

## Mini-symposium: Multiple pregnancy

# Paediatric consequences of multiple pregnancy

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Multiple birth rates have risen over the past decade and are expected to continue to rise with time. Multiple birth presents considerable risk to the infants involved. These risks have a significant effect in terms of immediate mortality, neonatal illness and also a more protracted impact on developmental outcome, especially in terms of congenital anomaly and cerebral palsy. The consequences of multiple birth may affect the whole family. Better education of parents and all professionals involved in the care of multiple births might help to lessen the disproportionate impact this small percentage of births has on medical care and family circumstance.

## INTRODUCTION

A multiple birth may be welcomed by fertile and infertile couples alike but the implications for medical care and family lifestyle are often underestimated. Multiple pregnancies are relatively rare in relation to total births, although the incidence appears to be rising. Their importance lies in the added risk that two or more fetuses have for the pregnancy and for the family after birth. These risks may be compounded by the additional effects of premature delivery. Only a small minority of doctors and other health care workers will experience the totality of care of a multiple pregnancy. As a result, medical and public knowledge about the problems posed is limited. In this paper we will focus on the epidemiology of multiple birth, the perinatal consequences of such deliveries and the long-term impact on the family.

## EPIDEMIOLOGY

Scandinavian countries have collected data on multiple births since the mid 18th century. In 1839, Queen

Victoria instituted a special crown bounty of one guinea payable to each child from a triplet or higher order birth. Eighty-nine years later, Ronald Fisher was commissioned by the Royal Society to undertake a survey of 166 triplet sets who were born in England and Ireland in the early 19th century and used records of this 'Kings Bounty' (sic) to trace them.<sup>1</sup> During the early 1930s payments from the press became a valuable source of income for some of these families, which has, to some extent, continued for higher order multiples, who remain newsworthy today as illustrated by recent media interest in cases of septuplets and octuplets.

In England and Wales, the Office of National Statistics (ONS) gathers information on a range of issues around multiple births that date back to 1938, when all infants born from a single delivery were recorded together for the first time.<sup>2</sup> However, terminations, miscarriages, early 'vanishing sacs' and selective fetal reduction were excluded from registration prior to 1 April 1991, and prevalence data that are based upon birth registers might not fully represent the true incidence of multiple births.

In 1996, multiple births made up only 1.4% of all births (14:1000 maternities). These were made up of 96.9% twins, 2.9% triplets, and 0.1% quadruplets and higher order pregnancies. The trends in multiple birth rates since 1988 are shown in Figure 1. The published incidence of multiple births increased from 10.4:1000 maternities in 1985 to 14:1000 in 1996, an overall

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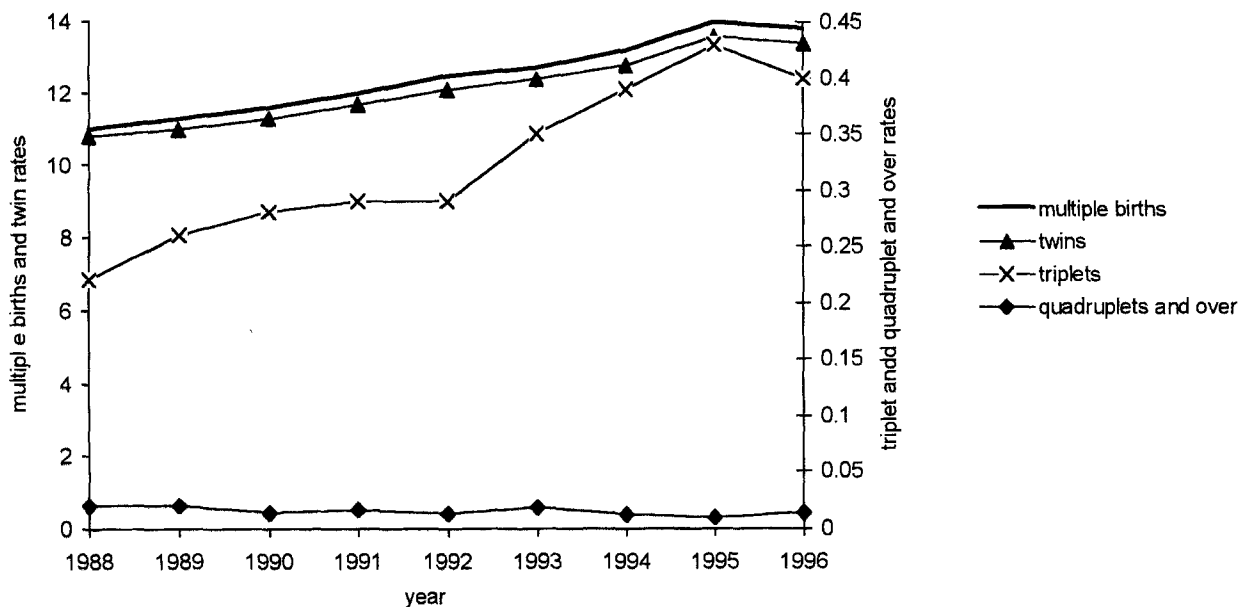


Fig. 1 Birth rates per 1000 live births by multiplicity (ONS data series FM1).

increase of 25%. The previous peak of 12.8:1000 was in 1950 and a trough of 9.8:1000 in 1980. Between 1985 and 1996 there has been an annual increase in rate of 2–4%. This increase differs according to the number of fetuses. The twin rate averaged 12.3:1000 maternities between 1938 and 1955 then fell to a low of 9.5:1000 in 1976. Since that time, it has risen steadily to 13.4:1000 in 1996, a rise of 22% over the 11 years from 1985. In contrast, the triplet rate rose from 0.1:1000 to 0.4:1000, an increase of 65% over the same period.

Multiple births are more common in older mothers and age specific incidence has similarly increased. In 1985 the multiple birth rate was 5.6:1000 for mothers aged less than 20 years, 8.7:1000 for those 20–24 years, 10.5:1000 for those 25–29 years, 13:1000 for those 30–34 years and 15.6:1000 for mothers over 35 years of age. By 1995 these rates had increased in each age group by 12%, 13%, 22%, 23% and 24% respectively.

Although the rise in multiple births has been largely attributed to the increased use of assisted fertility treatments (AFT), there are little data to directly support this. No routine data are collected for the number of women who are prescribed fertility drugs nor for couples who obtain private in-vitro fertilisation (IVF) and gamete intra-fallopian transfer (GIFT) procedures.

The risk of multiple pregnancy following ovarian hyperstimulation with clomiphene is quoted as 5%; that following gonadotrophin treatment is considerably greater being in the region of 15–45% for twins and 5–6% for triplets;<sup>3</sup> the risk following GIFT ranges from 19 to 38% and after IVF is around 22%.<sup>4</sup>

In 1990, an Australian study from Victoria identified a triplet and higher order birth rate of 1.09:1000 maternities which was associated with IVF or GIFT in 42% of cases.<sup>5</sup> In the most recent prospective UK

study of 156 triplet, 12 quadruplet and one quintuplet deliveries, 31% were conceived naturally, 34% resulted from ovarian stimulation, 24% followed IVF and 11% GIFT.<sup>6</sup> All quadruplet and quintuplet sets followed assisted reproduction. The high prevalence of couples who have undergone assisted reproduction among parents of twins and higher order births has significant consequences for the families as these children develop.

## NEONATAL CONSEQUENCES OF MULTIPLE BIRTHS

### Mortality

Early fetal death is said to be a common occurrence in multiple births following AFT. However, there are no routinely collected data to support this. Manzur and colleagues studied 38 triplet pregnancies with weekly vaginal ultrasound scans from day 21 to day 28 post AFT.<sup>7</sup> Eighteen (47.4%) progressed to deliver triplets, 12 (31.6%) delivered twins, seven (18.4%) resulted in singletons and one mother suffered complete miscarriage of all three sacs in the first trimester. Almost 90% of spontaneous reductions occurred during the first 7 weeks' gestation.

Stillbirth data have been routinely collected separately for multiple births since 1975.<sup>8</sup> Overall, the stillbirth rate has fallen from 29.3:1000 births in 1975 to 14.4:1000 in 1991. Compared with singleton deliveries in 1991, the stillbirth rate was 3.2 times higher for twins and 4.4 times higher for quadruplets. In 1995 these ratios had risen to 5.6 times higher and 8.3 times higher respectively.

The greatest disparity in mortality rates occurs in the case of neonatal deaths, where the twin rate is

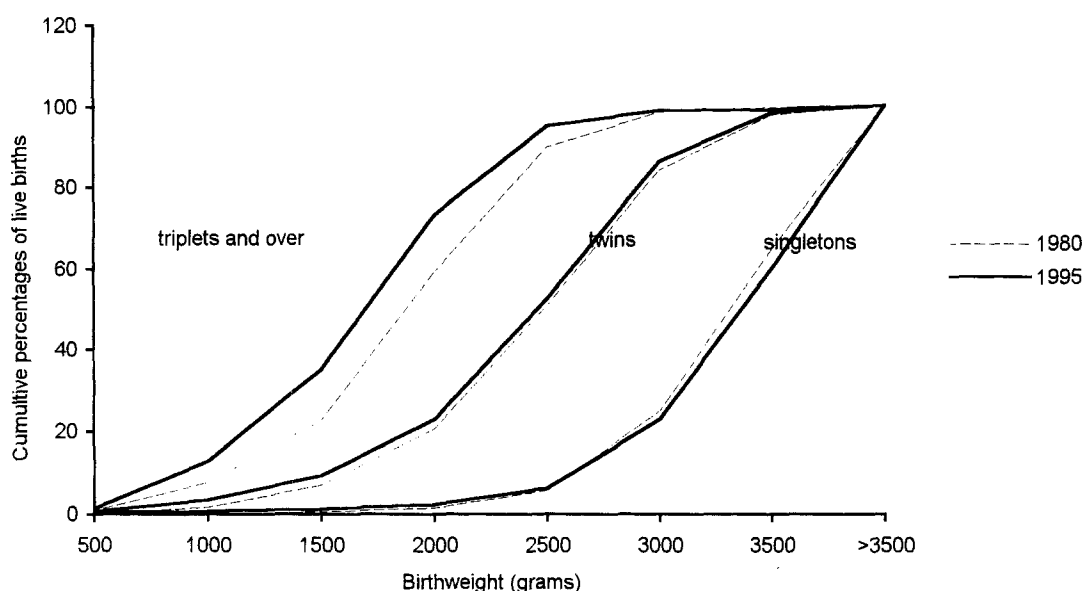


Fig. 2 Cumulative percentages of live birth by multiplicity and birth weight, England and Wales, 1980 compared with 1995<sup>11</sup>

seven times and the triplet rate 23.3 times higher than the singleton rate.<sup>8</sup> Despite a fall in infant mortality rates for multiple births by 50% between 1975 and 1991 (75.2–35.7:1000 births), infant mortality for multiple births is still almost six times greater than those for singletons (6.1:1000 births in 1991).<sup>8</sup>

Multiple births are disproportionately represented in mortality statistics in comparison with their prevalence. In 1991, they accounted for 2.5% of all births but 8% of all stillbirths, 19% of all neonatal deaths and 7% of all postneonatal deaths. Finally, mortality rates are consistently higher in like-sex twins compared with non-like-sex pairs, in which males seem to fair worse than females.

### Prematurity

Combined with low birth weight, prematurity is the most important cause for the increased mortality and morbidity amongst multiple births. Triplets and higher order births tend to be born at a lower gestation than twins, who in turn are born earlier than singletons. National figures show a median gestation at delivery of 40 weeks for singletons, 37 weeks for twins and 33 weeks for triplets.<sup>9</sup> The retrospective study of triplet and higher order births by Botting et al reported that by 32 weeks' gestation, (27.7%) of twins, (76.6%) of triplets and 90% of quadruplets had delivered.<sup>10</sup> A later prospective study by the British Association of Perinatal Medicine reported a median gestational age of 33 weeks (range 24–37 weeks) for both triplets and quadruplets.<sup>6</sup> Whilst these figures suggest an apparent maturity of these births, almost one-quarter of triplet and higher order births were delivered before 30 weeks' gestation. Monozygotic twins tend to have shorter gestations compared to

dizygotic, possibly because of poorer placental function.

The delivery of very premature triplets or higher-order multiple births constitutes a major strain on the resources of any neonatal intensive care unit (NICU). There are insufficient neonatal intensive care cots to contain all singleton births requiring admission in most areas of the UK, and the practice of holding beds whilst spontaneous delivery is awaited is impossible to achieve. However, with good planning most higher-order multiples births can be accommodated, but, on occasions, it is impossible to contain all babies initially within one service without putting other babies at risk.

### Low birthweight

Birthweight of multiples tends to be lower compared to singletons above 30 weeks' gestation. The incidence of low birthweight (LBW) (<2500 g) is higher in multiple births when compared with singletons, and increases with increasing birth order. Median birthweight is 3300 g for singletons, 2500 g for twins, 1800 g for triplets and 1500 g for quadruplets.<sup>10</sup> Figure 2 compares birthweights from 1980 and 1995.<sup>11</sup> Just over 50% of liveborn twins and 95% of triplets and higher order births were of LBW compared with only 6% of singletons. Liveborn singletons were slightly heavier in 1995 compared with 1980, but the reverse was true for multiple births, especially triplets and higher order births. The number of triplets who were very LBW (<1500 g) increased from 23 to 35% between 1980 and 1995. This may reflect a greater willingness to deliver triplets earlier as a result of better fetal assessment, and overall neonatal mortality rates at low weights and gestations.

## Morbidity

The main cause for excess morbidity amongst multiple births relates to premature delivery, although it is a commonly held view that multiple births have higher frequencies of complications, such as respiratory distress syndrome, intraventricular haemorrhage and periventricular leucomalacia, at equivalent gestational ages to singletons. Medical problems during the neonatal period are reported in 32% of twins, 53% of triplets and 68% of quadruplets and higher order births.<sup>10</sup>

*Congenital malformations* are more common amongst multiple births.<sup>12</sup> This is mainly confined to like-sexed pairs and probably monozygous (MZ) twins and reflects abnormalities which occur early in fetal life. Concordance of abnormality is likewise five times more common in MZ as opposed to dizygous (DZ) twins. Acardia and conjoined twins are particular anomalies confined to multiple births. Doyle and co-workers analysed 95 510 malformations reported voluntarily to the ONS from 1979 to 1980 and from 1982 to 1985.<sup>13</sup> The data collected from triplets provided only 33 reported malformations and was excluded from subsequent analysis. Five malformations, namely anencephaly, hydrocephalus, tracheoesophageal fistulae, atresias or stenosis of large bowel, rectum or anal canal, and patent ductus arteriosus (PDA), together with indeterminate sex, anomalies of the umbilical vessels and exomphalos were significantly more common in twins than in singletons. Some of these reported differences may be attributed to prematurity (hydrocephalus, PDA). Of interest is the fact that, of all types of neural tube defects, only anencephaly was more common in twins.

*Twin-twin transfusion* is a serious complication of both twin and higher order pregnancies. It can occur antenatally or in the intrapartum period. Fetus-fetus transfusion (FFT) occurs between monochorionic twins (approximately 20% of all twins). The prevalence is estimated to be 5–35% of MZ pregnancies (probably around 10%) and accounts for 20% of all perinatal twin mortality. A usually deep, placental arteriovenous anastomosis allows unidirectional blood flow from donor to recipient fetus. The donor suffers from anaemia, hydrops, hypovolaemia and intrauterine growth reduction; the recipient from polycythaemia, hyperviscosity and polyhydramnios. In extreme cases (1% FFTs) reversed flow in the umbilical artery of a 'pump' fetus occurs. This result in the 'perfused' fetus receiving deoxygenated blood which has a catastrophic effect on organ development. Antenatal treatment options may include conservative drug treatment, decompressive amniocentesis, selective fetocide and laser ablation of anastomoses.<sup>14</sup> The risk of later pregnancy loss or impairment in survivors is high if untreated, but at best around 60–65% will survive aggressive amnio-reduction regimes. At delivery the donor twin, who is usually growth

restricted, may require urgent transfusion and the plethoric recipient urgent plasma reduction to avoid hyperviscosity.

Acute perinatal twin-twin transfusion syndrome (TTS) may occur in the period between the clamping of the two cords, during which the second twin may receive a significant transfusion, being the sole twin attached to the whole placenta. This can produce a paradoxical situation where a growth restricted, anaemic, donor second twin may appear plethoric after birth. Acute TTS may require intervention, usually as a partial volume, exchange transfusion with plasma.

*Admission to a neonatal intensive care unit.* Levene and colleagues reported that 40% of their study population of triplet and higher order births required intensive care (level 1).<sup>6</sup> A further 51% needed special care (level 2) and only 9% did not require admission to a NICU. In 22% of cases, one or more infants needed to be transferred to another NICU because the unit in which the babies had been born was full. The average length of stay in NICU increases with increasing multiplicity with a median of 25 days. In the USA average lengths of stay are 4.6 days for singletons, 8.2 days for twins and 10 days for triplets and higher order births.<sup>15</sup>

*Neonatal respiratory illness* is found more frequently after multiple birth, possibly secondarily to prematurity, although there is a perception that it is more common in twins than equivalent gestation singletons. In MZ twins there is more often concordance than in DZ twins, where traditionally it occurs in the second twin, in whom there are often intact membranes.

*Retinopathy of prematurity* was initially more commonly found in multiple births after correction for gestation and birthweight differences, but more recent data from the USA seem to refute this among contemporary cohorts.<sup>16</sup>

*Breast feeding* twins is commonplace, milk supply rising to meet demand and professionals should reassure the anxious mother that this is so. Occasionally, triplets have been successfully breast fed, but more commonly the privilege of breast feeding is rotated among the sibship. Set against that is the perception that there will be an insufficient milk supply, that it will be too tiring and is unusual, none of which are born out in surveys. Nonetheless, mothers are often actively discouraged from breast feeding. Breast milk confers such an advantage to the mother and children that it should be actively encouraged. Expression of milk and administration via a bottle at night may facilitate mothers rest.

*Mother-infant relationship.* The new mother will always need support and understanding to develop her new relationship with two or more infants simultaneously. Where one or both are receiving intensive or special care, or even have been separated for specialist care, the quality of this support becomes of paramount importance. Parents will often notice

differences in temperament from early in the neonatal period and rapidly start to behave differently to each child. The mother will attempt to apportion her affection fairly but often feels guilty when this does not work out. She needs to be reassured that children do behave differently and require more or less of her time and that this is not abnormal, nor does it mean that there is any less love there. The additional stress of intensive care and problems of premature delivery with delayed oral feeding compromise a mother's feelings further still. There is a tendency to align with the healthier twin, which may lead to emotional difficulties during periods of critical illness.

Individuality is critical to the development of a bond between mother and one of a multiple birth. Staff should, therefore, be encouraged to develop identities for the individuals in the sibship, e.g. addressing each child by his or her name and avoiding like-dressing.

#### **FAMILY AND SOCIAL CONSEQUENCES**

The support and attention possible whilst the babies are in hospital often rapidly evaporate when they are taken home, however, even though a mother is often told she is lucky to have two or more children, the reality of child care is often very different. In the UK, mothers do not automatically qualify for additional help or financial support, and this can prove to be a great hardship for any parent. Twins clubs are a great source of both emotional and practical support, both before and after birth, but of little help for the mother with poor social networking, who is isolated by the burden of child care.

The demands of feeding multiple children continue after their discharge from hospital. Not only is it perceived that the supply of breast milk for more than one child harder to maintain, but the time taken to feed all the children becomes substantial. In the recent UK study, parents would have liked more help at night, with feeding and bathing.<sup>10</sup> Not all families can rely on help from within the family. Statutory facilities for help from health service sources are available but may not be very beneficial. The parents who responded to Botting and to Bendefy<sup>17</sup> felt that the experience of voluntary groups such as TAMBA or home start gave more experienced advice and help than other services. In addition, attendance at a specialist twins clinic gave reassurance, successful support for making applications for extra resources and useful information for the majority of cases.

The financial burden of higher order multiple birth is considerable. Although donations of food and milk are forthcoming, cash assistance is not so readily available. Child benefit rarely covers the costs incurred by changes in housing, transport, clinic attendance, baby-sitting, holidays and providing respite care. Attending outpatients or having one child in hospital

is also a major issue for many parents, who may be torn between needing to be with a sick child and the necessity of looking after the other children.

#### **LONG-TERM OUTCOMES**

Neurodevelopmental impairment in premature infants has been studied extensively, but few studies have looked specifically at the effect of multiple births, with the exception of studies from cerebral palsy (CP) registers. In multiple regression analysis with other perinatal markers for later disability, multiple birth has inconsistent independent association with excess impairment after controlling for gestation. Thus, in counselling parents, risk appropriate to the gestational age is usually used.

Epidemiological studies of CP reveal a different story, however. The crude prevalence rate of CP in the Mersey region ranged from 2.3:1000 livebirths in singletons to 12.6:1000 in twins and 44.8:1000 in triplets.<sup>18</sup> The number of triplets was small and this prevalence should, therefore, be interpreted with caution. In this study, birthweight-specific prevalence of CP was similar in singletons and multiple births at weights below 2500 g. In contrast, for birthweights over 2500 g, there was a difference of CP of 2.9:1000 between twins and singletons. However, a contemporaneous study from the North-East-Thames region of the UK observed an increase in relative risk for CP of 2.8 times in twins born before 33 weeks' gestation.<sup>19</sup>

Different findings were obtained from the Western Australia Register: the prevalence of CP per 1000 live births was 1.6 in singletons, 7.4 in twins and 26.7 in triplets.<sup>20</sup> All triplets and 78% of twins had spastic diplegia, hemiplegia or a combination of both. Before 1970, 5.3% of all CP occurred in multiple births, this rose to 10.3% in the 1980s. Low birth weight increased the risk of CP generally. In twins of >2500 g, the rate was almost four times higher than that for singletons.

#### **DEATH AND DISABILITY IN CO-TWINS**

A fetus from a multiple pregnancy may die antenatally (because of feto-fetal transfusion or other pathologies) or be lost postnatally following perinatal complications, usually of prematurity. In the case of antenatal death, the risk of necrotic neurological, renal, hepatic or cutaneous lesions in the surviving twin is in the order of 25%. There are two candidate pathogenetic theories: transfer of thromboplastin could result in disseminated intravascular coagulation and infarction in the survivor, alternatively, haemodynamic imbalance could lead to hypotensive ischaemic damage. Such neurological injury may lead to major impairment of the surviving child. It is important for professionals to realise the intense emotional conflict for parents who have lost one child of a multiple birth.

Recognition of the need to address this issue is critical, and parents should be allowed the opportunity to discuss their loss in the same way as a couple who have lost a singleton pregnancy are. The naming and individualization of the lost twin is one important stage in this process. Photographic records of the sibship together are likewise of great value to parents.

The risk of one of twins having a disability is around twice that of a singleton. In this situation parents again need the opportunity to grieve for their healthy child that might have been, and to be treated with support and sympathy when this process is prolonged because of the reminder provided by a healthy twin. Both parents and co-twins may have difficulties in adjusting to this scenario and specialist clinics for the support of families in this situation are available via TAMBA.

## CONCLUSION

The joy of parenting a multiple pregnancy must be tempered by the excess risk of mortality and morbidity posed. Health professionals should be aware of this increased risk, compared to singletons, and adjust their counsel accordingly.

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