Outcomes of Multiplets

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Abstract
Outcomes, both short and long term, differ between singletons and multiplets. Recently, a number of large, well-designed studies have clarified these differences, particularly in light of major changes in perinatal and neonatal care that have influenced changing outcomes. Accordingly, this article will review risks for singletons, twins and higher-order multiples as whole groups and also after correction for gestational age and other potential confounding variables that differ markedly between the groups. In addition, we will focus on the effects of certain factors such as antenatal steroid therapy and gender. Finally, we will detail the specific long-term risks for multiples in terms of growth and neurodevelopmental disabilities.

Introduction

Multiple births have been a source of universal fascination since Jacob grasped Esau’s heel while leaving his mother’s womb. Until about 30 years ago, human interest in multiples focused primarily on describing medical, social and psychological aspects of the twinning phenomenon. However, the development of artificial reproductive techniques has resulted in an epidemic of multiple pregnancies. As prematurity and intrauterine growth retardation (IUGR) are common in both twins and higher-order multiples (HOMs), neonatal intensive care units (NICUs) worldwide are now inundated with small premature multiples. Most recent data show that multiple births now comprise 3–4.5% of all births [1, 2]. Between 1980 and 1997, for example, triplet births rose in the USA by more than 400%, while twin births rose by over 50%. In parallel, the proportion of multiples among very low birth weight (<1,500 g; VLBW) infants in the NICHD Network database rose from 19% in the early 1990s to 26% in 2002 [3]. This alarming trend imposed a huge burden on often already overstretched neonatal services. At the same time, a consensus emerged whereby it was recognized that the need to resort to multifetal pregnancy reduction (MFPR) of triplets to twins should be considered a failure of medical therapy and a source of significant iatrogenic morbidity in both the mother and her offspring. These factors contributed to changes in embryo transfer guidelines in many countries [4]. As a result of the reduced embryo transfer policy, together with MFPR, most recent data have shown marked changes in multiple birth rates from a number of countries, including the USA, UK, Belgium and Israel [1, 4, 5]. Data from the USA have shown a 16% drop in the number of triplets between 1998 and 2005. However, despite this encouraging trend, the number of twins has continued to rise at a rate of approximately 3% per year [1]. Similar data have been generated by the Israel National VLBW database where the


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the number of triplets has fallen dramatically while the number of twins has remained stable as shown in figure 1 [5]. This was explained by a significant reduction in IVF-generated triplets while there was no change in triplets from ovulation induction (data not shown). As a result, we observed a marked reduction in the number of hospital admission days for VLBW triplets in Israel from a peak of almost 10,000 days per year in 2000 to less than 3,500 days per year in 2005.

While the reduction in triplet births is encouraging, it only partly alleviates the public health concerns resulting from the multiple birth epidemic. As the absolute numbers of triplets are very much lower than those of twins and as twins are at significant risk for both short- and long-term morbidity, the continuing increase in twin births remains a source of major concern that needs to be addressed at the levels of both individual caregivers and public health policymakers. Also, it is as yet unclear how much of the move from triplets to twins is a result of MFPR and how much from changed embryo transfer policy. This is of particular interest in view of the finding that MFPR may be associated with an increased risk of extremely preterm birth (<28 weeks) as compared with non-reduced twin pregnancies (4.8 vs. 1.8%, p = 0.004) [6].

**Risks for Singletons versus Multiples**

The risk of infant mortality in twins and HOMs may be expressed relative to the risk for singletons. Thus, data from a number of large studies show the relative risk of mortality to be 5- to 7-fold higher for twins and 10- to 12-fold higher for HOMs [7–10]. The primary explanation for this finding has been the increased rate of prematurity in multiples, together with increased IUGR as a secondary influence. Mean gestational age (GA) at birth is inversely correlated to plurality. In large population-based studies, mean GA was 39–40 weeks in singletons, 35.8–36 weeks in twins, and 32.5–34 weeks in triplets [2, 11]. Intrauterine growth in multiples is similar to that seen in singletons until approximately 28 weeks’ gestation when twins diverge from singletons, and around 35 weeks when triplets diverge from twins.

**Effect of Gestational Age**

In view of the marked differences in GA at birth between singletons and multiples, various investigators have studied mortality rates after correction for the week of gestation. Single-center studies have described relatively small samples of infants and, although potential confounding variables differed between the groups, no significant differences were found in the incidence of major morbidity and mortality [12–15]. Larger studies, albeit from more than 15 years ago, found twins to have increased mortality after correction for GA or adjusted birth weight (z-score) [16–18].

Large-scale data from Israel delineated infant mortality rates by week of gestation comparing singletons and twins. This sample included 988,202 infants during the years 2000–2006 and included approximately 90% of the births in the country during this period. Figure 2 shows...
the pattern of infant mortality which is higher in twins between 23 and 27 weeks but lower at 32–35 weeks. Term for twins is seen at 37–38 weeks and for singletons at 39–40 weeks [2].

However, the conclusions of these studies are limited by the marked confounding variables, such as use of fertility treatments, maternal age and ethnicity, IUGR, antenatal corticosteroid administration and mode of delivery.

**Effect of Confounding Variables**

A number of large studies have compensated for confounding variables. Donovan et al. [19] reported on neonatal morbidity and mortality in singletons and twins in a sample of 10,271 VLBW infants from 12 tertiary neonatal referral centers from the NICHD Neonatal Research Network. Mothers of twins received more prenatal care and more antenatal steroids and their infants were more often delivered by cesarean section and suffered more often from respiratory distress syndrome (RDS). After correction for these confounding variables, however, no statistically significant differences were found between singletons and twins in mortality or in the incidence of major morbidity such as bronchopulmonary dysplasia or intraventricular hemorrhage (IVH). Another large study that focused on VLBW multiples and added triplets to the previous comparison was conducted by the Israeli VLBW neonatal database [20]. This population-based study included VLBW singletons and complete sets of twins and triplets at 24–32 weeks’ gestation. Multiple logistic regression analyses were performed to account for confounding variables and assess the independent contribution of plurality. The sample included 3,717 singletons, 1,394 twins and 483 triplets born between 1995 and 1999. On univariate analysis, no significant differences were found between the groups regarding the incidence of the major adverse outcomes – chronic lung disease, adverse neurologic findings (severe IVH, periventricular leukomalacia, or ventricular dilatation), or death. After correction for confounding variables, RDS was found to be significantly more common in twins (70%; OR 1.58, 95% CI 1.32–1.89) and triplets (75%; OR 2.51, 95% CI 1.87–3.37) compared with singletons (60%), and it occurred despite higher exposure to antenatal steroids in these two groups. Mortality was similar in singletons and twins, but the risk for mortality was significantly higher for triplets (OR 1.54, 95% CI 1.13–2.11). The risk for chronic lung disease and adverse neurologic findings was similar in all groups.

Garite et al. [21] reported on neonatal outcomes from the Pediatrix group database of 23- to 35-week preterm infants. This study included 36,931 singletons, 12,302 twins and 2,155 triplets born during 1997–2002 in 124 NICUs, making it one of the largest, carefully conducted studies on this issue. No difference was found between the groups in mortality or a composite morbidity measure (discharge without necrotizing enterocolitis, severe IVH or severe retinopathy of prematurity (ROP)) at any GA. Antenatal steroid therapy was associated with lowered mortality at each week between 23–29 weeks in both singletons and twins. No statistically significant effect was seen for either route of delivery or birth order in twins. Mortality was increased when birth weight discordance was >40% and this discrepancy was primarily explained by increased mortality in the twin with IUGR.

A similarly large study has recently been reported from the Canadian Neonatal Network [22] that included 2,284 singletons and 958 multiples of <32 weeks’ gestation from 24 NICUs. In this study, multiples at <27 weeks were found to have significantly increased mortality. Multivariate analyses revealed increased adjusted risk for RDS (OR 1.3, 95% CI 1.0–1.6) and reduced risk for ROP (OR 0.5, 95% CI 0.3–0.9). The finding of reduced risk for ROP in multiples is supported by the findings of a single-center study reported by Friling et al. [23] that included 363 VLBW infants. In this study, twins and triplets were found to have a significantly reduced risk for ROP stages 2 and 3.

Extremely preterm infants who are born at or near the limits of viability represent a unique group in many respects. Accordingly, it is of interest to note that the differences in outcomes between singletons and twins noted above have recently been clarified for this particular subgroup. The NICHD network has reported neonatal morbidity and mortality and neurodevelopmental outcome at 18–22 months of age for a cohort of 4,192 infants born at 22–25 weeks during 1998–2003. Multiples were at a 30–40% increased risk for both death and severe neurologic impairment at 18–22 months of age when compared with singletons [24].

In summary, after appropriate adjustment for confounding variables, multiples appear to be at increased risk for RDS and perhaps mortality and reduced risk for ROP.

**Antenatal Steroids in Multiple Pregnancies**

Antenatal steroid therapy has been clearly shown to reduce the risk for RDS, IVH and death in preterm infants. However, the comparative efficacy in preterm in-
fants from multiple as compared to singleton pregnancies has been a source of debate in particular in view of the above data showing increased risk for RDS in multiples despite antenatal steroid therapy. Two recent population-based studies from the Israel VLBW Neonatal database have demonstrated that antenatal steroids reduce the risk for RDS and IVH in twins and triplets [25, 26]. However, the relative reduction in risk for RDS is plurality-dependent, being lowest in triplets. This finding has raised the question of the possible need for either a larger dose or repeated doses of steroids in multiple pregnancies. Appropriately powerful randomized controlled trials will be required to answer this question.

**Effect of Gender**

Preterm male infants are at a disadvantage when compared with female infants regarding the incidence of respiratory and neurologic morbidity and mortality. In order to clarify whether this represents a 'male disadvantage' or a 'female advantage', a large, population-based study in singletons and twins demonstrated a masculinizing effect on females from unlike-sex twin pairs as regards respiratory morbidity, but not neurologic morbidity and mortality [27]. This may be related to a transcortical paracrine effect as has been demonstrated in numerous animal studies.

**Long-Term Outcome**

In addition to the increased perinatal mortality and morbidity, multiples are at higher risk for long-term problems in growth and development that include cerebral palsy (CP), cognitive impairment, language and speech delay, learning disabilities and social-behavioral difficulties [28]. This part of the review will focus on the up-to-date literature regarding long-term developmental consequences of multiple births, will describe the problems with the available data that raise difficulties in parental counseling and will suggest areas for future research.

**Long-Term Growth in Multiples**

Twins and triplets have different fetal growth patterns that deviate from that of singletons from around 28 to 30 weeks (deviation of the multiples curve from that of singletons) and then, at around 35 weeks (deviation of triplets curve from that of the twins) [29]. Therefore, in order to define birth weight as appropriate for both GA and plurality, birth weight standards that are specific for multiples have been reported from different countries [30–32]. Data from the NICHD Neonatal Research Network demonstrate that between 1997 and 2002, multiple births accounted for 26% of VLBW infants, with a range of 18–40% among the different network centers [3]. Even higher proportions of multiples among VLBW infants (40%) were observed in the Israel National VLBW Infant Database during 1996–2005. Do these facts have an impact on the long-term somatic growth of multiples?

Follow-up of 2,029 pairs of normally developed Japanese twins revealed that the deficit in the size of twins compared with singletons was markedly large at birth, with a 20% weight and 6% length difference compared to the 50th percentile of the standard population growth curves. However, the deficits decreased rapidly in the first year of life and were below 2% at 4–6 years of age [33]. Similar trends were reported from the Netherlands Twin Register for 2,996 twin pairs at 5 years of age. Both sexes achieved height which was 0.6 standard deviation scores below the mean target height, calculated from parental height. However, all twins had lower body mass index than singletons [34]. Buckler and Green [35] in a study from England that measured height and weight of 1,533 twins between 2 and 9 years of age adjusted for gender and zygosity, found a disadvantage for boy twins, especially for those who were monozygotic and had low birth weight.

The fact that there is significant effect of intrauterine growth restriction on long-term postnatal growth in singletons, even when correcting for genetic height [36], has considerable value in growth prediction of multiples. However, conflicting data are available regarding childhood growth of twins who had severe intrauterine growth restriction or discordancy at birth, varying from growth within the normal population curves [37] to some degree of stunting in growth [38]. In a more recent study, Monset-Couchard et al. [39] reported that when examined at 3–17 years, most small for GA, extremely low birth weight (<1,000 g) twins and triplets did not catch up in size and remained significantly smaller in all growth parameters when compared to their appropriate for GA pairs while some even received growth hormone treatment.

When followed to adulthood, 270 Japanese twins had a shorter final height, on average of 2.6 cm smaller than singletons, mainly because of lower growth velocity between birth and prepuberty. The height difference was observed both in dizygotic and monozygotic twins, and
Cerebral Palsy in Multiples

The increased risk of CP in multiples has been reported all over the world. In 1992, Laplaza et al. [42] evaluated 12 case series in the USA and showed an average of 7.4% twins among CP cases, with CP frequency which was 5- to 10-fold higher than in singletons. Although population denominators were absent in the reviewed studies, later figures from CP registers in other parts of the world confirmed the data [43–46]. Moreover, it was shown that the prevalence of CP increases with plurality. Petterson et al. [47], examining rates of CP in multiples born from 1980 to 1989 in Western Australia, found that the risk of CP in triplets was higher than in twins that had a higher risk than singletons (28%, 95% CI 11–63; 7.3%, 95% CI 5.2–10; 1.6%, 95% CI 1.4–1.8, respectively). The same trend was found in England by Pharoah and Cooke [43]. Thus, it was shown that the higher the number of fetuses the greater is the risk for CP, with plurality having an exponential effect on the risk.

As regards the specific type of CP, data collected from 12 European population-based CP registers on 6,613 children reveal that in comparison to singletons, multiples have higher rate of spastic CP (91% vs. 87%, OR 1.59, p < 0.006), and the CP is more likely to be bilateral (73% vs. 65%, OR 1.57, p < 0.001) [45]. This type of CP correlates with brain MRI findings, reported in a study that investigated 351 children with CP, which was conducted in 8 European centers. The most common finding consisted of white matter injury including periventricular leukomalacia (42.5%) followed by basal ganglia lesions (12.8%) [48].

Several causative mechanisms have been suggested to explain the unique characteristics associated with higher rates of CP in multiples. CP is the result of brain damage occurring during pregnancy or in the early neonatal period and consists of a wide range of physiological disabilities. The prevalence of CP is commonly cited as being 2–2.5‰ live births. Although the diagnosis of CP is relatively easily made, the wide clinical spectrum and the possibility of relatively mild expression hinder the identification of causality. As discussed by Pharoah [49], after taking into account postnatal causes for CP (about 10%) and peripartum events related to asphyxia, which are not considered higher in multiples than in singletons (about 10%), it is estimated that approximately 80% of the causes of CP in multiples are prenatal. Some of the current concepts regarding CP in multiple gestations will be discussed.

Birth Weight and Gestational Age

Given the high prevalence of CP in VLBW and preterm infants and the increased CP rate among multiples, one may ask whether the process of twinning (particularly monozygotic) increases the risk of fetal cerebral damage that results in preterm birth with its long-term neurological consequences? By comparison, does the prematurity by itself, which is more common among multiples, lead to long-term neurological morbidity?

Several series stratified the prevalence of CP in twins and singletons according to birth weight and demonstrated that twins weighing >2,500 g at birth have an excess risk for CP (3.6- to 4.5-fold) over that of singletons [50, 51]. At birth weights of <2,500 g, no significant excess risk for CP was found when comparing twins and singletons; moreover, Scher et al. [52] reported that twins weighing <2,500 g at birth did better than singletons with respect to CP rates. This observation could be explained by fewer LBW survivors among multiples, whereas more survivors among multiples weighing >2,500 g at birth exhibit later CP.

With respect to GA, Yokoyama et al. [53] found that CP among multiples was 20 times higher in those born at <32 weeks than at 36 weeks and above. Williams et al. [51] reported that every additional week in twin preg-
nancy decreased the relative risk of CP by a factor of 0.76, yet the relative risk of CP was significantly increased for twins delivered ≥37 weeks of gestation. Thus, although LBW and preterm infants are significant risk factors for CP, the disadvantage for twins appears near term. This fact supports the contention that in twins, ‘term’ occurs earlier than in singletons, thus 38 weeks of pregnancy may be considered as post-term with its attendant complications.

**Zygosity and Chorionicity**

Monochorionicity appears to be one of the risk factors for CP in multiples. In this unique condition, a single fetal demise may cause brain damage in the survivor that eventually causes CP. Several suggested mechanisms have been introduced to explain the process of fetal brain injury in the survivor. These include the embolic theory in which thromboplastin-like material emboli are transferred through an open placental anastomosis to the survivor, the ischemic theory in which blood is shunted into the low resistance circulation of the dead fetus, and the hemodynamic instability theory in which bidirectional shunting leads to ischemic damage that may affect both fetuses [49].

As shown by several case series, the surviving twin after a co-twin death is at a significant risk of CP of 1 in 10, with the majority of these twins found in monozygotic-monochorionic pregnancies [43, 50, 52]. However, an important confounding factor to study this phenomenon is the inability to precisely know the zygosity status, as this parameter is not registered in many population studies. One tool to estimate zygosity was applied by Pharoah and Adi [54] as they compared CP rates in co-twin survivors of like-sex twin pairs (estimated to include all monozygotic + 50% of dizygotic pairs) to unlike-sex twin pairs (all dizygotic). They reported a higher CP rate of 106‰ (95% CI 70–150) and 29‰ (95% CI 6–83) in like and unlike-sex twin survivors, respectively. Clearly, their conclusion regarding CP rate in monochorionic twins could be inaccurate due to biased classification.

Some of the difficulties to categorize the type of twinning may stem from an early gestational death of one of the twins, a phenomenon called the ‘vanishing twin syndrome’. This observation has been described with the increasing use of ultrasonography during early pregnancy where more than one fetal sac was detected and subsequently, only a singleton was delivered. Thus, one of the hypotheses regarding the cause of CP in singletons is related to a vanishing twin [55].

The death of one of a pair of monochorionic twins during infancy is also associated with an increased risk of CP in the surviving twin. This curious phenomenon is called ‘co-twin infant death’ and the neurological consequences are thought to be related to vascular placental anastomoses that contribute to both the death of one twin and brain damage to the survivor [56, 57].

Similarly, twin-to-twin transfusion syndrome is limited to monochorionic twins, and the cerebral impairments are probably associated with hemodynamic disturbances during pregnancy [58, 59]. Long-term outcome results after intrauterine laser treatment are conflicting but still appear to include significant risks for neurologic impairment [60, 61].

**Assisted Reproductive Technologies**

The impact of using assisted reproductive technology (ART) as an infertility treatment on the proportion of multiples among LBW infants is remarkable. A population-based study of the Israel National Very Low Birth Weight Infant Database revealed that between 1995 and 1999, multiples comprised more than one-third of VLBW infants, 10 times of their prevalence in the entire population, and ART resulted in 10% of the singletons, 55% of twins and 90% of the triplets [20]. As such, concerns have been raised over the potential implications of ART on the prevalence of CP, as researchers have estimated that ART in the USA would contribute 8% to the annual number of CP cases [62]. In addition, it was calculated that the rate of CP would exponentially increase with the increasing number of transferred embryos [63]. ART also changed the proportions between monozygotic and dizygotic twins and among spontaneously conceived twins 55% were dizygotic whereas their percentage increased to 95% among assisted conceived twins [64].

However, recent studies suggest that singletons conceived by ART have significantly elevated risks of CP mainly because of the higher frequency of preterm births and low birth weight when compared to spontaneously conceived controls [65–67]. It was not clear whether ART conceived multiples are at higher risk for CP than their spontaneously conceived peers. Two population-based studies looked at this question: Pinborg et al. [68] established in Denmark a database of all singletons and twins born after ART between 1995 and 2000 (3,393 twins and 5,130 singletons conceived by ART, 10,239 spontaneous
twins) and followed the children between 2 and 7 years of age. However, diagnoses of neurological impairments classified as CP, mental retardation, and psychomotor delay were extracted from national registry centers and the children were not directly examined. The findings of this study were that twins born after ART had a similar risk of neurological complications as spontaneously conceived twins (even after exclusion of monozygotic twins) and as singletons born after ART. Adjustments were made for gender, year of birth, maternal age and GA. Moreover, the risk for CP was similar when comparing different infertility techniques (IVF or ICSI).

Stromberg et al. [69] performed a matched, population-based retrospective study in Sweden and followed 5,680 children born after IVF from 1982 and 1995, with 11,360 matched controls. For the 2,060 IVF twins, 4,120 (second set of controls) non-IVF twins were matched. Data on CP were obtained from rehabilitation centers. In contrast to the Danish study findings, this study showed that the risk for neurological complications, especially CP, was higher in IVF twins than in IVF singletons, however, they did not have greater risk of CP than non-IVF twin controls. Accordingly, one of the authors’ conclusions was that there is a need to shift from multiple to single embryo transfer upon infertility treatment, in order to decrease prematurity rate.

Both studies had methodological limitations, mainly related to the identification of CP cases, as probably not all the cases were registered in the official disability centers.

So far, very few studies have addressed the issue of long-term follow-up of iatrogenic multiples. Most of them are limited by small sample size and short follow-up periods, no validated examination systems are used, and controls are poorly matched. In a recent systematic review including controlled studies, no evidence for increased risk for CP was found in IVF twins compared to spontaneous twins [70]. Data gathered from well-designed studies will facilitate appropriate and more reliable counseling regarding the outcome of multiples for couples undergoing fertility treatment.

**Cognitive Outcome in Multiples**

From many cohorts and case studies it appears that during early childhood, the cognitive skills of twins are influenced by GA, birth weight and the zygosity-chorionicity status of the pregnancy [39, 71, 72]. Towards adulthood, genetic and environmental factors become more pronounced.

In a large retrospective cohort study from Scotland, Ronalds et al. [73] compared cognitive status of all 236 twins born in Aberdeen between 1950 and 1956 to their 9,832 singleton siblings. The researchers identified a significant lower IQ score in twins compared with the singleton family members: 5.3 points (95% CI 1.5–1.9) and 6 points (95% CI 1.7–10.2) at 7 and 9 years of age, respectively. Since the lower IQ scores could not be explained by maternal and socioeconomic characteristics or recruitment bias, the authors postulated that the lower intelligence in twins might be the result of low birth weight and GA. In contrast, a Dutch study using the same intra-family research design, however based on volunteer families, found no differences between adult twins and their non-twin siblings on cognitive performance [74]. Similarly, when comparing academic performance at age 15–16 years of all 3,411 Danish twins born during 1986–1988 to a random sample of 7,796 singletons, Christensen et al. [75] found similar results, although birth weight had a minimal negative effect on school performance.

Few data are available regarding cognitive outcome of triplets. Alin Akerman et al. [76] reviewed follow-up information at 4–6 years on 17 complete sets of triplets born at 33–36 weeks in Sweden during 1986–1989. Physical and mental development was similar in triplets compared with twins and singletons at the same GA and birth weight. However, triplets weighing <2,500 g at birth scored significantly less on the mental personal-social scale, compared with singletons and twins. More recently, Feldman et al. [77] reported that triplets (23 sets) overall scored lower than singletons and twins in the Bayley Mental Developmental Index at 6, 12 and 24 months. Of importance was the fact that discordant triplets demonstrated decreased cognitive skills at 12 and 24 months, when compared to their siblings. This finding was partially related to difficulties in providing maternal sensitivity to their children.

To summarize, the unique problems facing multiples include: (1) increased mortality, particularly in extremely preterm infants, (2) increased RDS, reduced ROP, (3) slower long-term growth, and (4) increased risk for CP and reduced cognitive function. This information should be made available to couples undergoing infertility treatment and when multiple pregnancy is diagnosed. However, the data supporting the above findings remain sketchy and there remains a need for unbiased, reliable data in order to estimate the impact of these risks.
References


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