Fetal growth and risk assessment: is there an impasse? POINT

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Fetal growth and risk assessment: is there an impasse?

The Issue

Fetal growth restriction is an indicator of placental insufficiency and is strongly associated with adverse perinatal outcome. There is a **point** that the recent dominance in the medical literature about which reference charts to use and dichotomization of fetal size at the 10th percentile overlooks the fact there is not a single cut-off in any growth chart that acts as an absolute divider between high and low risk for adverse outcome. Thus, the collective goal of all researchers to identify, monitor and effectively manage growth-restricted fetuses is better served by replacing dichotomisation of normal versus abnormal fetal growth at the 10th percentile by interpretation of fetal size in context with other known parameters of fetal risk - all as continuous parameters. The use of prospective comprehensive datasets should facilitate better risk assessment for the individual fetus, to help direct effective and appropriate interventions. The **counter argument** is that the debate about which growth standard to use was necessary and has been settled through evidence that size, and therefore growth, need customized limits to allow adjustment for constitutional variation, and to help distinguish between normal and abnormal growth. Implementation of a more precise standard has led to better detection of fetuses that are at risk due to growth restriction, improved application of additional investigations, enhanced clinical confidence in management including timely delivery, and ultimately increased prevention of adverse outcomes.

Key words: small for gestational age, SGA, fetal growth restriction, FGR, descriptive population references, customized standard, customised charts, prescriptive growth standards

POINT

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INTRODUCTION

In the February 2018 issue of the AJOG, important papers were published summarising some of the major issues in Fetal Growth Restriction (FGR).(1) Although all researchers undoubtedly share the same overall goal - to improve prevention, detection and outcomes of FGR, we think the issue of which reference chart should be used is predominant. We argue that this impasse distracts from the actual issue and wastes both clinical and academic resources. In this paper we highlight how the focus on fetal size as a proxy for fetal growth and adequate placental nutrition has been oversimplified as 'above' or 'below' the 10th percentile to distinguish between apparently normal and abnormal fetal growth. This dichotomization results in erroneous under diagnosis of growth-restricted fetuses among those that are apparently normally grown with the risk of adverse outcomes due to lack of medical attention. Conversely, among constitutionally small fetuses it leads to over diagnosis of FGR and risk from unnecessary obstetric intervention. FGR can result from any pathology affecting placental function and is associated with significant adverse short and long-term outcomes.(2-4) Accordingly, adequate detection and risk stratification is of paramount importance to guide perinatal care. With over 10,000 citations on "prenatal diagnosis" or "definition" of FGR in current medical literature we have achieved little progress beyond the initial landmark observation that fetal size is apparently optimally expressed by ascribing a percentile to its estimate.(5) This paper argues that we should progress beyond fetal size assessment alone and undertake a more comprehensive risk assessment using contemporary techniques.

WHICH FETAL GROWTH CHART?

Population-based reference charts

Population-based fetal size charts are created from retrospective datasets and by nature are descriptive – show how the fetuses in the observed population have grown. These references are skewed at the extremes of gestation where pathological conditions such as preeclampsia and preterm birth are concentrated, because these abnormal pregnancies are usually not excluded in their development.(5, 6) This still holds true for more recent descriptive reference charts.(7)

Customised fetal growth assessment

To overcome some of the methodological drawbacks of population-based growth charts, Gardosi *et al.* constructed growth charts that attempt to mathematically predict normal variation in growth at term.(8) This group introduced the idea of customisation: correcting for maternal characteristics that individualize the expected growth potential of the foetus.(9) Many variables have been used for correction such as fetal gender, maternal height, weight, ethnicity and parity. At first glance, ethnicity seems an intuitive variable for customisation, but ethnicity is often associated with poorer

socio-economic status which may be the determinant for adverse perinatal outcomes.(10)

Definition and self-reported categorisation of race is difficult, particularly in a multi-ethnic and continuously mingling society.(11) Additionally, it is unknown how much can change in transition from a generation of severe deprivation to a well-nourished and healthy generation. We suggest that individual variables should be comprehensively assessed for their individual putative merits and their well-known existing relationship with adverse outcomes. In the available datasets of second and third generation of migrants, we can test how many generations are required for adverse effects to subside. Similar interactions may be observed for maternal weight and parity, but fetal gender and maternal height may have a stronger argument to be used in customisation.(7) Even though there may be an academic discussion about the concept of customisation, the initiative to use back-calculated growth charts from a healthy term cohort, and serially plot growth assessments in a systematic manner have significantly improved awareness about growth and identification of fetuses at risk.(9, 12, 13)

Prescriptive growth standards

To a certain extent, healthy populations across the world are expected to have similar fetal growth, because only one species of humans exists without large phylogenetic differences.(14) Recent initiatives have prospectively followed healthy uncomplicated pregnancies with sequential ultrasound to develop prescriptive growth standards, defining how a healthy foetus grows.(15-19) In the Intergrowth-21 study performed in eight different countries, measurement variation between countries was significantly smaller than within-population variation.(16, 20) This uniformity suggests that prescriptive growth charts are the gold reference standard. However, there is persistent significant variation in fetal growth within each population when environmental constraints are not adequately controlled for. Apparently, these factors have a significant adverse influence on fetal growth and not all fetuses grow the same.(18, 19)

The way forward

Obviously, these approaches are conceptually different, and protagonists of either approach are in fundamental disagreement. Much effort is put into comparing how either approach performs retrospectively in large datasets.(21) These analyses have inherent methodological flaws. We postulate that if the strength of each approach is openly and academically appreciated we may come to a combined approach using prescriptive charts that use clinically validated using effective customisation. We propose a combined approach merging datasets on an individual level to test if variables included in customisation or the concept of conditional centiles may be used to determine optimal growth for the individual.(22) Next, the relationship between these variables nd adverse outcomes can and must be explored - although this will remain problematic in retrospective

datasets because of treatment paradox. Currently, many retrospective studies compare different strategies in their diagnostic capacity to identify small infants at birth or those with adverse outcomes. These comparisons are methodologically flawed because they analyse retrospectively if these strategies accurately predict birth weight category or adverse outcomes, whilst ignoring the effects of treatment paradox. Moreover, these comparisons also overlook the issue of the balance of detection rates and false-positive rates - prospective and randomised trials are lacking.(23) We propose that the combination of the two approaches will help achieve the penultimate goal to define normal individual fetal growth patterns. But we should not stop there...

WHAT WE ARE MISSING

How relevant is fetal size?

Size is a consequence of preceding fetal growth - reflecting fetal nutrition. Current practice dichotomises normal and abnormal fetal growth at the 10th percentile. But we need to move beyond 'good' or 'bad' fetal size. As for most continuous measures in human physiology, this is an oversimplification with significant sources of error. Firstly, most fetuses identified as small for gestational age (SGA) are constitutionally small and healthy. Secondly, many fetuses who have impaired growth and placental dysfunction are of apparent normal weight (schematically depicted in Figure 1).(24) Thirdly, fetal size only reflects nutrient transfer function of the placenta and points to the magnitude of placental dysfunction only by association.(25) Stillbirth risk decreases with higher birth weight percentiles, and the majority of fetuses born below the 3rd centile is known to have been exposed to significant intrauterine hypoxemia. However, there is no percentile above which this risk is excluded (Figure 2).(24) This is further complicated by the poor performance of ultrasound-based fetal growth assessment that detects only up to 50% of babies born weighing less than the 10th centile.(26) For the above reasons, fetal size would be better utilised as a continuous variable in risk calculation.

Clinical outcomes of relevance

The objective of obstetric care is not to diagnose fetal malnutrition, but to prevent the negative effects of placental dysfunction including fetal hypoxemia, brain damage and stillbirth. In postnatal life, protracted nutritional deprivation results in Kwashiorkor or Marasmus many weeks or months before infant demise. In contrast, an infant only survives a very short period with respiratory failure. The placenta is uniquely responsible for many critical body functions – namely nutrition and respiration. To date, clinicians have used fetal size/nutrition as a proxy for placental respiratory failure and risk of stillbirth, in order to avert this risk by timely delivery.(27) Many studies evaluate diagnostic tools or interventions by their ability to identify or prevent small babies. The outcomes

of relevance however, should be the variables that indicate fetal hypoxemia, such as stillbirth, the inability to withstand uterine contractions, and long-term neurodevelopmental outcomes.

A comprehensive approach

Focusing on fetal size parameters in isolation to detect compromise is a grossly oversimplified diagnostic approach and as such flawed.(28) Placental function is reflected across a number of variables associated with adverse outcomes that can be prenatally examined.(25) These include Doppler ultrasound of the fetal umbilical, middle cerebral and maternal uterine arteries, serum biomarkers and growth trajectory.{Gaccioli}{sovio} A recent international expert consensus recognised that parameters that indicate placental respiratory function should be included in the assessment.(29, 30) Currently, these risk factors are used in a categorical fashion, where they have a dose-dependent relationship with poor fetal growth and stillbirth. Risk factors and assessment variables are interdependent – a fact that is often disregarded in risk assessment tools recommended by national institutions. Finally, stillbirth is a time-dependent outcome rather than an overt disease – as such, it is extremely susceptible to the competing risk and intervention bias of elective delivery.

It is now possible to use contemporary software tools to generate competing algorithms to undertake comprehensive risk assessment. We propose the development of a predictive approach that takes into account relevant variables in a continuous, non-dichotomous manner. Large datasets with longitudinal prospective data are currently generated from on-going clinical intervention trials. We need aggregate individual data from these datasets to allow prediction modelling followed by internal and external validation. Within these algorithms, institutions will be able to choose either type of growth chart (prescriptive or customised) depending on local, regional or national interpretation. Once individual risk assessment is available, the rational next step is to feed intervention trials.

CONCLUSION

Currently, one issue dominates much of the debate amongst valued individual researchers - which growth chart to use to assess normal or abnormal fetal size? We argue that we need to abandon that gridlock because it obscures the bigger and more clinically relevant picture. The current standstill effectively prohibits progress towards the sketched horizon with a comprehensive risk assessment that will benefit the prenatal care for patients.

FIGURE LEGEND

Figure 1. Schematic depiction of the overlap and difference between FGR and SGA.
FGR = Fetal Growth Restriction; SGA = Small for Gestational Age; AGA = Appropriate for Gestational Age; LGA = Large for Gestational Age;
x-axis represents growth percentile, y-axis represents percentage of the population; red area represents fetuses with FGR;

Figure 2. Examples of linear relationship between birth weight percentile and clinical outcomes.
A. Percentage of 11.576 term fetuses with failure to reach growth potential (FRGP) according to their birth weight (BW) centile group (i.e. percentage of fetuses presenting an abnormal cerebroplacental ratio (CPR) calculated after subtracting those cases with abnormal CPR in the group with BW > 90th centile).(31)
B. Perinatal mortality according to birth weight centiles in Dutch Perinatal Registry in all (n=1.170.534) cases 28-43 weeks excluding congenital anomalies.(24)
C. Absolute risk per 10,000 pregnancies of term stillbirth by birth weight percentile among 784,576 singleton births in Scottish registries.(32)

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