Screening, Diagnosis, and Management of Intrauterine Growth Restriction

Andrea Lausman, MD, FRCSC,[1] Fergus P. McCarthy, MB, BCh, MRCPI,[2] Melissa Walker, MSc,[2] John Kingdom, MD, FRCSC, FRCOG, MRCP[2]

[1]Maternal-Fetal Medicine Division, Department of Obstetrics and Gynaecology, University of Toronto, St. Michael's Hospital, Toronto ON

[2]Maternal-Fetal Medicine Division, Department of Obstetrics and Gynaecology, University of Toronto, Mount Sinai Hospital, Toronto ON

Abstract

Objective: To provide comprehensive background knowledge relevant to the SOGC Maternal-Fetal Medicine Committee-approved guideline entitled "Intrauterine Growth Restriction: Screening, Diagnosis, and Management."

Methods: Publications in English were retrieved through searches of PubMed or Medline, CINAHL, and the Cochrane Library in January 2011 using appropriate controlled vocabulary via MeSH terms (fetal growth restriction and small for gestational age) and any key words (fetal growth, restriction, growth retardation, intrauterine growth restriction [IUGR], low birth weight, small for gestational age). Results were restricted to systematic reviews, randomized controlled trials or controlled clinical trials, and high-quality prospective and retrospective observational studies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Results: Evidence obtained from at least one properly randomized controlled trial, Cochrane Reviews, and high quality cohort data have been combined to provide clinicians with evidence to optimize their practice for screening, diagnosis, and management of intrauterine growth restriction.

Conclusion: Considerable advances have been made to improve clinicians' ability to screen, diagnose, and manage pregnancies with suspected IUGR more effectively, including several properly randomized controlled trials. Pregnancies with late-onset IUGR may be managed equally effectively by early delivery or delayed delivery (with increased surveillance) anticipating favourable outcomes. By contrast, many aspects of the management of early-onset IUGR require further clinical trials.

Key Words: Fetus, intrauterine growth restriction, IUGR, small for gestational age, screening, diagnosis, management, ultrasound, Doppler, placenta, aneuploidy, malformation

Conflict of Interest: None declared.

Received on January 26, 2011

Accepted on April 5, 2011

Résumé

Objectif : Offrir des connaissances de base exhaustives quant à la directive clinique intitulée « Retard de croissance intra-utérin : Dépistage, diagnostic et prise en charge » qui a été approuvée par le comité de médecine fœto-maternelle de la SOGC.

Méthodes : Des articles publiés en anglais ont été récupérés par l'intermédiaire de recherches menées, en janvier 2011, dans PubMed ou Medline, CINAHL et *Cochrane Library* au moyen d'un vocabulaire contrôlé approprié (termes MeSH – « *fetal growth restriction* » et « *small for gestational age* ») et de mots clés pertinents (« *fetal growth* », « *restriction* », « *growth retardation* », « *intrauterine growth restriction [IUGR]* », « *low birth weight* », « *small for gestational age* »). Les résultats ont été restreints aux analyses systématiques, aux essais comparatifs randomisés / essais cliniques comparatifs et aux études observationnelles prospectives et rétrospectives de grande qualité. La littérature grise (non publiée) a été identifiée par l'intermédiaire de recherches menées dans les sites Web d'organismes s'intéressant à l'évaluation des technologies dans le domaine de la santé et d'organismes connexes, dans des collections de directives cliniques, dans des registres d'essais cliniques et auprès de sociétés de spécialité médicale nationales et internationales.

Résultats : Les données issues d'au moins un essai comparatif bien randomisé, d'analyses Cochrane et d'études de cohorte de grande qualité ont été combinées pour permettre aux cliniciens d'optimiser leur pratique en ce qui a trait au dépistage, au diagnostic et à la prise en charge du retard de croissance intra-utérin.

Conclusion : Des percées considérables ont été accomplies (dont plusieurs sont issues d'essais comparatifs bien randomisées) en vue d'améliorer l'efficacité du dépistage, du diagnostic et de la prise en charge des grossesses chez lesquelles l'on soupçonne la présence d'un RCIU. Les grossesses qui présentent un RCIU d'apparition tardive peuvent être prises en charge tout aussi efficacement en procédant à un accouchement précoce ou à un accouchement différé (s'accompagnant d'une surveillance accrue) pour anticiper des issues favorables. En revanche, de nombreux aspects de la prise en charge du RCIU d'apparition précoce nécessitent la tenue d'autres essais cliniques.

J Obstet Gynaecol Can 2012;34(1):17–28

INTRODUCTION

An important consideration for all obstetrical caregivers is to ensure that reasonable efforts are made to identify and correctly manage pregnancies affected by intrauterine growth restriction. While most IUGR discovered during the third trimester is due to a degree of placental insufficiency, and therefore generally has a good perinatal prognosis, care must be taken to consider the extensive differential diagnosis of maternal, fetal and placental factors summarized in Table 1. Determining the likely etiology of IUGR during the antepartum period is important to reduce the rate of preventable perinatal loss, especially stillbirth of normally formed fetuses.[1] The risk factors for IUGR, including maternal age,[2] co-existent medical problems,[3,4] and assisted reproductive technology, have increased over time.[5–7] Neonatal mortality in both term and preterm neonates is significantly increased in those diagnosed with IUGR antenatally.[8] The potential morbidity from IUGR can be classified into short and long-term problems, which are summarized in Table 2.[9] Considerable advances in this area of perinatal medicine mean that increasing numbers of pregnancies with IUGR are identified during the antenatal period and survive with careful intensive fetal monitoring and coordinated delivery and neonatal care.[10]

METHODS

Publications in English were retrieved through searches of PubMed or Medline, CINAHL, and the Cochrane Library in January 2011 using appropriate controlled vocabulary via MeSH terms (fetal growth restriction and small for gestational age) and any key words (fetal growth, restriction, growth retardation, IUGR, low birth weight, small for gestational age). Retrieved publications were restricted to systematic reviews, randomized controlled trials or controlled clinical trials, and high-quality prospective and retrospective observational studies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

ABBREVIATIONS

AFI	amniotic fluid index
BPP	biophysical profile
EFW	estimated fetal weight
hCG	human chorionic gonadotropin
IPS	integrated prenatal screening
IUGR	intrauterine growth restriction
MCA	middle cerebral artery
MoM	multiples of the median
PAPP-A	pregnancy-associated plasma protein A
PI	pulsatility index
SFH	symphysis-fundal height
UPVI	uteroplacental vascular insufficiency
UtA	uterine artery

TERMINOLOGY

The terminology used to describe abnormal fetal growth is inconsistent and confusing. Obstetrical care providers desire to identify with confidence a sub-population of fetuses with pathological growth restriction while minimizing risks to normal pregnancies from false-positive screening test results. The refinement of ultrasound techniques, including detailed anatomical scanning, placental evaluation, and Doppler assessment of placental and fetal vessels, has allowed us to distinguish more accurately between pathological fetal growth restriction from a variety of fetal and placental causes and pregnancies with a small but healthy fetus whose growth is appropriate for its maternal host characteristics.

Intrauterine Growth Restriction

Since the risk of significant morbidity is increased in term newborns below the 10th percentile for weight, an estimated fetal weight of < 10th percentile will be used in this document to define the SGA fetus in utero.[11] This definition is recommended by most national societies including those of the United States[12] and the United Kingdom[13] though no current Canadian (SOGC) guideline has explicit definitions of SGA or IUGR. IUGR is distinct from SGA, in that it implies a pathological process in which one or more factors (summarized in Table 1) inhibit the pre-programmed genetic growth potential.[14,15] This distinction is important, because neonates with a prenatal diagnosis of IUGR have more perinatal morbidity than neonates who meet the criteria for a diagnosis of SGA, but have an otherwise healthy in-utero environment.[16] Therefore, IUGR is the key differential diagnosis of SGA when fetal biometry on ultrasound is below the 10th percentile.

Uteroplacental Vascular Insufficiency

The most common pathological finding at delivery in severe IUGR pregnancies[17] and in third trimester "unexplained" stillbirths[18] is gross and histopathologic evidence of uteroplacental vascular insufficiency. Not only can ultrasound assessment review fetal anatomy and therefore generally exclude rare fetal causes of IUGR, but

it can also look for direct evidence of abnormalities of placental formation and blood supply. Doppler studies of the uterine and umbilical arteries, together with ultrasound assessment of placental morphology, may be used to establish a diagnosis of placental insufficiency.[19]

Fetal Body Proportions

Evaluation of fetal symmetry by fetal biometry (relative size of head to abdomen and femur) was proposed more than 30 years ago as a tool to distinguish an intrinsic fetal growth problem (symmetric IUGR) from an extrinsic growth problem due to suspected placental insufficiency (asymmetric IUGR) in the third trimester.[20] Subsequent studies of fetal symmetry across a variety of underlying fetal causes of IUGR (aneuploidy, congenital infection, syndromes) indicate that this is a valid concept, but it should not be used in isolation to determine the underlying cause.[15,21,22] In current practice, with increased use of obstetric ultrasound,[23] the possibility of IUGR is often considered during the second trimester. These earlier and more severe forms of IUGR are also mostly asymmetric.[24] Moreover, fetuses with these forms have disproportionately short femurs, to the extent that inclusion of the femur length in biometry equations can significantly underestimate fetal weight.[25] Therefore simple review of fetal biometry is a valuable method of distinguishing an IUGR fetus that has made survival adaptations in the face of uteroplacental vascular insufficiency from a healthy symmetrically developed SGA fetus.

SCREENING FOR IUGR

There are currently no accurate predictive tests for IUGR, and it is not recommended to screen low risk populations with routine ultrasound.[26] Useful screening tools are embedded in the patient's history, physical examination, and general laboratory tests during routine antenatal care.

History

Screening for IUGR by clinical risk factor assessment is already routinely performed by obstetrical care providers. These risk factors can be divided into three broad categories: maternal, fetal, and placental, as shown in Table 1. Accurate dating is a prerequisite for pregnancy care and the tracking of fetal growth. This should be established from a careful history and correlated with the results of early ultrasound examinations in the first or second trimester.

Physical Examination

Fetal growth is estimated during routine antenatal care using either abdominal palpation or the more formal determination of symphysis–fundal height measurement. Abdominal palpation detects only 30% to 50% of IUGR fetuses[27–29] and has thus been replaced by the determination of SFH at clinical visits following the fetal anatomical ultrasound examination (after 20 weeks). The accuracy of SFH assessment of uterine growth is limited by abnormal fetal lie, fibroids, maternal obesity, and, in late gestation, by fetal head engagement. Within these limitations, a lag in uterine size of > 3 cm is a reasonable clinical guide to the need for prompt arrangement of a screening ultrasound examination to estimate fetal weight. A wide range of sensitivities (27% to 86%) and specificities (80% to 96%) have been reported for the detection of IUGR using SFH,[30–35] reflecting the inherent challenges of the method and the use of variable diagnostic criteria for IUGR.[11] The Cochrane database review of SFH measurements[36] includes the only randomized clinical trial comparing SFH measurements with abdominal palpation

Table 1. Maternal, fetal and placental risk factors for IUGR (modified from data contained in[121,169])

Maternal
Previous pregnancy with SGA or IUGR
Constitutionally small mother or low pre-pregnancy weight
Poor maternal weight gain and nutrition (< 1500 cal/day)
Low socioeconomic status
Smoking, alcohol, illicit drugs
Extremes of maternal age: < 16 years, > 35 years
Assisted reproductive technology
New partner for subsequent pregnancy
Teratogens: anticonvulsants, methotrexate, warfarin
Vascular disease: chronic hypertension, pre-gestational diabetes, antiphospholipid antibody syndrome, collagen vascular disease (e.g., systemic lupus erythematosus, thrombophilia, renal disease, Crohn's disease, ulcerative colitis)
Hypoxia—high altitude (> 10 000 ft)
Anemia including hemoglobinopathies
Fetal
Congenital infections: cytomegalovirus, syphilis, rubella, varicella, toxoplasmosis, tuberculosis, HIV, congenital malaria
Aneuploidies: triploidy, trisomy 13, 18, 21
Microdeletions: 4p-
Imprinting: Russell-Silver syndrome
Genetic syndromes or fetal anomalies
Discordant growth in multiple gestation
Placental
Uteroplacental vascular insufficiency
Chorionic separation (partial abruption, hematoma)
Extensive villous infarction
Marginal or velamentous cord insertion (chorion regression)
Major uterine malformations (unicornuate uterus)
Confined placental mosaicism
Advanced placental maturation[115,118]

Table 2. Perinatal and pediatric complications from IUGR[9]

Antepartum	Intrapartum	Neonatal	Pediatric
• Stillbirth • Iatrogenic prematurity • Abruption • Perinatal stroke	• Abnormal fetal status (fetal heart rate tracing) • Asphyxia • Emergency Caesarean section • Need for active neonatal resuscitation • Perinatal stroke	• Hypothermia • Hypoglycemia • Hypocalcemia • Polycythemia • Sepsis • Coagulopathy • Hepatocellular dysfunction • Respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, especially in premature IUGR neonates < 750 g • Hypoxic-ischemic encephalopathy	Increased risk of: • Short stature • Cerebral palsy • Developmental delay • Behavioural and emotional problems • Lower IQ scores • Chronic lung disease • Future cardiovascular disease and hypertension

that did not support use of SFH measurements.[37] Although SFH measurements are not associated with an improvement in perinatal outcomes,[27] they remain in clinical use in Canada, but are often supplemented by ultrasound examinations in pregnancies with additional clinical risk factors, including age, obesity, fibroids, and medical comorbidities, largely because of the unreliability of SFH measurements alone.

Use of customized growth curves

The validity of both SFH determined by clinical examination and EFW determined by ultrasound to identify IUGR fetuses may be improved though customized standards[38,39] that are designed to identify fetuses that measure < 10th percentile of their expected genetic growth potential. This approach adjusts the growth curve percentiles for anthropomorphic variables such as maternal height, weight, parity, and fetal sex.[16] Evidence from controlled, non-randomized trials supports this approach.[40,41] In addition, customized growth percentiles are better correlated with adverse pregnancy events and reduce the frequency of additional testing because of false-positive screening information.[40,42,43] Although most Canadian obstetrical practitioners still use population-based growth curves,[44] the website of the Gestational Network[45] provides further information and permits the GROW (Gestation Related Optimal Weight Chart) program to be downloaded free of charge. These tools have been incorporated into routine community obstetric practice in several multicultural urban areas of the United Kingdom to reduce false-positive interventions in cases of suspected IUGR.[46] This approach may be of particular value in multi-ethnic urban communities in Canada, although a recent study that simulated the improvement in the accuracy of the diagnosis of IUGR using Canadian data suggested only a limited benefit.[47]

Biochemical Screening for Pregnancies at Risk of IUGR

First trimester screening, second trimester quadruple maternal serum screening, or integrated prenatal screening tests are offered to varying degrees in Canada to screen singleton pregnancies for trisomy 21 and for fetal structural defects such as open neural tube defects.[48] These examinations determine maternal blood levels (expressed as multiples of the median value for gestation) of PAPP-A, alpha-fetoprotein, dimeric inhibin A, and free or total hCG. The results are reported in the context of a risk assessment for trisomy 21 or a structural anomaly; however, it is important to note the MoM levels of the above analytes, as significant deviations from normal may be a marker of early-onset placental insufficiency.

Low levels of PAPP-A[49–51] and elevated levels of the other three analytes (alpha-fetoprotein, dimeric inhibin A, and hCG)[52–56] are associated with IUGR, preeclampsia, and other adverse perinatal outcomes when the fetus is unaffected by trisomy 21 or neural tube defects. The choice of cut-off values will vary according to local capacity for additional ultrasound testing. The predictive accuracy characteristics for IUGR for any single analyte marker abnormality alone are too low to warrant intensive fetal surveillance without additional diagnostic testing. Exceptions include extreme (> 10 MoM) values for alpha-fetoprotein[52] or hCG.[53] The risk of IUGR and associated stillbirth is higher when two or more analytes are abnormal.[54,57–59] At a population-based level, two or more abnormal analytes may identify approximately one third of pregnancy losses and deliveries before 32 weeks of gestation.[48] Ultrasound assessment, using uterine artery Doppler and placental morphology, is of value to distinguish a subset of pregnancies at high risk of early severe IUGR.[56,60,61]

Ultrasound Examination

Dating

The importance of routine early dating in the first or early second trimester is evident. With the more widespread availability of IPS testing, the need to establish gestational age after 20 weeks is rare in Canada. Several parameters have been investigated for late dating purposes, including fetal liver volume,[62] humeral length,[63] subcutaneous tissue thickness,[64] superior cerebellar vermian width,[65] and transverse cerebellar diameter.[66] Of these, the transverse cerebellar diameter is the easiest to perform and the most effective, being normal in 75% of 73 previously dated IUGR fetuses.[66]

Fetal anatomy

The routine 19- to 20-week fetal anatomical examination includes several components that are relevant to the risk of developing IUGR. These are fetal biometry (asymmetry with short femurs),[67] fetal abdomen (echogenic bowel),[68] amniotic fluid (oligohydramnios), and assessment of the placenta and umbilical cord. The current International Society for Ultrasound in Obstetrics and Gynecology practice guideline for this examination requires only documentation of placental location, description of major abnormalities (hemorrhage, chorio-angioma), and consideration of invasive placentation in high-risk women; determination of cord vessel number is optional.[69] A recent large-scale population-based Canadian study underscores the importance of cord vessel documentation, demonstrating significant independent associations between a two-vessel cord and structural fetal abnormalities, aneuploidy, preterm delivery, and perinatal loss.[70] Follow-up ultrasound assessment in the third trimester is therefore recommended for pregnancies with a two-vessel cord.

Fetal biometry

Ultrasound determination of head circumference, biparietal diameter, femur length, and abdominal circumference can be used to derive an EFW using any one of several formulas available.[71–74] The Hadlock formula is the most widely accepted method,[75] although measurements of abdominal circumference alone are equally accurate and are of practical importance if the fetal head is engaged near term or difficult to visualize (for example, in multiple pregnancies).[11] It is important to appreciate that all biometry methods assessing fetal weight have significant error in the range of 10% to 15%,[76,77] especially at the two extremes of size. In general, EFW measurements within the normal range (10th to 90th percentile) exclude IUGR with a false-negative rate of < 10%.[78,79]

Repeated EFW measurement

Information obtained at a single ultrasound examination may be used to make a diagnosis of fetal growth restriction, but growth is a longitudinal process. When there are no acute concerns for fetal health, the accuracy of EFW for the diagnosis of IUGR may be improved by serial measurements. There is no value in repeating estimates of fetal weight before 14 days have elapsed[22,80] because of limitations in ultrasound accuracy and the rate of fetal growth. When fetal growth can be followed by serial estimates of fetal weight, a diagnosis of IUGR may be established from falling percentiles (e.g., from the 25th to the 10th) together with other features of IUGR such as changes in the umbilical artery Doppler waveforms (see below). These point estimates of fetal size are used to distinguish the healthy fetus that is growing normally along its biologically determined trajectory from an IUGR fetus whose growth potential is inhibited by one or more factors or diseases.

Amniotic fluid

The assessment of amniotic fluid is an integral part of any ultrasound examination of fetal growth. Amniotic fluid volume can be reported either as the maximum vertical pocket, or the four-quadrant AFI. AFI has a wide distribution and varies with gestational age.[81] Despite this limitation, low amniotic fluid volume may reasonably be defined after 37 weeks as an AFI < 5 cm or as a maximum vertical pocket < 2 cm. Isolated oligohydramnios is not associated with adverse perinatal outcomes.[82] However, the combination of IUGR and oligohydramnios is associated with fetal distress leading to Caesarean section in labour, admission to NICU, stillbirth, and neonatal death mostly attributable to placental insufficiency.[83–87] When oligohydramnios is found and IUGR is suspected from fetal biometry, umbilical cord artery Doppler studies are indicated. Additional Doppler studies may be required if the umbilical cord artery Doppler studies are abnormal, in order to refine the diagnosis (uterine artery Doppler) or prognosis (fetal arterial and venous Doppler). By contrast, the combination of IUGR and polyhydramnios (AFI > 25 cm) suggests non-placental fetal causes. In such circumstances a careful review of fetal anatomy is warranted to search for congenital abnormalities and to consider the possibility of aneuploidy.[88]

Umbilical artery Doppler studies

In contrast to amniotic fluid assessment, Doppler studies are not an integral part of a fetal biometry ultrasound. At present, there is no evidence to suggest that routine screening of low-risk pregnancies with umbilical artery Doppler reduces perinatal mortality or severe morbidity due to placental insufficiency.[26,89] However, in the context of a fetus with a diagnosis of IUGR by biometry, umbilical artery Doppler studies aid in diagnosing the cause of IUGR and the subsequent need for increased fetal surveillance (see below) that can reduce perinatal mortality and severe morbidity.[90,91]

Uterine artery Doppler studies

Uterine artery Doppler screening at 19 to 23 weeks of gestation has been evaluated as a screening tool for IUGR in the general obstetrical population. This is not recommended as an isolated screening test for IUGR in low-risk pregnancies,[92,93] but recent data illustrate the potential value of this screening test for pregnancies at risk of stillbirth before 36 weeks because of IUGR and placental disease.[94]

Comprehensive ultrasound in the third trimester

Routine, comprehensive ultrasound examination in the third trimester for low-risk pregnancies, reviewing fetal anatomy, presentation, and growth is an attractive concept with several potential benefits.[11,95] However a review of seven randomized clinical trials in a total of 25 036 low-risk women[26] found no evidence that this screening examination would reduce mortality or severe morbidity from IUGR in clinically low-risk women.[96–101]

Doppler Assessment in Pregnancies at High Risk for IUGR

The term "high-risk" refers to a pregnancy with one or more medical, biochemical, and/or obstetric risk factors for IUGR.

Umbilical artery Doppler studies

After 24 weeks of gestation, an ultrasound examination that includes umbilical artery Doppler studies is associated with a subsequent reduction in perinatal mortality and severe perinatal morbidity because of enhanced maternal-fetal surveillance of the subset with abnormal test results.[90,91] The identification of IUGR with abnormal umbilical artery Doppler studies merits consultation with the regional perinatal centre for comprehensive ultrasound assessment and clinical consultation because of the risk of spontaneous or indicated preterm delivery. Where available, MCA and ductus venosus Doppler studies may be useful because they in part define the fetal response to abnormal placental function, and they can identify a subset of pregnancies at risk of necessitating earlier delivery from IUGR to prevent stillbirth. Deteriorating umbilical artery Doppler studies and co-existent severe preeclampsia suggest progressive thrombotic placental pathology[102–104] and are an indication for increased fetal surveillance guided by fetal Doppler studies.

Umbilical artery Doppler waveforms should be obtained from either a free loop of cord or near the placental end, because false-positive waveforms with low end-diastolic velocities will be obtained when waveforms are obtained at the fetal cord root or within the fetal abdomen surrounding the bladder.[105] This is particularly relevant in IUGR fetuses.[106] An additional cause of false-positive reporting is discordant umbilical artery diameter; this can be recognized in real-time images of the umbilical cord in the context of variable waveforms.[107] In this situation the larger vessel should be insonated and its more normal waveforms reported, because these data correlate with fetal growth and pregnancy outcome.[108] A final caveat is in discordant growth in twin pregnancy, where for technical reasons insonating the umbilical arteries inside the fetus or at the cord root is necessary to be certain of waveform origin.[109] Use of colour Doppler, to track the cord out into a free loop to gate the waveforms, is encouraged to reduce the risk of false-positive reporting.

Uterine artery Doppler studies

Pregnancies with abnormal IPS biochemistry testing, such as low serum PAPP-A, elevated serum alpha-fetoprotein, or elevated inhibin, are at risk of IUGR from uteroplacental vascular insufficiency. If abnormal uterine Doppler waveforms are identified at 19 to 23 weeks, this further refines the risk of IUGR due to placental insufficiency, with likelihood ratios in the range of 3 to 5.[19,56,110–112] Since UtA Doppler waveform pulsatility declines with gestation in the second trimester, the phenomenon of "delayed normalization,"[113] which has an intermediate risk for IUGR,[114] may be seen. UtA Doppler waveforms, if initially abnormal, can be repeated at 26 weeks and at 30 weeks to define the extent of uteroplacental vascular insufficiency. When UtA Doppler studies remain persistently abnormal, placental ultrasound (see below) may identify a small or damaged placenta.

Placental ultrasound

Placental examination is emerging as a valid assessment tool in IUGR because a high proportion of IUGR placentas at delivery are small[17,104] and contain grossly visible lesions that correlate with ultrasound imaging.[115] The presence of a small or damaged placenta on ultrasound increases the likelihood of placental insufficiency as the cause of IUGR and may be more relevant than uterine artery Doppler studies (for example, in women with low PAPP-A).[61] The incorporation of placental morphology assessment at 19 to 23 weeks gestation (small thick placenta, with echogenic cystic lesions, or a jelly-like appearance due to abnormal formation of placental villi) with IPS blood tests and uterine artery Doppler studies can effectively refine the risk of extreme preterm birth in women judged to be at high risk for placental complications.[19] Placental ultrasound assessment at later gestations may be predictive of IUGR. In a cohort of 1011 low-risk women, advanced placental maturation at 36 weeks was strongly predictive of IUGR.[116]

MANAGEMENT OF INTRAUTERINE GROWTH RESTRICTION

Once a diagnosis of IUGR has been established, consideration of the need for further investigations, consultation or advice from a regional perinatal centre, and ongoing maternal–fetal surveillance should be instituted. Given the associations between placental injury, IUGR, and preeclampsia,[17] women with a diagnosis of IUGR should be educated about the relevant symptoms of hypertension in pregnancy. Simple measures such as smoking reduction or cessation, even during pregnancy, may improve fetal growth.[117–120] Although such measures may have only a small impact on birth weight or perinatal morbidity, they should not deter clinicians from emphasizing the broader maternal–infant health and economic benefits of smoking cessation to pregnant women.

Aneuploidy risk assessment is an important aspect of IUGR management and should be explicitly reviewed when a diagnosis of IUGR is made. Consideration of amniocentesis is appropriate, especially in the context of an abnormal fetal anatomical ultrasound examination (documentation of fetal anomalies or soft markers associated with aneuploidy). Amniocentesis in the context of IUGR in a younger woman with normal nuchal translucency at 11 to 13 weeks and a normal subsequent anatomical ultrasound (absence of soft markers) may confer more risk than benefit. Amniocentesis remains a logical choice for a subset of women with IUGR and fetal abnormalities diagnosed after the local termination of pregnancy limit (generally 22 weeks), because the discovery of a lethal aneuploidy (triploidy or trisomy 18[88]) may either guide obstetric decisions in labour (such as the avoidance of Caesarean section for fetal distress) or prompt induction of labour in the maternal interest. Given the multiple relevant factors, a decision to undertake amniocentesis in IUGR should be made with the woman and her partner on an individual basis.

Screening of maternal serum or amniotic fluid for congenital infections is warranted on a selected basis, although it tends to have a low detection rate (with the exception of cytomegalovirus[121]) in the absence of specific findings such as ventriculomegaly.

Selective referral for fetal echocardiography should be considered for several reasons and in certain circumstances: first, because a wide range of congenital heart lesions are associated with low birth weight after adjustment for confounding factors[122]; second, following an abnormal screening examination or if other evidence of aneuploidy is suspected[88]; and third, when no obvious explanation is found for abnormal umbilical artery Doppler studies.[123]

In general, following consideration of the above tests, the etiology of IUGR will fall into one of three categories: healthy small fetus (30%), aneuploidy (or other fetal pathology) (approximately 10%), or UPVI (approximately 60%).

The remainder of this review will focus on management of the pathologically growth restricted fetus secondary to UPVI. The initial step in management of IUGR secondary to UPVI is to establish the likely prognosis. This is determined by consideration of gestational age, the severity of IUGR based on evaluation of fetal biometry, umbilical artery and fetal Doppler studies, amniotic fluid volume, and relevant maternal comorbidities, especially the presence and severity of preeclampsia.[124] In referral practice, a subset of severe IUGR fetuses may be deemed pre-viable with experience.[61] Parental counselling regarding prognosis should ideally be carried out by a local interdisciplinary team including an obstetrician and neonatologist, ideally using locally derived newborn outcome data. Since most severe preterm IUGR fetuses with abnormal umbilical artery Doppler studies do not tolerate induction of labour, counselling should include discussion of the implications and advantages of planned Caesarean section. These patients are at high risk of developing preeclampsia or HELLP syndrome[125] and should be monitored weekly, as a minimum, for symptoms, biochemical or hematologic changes, hypertension, and proteinuria.[104] Since home blood pressure monitoring devices are now relatively inexpensive, we encourage their use in women with comorbidities that further increase their risk of preeclampsia.

Antenatal Fetal Surveillance in UPVI

Once viability has been established, and a plan of maternal–fetal monitoring agreed, a range of tools can be used to provide safe antenatal surveillance of the IUGR fetus leading to planned delivery, either by planned Caesarean section or induction of labour. These antenatal tests, which can be viewed as long-term (valid for > 2 weeks), medium-term (valid for 1 week), or short-term (valid for 1 to 3 days) tests of fetal well-being, are summarized in Table 3. Combinations of these tests can be used to monitor fetuses with IUGR. They include tests that can be provided easily by the local caregiver (non-stress test, biophysical profile including amniotic fluid volume assessment and umbilical artery Doppler studies, serial fetal biometry) in conjunction with additional examinations by a maternal-fetal medicine specialist or radiologist (fetal Doppler studies and the provision of inpatient care for early-onset preeclampsia or anticipated need for level 3 neonatal intensive care).

Initially, the commencement of long-term tests is adequate provided there are no significant maternal comorbidities (especially early-onset preeclampsia) and the

Table 3. Long-, medium-, and short-term tests of fetal well-being

Long term (valid for 2 weeks)	Medium term (valid for 1 week)	Short term (valid for 1 to 3 days)
Uterine artery Doppler studies	Umbilical artery Doppler studies	Non-stress test
Placental morphology including Grannum grade	Amniotic fluid	Fetal arterial and venous Doppler studies
Fetal biometry	Biophysical profile score	

umbilical artery Doppler studies are normal. The baseline assessment should include estimation of fetal weight, amniotic fluid volume, and umbilical artery Doppler studies. If repeat fetal biometry after two weeks shows reduced growth, especially in combination with reduced amniotic fluid, abnormal umbilical artery Doppler studies, or the development of preeclampsia, either medium-term tests should be added on a weekly basis or admission to hospital should be considered for easier access to more frequent testing, maternal assessment, and treatment of hypertension. Stepwise deterioration in umbilical artery Doppler studies, especially to absent end-diastolic flow velocity in a free loop of cord, is an indication for short-term testing. Preeclamptic women may ideally be managed with non-stress test monitoring and blood pressure control on an inpatient basis, while normotensive women with easier access to more specialist fetal Doppler studies could remain as outpatients with examinations twice per week. A full assessment using all tests is advised where no interval growth can be demonstrated over a two-week period.

Biophysical Profile

The biophysical profile is a method of assessing the presence of fetal asphyxia and/or chronic hypoxia.[126] It is based on five variables: fetal breathing, fetal movement, fetal muscle tone, non-stress fetal heart rate testing, and semi-quantitative amniotic fluid volume assessment. Each of these variables is scored 2 points if present and 0 points if absent. The first four variables are assessments of immediate fetal health, and the last is a measure of long-term fetal health; the average time for a chronically hypoxic fetus to develop severe oligohydramnios from normal amniotic fluid levels is 23 days.[127] In a large prospective study[128] of 86 955 high-risk patients undergoing biophysical profiling, the false-negative rate ranged from 0.7 to 2.3/1000 between two centres. In the 65 cases of fetal demise within seven days of having a "normal" BPP, the average interval from a normal BPP (e.g., 8/8 or 8/10 with normal amniotic fluid) to fetal demise was 3.6 days. Therefore, the use of biophysical profile has good negative predictive value in high-risk populations, and it can be considered a short-term test of fetal well-being. As a tool for fetal well-being, BPP has mostly been evaluated in near-term pregnancies.

Non-Stress Test

The non-stress test (cardiotocography) is a simple and readily accessible short-term method of fetal monitoring. However a meta-analysis of cardiotocography to assess fetal condition concluded that "antenatal CTG has no significant effect on perinatal outcome or interventions such as early elective delivery."[129] The rate of false-positive interpretation of non-stress tests may be reduced by the use of computerized interpretation.[129,130] Nevertheless, on the basis of current evidence, no method of non-stress testing should be used in isolation. The non-stress test is best used selectively; for example, it could be used to provide reassurance when a biophysical profile is 6/8 because of lack of sustained fetal breathing, to educate women in a day-unit setting to appreciate fetal activity, and for intensive fetal monitoring up to twice daily in an inpatient setting to advance gestational age in IUGR pregnancies at < 32 weeks' gestation. Significant concerns based on Doppler studies (see below) after 32 weeks are usually best managed by delivery, given the more favourable prognosis of the newborn and low incremental reduction in serious long-term morbidity.

Umbilical Artery Doppler Studies

The initial sign of feto-placental vascular insufficiency is a reduction in end-diastolic flow, reflected by an elevated PI value. The disease may progress to absent end-diastolic flow, and finally to reversed end-diastolic flow.[131] In our experience, one third of high-risk pregnancies with bilateral abnormal uterine artery Doppler studies at 19 to 23 weeks will develop severe IUGR with absent/reversed end-diastolic flow in the umbilical arteries.[104] The pathology of absent/reversed end-diastolic flow is complex, and involves combinations of abnormal early vascularization of the placental villi,[132] infarction or hemorrhage in placental segments,[17] thrombotic vasculopathy of the feto-placental circulation,[133] and finally fetal cardiac failure with reversed aortic isthmic flow diverting cardiac output to the fetal brain.[134] When low diastolic flow velocities are observed, care should be taken to ensure that either a free loop or the placental end is insonated[106] and that the pulsed gate placement and angle is guided by colour Doppler. Magnifying the screen and use of a narrow pulsed gate will

ensure that reversed end-diastolic flow is recognized, since using a wide pulsed gate may hide the reversed end-diastolic flow component in the umbilical venous flow channel. Umbilical artery Doppler studies generally deteriorate slowly, unless there is co-existent preeclampsia.[135] The prognosis for survival and neuro-developmental outcome in IUGR is dominated by gestational age at delivery and birth weight, but is compounded by the severity of umbilical Doppler waveform abnormalities.[136,137]

Fetal Arterial and Venous Doppler Studies

As changes occur in the umbilical arteries, fetal hypoxemia causes cerebral vasodilation—the "brain-spring" effect.[138] Assessment of the fetal cerebral circulation can be performed by MCA Doppler studies, with reduced PI values suggesting redistribution to the brain. This is an adaptive phenomenon and may be observed for some time. Serial MCA Doppler including assessment of the peak velocity[139] may be of prognostic value. Assessment of the MCA PI prior to induction of labour in term IUGR fetuses distinguishes a subset at high risk (> 50%) of Caesarean section from fetal distress that may benefit from planned Caesarean section.[140]

Doppler studies of the venous circulation are indicated when an IUGR fetus shows brain redistribution.[138] The free loop of the umbilical vein can be screened for pulsations, and the ductus venosus can be identified as the aliasing point at the top of the intrahepatic vein. Progressively deep a-waves in the ductus venosus waveform are indicative of right heart strain in the fetus and correlate with fetal metabolic acidosis at delivery.[141] Delivery is generally indicated in IUGR fetuses that have abnormalities of the MCA and ductus venosus waveforms in the context of abnormal umbilical artery Doppler studies.[137]

Umbilical artery Doppler studies are now widely available across Canada for the assessment of a suspected IUGR fetus. More detailed Doppler studies of the MCA/ductus venosus/umbilical vein in IUGR fetuses are best performed in level II or tertiary perinatal centres given the likely need for coordinated delivery with neonatal intensive care.

TREATMENT OF IUGR

Once the etiology of IUGR has been established, and the well-being of the fetus confirmed, various investigators have evaluated potential treatment modalities in the hope of either extending gestational age at delivery or increasing eventual birth weight. Unfortunately none have been very successful, and the evidence has been assessed in several Cochrane reviews. These potential treatments include maternal oxygen administration,[142] additional nutrient supplements,[143] hospitalization for bedrest,[144] calcium channel blockers,[145] hormones,[146] betamimetics,[147] plasma volume expansion,[148] low-dose ASA,[149] and heparin.[150]

Early diagnosis and treatment of co-existent preeclampsia, including education about the symptoms of severe preeclampsia, may contribute to reduced maternal mortality and long-term morbidity from severe untreated or fulminating disease. Hypertension is the most common maternal comorbidity in IUGR and frequently overrides fetal status in determining the timing of delivery.[151]

Anti-Platelet and Anticoagulant Agents

The use of low-dose ASA therapy in populations at high risk, such as those with abnormal uterine artery Doppler studies, is controversial.[149,152] The largest randomized control trial screening nearly 20 000 women showed no benefit of ASA,[153] although a meta-analysis of several earlier trials of smaller focused studies indicated some benefit.[152] This contrast suggests publication bias; however, low-dose ASA is commonly prescribed to prevent IUGR and/or preeclampsia despite having no impact on perinatal morbidity or mortality.

Several trials have evaluated the effectiveness of prophylactic dosing regimens of heparin to improve perinatal outcomes, including preventing IUGR, in women with and without an identifiable thrombophilia disorder. A recent systematic review of these trials shows no clear benefit of heparin for this indication, although use of low molecular weight heparin may significantly reduce the risk of severe preeclampsia.[150] Since low molecular weight heparin is an expensive parenteral drug with implications for anaesthetic safety at the time of delivery, its use should be restricted pending further trials. Pilot trials of chronic maternal oxygenation, in an effort to correct underlying chronic fetal hypoxemia in established IUGR with abnormal umbilical artery Doppler studies, have shown promising results and deserve further study, but this approach is not used in clinical practice.[142]

Inpatient Care

The importance of making a decision to transfer and/or admit a woman to hospital because of IUGR (especially with co-existent preeclampsia), and subsequently to be proactive with timing of delivery, must not be underestimated. Inpatient care solves geographic burdens of frequent hospital visits, especially to regional centres, and provides hypertension monitoring, daily non-stress testing, access to pediatric consultation, and immediate access to the appropriate level of anticipated neonatal pediatric care (most often in tertiary perinatal centres).

Because of a degree of pre-existing metabolic acidosis in IUGR fetuses, caution should be exercised when giving antenatal corticosteroids for lung maturation in an outpatient setting in the context of absent or reversed end-diastolic flow velocity in the umbilical arteries before 32 weeks of gestation.[154] Corticosteroids normally improve abnormal umbilical artery Doppler waveforms for up to one week, but in a subset of fetuses they may deteriorate.[155] Unless recognized, this phenomenon has the potential to confuse ultrasound interpretation in the days following a course of antenatal steroids.

Timing and Mode of Delivery

The optimal timing of delivery is currently the source of much controversy, because of the many relevant clinical and ultrasound factors that clinicians must consider in addition to patient preferences.

Late-onset IUGR

For the more common scenario of mild or late-onset IUGR, the recently published DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term) provides some guidance.[156] This multicentre randomized equivalence trial was conducted in singleton pregnancies of > 36+0 weeks' gestation with suspected IUGR. Three hundred twenty-one pregnant women were randomized to induction of labour and 329 to expectant monitoring. Induction group infants were delivered on average 10 days before babies in the expectant monitoring group and weighed 130 grams less. Delayed delivery increased both the risk of a postnatal diagnosis of IUGR and the risk of developing preeclampsia. Despite these incurred risks and utilization of health care resources, no differences were observed in the rate of Caesarean section (14% in each arm) or in composite adverse neonatal outcome (defined as death before hospital discharge [there were no perinatal deaths in either arm], 5-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, or admission to the intensive care unit). Several limitations of the study are important to consider. First, almost one third of recruited women did not have IUGR after delivery (i.e., had a false-positive diagnosis of IUGR). This finding nicely illustrates the challenges of diagnosing late-onset IUGR, but the number could have been reduced by the exclusion of healthy symmetrically small fetuses with normal amniotic fluid volume or the use of customized growth curves to recognize appropriately grown, yet small, fetuses. Second, fetal monitoring in the delayed delivery group did not include MCA Doppler studies, which are known from observational studies to be more relevant than umbilical artery Doppler studies.[140,157] Third, no specific information relevant to placental function, available at the point of randomization (discussed above), was included. Advanced placental maturation, identified by the Grannum grading system,[158] is a contentious subject in the context of IUGR management. A major risk factor for advanced (grade 3) placental maturation is smoking, but in the absence of this history a grade 3 placenta in the late third trimester is associated with a high rate of IUGR diagnosed postnatally.[159] Given the diagnostic challenges of making a direct diagnosis of IUGR after 36 weeks by biometry, the observation of a Grannum grade 3 placenta in a non-smoking woman may be considered a risk factor for late onset IUGR.[116] When subjected to a randomized controlled trial, weekly fetal assessment following the observation of a Grannum grade 3 placenta at 36 weeks of gestation reduced the risk of perinatal death.[160]

Presently we recommend that SGA fetuses with a normal BPP and non-stress test may safely remain undelivered after 37 weeks if they have the following ultrasound observations: symmetrical phenotype, normal uterine/umbilical/MCA Doppler waveforms, normal amniotic fluid volume and normal maturation of the placenta (Grannum grade 0 to 2), a reasonable prospect of a safe vaginal delivery (vertex presentation, no previous uterine scar), and that the mothers are normotensive with no relevant comorbidities (insulin-dependent diabetes, need for antepartum anti-coagulation). More than 50% of the women in the expectant arm of the DIGITAT trial[156] ultimately were induced for maternal or fetal indications, illustrating the relevance of close surveillance in late-onset IUGR if a decision is made not to deliver the fetus. The results of this trial illustrate the validity of induction of labour as an alternative to increased maternal–fetal surveillance. Induction may be especially relevant in practical terms for women with difficult access to the necessary maternal–fetal monitoring appointments.

Early-onset IUGR

In the context of earlier, more severe forms of IUGR, the European GRIT trial[151] showed no difference in perinatal outcomes when the timing of delivery for IUGR was delayed (the trial achieved an average delay of only 4 days, primarily because of the development of co-existent preeclampsia in the delayed delivery arm) using intensive fetal monitoring. Subsequent infant developmental assessment at two years showed no difference between the two arms, although those randomized to immediate delivery in a subset of deliveries < 31 weeks had a higher rate of severe disability (13% vs. 5%).[161] Despite the impressive achievements of the GRIT study investigators, two limitations of the study deserve consideration in the context of a decade of progress. First, a range of hospital

facilities (level II and level III) participated in the prenatal and postnatal care of IUGR pregnancies in the United Kingdom at that time. Second, fetal Doppler studies were not incorporated into the management of the delayed delivery arm as delivery end-points. In contemporary practice, the importance of centralization of perinatal care in early-onset IUGR is recognized; this process facilitates access to maternal–fetal medicine specialists who can perform detailed ultrasound assessments, integrating fetal Doppler studies (MCA and ductus venosus) with conventional ultrasound tests (umbilical artery Doppler studies and biophysical profile scoring), non-stress testing, and clinical parameters.[137,138] Traditional biophysical profile scoring was not originally intended for fetuses with extreme IUGR; observational data demonstrate that they may be significantly compromised, based on fetal Doppler studies and functional cardiac assessments, despite relatively normal amniotic fluid.[137,138] In addition, their physical activity may be suppressed by commonly used drugs, especially anti-hypertensives and corticosteroids used to improve fetal lung maturity. The European TRUFFLE study[162] specifically addresses the needs of such fetuses, by comparing fetal Doppler monitoring with computerized NSTs. This trial is expected to report in 2012.

Delivery and Postpartum Management

Careful surveillance is warranted for co-existent preeclampsia because this may present de novo following delivery, and it may require treatment and a surveillance plan following discharge. Women delivering by Caesarean section with risk factors such as obesity, age > 40, or coexistent severe preeclampsia should receive prophylactic subcutaneous heparin until discharge to prevent venous thromboembolism.[163]

The placenta should be examined at delivery and sent for pathologic examination. Gross examination may reveal reduced placental size, often with an eccentric cord (chorion regression in early pregnancy) and/or gross lesions (infarction, hemorrhage, intervillous thrombosis, massive peri-villous fibrin deposition). A range of histologic abnormalities may be found, including confirmation of gross pathology, lack of transformation or atherosis of the decidual portions of the uteroplacental vessels, defective formation of villi (distal villous hypoplasia), villous trophoblast abnormalities (focal necrosis or apoptosis of the syncytiotrophoblast), or fetal vascular pathology (fetal thrombotic vasculopathy). Typically, multiple abnormalities are found, suggesting that many cases of early-onset IUGR have a developmental origin in early pregnancy, consistent with their prediction by multiply abnormal IPS testing.[104,164] Thrombophilia screening is commonly performed following identification of thrombotic pathology, but thrombophilia is much less common (occurring in approximately 10%) than the underlying structural defects (70%) that are suggestive of abnormal development.[17]

A discussion of placental pathology alongside a review of the antenatal and delivery records, together with the progress of the infant, is a useful component of the postpartum visit when discussing the final diagnosis of IUGR and its implications for a future pregnancy. The recurrence risk of severe IUGR (with abnormal umbilical artery Doppler studies) and severe early-onset severe preeclampsia is approximately 10% in the absence of major maternal comorbidities such as chronic renal disease, thrombophilia, or chronic hypertension.[19] The postpartum visit can include discussion about the logic and effectiveness of screening for placental vascular insufficiency in a future pregnancy, because the combination of reinterpretation of IPS tests done at 11 to 13 weeks and at 15 to 20 weeks and ultrasound examination of placental morphology and uterine artery Doppler studies at 19 to 22 weeks may be an effective approach to defining the risk in a future pregnancy.[19] Such information can direct the plan of care for a future pregnancy. Addressing risk factors, such as components of the metabolic syndrome (obesity, hypertension), smoking, and optimal control of medical comorbidities may help to improve the future prognosis. Use of an online tool to derive BMI, with adjustment to the upper end of the normal range, is a useful way to discuss and set a realistic weight-reduction target over six to 12 months. Effective and appropriate birth control, especially in women who have delivered by Caesarean section, is important in order to defer a subsequent pregnancy. Following a pregnancy with IUGR, some women will have suffered either a perinatal loss or will still have an infant in a neonatal unit; therefore, a review of the need for mental health support is prudent. Finally, because documentation that IUGR was due to placental vascular disease has long-term health implications,[165–168] the postpartum discussion should include potentially useful interventions (diet, exercise, weight loss, blood pressure surveillance, smoking cessation) that may promote better long-term health with the assistance of the family physician.

CONCLUSION

IUGR is a common problem associated with significant perinatal morbidity and mortality. Currently existing Level I evidence will aid clinical practice, but is limited to only some aspects of decision-making. Several demographic factors, including advanced maternal age, assisted reproductive

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 attempt to improve the perinatal prognosis of IUGR due to placental insufficiency. Since IUGR has many additional causes, a detailed fetal anatomical ultrasound examination should be performed when it is suspected, including further testing when fetal abnormalities are suspected, when soft markers are seen, or when no supportive evidence of underlying placental insufficiency is evident. In uncomplicated IUGR attributed to placental insufficiency, no pharmacological interventions are of proven benefit, although the meta-analysis of data from several small trials of low-dose ASA therapy suggests some preventive benefit. By contrast, no evidence currently exists to support the use of 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, specialist examination of the placenta by a perinatal pathologist may provide key insights into the underlying cause. Maternal thrombophilia testing and a review of the results of both the placental pathology and pertinent neonatal investigations may refine the presumptive cause of IUGR that could alter the management plan in a subsequent pregnancy. Since the events leading up to, and following, delivery of a severe IUGR infant may trigger significant emotional stress, a review of maternal mental health status and family circumstances at this visit is prudent. Finally, women who have delivered an IUGR infant with placental vascular insufficiency have increased long-term risks of cardiovascular disease. This association may be due to vascular pathology (atherosis and inflammation) that is common to the uteroplacental vessels and to systemic vessels (e.g., carotid arteries).

References online
http://www.sogc.org and **http://www.jogc.com**