema. Three-vessel umbilical cord with one umbilical artery acute vasculitis.	No pathological abnormality in 1 and 2 placentas but in placenta 3 (for triplet C) revealed normal three-vessel cord, no umbilical vasculitis of funisitis. Membranes showed diffuse moderate to severe acute chorioamnionitis. Disc revealed patchy mild to moderate acute chorioamnionitis.	Placenta 1: Acute chorioamnionitis with a maternal inflammatory response equivalent to stage 3/3, grade 2/2. Three-vessel umbilical cord with peripheral funisitis. Placenta 2: Marginal acute retroplacental hematoma measuring 3 × 2.3 × 0.3 cm consistent with the significant clinical history of placental abruption. Subchorionic hematoma measuring 3 × 2.1 × 0.2 cm. Acute chorioamnionitis with a maternal inflammatory response equivalent to stage 2/3, grade 1/2. Three-vessel cord with no significant pathological diagnosis.

**Case 2**

A 32-year-old primigravida with unremarkable medical history conceived a DCDA twin by ovulation induction for a history of primary infertility. At 17<sup>3/7</sup> weeks, patient was admitted as a case of PPRM of the presenting twin and received ampicillin and erythromycin IV for latency. All the investigations were negative. During hospital admission, patient was counseled about the options of management and opted for conservative management and DID in case of miscarriage of affected twin. As patient was clinically stable, she was discharged home at 17<sup>6/7</sup> weeks on amoxicillin and erythromycin oral (PO). The following day, patient spontaneously delivered the first twin at home and placenta remained in situ. She was readmitted for management. The cord was cut short and close to the cervix, and patient was kept on IV antibiotics. Within 24 hours, she developed signs and symptoms of sepsis, and antibiotics were escalated. Patient underwent emergency evacuation and curettage of the entire pregnancy for septic shock secondary to chorioamnionitis. She recovered well and was kept for 7 days on ceftriaxone and metronidazole IV. Patient was discharged home in stable condition on metronidazole for 4 days.

The placental histopathology showed chorioamnionitis stage 3/grade 2 in first twin's placenta and stage 1/grade 1 in the second twin's placenta along with evidence of peripheral funisitis and acute villitis. **– Table 2**

**Case 3**

A 30-year-old pregnant woman, G4T1P2A0L1, with unremarkable medical history, conceived a DCDA twin pregnancy spontaneously. Obstetric history was significant for two preterm losses due to cervical insufficiency. During her index pregnancy, patient was on vaginal progesterone with serial cervical length assessments. At 18<sup>6/7</sup> weeks, patient was seen with PPRM of the presenting twin and started on antibiotics for latency for 24 hours. At 19 weeks, she spontaneously delivered the presenting twin and the placenta retained in situ. Patient opted for DID, so the cord was cut and ligated at the level of the cervix. She was hospitalized and received IV clindamycin and gentamycin for 7 days, then started on amoxicillin clavulanate PO. Cultures were positive for group B *Streptococcus* in the urine sample. She was discharged in stable condition at 20<sup>6/7</sup> weeks and advised to continue antibiotics for another 2 weeks.

At 21<sup>2/7</sup> weeks, she presented to the hospital in preterm labor. Patient progressed to spontaneous vaginal delivery of the second twin along with complete delivery of both placentas. The fetus weighed 339 g, nonviable (**– Table 1**). Patient was discharged on day 1 postdelivery in stable condition. No antibiotics were given upon discharge. She continued to have vaginal bleeding after delivery, an ultrasound on day 10 postpartum showed retained products of conception (RPOC), and there were no clinical signs of infection. Diagnostic hysteroscopy and curettage also revealed RPOC.

The placental histopathology showed chorioamnionitis stage 3/grade 2 in the first twin's placenta and stage 2/grade 1 in the second twin's placenta. **– Table 2**

**Case 4**

A 34-year-old primigravida conceived a trichorionic triamniotic triplet pregnancy by intrauterine insemination. She had an unremarkable medical history. At 19<sup>6/7</sup> weeks, she was hospitalized with preterm labor and progressed with PPRM. Antibiotics for latency were started. Her infection workup was negative. Presenting triplet was delivered a few hours later and the placenta remained in situ. Patient was counseled about the options of management and opted for DID for triplets B and C. The cord was cut and sutured high, close to the cervix. At 20<sup>2/7</sup> weeks, patient delivered the whole pregnancy spontaneously. None of the triplets were born alive. She received oral amoxicillin and was discharged in stable condition on the same day.

No pathological abnormalities were found in placentas for fetuses A and B. Membranes showed diffuse moderate to severe acute chorioamnionitis for triplet C. **– Table 2**

**Case 5**

A 31-year-old pregnant woman, G2TOP0A1, previous history of surgical abortion at 9 weeks, conceived a DCDA pregnancy by ovulation induction. Patient was a known case of short cervix on vaginal progesterone started at 15<sup>6/7</sup> weeks. At 21<sup>5/7</sup> weeks, she was hospitalized due to clinical diagnosis of threatened preterm labor. At 22<sup>2</sup> weeks, PPRM was confirmed and antibiotics for latency started. Betamethasone and MgSO<sub>4</sub> were not given at that point. All workup was negative for infection. At 22<sup>3/7</sup> weeks, she progressed to spontaneous vaginal delivery of twin A (nonviable). Vaginal and endocervical swabs were collected, and the umbilical cord was cut and ligated near the cervix. Patient was counseled about the options of management and opted for DID.

At 22+6 weeks, betamethasone was completed, and patient was discharged after completion of antibiotics for latency. She was readmitted a day later with threatened preterm labor and MgSO<sub>4</sub> was initiated for neuroprotection. Clinical signs of chorioamnionitis were recognized and evacuation of intrauterine contents was recommended; hence, augmentation with oxytocin was initiated. Twin B was delivered at 23<sup>2/7</sup> weeks (alive and admitted to NICU) and both placentas were delivered spontaneously. Patient's case was complicated with postpartum fever, and blood cultures showed *Bacteroides fragilis*. Clinical improvement was seen within hours of IV antibiotic therapy (ampicillin + gentamycin). Patient was discharged home on day 2 postdelivery on metronidazole for 5 days.

Acute chorioamnionitis with a maternal inflammatory response equivalent to stage 3/3 and grade 2/2 was found in first twin's placenta, and acute chorioamnionitis with a maternal inflammatory response equivalent to stage 2/3 and grade 1/2 in the second twin's placenta.

**Discussion**

We present the results of five cases of DID as first choice of management when the first twin is delivered previability. Our experience was mainly with DCDA twins; we had only

one case of trichorionic triamniotic triplets and no experience with high-order twins. Our patients were admitted between 17<sup>3/7</sup> and 21<sup>5/7</sup> weeks of gestation for the first twin. We achieved a delivery interval range between 1 and 36 days, averaging 18.5 days; 66% (four out of six) of fetuses candidates for DID did not survive. Two newborns who survived in DID stayed in the NICU (111 and 131 days, average 121 days) were discharged with a weight of 3,594 and 2,743 g, respectively. All births were delivered spontaneously except for two patients that required augmentation and evacuation due to maternal sepsis.

DID has been described as a management option in preterm or periviable multiple pregnancies, as it reduces morbidity and mortality for the subsequent fetus or fetuses.<sup>6</sup> In our case series, two patients (40%) developed serious maternal morbidity as they showed clinical signs of sepsis and underwent urgent surgical evacuation and augmentation. All cases had clinical findings of chorioamnionitis and confirmation was documented by placental pathology showing different stages and grades of the disease. One patient developed secondary postpartum hemorrhage due to remaining products of conception—a common complication of chorioamnionitis—which required surgical hysteroscopy for management. There was no maternal mortality in the cases described, but various stages of maternal morbidity were observed in all cases.

Similarly, a systematic review on DID reported serious maternal morbidity in 38.8% of pregnancies, but no maternal mortality.<sup>7</sup> Cases of maternal morbidity included local infection and/or sepsis, placental abruption, postpartum hemorrhage, hysterectomy, and a single case of uterovaginal fistula.<sup>6</sup>

In our case series, the delayed newborn survival rate was 33.3% (two out of six), and such rate of perinatal survival is similar to that seen in other studies of DID.<sup>6,8,9</sup>

Close clinical and laboratory monitoring is essential to reduce the risk of severe maternal morbidity, particularly sepsis. These patients are at high risk of morbidity and mortality due to complications associated with DID. Patients with DID may benefit from close monitoring with prophylactic antibiotics in a tertiary care center. We currently do not have a protocol for antibiotic regimen proposed for DID cases, so choice and duration of course were based on experts' opinions and individualized for each patient.

Steroids for lung maturation and IV MgSO<sub>4</sub> are indicated if delivery is imminent, as per guidelines. Decision-making regarding the timeline of steroids and MgSO<sub>4</sub> administration needs to be individualized as it depends on gestational age and the timing of delivery. It is not the scope of this work to debate the appropriate periviable gestational age for administration of steroids. Our practice is to decide the most appropriate timing of steroids in such cases after a multidisciplinary meeting is conveyed with neonatology and perinatology specialists; the patient's informed consent is also obtained.

There is no consensus in the literature regarding cervical cerclage for the second twin. Zhang et al reviewed seven

cases of DID and found no increase in intrauterine infection or maternal sepsis in patients treated by cerclage.<sup>10</sup> However, the risk of sutures acting as a source for infection or trapping a subclinical but ongoing infection is still concerning.<sup>11</sup> We did not offer cervical cerclage to any of our patients as our providers did not feel this was a risk-free procedure to be offered, with the potential to harm current and subsequent eventual pregnancies.

Cleansing the vagina with antiseptic after delivery of the first infant, leaving the placenta in situ with high ligation of the umbilical cord, and the use of prophylactic antibiotics is not standard practice at our hospital; however, these approaches are commonly used in DID cases.<sup>6</sup> In addition, it has been crucial at our center to closely monitor the pregnant individual via measurement of vital signs, regular physical examination, full blood count, and inflammatory markers. These practices were tailored to each case. The remaining fetus or fetuses should be also monitored by ultrasound. Moreover, some studies have avoided vaginal examinations and used transperineal ultrasound to assess cervical length, dilation, and funneling.<sup>10</sup>

DID of periviable multiple pregnancies in preterm labor is a rare window of opportunity, as most women will not settle after delivery of the first fetus, labor will progress and result in delivery of the whole pregnancy. However, when there is eligibility, DID can be a useful tool to reduce mortality of subsequent twin in those cases where the first fetus is delivered vaginally, contractions resolve, and there are no signs of infection that can preclude a watchful wait.

Our small sample size does not allow us to make recommendations about the management of DID cases to the general population; yet, it has increased our experience and empowered our team of specialists to offer patients counseling around this practice based on data from our institution. We are confident our data add to the current body of evidence as it is comparable to other institutions' results. We consider that future studies involving larger samples would be useful to examine the long-term outcome of these infants and may determine the success of prolonging the pregnancy of the second or third fetus.

## Conclusion

We shared our experience of five cases of DID intending to add to current published evidence regarding management of multiple pregnancies once the first fetus is born at nonviable gestation. Our goal was to understand the potential complications and outcomes, facilitate the decision-making, and management of cases of DID. Despite the high risk of maternal, fetal, and neonatal morbidity and mortality, if delivery of the first twin occurs before 20 weeks of gestation, DID could still be considered in selected cases to improve outcomes for the cotwin.

## Conflict of Interest

None declared.

**Acknowledgment**

We extend our sincere appreciation to Sara C. S. Souza (research coordinator at the Ottawa Hospital Research Institute) for her invaluable contributions and assistance throughout the course of this study.

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