GROWTH RESTRICTION IN MULTIPLE PREGNANCIES

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Summary

The frequently of small-for gestational-age (SGA) infants among multiples is unquestionably increased when defined by singleton standards. These SGA infants probably include genuine cases of intrauterine growth restriction (IUGR), however, these are less likely when SGA infants are defined by birth weight percentiles of twins or triplets. The inordinately high frequency of SGA infants and the characteristics of the growth discordance phenomenon both support the supposition of a physiological restriction of multiples and an adaptive pattern of the uterine environment to promote an advanced gestational age. Pathological growth restriction associated with adverse outcome may therefore be seen when adaptation fails. It is concluded that most SGA multiples are not a result of pathological IUGR but rather a consequence of a physiological adaptation of the uterus to the multiple pregnancy.

Introduction

The distinction between SGA and IUGR relates to the difference between cross-sectional and longitudinal observations, respectively. Nonetheless, it is believed that there is a cutoff level of birth weight percentiles below which the likelihood of an SGA fetus to be IUGR is most significant. The cross-sectional designation of SGA is based on birth weights by gestational age ("growth") curves. Ultrasonography and longitudinal studies led to better understanding IUGR and to defining the growth-restricted fetus as one whose intrauterine growth exhibited a decelerating pattern, i.e., the one whose growth potential is not maintained *in utero*.

It is self-evident that multiple gestations are frequently associated with IUGR. This statement, however, has not been scrutinized in depth because of three limitations. First, one should define IUGR by the growth curves of fetuses with comparable growth potentials. At present, it is believed that multiples do not have the same growth potential as singletons and, in fact, there are serious doubts concerning the appropriateness of singleton standards for multiples. Second, the growth patterns of late pregnancy are practically unknown merely because pre-term birth (by singleton standards) is the rule rather than the exception in multiple gestations. Finally, there are few longitudinal studies and most of our knowledge is derived from birth weight by gestational age relationships – the so-called "growth curves".

When is the average twin or triplet considered SGA?

Because of the increased likelihood of IUGR among SGA infants, it is customarily to designate a neonate as IUGR when its birth weight is less than an arbitrary birth weight percentile of the same gestational age. Alexander et al[1] used singleton standards to show that SGA twins and triplets occur from10 to 15% until 30 weeks, and are much increased thereafter. By singleton standards, more than 50% of triplets are considered SGA at 35 weeks and more than 50% of twins are considered SGA at 38 weeks. One may be hesitant to

consider a biological phenomenon with a frequency of over 50% as a pathological event; nonetheless, these frequencies did not deter authors to classify twin infants as IUGR by using a gender-, and gestational age-specific birth weight at or below the 10th percentile.[2-3] It is interesting to note that the conclusions of these studies were quite different, in accord with the questionable validity related to the definition of IUGR in multiples based on singleton SGA standards.

In re-evaluation of the data published by Alexander et al [1], the median birth weight percentile of twins and triplets was compared with the10th percentile for singletons. It could be shown that the average multiple is not "SGA" until well after the mean gestational age (i.e., 32 and 37 weeks for triplets and twins, respectively) and weighs more than the 10th birth weight percentile for singletons until 35 weeks in triplets and 38 weeks in twins.

The relationship between the average multiple and singleton pregnancies

The common growth curves show that deviations from singleton standards appear to be a third trimester (i.e., after 28 weeks) event.[4] It has been conceptualized that the uterine milieu, comprising utero-placental, maternal, and fetal components, limits the growth potential of the *individual* fetus in a multiple pregnancy. The concept implies that most multiples delivered after 28 weeks are *growth restricted* compared with singletons.[4-6] The overwhelmed uterine milieu, however, exhibits remarkable adaptation. Data derived from the 1995-7 Matched Multiple Birth Data Set complied by the National Center for Health Statistics and comprising 147,575 twin pairs and 5,172 triplet sets show that the total twin and total triplet birth weights exceed that of the 90th birth weight percentile for singletons as early as 25 week's gestation. The uterine potential adaptation to a multiple pregnancy is also appreciated by realizing that the average singleton birth weight at 40 weeks' gestation is reached as early as 32 weeks in twins and as early as 29 weeks in triplets. Put differently, the total twin birth weight at 36 weeks and the total triplet birth weight at 33 weeks by far exceed the 90th birth weight percentile of singletons at term.

It follows that at the same time that the individual multiple is relatively *growth restricted* compared to singletons, the entire pregnancy is *growth promoted*. It is hypothesized that only a *physiological* restriction enables concomitant growth of more than one fetus for as long as possible. In this case, the uterus should overcome the tremendous increase in volume, which leads to uterine overdistension and pre-term birth in multiple pregnancies. One way to decrease overdistension is to reduce fetal size. It was hypothesized that the adaptation is primarily directed to promote a more advanced gestational age[4-5] and hence, an adaptation in the form of *physiological growth restiction* is frequently seen.

The adaptation of the uterus changes throughout gestation. By calculating the ratio between the median birth weights of twins and triplets to that of singletons, four distinct phases can be observed.[4-6] In phase A, a ratio of 0.9 - 1.0 (i.e., birth weights are quite similar to those of singletons) is maintained until 28 and 30 weeks' gestation for triplets and twins, respectively. In this phase the uterine environment sustains the growth potential of the individual multiple to the same extent as is the case for singletons, but for some reason (i.e., cervical incompetence) is unable to promote an advanced gestational age. Multiples delivered during this phase are not likely to demonstrate growth restriction, albeit they are extremely low birth weight infants. Phase B is characterized by a steady decrease in birth weight of the individual multiple relative to singletons. In this phase, the uterine environment fails to maintain continued optimal growth, and if delivered during this phase, the multiples are smaller by 15 to 20% relative to singletons. At the same time, however, reduction in birth weight is associated with a 'compensatory' gain in gestational age. In phase C, the ratio does not change substantially over time. This phase, which in twins is longer than in triplets, continues until 40 weeks in twins and 36 weeks in triplets. During this phase, the uterus exhibits remarkable adaptation to the presence of twins, which cannot be maintained for a long period in the case of triplets. Phase C deliveries demonstrate the adaptive ability of the uterus to promote maturity in expense of maintaining growth of the already size-restricted individual multiples. Phase D, observed only in triplets, represents failure of the overwhelmed uterine environment to further adapt, and results in a striking decrease in triplet birth weight relative to singletons. Triplets delivered during phase D exhibit the most significant age promoting effect despite marked growth restriction.

Taken together, two distinct factors operating in parallel appears to operate - one promoting gestational age and maintaining size (phases A and C) and the other promoting age and restricting size (phase B and D).

What is the relationship between discordant growth and IUGR?

Discordant growth is another potential way to reduce uterine volume in order to promote an advanced gestational age. The problem was always to distinguish between natural variation and pathological growth restriction as the reason for inter-sib size differences. Differences as large as 15% may be a normal variation and by large have no clinical consequences, whereas 15-25% discordance may denote adaptation, and differences of more than 25% represent the inability to maintain growth.[7-8] The observed patterns of birth weight discordance did not substantiate a normal variation that might explain why the frequency of discordant pairs decrease as the total twin birth weight increases. The data suggest that the more favorable the uterine milieu for carrying twins, the smaller the likelihood of discordant twin growth. Indeed, higher birth weight discordance correlates with neonatal morbidities, including fetal abnormalities, low birth weight, intensive care admission, and respiratory distress, being associated with higher birth weight discordance.[9,10]

It is well known that even severely discordant pairs are not always associated with adverse outcome. This could be explained by the fact that not all severely discordant pairs include an SGA (and an IUGR) infant. Until recently, the frequency of SGA infants among growth discordant pairs was fairly unknown. By using data from the 1995-7 Matched Multiple Birth Data Set, we established the 10th and 50th birth weight percentiles among 259,036 individual twins delivered between 28 and 40 weeks' gestation.[11] We then classified 10,683 discordant (>25%) pairs (8.2% of the entire twin population) according to the birth weight of the smaller twin as being less than 10th %tile, between 11 to 50th %tile, or greater than 50th%tile. These subgroups correspond to severely discordant pairs who are growth restricted, growth adapted, or growth promoted, respectively. The frequencies of the 6668 (62.4%), 3514 (32.9%), and 501 (4.7%) severely discordant sets in the respective subgroups remained unchanged throughout the third trimester. There were significantly more nulliparas and fewer unlike-sex pairs in the growth restricted discordant pairs compared with the other subgroups. We found 368 (34.4‰) neonatal deaths in the smaller twin and 110 (10.3‰) in the larger twin (P<0.0001, OR 3.4, 95% CI 2.7, 4.3). Neonatal mortality rate was significantly higher (29.1‰) when the smaller twin weighs less than the 10th birth weigh percentile compared with the other subgroups (11.2 and 11‰). The data proves that even among severely discordant pairs – that could traditionally be termed as IUGR multiples – there are 40% appropriately grown twins, of which 6% are, in fact, growth promoted.

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