Published in final edited form as:

Lancet. 2015 November 21; 386(10008): 2038–2040. doi:10.1016/S0140-6736(15)00148-8.

Should serial fetal biometry be used in all pregnancies?

Roberto Romero, MD, D.Med.Sci.[1,2,3,4,*] and **Russell Deter, MD**[5]

[1]Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, and Detroit, MI, USA

[2]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA

[3]Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA

[4]Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

[5]Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA

Comment

Serial measurements of an infant's height, weight, and head circumference to monitor growth have been a cornerstone of routine pediatric care. This practice is based on the premise that detection of growth disorders, such as failure to thrive, can be manifestations of malnutrition, metabolic and genetic disorders, or infection and can be treated.[1] The frequency with which infant growth is monitored is associated with growth velocity. A general principle in developmental biology is that organisms are most susceptible to insults during periods of rapid growth.[2,3] Therefore, it is somewhat paradoxical that even though the human growth rate is particularly rapid during fetal life, monitoring such growth in women with low-risk pregnancies is not part of standard obstetrical care. This situation persists despite overwhelming evidence that fetal growth disorders are risk factors for adverse perinatal outcome and can predispose these infants to adult chronic diseases.[4] Routine assessment of fetal growth in women with low-risk pregnancies is not done because of a lack of compelling evidence that serial fetal biometry improves detection of smallness at birth and reduces infant morbidity.[5] A groundbreaking study by Ulla Sovio and colleagues,[6] published in The Lancet, now shows that serial assessment of fetal biometry in all pregnancies improves the detection of small-for-gestational-age (SGA) neonates and identifies a subset at risk for morbidity.

Sovio and colleagues6 report results of a prospective cohort study of unselected nulliparous women with a singleton viable gestation who underwent a dating ultrasound examination (typically at 10–14 weeks' gestation). Women who agreed to participate in the study were scheduled to undergo serial ultrasound examinations at roughly 20, 28, and 36 weeks of gestational age. About half of the patients (1666 [42%] of 3977 women) also underwent clinically indicated third trimester scans, in accordance with the UK's National Institute of

[*]**Correspondence:** prbchiefstaff@med.wayne.edu (RR).

Disclosure: We declare no competing interests.

Health and Care Excellence guidelines for low-risk[7] and high-risk pregnancies (eg, mothers who have diabetes, hypertension, or low symphyseal-fundal height).[8] Detection of SGA in the cohort was initially analysed on the basis of the results of selective or clinically indicated sonography. The analysis was then repeated with the results from universal or research sonography, and the diagnostic effectiveness of both approaches to detect SGA at birth were compared.

The results of fetal biometry and the anatomical survey to detect congenital anomalies at the time of the 20 weeks examination were reported for the entire cohort. However, the results of the 28 weeks and 36 weeks research ultrasound examinations were concealed from both clinicians and patients. This masking allowed for observation of the natural outcome of pregnancy in a subset of fetuses who had growth restriction or were small at birth and in whom no intervention was implemented, because these conditions had not been detected by a clinically indicated ultrasound. Ethical justification for concealing results derived from research ultrasounds was that third trimester sonography has not been shown to improve pregnancy outcome,[5] and is not recommended by professional societies. Yet women could still benefit from participating in this study[6] because incidental findings of importance noted during research sonographic examinations were conveyed to both patients and their clinicians (ie, congenital anomalies, placenta praevia, oligohydramnios, or non-cephalic presentation at 36 weeks' gestational age).

The key results from Sovio and colleagues' study[6] were, first, that universal sonography in the third trimester almost tripled the detection of SGA compared with clinically-indicated sonography (from 69 [20%] of 352, to 199 [57%] of 352). Second, among SGA neonates, those with an estimated weight of less than the 10th percentile and a fetal abdominal circumference growth velocity at the lowest decile or less (ie, abnormal) were at increased risk for neonatal morbidity (relative risk 3·9, 95% CI 1·9–8·1), whereas those with an estimated fetal weight less than the 10th percentile and abdominal circumference growth velocity above the lowest decile were not. Importantly, about 70% of fetuses diagnosed as SGA did not have abnormal abdominal circumference growth velocity. Third, abnormal umbilical artery or uterine artery Doppler velocimetry were not associated with an increased risk of neonatal morbidity.

However, the improved sensitivity in detection of SGA neonates achieved by universal sonography came at a cost, because for every additional SGA newborn detected, about two false positive diagnoses were made.[6] Therefore, whether universal sonography for fetal growth assessment should be implemented in clinical practice needs consideration of risks and benefits. Immediate challenges to address are, amongst others, to improve the accuracy of the sonographic diagnosis of SGA, to identify a small fetus at risk for morbidity, and to determine the interventions that could improve neonatal outcome.

The biometric parameters that Sovio and colleagues[6] assessed were head circumference, abdominal circumference, femur length, and estimated fetal weight, with the diagnosis of SGA being based only on estimated fetal weight. Errors inherent in sonographic estimations of fetal weight are well known. The value of other sonographic parameters that are representative of fetal soft tissue characteristics in improving the diagnostic accuracy of

SGA, and of novel statistical approaches that allow for personalised assessments of third trimester fetal growth[9] (ie, individualised fetal growth assessment) need to be explored. Although Doppler velocimetry of the uterine and umbilical arteries did not improve diagnostic effectiveness in Sovio and colleagues' study,[6] other Doppler parameters might be useful. An emerging body of evidence suggests that assessment of the middle cerebral artery and the cerebroplacental ratio[10] could help to identify a fetus at risk for neonatal complications, particularly near term when most diagnoses of SGA are made. Moreover, biomarkers in maternal blood and urine could assist in further enhancing the identification of an SGA fetus at risk. Indeed, maternal plasma concentrations of angiogenic and anti-angiogenic factors in preterm gestations with SGA fetuses are able to identify mothers at increased risk for pre-eclampsia, or those needing an indicated preterm delivery.[11] Such biomarkers seem to be of value to identify patients at risk of fetal death at or near term,[12] and might be helpful in pregnancies with an SGA fetus in which the risk for fetal death is increased.

We envision that a combination of fetal biometry, Doppler velocimetry, and biomarkers (such as placental growth factor, soluble vascular endothelial growth factor receptor 1, soluble endoglin, pregnancy-associated plasma protein A, human chorionic gonadotropin, and α-fetoprotein) would allow for identification of a population of SGA fetuses at especially high risk. Interventional studies focused on additional frequent fetal surveillance, timing of delivery, or administration of pharmacological agents could all be subjects of investigation.

The major contribution of Sovio and colleagues' important study[6] is that universal serial fetal biometry improves the detection of SGA neonates, and that assessment of abdominal circumference growth velocity contributes to identification of a subset of newborn babies at an increased risk of morbidity. This work, coupled with the development of international standards for fetal growth,[13] provides a solid foundation for future research to establish if routine fetal growth assessment can improve pregnancy outcome. Whether this can be accomplished with an observational study using standard obstetrical interventions, or if a randomised clinical trial is needed, is an important issue that warrants careful consideration.

Acknowledgments

Funding: This research was supported, in part, by the Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS) and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C. Dr. Romero has contributed to this work as part of his official duties as an employee of the United States Federal Government.

References

1. WHO Department of Nutrition for Health and Development, WHO Multicenter Growth Reference Study Group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization; 2006.
2. Bornstein, MH., Arterberry, ME., Lamb, ME. Development in infancy: a contemporary introduction. 5. New York: Psychology Press; 2014. p. 93

3. Fowden AL, Giussani DA, Forhead AJ. Intrauterine programming of physiological systems: causes and consequences. Physiology. 2006; 21:29–37. [PubMed: 16443820]

4. Gluckman PD, Hanson MA, Bateson P, et al. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. Lancet. 2009; 373:1654–57. [PubMed: 19427960]

5. Bricker L, Neilson JP, Dowswell T. Routine ultrasound in late pregnancy (after 24 weeks gestation). Cochrane Database Syst Rev. 2015; 6:CD001451.

6. 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. published online Sept 8. http://dx.doi.org/10.1016/S0140-6736(15)00131-2

7. National Collaborating Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman. London: Royal College of Obstetricians and Gynaecologists Press; 2008. NICE clinical guideline 62.

8. National Collaborating Centre for Women's and Children's Health. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. London: Royal College of Obstetricians and Gynaecologists Press; 2008. NICE clinical guideline 63.

9. Deter RL, Lee W, Sangi-Haghpeykar H, Tarca AL, Yeo L, Romero R. Individualized fetal growth assessment: critical evaluation of key concepts in the specification of third trimester size trajectories. J Matern Fetal Neonatal Med. 2014; 27:543–51. [PubMed: 23962305]

10. Flood K, Unterscheider J, Daly S, et al. 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. [PubMed: 24813969]

11. Chaiworapongsa T, Romero R, Whitten AE, et al. The use of angiogenic biomarkers in maternal blood to identify which SGA fetuses will require a preterm delivery and mothers who will develop pre-eclampsia. J Matern Fetal Neonatal Med. 2015; published online Aug 14. doi: 10.3109/14767058.2015.1048431

12. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia. Am J Obstet Gynecol. 2013; 208:287. [PubMed: 23333542]

13. Papageorghiou AT, Ohuma EO, Altman DG, et al. for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014; 384:869–79. [PubMed: 25209488]