GUIDELINE:

Fetal growth defects

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1. DEFINITIONS

A fetus is considered Small for Gestational Age (SGA) when it has an Estimated Fetal Weight (EFW) below the 10th and above the 3rd centiles (between the 3rd and 10th centiles) for its gestational age (GA) and a Doppler study within normal ranges. Intrauterine Growth Restriction (IUGR) is defined as: (i) the presence of an EFW below the 3rd centile; or (ii) the presence of an EFW below the 10th centile with a change in the cerebroumbilical or uterine arteries flow.

2. DIAGNOSIS

2.1. Clinical diagnosis

Fundal height should be measured from week 26 onwards. The methodology will be as follows: supine position, from uterine fundus to symphysis pubis, observation blinded from previous examination. If the fundal height is below the 10th centile for GA (Meler E. Progresos Obstetricia Ginecología, 2005; 48:480: 26 w-23 cm; 28 w-25 cm; 30 w-27 cm; 32 w-28 cm; 34 w-30 cm, 36 w-31 cm; 38 w -33 cm; 40 w -34 cm) and there is no EFW from the previous 2 weeks, an ultrasonographic assessment of the fetal weight is required.

2.2. Ultrasonographic diagnosis

The ultrasonographic estimation of the fetal weight requires 3 steps: (i) the correct assignation of a fetus to its gestational age, (ii) the estimation of the weight from fetal biometries, and (iii) the calculation of the weight centile for gestational age:

i. Gestational age will be determined according to the first ultrasonographic examination:

a. If Crown-Rump Length (CRL) <84 mm: GA is determined according to CRL (Robinson HP. BJOG, 1975-modified BUMS, 2008).
b. If CRL >84 mm and Biparietal Diameter (BPD) <70 mm: GA is determined according to BPD (Papageorghiou AT. IG 21st. Lancet, 2014).
c. If BPD >70 mm and Last Menstrual Period (LMP) is uncertain: GA is determined according to Head Circumference (HC) (Papageorghiou AT. IG 21st. Lancet, 2014).
d. If BPD >70 mm and LMP is certain: GA is determined according to LMP.

ii. EFW will be calculated according to the algorithm including BPD, HC, Abdominal Circumference (AC) and Femur Length (FL) (Hadlock FP. AJOG, 1985). If the head biometries are not technically measurable, the alternative algorithm using AC and FL should be used instead (Hadlock FP. Radiology, 1984).

iii. The fetal size centile adjusted for GA (step 1), the EFW (step 2), the fetal sex and the number of fetuses will be estimated (Figueras F. EJOGR, 2008 for singletons/ Torres X. Fetal Diagnosis and Therapy, 2017 for monochorionic/Kuno A. Hum Reprod, 1999 for multichorionic). In singleton pregnancies from mothers whose weight before pregnancy was <50 kg and/or whose height is <150 cm, the weight centile will be adjusted according to maternal characteristics (http://www.fetaltest.com/cgi-bin/ecopesofetal.cgi).

In the second trimester fetal growth will be evaluated according to the longitudinal growth between the first and second trimesters (Pedersen N. Obstet Gynecol, 2008). In those cases where the diagnosis at week <24 is only made from biometric measurements, fetal growth must be confirmed at 24 weeks of gestation.

The current version of the application "Calculadora Gestacional" provides automatic values for all calculations in this protocol.

Reassessments of the EFW should occur at intervals ≥ 15 days.

2.3. Diagnosis

2.3.1. Study protocol:

- Doppler study of the umbilical artery (UA), middle cerebral artery (MCA) and uterine arteries (UtA). Calculation of the cerebroplacental ratio (CPR): MCA PI/UA PI.
- Detailed anatomic examination upon diagnosis.
- Functional echocardiography and neurosonography: if severe IUGR stage I (<3rd %ile) or greater.
- Outpatient blood pressure (BP) control 2-3 times/week.
- Proteinuria determination:
  a) If BP <140/90 mmHg → request a protein/creatinine ratio (P/C) in fresh urine (normal if <0,300 mg/mg).
  b) If BP ≥140/90 mmHg → request 24 h proteinuria if GA <37 weeks or a protein/creatinine ratio if GA ≥37 weeks.
- Complete blood test (with both hepatic and renal work-up).

- The genetic study of the amniotic fluid is advised if one of the following criteria is met:
  a) QF-PCR and molecular karyotype:
    1. Severe IUGR (<3rd %ile) diagnosed before 24 weeks.
    2. Severe IUGR (<3rd %ile) diagnosed before 28 weeks along with ultrasonographic markers (excluding oligohydramnios)/minor structural anomaly or biometries (HC or FL) <-3 SD → additionally, perform a DNA reserve.
    3. EFW below the 10th centile along with any major structural anomaly → additionally, perform a DNA reserve.
  b) Study of bone dysplasias (add to QF-PCR and molecular karyotype)*:*
    1. If bone biometries <-3 SD or femur/foot ratio <0,85 → study of achondroplasia and hypochondroplasia.
    2. If there are dysplasia-associated malformations, morphologic bone anomalies (fractures, curvatures, hypomineralization) → request a

genetic counselling in order to consider further study of skeletal dysplasias.

c) *Study of specific genetic panels or exome sequencing:*

IUGR case with more than one structural anomaly affecting two systems (except hypospadias) with a high association with syndromes or biometries (HC or FL) <-4 SD without signs of placental insufficiency and a normal molecular karyotype → request genetic counselling in order to consider further studies.

- <u>Study of infections</u>:
  a) Rubella IgG: if Rubella-IgG negative or unknown in the first trimester.
  b) Syphilis: if IUGR (excluding SGA) (both treponemic and reaginic tests in maternal blood).
  c) Malaria: if IUGR (excluding SGA) and high-risk population.
  d) Cytomegalovirus (CMV):
     i. If indication for invasive technique: CMV-PCR in amniotic fluid.
     ii. If there is no indication for an invasive technique, maternal IgG and IgM will be requested only in IUGR (excluding SGA):
        - Both IgG and IgM are negative → infection is ruled out.
        - Positive IgM → perform amniocentesis for CMV-PCR in amniotic fluid.
        - Positive IgG and negative IgM → perform amniocentesis only if there is any ultrasonographic marker compatible with a CMV infection (CNS or extra-CNS) except isolated oligohydramnios (see specific protocol for TORCH infections).

2.3.2. Classification

According to the results in these tests, the following groups are established:

i. SGA: EFW ≥3rd %ile and <10th %ile with normal Doppler.

ii. IUGR:

- *Stage I* – if any of the following criteria are met:
  - EFW <3rd %ile (Figueras F. EJOGR, 2008).
  - CPR <5th %ile [in **two determinations** >12 h apart] (Bachat AA. UOG, 2003).
  - MCA PI <5th %ile [in **two determinations** >12 h apart] (Bachat AA. UOG, 2003).
  - UtA mean PI >95th %ile (Gómez O. UOG, 2008).
- *Stage II* – EFW <10th %ile + any of the following criteria:
  - UA-AEDF (absent end-diastolic flow) in >50% of the cycles measured in a free loop in both arteries and in **two determinations** >12 h apart.
- *Stage III* – EFW <10th %ile + any of the following criteria:
  - *Arterial*: UA-REDF (reverse end-diastolic flow) in >50% of the cycles measured in a free loop in both arteries and in **two determinations** >6-12 h apart.
  - *Venous*: Ductus venosus (DV) PI >95th %ile or absent diastolic flow in the DV or persistent dicrotic venous pulsations (in **two determinations** >6-12 h apart).
- *Stage IV* – EFW <10th %ile + any of the following criteria:
  - Pathological CTG tracing (variability <5 in the absence of sedative drugs and/or decelerative pattern).
  - Reverse diastolic flow in the DV (in **two determinations** >6-12 h apart).

2.4. Fetal wellbeing evaluation

2.4.1. Evaluation

Doppler study – when to perform the following determinations:

- CPR: in all visits
- UtA PI: upon diagnosis and every 4 weeks if normal or before if there are any clinical changes.
- DV: only if abnormal fetal Doppler (UA, MCA, CPR).

CTG: in stage II IUGR or greater (only from week 26 onwards).

2.4.2. Follow-up

EFW will be calculated throughout follow-up according to an algorithm comprising only HC and AC (Stirnemann J. IG 21st. UOG, 2017).

- SGA: every 2-3 weeks.
- Stage I IUGR: every 1-2 weeks.
- Stage II IUGR: every 2-4 days.
- Stage III IUGR: every 24-48 h.
- Stage IV IUGR: every 12-48 h.

*When **IUGR is accompanied with severe preeclampsia (PE)** → IUGR stage is increased by one in terms of follow-up.

2.4.3. Admission

Doppler study: according to follow-up (2.4.2)

CTG: from week 26 except if there is acute concurrent pathology (Threatened preterm labour (TPL), PROM (premature rupture of membranes), suspicion of placental abruption, preeclampsia)

- Stage I or II: once per day.
- Stage III or IV: twice per day.

3. OBSTETRICAL MANAGEMENT

3.1. Antenatal

3.1.1. General recommendations

- Home bed rest is to be discouraged
- Elimination of possible external factors (i. e. smoking) must be promoted.
- Patients will be admitted only in case of elective delivery and/or severe preeclampsia. In the rest of cases outpatient management is preferred.
- Fetal lung maturation will be performed only if criteria for elective delivery are met and GA >26 weeks (26-36+4 weeks). In cases of severe preeclampsia, suspicion of placental abruption, TPL or PROM, fetal lung maturation will be performed according to general recommendations.
- The criteria for neuroprophylaxis with $MgSO_4$ administration are: GA <34 weeks and >4 h prior to delivery.
- Fetal Functional Echocardiography allows the identification of those IUGR cases at higher risk of cardiovascular morbidity (mainly hypertension) during infancy. Therefore, those cases with signs of moderate or severe cardiac dysfunction (when 2 or more functional echocardiographic parameters are altered) will receive general lifestyle recommendations (breastfeeding promotion, polyunsaturated fatty acids (PUFA) rich diet encouraging, obesity avoidance) which have proved to decrease such cardiovascular risk (Rodríguez-López et al. Pediatr Res, 2016;79:100-6).
- A neonatal transfontanelar ultrasonography will be recommended in those cases where the fetus has a reverse aortic isthmus (Cruz-Martínez R et al. UOG, 2015;46(4):452-9).

3.1.2. Timing for delivery

- **SGA**: delivery from 40 weeks onwards. Vaginal delivery is not contraindicated.
- **Stage I IUGR**: delivery from 37 weeks onwards. Vaginal delivery is not contraindicated (if MCA PI <5th %ile, the risk for urgent caesarean section is 50%).
- **Stage II IUGR**: delivery from 34 weeks onwards. Elective caesarean section.
- **Stage III IUGR**: delivery from 30 weeks onwards. Elective caesarean section.

- **Stage IV IUGR**: delivery from 26 weeks onwards. Elective caesarean section.

<26 weeks: the neonate is considered periviable and the probabilities of survival without any severe sequelae are <50%. Prenatal paediatric assessment is required in case of indication of delivery. Hence, CTG before 26 weeks will only be performed in the context of concurrent acute pathology (TPL, PROM, suspicion of placental abruption, severe PE).

3.1.3. Induction of labour

Cervical ripening will be started with a PGE2 vaginal delivery system or oxytocic induction depending on the cervical conditions and uterine activity (according to the "Induction of labour and ripening methods" protocol).

3.2. Intrapartum

- Continuous monitoring.
- Reanimation: according to the baby's weight. Reminder: IUGR fetuses may present fetal distress and meconium emission.
- Request of anatomopathological evaluation of the placenta in IUGR cases

3.3. Postpartum

3.3.1. Immediate puerperium

- Protein/creatinine ratio and hepatic and renal profiles will be requested: in cases not studied antenatally or meeting IUGR criteria.
- Maternal CMV serologies (IgG): in cases not studied prenatally or meeting IUGR criteria who were delivered before 32 weeks or whose birthweight is <1500 g (to be able to process maternal milk before its administration and avoid CMV vertical transmission).

3.3.2. Puerperium

- Candidates for the study of thrombophilia will be selected: IUGR or PE who required delivery before 34 weeks or placental abruption.

  ** Blood collection must be more than 3 months apart from delivery.
- report of the placenta is to be handed and explained to the patient.

** The massive perivillous fibrin deposit is associated with a recurrence risk of 40-60%. The patient must be informed of the possibility of prophylaxis with heparin in the following pregnancy in order to decrease such risk.

4. Special situations

4.1. Dichorionic twin pregnancy with selective IUGR (sIUGR)

In case the other fetus does not have an IUGR, the following recommendations will be considered:

- **SGA/stage I IUGR**: delivery from 37 weeks onwards. No contraindication for vaginal delivery provided that an optimal intrapartum control of fetal wellbeing can be guaranteed.
- **Stage II IUGR**: delivery from 34 weeks onwards. Elective caesarean section.
- **Stage III IUGR**: delivery from 30 weeks onwards. Elective caesarean section.
- **Stage IV IUGR**: delivery from 28 weeks onwards. Elective caesarean section.
