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Case Report
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Severe early-onset fetal growth restriction as the first sign of preeclampsia: a case report and literature review

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Abstract

Early fetal growth restriction (IUGR/FGR) remains a challenging entity associated with an increased risk of perinatal morbidity and mortality and maternal complications. Placental dysfunction in the second trimester (early-onset FGR) is thought to arise from the inadequate remodeling of the spiral arteries in the first trimester, similar to preeclampsia. This paper aims to provide data regarding a rare case report of a patient with symptoms of early-onset severe FGR and preeclampsia during a singleton pregnancy in the 20th week of gestation obtained through in vitro fertilization (IVF). The patient had a history of severe preeclampsia, complicated by severe FGR, that imposed delivery at 27 weeks of gestation. This case was managed from the beginning with appropriate treatment to avoid complications and clinical symptoms related to preeclampsia. Despite the absence of proteinuria and adequate treatment of hypertension, severe FGR was revealed at 21 weeks of gestation. We suggested delivery at 27 weeks of gestation because of the severe alterations seen on Doppler velocimetry, but the patient refused. Intrauterine fetal demise occurred at 28 weeks of gestation, and the patient delivered a 470 g female fetus with no viability signs.

Keywords: preeclampsia, fetal grow restriction, pregnancy.

Introduction

Preeclampsia, pure or superimposed upon preexisting hypertension, increases the risk of both maternal and perinatal morbidity and mortality. Early recognition of high-risk factors and biomarkers for preeclampsia is critical to prevent maternal and fetal morbidity and mortality. Preeclampsia is defined by the appearance of hypertension and proteinuria during gestation, and it affects 5% of pregnancies [1]. Complications constitute a major issue encountered in cases of preeclampsia with an 8% complication rate described in the western world, rendering preeclampsia a significant factor of maternal and fetal mortality worldwide [2, 3]. Sixteen to eighteen percent of maternal deaths and up to 40% of fetal

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and neonatal deaths are attributed to cases of preeclampsia [4].

Intrauterine or fetal growth restriction (IUGR/FGR) is a pathological condition in which the fetus fails to grow to its biological potential, primarily because of poor placental function (Figure 1). Early-onset fetal growth restriction (FGR) is most often diagnosed based on a finding of a small-for-gestational-age (SGA) fetus with abnormal blood flow in the umbilical artery recorded by Doppler ultrasound. FGR is associated with an increased risk of intrauterine death and suboptimal neurodevelopment in survivors.

There is a solid but complex relationship between fetal growth restriction and preeclampsia. According to the International Society for the Study of Hypertension in Pregnancy, the coexistence of gestational hypertension and fetal growth restriction identifies preeclampsia with no need for other signs of maternal organ impairment [14]. While early-onset fetal growth restriction and preeclampsia are often strictly associated, such association becomes looser in the late preterm and term periods.

This paper aims to provide data regarding a rare case report of a patient with symptoms of early-onset severe FGR and preeclampsia during a singleton pregnancy in the 20th week of gestation obtained through in vitro fertilization (IVF). The patient has a history of severe preeclampsia, complicated by severe FGR, that imposed delivery at 27 weeks gestation. This case was managed from the beginning with appropriate treatment in order to avoid complications and clinical symptoms related to preeclampsia. Despite the absence of proteinuria and adequate treatment of hypertension, severe FGR was revealed at 21 weeks gestation. We suggested delivery at 27 weeks of gestation because of the severe modifications of Doppler velocimetry, but the patient refused. Intrauterine fetal demise occurred at 28 weeks of gestation, and the

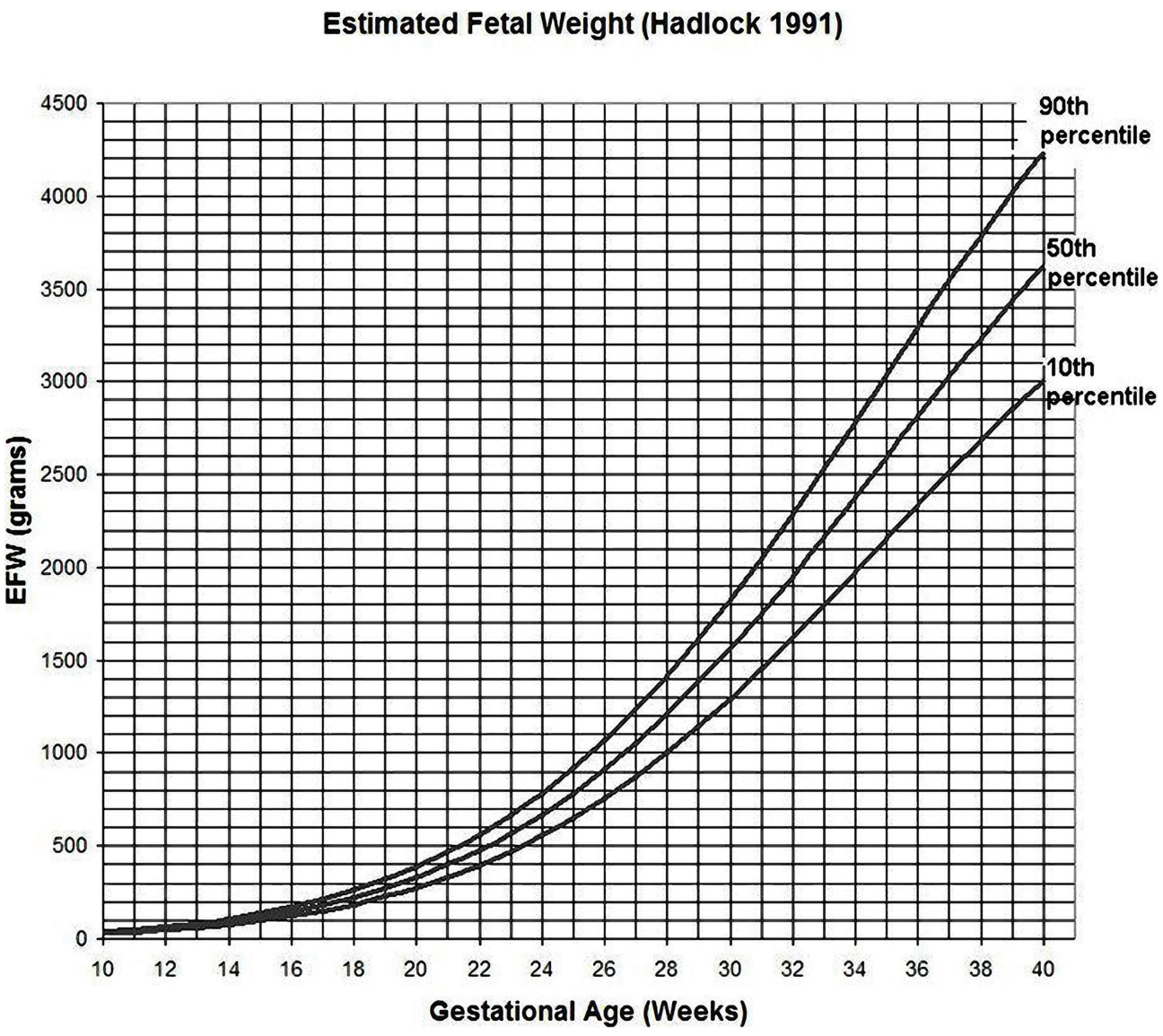

Figure 1. Fetal chart growth evolution from the early 20 weeks of gestation to the onset of fetal growth restriction (FGR).

patient delivered a 470 g female fetus with no viability signs.

Case report

A 42-year-old Caucasian woman, gravida 3, para 2 (GIIIPII), pursuing pregnancy, was subjected to single embryo transfer IVF.

The patient's body mass index (BMI) was 27 kg/m^2, and her medical history was marked by severe preeclampsia developed during the first IVF pregnancy; the patient was under treatment for autoimmune thyroiditis, free of smoking, infections, sexually transmitted diseases, and diabetes mellitus. Family medical history included maternal hypertensive disorder but free of hypertensive pregnancy disorders, including preeclampsia.

Her previous pregnancy was marked by severe early-onset preeclampsia, developed from the first trimester, and delivery was imposed at 27 weeks gestation due to maternal and fetal complications. Prematurity complications lead to perinatal death after 3 weeks.

Considering that the patient had advanced maternal age and diminished ovarian reserve and paternal age was advanced as well, she opted for in vitro fertilization with her embryo as a resort to pursuing a pregnancy.

Prior to the in vitro fertilization procedure, the woman was subjected to extensive clinical and biochemical investigation in the context of screening for any possible underlying pathologies, as certain conditions are typically evaluated prior to proceeding to a new pregnancy. Following examination, no signs of diabetes mellitus, antiphospholipid syndrome, thrombophilia, or other thrombophilic disorders were noted. Diagnostic hysteroscopy with endometrial sampling was performed and revealed a secretory endometrium.

Regarding the history and clinical evaluation and based on guidelines for preeclampsia management, the patient received treatment for hypertension from the beginning with Metildopa 750 mg/day and Labetalol 200 mg/day.

The patient underwent in vitro fertilization with one embryo. Four weeks following the recipient's last menstruation, a transvaginal ultrasound (TVUS) was performed, revealing the existence of one sonolucent sac surrounded by an echogenic ring of chorionic villi, indicating the successful implantation of the one blastocyst. Two weeks later, at the end of the sixth week, clinical pregnancy was confirmed via TVUS, indicating a single gestational sac and fetal heartbeats were present.

Following the confirmation of clinical pregnancy and until the 12th-week mark, the pregnancy progressed normally without any complications.

On the 12th week of gestation, the patient underwent a first-trimester nuchal translucency transabdominal scan that revealed a single pregnancy with measurements consistent with the gestational age estimated at the time.

The embryo had normal crown-rump length (CRL) as well as normal nuchal translucency (NT) measurements [5, 6]. A visible nasal bone was observed. There was no evidence or signs of any anatomical defects for the fetus. Along with NT, a Doppler ultrasound of the uterine artery was also performed, indicating a mean uterine artery pulsatility index (PI) of 2.2 (1.539 MoM).

The specialist who performed the NT measurements and transabdominal ultrasound assessed the preeclampsia risk while considering maternal characteristics and medical history following examination of blood pressure and blood flow in the uterus. Considering these assessments, the patient was classified to be at increased risk of developing early-onset preeclampsia. A low dose of aspirin (150 mg per day) was prescribed from that point onwards to prevent that.

At the same time, a double marker test was also performed via the evaluation of serum pregnancy-associated plasma protein-A (PAPP-A) and free beta-hCG levels. The result was that the fetus had a risk of 1/72 for Down's syndrome and 1/33 for Patau's syndrome.

The patient proceeded with non-invasive prenatal diagnosis testing, which did not detect an increased risk for aneuploidy for the embryo. Following that, diagnostic amniocentesis was performed, and the result revealed a normal karyotype.

Under clear guidance and consultation during the pregnancy, the patient's blood pressure (BP) was constantly 120/70 mmHg under the specific treatment. Urine analysis revealed normal urinary protein excretion.

Transabdominal ultrasonography scans were performed, indicating that the fetus was consistent with the gestational age. During the 21st week of gestation (21 weeks and 4 days), the patient was referred to our hospital for evaluation. The laboratory exams, the complete blood count, clotting, and liver function (serum glutamic-oxaloacetic transaminase, SGOT of 25 U/L and serum glutamic pyruvic transaminase, SGPT of 55 U/L) were normal. Renal function was normal, and the patient's 24-h urine protein was 0.2 g/day.

During the same gestational week, a transabdominal scan of the fetus was also performed. Ultrasound revealed oligohydramnios with an estimated weight of 220 g (<3rd centile according to Hadlock's formula). Close monitoring of the clinical and biochemical status of the patient was undertaken, and the patient underwent serial ultrasound scans.

At 23 weeks of gestation, the ultrasound revealed reversed end-diastolic flow in the umbilical artery and a normal pulsatility index for the mid-

Table 1. Fetal Medicine Foundation application for the management of pregnancies with small for gestational age fetuses. The essential fields are gestational age (24+0 – 40+0), estimated fetal weight (EFW) and presence or absence of preeclampsia. In some countries, assessment is primarily based on Doppler examination and fetal heart rate (FHR) pattern as well as biophysical profile score (BPS) in other countries. This application can suggest a management option using any combination [7].

Findings
The mother has preeclampsia
Absent or reversed ductus venosus a-wave
Absent umbilical artery end diastolic flow
Oligohydramnios
Abnormal biopshysical profile score
Suggested management
Consider administration of steroids, magnesium sulphate and delivery but the fetus may be previable

dle-cerebral artery. Following the Fetal Medicine Foundation (Table 1) [7] and Fetal Medicine Barcelona (Figure 2) [8] guidelines recommendation, serial ultrasound monitorization was performed. The patient was explained that the pregnancy was classified as having a high fetal risk.

At 27 weeks of gestation, we decided to perform fetal lung maturation with betamethasone 12 mg/day, two doses, according to the Fetal Medicine Foundation recommendations. The sustained IUGR ultrasonography revealed a fetus with an estimated weight of 525g (<1st centile according to Hadlock's formula), with a reversed end-diastolic flow in the umbilical artery (Figures 3 and 4) with decreased pulsatility index in the middle cerebral artery. Moreover, abnormal flow and spectrum in ductus venosus was detected.

According to the Fetal Medicine Foundation [7] and Fetal Medicine Barcelona [8] guidelines, we decided that delivery was imposed. Despite the severe IUGR diagnosis, increased fetal risk, and the recommendation for delivery, the patient denied our recommendation and chose to maintain the pregnancy until 28 weeks of gestation, based on her pregnancy history.

Figure 2. Fetal Medicine Barcelona's Fetal Growth calculator result. The essential fields are gestational age, estimated fetal weight, and ultrasound Doppler findings. There is no field for preeclampsia or the biophysical score. This application can suggest a management option using any combination [8].

At 28 weeks of gestation (28 weeks and 2 days), the patient was admitted to our hospital for the decreased perception of fetal movements, and intrauterine fetal demise was revealed. Clinical assessment and laboratory tests to assess maternal wellbeing were performed. The ultrasound findings revealed gross skin edema and maceration. We discussed with the patient, and we decided on the induction of labor with mifepristone and misoprostol following the guidelines recommendation. A 470 g female fetus with no viability signs was delivered. Following delivery, a comprehensive evaluation of the psychological and medical status was performed by a specialist. Postpartum, the patient received antihypertensive treatment to keep the values of arterial tension in range and extensive consultation during all stages of the decision-making process. She provided both verbal and written informed consent with regard to all medical interventions performed and approved her data to be employed for research purposes, authorizing the authors to collect all information related to this case report for further analysis. After acknowledging the scientific merit of the case's publication following consultation, the patient provided verbal and written informed consent for the publication of this case.

Discussion

The definition of preeclampsia has been thoroughly described and established in the literature. In clinical practice, the early onset of preeclampsia is considered an extremely critical condition. Certain

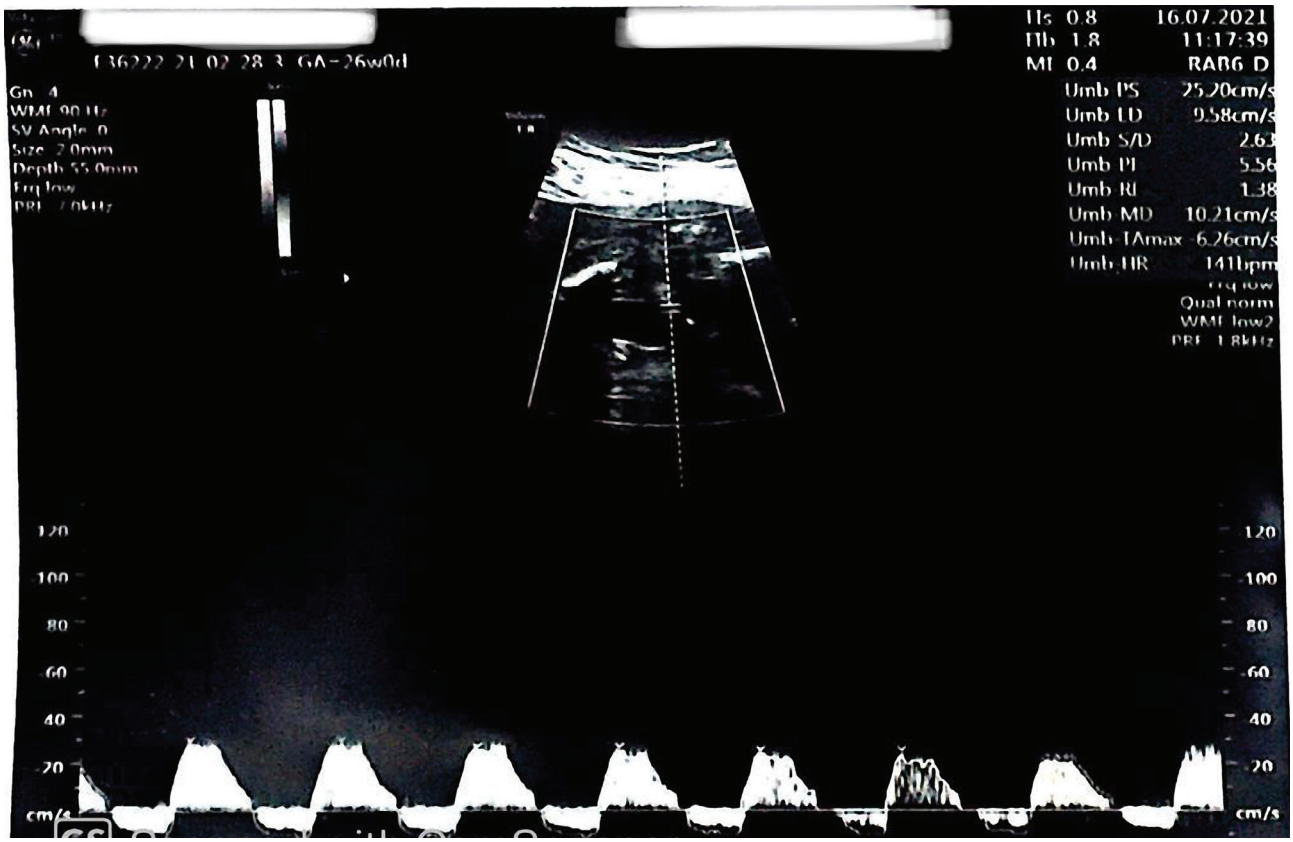

Figure 3. Abnormal umbilical artery flow with absent or reversed end-diastolic velocity (AREDV) during pregnancy is a strong indication of placental insufficiency.

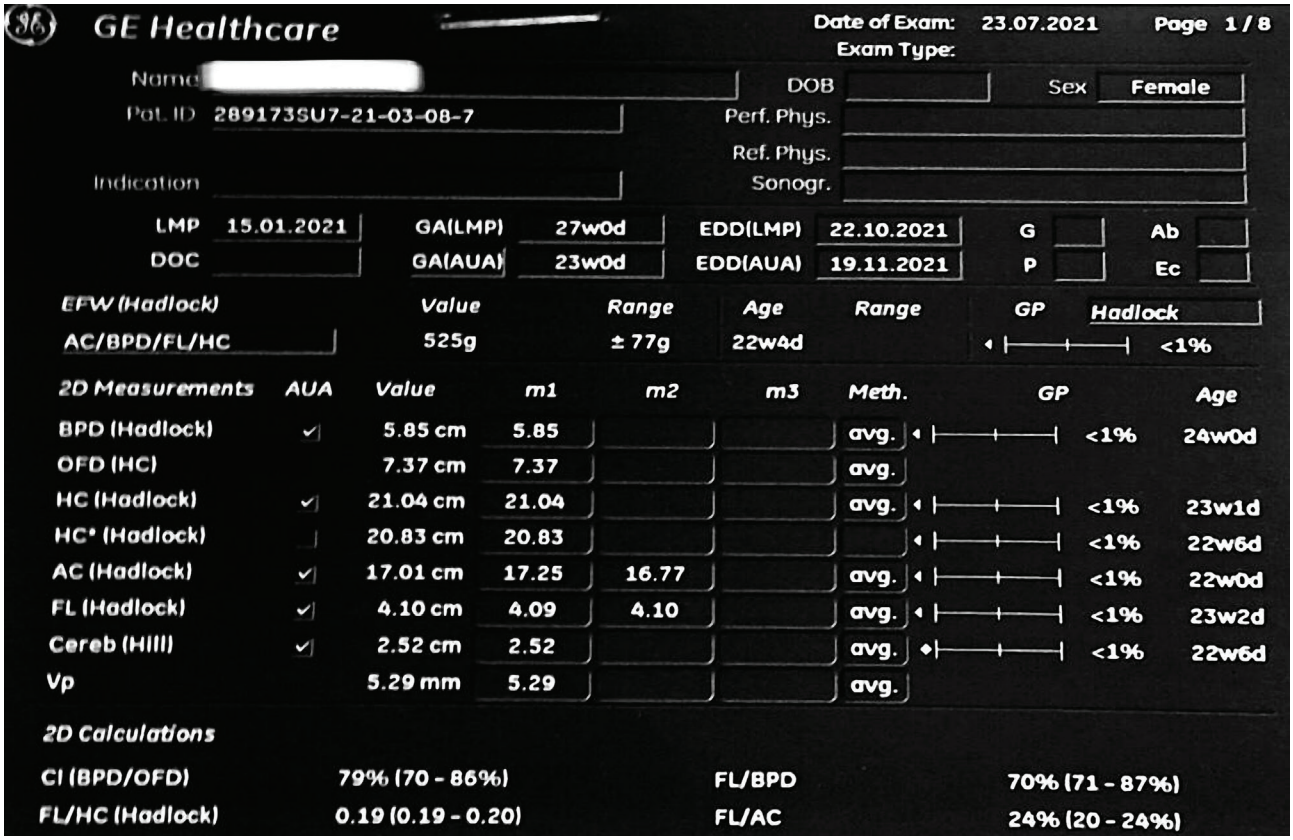

Figure 4. Fetal growth chart revealing a fetus with an estimated fetal weight of 525 g (<1st centile according to Hadlock's formula).

international guidelines on the recommended therapeutic approach have been proposed for clinicians in order to achieve efficient management of such cases [9–11]. On the contrary, when diagnosed prior to the 20th-week mark, early-onset preeclampsia recruits empirical management on behalf of the clinicians.

There is a solid but complex relationship between fetal growth restriction and preeclampsia. According to the International Society for the Study of Hypertension in Pregnancy, the coexistence of gestational hypertension and fetal growth restriction identifies preeclampsia with no need for other signs of maternal organ impairment. While early-onset fetal growth restriction and preeclampsia are often strictly associated, such association becomes looser in the late preterm and term periods.

Different placental and cardiovascular mechanisms underlie this trend: isolated fetal growth restriction has less frequent placental vascular lesions than fetal growth restriction associated with preeclampsia; moreover, late preterm and term fetal growth restriction show different patterns of maternal cardiac output and peripheral vascular resistance in comparison with preeclampsia.

Moreover, it has been voiced that early-onset preeclampsia is also associated with an increased risk of stillbirth, reporting 11.6 stillbirths per 1000 pregnancies in the 26th week of gestation. However, the risk for stillbirth is significantly reduced as pregnancy advances [12]. Impressively, studies have demonstrated that incidents of preeclampsia could also appear as early as prior to the 20 weeks milestone during gestation [13]. Nonetheless, only a few live births have been reported for cases where preeclampsia has been diagnosed prior to the 20th week of gestation. Moreover, preeclampsia may be present despite the absence of any symptoms indicating proteinuria or hypertension [14]. In the occurrence of antiphospholipid syndrome or partial molar pregnancy with triploidy, along with the detection of early-onset preeclampsia, the term 'atypical preeclampsia' is employed [15–18]. The cases where early-onset preeclampsia prior to the 20th-week mark is diagnosed in the absence of the aforementioned disorders are sporadic in literature, with only six cases published hitherto [19–24]. It should be noted that none of the published studies has reported a live birth following management of early-onset preeclampsia, indicating the knowledge gap in efficiently addressing and treating preeclampsia symptoms while ascertaining a positive pregnancy outcome. This very fact renders this study timely and essential.

Regarding the management employed in the present case report, and despite the lack of robust data indicating appropriate management of early-onset preeclampsia prior to the 20th-week mark, the clinical management and approach were strictly based on the guidelines set by the Romanian Society of Obstetrics and Gynecology [26] and The National Institute for Health and Care Excellence (NICE) regarding hypertension in pregnancy. Initially, a pharmaceutical regulation of hypertension was attempted by administering an appropriate scheme while monitoring its efficacy in ameliorating patient's symptoms. According to the NICE guidelines [25], labetalol has been the gold standard choice amongst antihypertensive drugs for treating pregnant women with preeclampsia since 2019. Nifedipine has been proposed as an alternative option if administration of labetalol is not allowed [24]. Additionally to the NICE guidelines, further clinical data indicate that methyldopa may also be considered if labetalol and nifedipine are not considered suitable for a prescription. According to the patient's medical history reporting a previous event of allergic asthma in her early adolescence, the option of labetalol was rejected.

In addition, during the publication of the NICE Guidelines [25] in June of 2019, certain nifedipine trademarks were contraindicated in pregnancy by manufacturers, based on the summary of their product's characteristics. Therefore, the coordinating physician and the clinic opted for administrating methyldopa as the optimal pharmaceutical treatment. Nonetheless, considering the mild antihypertensive effect of methyldopa and its delayed onset of action, additional actions for regulating the patient's blood pressure levels were required [24].

An efficient and safe strategy treatment outside the scope of empirical approaches remains the Holy Grail for pregnant women diagnosed with early-onset preeclampsia and severe FGR prior to the 20th week of gestation.

Conclusions

Severe early-onset fetal growth restriction is an obstetric condition with significant risks of perinatal mortality and major neonatal morbidity. The prognosis of a fetus is influenced by the extent of prematurity and fetal weight.

The reported case presents a sporadic clinical phenomenon of early-onset preeclampsia prior to the 20th week of gestation, manifested by IUGR, which aggravates the prognosis. Management is complex due to the lack of consensual and recommended therapeutic protocols. Clinical care is individually adjusted, and counseling patients with severe early-onset FGR about perinatal prognosis is difficult due to the uncertain influence of different prognostic variables of the condition. The maternal benefits of tight control could be achieved while minimizing any potentially negative effect on fetal growth by delaying initiation of antihypertensive therapy until later in pregnancy. An efficient

and safe strategy treatment instead of empirical approaches remains the target for pregnant women diagnosed with early-onset IUGR prior to the 20th-week mark.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

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