EDITORIAL

Early Detection and Prevention of Intrauterine Growth Restriction and Its Consequences

Paul Guerby, MD, PhD; Emmanuel Bujold, MD, MSc

Intrauterine growth restriction (IUGR) is a major public health problem and is the second leading cause of perinatal mortality and morbidity worldwide, behind preterm delivery.[1] IUGR refers to a condition in which a fetus is unable to achieve its genetically determined potential growth. IUGR is commonly reported in cases of an estimated fetal weight below the 10th percentile in combination with ultrasonographic evidence of impaired placental function.[2] This functional definition of IUGR seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes. Uteroplacental insufficiency is the most common cause of IUGR, associated with maternal vascular malperfusion, which is characterized by reduced placental size, multifocal infarction, hemorrhage, and diseased spiral arteries.[2] Fetuses with IUGR are at increased risk for significant perinatal morbidity and mortality after birth compared with infants with normal in utero growth.[2] IUGR is associated with a 5- to 10-fold increased risk of stillbirth.[2,3] Alteration in fetal growth may also be associated with developmental adaptation that permanently changes the child's physiologic makeup and metabolism, consistent with the fetal origins of adult disease hypothesis.[4] IUGR is associated with untoward long-term outcomes, including diabetes and cardiovascular diseases, and affects cognitive, socioemotional, and behavioral domains.[1,4]

Related article page 772

However, a large proportion of cases of IUGR remain undiagnosed before birth.[2,3] Although most neonates born small for gestational age (SGA; birth weight <10th percentile for gestational age) are constitutionally (and genetically) small without evidence of any impaired placental function, a substantial proportion of SGA is associated with undiagnosed IUGR.[1,2] As such, SGA is also associated with adverse perinatal and neonatal outcomes. Lawn et al[3] report that approximately half of stillbirths at term are neonates with SGA, and most are likely undiagnosed IUGR, emphasizing the importance of IUGR diagnosis before birth.

In this issue of *JAMA Pediatrics*, Sacchi et al[5] provide a systematic review and meta-analysis of cognitive outcomes in children who had IUGR and were SGA. The authors demonstrated poorer cognitive function during the first 12 years of life in neonates who had IUGR and were SGA compared with the neonates who were appropriate for gestational age matched for gestational age. In this well-conducted systematic review with robust methods, the authors observed that such findings were present in preterm and term-born individuals and highlighted that IUGR and SGA may be associated with an additional risk to that associated with preterm birth alone. Further studies are necessary to distinguish specific outcomes between IUGR and constitutional SGA. These important results emphasize the urgent need for improving IUGR prevention as well as antenatal detection and management, including for term IUGR and SGA. Prenatal diagnosis of IUGR and SGA and appropriate monitoring could result in a significant 4- to 5-fold reduction in perinatal morbidity and mortality.[6] On the basis of the study by Sacchi et al,[5] it could be suggested that early diagnosis and prevention of IUGR could potentially lead to specific intervention and improvement of long-term cognitive functions.

Early detection and diagnosis of IUGR has been a major topic of interest in obstetrics for several decades. At the end of the 20th century, ultrasonography in the early third trimester (approximately 30-34 weeks) was commonly performed in addition to serial measurement of the fundal height during pregnancy to detect IUGR. However, randomized clinical trials and meta-analyses demonstrated the poor predictability of both procedures.[7]

Previous studies[8-10] demonstrated that late third-trimester ultrasonography (approximately 35-37 weeks) combined with Doppler ultrasonography (uterine artery, middle cerebral artery, and fetal umbilical artery) would significantly improve the detection and the diagnosis of IUGR (61.4% vs 32.5%).[8] Moreover, the use of biochemical markers (placental growth factor and soluble FMS-like tyrosine kinase 1) could also be used to detect early uteroplacental insufficiency and identify women at greater risk for whom universal third-trimester ultrasonography may not be possible.[9] These new developments will allow for a better distinction between IUGR and constitutional SGA and could enable physicians to provide specific and appropriate management. Currently, identification and qualification of the severity of uteroplacental insufficiency allow for a better understanding of the fetal condition and help in decision-making regarding the optimal gestational age at which fetuses should be delivered with (or without in cases of SGA) IUGR. These improvements of detection methods with third-trimester ultrasonography and maternal biomarkers may enable secondary prevention of IUGR consequences. Unfortunately, although heparin and sildenafil provided several promises for the treatment and improvement of uteroplacental insufficiency in women with diagnosed IUGR, recent randomized clinical trials have demonstrated the absence of benefits from these treatments at this disease's stage.[10]

Although third-trimester management of diagnosed IUGR seems to be limited to the identification of the optimal time of delivery, there is increasing scientific evidence that a substantial proportion of placenta-mediated complications, including IUGR, and primarily the most severe complications can be detected as early as the first trimester of pregnancy and that a large

proportion of these could be prevented with the use of aspirin initiated in early pregnancy.[11,12] Bujold et al[12] observed that aspirin use initiated before 16 weeks of gestation in women who were at high risk of preeclampsia was associated with a significant reduction of IUGR. The current challenge is to identify the women at high risk of IUGR who could benefit from aspirin.

First-trimester screening tests that combine biophysical, ultrasonographic, and biochemical markers are now used to identify the most severe forms of preeclampsia that are also associated with deep placentation disorders and uteroplacental insufficiency.[13] Indirectly, such screening can be used to detect cases of preterm IUGR that are associated with preeclampsia, but the screening is not specifically focused on the early identification of IUGR and could therefore potentially be improved. Additional research on early placental growth and development could potentially help in the early identification of IUGR and could be included in early screening and prevention of IUGR with aspirin or other therapies. Recent evidence suggests that placental 3-dimensional ultrasonography, including 3-dimensional power Doppler angiography, could also improve IUGR screening in the first trimester of pregnancy.[14] However, to our knowledge, 3-dimensional measurements have never been included in combined models of IUGR screening.

Future research is targeting the uteroplacental circulation with novel therapeutics to treat or prevent IUGR, such as maternal vascular endothelial growth factor gene therapy[15] or nanoparticles and microRNAs to deliver drugs locally to the uterine arterial endothelium or trophoblast. In vitro and in vivo studies and animal models have shown promising results of nitric oxide donors, *N*-acetylcysteine supplementation, melatonin, hydrogen sulfide donors, statins, and proton pump inhibitors, with potential beneficial effects on maternal blood pressure, uterine artery pulsatility index, and angiogenic factors.[10] However, none of these methods have provided sufficient evidence in pregnant women and are therefore not currently recommended.

In conclusion, the study by Sacchi et al[5] emphasized the importance of fetal growth in long-term cognitive development of children. Moreover, an important body of scientific evidence suggests that several approaches, including ultrasonography and biochemical markers, could be used to (1) detect IUGR in its early process, (2) distinguish IUGR and constitutionally SGA, and (3) identify and prevent IUGR in high-risk women identified as early as the first trimester. Few available methods are currently available to prevent IUGR, and some simple recommendations seem to be required. Aspirin is a useful option in women identified as being at risk of IUGR, but the challenge is to accurately target those women to allow primary prevention. However, in these circumstances and to secure the resources necessary to perform such screening, the obstetric community will have to consider modifying the current pyramid of antenatal care that was originally based on increasing antenatal visits at the end of pregnancy rather than focused on the early recognition of pregnancy complications and their primary prevention.[13] An inverted pyramid of antenatal care[16] founded on an individualized medicine approach may be associated with a significant reduction of adverse perinatal outcomes, including IUGR, and with the long-term health of mothers and children.

ARTICLE INFORMATION

Author Affiliations: Research Center of CHU de Québec-Université Laval, Québec City, Québec, Canada (Guerby, Bujold); Department of Obstetrics and Gynecology, CHU Toulouse, Institute of Cardiovascular and Metabolic Diseases–Metabolic Diseases, Toulouse, France (Guerby); Department of Obstetrics and Gynecology, Faculty of Medicine, Université Laval, Québec City, Québec, Canada (Bujold).

Corresponding Author: Emmanuel Bujold, MD, MSc, Department of Obstetrics and Gynecology, Faculty of Medicine, Université Laval, 2705 Blvd Laurier, Québec City, Québec, G1W 3K5, Canada (emmanuel.bujold@crchudequebec.ulaval.ca).

Published Online: May 26, 2020. doi:10.1001/jamapediatrics.2020.1106

Conflict of Interest Disclosures: None reported.

LP;&-6QREFERENCES

1. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG*. 2015;122(8):1062-1072. doi:10.1111/1471-0528.13435

2. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 204: fetal growth restriction. *Obstet Gynecol*. 2019;133(2):e97-e109. doi:10.1097/AOG.0000000000003070

3. Lawn JE, Blencowe H, Waiswa P, et al; Lancet Ending Preventable Stillbirths Series Study Group; Lancet Stillbirth Epidemiology Investigator Group. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*. 2016;387(10018):587-603. doi:10.1016/S0140-6736(15)00837-5

4. Barker DJ, Eriksson JG, Forsén T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol*. 2002;31(6):1235-1239. doi:10.1093/ije/31.6.1235

5. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. *JAMA Pediatr*. Published online May 26, 2020 doi:10.1001/jamapediatrics.2020.1097

6. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol*. 2005;25(3):258-264. doi:10.1002/uog.1806

7. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). *Cochrane Database Syst Rev*. 2015;(6):CD001451. doi:10.1002/14651858.CD001451.pub4

8. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 vs 32 weeks' gestation: a randomized trial (ROUTE). *Ultrasound Obstet Gynecol*. 2015;46(4):391-397. doi:10.1002/uog.14915

9. Ciobanu A, Rouvali A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35-37 weeks' gestation. *Am J Obstet Gynecol*. 2019;220(5):486.e1-486.e11. doi:10.1016/j.ajog.2019.01.227

10. Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *Am J Obstet Gynecol*. 2018;218(2S):S829-S840. doi:10.1016/j.ajog.2017.11.565

11. Loussert L, Vidal F, Parant O, Hamdi SM, Vayssiere C, Guerby P. Aspirin for prevention of preeclampsia and fetal growth restriction. Prenat Diagn. Published online January 18, 2020.

12. Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol*. 2010;116(2 Pt 1):402-414. doi:10.1097/AOG.0b013e3181e9322a

13. Tan MY, Poon LC, Rolnik DL, et al. Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE. *Ultrasound Obstet Gynecol*. 2018;52(1):52-59. doi:10.1002/uog.19077

14. Bertholdt C, Eszto ML, Tournier M, et al. Assessment of uteroplacental vascularisation in early first-trimester pregnancy with contrast-enhanced ultrasound and 3D power Doppler angiography: protocol for a prospective, cross-sectional, multicentre and non-randomised open study ("HOPE Study"). *BMJ Open*. 2019;9(9):e030353. doi:10.1136/bmjopen-2019-030353

15. Spencer R, Ambler G, Brodszki J, et al; EVERREST Consortium. EVERREST prospective study: a 6-year prospective study to define the clinical and biological characteristics of pregnancies affected by severe early onset fetal growth restriction. *BMC Pregnancy Childbirth*. 2017;17(1):43. doi:10.1186/s12884-017-1226-7

16. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther*. 2011;29(3):183-196. doi:10.1159/000324320