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Early-onset fetal growth restriction with severe preeclampsia: our experience of a challenging topic

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ABSTRACT

Background. Early-onset foetal growth restriction is a critical condition of the pregnancy and the follow up and the best timing for the delivery could be challenging.
Case presentation. We present the case of a 38-year older woman, pregnant at 27 weeks+3 days of gestation, admitted to Obstetrics and Gynecology Unit complaining of lower limb oedema and hypertensive peak; after ultrasound assessment, we diagnosed early-onset foetal growth restriction with preeclampsia. We commenced a follow up with ultrasound doppler evaluation and computerized cardiotocography.
At the 31+5 of gestation, the maternal conditions worsened suddenly, and a caesarean section was carried out. The female newborn needed primary resuscitation, but she breathed ambient air spontaneously from the second day of life.
Conclusions. The present study revealed that an optimal monitoring and timing of delivery remain crucial in the management of early-onset foetal growth restriction, to find the best balance between prolonging pregnancy and preventing mortality/morbidity.

INTRODUCTION

Fetal growth restriction (FGR), also called intrauterine growth restriction, describes a pregnancy condition in which the fetus does not achieve its potential growth because of an unfavorable intrauterine environment – above all, placental insufficiency [1]. Fetuses with FGR present an increased risk of perinatal morbidity, neurological and cognitive impairment, and academic and social performance decrements.

Moreover, these outcomes are strongly associated with gestational age at birth [2-6]. Determining foetal biological growth "potential" is complex and, consequently, a unanimous consent regarding proper management could be challenging.
For a long time, the terminology and definitions on this topic were imprecise and not shared. Today, FGR is usually diagnosed as fetal size or abdominal circumference below the lower threshold (10^{th}, 5^{th} or 3^{rd}) [1]. FGR could be divided into asymmetric and symmetric types based on whether the growth restriction is limited to the abdomen or involves other structures such as the head. Moreover, FGR should be differentiated from a fetus "small for gestational age" (SGA), defined as a birth weight less than the 10^{th} centile from a population-based reference but with no abnormal growth kinetic: it is considered constitutionally small but not associated to an increased risk in perinatal outcomes [7].
The different entities of FGR have been recognized according to the gestational age. Early FGR represents 20-30% of all FGR developed before 30-32 weeks and is associated with early preeclampsia (PE) in up to 50% of cases and increased perinatal morbidity [8-10]. In addition, it is known that a critical sign for this type of FGR is the change in the umbilical artery due to placenta dysfunction.
Late FGR is characterized by a milder degree of placental dysfunction and is less likely to be associated with preeclampsia, and changes in umbilical artery Doppler are less common [1].
Currently, there the causes of abnormal placentation are still unknown, but two molecules have been recognized to have a significant impact on the ischaemia process: sFLT1 (soluble fms-like tyrosine kinase 1) and endoglin (soluble TGF-β co-receptor) [11, 12].
Therefore, chronic ischaemia could lead to a low weight placenta with a narrow umbilical cord [11]. However, the challenge for obstetricians is finding the best balance between minimizing foetal injury and the risks of iatrogenic preterm delivery. Given the above, we aim to present the case of an early onset FGR complicated by preeclampsia and our management from the admission to the hospital to the delivery.

CASE PRESENTATION

Patient features

A 38-year old Caucasian woman, G2P1, spontaneous conception, pregnant at 27 weeks and three days of gestation, presented to our Obstetrics and Gynecology Unit of "Villa Sofia Cervello" Hospital, Palermo (Italy), complaining of lower limb oedema and hypertensive peak (160/110 mmHg). The patient had no pertinent past medical or surgical history. She performed the first trimester screening for trisomies that came back low risk, and the anomaly scan did not reveal any obvious fetal defect. She was not a smoker, and no antibody seroconversion was detected for *Toxoplasma gondii*, *Rubella*, *Cytomegalovirus* and *Herpes simplex* virus types 1 and 2.
Her previous pregnancy had no complications with vaginal delivery in 2015, and the baby born was 3700 g. The local obstetric finding was negative, and the cervical exam was 1/0/-3 (respectively dilatation, effacement, and station). The patient was informed of all procedures she was to sustain; she signed an informed consent allowing data collection for research purposes. The Institutional Review Board approved the study; informed consent was obtained in accordance with Declaration of Helsinki. This case is in accordance with the Consensus-based Clinical Case Reporting Guideline Development (http://www.equator-network.org/) [13].

Management and follow up

Therefore, we administered 20 mg of nifedipine for the high blood pressure and started the prophylaxis for respiratory distress syndrome with two injections of 12 mg betamethasone intramuscularly 24 hours apart. The ultrasound assessment showed abdominal circumference (AC) and the estimated fetal weight < 5^{th} centile; umbilical artery (UA) doppler assessment presented the absence of end-diastolic flow (AEDF), while the ductus venosus (DV) doppler was within normal limits; computerized cardiotocography (cCTG) and amniotic fluid were normal. Therefore, we diagnosed an early-onset FGR complicated by preeclampsia. The 24-hour urine collection showed 6.4 g proteinuria/24 hours, associated with increased lactate dehydrogenase value (297 mg/dl). Foetal ultrasound was performed daily by a skilled operator (with systematic evaluation of UA doppler, DV doppler, amniotic fluid), and cCTGs with foetal movements were evaluated at least three times/day. Patient monitoring maintained normal values. Due to hypertensive instability, several variations of therapy were performed over time, as follows: nifedipine

20 mg - 2/daily (at 27+3 weeks), nifedipine 20 mg - 3/daily (at 28+1 weeks); nifedipine 20 mg - 3/daily + labetalol 100 mg (28+4 weeks), nifedipine 20 mg - 2/daily + labetalol 100 mg - 2/daily (29+0 weeks). At the 31+5 weeks of gestation, the maternal conditions worsened suddenly, exhibiting hypertensive peak, headache, blurred vision and epigastric pain; although blood tests, cCTG and ductus venosus waveform were still regular, the neuroprotection with magnesium sulfate according to the protocol was performed. Then, the caesarean section was carried out.

Maternal and fetal outcome

The newborn was a 1070 g girl, APGAR score was 8-9. The newborn required primary resuscitation, up to continuous positive airway pressure breathing with a positive end-expiratory pressure of 6 cm-H_2O and a FiO_2 of 24%; from the second day of life, the baby established spontaneous regular breathing. Therefore, the baby was discharged after 34 days.

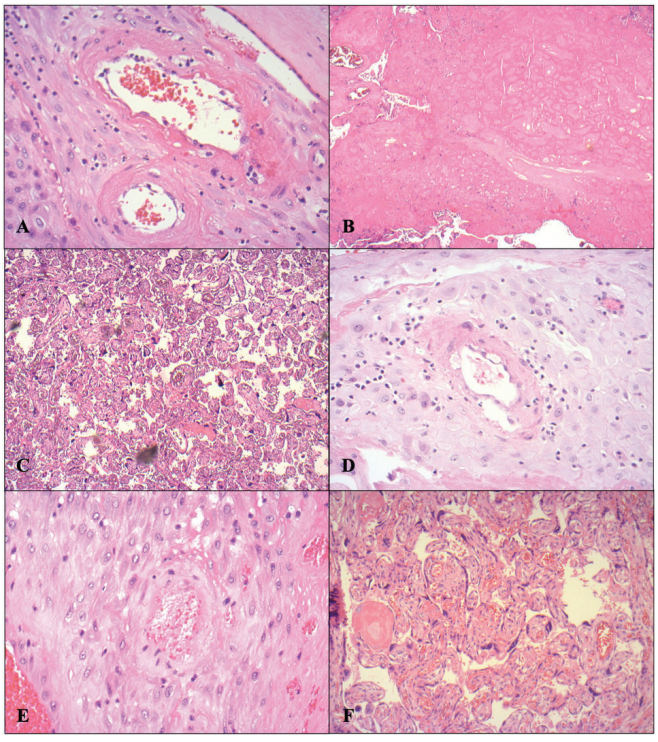

Figure 1. *Histological aspects of the placenta.*
(A) *Decidual atherosis - red glassy fibrinoid necrosis of muscolar wall of spiral artery, with foamy macrophages in sub-endothelium and wall of the vassel (H&E, original magnification x10).* ***(B)*** *Remote Infarct - villous populations are losing nuclear basophilia; an eosinophilic basement membrane with fibrin is seen where syncytiotrophoblast cells once were present (H&E, original magnification x2.5).* ***(C)*** *Accelerated villous maturation, with small or short hyper-mature villi for gestational period, usually accompanied by an increase in syncytial knots (H&E, original magnification x2.5).* ***(D)*** *Decidual vasculitis (H&E, original magnification x20).* ***(E)*** *Decidual thrombosis (H&E, original magnification x40).* ***(F)*** *Tenney-Parker Change - clusters of richly capillarized, short, highly branched, and notched terminal villi, showing increased syncytial knots (H&E, original magnification x10).*

After the caesarean section, maternal symptoms improved, and the mother was discharged after four days of hospitalization. Pathological examination of the placenta presented pathognomonic histological aspects of preeclampsia as decidual vasculopathy and thrombosis, cause of an incomplete invasion of the trophoblast into maternal tissues (**Figure 1**).

DISCUSSION

Here we presented a challenging case of early-onset FGR complicated by preeclampsia and handled with attending management until the mother's condition worsened and required delivery by cesarean section. PE is considered one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition appears before 34 weeks; moreover, early-onset PE is associated with an increased risk for FGR [14].
Globally, FGR affects nearly 10% of all pregnancies, and in Europe, the incidence is between 3-9% [15]. Both preeclampsia and fetal growth restriction result from abnormal placental implantation in early pregnancy [16]. It is supposed to be a trophoblasts' failure in remodeling the spiral arteries during placentation. It contributes to pregnancy-related pathologies, such as PE and FGR, due to increased reactive oxygen species [17]. Placental oxidative stress is also associated with damage to the syncytiotrophoblast seen in cases of miscarriages [18, 19]. However, risk factors of placental disorders such as previous cesarean section, assisted reproductive technology, elderly, smoking, and history of previous placental problems, seriously impact on maternal and fetal outcomes [20-22].
Recent evidences suggested that the PE associated with FGR presents a more severe pre-eclamptic phenotype than those with PE but without FGR [23, 24].
In order to improve the definition of FGR, Gordijn *et al*. in 2016 published for the first time the consensus-based definitions for both early and late FGR due to placental insufficiency established through a Delphi procedure, including biometric and functional parameters [1]. Early-onset FGR is defined as foetal abdominal circumference below the 10th percentile and abnormal UA doppler pulsatility index (PI) above the 95th percentile, irrespective of absent or reversed end-diastolic flow [2]. In addition, it is associated with doppler signs suggesting hemodynamic redistribution (as a reflection of foe-

tal adaptation to undernutrition/hypoxia), histological and biochemical signs of placental disease and a higher risk of preeclampsia [8].
The challenge for obstetricians is finding the best timing for the delivery minimizing foetal injury due to preterm complications. An early delivery potentially exposes the neonate to the morbidity associated with immaturity, whereas delivering too late risks severe morbidity due to critical foetal hypoxia [25].
There is a broad consensus to deliver electively in the case of FGR when lung maturation can be presumed or earlier if signs of foetal deterioration are observed [4]. A delivery between 26+0 and 31+6 weeks presents the worst scenario, particularly if the fetal weight is < 500 g; the timing of delivery mainly depends on cCTG analysis and DV doppler [1, 3, 26]. Maternal indication for delivery should be considered as independent of fetal condition.
The optimal management of FGR should integrate clinical, doppler, and cCTG parameters to ensure safe deferral of delivery for the fetus and the mother or timely intervention. DV seems to be the most decisive single doppler parameter to predict the short-term risk of fetal death in early-onset FGR [4]. The monitoring timing (cCTG, DV) should be based on the severity of FGR and UA doppler abnormalities [3]. The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) of management of preterm FGR between 26-32 weeks provides evidence that waiting until late changes occur in the DV or abnormal CTG is associated with improved outcomes at two years of age [26].
In consideration of the UA abnormalities, we monitored our patient with cCTG and DV doppler daily (in the range of normality until 31+5 weeks), and at the same time, all the maternal parameters. As reported in the results of a recent review on the topic, most authors suggested cesarean section as a modality of delivery, mainly based on the severe doppler abnormalities [27]. Furthermore, most international guidelines emphasized the importance of neuroprotection in early gestations ages: there is consensus on the use of magnesium sulfate for neuroprotection in early-onset FGR (< 32 weeks) [25, 28]. Moreover, there is universal agreement on the use of corticosteroids before birth at < 34 weeks and the Royal College of Obstetricians and Gynaecologists, promotes the improvement of lung maturation up to 35+6 weeks [29].
Indeed, predicting the development of FGR is one of the primary healthcare goals in fetal medicine. Unfortunately, although many researches focused on first-trimester screening for FGR and multiple biomarkers have been investigated (such as PAPP-A and Placental Growth Factor), an adequate biomarker has not yet been defined as a standard test. However, FGR biomarker prediction is improved by adding maternal characteristics and uterine artery doppler studies at the 12-week evaluation; this data seems to be mainly due to the increased prediction of FGR cases associated with preeclampsia. Particularly, Nicolaides *et al*. revealed that the combination of PAPP-A and Placental Growth Factor values with maternal characteristics, increase the detection of FGR [30]. Crovetto *et al*., instead, underlined that the screening algorithm for FGR should be different for early and late FGR, as they represent two clinical forms with a different impact of preeclampsia [31].
Moreover, other authors proposed different molecular markers in the prediction of early PE, FGR and also stillbirth [12, 19, 32-35]. Particularly, the role of miRNAs has been found to be selectively up- and down-regulated both in placenta and serum of women with onset of PE [33].
Finally, an important role has the placental examination in pregnancies complicated by PE; it can show several pathological findings, due to chronic ischaemia. However, the presence of these features is essentially restricted to cases of severe preterm PE; in fact, they could not be present in term pregnancies, suggesting that late onset PE is due to a different biology than abnormal implantation [11, 36].
Although it is a case report, the strength of our study is the importance of the successful conduction of the difficult condition of early-onset FGR, with optimal step-by-step management based on repeated doppler evaluation and cCTG monitoring in the clinical practice. Moreover, the timing of delivery to minimize fetal injuries represents a crucial point as there is still a lack of evidence about the topic. However, our results should be interpreted with the acknowledgement of the limitations of a case report design and that it is a single experience.

CONCLUSIONS

The optimal management of FGR should consider clinical, doppler, and cCTG parameters to ensure safe deferral of delivery. DV is considered the most decisive doppler parameter to predict the short-term risk of fetal death in early-onset FGR. In addition, the pathological examination of the placenta

should be included in the care of all such pregnancies, to confirm a diagnosis of placental impairment. Ongoing and future prospective studies will probably shed more light on this topic and particularly, propose a common consensus regarding the management of early-onset FGR.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

G.C, F.P.: Conceptualization and writing. A.S., R.A.G., M.L.: Data curation. B.A.: Help and advice on histological aspects. P.D.F., G.C.: Investigation and supervision. G.C.: Validation, writing – review & editing. All authors contributed to editorial changes in the manuscript.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The Institutional Review Board approved the study.

Informed consent

Informed consent was obtained in accordance with Declaration of Helsinki.

Data sharing

N/A.

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