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Prospective risk of intrauterine death of monochorionic-diamniotic twins

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Objective: The purpose of this study was to calculate the prospective risk of fetal death in monochorionic-diamniotic twins.
Study design: We evaluated 193 monochorionic diamniotic twin pregnancies that were followed and delivered after 24 weeks. Surveillance included cardiotocography and sonography performed at least once weekly. The prospective risk of fetal death was calculated as the total number of deaths at the beginning of the gestational period divided by the number of continuing pregnancies at or beyond that period.
Results: The fetal death rate was 5 of 193 pregnancies (2.6%; 95% CI, 1.1, 5.9); the prospective risk of stillbirth per pregnancy after 32 weeks of gestation was 1.2% (95% CI, 0.3% - 4.2%).
Conclusion: Under intensive surveillance, the prospective risk of fetal death in monochorionic-diamniotic pregnancies after 32 weeks of gestation is much lower than reported and does not support a policy of elective preterm delivery.

Monochorionic twins, comprising approximately 20% of all spontaneous twins and nearly 5% of iatrogenic twins,[1] are at a substantial higher risk of perinatal morbidity and death than their bichorionic counterparts.[2-4] This risk is attributed to the inherent pathologic condition that is associated with delayed zygotic splitting that leads to the increased prevalence of fetal and placental malformations. However, in monochorionic-diamniotic pregnancies, the precise cause of the high rate of adverse perinatal outcomes in pregnancies that are not complicated by congenital anomalies, twin-twin transfusion syndrome (TTTS), and/or growth restriction is not clear.

Evidently, not all monochorionic twin pregnancies are complicated a priori. A recent analysis of a large cohort of 455 monochorionic twins showed that 181 (39.8%) twin pairs were considered "uncomplicated" (ie, without signs of TTTS and exhibiting appropriate and concordant growth in each of the structurally normal twins).[5] This subset of "uncomplicated" monochorionic twins, however, was found to be at a considerable excess

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risk of intrauterine fetal demise (IUFD), despite being without apparent risk except of sharing a monochorionic placenta. The invariable presence of intertwin vascular connections in these placentas was suspected to be involved in some form of unexpected and acute TTTS. In that study,[5] the prospective risk of such unexpected IUFD after 32 weeks of gestation was 1 in 23 monochorionic-diamniotic pregnancies (4.3%; 95% CI, 1/11-1/63). With this risk in mind, one might question the wisdom of continuing the pregnancy of "uncomplicated" monochorionic twins after 32 weeks of gestation. In their commentary on this study, Cleary-Goldman and D'Alton[6] focused on the important dilemma that many practitioners are confronting increasingly often, namely the ideal gestational age at which to deliver apparently uncomplicated monochorionic twins. Whereas the results of the study of Barigye et al[5] seem to suggest that 32 weeks of gestation may be a reasonable date for elective preterm delivery to avoid unexpected IUFDs, the inherent risks of prematurity at that gestational age remain significant.[6]

In the absence of randomized studies, balancing the risk of elective preterm birth versus the risk of single or double IUFD is still challenging.[6] As a result, we carried out this retrospective cohort study to reassess the prospective risk of IUFD in our monochorionic twin population.

Material and methods

During the period September 1994 through March 2005, there were 893 twin pregnancies that were followed and delivered at the Maternity Dr Alfredo da Costa, Lisbon, Portugal, which is a tertiary perinatal center that cares for the Lisbon area and serves as a referral center for the south of Portugal. This figure represents approximately 1% of all deliveries. During this period, information about the pregnancy and delivery was registered prospectively on a preset form and subsequently entered into a computerized system. We excluded twin gestations that were delivered only and were not followed at our service.

For this study, we identified monochorionic twins. Monochorionicity was established by standard ultrasonographic criteria performed by level III ultrasonographers, confirmed by careful examination of the delivered placenta by experienced obstetricians, and double-checked by pathologic examination of the placentas. We restricted our analysis to twin births at >24 weeks of gestation.

Gestational age was derived from the last menstrual period that was confirmed by first trimester ultrasound scans and from the day of oocyte retrieval in pregnancies after assisted reproduction (ie, oocyte retrieval day minus 14). Prenatal diagnosis in the form of nuchal translucency thickness measurements, level III detailed anatomic scan, and genetic amniocentesis (when indicated) were performed in all cases. Our surveillance protocol in monochorionic twins included biweekly assessments between 24 and 30 completed weeks of gestation and weekly assessment thereafter. The prenatal care included nonstress testing of the 2 fetal heart rates and biophysical profile of both twins. Longitudinal growth assessment is performed biweekly. After 30 weeks of gestation, we performed Doppler analyses of the umbilical arteries supplemented with measurements of the peak systolic velocity in the middle cerebral artery, if signs of aberrant fetal growth were found. These measures were implemented during the study period as they became available in terms of equipment and experience. Subjects with either nonreassuring fetal findings or with maternal complications were submitted to daily to twice weekly maternal-fetal evaluations that were performed during hospitalization or during visits at an outpatient clinic setting. No elective preterm deliveries are done; however, indicated preterm deliveries were carried out on the basis of maternal and/or fetal conditions. Prophylactic antenatal corticosteroids (2 intramuscular doses of 12 mg betamethasone, 24 hours apart) were administered only if a preterm delivery was considered. In otherwise normally progressing gestations, we offered, after detailed counseling, elective deliveries at 36 to 37 completed weeks of gestation without lung maturity assessment.

The analysis was made per pregnancy or per fetus, as required. We excluded the stillborn fetuses from the analysis of birth weights and birth weight discordance because of the maceration that is associated with the prolonged interval between IUFD and delivery. The following variables were considered in our analysis: maternal age and parity, mode of conception (spontaneous vs iatrogenic), maternal complications such as premature contractions (<34 weeks of gestation), hypertensive disorders (preeclampsia, pregnancy-induced hypertension, and chronic hypertension), diabetes mellitus (gestational and pregestational), preterm rupture of membranes at <34 weeks of gestation, mode of delivery, gestational age at birth, birth weight, birth weight discordance of $>25\%$ (intertwin birth weight difference expressed as percentage of the heavier twin), frequency of TTTS, Apgar scores at 5 minutes (not available for 1 pair because of extreme prematurity), major malformations (excluding stillbirths), early (≤ 7 days of life) neonatal death, and major neonatal morbidity (respiratory complications, sepsis, and intraventricular hemorrhage).

Using the same method of "fetuses-at risk" that was employed by Barigye et al,[5] we derived the rate of fetal death in continuing pregnancies for each 2-week gestational period, starting at 24 weeks of gestation. This rate was calculated as the number of IUFDs that occurred within the 2 weeks after the beginning of the week divided by the number of continuing pregnancies

Table I Maternal and fetal/neonatal characteristics of 193 intensively monitored monochorionic diamniotic twin gestations that were delivered after 24 weeks of gestation

Characteristic	Measurement
Maternal age (y)	28.2 ± 4.8
Nulliparous women (n)	105 (54.4%)
Spontaneous conceptions (n)	183 (94.8%)
Pregnancy complications (n)*	
Premature contractions	79 (40.9%)
Hypertensive disorders	37 (19.2%)
Premature preterm rupture of membranes	13 (6.7%)
Diabetes mellitus	14 (7.3%)
Mode of delivery (n)	
Vaginal	63 (32.6%)
Cesarean birth in labor	26 (13.5%)
Elective cesarean	104 (53.9%)
Gestational age at delivery (wk)	34.8 ± 2.5
<32 (n)	18 (9.3%)
32-35 (n)	89 (46.1%)
≥36 (n)	86 (44.6%)
Birth weight (g)†	2156 ± 534
<1500 (n)†	43 (11.3%)
1500-2499 (n)†	230 (60.4%)
>2500 (n)†	108 (28.3%)
Birth weight discordance >25% (n)†	28 (14.5%)
Major malformations (n)†	16 (4.2%)
Twin-twin transfusion syndrome (n)	15 (7.8%)
IUFD (n)	
Per fetus	5 (1.3%)
Per pregnancy	5 (2.6%)
5-Minute Apgar score <7 (n)	5 (1.3%)
Early neonatal deaths (n)	7 (1.8%)
Major neonatal morbidity (n)*	
Respiratory	55 (14.4%)
Sepsis	7 (1.8%)
Intraventricular hemorrhage	2 (0.5%)

* Subjects may have >1 condition.
† Data excludes stillbirths.

at the beginning of that week. The prospective risk of IUFD was calculated as the total number of IUFDs at the beginning of the gestational period divided by the number of continuing pregnancies at or beyond that period.[5,7] Because few pregnancies continued beyond the 2-week period at ≥36 weeks of gestation, the prospective risk was not determined for this period. Our pediatricians followed the surviving infant in cases with single IUFD, and their condition was recorded in our database. We derived the binomial distribution 95% CI for rates with standard statistical formulas.

The study has been approved by local institutional review board.

Results

We identified 193 monochorionic diamniotic sets among the 893 twins who were followed and delivered during the study period (21.6%). None of the sets were excluded from the analysis; the characteristics of this monochorionic-diamniotic twin cohort are shown in Table I. In our cohort, 107 pregnancies (approximately 55% of all cases) were delivered at <36 weeks of gestation; 39 pregnancies (36.4%) had a spontaneous preterm labor, and in 68 cases we delivered the pregnancy prematurely because of fetal indication (63/68; 92.6%) or maternal indications (5/68; 7.4%). The IUFD rates were 5 of 193 pregnancies (2.6%; 95% CI, 1.1, 5.9) and 5 of 86 fetuses (1.3%; 95% CI, 0.5, 3.0).

Major fetal malformations included 2 concordant chromosomal anomalies (inversion of chromosome 3, also present in the mother), 9 congenital heart anomalies, 2 kidney anomalies, and 1 omphalocele. All IUFDs occurred in the nonpresenting twin (ie, in twin B). Four of the 5 IUFDs occurred remote from term (Table II) and were delivered with their apparently normal co-twin at an interval of 3 to 7 weeks. Because of severe maceration, autopsies were unreliable in terms of anomaly detection; however, all these pregnancies were under close observation because of early onset severe discordant growth (>25% as estimated from the last sonography), but without signs of TTTS. The fifth IUFD occurred at 34 weeks of gestation in a fetus with a nonreassuring fetal heart rate tracing in a pregnancy that was complicated with severe preeclampsia. IUFD occurred just before the planned cesarean delivery, and the stillborn fetus weighed 1780 g (19% discordant). Because no other cause was found, this potentially avoidable death was presumably related to acute fetal distress. All but 1 of the survivors are developing normally at a follow-up of at least 3 years. One survivor, however, has cerebral palsy. This child lost its co-twin at 25 weeks of gestation, was growing normally, was delivered by elective cesarean 7 weeks later, and had a 5-minute Apgar score of 10. This event occurred before we implemented antepartum level III ultrasound scans and serial magnetic resonance imaging of the surviving single twin. Thus, we are unable to exclude the possibility that brain lesions could have been detected before birth in this case.

Four of the 7 early neonatal deaths were a result of a congenital heart anomaly (including 1 pair with a concordant cardiac anomaly): One death was the result of a traumatic forceps delivery of a 31 weeks of gestation (1545 g, second twin); 1 death was the result of sepsis at 33 weeks of gestation in a 1845-g infant; and one death was the lighter twin who weighed 695 g from a pregnancy that was complicated by TTTS and underwent spontaneous preterm delivery at 29 weeks of gestation. The uncorrected perinatal (stillbirth plus early neonatal) mortality rate of this cohort was 12 of 381 infants (3.1%) or 31.5 of 1000 live born infants. The uncorrected for anomalies early neonatal mortality rate was 7 of 381 infants (1.8%, 18.3 of 1000 live born infants), and the corrected for

Table II Rate and prospective risk of unexpected fetal demise in 193 intensively monitored monochorionic-diamniotic twin gestations that were delivered after 24 weeks of gestation

	Continuing (n)		Deaths per period (n)		IUFD rate per period (n/N)		Deaths in continuing (n)		Prospective risk of IUFD (n/N)*	
Gestational age (wk)	Pregnancies	Fetuses	Per pregnancy	Per fetus	Per pregnancy	Per fetus	Pregnancies	Fetuses	Per pregnancy	Per fetus
24-25	193	386	2	2	2/193 (1/97)	2/386 (1/193)	5	5	5/193 (1/37), 2.6%, [1.1,5.9]	5/386 (1/77), 1.3%, [0.5, 3.0]
26-27	193	384	1	1	1/193	1/384	5	5	5/193 (1/37), 2.6%, [1.1,5.9]	5/384 (1/77), 1.3%, [0.5, 3.0]
28-29	191	379	0	0	0/191	0/379	4	4	4/191 (1/48), 2.1%, [0.8, 5.2]	4/379 (1/95), 1.0%, [0.4, 2.7]
30-31	183	363	1	1	1/183	1/363	4	4	4/183 (1/46) 2.2% [0.9, 5.5]	4/363 (1/91) 1.1% [0.4, 2.8]
32-33	168	332	0	0	0/168	0/332	2	2	2/168 (1/84), 1.2%, [0.3, 4.2]	2/332 (1/166), 0.6%, [0.1, 2.2]
34-35	140	276	1	1	1/140	1/276	1	1	1/140, 0.7%, [0.1, 3.9]	1/276, 0.4%, [0.06, 2.0]
≥36	88	171	0	0	0/88	0/171	0	0		

* 95% CI is given in brackets.

anomalies early neonatal mortality rate was 3 of 381 (0.8%, 7.9 of 1000 live born infants).

Comment

Elective preterm delivery of presumably "uncomplicated" pregnancies is reserved for cases in which evidence shows that continuing the pregnancy undoubtedly may increase the risk for the fetus(es) and that this potential risk outweighs the risks that are associated with preterm birth. Such a "ticking bomb" situation that warrants intensive antenatal care and elective preterm delivery has been described for monoamniotic twin pregnancies in which cord entanglement with a potential to become dangerously tightened is almost invariably seen.[8,9] However, the extension of this approach to all diamniotic-monochorionic twins,[10] including those who are apparently "uncomplicated," has been suggested only recently in the seminal study that was conducted by Barigye et al.[5] In this study, the authors reiterated the well-known association of monochorionicity and the risk for an unexpected single or double fetal death past 32 weeks of gestation. Single fetal death is of special importance because, as opposed to dichorionic twins, intertwin agonal transfusion results in up to a 38% risk of death and a 46% risk of neurologic damage to the co-twin.[10] The authors concluded that the significant prospective risk merits further studies that will examine the potential salvage of these IUFDs by elective preterm delivery.

Our study, although inspired by that of Barigye et al,[5] is different in 2 main aspects. First, their seminal study was comprised of presumably "uncomplicated" cases, whereas our study did not exclude malformations, growth problems, and TTTS. This difference was expected to increase the prospective risk of IUFD in our cohort. However, our results show a much lower prospective risk per pregnancy and per fetus in each stratum of gestational ages (Table II) compared with the risks reported by Barigye et al.[5] Importantly, the prospective risk of antepartum stillbirth after 32 weeks of gestation was 4.3% (95% CI, 1.6% - 9.1%) as compared with 1.2% (95% CI, 0.3% - 4.2%) in our series. Thus, according to our data, 1 case of IUFD would be prevented for every 84 monochorionic pregnancies that are delivered at 32 weeks of gestation and 1 case of IUFD for every 140 pregnancies at 34 weeks of gestation, compared with 23 and 30 pregnancies in the series of Barigye et al.[5]

The second main difference between our study and that of Barigye et al[5] is the more intensive antenatal surveillance that is used in our service in terms of frequency (weekly vs biweekly) and methods (cardiotocography and sonography vs sonography alone). We acknowledge that there are no data to support the frequency of antenatal testing in uncomplicated twins and that these are scheduled empirically rather than according to evidence-based recommendations. However, because all IUFDs occurred between 1 and 2 weeks after the last scan in the study of Barigye et al,[5] it is likely that

more frequent assessments of fetal well-being may reduce, at least in part, the prospective risk of IUFD. In our cohort, nearly 55% of the pregnancies were delivered preterm as a result of our surveillance protocol; in the majority of pregnancies, the preterm delivery was for fetal indications. Nevertheless, it is unknown and probably can never be known how many unanticipated fetal deaths have been avoided by our antenatal surveillance protocol.

Increasing the frequency of antenatal assessments and implementing more sophisticated surveillance methods are undeniably more expensive. However, if the alternative to intensive antenatal assessments is elective preterm delivery, the cost of a prolonged stay in the neonatal intensive care unit as a result of iatrogenic prematurity should certainly be added to the equation and conceivably would offset the costs that are involved in intensive monitoring.

The American College of Obstetricians and Gynecologists, in its most recent practice bulletin on complicated twin and other multiple gestations[11] did not differentiate between the risk of dichorionic and monochorionic twins and therefore did not describe specifically the necessary fetal well-being assessment of monochorionic twins nor the possibility of elective preterm birth. However, as Cleary-Goldman and D'Alton[6] pointed out, some maternal-fetal medicine centers in the United States are conducting antenatal surveillance more frequently than once every 2 weeks and are using cardiotocography in addition to ultrasound and Doppler studies.

Another pertinent question is the timing of elective preterm delivery for twins. Most clinicians would probably agree that 32 weeks of gestation is too early. Similarly, many clinicians would agree that 37 to 38 weeks of gestation is the optimal gestational age for twins.[12] One possible concession is to offer delivery of these apparently uncomplicated monochorionic twins at approximately 34 to 35 weeks of gestation after antenatal corticosteroid administration and appropriate counseling regarding the pros and cons of expectant management versus elective preterm delivery.[6] Based on our results and on recent observations regarding the excess risk of respiratory complications after near term twin delivery,[13,14] we believe that our policy of offering elective preterm birth after 36 completed weeks of gestation is a more reasonable compromise.

The differences between our study and that of Barigye et al[5] may relate to difference in the referral populations. Although the 2 maternal-fetal medicine services are considered tertiary and although the prevalence of fetal malformation in our series (4.2%; Table I) was similar to that reported by Barigye et al[5] (27/480; 5.6%), we had only approximately 8% TTTS cases (Table I), whereas Barigye et al excluded 164 of 480 cases (34.2%) of TTTS from the analysis. Our low TTTS prevalence is because many patients (data not available) opted for induced late abortion rather than continuation of pregnancy after 24 weeks of gestation. Given the strict criteria that were used by Barigye et al, the nearly twice higher than the accepted 15% to 20% prevalence of TTTS may suggest that a different referral policy may account for the higher intrauterine death. Because of the long interval between fetal death and delivery, we were unable to reproduce the pathologic observation that suggests that death occurred because of some form of acute TTTS.[5]

Finally, IUFDs among dichorionic twins does also exist. However, this risk is considerably higher in monochorionic twins[4,15] and highlights the special attention that is required for monochorionicity, which should translate into more intensive antenatal assessments. However, the prospective risk of IUFD that was found in our study does not indicate preterm elective delivery of monochorionic twins.

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