No. 295, August 2013

Intrauterine Growth Restriction: Screening, Diagnosis, and Management

This clinical practice guideline has been prepared by the Maternal Fetal Medicine Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Andrea Lausman, MD, Toronto ON

John Kingdom, MD, Toronto ON

MATERNAL FETAL MEDICINE COMMITTEE

Robert Gagnon, MD (Chair), Verdun QC

Melanie Basso, RN, Vancouver BC

Hayley Bos, MD, London ON

Joan Crane, MD, St. John's NL

Gregory Davies, MD, Kingston ON

Marie-France Delisle, MD, Vancouver BC

Lynda Hudon, MD, Montreal QC

Savas Menticoglou, MD, Winnipeg MB

William Mundle, MD, Windsor ON

Annie Ouellet, MD, Sherbrooke QC

Tracy Pressey, MD, Vancouver BC

Christy Pylypjuk, MD, Saskatoon SK

Anne Roggensack, MD, Calgary AB

Frank Sanderson, MD, Saint John NB

Disclosure statements have been received from all members of the committee.

Key Words: intrauterine growth restriction (IUGR), screening, diagnosis, management, ultrasound, Doppler, placenta.

Abstract

Background: Intrauterine growth restriction (IUGR) is an obstetrical complication, which by definition would screen in 10% of fetuses in the general population. The challenge is to identify the subset of pregnancies affected with pathological growth restriction in order to allow intervention that would decrease morbidity and mortality.

Objective: The purpose of this guideline is to provide summary statements and recommendations and to establish a framework for screening, diagnosis, and management of pregnancies affected with IUGR.

Methods: Affected pregnancies are compared with pregnancies in which the fetus is at an appropriate weight for its gestational age. History, physical examination, and laboratory investigations including biochemical markers and ultrasound characteristics of IUGR are reviewed, and a management strategy is suggested.

Evidence: Published literature in English was retrieved through searches of PubMed or MEDLINE, CINAHL, and The Cochrane Library in January 2013 using appropriate controlled vocabulary via MeSH terms (fetal growth restriction and small for gestational age) and key words (fetal growth, restriction, growth retardation, IUGR, low birth weight, small for gestational age). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table).

Benefits, harms, and costs: Implementation of the recommendations in this guideline should increase clinician recognition of IUGR and guide intervention where appropriate. Optimal long-term follow-up of neonates diagnosed as IUGR may improve their long-term health.

J Obstet Gynaecol Can 2013;35(8):741–748

This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.

Summary Statements

1. The definition of small-for-gestational age for a fetus in utero is an estimated fetal weight that measures < 10th percentile on ultrasound. This diagnosis does not necessarily imply pathologic growth abnormalities, and may simply describe a fetus at the lower end of the normal range. (III)
2. Intrauterine growth restriction refers to a fetus with an estimated fetal weight < 10th percentile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential. (III) A clinical estimation of fetal weight or symphysis-fundal height has poor sensitivity and specificity and should not be relied upon to diagnose intrauterine growth restriction. Intrauterine growth restriction should be considered in the differential diagnosis when the fetus is found to be small for gestational age. (II-1)
3. Effective screening for intrauterine growth restriction requires accurate dating and includes a review of the mother's menstrual history, relevant assisted reproductive technology information, and either a first trimester or early second trimester dating ultrasound. (I)
4. Symphysis-fundal height determination is of limited value in routine obstetrical care, but continues to be the only physical examination screening test available. (I)
5. Fetal weight determination in fetuses between the 10th and 90th percentiles by ultrasound biometry alone has at least a 10% error rate across gestation, but is effective equally when measuring with abdominal circumference alone or in combination with head size (biparietal diameter or head circumference) and/or femur length to establish an estimated fetal weight. (II-2)
6. Determining whether intrauterine growth restriction is symmetric or asymmetric is of less clinical importance than careful re-evaluation of fetal anatomy and uterine and umbilical artery Doppler studies. (I)
7. In women with risk factors for intrauterine growth restriction, uterine artery Doppler screening at 19 to 23 weeks may identify pregnancies at risk of antepartum stillbirth and preterm delivery due to intrauterine growth restriction and placental disease. (II-2)
8. In pregnancies in which intrauterine growth restriction due to uteroplacental vascular insufficiency is diagnosed, maternal surveillance for the development of severe preeclampsia with adverse features is warranted. (II-1)
9. Once surveillance of a fetus with intrauterine growth restriction is instituted, umbilical artery Doppler studies and biophysical profile scoring can be used as short-term predictors of fetal well-being. (I)
10. In the presence of abnormal umbilical artery Doppler studies, further investigation of the fetal circulatory system by Doppler

ABBREVIATIONS

AC	abdominal circumference
AFV	amniotic fluid volume
BPP	biophysical profile
DV	ductus venosus
DVP	deepest vertical pocket
EFW	estimated fetal weight
IUGR	intrauterine growth restriction
MCA	middle cerebral artery
NST	non-stress test
SFH	symphysis fundal height

examination of the middle cerebral artery, ductus venosus, and umbilical vein can be considered. (II-2)

11. For a fetus with intrauterine growth restriction, the decision for obstetrical intervention, including Caesarean section, in cases of abnormal fetal heart rate or malpresentation is largely based on fetal viability, as assessed by ultrasound. (II-2)
12. Maternal surveillance for the development of preeclampsia is warranted. (II-2)

Recommendations

1. Women should be screened for clinical risk factors for intrauterine growth restriction by means of a complete history. (II-2B)
2. Women should be counselled on smoking cessation at any time during pregnancy. (II-2A)
3. First and second trimester screening tests for aneuploidy maybe useful tests of placental function. If two screening test results are abnormal, health care providers should be aware that the fetus is at increased risk of preterm intrauterine growth restriction and associated stillbirth. (II-1A)
4. If intrauterine growth restriction is suspected, further assessment can assist in making the diagnosis. If available, detailed ultrasound examination of the placenta (looking for evidence of a small, thickened placenta, or abnormal morphology) and uterine artery Dopplers should be considered at 19 to 23 weeks. In the absence of available diagnostic testing, closer surveillance should be offered. A maternal–fetal medicine consultation can be considered if the placenta appears abnormal on ultrasound, especially in the context of a growth-restricted fetus and abnormal uterine artery Doppler. In a rural setting, the caregiver needs to decide whether the patient should be delivered immediately, or whether transfer to a tertiary centre is appropriate. A telephone consultation and telemedicine may help. (II-2A)
5. In women without risk factors for intrauterine growth restriction, comprehensive third trimester ultrasound examination including biophysical profile, fetal biometry, amniotic fluid volume, and umbilical artery Doppler studies is not recommended. (II-2D)
6. Low-dose aspirin should be recommended to women with a previous history of placental insufficiency syndromes including intrauterine growth restriction and preeclampsia. It should be initiated between 12 and 16 weeks' gestation and continued until 36 weeks. (I-A)
7. Low-dose aspirin should also be recommended to women with two or more current risk factors in pregnancy including, but not limited to, pre-gestational hypertension, obesity, maternal age > 40 years, history of use of artificial reproductive technology, pre-gestational diabetes mellitus (type I or II), multiple gestation, previous history of placental abruption, and previous history of placental infarction. It should be initiated between 12 and 16 weeks' gestation and continued until 36 weeks. (I-A)
8. Umbilical artery Doppler studies are not recommended as a routine screening test in uncomplicated pregnancies. (I-E)
9. An ultrasound examination for estimated fetal weight and amniotic fluid volume should be considered after 26 weeks if the symphysis-fundal height measurement in centimetres deviates by 3 or more from the gestational age in weeks or there is a plateau in symphysis-fundal height. (II-2B)
10. In cases in which the fetus measures < 10th percentile by estimated fetal weight or abdominal circumference measurement, the underlying cause of intrauterine growth restriction may be established by an enhanced ultrasound examination to include a detailed review of fetal anatomy, placental morphology, and Doppler studies of the uterine and umbilical arteries. (II-2A)
11. In cases of intrauterine growth restriction, determination of amniotic fluid volume should be performed to aid in the differential diagnosis of intrauterine growth restriction and increase the accuracy of the diagnosis of placental insufficiency. (II-2B)
12. Umbilical artery Doppler should be performed in all fetuses with an estimated fetal weight or an abdominal circumference < 10th percentile. (I-A)
13. In pregnancies affected by intrauterine growth restriction, umbilical artery Doppler studies after 24 weeks may prompt intervention that reduces perinatal mortality and severe perinatal morbidity due to intrauterine growth restriction. (I-A)
14. In pregnancies in which intrauterine growth restriction has been identified, invasive testing to rule out aneuploidy may be offered where fetal abnormalities are suspected, soft markers are seen, or no supportive evidence of underlying placental insufficiency is evident. (II-2A)
15. In patients presenting with intrauterine growth restriction, maternal screening for infectious etiology may be considered. (II-2A)
16. When intrauterine growth restriction is diagnosed, surveillance should be initiated. Serial ultrasound estimation of fetal weight (every 2 weeks), along with umbilical artery Doppler studies should be initiated. If available, a placental assessment and other Doppler studies such as middle cerebral artery, umbilical vein, and ductus venosis can be performed. Increased frequency of surveillance may be required. (II-2A)
17. If fetal growth starts to plateau, amniotic fluid index starts to decline, or fetal tone or gross movements are diminished or absent, then more intensive surveillance (e.g., 2 to 3 times per week) or admission to hospital and delivery planning is required. (II-2A)
18. Abnormal umbilical cord Doppler (e.g., absent or reversed end-diastolic flow) in the presence of intrauterine growth restriction is an ominous finding that requires intervention and possible delivery. (I-A)
19. Cardiotocography (non-stress testing) performed antenatally as a test of fetal well-being should not be used in isolation to monitor fetuses with intrauterine growth restriction. (II-2E)
20. Maternal administration of corticosteroids is indicated if there is a significant possibility of delivery at < 34 weeks' gestation, as administration may positively affect umbilical Doppler studies. (I-A)
21. If delivery was not indicated prior to 37 weeks in a patient diagnosed with intrauterine growth restriction, expectant management with close fetal and maternal surveillance versus delivery should be discussed after 37 weeks. (I-A)
22. Site of planned delivery should take into consideration facilities and expertise available at each institution including obstetricians, pediatricians or neonatologists as appropriate, anaesthesiologists, and access to Caesarean section. (III-A)

INTRODUCTION

Intrauterine growth restriction is a problem faced by obstetrical care providers on a daily basis. Neonatal mortality in both term and pre-term neonates is significantly increased in those diagnosed antenatally with IUGR. Despite the importance of the topic, there is a paucity of level I evidence. The purpose of this guideline is to provide summary statements and recommendations and to establish a framework for screening, diagnosis, and management of pregnancies affected with IUGR. A previously published review (Lausman et al., 2012) provides further background.

Summary Statements

1. The definition of small-for-gestational age for a fetus in utero is an estimated fetal weight that measures < 10th percentile on ultrasound. This diagnosis does not necessarily imply pathologic growth abnormalities, and may simply describe a fetus at the lower end of the normal range. (III)
2. Intrauterine growth restriction refers to a fetus with an estimated fetal weight < 10th percentile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential. (III) A clinical estimation of fetal weight or symphysis-fundal height has poor sensitivity and specificity and should not be relied upon to diagnose intrauterine growth restriction. Intrauterine growth restriction should be considered in the differential diagnosis when the fetus is found to be small for gestational age. (II-1)
3. Effective screening for intrauterine growth restriction requires accurate dating and includes a review of the mother's menstrual history, relevant assisted reproductive technology information, and either a first trimester or early second trimester dating ultrasound. (I)
4. Symphysis-fundal height determination is of limited value in routine obstetrical care, but continues to be the only physical examination screening test available. (I)
5. Fetal weight determination in fetuses between the 10th and 90th percentiles by ultrasound biometry alone has at least a 10% error rate across gestation, but is effective equally when measuring with abdominal circumference alone or in combination with head size (biparietal diameter or head circumference) and/or femur length to establish an estimated fetal weight. (II-2)
6. Determining whether intrauterine growth restriction is symmetric or asymmetric is of less clinical importance than careful re-evaluation of fetal anatomy and uterine and umbilical artery Doppler studies. (I)
7. In women with risk factors for intrauterine growth restriction, uterine artery Doppler screening at 19 to 23 weeks may identify pregnancies at risk of antepartum stillbirth and preterm delivery due to intrauterine growth restriction and placental disease. (II-2)
8. In pregnancies in which intrauterine growth restriction due to uteroplacental vascular insufficiency is diagnosed, maternal surveillance for the development of severe preeclampsia with adverse features is warranted. (II-1)
9. Once surveillance of a fetus with intrauterine growth restriction is instituted, umbilical artery Doppler studies and biophysical profile scoring can be used as short-term predictors of fetal well-being. (I)
10. In the presence of abnormal umbilical artery Doppler studies, further investigation of the fetal circulatory system by Doppler examination of the middle cerebral artery, ductus venosus, and umbilical vein can be considered. (II-2)
11. For a fetus with intrauterine growth restriction, the decision for obstetrical intervention, including Caesarean section, in cases of abnormal fetal heart rate or malpresentation is largely based on fetal viability, as assessed by ultrasound. (II-2)
12. Maternal surveillance for the development of preeclampsia is warranted. (II-2)

Recommendations

1. Women should be screened for clinical risk factors for intrauterine growth restriction by means of a complete history. (II-2B)
2. Women should be counselled on smoking cessation at any time during pregnancy. (II-2A)
3. First and second trimester screening tests for aneuploidy maybe useful tests of placental function. If two screening test results are abnormal, the fetus is at increased risk of preterm intrauterine growth restriction and associated stillbirth. (II-1A)
4. If intrauterine growth restriction is suspected, further assessment can assist in making the diagnosis. If available, detailed ultrasound examination of the placenta (looking for evidence of a small, thickened placenta, or abnormal morphology) and uterine artery Dopplers should be considered at 19 to 23 weeks. In the absence of available diagnostic testing, closer surveillance should be offered. A maternal–fetal medicine

consultation can be considered if the placenta appears abnormal on ultrasound, especially in the context of a growth-restricted fetus and abnormal uterine artery Doppler. In a rural setting, the caregiver needs to decide whether the patient should be delivered immediately, or whether transfer to a tertiary centre is appropriate. A telephone consultation and telemedicine may help. (II-2A)

5. In women without risk factors for intrauterine growth restriction, comprehensive third trimester ultrasound examination including biophysical profile, fetal biometry, amniotic fluid volume, and umbilical artery Doppler studies is not recommended. (II-2D)
6. Low-dose aspirin should be recommended to women with a previous history of placental insufficiency syndromes including intrauterine growth restriction and preeclampsia. It should be initiated between 12 and 16 weeks' gestation and continued until 36 weeks. (I-A)
7. Low-dose aspirin should also be recommended to women with two or more current risk factors in pregnancy including, but not limited to, pre-gestational hypertension, obesity, maternal age > 40 years, history of use of artificial reproductive technology, pre-gestational diabetes mellitus (type I or II), multiple gestation, previous history of placental abruption, and previous history of placental infarction. It should be initiated between 12 and 16 weeks' gestation and continued until 36 weeks. (I-A)
8. Umbilical artery Doppler studies are not recommended as a routine screening test in uncomplicated pregnancies. (I-E)
9. An ultrasound examination for estimated fetal weight and amniotic fluid volume should be considered after 26 weeks if the symphysis-fundal height measurement in centimetres deviates by 3 or more from the gestational age in weeks or there is a plateau in symphysis-fundal height. (II-2B)
10. In cases in which the fetus measures < 10th percentile by estimated fetal weight or abdominal circumference measurement, the underlying cause of intrauterine growth restriction may be established by an enhanced ultrasound examination to include a detailed review of fetal anatomy, placental morphology, and Doppler studies of the uterine and umbilical arteries. (II-2A)
11. In cases of intrauterine growth restriction, determination of amniotic fluid volume should be performed to aid in the differential diagnosis of intrauterine growth restriction and increase the accuracy of the diagnosis of placental insufficiency. (II-2B)
12. Umbilical artery Doppler should be performed in all fetuses with an estimated fetal weight or an abdominal circumference < 10th percentile. (I-A)
13. In pregnancies affected by intrauterine growth restriction, umbilical artery Doppler studies after 24 weeks may prompt intervention that reduces perinatal mortality and severe perinatal morbidity due to intrauterine growth restriction. (I-A)
14. In pregnancies in which intrauterine growth restriction has been identified, invasive testing to rule out aneuploidy may be offered where fetal abnormalities are suspected, soft markers are seen, or no supportive evidence of underlying placental insufficiency is evident. (II-2A)
15. In patients presenting with intrauterine growth restriction, maternal screening for infectious etiology may be considered. (II-2A)
16. When intrauterine growth restriction is diagnosed, surveillance should be initiated. Serial ultrasound estimation of fetal weight (every 2 weeks), along with umbilical artery Doppler studies should be initiated. If available, a placental assessment and other Doppler studies such as middle cerebral artery, umbilical vein, and ductus venosis can be performed. Increased frequency of surveillance may be required. (II-2A)
17. If fetal growth starts to plateau, amniotic fluid index starts to decline, or fetal tone or gross movements are diminished or absent, then more intensive surveillance (e.g., 2 to 3 times per week) or admission to hospital and delivery planning is required. (II-2A)
18. Abnormal umbilical cord Doppler (e.g., absent or reversed end-diastolic flow) in the presence of intrauterine growth restriction is an ominous finding that requires intervention and possible delivery. (I-A)
19. Cardiotocography (non-stress testing) performed antenatally as a test of fetal well-being should not be used in isolation to monitor fetuses with intrauterine growth restriction. (II-2E)
20. Maternal administration of corticosteroids is indicated if there is a significant possibility of delivery at < 34 weeks' gestation, as administration may positively affect umbilical Doppler studies. (I-A)
21. If delivery was not indicated prior to 37 weeks in a patient diagnosed with intrauterine growth restriction, expectant management with close fetal and maternal surveillance versus delivery should be discussed after 37 weeks. (I-A)

22. Site of planned delivery should take into consideration facilities and expertise available at each institution including obstetricians, pediatricians or neonatologists as appropriate, anaesthesiologists, and access to Caesarean section. (III-A)

FRAMEWORK FOR APPROACHING INTRAUTERINE GROWTH RESTRICTION IN CLINICAL PRACTICE

Screening for intrauterine growth restriction

History: maternal, fetal, and placental risk factors; establish dates by first trimester ultrasound and last menstrual period

Physical: SFH measurement

Investigations to consider:

- biochemical screening tests for Trisomy 21 as a test of placental insufficiency;
- first trimester ultrasound for dating and nuchal translucency;
- uterine artery Doppler at 19 to 23 weeks if biochemical markers are abnormal;
- if SFH (in centimetres) is less than gestational age (in weeks) by > 3, arrange ultrasound for EFW, AFV or DVP, biophysical profile, and/or umbilical Doppler studies.

Diagnosis of intrauterine growth restriction

EFW or AC < 10th percentile

Management of intrauterine growth restriction

Investigations:

- Offer amniocentesis if there is high risk of aneuploidy;
- Consider TORCH screen.

Maternal management:

- Conduct ongoing monitoring for preeclampsia;
- Encourage patient to quit smoking;
- Consider adding low-dose aspirin early in the pregnancy if patient fulfills the criteria for its use.

Fetal management:

- If pre-viable (< 500 g ± < 24 weeks): offer counselling by multi-disciplinary health care team regarding fetal monitoring and obstetrical intervention until viability.
- If viable (> 500 g and > 24 weeks): conduct initial ultrasound assessment: EFW, AFV, umbilical Doppler; in third trimester (~ 26 weeks) consider weekly BPP and growth every 2 weeks.
- If growth continues along growth curve: conduct weekly biophysical profile and umbilical artery Doppler; add growth every 2 weeks; consider delivery near term (38 to 40 weeks) if no other issues.
- If growth plateaus or stops < 34 weeks: administer corticosteroids; increase surveillance to 2 to 3 times per week; consider hospitalization; consider maternal–fetal medicine consultation; consider pediatric consultation.
- If abnormal umbilical artery Doppler studies: add MCA and DV studies.
- If abnormal umbical artery, MCA, and DV Doppler studies and abnormal NST: deliver.

  NST can be used selectively if the BPP is abnormal.
- If abnormal Doppler studies (e.g., absent or reversed end-diastolic flow) and normal BPP and NST: continue intensive monitoring with BPP and umbilical Dopplers 2 to 3 times per week; deliver if BPP or umbilical Dopplers worsen or if MCA/DV are abnormal.
- If > 34 weeks.
- If normal AFV and DVP, BPP, and Doppler studies: conduct weekly surveillance and discuss delivery or ongoing monitoring after 37 weeks.
- If abnormal fluid (AFV < 5 cm or DVP < 2 cm), BPP, and/or Doppler studies: consider delivery.

DISCUSSION

IUGR is a problem associated with significant perinatal morbidity and mortality. Level 1 evidence to direct clinicians in practice does exist, but is limited to a few high quality trials. Several demographic factors, including advanced maternal age, assisted conception technologies, and pregnancy with maternal comorbidities, interact to steadily increase the risk of IUGR and stillbirth in the third trimester. More effective use of current evidence may reduce this risk, but further studies, especially to evaluate the role of systematic screening of placental function in the second trimester, are needed to improve the perinatal prognosis of IUGR due to placental insufficiency. Since IUGR has many additional causes, when it is suspected, a detailed fetal anatomical ultrasound examination should be performed including further testing when fetal abnormalities are suspected, soft markers are seen, or there is no apparent supportive evidence of underlying placental insufficiency.

In uncomplicated IUGR attributed to placental insufficiency, no pharmacological interventions are of proven benefit, although the accumulated data from several trials and meta-analyses of low-dose aspirin demonstrate

some preventive benefit. By contrast, no evidence currently exists to support the preventive use of the parenteral anticoagulant drug heparin for either the prevention or treatment of IUGR. After 36 weeks of gestation, IUGR due to suspected placental insufficiency can be managed equally effectively by early delivery or delayed delivery with increased fetal surveillance.

Further research is needed to define optimum management of early-onset IUGR. Following delivery, pathological examination of the placenta may provide key insights into the underlying cause and form the basis of an effective postpartum counselling visit to discuss that cause. Since the events leading up to and following delivery of an infant with severe IUGR may trigger significant emotional stress, a review of mental health status and family circumstances at this visit is prudent.

BIBLIOGRAPHY

Abdel-Fattah SA, Bhat A, Illanes S, Bartha JL, Carrington D. TORCH test for fetal medicine indications: only CMV is necessary in the United Kingdom. Prenat Diagn 2005;25:1028–31.

Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: systematic review with meta-analysis. Am J Obstet Gynecol 1995;172:1379-87.

Alley MH, Hadjiev A, Mazneikova V, Dimitrov A. Four-quadrant assessment of gestational age-specific values of amniotic fluid volume in uncomplicated pregnancies. Acta Obstet Gynecol Scand 1998;77:290-4.

American College of Obstetricians and Gynecologists. Intrauterine Growth Restriction. ACOG Practice Bulletin No. 12. Washington DC: ACOG; 2000.

Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. Chronobiol Int 2013;30:260-79. doi: 10.3109/07420528.2012.717455.

Bamberg C, Kalache KD. Prenatal diagnosis of fetal growth restriction. Semin Fetal Neonatal Med 2004;9:387–94.

Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109(2 Pt 1):253–61.

Becker R, Keller T, Kiesewetter H, Fangerau H, Bittner U. Individual risk assessment of adverse pregnancy outcome by multivariate regression analysis may serve as basis for drug intervention studies: retrospective analysis of 426 high-risk patients including ethical aspects. Arch Gynecol Obstet 2013; 288:41–8. doi: 10.1007/s00404-013-2723-1.

Boers KE, van Wyk L, van der Post JA, Kwee A, van Pampus MG, Spaanderdam ME, et al.; DIGITAT Study Group. Neonatal morbidity after induction vs expectant monitoring in intrauterine growth restriction at term: a subanalysis of the DIGITAT RCT. Am J Obstet Gynecol. 2012;206:344.e1–e7. doi: 10.1016/j.ajog.2012.01.015.

Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ 2010;341:c7087.

Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. Am J Obstet Gynecol 1976;126:555–64.

Bricker L, Neilson JP. Routine Doppler ultrasound in pregnancy. Cochrane Database Syst Rev 2000;2:CD001450.

Bricker L, Neilson JP, Dowswell T. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev 2008;4:CD001451.

Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, 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):402-14. doi: 10.1097/AOG.0b013e3181e9322a.

Carberry AE, Gordon A, Bond DM, Hyett J, Raynes-Greenow CH, Jeffery HE. Customised versus population-based growth charts as a screening tool for detecting small for gestational age infants in low-risk pregnant women. Cochrane Database Syst Rev 2011 Dec 7;12:CD008549. doi: 10.1002/14651858.CD008549.pub2.

Chauhan SP, Magann EF. Screening for fetal growth restriction. Clin Obstet Gynecol 2006;49:284–94.

Dayal AK, Manning FA, Berck DJ, Mussalli GM, Avila C, Harman CR, et al. Fetal death after normal biophysical profile score: an eighteen-year experience. Am J Obstet Gynecol 1999;181(5 Pt 1):1231–6.

Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 2005;25:80–9.

Dugoff L. First- and second-trimester maternal serum markers for aneuploidy and adverse obstetric outcomes. Obstet Gynecol 2010;115:1052 61.

Dugoff L, Hobbins JC, Malone FD, Vidaver J, Sullivan L, Canick JA, et al. Quad screen as a predictor of adverse pregnancy outcome. Obstet Gynecol 2005;106;2:260–7.

Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol 2011;204:288–300. doi: 10.1016/j.ajog.2010.08.055.

Gardosi J. Customised assessment of fetal growth potential: implications for perinatal care. Arch Dis Child Fetal Neonatal Ed 2012;97:F314-7. doi: 10.1136/fetalneonatal-2012-301708.

Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992;339:283–7.

Grivell RM, Alfirevic Z, Gyte GM, Devane D. Antenatal cardiotocography for fetal assessment. Cochrane Database Syst Rev 2010;1:CD007863.

Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. Cochrane Database Syst Rev 2012 Jun 13;6:CD007113. doi: 10.1002/14651858.CD007113.pub3.

Haram K, Softeland E, Bukowski R. Intrauterine growth restriction. Int J Gynaecol Obstet 2006;93:5–12.

Konchak PS, Bernstein IM, Capeless EL. Uterine artery Doppler velocimetry in the detection of adverse obstetric outcomes in women with unexplained elevated maternal serum alpha-fetoprotein levels. Am J Obstet Gynecol 1995;173:1115–9.

Lackman F, Capewell V, Richardson B, daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. Am J Obstet Gynecol 2001;184(5):946−53.

Lausman A, McCarthy FP, Walker M, Kingdom J. Screening, diagnosis, and management of intrauterine growth restriction. J Obstet Gynaecol Can 2012;34:17–28.

Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sorensen HU, Roseno H. The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial. Br J Obstet Gynaecol 1990;97:675–80.

Mari G, Hanif F, Kruger M, Cosmi E, Santolaya-Forgas J, Treadwell MC. Middle cerebral artery peak systolic velocity: a new Doppler parameter in the assessment of growth-restricted fetuses. Ultrasound Obstet Gynecol 2007;293:310–6.

Maulik D. Fetal growth compromise: definitions, standards, and classification. Clin Obstet Gynecol 2006;49:214–8.

McCowan LM, Dekker GA, Chan E, Stewart A, Chappell LC, Hunter M, et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. BMJ 2009;338:b1081.

Mitani M, Matsuda Y, Makino Y, Akizawa Y, Ohta H. Clinical features of fetal growth restriction complicated later by preeclampsia. J Obstet Gynaecol Res 2009;35:882–7.

Neilson JP. Symphysis-fundal height measurement in pregnancy. Cochrane Database Syst Rev 2000;2:CD000944.

Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. Cochrane Database Syst Rev 2000;2:CD000073.

Nyberg DA, Abuhamad A, Ville Y. Ultrasound assessment of abnormal fetal growth. Semin Perinatol 2004;28:3–22.

Pinar H, Carpenter M. Placenta and umbilical cord abnormalities seen with stillbirth. Clin Obstet Gynecol 2010;53:656–72.

Proctor LK, Whittle WL, Keating S, Viero S, Kingdom JC. Pathologic basis of echogenic cystic lesions in the human placenta: role of ultrasound-guided wire localization. Placenta 2010;31:1111–5.

Reeves S, Bernstein I. Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. Expert Rev Obstet Gynecol 2008;3:719–30.

Roberge S, Giguère Y, Villa P, Nicolaides K, Vainio M, Forest JC, et al. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. Am J Perinatol 2012;29:551-6. doi: 10.1055/s-0032-1310527.

Roberge S, Nicolaides K, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. Ultrasound Obstet Gynecol 2013;41:491-9. doi: 10.1002/uog.12421.

Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal Diagn Ther 2012;31:141-6. doi: 10.1159/000336662.

Robert Peter J, Ho JJ, Valliapan J, Sivasangari S. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. Cochrane Database Syst Rev 2012 Jul 11;7:CD008136. doi: 10.1002/14651858.CD008136.pub2.

Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Sys Rev 2006 Jul 19;3:CD004454.

Royal College of Obstetricians and Gynecologists (RCOG). The investigation and management of the small-for-gestational age fetus. Guideline No. 31. London: RCOG; 2002.

Siddiqui N, Hladunewich M. Understanding the link between the placenta and future cardiovascular disease. Trends Cardiovasc Med 2011;21:188-93. doi: 10.1016/j.tcm.2012.05.008.

Simchen MJ, Alkazaleh F, Adamson SL, Windrim R, Telford J, Beyene J, et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. Am J Obstet Gynecol 2004;190:296304.

Smith GC, Smith MF, McNay MB, Fleming JE. The relation between fetal abdominal circumference and birthweight: findings in 3512 pregnancies. Br J Obstet Gynaecol 1997;104:186–90.

Smith GC, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH. Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth. Obstet Gynecol 2007;109:144–51.

Snijders RJ, Sherrod C, Gosden CM, Nicolaides KH. Fetal growth retardation: associated malformations and chromosomal abnormalities. Am J Obstet Gynecol 1993;168:547–55.

Toal M, Chaddha V, Windrim R, Kingdom J. Ultrasound detection of placental insufficiency in women with elevated second trimester serum alpha-fetoprotein or human chorionic gonadotropin. J Obstet Gynaecol Can 2008;30:198–206.

van Wyk L, Boers KE, van der Post JA, van Pampus MG, van Wassenaer AG, van Baar AL, et al.; DIGITAT Study Group. Effects on (neuro)developmental and behavioral outcome at 2 years of age of induced labor compared with expectant management in intrauterine growth-restricted infants: long-term outcomes of the DIGITAT trial. Am J Obstet Gynecol 2012;206:406.e1–e7. doi: 10.1016/j.ajog.2012.02.003.

von Beckerath AK, Kollmann M, Rotky-Fast C, Karpf E, Lang U, Klaritsch P. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. Am J Obstet Gynecol 2013;208:130.e1–e6. doi: 10.1016/j.ajog.2012.11.014.

Zhang J, Troendle J, Meikle S, Klebanoff MA, Rayburn WF. Isolated oligohydramnios is not associated with adverse perinatal outcomes. BJOG 2004;111:220–5.