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Factors Associated with Neonatal Problems in Twin Gestations

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Abstract. We examined the neonatal outcome of 644 twins weighing 500 g or more and 656 singletons, born in the years 1984-1986 in the Soroka Medical Center, Beer-Sheva, Israel. There was nearly a four-fold risk of antepartum death in twins vs singletons, which disappeared when birth weight was controlled for. The risks for intrapartum and early neonatal mortality were not raised in this population. A statistically significant relative risk for congenital heart malformations in twins vs singletons remained (RR = 5.0, 95% CI = 1.5-16.3), after controlling for maternal age. Significantly higher rates of hyalin membrane disease, hypoglycemia, hyperbilirubinemia, anemia and septicemia were found in twins. Controlling for the confounding of the association between twinning and mortality or morbidity caused by differences in distributions of mode of delivery or gestational age between twins and singletons, was not as efficient as the controlling for birth weight. Thus, adjustment for birth weight removed all the excess risks detected except in hypoglycemia. Our findings suggest that the lower birth weight of twins, which is so intimately associated with multiple gestations, is probably the single most important factor associated with neonatal problems found in twin births.

Key words: Twins, Mortality, Morbidity, Congenital malformations, Birth weight

INTRODUCTION

Multiple gestation is well known to be associated with higher rates of neonatal problems. Perinatal mortality, congenital malformations, prematurity, low birth weight and morbidity are all more common in twins than in singletons [4,6,8,9,11,12,15]. Some studies have suggested that the differences between twins and singletons lie not in the multiplici-

ty of embryos, but in the other factors associated with twin deliveries. Thus, some of the differences in mortality rates between twins and singletons, although by no means all, disappear when birth weight specific rates are examined [3,7]. Ghai and Vidyasagar [4] found that, while some of the differences between twins and singletons in rates of mortality, hyalin membrane disease, other respiratory morbidity, birth asphyxia and seizures are accounted for by birth weight, significant differences persist, particularly in larger twins. Windham and Bjerkedal [17] found that the higher rates of congenital malformations in twins are due to differences in maternal age, as higher parity and maternal age are associated with twin gestation.

Our study will examine the contribution of twin gestation, gestational age, mode of delivery and birth weight to neonatal complications associated with twin births. We will attempt to determine whether twin gestation itself, which cannot be controlled, or other factors on which intervention can be based, are responsible for neonatal problems in twins.

MATERIALS AND METHODS

This study compares the neonatal outcome of 644 twins born in the years 1984 to 1986, and 656 singleton births randomly chosen from the 1986 births which occurred at the Soroka Medical Center in Beer-Sheva, Israel. "Soroka" is the only and central hospital of the Negev and serves almost 300,000 inhabitants. As there are no private maternity institutions, nearly all the deliveries, approximately 7500 annually, occur in this hospital. In our study population, 97.2% of the twins and 98.4% of the singletons were delivered in hospital. All births are registered, however, as a monetary incentive exists for mothers to bring the newborns to hospital immediately after birth.

Information regarding maternal age, parity, sex, weight of newborn, date of birth and origin of the mother, and the mode of delivery, was collected retrospectively for the twin and singleton births from the delivery room records and the maternity ward charts of the Division of Obstetrics and Gynecology. It was unfortunately not possible to obtain information useful for zygosity diagnosis. Maternal age and mode of delivery data are available for 98.1% and 96.2% of the twin and singleton deliveries of the study, respectively. Data on the infants was collected retrospectively from that recorded on the discharge sheet of the Neonatology Unit, which summarizes the delivery hospitalization, and were used to determine the rates of morbidity and congenital malformations recorded. Twins and singletons had routine care while hospitalized, and only laboratory tests clinically indicated were performed. Mortality data were collected from the delivery room records and from the infants discharge records. Only mortality which occurred up to the discharge of the infant following the delivery hospitalization (early neonatal mortality) was recorded.

Statistical Analysis

The rates of mortality, of recorded congenital malformations and morbidity, and the distribution of qualitative variables, were compared between twins and singletons using

chi-square or Fisher's exact test where appropriate. The relative risk (RR) of a recorded event (early delivery, mortality, congenital malformation or morbidity) in twins as compared with singletons was calculated, and 95% confidence intervals (95% CI) were computed. The relative risk is the rate of the event, calculated using the population at risk in the denominator, in twins, divided by the rate for the same event in singletons. A relative risk which equals 1.0 or is not statistically different from 1.0 (ie, the 95% CI include the value 1.0) denotes equality of risk in the two groups. A 95% CI from which 1.0 is excluded indicates that the RR is statistically significant at the level of $p < 0.05$. Where a relative risk could not be computed, as no events had been recorded for one of the study groups, the probability of Fisher's exact test is given.

Maternal age and high parity are known to be associated with twin births. This was also found in our population [13], and because twins tend to have lower gestational age and birth weight, and are more often delivered by a cesarean section, the Mantel-Haenszel summary RR estimates [14] were calculated. To control for mode of delivery, two categories were used, cesarean delivery and others combined. Controlling for gestational age was performed in three categories, < 34 weeks, 34-36.9 and 37 weeks or more, and controlling for birth weight was performed using the three categories of 500-1499 g, 1500-2499 g, and 2500 g or more. The RR for congenital malformations was controlled for maternal age in the categories of ≤ 25 years, 26-31, and 32 years or older.

Only twin sets where both twins had birth weights ≥ 500 g were included in the analysis. P values ≤ 0.05 were considered statistically significant.

RESULTS

Twin deliveries differed from those of singletons in several important characteristics (Table 1). The mothers of twins tended to be older, more twins were born by cesarean sections, the birth weight of twins was much lower, and twin deliveries occurred earlier than did those of singletons. Whereas 8.7% of twin deliveries occurred before 32 weeks of gestation, only 1.2% of singleton infants were delivered by this gestational age, yielding a relative risk (RR) of an early delivery in twins vs singletons of 7.1 (with 95% CI = 3.3-15.5, $p < 0.0001$). A similar risk was found for twin births below 34 weeks of gestation, RR = 7.5 (95% CI = 4.1-13.7, $p < 0.0001$). Our sample of singletons is representative of all singleton births from 1986. For example, the maternal age distribution of all singleton births from 1986 was 35%, 38.3%, and 26.7%, for ages < 25, 26-31, and 32 years and older, respectively, which is not significantly different from the age distribution of our sample of singletons.

The rates of mortality, and the relative risks in twins vs singletons are shown in Table 2. The risk of antepartum death in twins vs singletons was 3.7 (95% CI = 1.1-13.3). As twin births differ from those of single infants, it was deemed necessary to control for the differences in rates of cesarean section, and the distributions of gestational age and birth weight. The excess risk of antepartum mortality remained when the RR was controlled for mode of delivery and gestational age. Twins of gestational age ≥ 37 weeks were at 7.4 fold higher risk of antepartum death than singletons of that age (95% CI = 1.6-33.9, $p < 0.005$). The differences in risk of antepartum death disappeared, however, once the infants' birth weights were controlled for.

Table 1 - Percent distribution of selected characteristics in twins and singletons

Characteristic	Twins (N = 644)	Singletons (N = 656)	p
Maternal age (years)			
≤ 25	25.6	38.0	
26-31	42.7	36.0	
≥32	31.7	26.0	< 0.0001
Mode of delivery			
Cesarean	37.3	9.8	
Other	62.7	90.2	< 0.0001
Birth weight (g)			
500-1499	11.6	0.6	
1500-2499	46.0	6.4	
2500+	42.4	93.0	< 0.0001
Gestational age (weeks)			
< 34	14.9	2.0	
34-36.9	26.4	3.8	
⩾ 37	58.7	94.2	< 0.0001

There was no excess risk of intrapartum death in this population of twins, nor was the early neonatal death rate significantly different from that of singletons, once gestational age or birth weight were controlled for.

Table 2 - Rates, relative risks (RR) and 95% confidence interval (95% CI) of antepartum (APD), intrapartum (IPD), and early neonatal (ENND) mortality in twins as compared with singletons

Birth outcome	Twins (N = 644)		Singletons (N = 656)		RR (95% CI)	RR^a (95% CI)	RR^b (95% CI)	RR^c (95% CI)
	N	%	N	%				
APD	11	1.7	3	0.5	3.7* (1.1-13.3)	4.4* (1.1-17.0)	3.7* (1.2-10.5)	0.8 (0.2-2.5)
IPD	2	0.3	1	0.2	2.0 (0.2-22.4)	3.0 (0.3-32.5)	0.3 (0.0-2.8)	0.2 (0.0-1.1)
ENND	22	3.4	3	0.5	7.5* (2.3-24.8)	5.6* (2.1-14.8)	1.5 (0.3-7.5)	0.2 (0.0-2.9)

RR^a = Relative risk controlling for mode of delivery.
RR^b = Relative risk controlling for gestational age.
RR^c = Relative risk controlling for birth weight.
* $p < 0.05$.

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An excess risk in twins for congenital anomalies of the cardiovascular system was found (RR = 5.8, 95% CI = 1.7-19.6) (Figure), which was not explained by the older age of the mothers (RR adjusted for maternal age 5.0, 95% CI = 1.5-16.3). A statistically significant higher rate of skeletal congenital malformations was found in the twins, which lost its statistical significance (p = 0.06) once maternal age was controlled for. The higher rates of 'Other' malformations were not statistically significant (RR = 7.1, 95% CI = 0.9-57.7), and remained so after adjusting for maternal age.

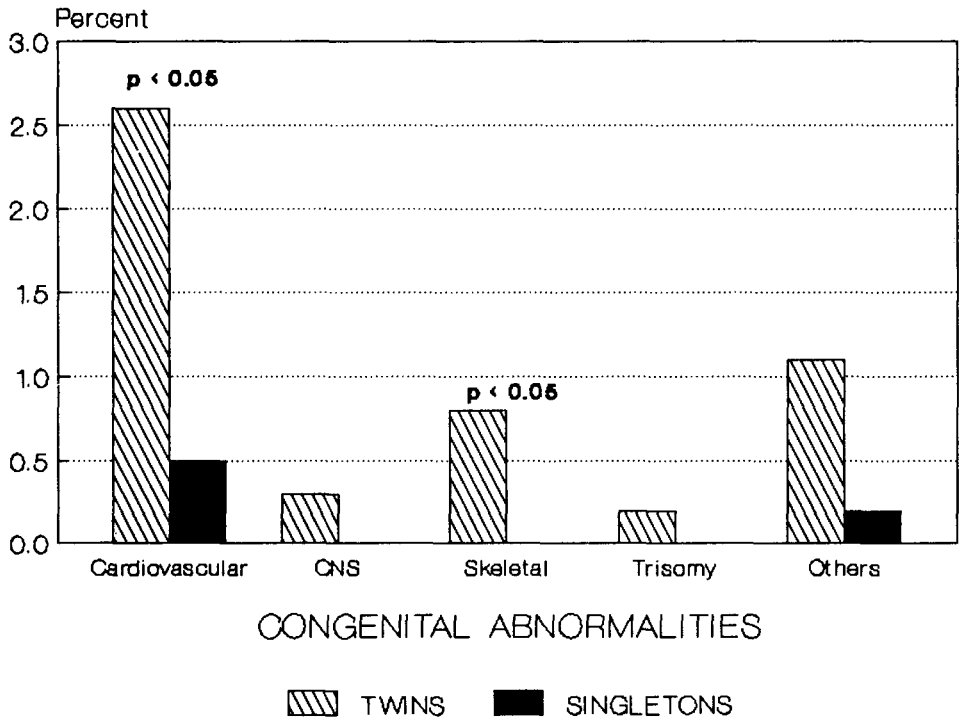

Figure. Congenital malformations (percent values) detected in 644 twins and 656 singletons.

Twins were found to have higher rates of recorded diagnoses than singletons (Table 3). Significantly higher risks were found for hyalin membrane disease, hypocalcemia, hyperbilirubinemia, anemia and septicemia, and the rate of hypocalcemia was also significantly higher in twins.

Hyaline membrane disease in this population was found to be related to cesarean sections, thus for all study births the risk of the disease associated with delivery by cesarean section, as compared with other modes of delivery, was 8.0 (95% CI = 1.6-41.2, $p < 0.05$). Twins delivered by cesarean section, however, still had higher risk of the disease than singletons, but the excess risk disappeared once the gestational age or birth weights of the infants were controlled for. The only relative risk which remained significantly

Table 3 - Rates, relative risks (RR) and 95% confidence interval (95% CI) for recorded diagnoses in live births of twins compared with singletons. For diagnoses which were found in more than 1% of the infants, the relative risks adjusted for birth weight (RR^a) were also calculated.

Diagnosis	Twins (N = 631)		Singletons (N = 652)		RR (95% CI)	RR^a (95% CI)
	N	%	N	%		
Hyalin membrane disease	27	4.3	3	0.5	9.3* (2.8-30.5)	1.4 (0.4-5.3)
Wet lung	6	1.0	1	0.2	6.2 (0.8-51.4)	7.8 (0.7-88.1)
Pneumothorax	6	1.0	2	0.3	3.1 (0.6-15.3)	1.0 (0.2-5.1)
Hypoglycemia	27	4.3	2	0.3	14.0* (3.3-58.4)	4.4* (1.1-18.0)
Hyperbilirubinemia	57	9.0	5	0.8	11.8* (4.8-29.2)	2.6 (1.0-6.5)
Hypocalcemia	6	1.0*	—	—	—	—
Anemia	33	5.2	4	0.6	8.5* (3.0-23.9)	1.5 (0.4-5.3)
Convulsions	2	0.3	—	—	—	—
Septicemia	21	3.3	3	0.5	7.2* (2.2-24.1)	1.5 (0.3-7.9)
Intraventricular hemorrhage	7	1.1	1	0.2	7.2 (0.9-58.9)	2.4 (0.1-112)

* $p < 0.05$

higher in infants was hypoglycemia. In addition, twins of birth weight 2500 g or more had a RR for hypoglycemia of 9.0 (95% CI = 1.1-79.8, $p < 0.05$), compared with singletons of the same birth weight.

DISCUSSION

Twins suffer from higher rates of mortality, morbidity and congenital malformations than do singletons. It is becoming more apparent, from other publications as well as from our results, that most of the risks of multiple gestations are probably less related to the multiplicity of the embryos then to their lower birth weight. Thus, all the differences between twins and singletons in mortality found in this study disappered once birth weight was controlled for, while the adjustments for gestational age or mode of delivery did not remove the apparent increase in risk as efficiently. With regard to morbidity, the excess risk in twins for all recorded diagnoses, except for hypoglycemia, disappeared once birth weight was controlled for. Controlling for mode of delivery did not

alter the relative risks greatly, while the effect of adjusting for gestational age differences was intermediate.

The excess risk in congenital malformations of the cardiovascular system, which remained after maternal age adjustment, may be due in part to ascertainment bias [16]. These malformations are relatively difficult to detect, and in twins, once a defect is found in one twin, a more detailed examination is given to the apparently healthy cotwin.

In our data, the higher rates of hyaline membrane disease disappeared once gestational age was controlled for. Our findings agree with those of other workers [2,5,10], that the higher incidence of the disease in twins, is related to lung immaturity as it is in singletons. In addition, we feel that, in twin populations, it may also be related to the increased risks of birth asphyxia resulting from the more traumatic birth associated with malpresentation, which is more prevalent in twin deliveries. The higher rates of hypoglycemia found in this study may be due to the same causes, as twins are more liable to suffer from asphyxia [1,4] and have difficulties in maintaining homeostasis.

It should be noted that, in seven of the eight diagnoses for which relative risks could be calculated, the resulting RR, even after controlling for birth weight, and although not statistically significant, were greater than 1.0. This could be due to the fact that, while we have achieved considerable control for confounding by birth weight, using the three categories described, it was not sufficient to remove all of the association between twin births and morbidity caused by birth weight. Alternatively, there may genuinely be an excess risk of morbity in twin neonates, which in our sample did not reach statistical significance. The latter possibility is supported by the findings of Ghai and Vidyasagar [4], who examined 998 twin pregnancies and over 80,000 singleton pregnancies, finding significantly elevated birth-weight specific risks in twins for birth asphyxia, hyaline membrane disease, other respiratory disorders, and mortality.

In conclusion, our results tend to confirm the opinion that higher rates of neonatal problems in twins are not particularly associated with either frequent delivery by cesarean section or earlier gestational age, but rather result from low birth weight.

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