ORIGINAL ARTICLE

Perinatal Loss Among Twins

By Anne Lynch, MD, MSPH
Robert McDuffie Jr, MD
Ella Lyons, MS
Mary Chase
Miriam Orleans, PhD

Abstract

Objective: We evaluated prenatal factors related to perinatal loss in twins, using medical records and death certificates, to determine the main perinatal event that contributed to babies' deaths.

Design: This was a retrospective cohort study of 550 monochorionic diamniotic or diamniotic dichorionic twins who were delivered at Kaiser Permanente Colorado between 1994 and 2001.

Main Outcome: The main outcome of the study was perinatal loss (stillbirth or neonatal death).

Outcomes Measures: Select maternal risk factors (maternal age, race, marital status, assisted conception, past history of preterm birth, cigarette smoking, and placentation) were included in the univariable and multivariable logistic regression analysis. Data on these risk factors came from review of records from our multiple-birth perinatal database. A comprehensive review of clinical events recorded in the medical records and on the death certificate was conducted to assess the main event that contributed to the loss.

Results: In the cohort of 1100 babies, there were 12 stillbirths and 34 neonatal deaths, with an overall frequency of perinatal loss of 4.2%. We found a strong association between a monochorionic diamniotic placentation and perinatal loss (adjusted odds ratio, 3.9; 95% confidence interval, 2, 7.7). At delivery, placental pathology and spontaneous preterm birth accounted for 36% and 41%, respectively, of the clinical events contributing to the demises. Compared with the medical record, review of death certificate information did not contribute significantly to the understanding of the sequence of perinatal events leading to the demise.

Conclusions: We conclude that loss in twins is most strongly associated with monochorionic diamniotic placentation. Although this condition is not preventable, early identification (by ultrasound) and referral to subspecialists may decrease the chances of perinatal loss. Prevention of spontaneous preterm birth in all women remains an important initiative in obstetric care to reduce perinatal mortality and neonatal morbidity. We believe that improvements in the reporting on death certificates will allow future research on large data sets and may provide further insight into perinatal loss in twins. We emphasize the importance of a comprehensive clinical review of each case of perinatal loss to fully understand the sequence of clinical events leading to this adverse pregnancy outcome.

Introduction

In the United States the twinning rate has increased 38% since 1990 and 65% since 1980.[1] Two principal reasons for this upsurge are the increased availability of and demand for assisted conception and the larger numbers of women who are deferring childbearing until later in life.[2] We have known for many years that multiple births are associated with a higher risk of perinatal loss.[3,4] The natural history of events preceding multiple birth demise is complex, however. Its study requires assimilation of information from many sources. We now recognize that risk factors early in the antenatal history and course may have a significant impact on the outcome, yet these major contributory factors may be viewed as remote and may be overlooked or not made available to health care professionals completing death certificates.

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The changing epidemiology of multiple births led our research group to study the incidence and factors contributing to perinatal loss among twins in a Colorado multiple-birth cohort. We designed our own system for reviewing each case of perinatal loss. After this review, we developed a model of prenatal risk factors for perinatal loss and determined the main perinatal clinical event that contributed

Anne Lynch, MD, MSPH, is an assistant professor and epidemiologist in the Department of Obstetrics and Gynecology at the University of Colorado at Denver and Health Sciences Center. E-mail: anne.lynch@uchsc.edu.
Robert McDuffie, Jr, MD, is Chief of Perinatology at Kaiser Permanente Colorado. He is also a clinical professor in obstetrics and gynecology at the University of Colorado at Denver and Health Sciences Center. E-mail: robert.mcduffie@kp.org.
Ella Lyons, MS, is the manager of Analytic Services/Biostatistician at the Clinical Research Unit, Kaiser Permanente Colorado. E-mail: ella.e.lyons@kp.org.
Mary Chase is a statistician in the Health Statistics Section at the Colorado Department of Public Health and Environment. E-mail: Mjchase@smtpgate.dphe.state.co.us.
Miriam Orleans, PhD, is a professor emerita in the Department of Preventive Medicine and Biometrics at the University of Colorado at Denver and Health Sciences Center. E-mail: pmorleans@earthlink.net.

to the baby's death using information from the medical record and the death certificate.

Materials and Methods

Review of the records of this retrospective cohort of 550 twins (delivered between 1994 and 2001) was approved by the Kaiser Permanente (KP) Northern California Institutional Review Board. The twins were born to women who were KP members at the time of delivery. All mothers received coordinated care from KP obstetric providers. Routine referral to maternal fetal medicine specialists was made by 20 weeks' gestation for consultation and development of a plan for care in the second half of pregnancy. Women were monitored with serial ultrasound examinations of twins and digital cervical examinations. Repeat twin births, twins born before 20 weeks' gestation, and monochorionic monoamniotic twins were excluded from the data analysis.

The purpose of the review was to determine the main perinatal event that contributed to the baby's death.

Study outcomes were stillbirth, neonatal mortality, and perinatal mortality (a composite of stillbirths and neonatal deaths). Stillbirth was defined as the intrauterine demise of the fetus after 20 weeks' gestation. A neonatal death was the death of the baby during the first 28 days of life. Data on stillbirth and early neonatal death (within the first few hours of life) were obtained from a multiple-birth perinatal database, described in detail elsewhere.[5–7] Information on deaths later in the neonatal period was primarily obtained from the KP Colorado administrative databases (where information is routinely gathered on deaths of members). We also investigated all stillbirths and neonatal deaths among twins born at Colorado's KP facilities during the study period using the Colorado Department of Public Health and Environment (CDPHE) matched infant birth and death database. In the state of Colorado, all cases of fetal death are required by law to be submitted to the CDPHE irrespective of gestational age. We reviewed data from multiple sources to ensure that we were missing no cases of perinatal loss. We linked deaths from the CDPHE database to our twin database using the mother's date of birth and the delivery date of the baby. We imported fields from this database describing the main cause of death, contributory causes of the baby's death, and pregnancy complications. The fields contained codes from *International Classification of Diseases, 9th Revision,* and *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, that were subsequently decoded to assist our review.

Risk factors examined in this study included maternal age (≥35 years versus <35 years), race (African American versus others), marital status (married versus single), assisted (ovulation induction or assisted reproductive technologies) conception (yes or no), past history of a preterm delivery (yes or no), cigarette smoking during pregnancy (yes or no), and placentation as outlined below. Data on these risk factors were obtained from our multiple-birth perinatal database. These factors were chosen on the basis of our previous experience with this cohort[5–7] and of the existing literature on this topic.[8]

Placentation was classified as monochorionic diamniotic or dichorionic diamniotic. We assumed that all twins who were of the opposite sex (n = 72) were dichorionic diamniotic. The placental histology was reviewed on the remaining 478 sets of twins to determine their chorionicity. A diagnosis of twin-to-twin transfusion was made on the basis of prenatal ultrasound evidence of monochorionic diamniotic placentation (single placenta, absence of twin peak sign, thin membrane, same twin sex), clinical evidence of polyhydramnios in the recipient twin and oligohydramnios in the donor twin, discordant growth, and findings on postnatal placental examination confirming diamniotic monochorionic placentation with shared placental vascularity. All cases of twin-to-twin transfusion were managed by maternal fetal medicine specialists and were treated with reduction amniocentesis at the discretion of the provider. None of these patients had laser ablation of the vascular connections in the placenta.

All cases of perinatal death were reviewed by Drs Lynch and McDuffie. The maternal medical record, the baby's medical record, pathology records, and information on the death certificate were studied and discussed on each of the 46 cases of perinatal death. The purpose of the review was to determine the main perinatal event that contributed to the baby's death. A third reviewer was consulted on four cases where there was difficulty reaching a consensus about the cause of death.

Statistical Analysis

The data were analyzed in SAS 9.1 (SAS Institute, Cary, NC). First, we determined the association of the risk factors with perinatal loss. The relative risk (RR) was used as a measure of association. Measures of association were tested using the χ–square or Fisher exact test. Statistics are presented with 95% confidence intervals (CI; $p < .05$). We developed a multivariable logistic regression model to determine the independent association of each of these risk factors with perinatal loss.

The odds ratio (OR) was used as an approximation of the RR. We described the major determinant of perinatal death as concluded from our medical record review and the clinical information on the death certificate using descriptive univariable statistics.

Results

There were 550 women with twin gestations in the cohort. Of those, 424 (77%) women were non-Latina White, 61 (11%) were Latina, 48 (9%) were African American, and 17 (3%) were of other races. There were 193 pregnancies (35%) that resulted from assisted conception. Diamniotic dichorionic placentas were found in 439 (80%) of the twin gestations, and the remaining 110 (20%) placentas were monochorionic diamniotic. Histology of the placenta for one set of twins was missing. Eighteen (3.3%) pregnancies resulted in the twin-to-twin transfusion syndrome.

Table 1 shows the RR of early pregnancy risk factors for perinatal loss. There was a strong association between monochorionic placentation and perinatal death. In addition, we found that women whose fetuses had twin-to-twin transfusion syndrome were over nine times more likely to have a perinatal loss than women whose fetuses did not have the syndrome. Race (African American), marital status (single), nulliparity, and cigarette smoking were associated with an elevated risk of perinatal loss. However, these associations were not statistically significant. Adjusted for other risk factors, the OR of monochorionicity for perinatal loss was 3.9 (CI, 2, 7.7).

There were 46 (4.2%) perinatal deaths during the study period. However, when we removed cases of twin-to-twin transfusion from the data set, the incidence of perinatal death decreased to 3.3%. Twelve were stillbirths and 34 were neonatal deaths (Table 2). The mean (± SD) gestational ages (weeks) at delivery of the stillborn infants and of the infants who died after birth were 30 ± 6 and 25 ± 4 weeks, respectively. Fifteen pairs of twins died. In the remaining 16 perinatal deaths, one of the twin pair survived (twin A = 6; twin B = 10).

The main perinatal events contributing to loss are shown in Table 2. After medical record review, we found that in 17 (37%) cases, a significant perinatal event preceded the death and was related to a problem with the placenta (twin-to-twin transfusion, placenta previa, placental abruption). The incidence of perinatal mortality due to twin-to-twin transfusion was evenly distributed among the stillbirths and neonatal deaths. Deaths as a result of placental abruption or placenta previa were limited to the neonatal period. Further, we found that 19 (41%) were related to spontaneous preterm birth (preterm premature rupture of the membranes, cervical incompetence, preterm labor, primary chorioamnionitis with preterm birth). All of the perinatal deaths associated with chorioamnionitis, preterm labor, or congenital anomalies occurred in the neonatal period. Of five cases of cervical incompetence, three involved a congenital uterine anomaly that had been surgically corrected. Four deaths were due to congenital anomalies. Five perinatal deaths could not be assigned a definite cause of death. Interestingly, all of these five babies

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Table 1. The relative risk of selected risk factors for perinatal loss among 1110 births from 550 twin pregnancies

Risk factor	Total	Incidence perinatal loss	RR[a]	(95% CI)
Assisted conception				
Yes	386	14 (3.6)	0.8	(0.4, 1.5)
No[b]	714	32 (4.5)	1.0	
Maternal age ≥35 years	236	8 (3.4)	0.8	(0.4, 1.6)
Maternal age <35[b]	864	38 (4.4)	1.0	
African American	96	7 (7)	1.9	(0.9, 4)
Non-Latina White, Latina White, Asian, others[b]	1004	39 (4)	1.0	
Marital Status				
Single	180	12 (6.7)	1.8	(0.9, 3.4)
Married[b]	920	34 (3.7)	1.0	
Nulliparity	502	25 (5)	1.4	(0.8, 2.5)
Multiparity[b]	598	21 (3.5)	1.0	
History of preterm delivery				
Yes	68	3 (4.4)	1.0	(0.3, 3.3)
No[b]	1032	43 (4)	1.0	
Cigarette smoking				
Yes	135	9 (6.7)	1.7	(0.8, 3.5)
No[b]	965	37 (3.8)	1.0	
Monochorionic diamniotic placentation	220	20 (9)	3.0	(1.7, 5.4)
Diachorionic diamniotic placentation[b]	878	26 (3)	1.0	
Twin-to-twin transfusion syndrome				
Yes	36	11 (31)	9.3	(5, 17)
No[b]	1064	35 (3.3)	1.0	

[a] RR = relative risk—incidence of perinatal loss among women with a select risk factor divided by incidence of perinatal loss among women without a select risk factor (CI = 95%, confidence interval).
[b] Referent group

Table 2. Major clinical events among 46 cases of perinatal loss in a cohort of 1100 babies from 550 twin pregnancies

	Total number of cases of perinatal loss (n = 46)		Stillbirth (n = 12)		Neonatal loss (n = 34)	
	N	Percentage	N	Percentage	N	Percentage
Twin-to-twin transfusion	11	24	3	25	8	24
Placental abruption	4	8.6			4	12
Placenta previa	2	4.3			2	6
Chorioamnionitis with preterm labor	6	13			6	18
Preterm premature rupture of membranes	4	8.6	2	17	2	6
Cervical incompetence	5	11	1	8	4	12
Preterm labor	4	8.6			4	12
Diabetes mellitus	1	2.2	1	8		
Congenital anomalies	4	8.6			4	12
Unexplained	5	11	5	42		

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died in utero. In spite of repeated review of these cases, we were unable to identify a major clinical event in the time near the demise. The only indication of an intrauterine disturbance was the finding of unexplained intrauterine growth restriction in two of these unexplained cases.

All of the stillbirths and neonatal deaths in our database were also found in the database at the CDPHE. The cause of death was listed as "stillbirth" on the death certificate in 11 cases. One stillborn infant who died from complications of twin-to-twin transfusion was assigned an underlying cause of death of "renal disease." Twenty-one (61%) of the neonatal deaths were attributed to prematurity on the death certificate. The congenital anomalies were classified correctly on the death certificate. Two of the six cases of chorioamnionitis were correctly classified. The underlying cause of death in the remaining four cases was listed as prematurity. In all of the cases of neonatal death that we attributed to cervical incompetence, placenta previa, placental abruption, preterm premature rupture of the membranes, or preterm labor by our review, the death certificate listed prematurity as the cause of death. Among the eight neonatal cases of loss from the twin-to-twin transfusion, two were correctly classified. In the remaining six cases, the cause of death was listed as atelectasis, preterm rupture of the membranes, prematurity, and renal disease.

Discussion

We found a monochorionic diamniotic placenta was the leading prenatal risk factor for perinatal loss. Adjusted for other risk factors, women with a monochorionic diamniotic placenta were over three times more likely to have a perinatal loss compared with women with a dichorionic diamniotic placenta. Women whose pregnancies later developed twin-to-twin transfusion were nine times more likely to have an infant who died than were women whose pregnancies did not have this adverse complication. The leading perinatal events that contributed to perinatal loss were abnormalities of the placenta and spontaneous preterm birth. Compared with the medical record, review of the information from the death certificate did not contribute significantly to the understanding of the sequence of perinatal events leading to the demise.

The finding of monochorionic diamniotic placentation as the leading early risk factor for perinatal loss agrees with the results of a similar study from Norway.[9] None of the other risk factors included in our analysis were significantly associated with perinatal death. We acknowledge that this is a study with a small sample size and a retrospective review of clinical information. We were unable to confirm the contribution of some risk factors to perinatal loss (eg, race, birth order), possibly because of the small number of study subjects. We did not examine the contribution of the route of delivery to the outcome because the decision to perform a cesarean delivery was based on standard maternal fetal indications, and in fact, all of the stillbirths occurred prior to delivery, so the route of delivery did not make a difference to this outcome. However, the study's strengths include its population-based nature, completeness of ascertainment thorough confirmation by state records, and uniform care by one group of health care providers.

Monochorionic diamniotic placentation occurs because of division of the embryo three to four days after conception. It is therefore an event that occurs very early in pregnancy and is associated later with twin-to-twin transfusion syndrome.[10–12] Although we determined placentation

in the postnatal period, we believe that it is justified to include placentation as a risk factor because determination of chorionicity can be made reliably in the first half of pregnancy on the basis of ultrasound criteria (eg, single placenta, same sex, thin membrane separating embryos).

There were five deaths for which we could find no cause. Interestingly, these were all stillbirths. The fetuses were delivered at somewhere between 30 and 35 weeks' gestation. In two cases, the mothers had intrauterine growth restriction, which brings into question the role of the placenta in this select group of unexplained stillbirths.[13,14] It is concerning that in a high proportion of the stillbirths, the cause of death on the death certificate was listed as stillbirth or prematurity, with no further details given. The use of these terms does not reflect the pathophysiology of loss and contributes little to the understanding the predominant clinical events leading to the loss. The National Institute of Child Health and Human Development and other researchers[8,15–17] acknowledge these frustrating gaps in our explanation of the cause and other issues surrounding stillbirth. These and other data gaps have also been discussed by other authors.[18,19] In 2001, a workshop was convened to set a national agenda for stillbirth research. This workshop resulted in funds being allocated for the study of the scope, cause, and pathogenesis of stillbirth, which is currently underway at five sites across the United States.[20] Our review concluded that cause-of-death information on the death certificates reflected the dominant clinical event in the baby at the time of death. In the majority of cases, these were prematurity-related problems. However, the cause of death did not take into account the prenatal problems that contributed to the prematurity. We emphasize the need to retrace the sequence of events that leads to these adverse outcomes and to comprehensively review each case of perinatal death. We were encouraged that all stillbirths were reported to the CDPHE and that there was no discordance in the reporting of congenital anomalies. These are problems that have been reported by other authors.[17]

Among most cases of perinatal death in our cohort, the main perinatal event contributing to the demise of the baby was determined clinically, and in only a small proportion of cases was the underling cause unclear, requiring closer investigation and a second opinion. However, to the emotionally traumatized parents, all of these events are complex and require explanation. We propose a comprehensive review of all cases of perinatal death followed by an interview with the parents, which should include not only a complete explanation of the events leading to the demise but also a referral to local and national perinatal loss support organizations (see sidebar).[21,22]

Prevention of spontaneous preterm birth in all women remains an important initiative in obstetric care …

We conclude that loss in twins is most strongly associated with monochorionic diamniotic placentation. Although this condition is not preventable, early recognition and referral to subspecialists may improve the outcome. Prevention of spontaneous preterm birth in all women remains an important initiative in obstetric care to reduce perinatal mortality and neonatal morbidity. We hope that improvements in the reporting on death certificates will allow future research on large data sets and may provide further insight into perinatal loss in twins. ❖

Some suggested resources for patients suffering perinatal loss

www.CLIMB-support.org
www.twinlesstwins.org
www.compassionatefriends.org
www.nationalSHAREoffice.com
www.marchofdimes.com
www.forgottengrief.com
www.missfoundation.org
www.coloradopregnancyloss.org
www.hospicecareonline.org
Resource specifically addressing twin-to-twin transfusion:
www.tttsfoundation.org

These are just a few of the national resources available on the Internet; many more local and national resources are available.

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A Hard Battle

Be kind, for everyone you meet is fighting a hard battle.

— Plato, C 427-347 BCE, Greek philosopher and educator