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Delayed interval delivery in twin pregnancies in the United States: Impact on perinatal mortality and morbidity

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KEY WORDS
Multiple pregnancy
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Objective: To estimate the incidence of delayed interval delivery in twin pregnancies in the United States and evaluate the impact of delayed delivery on perinatal outcomes.
Study design: A population-based retrospective cohort study was performed using the U.S. "matched multiple birth" file (1995 to 1998), restricting our analysis to twin sets in which the first twin was delivered vaginally at 22 to 28 weeks (n = 4257). Outcomes examined included perinatal and infant mortality and small-for-gestational-age births. Outcomes of second twins in pregnancies that underwent delayed interval delivery of 1, 2, 3, and ≥4 weeks were compared with those in which both twins were delivered contemporaneously.
Results: In this cohort, 6.1% (n = 258) of twins had delayed delivery (≥1 week) of the second twin. Decreases in perinatal and infant mortality were observed only when the first twin was delivered at 22 to 23 weeks and when the delivery interval was ≤3weeks. However, for intervals ≥4 weeks or when the first twin was delivered at 24 to 28 weeks (regardless of delivery interval), there was no benefit in perinatal or infant mortality. Delayed delivery of ≥4 weeks was associated with increased risk of small-for-gestational-age birth in the second twin, regardless of gestational age at delivery of the first.
Conclusion: When a first twin was delivered at 22 to 23 weeks, delayed delivery of the second twin was associated with reduced perinatal and infant mortality of the second twin if the interval was less than 3 weeks. Delayed delivery of the second twin when the first was delivered at ≥24 weeks had no benefit on mortality.

The incidence of multiple pregnancies has increased dramatically in recent years.[1] These pregnancies are commonly delivered prematurely and contribute disproportionately to perinatal mortality and morbidity.[2] Women with twin pregnancies may present in premature labor or with ruptured membranes in the second trimester at the lower limit of viability. Frequently delivery of the first fetus is inevitable. Traditionally, this scenario is

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managed by delivery of both fetuses, either vaginally or by cesarean. However, an increasing number of case reports have described delaying delivery of the second twin for days and even weeks after delivery of the first.[3-11] Gestational age is the most important predictor of neonatal survival in infants delivered at <25 weeks gestation.[12] In twins, survival to discharge following delivery at 22, 23, 24, and 25 weeks are 11%, 11%, 23%, and 51% respectively.[12] Similarly, at these extremely premature gestational ages, even small increases in fetal weight have tremendous impact on neonatal survival.[12] Thus, in pregnancies presenting at the lower limit of viability, significant prolongation of gestation and increase in fetal weight would be expected to improve fetal outcome.

Information on delayed interval delivery has been available only from sporadic case reports, most of which shows an improved outcome for the second fetus.[3-11] However, these data may be affected by significant selection bias because unsuccessful cases are unlikely to be reported. Consequently, the true incidence of delayed interval delivery, and its impact on perinatal outcomes, is unknown. The potential benefit of delaying delivery of second twins would be expected in very preterm gestations. Therefore, we performed a population-based, retrospective cohort study to determine the incidence of delayed interval delivery in extremely premature twin pregnancies in the United States and evaluated the impact of this management on perinatal and infant survival and morbidity.

Material and methods

Data from the "matched multiple birth" file of the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) were used.[13] These data comprise all twin live births, stillbirths and infant deaths in the United States during the period 1995 to 1998. The data were abstracted from live birth, fetal, and infant death certificates. The two fetuses from a twin pregnancy were linked based on a 3-stage matching algorithm developed by the NCHS.[14] The algorithm has been validated and found to be 99% accurate in being able to link the 2 fetuses to a twin pregnancy. The details of the algorithm have been described elsewhere.[14]

Our study population consisted of all twin pregnancies in which a first twin was delivered vaginally between 22 and 28 weeks with birth weights corresponding to these gestational ages. The birth weight cut-off ranges were based on a twin birth weight-for-gestational age nomogram corresponding to the 5th (350 g) and 95th (1459 g) centiles for birth weights at 22 and 28 weeks, respectively.[15] These gestational ages and birth weight ranges were chosen because neonatal survival after 28 weeks' gestation is generally favorable.

Gestational age in these data files was predominantly based on the last menstrual period. In a small fraction of births (<5%), it was based on a clinical estimate. The clinical estimate was used when the last menstrual period-based estimate was implausible for a given birth weight. When both the clinical estimate and the menstrual estimate of gestational age were incorrect or missing, it was imputed by the NCHS prior to release of the data.[16,17]

Delayed interval delivery between the first and second twin was expressed in completed weeks and was defined as 1 week or greater between the gestational age at delivery of the first and second twins. Risks of perinatal and infant mortality were the primary outcomes evaluated. Perinatal mortality was defined as the number of stillbirths (at 22 to 28 weeks) plus the number of neonatal deaths within the first 28 days and was expressed per 1000 total twin births. Infant mortality was defined as the number of infant deaths within the first year and was expressed per 1000 total twin live births. Secondary outcomes that were evaluated included stillbirths (defined as a fetus born without signs of life), neonatal deaths (defined as deaths within the first 28 days of life), mean birth weight, rates of small-for-gestational age (SGA) births (defined as birth weight <10th centile for gestational age), and respiratory distress syndrome with or without the need for assisted ventilation (for at least 30 minutes).

Perinatal and infant mortality rates in first and second twins were derived in relation to delayed interval delivery. In addition, these mortality rates were calculated in second twins in relation to delayed interval delivery categories separately for each week of gestation between 22 and 28 weeks. Relative risk (RR) with 95% confidence interval (CI) was derived as the measure of effect. Two sets of RRs were derived: (1) for perinatal mortality in second twins, compared with first twins, at each delivery interval strata (1, 2, 3, and ≥4 weeks), using 0 weeks as the reference; and (2) for perinatal mortality in second twins with delayed intervals, compared with those (second twins) that were delivered contemporaneously with the first twin (0 week interval). This latter comparison allowed us to evaluate the benefit of postponing delivery of second twins as opposed to delivering both fetuses contemporaneously.

We fitted multivariable logistic regression for categorical outcomes and linear regression for continuous outcomes to adjust for potential confounders. These confounders included maternal age (categorized as <20, 20 to 24, 25 to 29, 30 to 34, 35 to 39, and ≥40 years), gravidity (primigravida or gravida ≥2), maternal education (<12 or ≥12 completed years of schooling), marital status (married or single), maternal race/ethnicity (white, black, or other race/ethnicity), and lack of prenatal care. All statistical analyses were further adjusted for gestational age at delivery of the first twin to eliminate any bias because of residual confounding by gestational age. This study was approved by the ethics review committee of the Institutional Review Board of the University of

Table I Distribution of selected maternal characteristics based on categories of delayed interval delivery: United States twin births, 1995–1998

Maternal characteristics	Delayed interval delivery group: Yes (n = 258)	No (n = 3999)	*P* value
Maternal age, y (%)			.144
<20	13.2	13.7	
20–24	26.4	23.7	
25–29	21.3	28.2	
30–34	24.4	22.6	
≥35	14.7	11.9	
Primigravidity (%)	14.3	9.4	.010
Maternal race (%)			.895
White	66.3	66.4	
Black	30.6	30.0	
Other	3.1	3.6	
Maternal education, y (%)			
<12	17.5	19.7	.408
Smoking (%)	8.7	13.0	.074

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Results

In the United States between 1995 and 1998, 24,194 sets of twins were delivered between 22 and 28 weeks' gestational age. Of these, there were 4257 sets of twins in which the first twin was delivered vaginally at 22 to 28 weeks. In 258 (6.1%, 95% CI 5.4, 6.8) of these sets, the second twin was delivered at least a week after the first. Group-specific demographic characteristics of the studied population are presented in Table I. Because the benefit of delaying delivery on perinatal mortality of the second twin was evident only when the first twin was delivered at 22 to 23 weeks and not at later gestational ages (the Figure), we stratified all our analyses on the basis of the gestational age at delivery of the first twin at 22 to 23 and 24 to 28 weeks.

Perinatal mortality rates based on the gestational age at delivery of the first twin from 22 to 28 weeks in relation to delivery intervals are shown in Table II. For pregnancies in which the first twin was delivered at 22 to 23 weeks, as the delivery interval increased, there was a progressively significant decline in perinatal mortality of the second twin for up to 3 weeks' delivery interval. No statistically significant benefit existed for delivery intervals of 4 weeks or greater. The pattern of association between delayed interval delivery and stillbirths and neonatal deaths showed similar results (not shown). Analysis of infant mortality in relation to delayed

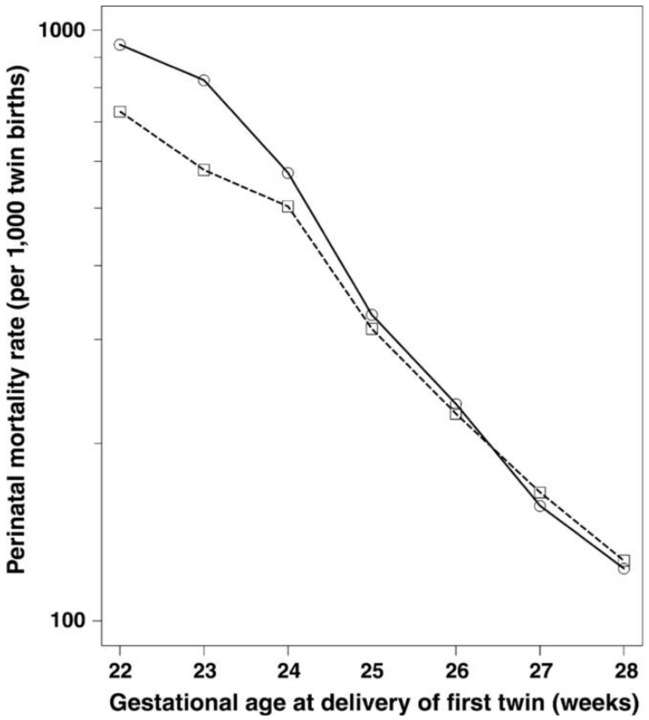

Figure Perinatal mortality for second twin by gestational age at delivery of the first twin in relation to delayed interval delivery: United States twin births 1995to 1998. The *open circles/solid line* represent no delivery interval, and *squares/dotted line* represent any delivery interval (≥1 week). Perinatal mortality rates were significantly different ($P < .05$) for twins with and without delayed interval delivery when the first twin was delivered at 22 to 23 weeks but not when the first twin was delivered at ≥24 weeks.

interval delivery was similar to those for perinatal deaths (Table III).

With increasing delay between delivery of the twins, there was a progressive increase in mean birth weight of the second twin over the first (Table IV). However, the rates of SGA births in the second twin increased with increasing delivery interval; this reached statistical significance for ≥4 weeks' interval (for delivery at 22 to 23 weeks) and ≥2 weeks for delivery of the first twin at 24 to 28 weeks (Table V).

Delayed delivery did not result in a reduction in the rates of respiratory distress syndrome or assisted ventilation support for over 30 minutes in the second twin. Delayed delivery led to a lower incidence of 5-minute Apgar scores <7 for the delayed twin over the first (not shown). This effect, however, reached statistical significance only for 1- to 2-week interval when the first twin was delivered at 22 to 23 weeks.

Comment

This population-based study evaluates delayed interval delivery in extremely preterm twin pregnancies and

Table II Perinatal mortality (fetal plus neonatal deaths) in first- and second-born twins in relation to interval between deliveries: United States twin births, 1995–1998

Delivery interval (wk)	Gestational age of first twin: 22–23 wks				Gestational age of first twin: 24–28 wks			
	Number of twins	Perinatal mortality*		Adjusted RR (95% CI)†	Number of twins	Perinatal mortality*		Adjusted RR (95% CI)†
		First	Second			First	Second	
0	1450	851.0	888.3	1.00 (Ref)	2549	282.1	302.5	1.00 (Ref)
1	68	852.9	691.2	0.28 (0.16, 0.49)	56	339.3	303.6	1.11 (0.60, 2.04)
2	23	739.1	521.7	0.12 (0.05, 0.30)	42	381.0	309.5	0.90 (0.44, 1.84)
3	9	666.7	444.4	0.08 (0.02, 0.35)	18	277.8	111.2	0.31 (0.07, 1.38)
≥4	14	928.6	857.1	0.66 (0.14, 3.05)	28	464.3	214.3	0.65 (0.24, 1.75)
Any interval ≥1 wk	114	824.6	657.9	0.29 (0.15, 0.35)	144	368.1	263.9	0.83 (0.55, 1.25)

* Perinatal mortality rates are expressed per 1000 total twin births, separately for first and second twins.
† Relative risks denote comparison of perinatal mortality rates in second twins with delayed interval, relative to those with an interval of 0 weeks. Relative risks were adjusted for maternal age, gravidity, maternal education, marital status, lack of prenatal care, maternal race/ethnicity, and gestational age at delivery of first twin.

Table III Infant mortality rates in first and second live-born twins in relation to interval between deliveries: United States twin births, 1995–1998

Delivery interval (wk)	Gestational age of first twin: 22–23 wks				Gestational age of first twin: 24–28 wks			
	Number of twins	Infant mortality*		Adjusted RR (95% CI)†	Number of twins	Infant mortality*		Adjusted RR (95% CI)†
		First	Second			First	Second	
0	1106	804.7	834.5	1.00 (Ref)	2324	212.6	211.9	1.00 (Ref)
1	52	807.7	618.2	0.27 (0.15, 0.48)	46	195.7	231.3	0.98 (0.51, 1.90)
2	19	684.2	266.7	0.06 (0.02, 0.19)	33	212.1	194.4	0.70 (0.30, 1.61)
3	6	500.3	166.7	0.03 (0.01, 0.28)	15	133.3	58.8	0.19 (0.03, 1.46)
≥4	9	888.9	700.0	0.63 (0.13, 3.08)	24	375.0	185.2	0.74 (0.28, 1.99)
Any interval ≥1 wk	86	767.4	546.5	0.20 (0.12, 0.32)	118	228.8	190.8	0.73 (0.47, 1.15)

* Infant mortality rates are expressed per 1000 twin live births, separately for first and second twins.
† Relative risks denote comparison of infant mortality rates in second twins with delayed interval, relative to those with an interval of 0 weeks. Relative risks were adjusted for maternal age, gravidity, maternal education, marital status, lack of prenatal care, maternal race/ethnicity, and gestational age at delivery of first twin.

assesses its impact on perinatal and infant outcomes. Our data demonstrate that, in this population, perinatal outcomes for second twins were improved when the first twin was delivered at 22 to 23 weeks and delivery of the second twin was delayed by up to 3 weeks. Furthermore, this improvement was proportional to the number of weeks by which the pregnancy was prolonged up to 3 weeks. Although perinatal and infant mortality was reduced in second twins when the first twin was delivered at 24 to 28 weeks, this reduction in mortality was not statistically significant when compared with pregnancies in which both twins were delivered contemporaneously.

These data suggest that delayed delivery may be a reasonable strategy when delivery of the first twin occurs at 22 to 23 weeks' gestation. A variety of approaches have been used to postpone delivery and improve outcomes of second twins. These include aggressive tocolysis, cervical cerclage in selected cases, corticosteroids to induce fetal lung maturation, and antibiotics.[3-11] Our study did not allow us to evaluate the impact of these different strategies on outcomes when delivery of the second twin was delayed. Therefore, our study does not permit recommendations as to which strategies are best for delaying delivery.

Although these initial data are promising, data on long-term outcomes of the infants who had been delivered as a consequence of delayed interval delivery are lacking. It is possible, for example, that the second-born twins may have an unacceptably high incidence of periventricular leukomalacia, intraventricular hemorrhage, and cerebral palsy. It is known that premature rupture of the membranes, especially when associated with intra-amniotic infection, is an antecedent of these conditions.[18,19] One unexpected finding from this study is the higher risk for SGA in the second twin with increasing delivery intervals. This is an issue that requires examination in future studies.

Our study has some limitations. We assumed that pregnancy dating was accurate and that the recorded

Table IV Mean birth weight in first and second live-born twins in relation to delayed interval delivery: United States twin births, 1995–1998

	Gestational age of first twin: 22–23 wks			Gestational age of first twin: 24–28 wks		
	Birth weight (mean SD)			Birth weight (mean SD)		
Delivery interval (wk)	First twin	Second twin	Difference* (95% CI)	First twin	Second twin	Difference*‡ (95% CI)
0	527 (91)	578 (155)	Reference	877 (220)	923 (686)	Reference
1	538 (84)	564 (99)	−8 (−223, 206)	855 (244)	922 (280)	26 (−154, 206)
2	555 (74)	674 (96)	13 (−390, 416)	923 (265)	1072 (353)	74 (−139, 287)
3	563 (121)	801 (173)	103 (−532, 738)	904 (284)	1127 (482)	146 (−163, 455)
≥4	530 (66)	869 (601)	349 (196, 502)	903 (249)	1324 (456)	453 (208, 698)
Any interval ≥1 wk	541 (81)	713 (364)	92 (−83, 267)	890 (254)	1059 (394)	129 (15, 243)

* Birth weight differences correspond to differences in mean birth weight in second twins with delayed interval, relative to those with an interval of 0 weeks. Analyses were adjusted for maternal age, maternal education, marital status, maternal race/ethnicity, and gestational age at delivery of first twin.

Table V Rates of small-for-gestational age in first and second live-born twins in relation to delayed interval delivery: United States twin births, 1995–1998

	Gestational age of first twin: 22–23 wks				Gestational age of first twin: 24–28 wks			
		SGA (%)				SGA (%)		
Delivery interval (wk)	Number of twins	First	Second	Adjusted RR* (95% CI)	Number of twins	First	Second	Adjusted RR* (95% CI)
0	1106	–	3.2	1.00 (Ref)	2324	–	3.1	1.00 (Ref)
1	52	–	3.6	1.18 (0.27, 5.13)	46	–	2.0	0.60 (0.08, 4.41)
2	19	–	6.7	2.37 (0.30, 18.96)	33	–	13.9	5.22 (1.94, 14.04)
3	6	–	–	–	15	–	35.3	16.40 (5.66, 47.52)
≥4	9	–	70.0	20.1 (2.41, 98.9)	24	–	25.9	11.12 (4.49, 27.56)
Any interval ≥1 wk	86	–	11.6	4.06 (1.90, 8.68)	118	–	14.5	5.20 (2.99, 9.04)

* Relative risks denote comparison of small-for-gestational-age rates in second twins with delayed interval, relative to those with an interval of 0 weeks. Relative risks were adjusted for maternal age, gravidity, maternal education, marital status, lack of prenatal care, maternal race/ethnicity, and gestational age at delivery of first twin.

gestational ages at delivery were reliable. Bleeding in early pregnancy may lead to errors in gestational age assessment.[20] Furthermore, in the data set available to us, the gestational age at delivery was recorded only in completed weeks. As a result, pregnancies in which the pair of twins were born a few hours apart, ie, 24 weeks 6 days and 25 weeks 0 days, would be recorded in such a manner as to give the impression that the twins were born a week apart (24 and 25 weeks). Similarly, in cases in which twins were born days apart but within the same week of gestation, the gestational ages were recorded in a manner that would suggest that there was no interval between the deliveries. Nevertheless, there would be a genuine interval of at least 1 week when the recorded interval was 2 weeks. Because our findings demonstrate a definite improved survival with increasing delivery interval between twins, the conclusion that delayed interval delivery may improve perinatal and infant survival and birth weight when the first twin is delivered at 22 to 23 weeks' gestation and the delivery interval is ≤3 weeks is reasonable. Because we did not have data on delays of days, rather than weeks, we were unable to determine whether delays of a few days improved outcomes, as would be expected at these extremely premature gestational ages. We also did not address pregnancies in which the first twin was delivered at less than 22 weeks' gestational age. A review of the literature suggests an improved outcome for the second twin in this situation is possible.[7]

Another weakness of this study is that we did not obtain data on maternal morbidity and outcomes. Delayed delivery would conceivably put the mother at significant risk of infectious morbidity, deep venous thrombosis due to bed rest, coagulation disorders, and adverse effects of tocolytics and other medications; these complications could occasionally lead to maternal death. Therefore, the true risk to the mother remains unevaluated. However, there have been no reported instances of maternal death in the published literature.[7,9]

It was not possible, with the data available for our study, to determine how often delayed delivery was attempted but unsuccessful. Although previous studies have been optimistic about outcomes of delayed interval delivery, the majority has suffered from selection bias. In the only study in which a uniform policy of attempting delayed delivery on all eligible multiple pregnancies was employed, Farkouh et al[8] reported their experience with 24 consecutive twin and triplet pregnancies ranging between 16.4 and 28.6 weeks at delivery of the first fetus. They achieved a mean delay of 36 days (range 3 to 123 days) between delivery of the first-born and after-coming fetuses. The mortality among the first-born infants was 84% (21/25), compared with 37% in the retained siblings (10/27). In contrast, a recent retrospective study of 14 cases by Livingston and colleagues[11] found a high perinatal mortality of 61% associated with delayed interval delivery. In the same study, only 1 of 19 retained fetuses survived without major sequelae.

We do not know in which cases there was a deliberate attempt to delay delivery. There have been reports of cases in which following the delivery of the first twin, the authors attempted to induce delivery of the second with oxytocin. In some of these, it was only when attempted induction was unsuccessful that attempts at delivering the second twin were aborted, with resulting delayed interval delivery.

The failure of our study in demonstrating any benefit in reducing mortality for the second twin when the first was delivered at $\geq$24 weeks or when the delivery interval was $\geq$4 weeks may be a consequence of small numbers (Table II). A *post hoc* analysis indicates that one would need 140 cases to demonstrate a benefit of delaying delivery of the second twin beyond 4 weeks (i.e., $\geq$4 weeks) when the first twin was delivered at 22 to 23 weeks. However, our analysis had a power of 76% in being able to demonstrate a reduction in perinatal mortality in the second twin when the first was delivered at 24 to 28 weeks.

In conclusion, delayed interval delivery appears to be associated with improved outcomes for the twin whose delivery is delayed when the first twin is delivered at 22 to 23 weeks and the delivery interval is $\leq$3 weeks. However, we urge caution in applying the results of our study to decision making for the individual case. The management of each clinical situation must be individualized according to its own merit, after thorough counseling of the expectant couple. Prospective studies that examine the long-term outcomes of infants whose delivery is delayed are necessary, as are studies examining the risks and complications of pregnant women who undergo this management approach.

Authors' note

Since the acceptance of our manuscript for publication, a study addressing delayed interval delivery in twins in the United States using the same dataset has been published in the *American Journal of Obstetrics and Gynecology*.[21] At the time we submitted our manuscript, we were unaware that such a paper had already been accepted for publication and was "in press" in the *American Journal of Obstetrics and Gynecology*.

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