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Intrauterine growth in multiple pregnancies in relation to fetal number, chorionicity and gestational age

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ABSTRACT

Objectives *To examine birth weight in dichorionic and monochorionic twins and trichorionic triplets, and to estimate the relative independent importance on growth of fetal number, chorionicity and gestational age.*

Methods *Four groups of pregnancies were examined: 12 816 singleton pregnancies, 302 monochorionic twin pregnancies, 569 dichorionic twin pregnancies, and 97 trichorionic triplet pregnancies. Chorionicity was determined at 10–14 weeks on the basis of the presence or absence of the lambda sign in twins, and by examining the ipsilon zone in triplets. The relationship between birth weight and gestational age in singletons was established, and using this equation the expected mean birth weights for all gestational ages were calculated. For each case in all groups, the difference between the observed birth weight for each fetus and the appropriate normal mean for gestation in singletons was calculated (Z-score). Multiple regression analysis was used to examine the independent contribution of gestational age, number of fetuses and chorionicity in the prediction of actual birth weight and birth weight Z-score.*

Results *Birth weight Z-score was significantly lower than the expected mean in singletons for dichorionic twins, monochorionic twins and trichorionic triplets ($t = 15.4$, $P < 0.0001$, $t = 21.7$, $P < 0.0001$ and $t = 19.9$, $P < 0.0001$, respectively). Furthermore, the reduction in expected birth weight was significantly greater for monochorionic twins and trichorionic triplets compared with dichorionic twins ($t = 6.3$, $P < 0.0001$ and $t = 7.8$, $P < 0.0001$, respectively). Multiple regression analysis demonstrated that number of fetuses, presence of a monochorionic placenta and gestational age were independently associated with birth weight Z-score, the strongest effect being fetal number, followed by monochorionicity ($t = -23.4$, $P < 0.0001$, $t = -8.3$, $P < 0.0001$ and $t = -4.9$, $P < 0.0001$, respectively).*

Conclusions *The finding that monochorionic twins were of lower adjusted birth weight than dichorionic twins, and the significant independent effect of chorionicity on birth weight suggest that monochorionic placentation in itself has an effect on intrauterine growth. The effect of fetal number independent of chorionicity is demonstrated by the lower birth weight of trichorionic triplets compared with dichorionic twins.*

INTRODUCTION

At all gestational ages beyond 24 weeks the average birth weight of a fetus from a twin pregnancy is lower than that of a corresponding singleton[1]. Furthermore, previous studies have reported that the birth weight of monochorionic twins is lower than that of dichorionic twins[2,3]. Chorionicity can now be determined prenatally by ultrasonography[4]. The aim of this study was to examine birth weight in dichorionic and monochorionic twins and trichorionic triplets, and to estimate the relative independent importance on growth of fetal number, chorionicity and gestational age.

METHODS

Four groups of patients were examined for this study: 12 816 unselected singleton pregnancies, 302 monochorionic twin pregnancies, and 569 dichorionic pregnancies, all attending the Harris Birthright Centre for calculation of risk for trisomy 21 on the basis of maternal age and fetal nuchal translucency thickness. In addition, there were 97 trichorionic triplet pregnancies referred

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to the Harris Birthright Centre from other hospitals for counseling concerning the option of embryo reduction, but the parents decided to continue with the pregnancy without reduction. The control group of 12 816 singleton pregnancies was used to derive the normal range of birth weight for gestation in singletons.

In all groups, the inclusion criteria were, first, an ultrasound examination demonstrating live fetuses at 10–14 weeks and, second, pregnancies resulting in registered live births at or after 23 weeks of gestation. Gestation was determined on the basis of the crown–rump length and in multiple pregnancies the crown–rump length of the largest fetus was used. In twins, chorionicity was determined at 10–14 weeks on the basis of the presence or absence of the lambda sign or a projection of choriodecidual tissue into the intertwin membrane[5], and in triplet pregnancies by examining the ipsilon zone[6]. Pregnancy outcome was obtained from the patients themselves, the referring hospitals or general practitioners.

Statistical analysis

The relationship between (log) birth weight and gestational age in singletons was established. The expected mean birth weight and SD at all gestational ages beyond 23 weeks were calculated. For each case in all groups the difference, in SD, between the observed birth weight for each fetus and the appropriate normal mean for gestation in singletons was calculated (Z-score). Students t-test was then used to examine the significance of differences in Z-score between the groups. Multiple regression analysis was used to examine the independent contribution of gestational age, number of fetuses and chorionicity in the prediction of actual birth weight and birth weight Z-score.

RESULTS

The median gestational age at delivery in singleton pregnancies was 40 weeks (Figure 1). Gestational ages at delivery and birth weight Z-score of the four groups of pregnancies are given in Table 1, and the individual birth weights are plotted on the reference range for singletons in Figure 2. The relationship between (log) birth weight and gestational age in singletons could be described as log birth weight (g) = (gestation in weeks $\times$ 0.03315) + 2.229 (SD, 0.0827; $t = 95.7$, $P < 0.0001$). Birth weight Z-scores were significantly lower than the expected mean in singletons for dichorionic twins, monochorionic twins and trichorionic triplets ($t = 15.4$, $P < 0.0001$, $t = 21.7$, $P < 0.0001$ and $t = 19.9$, $P < 0.0001$, respectively) (Table 2). Furthermore, the reduction in expected birth weight was significantly greater for monochorionic twins and trichorionic triplets compared with dichorionic twins ($t = 6.3$, $P < 0.0001$ and $t = 7.8$, $P < 0.0001$, respectively) (Table 2).

Multiple regression analysis demonstrated that number of fetuses, presence of a monochorionic placenta and gestational age were independently associated with birth weight Z-score, the strongest effect being fetal number, followed by monochorionicity. ($t = -23.4$, $P < 0.0001$, $t = -8.3$, $P < 0.0001$ and $t = -4.9$, $P < 0.0001$, respectively).

DISCUSSION

The median gestational age at delivery and adjusted birth weight were progressively lower through dichorionic twins, monochorionic twins and trichorionic triplets. This reduction in birth weight was a real reduction rather than being a purely gestational effect because the birth weight Z-score was significantly reduced in a similar fashion through the groups.

The finding that monochorionic twins were of lower adjusted birth weight than dichorionic twins, and the significant independent effect of chorionicity on birth weight demonstrated by the multiple regression model, both suggest that monochorionic placentation in itself has an effect

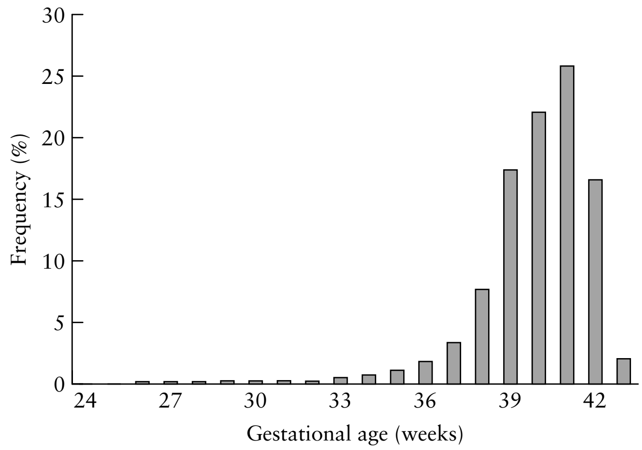

Figure 1 Frequency distribution of gestational age at delivery in singleton pregnancies.

Table 1 Gestational age at delivery, birth weight and birth weight Z-score for singleton, monochorionic and dichorionic twins, and trichorionic triplet pregnancies

Type of fetus	*Number of fetuses*	*Gestation (weeks, median (range))*	*Birth weight (kg, mean (95% CI))*	*Z-score (range)**
Singleton	12 816	40 (23–43)	3.46 (0.42–5.10)	0.01 (−0.01 to 0.03)
DC twins	1138	36 (24–42)	2.50 (0.41–4.66)	−0.47 (−0.55 to −0.39)
MC twins	604	35 (23–40)	2.15 (0.43–3.54)	−0.88 (−0.97 to −0.78)
TC triplets	291	34 (24–38)	1.81 (0.65–2.61)	−1.14 (−1.27 to −1.01)

*Relative to appropriate normal mean for gestation in singletons. DC, dichorionic; MC, monochorionic; TC, trichorionic.

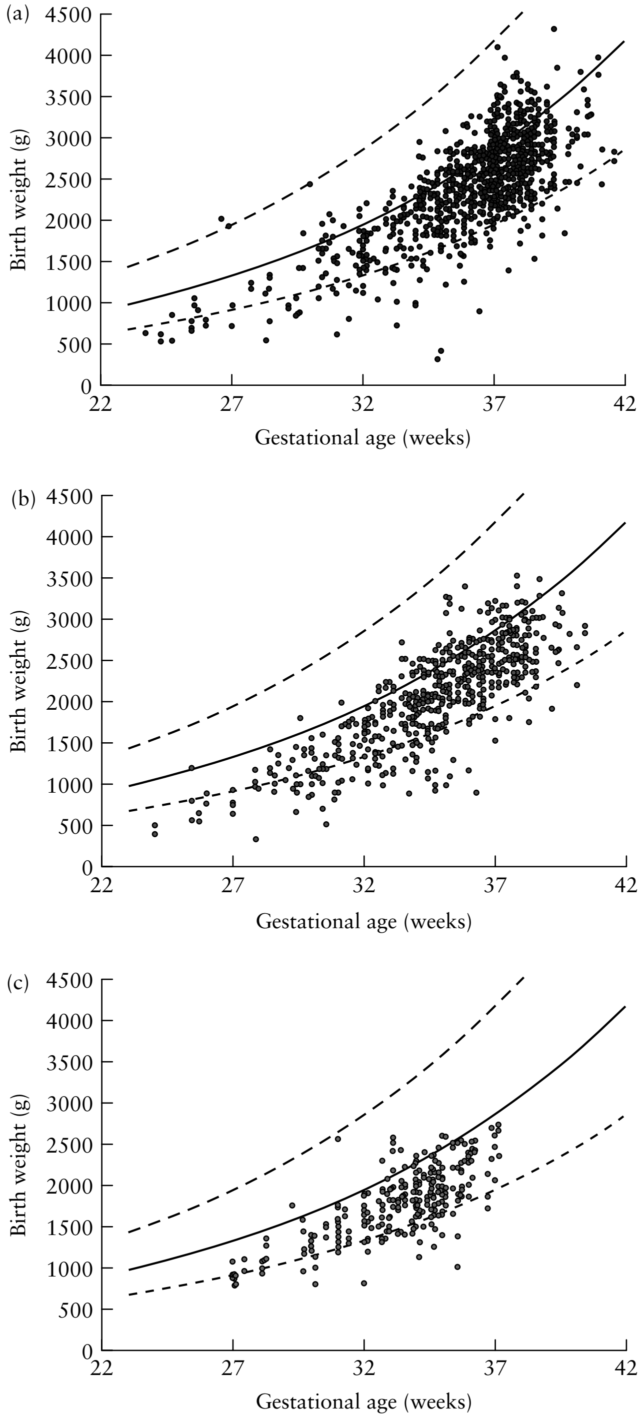

Figure 2 Birth weight for individual fetuses from dichorionic (a) and monochorionic (b) twin pregnancies, and trichorionic triplet pregnancies (c), plotted on the normal range for gestation in singletons (shown as mean, 5th and 95th centiles).

on intrauterine growth. The effect of chorionicity independent of zygosity was examined by Derom *et al.*, who demonstrated that the average birth weight of dichorionic monozygotic twins was more than for monochorionic monozygotic twins[7]. Differences owing to chorionicity cannot be due to differences in uterine surface area or genetic differences so must be caused by environmental differences. Underlying mechanisms could be alterations in the fetal circulation and/or differences in uterine blood

Table 2 Birth weight *Z*-scores for singleton, monochorionic and dichorionic twins, and trichorionic triplet pregnancies compared using regression analysis

Parameter	t	P
Birth weight *Z*-score group		
DC twins vs. singletons	15.4	< 0.0001
MC twins vs. singletons	21.7	< 0.0001
TC triplets vs. singletons	19.9	< 0.0001
MC twins vs. DC twins	6.3	< 0.0001
TC triplets vs. DC twins	7.8	< 0.0001
TC triplets vs. MC twins	3.1	0.002
Regression analysis contribution to birth weight *Z*-score		
Fetal number	−23.4	< 0.0001
Monochorionicity	−8.3	< 0.0001
Gestational age	−4.9	< 0.0001

DC, dichorionic; MC, monochorionic; TC, trichorionic.

flow in monochorionic compared with dichorionic twins. A study by Loos *et al.* suggests that the relative frequency of peripheral cord insertion, which occurs most frequently in monochorionic twins, may also play a role[8]. The latter study also confirmed that fetal gender has an effect on birth weight; female fetuses were smaller from as early as 27–31 weeks[8]. Although we did not have information on gender, given the large number of cases it is very unlikely that gender distribution would be unequal enough to influence the results significantly. An aternative hypothesis could be that the defect that leads to monochorionic twinning also leads to reduced fetal size, perhaps via a reduction in the total totipotential cell mass, but this appears unlikely because chorionicity rather than zygosity is important in determining fetal size.

The effect of fetal number independent of chorionicity is demonstrated by the lower birth weight in trichorionic triplets compared with dichorionic twins and the findings of the regression model. Such findings, of reduced fetal weight with increasing litter size, are well recognized in animal studies of pups[9] and rabbits[10]. In this case the most obvious explanation is simply a reduction in total placental mass per fetus as the available decidual surface of the uterus is the limiting factor once the fetal number becomes greater than two. Evidence for such a hypothesis in humans is also provided by the finding that maternal serum PP14 (a decidual protein) concentration in maternal serum from multifetal pregnancies reaches a maximum with twins rather than higher-order multiples. However, a mechanical reduction in placental size should not lead to a reduction in fetal size unless it is of at least 30–40% because of the normally large functional reserve capacity of the placenta[11]. Therefore, it is unlikely that reduction in placental size leads to a reduction in fetal size purely due to reduced nutrient transfer capability. It is possible, however, that cell–cell interaction limits the placental implantation site and, to maintain the reserve, the placenta mediates fetal growth via growth factors such as insulin-like growth factors[12]. The finding that the gestational age-adjusted birth weight in twin pregnancies following embryo reduction remains lower than that in non-reduced twins but higher than in triplets[13] further suggests that the controlling mechanisms for fetal growth in multiple pregnancies are in part determined very early in the pregnancy according to fetal number and in part by ongoing influences during the course of the pregnancy.

The pathophysiological implications of the lower birth weight in multiple pregnancies remain unclear. If the underlying defect is reduced growth potential owing to small placental size then the mechanism of the reduced growth would be expected to be similar to that in singletons with primary uteroplacental insufficiency, with the resulting potential adverse effects into adulthood[14]. An alternative explanation is that in multiple pregnancies, and particularly those that are monochorionic, there is a mechanism operating in early pregnancy that optimizes fetal growth potential according to the fetal number and total placental function. This is compatible with the finding that twins generally remain smaller than singletons into childhood but the reduction is primarily in weight rather than height, suggesting a lower body fat content owing to intrinsically altered metabolism. This effect could potentially be beneficial as obesity and the development of adult cardiovascular disease are linked. Evidence for such a postnatal effect is also provided by the finding in rats that body weight remains lower for about 90 days with increasing litter size[15].

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