FETAL GROWTH DISORDERS

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1. DEFINITIONS

Small for gestational age (SGA) is defined as a estimated foetal weight (EFW) for gestational age < 10th percentile and 3rd percentile with normal Doppler study. Foetal growth restriction is defined as an EFW ≥ 3rd percentile or EFW < 10th percentile plus abnormal umbilical, brain or uterine arteries Doppler.

2. DIAGNOSIS

2.1 CLINICAL DIAGNOSIS

Fundal height should be assessed in each control from 26 weeks of gestation. The distance from pubis to fundus should be measured with patient in supine decubitus and without knowing previous measurement.

If fundal height is < 10th percentile for gestational age (Meler E. *Progresos Obstetricia Ginecología* 2005: 26w-23cm; 28w-25cm; 30w-27cm; 32w-28cm; 34w-30cm; 36w-31cm; 38w-33cm; 40w-34cm) and EFW is not available within the previous 2 weeks, it is required to perform an EFW by ultrasound.

2.2 ULTRASOUND DIAGNOSIS

Ultrasound foetal weight estimation requires 3 steps: (A) correct foetal dating to its gestational age; (B) estimation of weight based on foetal biometrics; and, (C) calculation of weight percentile for gestational age.

(A) Gestation should be dated according to the first ultrasound:

a. If Crown-Rump Length (CRL) < 84 mm, dating is recommended to be performed by CRL (Robinson HP. BJOG 1975-Modified BUMS 2008)
b. If CRL ≥ 84 mm and BPD < 60 mm, dating is recommended by BPD (Papageorghiou AT. IG 21st. Lancet 2014)
c. If Biparietal Diameter (BPD) ≥ 60 mm with certain Last Menstrual Period (LMP), dating is preferred by LMP
d. If BPD ≥ 60 mm with uncertain LMP:
    i If BPD < 85 mm, dating is to be performed by BPD (Papageorghiou AT. IG 21st. Lancet 2014).
    ii If BPD > 85 mm, dating is to be performed by head circumference (HC) and femur length (FL) (Papageorghiou AT. IG 21st. UOG 2016)

(B) EFW should be calculated according to an algorithm including BPD, HC, abdominal circumference (AC) and FL (Hadlock FP AJOG1985). If cephalic parameters are not measurable, an alternative algorithm with FL and AC should be used (Hadlock FL Radiology 1984).

(C) Foetal weight percentile should be estimated, adjusted for gestational age, EFW, foetal sex and number of foetuses (Figueras F EJOGR 2008, for singleton / Torres X Foetal Diagnosis and Therapy 2017 for monochorionic twins / Kuno A Hum Reprod 1999 for multichorionic twins).

In those women with height ≤ 150 cm or maternal weight at first appointment < 50 kg, foetal weight should be customised according to maternal characteristics. For this, the website http://fetaltest.com can be used.

In the second trimester, foetal growth should be assessed according to the longitudinal growth between the first and second trimester (Pedersen N. Obstet Gynecol 2008). In cases where the diagnosis of SGA or FGR (Foetal Growth Restricted) at 20 weeks is only based on biometrical parameters (no Doppler abnormalities), it should be confirmed at 24 weeks of gestation.

All calculations of this guideline can be performed automatically using the calculator available on the website http://medicinafetalbarcelona.org/calc/.

2.3 DISORDER TYPE DIAGNOSIS

2.3.1 Study protocol

The following work-up should be performed:

- Doppler evaluation of umbilical artery (UA), middle cerebral artery (MCA) and uterine arteries (UtA); and calculation of cerebroplacental ratio (CPR): MCA PI/UA PI
- Detailed anatomical examination at diagnosis
- Ambulatory monitoring of blood pressure (BP) 2-3 times/week.
- Proteinuria quantification:
    a. If BP < 140/90 mmHg, request protein/creatinine ratio in fresh urine (normal < 0.300 mg / mg).
    b. If BP ≥ 140/90 mmHg, 24-hour proteinuria below 37 weeks and protein/creatinine ratio above 37 weeks
- Complete blood work-up (with hepatic and renal profile).

- Genetic study in amniotic fluid is recommended if any of following criteria are met:

    a. QF-PCR and molecular karyotyping:
        1. Severe FGR (< 3rd percentile) diagnosed before 24 weeks
        2. Severe FGR (< 3rd percentile) diagnosed before 28 weeks with ultrasound markers (excluding oligohydramnios) / minor structural anomaly or biometries (FL or HC) < -3 SD. In these cases, if available, DNA should be stored to extend the study in a later stage if required.
        3. EFW < 10th percentile with major structural anomaly. In these cases, if available, DNA should be stored to extend the study in a later stage if required.

    b. Study of skeletal dysplasia (to be added to QF-PCR and molecular karyotyping):
        1. If bone biometries < -3 SD or (< 2.5 SD and femur/foot ratio < 0.85), perform study for achondroplasia and hypochondroplasia.

2. If there are malformations associated with dysplasia, bone morphological alterations (fractures, curvatures, hypomineralisation), genetic counselling should be requested to assess the study of skeletal dysplasia.

c. Study specific genetic panels or exome sequencing:
Indicated if FGR with more than one structural anomaly of two systems (except hypospadias) or biometries (FL or HC) < -4 SD without signs of placental insufficiency and normal molecular karyotype result.

d. Suspected Silver-Russell Syndrome:
FGR with relative macrocephaly HC/AC > 90th percentile or asymmetry of long bones > 15%:
1. 11p15 methylation MLPA: in 40% of cases, Silver-Russell syndrome is caused by hypomethylation of paternal IC1 imprinting centre.
2. Maternal UPD7 in amniotic fluid (10% of cases) in case of normal methylation study.

- Infections study:
  a. IgG Rubella testing: If IgG-Rubella negative or unknown in first trimester.
  b. Syphilis testing (treponemal and reagin test in maternal blood): If FGR (excluded SGA).
  c. Malaria testing: If FGR (excluded SGA) and at-risk population
  d. CMV testing:
     1. If invasive technique indicated, CMV PCR in amniotic fluid should be performed.
     2. If invasive technique is not indicated, testing for maternal IgG and IgM serology is indicated only in FGR (excluded SGA).
        i If IgG and IgM are negative, infection can be ruled out.
        ii If IgM is positive, perform amniocentesis for CMV PCR in amniotic fluid.
        iii If IgG is positive and IgM is negative: amniocentesis for PCR is indicated only if there is any ultrasound marker suggestive of CMV infection (CNS or extra-CNS), except isolated oligohydramnios

- Neurosonography and functional echocardiography if severe FGR stage I (< 3rd percentile) or higher. In cases of FGR I, both evaluations should be performed at 32-34 weeks. In other stages, the timing of both evaluations should be decided according to the evolution.

3. CLASSIFICATION

Based on the study protocol detailed above, the following stages are defined:

SGA: EFW ≥ 3rd centile and < 10th centile with normal Doppler

FGR:

- Stage I (any of following criteria):
  - EFW < 3rd percentile (Figueras F EJOGR 2008)
  - CPR < 5th percentile [on two separate occasions > 12h] (Bachat AA UOG 2003)
  - MCA PI < 5th percentile [on two separate occasions > 12h] (Bachat AA UOG 2003)
  - Mean UtA PI > 95th percentile (Gomez O, UOG 2008)

- Stage II (EFW < 10th percentile and the following criterion)
  - AEDF-UA (absent end-diastolic flow in free-loop UA, > 50% of cycles, in both arteries and on two separate occasions > 12h)
- Stage III (EFW < 10th percentile and any of following criteria)
  - Arterial: UA (free-loop) with reverse end-diastolic flow (in > 50% cycles, in both arteries and on two separate occasions > 6-12h)
  - Ductus venous (DV) PI > 95th percentile or DV with absent end-diastolic flow (in two separate occasions > 6-12h)
- Stage IV (EFW < p10 and any of following criteria):
  - DV with reverse end-diastolic flow (on two separate occasions > 6-12h)
  - Pathological variability in cardiotocography (CTG):
    i. Short-term variability on 1-hour computerised CTG (cCTG):
       - < 2.6 ms between 26 and 28+6 weeks
       - < 3ms above 29 weeks
    ii. If computerised CTG is not available, pathological variability is defined as < 5 bpm in 1-hour recording.
  - CTG with deceleration pattern:
    i. > 2 spontaneous decelerations every 10 min for 30 min.

4. EVALUATION OF FETAL WELLBEING

4.1 FOLLOW-UP STUDIES

- Doppler evaluation:
  a. CPR: at all visits
  b. Uterine arteries: at diagnosis and, afterwards, every 4 weeks if normal, or earlier if clinical change.
  c. DV: only if any abnormal foetal Doppler (UA, MCA, CPR) is observed.

- CTG: FGR stage II or higher (only above 26 weeks of gestation).

- EFW: at minimum intervals of 2 weeks

  For follow-up, EFW should also be calculated according to an algorithm that includes BPD, HC and AC (Hadlock FP AJOG 1985); and, if cephalic parameters are not measurable, an alternative algorithm with FL and AC should be used (Hadlock FL Radiology 1984). This is the same systematic approach as for diagnosis.

4.2 FOLLOW-UP TIMING

Follow-up visits for Doppler study control should be adapted to the stage of foetal involvement.

- SGA: every 2-3 weeks
- FGR stage I: every 1-2 weeks
- FGR stage II: every 2-4 days
- FGR stage III: every 24-48 hours
- FGR stage IV: every 12-48 hours

- When FGR is **associated with severe preeclampsia**, follow-up intervals should be those indicated in the immediate upper stage (as stage II in stage I, as stage III in stage II, and as stage IV in stage III).

4.3. MANAGEMENT ON ADMISSION

- Doppler study: as per follow-up (4.2)
- CTG: above 26 weeks of gestation, except if acute concurrent pathology (PTL, PROM, suspected NIPPD).
    - FGR I or FGR II: once daily
    - FGR III or IV: twice daily.

5. OBSTETRIC MANAGEMENT

5.1 PRENATAL

5.1.1 General recommendations

- Discourage absolute rest at home and promote elimination of possible external factors (smoking or other environmental risk factors)

- Only the indication for delivery (see following section) and preeclampsia are necessary criteria for admission. In all other cases, outpatient monitoring is preferred.

- **Lung maturation should be performed between 25.5 - 34.6 weeks in the following cases**:
    - Confirmed FGR II: from 33 weeks.
    - Confirmed FGR III: from 26 weeks.
    - FGR IV: from 25.5 weeks if confirmed, and from 26 weeks without waiting for confirmation.
    - When delivery criteria are met and lung maturation has not yet been performed, this should be completed, and then delivery of pregnancy should take place within 6-12 hours. In cases of FGR IV due to pathological CTG, delivery should not be postponed for lung maturation.
    - In case of severe preeclampsia, suspected NIPP, PTL or PROM, lung maturation should be performed according to general recommendations.
    - A booster dose or a new round of lung maturation should only be administered if there is a new indication for termination after 7 or 14 days, following general recommendations.

- **The criteria for neuroprophylaxis with magnesium sulphate are: less than 34 weeks** and more than 4 hours prior to birth whenever possible. In case of pathological CTG, immediate delivery is recommended.

- Foetal functional echocardiography allows selection of those cases of FGR with increased cardiovascular risk (mainly, risk of hypertension) in infancy. Therefore, in those cases with signs of moderate or severe cardiac dysfunction (with 2 or more altered functional echocardiographic parameters), general lifestyle recommendations should be provided (breastfeeding, diet rich in polyunsaturated fatty acids, and avoidance of obesity) that have been shown to reduce cardiovascular risk.
    - A neonatal transfontanellar ultrasound is recommended in those foetuses with aortic isthmus retrograde diastolic blood flow.

5.1.2 Delivery timing

- SGA: Delivery from 40 weeks. Vaginal delivery is recommended as per obstetric indications.

- FGR I: Delivery from 37 weeks. Vaginal delivery is not contraindicated. (If MCA PI < 5h percentile, the risk of emergency caesarean section is 50%).
- FGR II: Delivery from 34 weeks. Elective caesarean section.
- FGR III: Delivery from 30 weeks. Elective caesarean section.
- FGR IV: Delivery from 26 weeks. Elective caesarean section.

Before 26 weeks of pregnancy, the probability of survival without serious sequelae is less than 50%. For this reason, CTG should be performed before 26 weeks of gestation only in the context of acute concurrent pathology (PTL, PROM, suspected NIPPD). Below this gestational age, when delivery is considered, prenatal neonatal counselling is recommended.

5.1.3 Induction method:

Cervical ripening with PGE2 slow-release device or oxytocic induction is recommended, depending on cervical conditions and uterine dynamics.

5.2 INTRAPARTUM

- Continuous monitoring is recommended
- Resuscitation: according to the newborn weight. FGR is a risk factor for meconium aspiration.
- In all cases, placental anatomopathological evaluation is recommended.

5.3 POSTPARTUM

5.3.1 Immediate postpartum

- Protein/creatinine ratio and hepatic and renal profile should be requested in those cases not studied prenatally with FGR criteria.

- Maternal serological assays for CMV (IgG) should be requested in those cases not studied prenatally and with FGR criteria that required delivery before 32 weeks of gestation or with birth weight less than 1500 g, in order to process breast milk prior to administration and avoid vertical transmission of CMV.

5.3.2 Post-partum visit

- Work-up for thrombophilia testing (later than 3 weeks after delivery) is recommended in FGR or preeclampsia cases requiring delivery before 34 weeks or in the presence of placental abruption.

  Placental histological findings and their consistency with the clinical findings are to be discussed. Massive perivillous fibrin deposition of the placenta and histiocytic intervillositis are associated with a 40-60% risk of recurrence. In these cases, prophylaxis with heparin in a subsequent pregnancy is empirically recommended.

6. SPECIAL SITUATIONS

6.1 Dichorionic twin gestation with discordant growth problems

In discordant SGA/FGR bicorial twin pregnancies, recommended timings of delivery are:

- SGA/FGR stage I: Delivery from 37 weeks. Vaginal delivery is not contraindicated if correct intrapartum foetal wellbeing can be assured.
- FGR stage II: Delivery from 34 weeks. Caesarean section.
- FGR stage III: Delivery from 30 weeks. Caesarean section.
- FGR stage IV: Delivery from 28 weeks. Caesarean section.

ANNEX 1. Algorithms for follow-up and delivery in singleton pregnancies

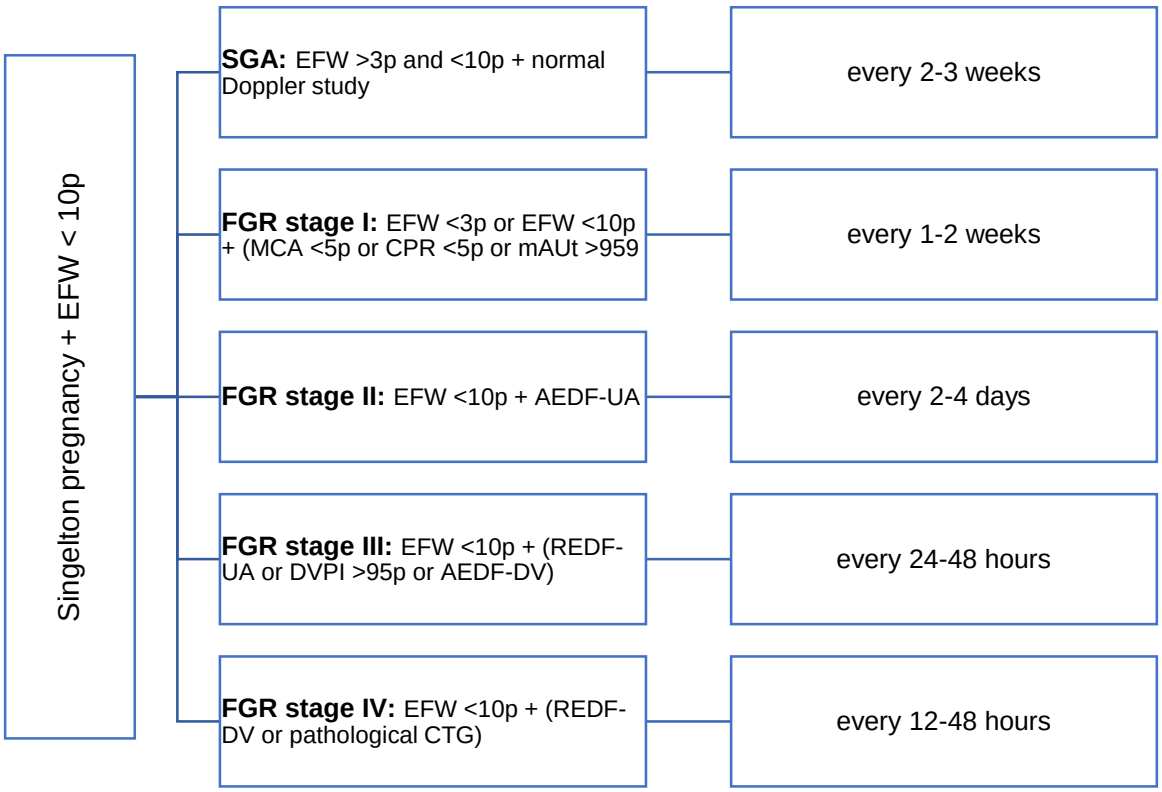

Figure 1. Algorithm for follow-up

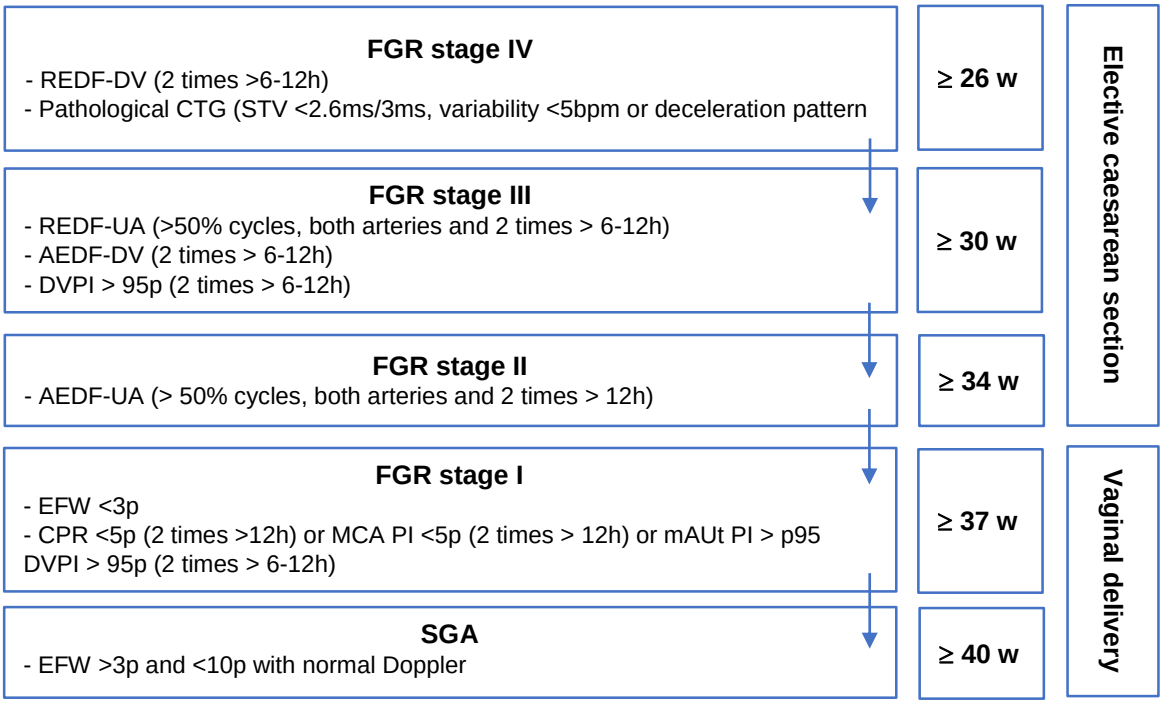

Figure 2. Algorithm for delivery

ANNEX 2. Algorithm for invasive technique

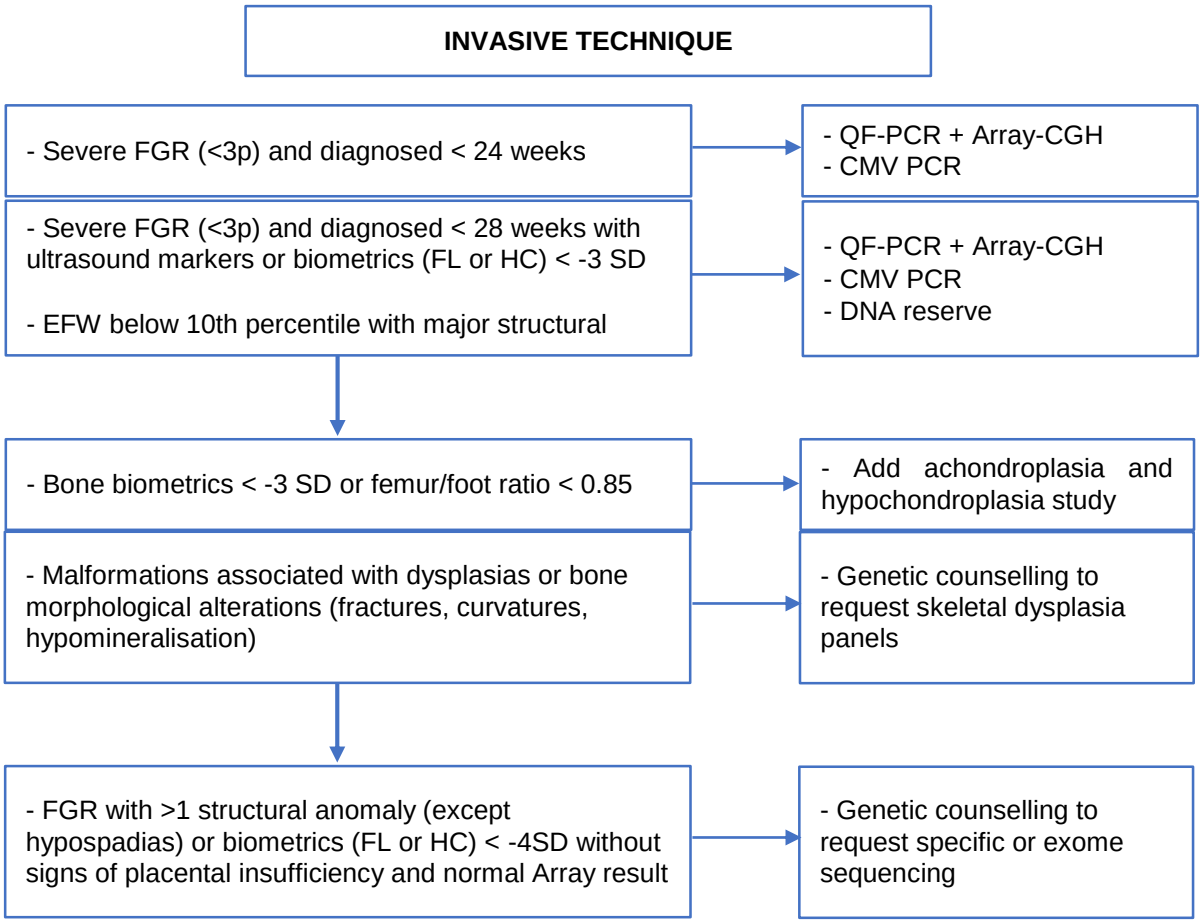

Figure 3. Algorithm for invasive technique