Toward safe standards for assessment of fetal growth in twin pregnancy

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Twin pregnancies have many increased risks of adverse outcome for mothers and babies. Fetal growth restriction is a major and frequent complication, in dichorionic as well as monochorionic pregnancies, and appropriate monitoring of growth is a particular challenge.

Serial fundal height measurement, the primary method of surveillance in many health systems, is inappropriate in multiple pregnancies because one cannot make inferences from the size of the uterus to the size and growth of each baby. Ultrasound biometry can also be difficult, especially for the fetus that is free and high in the uterus. The usually adopted clinical protocol is to monitor fetal parameters and estimated weight serially—to assess whether the growth of each twin is adequate, and to look out for discordant growth.

Such close surveillance requires an appropriate growth standard, which will help determine the best compromise between the ability to recognize and act on insufficient growth while providing reassurance and avoiding unnecessary intervention when growth is satisfactory. Two main influences are at play: each fetus's genetic potential, and the maternal and placental factors that affect, mostly restrain, intrauterine growth.

Ghi et al[1] present a study on fetal growth in twins based on data from their Italian network. Their report makes 2 main points: (1) the growth standard benefits from being customized according to physiological pregnancy characteristics and (2) it is lower overall for mono- as well as dichorionic twins compared with singleton pregnancies. Each of these findings warrant consideration.

Physiological variation in growth

Most of the work on the effect of customization has been done on singleton pregnancies and confirmed that maternal height, maternal weight in early pregnancy, parity, and ethnic origin as well as fetal sex have significant physiological effects on birthweight[2-5] as well as fetal biometry[6-8] and has recently also included the Italian group's own customized singleton growth standard.[9] The ability of the model to predict normal birthweight increases stepwise with each added physiological variable.[10] The standard is further optimized by including only pregnancies that have reached term, and excluding pathological factors such as smoking, hypertension, or diabetes in the multivariable analysis.[2]

In determining the genetic potential of twins, the authors confirm most of the maternal and pregnancy-related factors that affect fetal growth in singleton pregnancies. Maternal weight did not show a significant association in the analysis of twin growth, which is consistent with a previous study from the United States that based their analysis on birthweight data.[11] This finding is not unexpected because maternal weight is affected by a pregnancy with 2 fetuses, while the effect on each twin's growth is being measured. The Italian study[1] was underpowered for ethnicity because of the low percentage of mothers from different ethnic origins, but the aforementioned American study[11] confirmed that it was also a significant factor of influence in American blacks.

A different approach has been advocated by the Intergrowth project,[12,13] which put forward a prescriptive model with measurements derived from low-risk populations in 8 countries, proposing a single standard to be used globally, which would better identify pregnancies with suboptimal growth due to pathological factors including malnutrition. However, even within their selected low risk, well-nourished maternity population, between-country differences in term birthweight were substantial and amounted up to 600 g at term,[12] without accounting for the composite causes of such variation. Reports have started to appear suggesting that the Intergrowth standard is not appropriate when applied to maternity populations in New Zealand,[14] Hong Kong,[15] or the United Kingdom.[16]

More recently, the World Health Organization (WHO) Fetal Growth project,[17] using a similar, WHO-originated methodology and also focussing on low-risk pregnancies, reported significant variation between different countries, thereby contradicting Intergrowth's one-size-fits-all approach.

These findings are consistent with a previous report by Mikolajczyk et al[18] using WHO survey birthweight data from 24 countries in Africa, Asia and Latin America, which found that small for gestational age (SGA) defined according to country-specific average weights were better predictors of perinatal outcome than a single universal standard.

Individual adjustment added little in this study at country level but the advantages of customized assessment are best demonstrated when the analysis is within subgroups of the population—eg, within different maternal size or parity categories.[19] Using the same Hadlock derived fetal weight curve with and without adjustment for maternal variables showed

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significant improvements in the association between SGA and perinatal mortality when SGA was based on a customized definition. The uncustomized standard tended to overdiagnose SGA in small mothers and underdiagnose it in large mothers, thereby reducing the association between SGA and perinatal mortality risk.[19]

Similar evidence of advantages of customized fetal measurements in twin pregnancies is still lacking, although Odibo et al[11] did find that their customized birthweight standard for twins is more significantly correlated with perinatal deaths.

Slower growth in twins

Ghi et al[1] present reference values that are lower than those for singletons, suggesting that twin growth slows in the third trimester. This is in agreement with other fetal measurement studies[20,21] as well as a birthweight-based report showing lower optimal weights for twins than singletons at their respective lowest points for neonatal mortality and morbidity.[22]

The fetal biometry studies show a divergence of the twin curve compared with that of singletons, which tends to be observed as a flattening of the growth trajectory from 30 to 32 weeks for different ultrasound parameters. The question arises whether this difference is a physiological adaptation or a pathological consequence of multiple pregnancies, manifesting by late-onset fetal growth restriction as also evidenced in singleton pregnancies[10] but more likely to occur in multifetal pregnancies because of environmental constrains. Unlike early-onset growth restriction, late onset is characterized by relative placental insufficiency, is more insidious, and is often not detected antenatally. Growth restriction is also not easily recognized postnatally because we have no gold standard to assess whether a fetus's growth potential has been reached or whether a relative growth deficit has occurred.

Ghi et al[1] sought to study a cohort with good placental function after excluding all pregnancies below the fifth centile of their national population standard for singletons. While this may have excluded many or most SGA fetuses, in many instances growth may have been *relatively* reduced (eg, from a potential 70th to the 30th centile) without falling below any set centile limit. If such "slow growing but normal size" cases are common and not excluded from the cohort, the overall values would be shifted downward, thereby normalizing a pathological effect. The result would be a reference curve describing the population as is, including potentially frequent instances of pathological growth, rather than an optimal standard with which to identify fetuses at risk.

Further evidence to support the possible preponderance of growth restriction in twin pregnancy is the shorter average length of gestation (37 weeks), not only because of iatrogenic intervention but also by births following spontaneous onset of labor.[23] This is consistent with the notion that fetal growth restriction can be causal in determining gestational age at delivery,[24] and with the conclusion of a recent systematic review that in uncomplicated dichorionic twin pregnancies, the lowest risk of perinatal deaths is for deliveries at 37 weeks.[25]

Monochorionic twins have even smaller biometry values and earlier flattening of the curve than dichorionic twins.[1,26,27] They also have an earlier point of lowest perinatal mortality: 36 weeks.[25] The model of late-onset fetal growth restriction again applies, with potentially increased severity, with the single placenta even more challenged to keep up with the growth of both fetuses. Twin-twin discordance is also more prevalent and, even when not clinically apparent, may contribute to the downward trend of the average curve, especially when both twins are used to derive the standard, as was the case here.[1]

Validation

It is advisable therefore to tread with caution when considering adopting new charts for twin pregnancies. The principle of adjusting for maternal and pregnancy characteristics has now been established in singletons[20,27-30] as well as twins.[11] But whether third-trimester growth tailing off can be considered normal or instead represents frequent pathological occurrence with mostly normal outcome is a question yet to be answered.

The authors acknowledge the need for prospective studies before implementation,[1] and these will need to include neonatal outcomes to better define the balance between intrauterine risk and iatrogenic prematurity. While an argument can be made against a standard that categorizes most twin pregnancies as growth restricted, the onus of proof ought to be on ensuring that lowering of the standard does not adversely affect the ability to recognize pregnancies that are at risk because of placental insufficiency. ■

REFERENCES

1. Ghi T, Prefumo F, Fichera A, et al. Development of customized fetal growth charts in twins. Am J Obstet Gynecol 2017;216:514.e1-17.
2. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol 1995;6:168-74.
3. Gardosi J, Francis A. A customized standard to assess fetal growth in a US population. Am J Obstet Gynecol 2009;201:25.e1-7.
4. Anderson N, Sadler L, Stewart A, McCowan L. Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study: maternal characteristics in customised birthweight centiles. BJOG Int J Obstet Gynaecol 2012;119:848-56.
5. Larkin JC, Speer PD, Simhan HN. A customized standard of large size for gestational age to predict intrapartum morbidity. Am J Obstet Gynecol 2011;204:499.e1-10.
6. De Jong CLD, Francis A, Van Geijn HP, Gardosi J. Customized fetal weight limits for antenatal detection of fetal growth restriction. Ultrasound Obstet Gynecol 2000;15:36-40.
7. Mongelli M, Gardosi J. Reduction of false-positive diagnosis of fetal growth restriction by application of customized fetal growth standards. Obstet Gynecol 1996;88:844-8.
8. Gaillard R, de Ridder MAJ, Verburg BO, et al. Individually customised fetal weight charts derived from ultrasound measurements: the Generation R Study. Eur J Epidemiol 2011;26:919-26.
9. Ghi T, Cariello L, Rizzo L, et al. Customized fetal growth charts for parents characteristics, race, and parity by quantile regression analysis: a cross-sectional multicenter Italian study. J Ultrasound Med 2016;35:83-92.
10. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol 2011;204:288-300.

11. Odibo AO, Cahill AG, Goetzinger KR, Harper LM, Tuuli MG, Macones GA. Customized growth charts for twin gestations to optimize identification of small-for-gestational age fetuses at risk of intrauterine fetal death: customized growth charts in twin pregnancies. Ultrasound Obstet Gynecol 2013;41:637-42.

12. Villar J, Papageorghiou AT, Pang R, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. Lancet Diabetes Endocrinol 2014;2:781-92.

13. Stirnemann J, Villar J, Salomon LJ, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol 2016. Available at: http://onlinelibrary.wiley.com/doi/10.1002/uog.17347/full. Accessed March 19, 2017.

14. Anderson NH, Sadler LC, McKinlay CJD, McCowan LME. INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity. Am J Obstet Gynecol 2016;214:509.e1-7.

15. Cheng Y, Leung T, Lao T, Chan Y, Sahota D. Impact of replacing Chinese ethnicity-specific fetal biometry charts with the INTERGROWTH-21st standard. BJOG Int J Obstet Gynaecol 2016;123:48-55.

16. Poon LCY, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birthweight in live births and stillbirths. Ultrasound Obstet Gynecol [Internet]. 2016 (cited Nov. 1, 2016]. Available at: http://doi.wiley.com/10.1002/uog.17287. Accessed March 19, 2017.

17. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. Myers JE, ed. PLOS Med 2017;14:e1002220.

18. Mikolajczyk RT, Zhang J, Betran AP, et al. A global reference for fetal-weight and birthweight percentiles. Lancet 2011;377:1855-61.

19. Gardosi J, Clausson B, Francis A. The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size: value of customising centiles for parity and maternal size. BJOG Int J Obstet Gynaecol 2009;116:1356-63.

20. Grantz KL, Grewal J, Albert PS, et al. Dichorionic twin trajectories: the NICHD Fetal Growth Studies. Am J Obstet Gynecol 2016;215:221.e1-16.

21. Shivkumar S, Himes KP, Hutcheon JA, Platt RW. An ultrasound-based fetal weight reference for twins. Am J Obstet Gynecol 2015;213:224.e1-9.

22. Joseph KS, Fahey J, Platt RW, et al. An outcome-based approach for the creation of fetal growth standards: do singletons and twins need separate standards? Am J Epidemiol 2008;169:616-24.

23. Mahomoud S, Francis A, Gardosi J. Timing of elective caesarean section for twin pregnancy. J Obstet Gynaecol 2004;3:S48-9. Available at: http://perinatal.org.uk/pdfs/Timing_of_CS_in_twins.pdf. Accessed March 19, 2017.

24. Gardosi JO. Prematurity and fetal growth restriction. Early Hum Dev 2005;81:43-9.

25. Cheong-See F, Schuit E, Arroyo-Manzano D, et al. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. BMJ 2016:i4353.

26. Stirrup OT, Khalil A, D'Antonio F, Thilaganathan B. on behalf of the Southwest Thames Obstetric Research Collaborative (STORK). Fetal growth reference ranges in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. Ultrasound Obstet Gynecol 2015;45:301-7.

27. Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. Am J Obstet Gynecol 2009;201:28.e1-8.

28. Figueras F, Figueras J, Meler E, et al. Customised birthweight standards accurately predict perinatal morbidity. Arch Dis Child Fetal Neonatal Ed 2007;92:F277-80.

29. Odibo AO, Francis A, Cahill AG, Macones GA, Crane JP, Gardosi J. Association between pregnancy complications and small-for-gestational-age birth weight defined by customized fetal growth standard versus a population-based standard. J Matern Fetal Neonatal Med 2011;24:411-7.

30. Kase BA, Carreno CA, Blackwell SC. Customized estimated fetal weight: a novel antenatal tool to diagnose abnormal fetal growth. Am J Obstet Gynecol 2012;207:218.e1-5.