FETUS, PLACENTA, AND NEWBORN

Twins: Causes of perinatal death in 12 United States cities and one African city

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The perinatal mortality rate in a large U. S. study was 139 per 1,000 births for twins and 33 per 1,000 for singletons. Sixteen per cent of the twin deaths were due to amniotic fluid infections, 11 per cent to premature rupture of the membranes, 8 per cent to the monovular twin transfusion syndrome, 8 per cent to large placental infarcts, 7 per cent to congenital anomalies, and the rest to over 20 other disorders. The perinatal mortality rate for monozygotic twins was 2.7 times that for dizygotic twins, mainly due to more amniotic fluid infections, congenital anomalies, and the twin transfusion syndrome in the monozygotic pairs. To study the role of poor maternal nutrition on twins, a similar study of perinatal mortality rates was undertaken in Addis Ababa, Ethiopia. Addis Ababa twins had 2.5 times the mortality rate of U. S. twins, mainly due to a higher frequency of amniotic fluid infections, abruptio placentae, cord accidents, obstructed labors, congenital syphilis, and the twin transfusion syndrome in the Ethiopians. (AM. J. OBSTET. GYNECOL. 131: 267, 1978.)

IT HAS LONG BEEN known that perinatal death is several times more frequent in twins that in single-born infants.[1-3] Most of these deaths in twins are reportedly due to more frequent premature deliveries, congenital anomalies, premature separation of the second placenta, and other causes of intrapartum hypoxia.[1-3] Although higher incidence of premature deliveries is partially due to hydramnios or to maternal toxemia, it has, for the most part, been unexplained.[1-4] Data now available from a large U. S. prospective study of pregnancy make it possible to analyze the causes of most perinatal deaths in monozygotic and dizygotic twins, including the causes of premature deliveries. The present paper is a report of these analyses.

Twins substantially increase the nutritional requirements of pregnancy. To explore the role of these increased requirements on the various disorders responsible for fetal and neonatal death, data on the twins were compared with findings on single-born infants and with data on twins from a large study in Addis Ababa, Ethiopia, where poor nutrition is common in

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Table I. Causes of perinatal deaths in the United States

	Causes of perinatal deaths per 1,000 births	
	Twins	*Singletons*
Amniotic fluid infection syndrome	22.6 (19)*	5.9 (34) $p < 0.001$
Premature rupture of membranes	15.9 (11)	3.5 (30) $p < 0.001$
Fetal hypoxia of unknown cause	15.1 (37)	2.6 (64) $p < 0.001$
Monovular twin transfusion syndrome	11.7 (50)	0
Large placental infarcts	10.9 (62)	2.1 (87) $p < 0.001$
Congenital anomalies	10.1 (17)	3.2 (34) $p < 0.04$
Hydramnios	8.3 (0)	0.1 (40) $p < 0.001$
Abruptio placentae	7.5 (67)	3.8 (65) $p < 0.03$
Postnatal respiratory tract infections	6.7 (0)	0.4 (0) $p < 0.001$
Umbilical cord compression	2.5 (40)	1.2 (81) $p < 0.04$
Birth trauma	2.5 (33)	0.5 (12) $p < 0.004$
Incompetent cervix	2.5 (67)	0.2 (32) $p < 0.001$
Placenta previa	1.7 (100)	0.7 (38) $p > 0.1$
Trauma to gravida	1.7 (50)	0.1 (100) $p < 0.001$
Rhesus erythroblastosis fetalis	1.6 (100)	1.6 (71) $p > 0.01$
Umbilical cord knots, stenosis	0.8 (100)	0.5 (53) $p > 0.01$
Placenta markedly growth retarded	0.8 (100)	0.9 (66) $p > 0.01$
Thrombosis, placental vessels	0.8 (100)	0.5 (67) $p > 0.01$
Cesarean section	0.8 (0)	0.3 (0) $p > 0.01$
Therapeutic abortion	0.8 (100)	0.1 (69) $p > 0.01$
Obstructed labor	0	0
Congenital syphilis	0	0.1 (75) $p > 0.01$
Hepatitis	0	0
Other disorders	5.9 (29)	0.5 (32) $p < 0.001$
Diagnosis unknown	7.5 (78)	4.6 (64) $p < 0.1$
Totals	138.7	33.4 $p < 0.001$

*Per cent of stillborn babies are in parentheses. Chi square was the statistical method used.

gravid women.[5] Poor nutrition may also increase the frequency in twins of those perinatal disorders that have a nutritional origin.

Patients

The Collaborative Perinatal Project of the National Institute of Neurological Communicative Disorders and Stroke recorded events of gestation, labor, delivery, and the neonatal period in 53,518 pregnancies at 12 urban hospitals in different regions of the United States between 1959 & 1966.[6] Autopsies were performed in 1,435 of the 1,993 deaths that occurred between 20 weeks of gestation and 28 days after birth. These are the age brackets in which deaths are included in calculations of perinatal mortality rates. Of the deaths, 171 were of twins. Four specially trained technicians reviewed microscopic sections from the placentas collected for the study. The senior author reviewed the clinical, placental, and postmortem material, including microscopic sections, in all neonatal deaths studied to standardize diagnoses.[7] The study separately analyzed the causes of deaths in twins and those in single-born infants.

A similar study of perinatal mortality rates was undertaken in Addis Ababa, Ethiopia, in 1974 and 1975 in the hospitals and clinics affiliated with the Addis Ababa University Faculty of Medicine.[8] About 40 per cent of the births in the city took place in these facilities, which serve all segments of the population. Postmortem examinations were carried out on 1,019 stillborn and live-born neonates from all the clinics and hospitals, representing 72 per cent of all perinatal deaths in these facilities. A total of 134 autopsies were performed on twins. Using clinical, placental, and postmortem information, the senior author used the same diagnostic criteria as were used in the U. S. study to assign diagnoses to the cases.

Methods

Primary and secondary diagnoses were assigned to each case. The primary diagnosis was intended to identify the disorder that initiated the course to death and the present paper is an analysis of these primary diagnoses. Twins were classified as monozygotic when their fetal membranes were monochorionic by histologic examination. Twins were classified as dizygotic when the membranes were dichorionic or the twins were of different sex or blood type. We recognize that some dichorial twins are monozygotic, but we had no phenotypic data which would enable us to differentiate those twins who had the same blood types.

Cases were placed in the category of *acute amniotic*

fluid infection syndrome with intact membranes when acute funisitis and inflammation of the chorionic plate of the placenta were associated with congenital pneumonia. For this diagnosis, membranes had to be intact at the onset of labor. Previous studies have shown that bacteria are responsible for most of these infections.[5, 9] In the Ethiopian study, 76 per cent of lung and 66 per cent of placental cultures were positive for one or more bacteria in infants with this diagnosis, whereas only 17 per cent of placentas from the infants who survived had positive cultures.[5] *Premature rupture of the membranes* was diagnosed when the membranes had ruptured before the onset of labor prior to 37 weeks of gestation. Cases were also entered into this category when the gestational period was longer than 37 weeks but labor did not begin until 20 or more hours following membrane rupture. Cases were placed in the category of *fetal hypoxia of unknown cause* when aspirated squamae and organ petechiae were present as evidence of antenatal hypoxia without its cause being known. In two thirds of these cases no placenta was available for examination. Some would undoubtedly have been placed in another diagnostic category if the placenta had been examined.

Criteria for the *monovular twin transfusion syndrome* have been previously published.[4] Cases were placed in the category *large placental infarcts* when 25 per cent or more of the placenta was involved by one or more infarcts greater than 3 cm. in diameter and there was no other explanation for death. Perinatal death was ascribed to *congenital anomalies* when such anomalies were severe and incompatible with fetal or neonatal survival. The category *hydramnios* was used when excess fluid initiated premature labor and the infant died of the consequences of immaturity. Cases were placed in the *abruptio placentae* category when gross inspection showed an adherent retroplacental clot with depression or disruption of the underlying placental tissue or when there were otherwise classical clinical findings including external or occult bleeding and fetal or neonatal death with evidences of hypoxia including aspirated squamae in the lungs and petechiae on the serosal surfaces of the visceral organs.

Umbilical cord compression deaths included breech deliveries in which the head compressed the cord, cases of cord prolapse, and instances where the cord was tightly wound about the infant's neck. Most cases placed in the category of *birth trauma* had tentorial tears. The category *placenta previa* included cases in which the placenta encroached on the cervical os and death was due to blood loss or to the consequences of premature delivery. The diagnosis of rhesus erythroblastosis fetalis was based on the following criteria: (1) rising titers of maternal rhesus antibodies, (2) hepatosplenomegaly, (3) erythroblastic hyperplasia in the bone marrow, spleen, liver, and adrenal glands and, (4) severe neonatal anemia in live-born infants. Deaths were ascribed to *cesarean section* when the gestational age of the fetus had been overestimated and a prematurely born infant died of the consequences of immaturity.

Table II. Perinatal mortality rates in monozygotic and dizygotic twins in United States according to specific primary diagnoses

	Causes of perinatal deaths per 1,000 births	
	Monozygotic	*Dizygotic*
Amniotic fluid infection syndrome	33.7	6.4 $p < 0.004$
Premature rupture of membranes	19.6	9.6 $p > 0.1$
Fetal hypoxia of unknown cause	19.7	8.0 $p > 0.1$
Monovular twin transfusion syndrome	28.1	0 $p < 0.001$
Large placental infarcts	11.2	6.4 $p > 0.1$
Congenital anomalies	22.5	1.6 $p > 0.004$
Hydramnios	14.0	4.8 $p > 0.1$
Abruptio placentae	5.6	8.0 $p > 0.1$
Postnatal respiratory tract infections	5.6	4.8 $p > 0.1$
Umbilical cord compression	5.6	1.6 $p > 0.1$
Birth trauma	2.8	3.2 $p > 0.1$
Incompetent cervix	0	3.2 $p > 0.1$
Placenta previa	0	3.2 $p > 0.1$
Rhesus erythroblastosis fetalis	0	1.6 $p > 0.1$
Placenta markedly growth retarded	2.8	0 $p > 0.1$
Thrombosis, placental vessels	0	1.6 $p > 0.1$
Cesarean section	0	1.6 $p > 0.1$
Therapeutic abortion	0	1.6 $p > 0.1$
Other disorders	11.2	4.8 $p > 0.1$
Diagnosis unknown	8.4	3.2 $p > 0.1$
Total	190.8	75.2 $p < 0.001$

Death was ascribed to *cord knots* when the knots were tight and there was no other explanation for the postmorten evidence of antenatal hypoxia in the neonate. Cases were placed in the category *placental growth retardation* when the placenta was 40 per cent or more below normal weight for gestational age and there was no other explanation for perinatal death. A recent study found that placentas this small were associated with an increased perinatal mortality rate near term.[10] There were no other placental abnormalities to explain the deaths and the victims had postmortem evidences of antenatal hypoxia. The primary diagnosis of *congenital syphilis* was established by finding chronic inflammation and fibrosis in association with spirochetes in infants' organs. Cases were placed in the category of *obstructed labor* when cephalopelvic disproportion or transverse lie led to prolonged labor and intrapartum

Table III. Causes of perinatal death in Addis Ababa, Ethiopia

	Causes of perinatal deaths per 1,000 births	
	Twins	*Singletons*
Amniotic fluid infection syndrome	128.1 (40)*	17.5 (62) $p < 0.001$
Premature rupture of membranes	5.5 (100)	1.1 (71) $p < 0.1$
Fetal hypoxia of unknown cause	21.8 (100)	3.6 (84) $p > 0.001$
Monovular twin transfusion syndrome	46.3 (82)	0 $p < 0.001$
Large placental infarcts	8.2 (100)	1.5 (96) $p < 0.03$
Congenital anomalies	2.7 (19)	2.4 (73) $p < 0.1$
Hydramnios	0	0.1 (100) $p > 0.1$
Abruptio placentae	27.3 (40)	4.5 (86) $p < 0.001$
Postnatal respiratory tract infections	0.5 (0)	0 $p > 0.1$
Umbilical cord compression	38.1 (57)	3.4 (85) $p < 0.001$
Birth trauma	0	0.9 (72) $p > 0.1$
Incompetent cervix	0	0
Placenta previa	2.7 (0)	1.6 (72) $p > 0.1$
Trauma to gravida	0	0.1 (100) $p > 0.1$
Rhesus erythroblastosis fetalis	0	0.2 (100) $p > 0.1$
Umbilical cord knots, stenosis	0	0.7 (73) $p > 0.1$
Placenta markedly growth retarded	2.7 (100)	0.2 (100) $p > 0.1$
Thrombosis, placental vessels	0	0.1 (100) $p > 0.1$
Cesarean section	0	0
Therapeutic abortion	0	0
Obstructed labor	24.5 (56)	8.4 (82) $p < 0.03$
Congenital syphilis	13.6 (60)	4.3 (72) $p < 0.05$
Hepatitis	8.2 (100)	0.7 (100) $p < 0.001$
Other disorders	8.2 (0)	1.9 (63) $p < 0.01$
Diagnosis unknown	0	0.2 (100) $p > 0.1$
Totals	338.4	53.4 $p < 0.001$

*Per cent of stillborn infants are in parentheses.

or neonatal death. Death was ascribed to *viral hepatitis* when it was intrauterine and secondary to the death of the gravid woman from the disease.

Results

The perinatal mortality rate for U. S. twins was 139 per 1,000 births and for single-born infants 33 per 1,000. The ratio of stillborn to neonatal deaths for the twins was 1.0:1.6 and for single-born infants 1.0:0.9. The following disorders were mainly responsible for the more frequent deaths of U. S. twins than of single-born infants: amniotic fluid infections, premature rupture of the membranes, large placental infarcts, abruptio placentae, umbilical cord compression, birth trauma, congenital anomalies, incompetent cervix, hydramnios, pneumonia arising after birth, and the monovular twin transfusion syndrome (Table I). Zygosity was established for 101 of the twins who were stillborn or died in the neonatal period. The over-all perinatal mortality rate for monozygotic twins was 2.5 times greater than that for the dizygotic twins (Table II). The greater mortality rate in the monozygotic twins was mainly due to amniotic fluid infections, the monovular twin transfusion syndrome, and congenital anomalies.

The perinatal mortality rate for Addis Ababa twins was 338 per 1,000 births and for single-born infants 53 per 1,000 (Table III). The ratio of stillborn to neonatal deaths for the twins was 1.0:0.8 and for single-born infants 1.0:0.4. The primary disorders responsible for death were similar to those in the United States except that the following disorders were much more frequent in Addis Ababa: amniotic fluid infections, abruptio placentae, umbilical cord compression, the monovular twin transfusion syndrome, obstructed labor, hepatitis, and congenital syphilis (Table III).

There were no significant differences between the overall perinatal death rates of first and second-born twins in either the United States or Addis Ababa, but there were some differences for individual disorders in the U. S. twins. Perinatal death due to large placental infarcts was 2.3 times more frequent in the second than in the first born ($P < 0.02$). Fetal hypoxia of unknown cause was 1.7 times more frequent in the second than in the first born ($P < 0.1$).

Comment

The study attempted to identify the disorders responsible for the excessive perinatal mortality rate in U. S. urban-born twins and in those in a third-world city, Addis Ababa, Ethiopia. The U. S. data were drawn from medical school–affiliated urban hospitals in many parts of the nation. The cases utilized included a somewhat larger proportion of nonwhites and those in

the lower socioeconomic strata than are represented in the U. S. urban population as a whole.[6] The Addis Ababa cases were relatively representative of the delivery population in that city.[8] Comparisons between the two nations and between twins and single-born infants give clues to the pathogenesis of several major perinatal disorders.

The amniotic fluid infection symdrome with intact membranes was the leading cause of perinatal death in both the United States and in Addis Ababa and was several times more frequent in twins than in single-born infants. Passage of maternal microorganisms through the cervical os is responsible for most of these infections.[5, 9] Many of the fetuses were directly killed by the infections, but a large proportion died of the complications of immaturity which resulted from infection-initiated premature deliveries. The much higher rate of the fatal infections in twins than in singletons may be due in part to overdistention of the uterus in twins with consequent greater exposure of the fetal membranes at the cervical os to the bacterial flora of the vagina.[5, 11] Poor nutrition may play an even larger role. In the United States such infections are most common in undernourished gestations and twins are usually more poorly nourished than singletons, particularly in late gestation.[11, 12] In Addis Ababa, poor maternal nutrition during pregnancy commonly leads to a deficiency of antimicrobial activity in the amniotic fluid, which in turn permits bacteria to grow in the fluid and infect the fetus.[5, 11, 13] This explains the higher rate of fatal infections in Addis Ababa.[5]

The second most frequent cause of perinatal death in the U. S. twins was premature rupture of the membranes. Overdistention may explain some of these ruptures, but a recent study found evidence that most such ruptures are the consequence of amniotic fluid infections.[14] In Addis Ababa a large proportion of the amniotic fluid infections involved bacteria of relatively low virulence.[5] This may help explain the lower frequency of premature ruptures in that city because such bacteria seem less often involved in premature membrane ruptures than are more virulent bacteria. The more virulent bacteria may more often damage the tissues in the fetal membranes, thereby reducing their tensile strength and predisposing to rupture.

There have been many clinical reports that death is more frequent in the second born than in the first born of twins.[2, 3] The present study found only a statistically insignificant greater death rate in the second born. The small difference that was found was due to a greater frequency of intrapartum hypoxia in the second born, due either to placental infarcts or to unknown causes.

Abruptio placentae proved to be an important cause of perinatal deaths in twins in both the United States and Addis Ababa. Such abruptions have been claimed to affect mainly the second twin and to be due to the shearing effect of the decompression that follows the delivery of the first twin. In the present study, abruptio placentae was nearly as frequent a cause of death in the firstborn as in the second born of twins. It was also a frequent cause of premature delivery. In the United States about 20 per cent of abruptions that lead to perinatal deaths are due to cigarette smoking, which causes a selective necrosis of the decidua basalis at the margin of the placenta.[15] No placental lesions were found to explain the frequent abruptions in Addis Ababa. However, the abruptions were strongly associated with undernutrition and malnutrition in the poorest Ethiopian gravid women.[16] Nutrition may also play a role in some U. S. placental abruptions. Suboptimal maternal weight gain was common in a recently studied series of U. S. pregnancies that ended with fatal placental abruptions.[15] Twins increase the nutritional requirements of pregnancy so the excess rate of fatal abruptions in both Ethiopian and U. S. twins provides some support for the view that inadequate nutrition may play a role in the genesis of the disorder.

The greater perinatal mortality rate in monozygotic than in dizygotic twins was mainly due to the monovular twin transfusion syndrome and to an excess of amniotic fluid infections and congenital anomalies in the monozygotic twins. Monovular twinning might be considered a biologic accident and the events responsible for it may sometimes be teratogenic. Most, but not all, prior studies of congenital anomalies have found more anomalies in twins than in the single born.[17] The excess of amniotic fluid infections in monozygotic twins may be due to a higher frequency of unrecognized hydramnios in such gestations which overdistend the uterus, exposing more membranes at the cervical os to the bacterial flora of the vagina. Overt hydramnios is much more frequent in monozygotic than in dizygotic twin gestations due to mild forms of the monovular twin transfusion syndrome which occur in many monozygotic twin pregnancies.[4]

The present study documented several other well-known causes of the excessive perinatal mortality rate in twins, including umbilical cord accidents, birth trauma, and placenta previa.[2] Obstructed labor was a serious problem in Addis Ababa because many of the gravid women with abnormal presentations delayed seeking professional obstetric aid.

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