# Contribution of Multiple Pregnancies to Perinatal Mortality and Morbidity

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**ABSTRACT**

Multiple pregnancies have increased from 9 per 1000 pregnancies in the 1970s to 14 per 1000 pregnancies. Multiple births account for 10% of perinatal deaths (8% of fetal deaths and 14% of neonatal deaths). Compared to singletons births, the perinatal mortality rate is four times higher in twins, and nine times higher in multiple births of a higher order. The cerebral palsy rate among survivors is five times higher in twins and nineteen times higher is multiple births of a higher order. Monochorionic monozygotic twins are at the highest risk, due firstly to the cell division process leading to chromosomal or other anomalous lethal aberration in one fetus, and secondly to twin-to-twin transfusion syndrome (TTTS) and its adverse consequences on the surviving fetus if there is fetal death of its co-twin. The incidence of TTTS is 15-30% in monochorionic monozygotic twins. Data are emerging on the obstetric risks, survival and neurological outcome associated with interventions for treating TTTS (serial amnioreduction, fetoscopic laser ablation of placental vascular anastomoses, amniotic septostomy, and selective feticide), and several randomised controlled trials are in progress.

**Keywords:** Multiple births, perinatal mortality, perinatal morbidity, twin-to-twin transfusion

## Introduction

There is a worldwide trend for an increase in the rate of twinning and higher order multiple births from the late 1980s [7, 10, 18]. This has been attributed to increasing maternal age and the increasing use of fertility enhancing therapies [9, 19]. The true incidence of multiple pregnancies is higher than was reported, because for every twin pair born, at least 10 singletons are conceived as one of a twin pair (the vanishing twin syndrome) [2]. The monozygotic twinning rate is constant worldwide at 3-5 per 1000 pregnancies until an unexplained increase recently. The dyzygotic twinning rate is highest in Africa and lowest in the Far East, in between in Caucasians and Indians, and increases with maternal age and parity. Multiple pregnancies, especially those from monochorionic monozygotic twins, are associated with an increased risk of perinatal mortality and morbidity. This can result in serious consequences to the long-term outcome among survivors, including an increased risk of cerebral palsy (CP).

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## Incidence of multiple pregnancies

An upward trend for multiple pregnancies in Australia has been documented in the last 20 years. The rate of 9 per 1,000 confinements in 1977 has progressively increased to 14 per 1,000 confinements in 1993 [11]. This national perinatal data collection reported 3,520 multiple pregnancies out of 256,956 fetuses remaining in utero at 20 weeks' gestation. It reported 3,420 twin pregnancies, 99 triplet pregnancies and one quintuplet pregnancy. In Australia, as with other developed countries, the dizygotic to monozygotic (Dz:Mz) ratio for twins was over 2.0, but is now under 1.0 [8, 16].

## Perinatal mortality

Fetal death (stillbirth) is defined as death prior to complete expulsion or extraction from its mother of a product of conception of 20 or more comple-

**Table I. Fetal, neonatal and perinatal deaths in singleton and multiple births. Based on Lancaster et al, 1996 [11].**

| | Singletons | | Twins | | Other multiple births | |
|---|---|---|---|---|---|---|
| | Number | Rate[a] | Number | Rate[a] | Number | Rate[a] |
| Fetal death | 3,878 | 5.1 | 315 | 15.7 | 22 | 24.2 |
| Neonatal death | 2,498 | 3.3 | 371 | 18.8 | 44 | 49.5 |
| Perinatal death | 6,376 | 8.3 | 686 | 34.1 | 66 | 72.5 |

[a]Rate per 1,000 births.

ted weeks of gestation or of 400 grams or more birthweight; the death is indicated by the fact that after such separation, the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Neonatal death is defined as death of a liveborn infant within 28 days of birth. Based on these definitions, our Australian national data for the three years, 1991-1993, showed that there were 4,215 fetal deaths (5.4 per 1,000 births), 2,913 neonatal deaths (3.7 per 1,000 births) and 7,128 perinatal deaths (9.1 per 1,000 births) [11]. Multiple births accounted for 10.5% of all perinatal deaths (8.0% of fetal deaths and 14.2% of neonatal deaths). Compared to singletons births, the perinatal mortality rate was 4.1 times higher in twins, and 8.7 times higher in multiple births of a higher order (Table I).

### Cerebral palsy

A population-based study from the United Kingdom showed that multiple birth infants are at a higher risk of CP compared to those who were of singleton birth [13]. The CP rate was 2.3 per 1,000 in 254,360 singleton survivors, 12.6 in 5,207 twins and 44.8 in 142 triplets. The difference is partly due to the lower birthweight distribution and partly due to the increased risk of CP among multiple births born at more than 2,500 grams. Among the extremely low birthweight (<1000 g) subgroup, the CP rates were 8.6%, 15.8%, and 22.2% in singletons, twins, and triplets, respectively. The higher risk of CP in twins is not entirely explained by their increased risk of prematurity [20]. The infant death and CP rates for a cohort of over 104,000 live births reported for different gestations from that study are shown in Table II.

### Monozygotic versus dizygotic twins

Mz twins are at considerable higher risks than Dz twins. Firstly, in Mz twins, the cell division process leads to a chromosomal or other anomalous lethal aberration in the fetus. Mz twins are responsible for the increase in the rate of congenital anomalies in twins compared to singletons [3]. Conjoined twins (1 in 50,000) are a form of Mz twinning in which the division of the zygote is incomplete. Acardia (1 in 30,000) is caused by an imbalance of the interfetal circulation in monochorionic Mz pregnancies. Secondly, twin-to-twin transfusion syndrome (TTTS) can occur and, after the fetal death of one twin, adverse consequences can result in the surviving co-twin. About 70-75% of Mz twin pregnancies have monochorionic placentas in which vascular connections are common. These anastomoses can be superficial (artery-to-artery, vein-to-vein) or deep (artery-to-vein). Most shunts are balanced but an imbalance will result in donor to recipient transfusion. The incidence of TTTS is 1 in 4000 of all pregnancies and 1 in 60 of twin pregnancies. It is as high as

**Table II. Infant death and cerebral palsy rates in singleton and twin births. Based on Williams et al, 1996 [20].**

| Gestation (weeks) | Infant death | | Cerebral palsy | |
|---|---|---|---|---|
| | Singleton | Twin | Singleton | Twin |
| 28 or less | 41.0% | 54.9% | 3.2% | 6.3% |
| 29-32 | 8.8% | 8.9% | 2.8% | 5.1% |
| 33-36 | 2.5% | 2.5% | 3.0% | 9.0% |
| 37 or over | 0.5% | 2.0% | 0.07% | 0.4% |

1 in 5 in monochorionic monozygotic twinning (range 15-30%). TTTS can present acutely, with profound haemodynamic imbalance and death of one twin, usually the recipient. It also has a chronic presentation: the recipient (usually appropriately grown for gestational age) developing polyuria, polyhydramnios, polycythaemia, hyperviscosity, intravascular thrombosis, right heart failure, tricuspid incompetence, hydrops fetalis, and hyperbilirubinaemia, and the donor (usually small for gestational age) developing oliguria, oligohydramnios, stuck twin syndrome, abnormal umbilical artery Doppler flow, anaemia, and hypoproteinaemia.

### Adverse outcome in monozygotic twins

Death of a co-twin in monochorionic Mz pregnancies can be a result of thrombo-embolisation from thromboplastin being released from the dead twin's tissues, crossing the placental anastomoses, and causing disseminated intravascular coagulation in the surviving twin. However, a more probable explanation is profound circulatory collapse when the vascular resistance falls in the dead fetus, with the surviving twin exsanguinating into the dead twin, and suffering hypoxia-ischaemia from severe hypotension. In the surviving co-twin, there is an increased risk of significant neonatal morbidity [4, 15]. Central nervous system complications had been reported in 72% of cases, including microcephaly, porencephaly and hydrancephaly. This can result in CP, low IQ and severe learning disability. Gastrointestinal complication had been reported in 19% of cases, primarily intestinal atresia. Renal complications had been reported in 15% of cases, for example, renal tubular dysgenesis. Cardiorespiratory malformations had been reported in 8% of cases. Other miscellaneous complications include aplasia cutis. In a national survey from the United Kingdom, Mz twins compared to Dz twins were found to have a relative risk of 18.91 for both twins being stillborn (1.1% vs 0.1%), and 1.63 for one twin being a stillbirth (3.1% vs 1.9%) [17]. Where there is one stillbirth and one livebirth, the relative risk is 2.26 for the liveborn Mz co-twin dying as a neonate compared to a Dz co-twin (7.6% vs 3.2%). Abnormal neonatal cerebral ultrasound findings are common in Mz twins [1, 4, 5, 6]. These were reported in up to 30% in Mz twins compared to 3% in Dz twins, especially after in utero death of the co-twin. Evidence of brain injury was found in 27-35% of twins with TTTS (incidence of periventricular leukomalacia was 10%). Both the donor twin and recipient twin are at risk of brain injury. The rate of CP and developmental delay is high among TTTS survivors (up to 22% reported in one series). In a population study, the rate of CP after the death of a co-twin was reported to be 83 per 1000 (95% CI 57-117), a 40-fold increase over the general population [12]. In addition, the incidence of other forms of cerebral impairment was 115 per 1000 (95% CI 83-153). Together, they result in an overall risk of brain injury of 20% when one twin died in utero and the co-twin survives infancy. In truly monochorionic MZ twin pregnancies, the risk is even higher at 40%.

### Outcome of obstetric interventions

Interventions for the treatment of TTTS include serial amnioreduction, fetoscopic laser ablation of placental vascular anastomoses, amniotic septostomy, and selective feticide [14]. Serial amnioreduction improves uteroplacental blood flow and reduces rate of amniotic fluid accumulation. The procedure-related complication rate is 10%. With this intervention, the survival rate was reported as 37-63% and the neurological damage rate 17-33%. Laser coagulation might not be successful, as the anastomoses causing unbalanced TTTS are more likely to be deep rather than superficial. It is an invasive procedure associated with a high maternal morbidity. Further amnioreduction is required in about 20% of cases. With this intervention, the survival rate was reported as 53-80% and the neurological damage rate 4%. Amniotic septostomy creates a puncture in the inter twin membrane to equalises the pressure in the two sacs, thus relieving the pressure on the placenta. The major risk is cord entanglement. With this intervention, the survival rate was reported as 57-83% but the neurological damage rate remains unknown. The selective feticide technique used must not affect the circulation of the surviving twin (fetoscopic cord ligation, ultrasound guided vascular embolisation). It is usually only performed where the death of the co-twin is certain. With this intervention, the rates of survival and neurological damage are unknown. The Cochrane Review did not find any published randomised controlled trial (RCT) in the treatment of TTTS [14]. Three ongoing RCTs have been identified: Y Ville (Eurofetus Group), N Fisk (London, United Kingdom) and K Moise (Chapel Hill, North Carolina, USA).

### The Australian and New Zealand TTTS registry

Over a three-year period (1995-1998) 112 cases of TTTS were registered in Australia and New Ze-

aland [6]. The median age at diagnosis was 21.5 weeks (range 14-35 weeks). The oligohydramnios-polyhydramnios sequence was the most common presentation in 84% of cases. Hydrops fetalis developed in 16% of cases. Absent end-diastolic umbilical artery flow was found in 16% (72% of donor twins and 28% of recipient twin). Therapeutic amnioreduction was performed in 92 cases (82%) started at a median gestation of 22.5 weeks. A total of 281 amnioreductions were performed (median 2 per case, range 1-23). The median volume of amniotic fluid removed per procedure was 1725 ml (range 300-5200 ml). Complications reported within 24 hours of the procedure included chorioamnionitis and preterm labour (2 cases), prelabour membrane rupture (5 cases), and umbilical cord entanglement (2 cases). Delivery occurred at a median gestation of 29 weeks (range 18-38 weeks). The prematurity rate was 90% (44% of infants were born <28 weeks). The caesarean section rate was 52%. The fetal death rate was 18%, and the neonatal death rate was 19%. Perinatal survival rate was 63% (recipient 67%, donor 58%). Both twins survived in 46% of the pregnancies, one twin survived in 26%, and both twins died in 28%. In the neonatal period, 27% had an abnormal cerebral ultrasound scan: intraventricular haemorrhage 12%, periventricular leukomalacia 10%, ventriculomegaly without intraventricular haemorrhage 6%, and porencephalic cysts 1%. Renal failure developed in 8%, necrotising enterocolitis in 3%, hypertrophic cardiomyopathy in 3% and severe ischaemia of lower limb in 2%. Prognostic factors that were found to be predictive included gestation at delivery (survival rate was 0% <25 weeks, 26% <28 weeks, and 99% >32 wks), absent or reversed diastolic flow on umbilical artery Doppler velocimetry (associated with a fetal death rate of 56%, and an abnormal cerebral ultrasound in 53%), and hydrops fetalis (associated with a perinatal death rate of 61%, and cerebral and cardiac morbidity in 75%).

### Conclusions

Multiple pregnancies are associated with significant perinatal mortality and morbidity and an increased risk of CP among survivors. Their perinatal management consumes a large amount of physical, emotional and financial resources. Adverse outcomes following assisted reproductive technologies are partly due to the increased risk of multiple pregnancies and partly due to preterm and low birthweight birth. This fact and the lack of evidence that the transfer of more than two embryos improves pregnancy rates, make it advisable to limit the number of embryos transferred to no more than one or two per cycle. Perinatal mortality and morbidity are particularly high in monochorionic Mz twins, due to an increased risk of congenital anomalies and the development of TTTS, especially when in-utero death of a co-twin occurs. Results of RCTs of current management strategies for TTTS in these pregnancies are awaited with interest. Long-term neurodevelopmental follow-up of monochorionic Mz children who survive TTTS is also needed.

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