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Infant and perinatal outcomes of triplet pregnancy in Auckland: better than expected?

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Abstract

Aim There were two aims to the study: (1) to provide local outcome data that would be useful in counselling prospective parents of triplets; and (2) to address the deficit in accurate contemporary data on neurodevelopmental outcome and neonatal morbidity for those infants weighing less than 1500 g at birth.

Methods We reviewed the outcome of triplet pregnancies born at National Women's Hospital / Auckland City Hospital (Auckland, New Zealand) for 1995–2005 inclusive. For this study triplet pregnancy was defined as a pregnancy beyond 20 weeks leading to registration of at least one birth.

Results For the study period, 55 triplet pregnancies were identified. Forty-five percent of the pregnancies were reported as spontaneously conceived and 60% had no major complications other than premature delivery. One pregnancy spontaneously aborted; three fetuses from one pregnancy were stillborn, and four infants died in delivery suite. The median gestational age at birth was 32 (23–37) weeks and birth weight 1620 (530-2780) g. The median (range) Apgar score, for liveborns, was 8 (2–10) and 10 (4–10) for 1 and 5 minutes respectively.

There were five neonatal deaths. Fifty-three infants, <1500g at birth, underwent formal developmental assessment. Three had cerebral palsy (2 hemiplegia and 1 spastic diplegia); one had marked motor delay and one hearing impairment requiring aids. The median Bayley II MDI was 95 (71–105) and PDI 94 (65–110). Outcomes were categorised in surviving triplets <1500 g as normal in 66%, mild abnormality in 17%, moderate abnormality in 15% and severely abnormal in only 2%.

Conclusion Although triplets represent a significant burden on the regional NICUs the outcome, including those <1500 g at birth, compares favourably with that reported.

The triplet birth rate has generally increased worldwide since the 1970s.[1,2] Two important factors associated with this are the tendency towards increased maternal age, which may be associated with higher rates of spontaneous multiple births,[3] and the rising use of medical assistance to become pregnant.[4–7] Locally, there has certainly been a significant increase over time in the proportion of multiple pregnancies conceived following fertility treatments.[8]

A triplet pregnancy has significant implications for the mother, the infant, the family,[9] and society as a whole.[10] Triplet pregnancies are reported to have high rates of complications,[11–13] the most common of which is preterm delivery.[12,13] Indeed, the recent literature on triplet pregnancies reports delivery to occur at a mean gestation of approximately 32–34 weeks.[4–6,12,13]

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Other important pregnancy complications that occur more frequently are preeclampsia,[13,14] excessive postnatal haemorrhage[11,13] and growth restriction, which is associated with an increased rate of perinatal mortality.[15] In addition there is a two-fold increase in risk of maternal mortality over singleton pregnancies.

Postnatally, there are reports of an increased rate of neonatal morbidity including respiratory distress syndrome (RDS),[5,12] intraventricular haemorrhage (IVH)[5,12] and retinopathy of prematurity (ROP).[5,16] Lastly triplet pregnancy carries an increased risk of cerebral palsy (CP).[17] In twins the highest risks for CP are in monochorionic twins, especially in association with discordant growth or fetal demise of a co-twin.[18] Most triplet pregnancies are polyzygotic and polychorionic / polyamniotic but some contain a monochorionic pair.

The combination of the growing number of triplet pregnancies and the potential for problems make it important to review the available data on perinatal and neonatal outcomes. Although there have been reports of neonatal outcome in recent cohorts of triplets published,[16,19-21] a recent review highlighted the need for quality neurodevelopmental outcome data.[18] Particularly, there is a lack of data on neurodevelopmental follow up of triplets born with a birth weight below 1500 grams, i.e. those who may be expected to have the highest mortality and morbidity.

Accordingly, we have reviewed the neonatal, maternal and perinatal outcomes of triplet pregnancies born at NWH in Auckland during the period 1995 to 2005 inclusive. There were two broad aims. Firstly, to provide local outcome data that would be useful in counselling prospective parents of triplets. Hence a basic analysis of gestation, birth weight and survival data are presented for all triplet pregnancies during this period. Secondly, to address the deficit in accurate contemporary data on neurodevelopmental outcome and neonatal morbidity for those infants weighing less than 1500 g at birth.

Methods

All women who had given birth to triplets, at National Women's Hospital (subsequently National Women's Health, Auckland City Hospital), Auckland, New Zealand during the years 1995–2005, were identified from the Healthware database. A triplet pregnancy for the purpose of this study was defined as a pregnancy beyond 20 weeks that lead to registration of at least one birth. The mothers' and babies' paper and electronic medical records were searched for clinical and demographic details including pregnancy and neonatal histories.

Pregnancy details included maternal age at conception, delivery method, gestational age at delivery, conception details, maternal complications, and antenatal steroid use. Method of conception was defined as spontaneous or with fertility treatments. Details of any fertility treatment were recorded including ovulation induction (OI) with Clomiphene Citrate or Gonadotrophins, Assisted Reproductive Technologies (ART) such as *in vitro* fertilisation (IVF) with embryo transfer or other IVF techniques such as intracytoplasmic sperm injection (ICSI) and gamete intra-fallopian transfer (GIFT).

Neonatal data included details of resuscitation, sex, birth weight, neonatal morbidity, neonatal follow up and outcome. All identified infants were cross referenced with the neonatal database to confirm data. Major neonatal morbidity included chronic lung disease (CLD), confirmed necrotising enterocolitis (NEC), retinopathy of prematurity (ROP) stage 3 or 4, intraventricular haemorrhage (IVH) grade 3 or 4, periventricular leucomalacia, porencephalic cyst, or hydrocephalus. CLD was defined as the need for respiratory support (oxygen, CPAP, or ventilation) at 36 weeks of corrected postmenstrual age.

Infants with a birth weight below 1500 g are enrolled in a follow-up programme when they graduate from the NICU, including physical examination and formal developmental assessment using the

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Bayley scales of infant development[22] at 18 months of age. In addition to Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI), outcome category is formally allocated on a scale of 1-4, according to published criteria,[23] where 4 is normal and 1 severely abnormal.

The outcome for infants with a birth weight above 1500 g is generally good thus their follow up arrangements will vary and includes: neonatologist clinic, at a tertiary centre; local paediatric follow; GP; and Bayley assessment is only performed if requested. Infants undergo routine formal hearing assessments and ophthalmological assessments as indicated from gestation and clinical course.

Data are presented as mean and standard deviation if normal or median (range) if not normally distributed. Incidences were compared by Chi squared or Fisher's exact test as appropriate. Pregnancy and delivery data is presented as a percent of total triplet pregnancies whilst neonatal data is presented as a percent of the number of babies (either total number or number of neonatal admissions). For the calculations based on the number of babies (such as birth weight, neonatal morbidity, and perinatal mortality) any fetus born before 20 weeks gestation was excluded.

Results

For the study period, 1995 to 2005 inclusive, 55 triplet pregnancies were identified and the charts reviewed. The mean age of the women was 32 years (Table 1). Twenty-five pregnancies (45.4%) were known to be spontaneously conceived. Thirty-three women (60%) had no major complications other than multiple pregnancy. All but one set of triplets delivered in the same way. Eight women (14%) delivered vaginally, and of these, 3 were less than 24 weeks. The number of infants delivered each year varied from 6 to 33 with a peak in 2000 (Figure 1).

Table 1. Maternal, pregnancy and birth characteristics

Variables	Number of women (N= 55)	%
Median maternal age at delivery (range)	32 (19–39)	
Method of conception		
Unknown	7	13
Spontaneous	25	45
Ovulation Induction	11	20
IUI (Intrauterine insemination)	1	2
IVF	11	20
Number of embryos transferred = 2	3	
Number of embryos transferred = 3	4	
Number of embryos transferred unknown	4	
Pregnancy-related maternal complications		
Gestational hypertension ± proteinuria	8	14
APH	5	9
PPH (> 1000 mL)	5	9
Other (GDM, increased LFTs)	4	7
Nil	33	60
Mode of delivery		
Vaginal birth	8	14
Emergency LSCS during labour*	19	34
Emergency LSCS without labour	11	20
Elective LSCS	17	31

* Includes the set of triplets where Triplet A delivered vaginally and Triplets B and C by CS; APH=antepartum haemorrhage, PPH=Post partum haemorrhage (>1000 mL), GDM=gestational diabetes mellitus, LFTs=liver function tests, LSCS=lower segment caesarean section.

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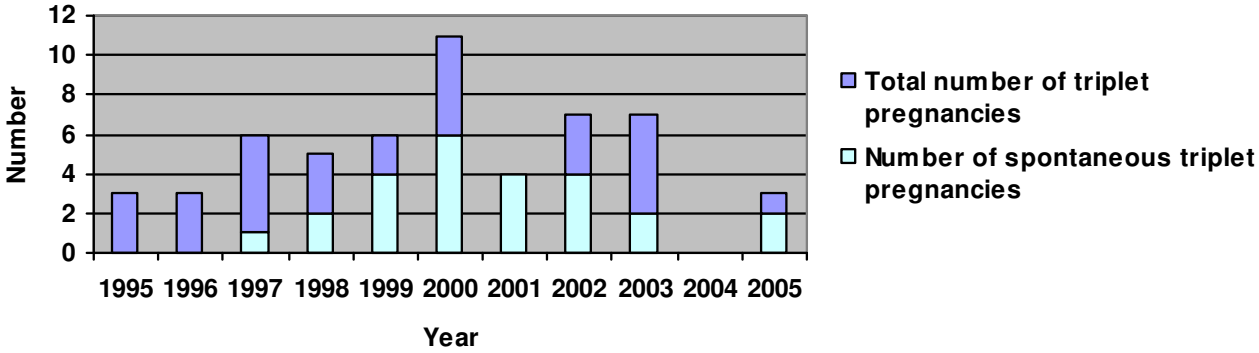
Figure 1. Distribution of triplet pregnancies by year and showing proportion that were spontaneously conceived.



*Conception data unavailable for 7 triplet pregnancies

Of the 165 fetuses, 10 died prior to admission to the neonatal unit. These included three infants from one pregnancy who were liveborn at 22 weeks gestation but died in the delivery suite; three were stillborn, one at 27 and two at 29 weeks; and one 23 week infant who weighed 475 grams was not resuscitated and died in delivery suite. In addition, there were three fetuses from one pregnancy that spontaneously aborted prior to 22 weeks gestation.

Although two delivered at 19 weeks plus 6 days the third was delivered at 20 plus 5 days so the pregnancy was included in the current report. There was also one set of triplets born at 37 weeks gestation who did not require admission to the neonatal unit. The overall sex distribution was even with 84 (51%) males and 81(49%) females.

Of the infants actively resuscitated and/or admitted to NICU (n=152), the median gestational age at birth was 32 (range 23–-35) weeks and birth weight 1620 g (530–2780) g respectively. Two infants were born prior to 24 weeks gestation, 17 infants between 24 and 27 weeks plus 6 days, 49 infants between 28 weeks and 31 weeks plus 6 days and 84 infants between 32 weeks and 35 weeks 6 days. At birth 19 (12.5 %) infants required intubation for resuscitation and the median (range) Apgar score, for the liveborn infants, was 8 (2–10) and 10 (4–10) for 1 and 5 minutes respectively.

There were five neonatal deaths (3.3%), including the one 23-week infant who died in delivery suite, with each of these occurring in infants born at 25 weeks gestation or less. Thus the overall number (i.e. including stillbirths, spontaneous abortions and pre viable live born infants) of perinatal deaths was 14/165, which equated to a crude perinatal mortality rate for triplet pregnancies of 83/1000 and a neonatal mortality rate of 33/1000 births respectively.

Neonatal course and morbidity—In 35 infants the main respiratory diagnosis was respiratory distress syndrome (RDS); of these, 28 infants received surfactant. There were also 11 cases of transient tachypnoea and one case of pulmonary hypertension. The median (range) duration of ventilation was 0 days (0–70) and median duration of CPAP was 2 (0–317) days.

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Respiratory morbidity included six infants who developed air leak, five with chronic lung disease and one who required home oxygen. Other neonatal morbidities included one case of proven necrotising enterocolitis and serious cerebral ultrasound abnormalities in nine infants that included various combinations of grade 4 intraventricular haemorrhage (five infants), ventriculomegaly / hydrocephalus (six infants) and cyst formation (five infants).

Congenital anomalies were present in six infants (4%) and included one case each of polycystic dysplastic kidney, arachnoid cyst, two vessel cord, massive facial haemangioma, tracheal oesophageal atresia and hydrops.

Outcome data—Infants below 1500 g are routinely followed in clinic and undergo developmental review including Bayley assessment. Fifty-three infants weighed less than 1500 g at birth, with a mean gestation of 29 (23–35) weeks and birth weight 1040 (530–1480) g. In this group, 39 infants had received a complete antenatal steroid course, 10 an incomplete course and in only four cases no antenatal steroids had been received. Six infants died, including one at 7 months unrelated to neonatal period; three developed cerebral palsy, two cases of hemiplegia and one spastic diplegia; one infant had marked motor delay and one infant hearing impairment requiring aids.

Bayley scores were performed in 30 infants with a median MDI 95 (71–105) and 94 (65–110). Outcomes were categorised for all surviving infants below 1500 g as normal (4) in 31/47 (66%) of survivors, mild abnormality in 8/47 (17%), moderate abnormality in 7/47 (15%) and severely abnormal in only 1/47 (2%) infants. The one infant born prior to 24 weeks gestation (23 + 6) who survived the period and had a good neurodevelopmental outcome on follow-up.

Of the 64 infants above 1500 g some limited follow up information is available. Twenty-four were normal when last reviewed at a median of 14 (range 3–24) months and two had died from conditions presumed not to be related to the neonatal course (SIDS and aspiration secondary to epilepsy associated with an arachnoid cyst). The median birth weight of this group was 1795 g and median gestation was 33.5 weeks, which would normally be expected to be associated with a reassuring outcome.

Discussion

In this paper we report the outcome, including mortality and neonatal morbidity, for an 11 year cohort of 165 triplets born at a single large perinatal centre in New Zealand. The overall fetal losses for pregnancies that reached 20 weeks gestation were low with only 9 fetuses resulting in stillbirth, spontaneous abortion or pre-viable delivery. Furthermore, there were only five neonatal deaths, all of which occurred before one week of age.

Consistent with our expectation, mortality was focused in those pregnancies that delivered at the very premature end of the spectrum, indeed 1/3 cases in infants born before 24 weeks gestation died. In general the crude perinatal mortality rate of 83/1000 and a neonatal mortality rate of 33/1000 for triplet births compares favourably to reported rates of 41-121/1000[5,12,13,16,23,24] and 51–59[5,6] respectively.

Even though neonatal mortality was quite low for a group of premature infants there was morbidity. Approximately 6% had cerebral ultrasound abnormality and 3% developing chronic lung disease but below 1% of infants required home oxygen or

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developed proven necrotising enterocolitis. These morbidities with potential long-term consequences were also largely focused in those pregnancies below 28 weeks gestation. Congenital anomalies occurred sporadically with a rate that was consistent with that reported from other studies.[21,26]

Review of the neurodevelopmental outcome for triplet infants <1500g revealed over 80 % of the survivors, categorised as normal or only mildly abnormal (66%+ 17%) and only 1/47 (2%) infant categorised as severely abnormal. These results were comparable with those reported from a cohort of triplets from Israel;[27] however, that study reported outcome of a slightly more mature group of triplets with a mean BW of 1660 g and gestation of 32 weeks.

In the New Zealand data the scores encompass a broad range and the values of 65 and 71 for minimum MDI and PDI respectively represent a significant degree of impairment. Also three of these infants developed cerebral palsy with two cases of hemiplegia and one spastic diplegia plus one infant had marked motor delay and one infant with hearing impairment requiring aids.

There are very limited data available on neurodevelopmental follow up of triplets with a birth weight below 1500 g but the one report from Zagreb described the outcome to be normal in 15 infants, CP in seven and minimal abnormality on neurological testing in seven infants.[19] Although it should be noted that in the centre reporting this data there was not a specific follow up program for infants born at this weight and findings were from neurological assessments by a neurologist so there may be some referral and / or ascertainment bias in that data.

Although the data described in the current study are from a single high risk centre so represent a fairly homogeneous pattern of management there are some limitations. Specifically, there are quite small numbers that mean it is not possible to perform meaningful comparisons within the cohort such as the outcomes of triplet pregnancies conceived spontaneously versus those conceived using assisted techniques.

The other potential limitation is the lack of complete follow up data on those infants who were not enrolled in the follow up program. Nevertheless a minimum data set of gestation, birth weight, neonatal survival and neonatal morbidity were established. Furthermore, if the clinician following the child considers development to be abnormal then formal assessment can be performed on request.

The role of fertility treatment in triplet pregnancies is well recognised.[8] Locally there have been strong moves to decrease the number of multiple births secondary to assisted fertility.[28] During the study period the number of triplet pregnancies fluctuated from none to 11 per year and there is the suggestion that numbers are declining since the peak in 2000. This experience is consistent with that of others with recent UK data on triplet and higher order births demonstrating that the rate has decreased by one-quarter since 1998.[29] NZ has already taken steps to reduce the number of multiple births following ART by implementing policy limiting the number of embryos transferred.

It is of interest to explore the relative contribution of multiple pregnancy and prematurity to any adverse outcome for the infant. Some authors have compared data obtained from triplets to singletons of same gestation and report survival and major short term morbidity to be very similar once controlled for appropriate variables.[4,16,21]

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Although neonatal stay is reported to be generally longer for triplets than twins[4,30] and in one study [16] there was still an increased rate of mild IVH and severe ROP associated with triplet pregnancy. A logical extension to this is to examine the role of selective fetal reduction on subsequent neurodevelopmental outcome. Although it is well described in the literature,[31–35] the published results in terms of neurodevelopmental outcome are somewhat contradictory and this procedure was not performed on any of the triplet pregnancies in the current cohort.

The Cochrane Review[36] concludes there is no strong evidence about the effects of reducing the number of fetuses in women pregnant with triplets or higher order multiples. A subsequent systematic review[37] suggests that embryo reduction reduces the rate of preterm delivery, with a number needed to treat 7 (95%CI: 5–9) but there is an increased rate of miscarriage, with a number needed to treat of 26 (95%CI: 14–193).

Although this suggests embryo reduction may have a role in reducing prematurity, there is still a lack of data on the effect, if any, on subsequent long term neurodevelopmental outcome. One retrospective study has examined cerebral palsy (CP) rates in a large cohort of trichorionic triplets, where the decision to have ER or not was determined by parent choice.[38]

The mean gestation at birth was 35.6 weeks versus 33.8 weeks and CP rate was 13.8 versus 18 per 1000 live births respectively for those managed with reduction to twins or expectant management. The authors suggested that there was a significant difference in gestation at birth but the rates of cerebral palsy were similar and concluded there was a need for further data.[38]

In summary, this study provides local data on the outcome of New Zealand triplets. This will be useful not only for counselling prospective parents of triplets but also in planning services and potentially as a baseline for monitoring impact of ongoing developments in the care of triplet pregnancies. In addition, the detailed neurodevelopmental follow up data may be used to counsel the parents of preterm triplet infants admitted to the neonatal unit.

Competing interests: None known.

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