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Fetal growth restriction - clinical manifestations through the perspective of pathophysiological changes

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Abstract

Intrauterine restriction of fetal growth is one of the most interestings and nowadays intensively studied problems of modern obstetrics. Fetal growth restriction can lead to significant obstetric complications, as well as consequences after delivery. For the obstetricians the fetal growth means iatrogenic prematurity, fetal distress, perinatal morbidity but also long term consequences as metabolic disease, cardiovascular pathology and Alzhaimer disease. There was considerable controversy as to how fetal growth restriction should be defined and diagnosed. Biometric and biophysical tests have been proposed to diagnose growth restriction, but until recently there were no unanimously accepted standards for the diagnosis of this pathology. This definition was reached in 2021 by the FIGO publication. Under the condition of intrauterine hypoxia adaptation mechanisms are activated. Understanding the ongoing pathophysiological process of adaptation in a hypoxic media helps to better understand proposed diagnosis criteria and the classification.

Key words: fetal growth restriction, hypoxia adaptation.

Introduction

Birth weight is one of the parameters used to describe the "health" of the newborn. Thus, the healthy newborn is a child born at 37-42 weeks' gestation, with a birth weight of 2500-4000 g and who during the examination looks vigorous, without congenital developmental anomalies or other pathological signs [1].

Fetal weight depends on genetically predetermined growth potential (parental weight, sex, ethnicity), but can be modulated by internal (fetal, placental, maternal) and external factors. Low fetal weight at birth can be an indicator of pathological damage, associated with perinatal complications, but it can also be found if low weight is genetically determined (constitutionally small newborns) [2].

A "normal" fetus, with "appropriate for gestational age" growth, is one that maintains constant growth and whose biometric parameters (cranial circumference, abdominal circumference, biparietal diameter, estimated weight) lie between the 10th and 90th percentiles [3]. A fetus whose estimated mass and/or abdominal circumference falls on the growth curves below the 10th percentile is defined as a "small for gestational age" (SGA) fetus. In the case of intrauterine growth restriction, fetal growth will be affected by an external or internal factor, fetal growth will be diminished, flattened, most frequently, lower than the 10th percentile [4].

The group of fetuses with a weight below the 10th percentile is a heterogeneous group and includes:

1) constitutionally small fetuses (50-70%);

2) fetuses who are small due to the action of an etiological factor, and in this case the diagnosis is fetal growth restriction (FGR).

Fetal growth restriction is the third leading cause of perinatal death. In specialized literature, this pathology is associated with iatrogenic prematurity, intraventricular hemorrhage, necrotizing enterocolitis, convulsions, sepsis, respiratory distress syndrome, retinopathy of prematurity, cerebral palsy, perinatal death [5]. Along with the profound perinatal impact, the consequences may continue into adulthood in the form of metabolic disease as a result of prenatal reprogramming and compensatory postnatal growth. It is now well established that children born with intrauterine growth restriction have poorer school performance and lower rates of neurobehavioral development. Adults who suffered intrauterine growth restriction have an increased risk of metabolic syndrome, hypertension, insulin resistance and type 2 diabetes, coronary heart disease and stroke [6].

Methods and materials

Research was conducted in international databases PubMed, Cochrane Library, and DOAJ by applying the key words and the combinations of terms including pregnancy, oxygen, fetal growth restriction, hypoxia, adaptation, hypoxic stress. The authors then compiled and analyzed the data, attempting to answer the following questions:

1. What are the hypoxic modifications in the growth restricted fetus?

2. What are long term and short term complications of these modifications?

3. Is there an interrelation between the hypoxic modification in fetuses and criteria proposed for diagnosis of FGR?

References from primary and review articles were cross-referenced to identify additional reports that met the inclusion criteria but were not identified by the initial search. Excluded were short reports, case reports, and letters to the editor.

Results

Antepartum fetal assessment is based on the hypothesis that the fetus responds to progressive hypoxia with a series of biophysical changes that can be detected by instrumental investigations.

Physiological and pathological mechanisms in intrauterine hypoxia have been studied since the 17th century, the first publication on fetal respiration appeared in 1674 - "De respiratione foetus in utero et ovo" by John Mayow [7]. Until now, the focus of international study is on the physiological reactions during the exposure to hypoxic episodes during intrauterine life and the cardiovascular adaptation of the fetus [8].

The heart rate, breathing, muscle tone and other biophysical activities of the fetus are dependent on the level of oxygenation. Under conditions of hypoxic stress, physiological adaptation mechanisms are activated. This determines the centralization of blood circulation for the protection of vitally important organs [9]. Thus, in the experimental and human models, under conditions of hypoxia, vasodilatation was determined in the vessels of the heart, central nervous system and adrenal glands, and in the vessels of other fetal regions – vasoconstriction (Figure 1). In the animal models, there was 70% increasing blood flow through the cerebral vessels in the hypoxic fetuses in comparison with the controls [10]. Prospective studies on fetal vessels confirmed higher middle adrenal artery-peak systolic velocity and increasing of the fetal adrenal gland dimensions in the pregnancies with FGR [11]. Finally, the greater vessel lumen diameter profiles were obtained for the right coronary artery, left coronary circumflex artery, and left anterior descending artery in the FGR in comparison with the normal weight fetuses [12]. An increase of the pulsatility index in tibial arteries as a sign of remarkable constriction of the peripheral arteries was found in human growth restricted fetuses [13]. Absolute brain volume did not differ between the chronic hypoxia fetuses and controls, indicating protection of brain growth. However, the liver and lung volumes were 22 and 27% smaller in the fetuses exposed to chronic maternal hypoxia compared to controls [14]. In the same time, the elevations in uric acid and other ammoniagenic amino acids identified in studies supports the global metabolic changes in a sheep model of intrauterine growth restriction fetuses [15].

The redistribution of blood flow has the following consequences: decreased fetal movements due to vasoconstriction on the striated muscles, decreased renal perfusion and the development of oligoamnios, asymmetric growth with decreased abdominal diameters, intrauterine growth restriction, fetal death [16].

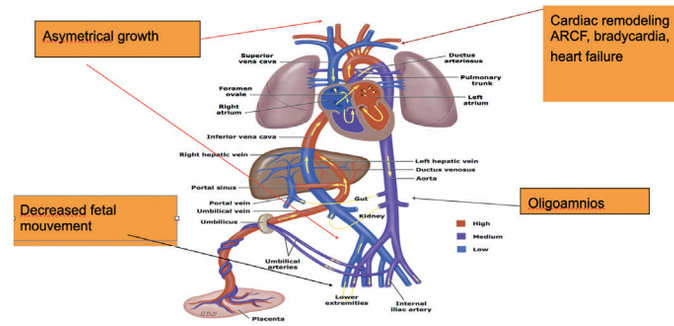

Figure 1 - Fetal response to hypoxia. Short term complications.

It should be noted that fetal biophysical parameters can also be affected by factors unrelated to hypoxemia, such as gestational age, maternal medication, sleep-wake rhythm, and fetal anomalies [17]. These parameters are taken into consideration during the antenatal assessment [18].

Centralisation of the circulation to the vital organs, eg. towards the fetal heart, the fetal brain and fetal adrenal glands have as consequences the cerebral vasodilation and cardiac remodeling. Vasoconstriction on the peripheral segments (renal, digestive, striated muscles) is responsible for the clinical manifestation of FGR such as oligoamnios, asymmetrical growth and decreased fetal movements.

Discussion

FGR of the fetus is defined as the inability to reach its growth potential corresponding to its gestational age, due to one or more determining factors. Classically, the factors involved in the occurrence of fetal growth restriction are divided into: maternal, fetal and placental (table 1) [19]. The detailed collection of anamnesis at the preconception visit or at the first antenatal visit allows the identification of patients with risk factors for the development of fetal growth restriction and their more careful monitoring during pregnancy [20]. Considering the association of fetal growth restriction and genetic syndromes, aneuploidy and intrauterine infection, a careful evaluation of the parents' morphotype, personal and family medical history is indicated [21].

Table 1 Maternal, fetal, and placental factors in fetal growth restriction

Maternal factors	Age <20 and >35 years Primiparity or multiparity Chronic hypertension, preeclampsia, pregnancy-induced hypertension History of preeclampsia, fetal growth restriction in previous pregnancies Causes of chronic hypoxia (cyanotic heart disease, anemia, hemoglobinopathy) Antiphospholipid syndrome, systemic lupus erythematosus, autoimmune diseases, diabetes with vascular damage Unfavorable socioeconomic environment Use of tobacco, alcohol, drugs Malnutrition/underweight or obesity Uterine malformations, uterine hypoplasia
Fetal factors	Infections: toxoplasmosis, rubella, chicken pox, cytomegalovirus, syphilis, parvovirus, enterovirus, herpes, Epstein-Barr virus Chromosomal abnormalities Genetic syndromes Multiple pregnancy
Placental factors	Placental insufficiency, usually as part of preeclamptic syndrome Placental infarction Placenta previa Placental chorioangioma Pathology of the cord: velamentous insertion, veridical ombilical knot

For the diagnosis of fetal growth restriction, biometric tests and fetal functional tests are combined. An important condition for the ultrasonographic examination is the accurate assessment of the gestational age. Thus, the first step in the evaluation of a pregnant woman with a risk of reduced fetal growth is the correct assessment of the gestation period by taking into account the date of the last menstruation and/or the ultrasound data from the first trimester of pregnancy [22]. Considering the association of fetal growth restriction with chromosomal abnormalities, genetic syndromes, intrauterine infection, a careful and detailed evaluation of the fetal anatomy will be performed each time. Following the ultrasound examination, the presence/absence of fetal structural abnormalities, markers for genetic pathology, chromosomal abnormalities, polyhydramnios, markers for intrauterine infection will be noted. In case of suspicion of growth restriction due to chromosomal or genetic causes, the pregnant woman will be consulted in order to perform non-invasive antenatal tests, amniocentesis; when an infectious cause is suspected, serological tests will be performed [23].

Table 2 Ultrasonographic tests used for the diagnosis of fetal growth restriction

Biometric tests	Functional tests
Estimated Fetal Weight (GFE) Biparietal diameter (DBP) Cranial Circumference (CC) Abdominal circumference (CA) Femur length (LF)	Evaluation of pulsatility indices at the level of the uterine arteries Evaluation of the pulsatility index at the level of the umbilical artery Evaluation of the pulsatility index at the level of the middle cerebral artery Calculation of cerebroplacental ratio Assessment of amniotic fluid volume Evaluation of the fetal biophysical score Cardiotocography with the non-stress test Doppler flow evaluation at the level of the ductus venosus Doppler flow evaluation at the level of the aortic isthmus

During the ultrasonography examination the fetal biometric and functional parameters are evaluated: the biparietal diameter, the cephalic circumference, the abdominal circumference, the femoral lengths with the calculation of the fetal weight, the uterine artery pulsatility index, umbilical cerebral Doppler, and the cerebroplacental index [24]. All the results are expressed in percentile. To establish the diagnosis, the presence of one major pathological parameter or two minor parameters is necessary. The major parameters are: estimated fetal weight or abdominal circumference less than 3rd percentile, flattening of the growth curve, absent or reverse-flow umbilical Doppler. The minor parameters are: estimated fetal weight or abdominal circumference less than the 10th percentile, pathological Doppler on the uterine arteries, increased resistance on the umbilical artery, pathological cerebroplacental index [25].

The proposed criteria perfectly reflect the fetal answer to hypoxia, and not only the general compensating mechanism, but also the tiny modifications that occur in the fetal cardiovascular system depending on the gestational term of installation of hypoxia. So knowing FIGO diagnosis criteria helps us also to describe the ongoing processes in a hypoxic intra-uterin media [26].

The current classification proposes the differentiation of fetal growth restriction according to the onset of the pathological process: FGR with early onset is diagnosed up to 32 gestational weeks and FGR with late onset, after 32 gestational weeks. This classification corresponds to the clinical course of the disease [27].

Early-onset fetal growth restriction is frequently associated with preeclampsia, severe placental insufficiency. This insufficiency translates into pathological Doppler on the uterine arteries. Insufficient transit through the placenta causes chronic fetal hypoxia. Fetal condition deteriorates with progression to hypoxia and decompensated acidosis. Decompensated acidosis translates negative or reverse flow Doppler on the umbilical artery, decreased resistance in the cerebral artery and pathological venous duct. The latency of severe fetal damage may vary in individual cases, but normally lasts for weeks [28]. It can be associated with antenatal death, or neonatal morbidity. Late-onset growth restriction is associated with preeclampsia only in about 10% of cases. Fetal adaptation to hypoxia results in blood redistribution phenomena, with cerebral vasodilation and vasoconstriction in the peripheral segment, due to which the cerebroplacental ratio is pathological. Fetal damage occurs rapidly, suddenly, manifesting as fetal distress during labor and neonatal acidosis, and impairment of neurological development after delivery [29, 30]. Centralisation of the circulation in intrauterine life induces long duration vasospasm in the renal arteries, digestive system vessels and is responsible for the late clinical consequences such as metabolic syndrome, diabetes, kidney disease. The cardiac remodeling due to vasodilation in the coronary segment increases the risk of cardiac pathology in adult life (Figure 2) [31].

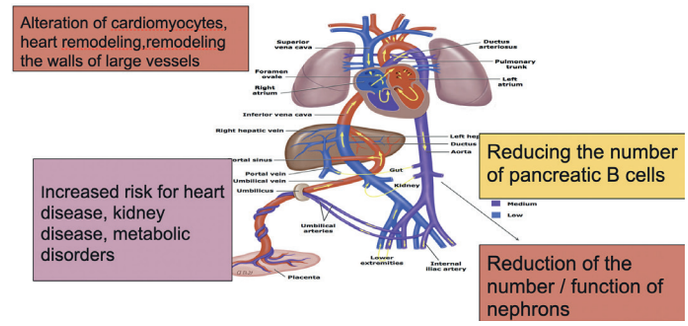

Figure 2 - Fetal response to hypoxia. Long term consequences

Conclusion

The fetus responds to progressive hypoxia with a series of pathophysiological changes. In conditions of hypoxic stress, physiological adaptation mechanisms that are activated determine the centralization of blood circulation to ensure the protection of organs of vital importance: vasodilation is determined in the vessels of the heart, central nervous system and adrenal glands, and in other fetal regions - vasoconstriction. These effects will determine short term complications in the restricted fetus that are nowadays used for the diagnosis: growth retardation, oligoamnios, pathological Doppler, fetal rhythm anomalies etc. The exposure of the fetus to the hypoxic media during prenatal life will induce long term system modifications causing adult pathology : metabolic syndrome, diabetes, renal disease, cardiac pathology.

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References

1. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol.* 2013; 121(5): 1122-1133. https://doi.org/10.1097/01.AOG.0000429658.85846.f9. PMID: 23635765.
2. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl.* 2006; 450: 76-85. https://doi.org/10.1097/10.1111/j.1651-2227.2006.tb02378.x. PMID: 16817681.
3. Nardozza LM, Araujo Júnior E, Barbosa MM, Caetano AC, Lee DJ, Moron AF. Fetal growth restriction: current knowledge to the general Obs/Gyn. *Arch Gynecol Obstet.* 2012; 286(1):1-13. https://doi.org/10.1007/s00404-012-2330-6. Epub 2012 Apr 24. PMID: 22526452.
4. Damhuis SE, Ganzevoort W, Gordijn SJ. Abnormal Fetal Growth: Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology. *Obstet Gynecol Clin North Am.* 2021; 48(2): 267-279. https://doi.org/10.1016/j.ogc.2021.02.002. PMID: 33972065.
5. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol (Lausanne).* 2019; 10: 55. https://doi.org/10.3389/fendo.2019.00055. PMID: 30792696; PMCID: PMC6374308.
6. D'Agostin M, Di Sipio Morgia C, Vento G, Nobile S. Long-term implications of fetal growth restriction. *World J Clin Cases.* 2023; 11(13): 2855-2863. https://doi.org/10.12998/wjcc.v11.i13.2855. PMID: 37215406; PMCID: PMC10198075.
7. Mayow, J. Tractatus quinque medico-physici; Quorum primus agit De salnitro, et spiritu nitro-aereo; Secundus De respiratione; Tertius De respiratione foetus in utero, et ovo; Quartus De motu musculari, et spirtitibus animalibus; Ultimus De rhachide. E. Theatro Sheldonian, Oxonii. 1674
8. Capros H, Scoricova I, Mihalcean L. Intrauterine growth restriction: contemporary issues in diagnosis and management. *The Moldovan Medical Journal.* 2017; 60 (2): 26-31. ISSN 2537-6373.
9. Maršál K. Physiological adaptation of the growth-restricted fetus. *Best Pract Res Clin Obstet Gynaecol.* 2018; 49: 37-52. https://doi.org/10.1016/j.bpobgyn.2018.02.006. Epub 2018 Feb 24. PMID: 29753694.
10. Cahill LS, Hoggarth J, Lerch JP, Seed M, Macgowan CK, Sled JG. Fetal brain sparing in a mouse model of chronic maternal hypoxia. *Journal of Cerebral Blood Flow & Metabolism.* 2019; 39(6):1172-1184. https://doi.org/10.1177/0271678X17750324.
11. Uyan Hendem, Derya, Ocal, Fatma Doga, Oluklu, Deniz, et al. Evaluation of fetal middle adrenal artery Doppler and fetal adrenal gland size in pregnancies with fetal growth restriction: a case-control study. *Journal of Perinatal Medicine.* 2023; 51 (4): 492-499. https://doi.org/10.1515/jpm-2022-0270.
12. Garcia-Canadilla P, de Vries T, Gonzalez-Tendero A, Bonnin A, Gratacos E, Crispi F, et al. Structural coronary artery remodelling in the rabbit fetus as a result of intrauterine growth restriction. *PLoS One.* 2019; 14(6): e0218192. https://doi.org/10.1371/journal.pone.0218192. PMID: 31226127; PMCID: PMC6588274.
13. Norvilaitė K, Ramašauskaitė D, Bartkevičienė D, Šliachtenko A, Kurmanavičius J. Fetal Tibial Artery Doppler in Late IUGR Fetuses: A Longitudinal Study. *J Clin Med.* 2022; 12(1): 82. https://doi.org/10.3390/jcm12010082. PMID: 36614891; PMCID: PMC9821295.
14. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS. 2018; 126(7): 561-569. https://doi.org/10.1111/apm.12849. PMID: 30129125.
15. Chang EI, Wesolowski SR, Gilje EA, Baker PR 2nd, Reisz JA, D'Alessandro A, et al. Skeletal muscle amino acid uptake is lower and alanine production is greater in late gestation intrauterine growth-restricted fetal sheep hindlimb. *Am J Physiol Regul Integr Comp Physiol.* 2019 1; 317(5): R615-R629. https://doi.org/10.1152/ajpregu.00115.2019. Epub 2019 Sep 4. PMID: 31483682; PMCID: PMC6879841.
16. Boddy K, Dawes GS, Fisher R, Pinter S, Robinson JS. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. *J Physiol.* 1974; 243(3): 599-618. https://doi.org/10.1113/jphysiol.1974.sp010768. PMID: 4475694; PMCID: PMC1330726.
17. Indications for Outpatient Antenatal Fetal Surveillance: ACOG Committee Opinion, Number 828. *Obstet Gynecol*. 2021; 137(6): e177-e197. https://doi.org/10.1097/AOG.0000000000004407. PMID: 34011892.
18. Capros H, Mihalcean L, Surguci M. Fetal growth restriction. New terminology and classification. *Obstetrics and Gynaecology of Saint-Petersburg.* 2020; 1(2): 6-10. ISSN: 2541-8491.
19. Unterscheider J, O'Donoghue K, Malone FD. Guidelines on fetal growth restriction: a comparison of recent national publications. *Am J Perinatol.* 2015; 32(4): 307-16. https://doi.org/10.1055/s-0034-1387927. Epub 2014 Sep 13. PMID: 25217738.
20. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small-for-Gestational-Age Fetus. RCOG Green-top Guideline No. 31.
21. Vayssière C, Sentilhes L, Ego A, Bernard C, Cambourieu D, Flamant C et al. Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. *Eur J Obstet Gynecol Reprod Biol.* 2015; 193: 10-8. https://doi.org/10.1016/j.ejogrb.2015.06.021. Epub 2015 Jul 2. PMID: 26207980.
22. Lausman A, Kingdom J; Maternal fetal medicine committee. Intrauterine growth restriction: screening, diagnosis, and management. *J Obstet Gynaecol Can.* 2013; 35(8): 741-748. English, French. https://doi.org/10.1016/S1701-2163(15)30865-3. PMID: 24007710.
23. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. *Ultrasound Obstet Gynecol*. 2019; 53(6): 715-723. https://doi.org/10.1002/uog.20272. PMID: 31169958.

24. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol.* 2016; 48(3): 333-9. https://doi.org/10.1002/uog.15884. PMID: 26909664.
25. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet.* 2021; 152 (51): 3-57. https://doi.org/10.1002/ijgo.13522. PMID: 33740264; PMCID: PMC8252743.
26. Lees CC, Romero R, Stampalija T, Dall'Asta A, DeVore GA, Prefumo F, et al. Clinical Opinion: The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. *Am J Obstet Gynecol.* 2022; 226(3): 366-378. https://doi.org/10.1016/j.ajog.2021.11.1357. Epub 2022 Jan 10. PMID: 35026129; PMCID: PMC9125563.
27. Lawin-O'Brien AR, Dall'Asta A, Knight C, Sankaran S, Scala C, Khalil A, et al. Short-term outcome of periviable small-for-gestational-age babies: is our counseling up to date? *Ultrasound Obstet Gynecol.* 2016; 48(5): 636-641. https://doi.org/10.1002/uog.15973. PMID: 27854384.
28. Visser GH, Nicholson WK, Barnea ER, Ramasauskaite D, Nassar AH; FIGO Safe Motherhood, Newborn Health Committee. FIGO position paper on reference charts for fetal growth and size at birth: Which one to use? *Int J Gynaecol Obstet.* 2021; 152(2): 148-151. https://doi.org/10.1002/ijgo.13500. Epub 2020 Dec 29. PMID: 33247958.
29. Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. *Ultrasound Obstet Gynecol*. 2011; 37(2): 135-42. https://doi.org/10.1002/uog.7767. Epub 2011 Jan 12. PMID: 20922778.
30. Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. *Ultrasound Obstet Gynecol*. 2011; 37(5): 501-14. https://doi.org/10.1002/uog.9008. PMID: 21520312.
31. Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *Am J Obstet Gynecol.* 2018 Feb; 218 (2S): 869-879. https://doi.org/10.1016/j.ajog.2017.12.012. PMID: 29422215.