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Opinion

Temporal variation in definition of fetal growth restriction in the literature

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Fetal growth restriction (FGR) is a major obstetric problem contributing significantly to perinatal morbidity and mortality[1,2]. The adverse intrauterine environment associated with FGR also has an impact on long-term health outcomes, such as neurological and cognitive impairment, and cardiovascular and endocrine diseases[3]. Although its impact is acknowledged universally, FGR is defined poorly. In many studies, the term FGR is used for fetuses that are in fact small-for-gestational age (SGA). Birth weight, estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile is often used as a cut-off to define FGR[4,5]. However, SGA and FGR are principally different. SGA is the statistical deviation of fetal size from a reference, and may describe a healthy fetus at the lower end of the normal growth range. FGR is a pathological condition in which the fetus does not reach its intrinsic growth potential.

Fetal size at a certain gestational age can reflect past growth, but it does not provide any information about fetal growth velocity and placental function over time. As fetal growth is a dynamic process, it can be evaluated adequately only through sequential measurements. Detection of growth restriction by observation of reduced or declining growth velocity is difficult because it may take weeks before it is apparent on ultrasound measurements. Another way to gain insight into placental function is by evaluating functional parameters, such as Doppler measurements and placental biomarkers. The combination of Doppler measurements and fetal biometry has higher sensitivity in detecting FGR than do biometric measurements alone[6–10]. Moreover, serum markers for placental function have been identified to be associated with placental pathology[11–14]. Based on these new insights, contemporary research is focused increasingly on the combination of functional parameters and biometric measurements to identify fetuses at risk for growth restriction and define FGR.

We aimed to describe different definitions of FGR used in the literature and how these changed over the past two decades, between 1994 and 2014, before a consensus-based definition for early and late FGR was established through a Delphi procedure[15].

We reviewed the definition of FGR used in all studies with focus on FGR published in the years 1994, 2004 and 2014. Animal studies, reviews, editorials, case reports and unpublished studies were excluded. We also excluded studies that focused on neonatal growth or SGA when the term was not used synonymously with FGR. Only records available in English were included. The literature search yielded 118 records published in 1994, 191 records in 2004 and 307 records in 2014. After screening the title, abstract and (if necessary) the full text, 56, 75 and 115 records published in 1994, 2004 and 2014, respectively, met the inclusion criteria (Appendix S1). In total, 28 (11%) records were excluded because no definition for FGR was reported, even though the articles were dedicated specifically to FGR.

A total of 31, 33 and 44 different definitions of FGR were identified in articles published in 1994, 2004 and 2014, respectively (Tables S1–S3). The majority of the studies published in any of the 3 years used birth weight $< 10^{th}$ percentile to define FGR, indicating that growth restriction was identified only after birth (Figure 1). Diagnosis of FGR postpartum precludes the opportunity to reduce the effects of this pathological condition by frequent fetal monitoring and/or planned timing of delivery. The proportion of studies that used FGR definitions based on antenatal parameters increased with time. The definition of FGR was based on antepartum findings alone in 47% of studies published in 2014, *vs* in 34% and 30% of studies published in 1994 and 2004, respectively (Figure 1). This reflects the improved ability to determine accurately fetal size using ultrasound and the increased availability of other ultrasound parameters that assess reduced fetal growth.

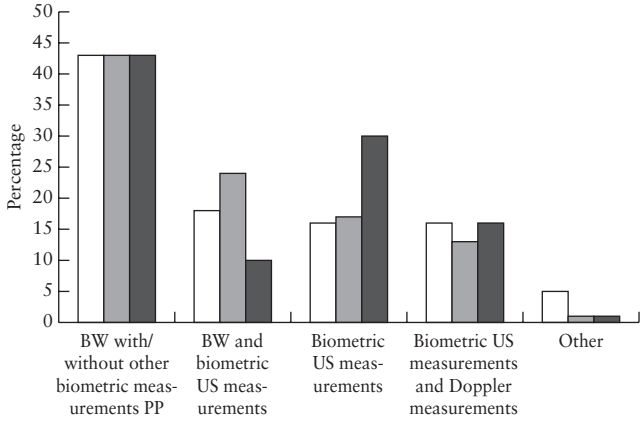

Figure 1 Variation in definition of fetal growth restriction used in studies published in 1994 (□), 2004 (▩) and 2014 (■). BW, birth weight; PP, postpartum; US, ultrasound.

In addition to the variability in the definition of FGR, different reference growth charts were also used between the studies to define FGR. In all three publication years, the most commonly used charts were local population-based growth charts (30%, 39% and 43% of studies published in 1994, 2004 and 2014, respectively), defined as hospital-, country- or area-based. Approximately a quarter of all included studies did not describe which reference chart they used. In all definitions of FGR, abnormal growth was based on cut-offs beyond a certain percentile of the reference growth charts. However, since different growth charts are based on different reference populations, a fetus of a certain size might be considered growth-restricted on one chart but normal on another.

The findings of our review point out the major heterogeneity and weaknesses in definitions of FGR used over the past two decades. The lack of a uniform definition of one of the major and most common obstetric problems hampers adequate interpretation from a clinical perspective as well as data synthesis from a research perspective.

The terms FGR and SGA are frequently used interchangeably, despite the fact that they are not synonymous and reflect different patient populations with different perinatal risks. Using the definition of SGA to define FGR, up to 72% of fetuses would have normal perinatal outcome[16]. This reflects the lack of a gold standard for the definition of FGR, which poses a difficulty in pinpointing an exact definition for this condition. For this reason, researchers resort to a definition that is exact yet faulty. In the absence of a gold standard, SGA may be a sensible surrogate population to study, as almost half of SGA fetuses are thought to be growth-restricted. The lower the cut-off for size the higher is the risk for FGR and adverse outcome[17]. However, it should be taken into account that study results and effects are diluted by healthy fetuses[18]. This hampers correlation studies for etiologic factors and intervention studies of FGR.

A Delphi procedure was conducted in 2015 among recognized FGR experts and consensus was reached, based on contemporary knowledge, on definitions for early and late FGR due to placental insufficiency[15]. These included not only size parameters but also functional parameters that reflect placental function. Although less than exact, these definitions probably narrow down more accurately the patient group of interest. If new and stronger markers for FGR become available, it may become opportune to repeat such a procedure in due time to decide if the evidence is strong enough to add the variable to the definition.

The present literature analysis highlights the importance of a uniform definition of FGR in order to allow comparison of different study cohorts and implementation of findings in clinical practice. Henri Ford was exemplary in thinking of the benefits of standardization as the best that we know today but which is to be improved tomorrow[19]. We propose that researchers adopt the contemporary definition of FGR established by the Delphi consensus[15].

REFERENCES

1. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico A, Visser GH, Wolf H; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013; **42**: 400–408.
2. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. *BMJ* 2013; **346**: f108.
3. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. *BMJ* 2014; **348**: g14.
4. Lausman A, Kingdom J, Maternal Fetal Medicine Committee. Intrauterine growth restriction: screening, diagnosis, and management. *J Obstet Gynaecol Can* 2013; **35**: 741–748.
5. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol* 2013; **121**: 1122–1133.
6. Flood K, Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study. *Am J Obstet Gynecol* 2014; **211**: 288.e1–5.
7. Cruz-Martinez R, Savchev S, Cruz-Lemini M, Mendez A, Gratacos E, Figueras F. Clinical utility of third-trimester uterine artery Doppler in the prediction of brain hemodynamic deterioration and adverse perinatal outcome in small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 2015; **45**: 273–278.
8. Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2015; **213**: 54.e1–10.
9. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385**: 2162–2172.
10. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015; **386**: 2089–2097.
11. Schwartz N, Sammel MD, Leite R, Parry S. First-trimester placental ultrasound and maternal serum markers as predictors of small-for-gestational-age infants. *Am J Obstet Gynecol* 2014; **211**: 253.e1–8.
12. Benton SJ, Hu Y, Xie F, Kupfer K, Lee SW, Magee LA, von Dadelszen P. Can placental growth factor in maternal circulation identify fetuses with placental intrauterine growth restriction? *Am J Obstet Gynecol* 2012; **206**: 163.e1–7.
13. Odibo AO, Patel KR, Spitalnik A, Odibo L, Huettner P. Placental pathology, first-trimester biomarkers and adverse pregnancy outcomes. *J Perinatol* 2014; **34**: 186–191.
14. Gaccioli F, Aye I, Sovio U, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. *Am J Obstet Gynecol* 2018; **218**: S725–S37.
15. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48**: 333–339.
16. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. *Am J Obstet Gynecol* 2013; **208**: 290.e1–6.
17. Vasak B, Koenen SV, Koster MP, Hukkelhoven CW, Franx A, Hanson MA, Visser GH. Human fetal growth is constrained below optimal for perinatal survival. *Ultrasound Obstet Gynecol* 2015; **45**: 162–167.
18. Griffin M, Seed PT, Webster L, Myers J, MacKillop L, Simpson N, Anumba D, Khalil A, Denbow M, Sau A, Hinshaw K, von Dadelszen P, Benton S, Girling J, Redman CW, Chappell LC, Shennan AH. Diagnostic accuracy of placental growth factor and ultrasound parameters to predict the small-for-gestational-age infant in women presenting with reduced symphysis-fundus height. *Ultrasound Obstet Gynecol* 2015; **46**: 182–190.
19. Ford H, Samuel Crowther. *Today and Tomorrow*. Doubleday, Page & Co: New York, 1926.

SUPPORTING INFORMATION ON THE INTERNET

Appendix S1 and **Tables S1–S3** may be found in the online version of this article.