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Intrauterine growth restriction: new standards for assessing adverse outcome

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The study of associations between intrauterine growth restriction (IUGR) and adverse outcome benefits from the use of a birthweight standard which is based on customised growth potential. Its application is able to retrospectively quantify the strength of the link with IUGR, whether fetal growth problems were identified antenatally or not. Furthermore, growth failure hitherto unrecognised by conventional standards, such as the average size but *relatively* small babies of mothers with high body mass index, identify IUGR as a cause of the increased perinatal mortality risk in obese pregnancies. Fetal growth restriction is found to be a frequent antecedent of perinatal morbidity and mortality, pointing to the need to improve its timely antenatal detection as a mainstay of management and prevention.

An understanding of the effects of intrauterine growth restriction (IUGR) on pregnancy outcome has to start with the right definition. Often, terms are confused, and their relevance to pathology uncertain. Smallness for gestational age (SGA) is taken as synonymous with fetal growth restriction. Yet, SGA is merely a statistical construct, a size limit which cannot differentiate between physiological and pathological smallness. Such a distinction first requires the assessment of the growth potential, the optimal weight which a baby can achieve. From then on, it becomes easy to define 'IUGR' as *the failure of the fetus to reach its growth potential.*

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Defining the fetal growth potential

Establishment of a baby's individual growth potential follows three basic principles:

1. The standard needs to be adjusted for physiological variation, due to maternal characteristics (height, weight in early pregnancy, ethnic origin), parity/birth order and the sex of the baby (if already known).[1,2]
2. The standard has to exclude pathology which can affect birthweight – such as smoking, hypertensive diseases or diabetes. The most obvious example is smoking, known to affect birthweight in a dose–response relationship with a deficit of up to 250 g at term.[2] However, rather than predicting the birthweight, the growth potential should define a standard with a weight which the baby should be able to achieve if the mother did NOT smoke during pregnancy. Against this standard, it is more likely that IUGR is detected if it did occur during this pregnancy.
3. The standard needs to exclude prematurity, which is known to be linked with growth restriction.[3,4,5] By definition, babies born preterm had a pathological pregnancy. Their birthweight distribution is negatively skewed, that is, they are lighter than fetuses (at the corresponding gestational age) which continue *in utero* growth towards a normal term delivery. Thus the 'term optimal weight' (TOW) is linked to a growth curve which is not based on neonatal weight, but a fetal weight curve derived from a set of normal pregnancies born at term, such as that described by Hadlock.[6] The growth equation is expressed as a proportionality formula, which is then combined with TOW to show the weight that should be expected at each gestation week in an 'optimal' pregnancy – the gestation-related optimal weight (GROW) curve.[2]

In practice, the growth potential, and thus individually adjusted or customised normal limits (e.g., 10th and 90th centile) are calculated by computer software[7] because of the infinite number of possible combinations. Fig. 1 illustrates this by two examples.

Depending on the availability of suitable databases, coefficients are calculated for different populations. To date, they have been derived for the United Kingdom,[2] Australia,[8] New Zealand,[9] France,[10] Spain,[11] United States[12] and Sweden,[13] with others in preparation. Standard mother comparisons have demonstrated remarkable similarities in growth potential between different countries.[8,12]

Lack of adjustment for individual variation affects the number of babies considered SGA. For example, in a population with an SE of 382.6 g, a 200-g shift would mean that about two-thirds of the babies previously considered SGA are not SGA, and vice versa (Fig. 2).

Cut-off limits

Limits to define 'SGA' or 'IUGR' are used arbitrarily, usually as 10th, 5th or 3rd centile, or –2SD. In light of the mix of physiological and pathological smallness in traditional definitions, the reasoning often is that the smaller the cut-off, the more likely that those below the limit are truly 'IUGR'. The problem with this reasoning is that it excludes a lot of other babies which are also pathologically small.

The definition depends to some extent on the purpose for which it is intended. For example, for postnatal assessment, the likelihood of a baby having been affected and experiencing subsequent complications is indeed related to the severity of its growth deficit, and it is more likely that neonatologist would prefer a 5th or 3rd centile limit. For prospective management, however, the bar needs to be set higher, as:

1. 'mildly' growth-restricted fetuses, for example between the 3rd and the 10th *birthweight* centile, are also at increased risk[14];
2. antenatal estimation of fetal weight is less reliable than measuring birthweight with scales; EFW can err in either direction, crucially also towards over-estimation, which suggests the need of an additional safety zone;
3. the judgement that the pregnancy is safe to continue has to 'last' until the next assessment.