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# PERINATAL OUTCOMES AND PROGNOSTIC FACTORS IN EARLY AND LATE-ONSET FETAL GROWTH RESTRICTION

## ERKEN VE GEÇ BAŞLANGIÇLI FETAL GELİŞİM KISITLILIĞINDA PERİNATAL SONUÇLAR VE PROGNOSTİK FAKTÖRLER

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### ABSTRACT

**Objective:** To evaluate the obstetric and perinatal outcomes of fetuses with early (EO) and late-onset (LO) fetal growth restriction (FGR), and to explore the prognostic factors on perinatal survival and adverse perinatal outcome.

**Materials and Methods:** We retrospectively reviewed 105 EO- and 55 LO-FGR singleton pregnancies. Umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV) Doppler parameters and cerebroplacental ratio (CPR) were assessed. Prognostic significance of gestational age at delivery, birth weight and Doppler parameters were evaluated.

**Results:** Gestational age at delivery greater than 27 weeks (sensitivity 87.5%, specificity 76%) and birth weight of 665 g (sensitivity 88.8%, specificity 92%) provided the best prediction of survival in EO-FGR. Logistic regression analysis of UA absent or reversed end diastolic flow (EDF), abnormal DV Doppler, and absent/reversed DV a-wave revealed Odds Ratios of 2.57, 6.97, 4.51 and 8.75 respectively for perinatal mortality in EO-FGR. The incidence of CPR below the 5$^{th}$ percentile was significantly higher in LO-FGR pregnancies with the composite adverse outcome than normal outcome ($p<0.001$).

**Conclusion:** Gestational age at delivery and birth weight are the strongest predictors of perinatal mortality in EO-FGR. In LO-FGR, CPR <5$^{th}$ percentile is associated with an increased risk of delivery complications.

**Keywords:** Early-onset fetal growth restriction, late-onset fetal growth restriction, perinatal outcome, Doppler parameters

### ÖZET

**Amaç:** Erken (EB) ve geç (GB) başlangıçlı fetal gelişim kısıtlılığı (FGK) olgularında obstetrik ve perinatal sonuçların değerlendirilmesi ve perinatal sağ kalım ile olumsuz perinatal sonuçlar üzerine etkili prognostik faktörlerin saptanması.

**Gereç ve Yöntem:** Tekil 105 EB- ve 55 GB-FGK olan gebelik retrospektif olarak derlendi. Umblikal arter (UA), orta serebral arter (MCA) ve duktus venozus (DV) Doppler parametreleri ile serebroplasental oran (CPR) değerlendirildi. Doğumdaki gebelik haftası, doğum ağırlığı ve Doppler parametrelerinin prognostik anlamı incelendi.

**Bulgular:** Doğumun 27. gebelik haftasından sonra gerçekleşmesi (duyarlılık %87,5, özgüllük %76) ve doğum ağırlığının 665 gr'ın üzerinde olması (duyarlılık %88,8, özgüllük %92) EB-FGK olgularında en iyi sağ kalım öngörüsünü sağladı. Lojistik regresyon analizinde, UA diyastol sonu akımın (EDF) kaybı ve ters akım olması, anormal DV Doppler ve DV a dalgasının kaybı/ters a dalgası EB-FGK'da perinatal mortalite ile ilişkili bulundu (sırasıyla olasılık oranları %2,57, 6,97, 4,51 ve 8,75). Olumsuz sonuçların eşlik ettiği GB-FGK'da, normal sonuçların izlendiği olgulara kıyasla, CPR'ın 5. persentilin altında olma oranı istatiksel olarak anlamlı bulundu ($p<0,001$).

**Sonuç:** EB-FGK'da doğumdaki gebelik haftası ve doğum ağırlığı en kuvvetli prediktörlerdir. GB-FGK'da, CPR'ın <5. persentil olması doğum komplikasyonları açısından artmış risk ile ilişkilidir.

**Anahtar Kelimeler:** Erken başlangıçlı fetal gelişim kısıtlılığı, geç başlangıçlı fetal gelişim kısıtlılığı, perinatal sonuç, Doppler parametreleri

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## INTRODUCTION

Fetal growth restriction (FGR) is defined as the inability of the fetus to reach its growth potential with increased risks of perinatal mortality and morbidity (1). FGR is classified as early-onset (EO-) (<32 weeks) or late-onset (LO-) (≥32 weeks) FGR based on the gestational age at diagnosis (1). EO- and LO-FGR seems to be caused by different placental pathologies, where EO-FGR originates from the reduction of villous vascular area; LO-FGR is associated with impaired maturation of the villi with mild placental insufficiency (2, 3). EO-FGR affects 1-2% of births and is frequently associated with preeclampsia, abnormal Doppler indices, fetal hypoxia, and increased perinatal mortality (4). LO-FGR affects 3-5% of births, although associated with a lower risk of fetal hypoxia and abnormal Doppler indices, is related to stillbirth, neonatal morbidity and intrapartum fetal distress (5).

Clinical management of FGR pregnancies mostly relies on optimizing the timing of delivery. Doppler evaluation of uterine artery (UtA), umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV) are commonly used in the management of FGR pregnancies. The major concern in EO-FGR is to prevent fetal death and severe neonatal morbidity, balancing the risks of preterm delivery. The typical pattern of fetal Doppler parameters' deterioration, which guides the timing of delivery, has been shown to be present in EO-FGR (4). Absent or reversed end diastolic flow (EDF) in UA is related to increased risk of fetal demise, and delivery is recommended after 32-34 weeks (6). Abnormal DV Doppler parameters (increased PI, absent or reversed atrial contraction wave (a-wave)) and cardiotocography findings are indications for delivery before 32 weeks (6). LO-FGR is associated with low fetal tolerance to the hypoxic conditions induced by normal labor (5). Cerebroplacental ratio (MCAPI/UAPI, CPR) has been reported to be useful in identifying fetuses with poor perinatal outcome in LO-FGR (7).

The aim of the present study was to evaluate the obstetric and perinatal outcomes of fetuses with EO- and LO-FGR. And also, to explore the significance of prognostic factors on perinatal survival and adverse perinatal outcome in EO- and LO-FGR pregnancies.

## MATERIALS AND METHODS

This was an observational retrospective cohort study of 105 EO-FGR and 55 LO-FGR singleton pregnancies conducted at the Maternal-Fetal Unit, between January 2015 and December 2019. Approval for this study was obtained by the institution's ethics committee. Fetuses with chromosomal and structural abnormalities, infections and genetic syndromes were excluded from the study. Gestational age was determined based on last menstrual period and was confirmed with crown-rump length of first trimester ultrasound. EO-FGR was defined when the gestational age at diagnosis was <32 weeks and delivery was ≤34 weeks and the following criteria were present: estimated fetal weight (EFW) or abdominal circumference (AC) below the 3$^{rd}$ percentile for the gestational age or absent EDF UA; EFW or AC below the 10$^{th}$ percentile for the gestational age, associated with a mean UtA PI or UA PI above the 95$^{th}$ percentile for gestational age (1). LO-FGR is defined, when the gestational age at diagnosis is ≥32 weeks and delivery is >34 weeks in the presence of EFW or AC below the 3$^{rd}$ percentile for gestational age; EFW or AC below the 10$^{th}$ percentile for the gestational age, associated with a mean UtA-PI above the 95$^{th}$ percentile for the gestational age, CPR below the 5$^{th}$ percentile for the gestational age (1).

Ultrasound and Doppler assessments were performed using Voluson E10 (GE Medical Systems, USA). Fetal biometric parameters and amniotic fluid index were measured and EFW was calculated using the Hadlock formula (8). Doppler velocity waveforms from UtA, UA, MCA and DV were obtained and measured according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines (9). In all cases the last Doppler evaluation was performed within 24 hours before delivery. Abnormal UtA Doppler was defined as mean PI (right+left UtA PI/2) above the 95$^{th}$ percentiles or the presence of a diastolic notch in both uterine arteries (10). Abnormal UA, MCA and DV Doppler parameters and CPR were defined as UA-PI>95$^{th}$, MCA-PI<5$^{th}$, DV-PI>95$^{th}$ and CPR<5$^{th}$ for the gestational age respectively (11-13). The UA was also qualitatively assessed for absent or reversed EDF.

Follow-up ultrasound assessments were carried out at least every 1-2 weeks and up to every day depending on the type and severity of FGR. Timing of delivery was based on evidence from randomized controlled trials considering gestational age, severity of FGR, and results of fetal surveillance (6, 12). In cases of EO-FGR with absent or reversed EDF in UA, delivery was recommended at 32 weeks or sooner if DV Doppler parameters were abnormal (6). Evident cardiotocographic abnormalities such as recurrent late decelerations or loss of variability and maternal condition such as severe preeclampsia were also indications for delivery. Antenatal steroids were administrated for fetal lung maturity in EO-FGR. Cases with LO-FGR were followed weekly or twice weekly with amniotic fluid volume measurement, Doppler examination and cardiotocography. Induction of labor was performed in case of maternal medical complications, decreased amniotic fluid index, fetal movement and gestational age ≥39 weeks.

Demographic data, obstetric, and perinatal outcomes were evaluated. Incidences of preeclampsia (BP>140/90 on two separate occasions and proteinuria (>300 mg/day) arising de novo after the 20$^{th}$ week of pregnancy),

cesarean section (CS), fetal death (death after 22 completed weeks of gestation and before birth), neonatal death (death before 28 completed days after birth), perinatal mortality (obtained as the sum of fetal and neonatal death), 5-min Apgar score <7, birth weight, umbilical artery pH and admission to the neonatal intensive care unit (NICU) were studied. The diagnosis of intrapartum fetal distress was based on abnormal CTG tracing according to the FIGO classification system (14). The composite adverse outcome for LO-FGR was defined as 5-min Apgar score <7, umbilical artery pH<7.20, emergency CS for fetal distress and neonatal admission to special care unit.

### Statistical analysis

Non-parametrical Kruskal-Wallis, Mann-Whitney U and chi-square test were used to compare categorical data and One-way ANOVA or Student's t-test were used to compare non-categorical data as appropriate. Association between the different Doppler indices and perinatal mortality were assessed by binary logistic regression analysis and results were reported as odds ratios (ORs) with their 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves and the area under the curve (AUC) and 95% confidence interval (CI) of the ROC curve were analyzed for continuous variables that contribute to perinatal mortality, and predictive cut-offs were determined. Statistical Package for Social Sciences software version 20.0 for Windows (SPSS Inc., Chicago, USA) was used.

## RESULTS

The clinical characteristics and pregnancy outcomes of women with EO- and LO-FGR are presented in Table 1. There were no statistically significant differences between the study groups with respect to maternal age, nulliparity and interval from diagnosis to delivery (p>0.05). Incidences of preeclampsia and abnormal uterine artery Doppler waveform were 20% vs 5.5% and 80.9% vs 9.1% in the EO- and LO-FGR groups, (p<0.01) respectively. Incidences of cesarean section rate, 5-min Apgar score <7, and NICU admission were significantly higher in the EO-FGR group (p<0.01). In the EO-FGR group, there were 12 fetal (11.4%) and 15 neonatal deaths (14.3%) with a perinatal mortality rate of 25.7%. No fetal or neonatal death was observed in cases with LO-FGR.

Perinatal outcomes of fetuses according to gestational age at delivery for the EO-FGR group are illustrated in Table 2 and Figure 1. Fetal deaths occurred between 25 and 27 weeks of gestation (mean 25.7±0.6 weeks), and in all these cases, parents had decided against intervention. The mean interval between diagnosis of EO-FGR and fetal death was 3.1±1.6 weeks (range: 3 days to 5 weeks). Of the 12 fetuses which died in utero, all had ab-

**Table 1:** The clinical characteristics and pregnancy outcomes of women with early-onset and late-onset fetal growth restriction

| | Early-onset FGR | Late-onset FGR | p value |
|---|---|---|---|
| n | 105 | 55 | |
| Maternal age (y) | 29.3±4.9 | 28.3±6.5 | 0.229 |
| Nulliparity | 54 (51.4) | 25 (45.5) | 0.508 |
| Gestational age at diagnosis (weeks) | 26.7±3.4 | 34.9±1.5 | 0.000 |
| Diagnosis to delivery time (weeks) | 2.9±2.7 | 2.5±1.5 | 0.209 |
| Preeclampsia | 21 (20) | 3 (5.5) | 0.015 |
| Abnormal uterine artery Doppler | 85 (80.9) | 5 (9.1) | 0.000 |
| Umbilical artery absent/reversed EDF[a] | 55 (52.4) | - | 0.000 |
| Gestational age at delivery (weeks) | 29.7±2.9 | 37.4±1.2 | 0.000 |
| Birth weight (g) | 948±428 | 2375±417 | 0.000 |
| Cesarean section rate | 89/93 (95.7) | 17 (30.9) | 0.000 |
| 5-min Apgar score <7 | 37/93 (39.8) | 1 (1.8) | 0.000 |
| Umbilical artery pH | 7.30±0.10 | 7.35±0.04 | 0.008 |
| NICU[b] admission | 87/93 (93.5) | 9 (16.4) | 0.000 |
| Fetal death | 12 (11.4) | - | 0.009 |
| Neonatal death | 15 (14.3) | - | 0.002 |

Data are expressed as mean±standard deviation or n (%) where appropriate
[a]: EDF; end-diastolic flow, [b]: NICU; Neonatal intensive care unit

**Table 2:** Perinatal outcomes of fetuses according to gestational age at birth for early-onset fetal growth restriction group

| | Gestational age at birth (weeks) | | | | |
|---|---|---|---|---|---|
| | **25-26 weeks** | **27-28 weeks** | **29-30 weeks** | **31-32 weeks** | **33-34 weeks** |
| n | 23 | 16 | 21 | 26 | 19 |
| Fetal death | 11 (47.8) | 1 (6.3) | 0 (0) | 0 (0) | 0 (0) |
| Neonatal death | 6 (26.1) | 6 (37.5) | 2 (9.5) | 1 (3.8) | 0 (0) |
| Survival | 6 (26.1) | 9 (56.2) | 19 (90.5) | 25(96.2) | 19 (100) |

Data are expressed n (%)

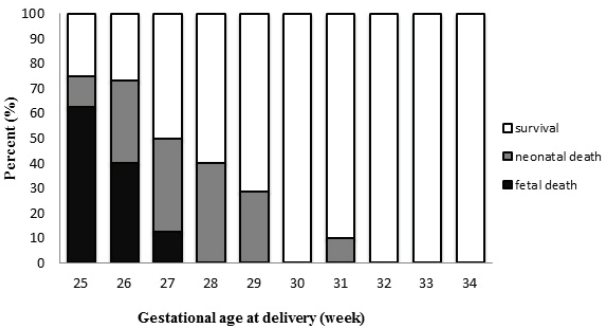


**Figure 1:** Outcome for fetuses according to gestational age at delivery for early-onset fetal growth restriction group

sent/reversed EDF in UA and 4 (33.3%) had absent/reversed a-wave in DV. In the EO-FGR group, there were 15 neonatal deaths with a mean gestational age at delivery of 27.3±1.5 weeks and mean birth weight of 549±138 g. Causing factors of neonatal deaths were perinatal asphyxia (n=10), RDS (n=2), neonatal sepsis (n=1), and NEC (n=2).

The obstetric characteristics and Doppler features of EO-FGR pregnancies that had perinatal mortality and survival are shown in Table 3. The mean gestational age at diagnosis, delivery and birth weight were significantly higher in pregnancies that survived than with perinatal mortality (p<0.001). ROC curve analysis demonstrated that gestational age greater than 27 weeks (sensitivity 87.5%, specificity 76%, AUC 0.908, p<0.001) and birth

**Table 3:** The obstetric characteristics and Doppler features of early-onset fetal growth restriction pregnancies that had perinatal mortality and survival

| | **Perinatal mortality** | **Survivors** | **p** | | |
|---|---|---|---|---|---|
| n | 27 | 78 | | | |
| Gestational age at diagnosis (weeks) | 24.1±2.5 | 27.6±3.2 | 0.000 | | |
| Gestational age at delivery (weeks) | 26.6±1.5 | 30.8±2.5 | 0.000 | | |
| Birth weight (g) | 483±155 | 1109±371 | 0.000 | | |
| Abnormal uterine artery Doppler | 24 (88.9) | 61 (78.2) | 0.225 | | |
| Umbilical artery [a]PI | 2.9±0.9 | 1.6±0.8 | 0.000 | | |
| Middle cerebral artery PI | 1.2±0.4 | 1.5±0.4 | 0.002 | | |
| Ductus venosus [a]PI | 1.3±0.4 | 0.7±0.3 | 0.000 | | |
| Umbilical artery end diastolic velocity | | | | OR[b] (95% CI) | |
| Absent | 14 (51.8) | 23 (29.4) | 0.037 | 2.57 (1.05±6.32) | 0.039 |
| Reversed | 11 (40.7) | 7 (8.9) | 0.000 | 6.97 (2.34±20.77) | 0.000 |
| Ductus Venosus | | | | | |
| Elevated [a]PI | 15 (55.6) | 16 (20.5) | 0.002 | 4.51 (1.71±11.92) | 0.002 |
| Absent/reversed atrial systolic velocity | 7 (25.9) | 3 (3.8) | 0.001 | 8.75 (2.07±36.92) | 0.003 |

Data are expressed as mean±standard deviation or n (%) where appropriate
[a:] PI; Pulsatility index, [b:] OR; Un-adjusted Odds Ratio

weight of 665 g (sensitivity 88.8%, specificity 92%, AUC 0.970, p<0.001) provided the best prediction of survival. Mean UA and DV PI were significantly higher and MCA PI was significantly lower in pregnancies that survived than those that had perinatal mortality (p<0.01). ROC curve for the detection of perinatal mortality by UA, DV and MCA PI is illustrated in Figure 2 and the areas under the curve equal to 0.875, 0.867 and 0.729 (p<0.001) for UA, DV, and MCA PI respectively were determined. Incidences of absent/reversed EDF in UA and absent/reversed DV a-wave were significantly higher in pregnancies with perinatal mortality than survival (p<0.01). Logistic regression analysis of UA absent/reversed EDF, abnormal DV Doppler, and absent/reversed DV a-wave revealed ORs of 2.57, 6.97, 4.51 and 8.75, respectively for perinatal mortality in EO-FGR group (Table 3).

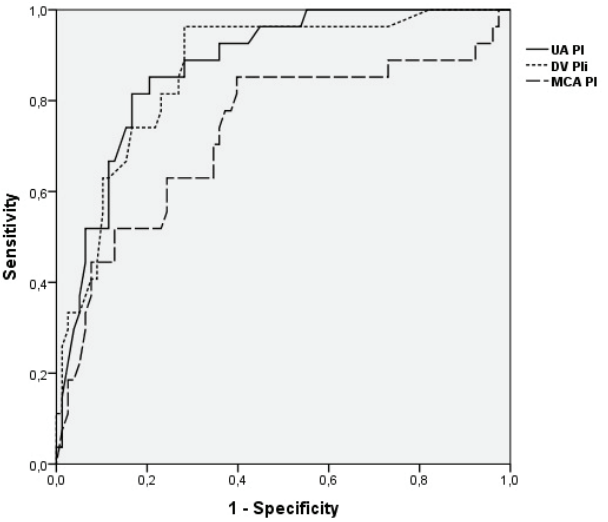


**Figure 2:** Receiver operating characteristics (ROC) curve analysis of umbilical artery, ductus venosus and middle cerebral artery for the detection of perinatal mortality in the early-onset fetal growth restriction group

In the LO-FGR group, there was no perinatal mortality and 11 (20%) composite adverse outcomes. Of the pregnancies with LO-FGR, 11 had spontaneous vaginal delivery, 9 had CS due to previous CS or breech presentation and 29 had induction of labor, of which 8 was emergency CS performed due to fetal distress. The obstetric characteristics and Doppler features of LO-FGR pregnancies with composite adverse and normal perinatal outcomes are shown in Table 4. The mean gestational age at diagnosis and delivery were not significantly different (p>0.05), whereas mean birth weight was significantly lower in LO-FGR pregnancies with composite adverse outcome than the normal outcome (p<0.001). The incidence of CPR below the 5$^{th}$ percentile was significantly higher in LO-FGR pregnancies with the composite adverse outcome than the normal outcome (p<0.001).

## DISCUSSION

The present study, comparable with previous studies, demonstrates that EO- and LO-FGR have completely different perinatal and obstetric outcomes with higher incidences of perinatal mortality, preeclampsia and Doppler abnormalities in EO-FGR pregnancies (3, 15, 16). Defective placentation reflected by abnormal UtA and UA Doppler velocimetry findings is the main cause of EO-FGR, in which pregnancy is not accepted to continue beyond 34 weeks with such improper placenta formation (4, 17). Whereas in LO-FGR, although the placenta is formed properly, villous immaturity seems to be the main cause of mild placental insufficiency with mostly normal UA and UtA Doppler velocimetry (2, 5). We have observed high incidence of UtA Doppler abnormality (81%) and absent/reversed EDF in UA (52%) in EO-FGR pregnancies; however, all of the LO-FGR fetuses had UA PI within normal limits.

In our study group, all of the perinatal mortalities were observed in the EO-FGR pregnancies. Survival rates according to gestational age at delivery were similar to those

**Table 4:** The obstetric characteristics and Doppler features of late-onset fetal growth restriction pregnancies that had composite adverse outcome and normal outcome

| | Normal outcome | Composite adverse outcome | p |
|---|---|---|---|
| n | 44 | 11 | |
| Gestational age at diagnosis (weeks) | 35.2±1.5 | 34.7±2.1 | 0.380 |
| Gestational age at delivery (weeks) | 37.9±1.1 | 37.3±1.2 | 0.119 |
| Birth weight (g) | 2450±352 | 1985±282 | 0.000 |
| Abnormal uterine artery Doppler | 4 (9.1) | 1 (9.1) | 1.000 |
| CPR[a] below the 5$^{th}$ | 5 (11.3) | 7 (63.6) | 0.000 |

[a]: CPR; Cerebroplacental ratio
Data are expressed as mean±standard deviation or n (%) where appropriate

reported by multicentric TRUFFLE study (18). Gestational age at delivery and birth weight were the strongest predictors of perinatal mortality in the EO-FGR group, these findings were in accordance with the literature (18, 19). Gestational age greater than 27 weeks and birth weight of 665 g provided the best prediction of survival, which also were similar to previous studies (20, 21). Doppler evaluation of fetal vessels has become the primary method of fetal surveillance and management of EO-FGR pregnancies. UA Doppler reflects placental dysfunction, whereas MCA and DV Doppler reflect a brain sparing effect and myocardial dysfunction (4, 6). In our EO-FGR group, UA and DV PI were more effective than MCA PI in predicting perinatal mortality. In accordance with previous studies, our data also supports that MCA PI is unlikely to be helpful for targeting the best time of delivery in EO-FGR (22). Meta-analysis evaluating Doppler indices in EO-FGR fetuses has demonstrated that UA and/or DV absent/reversed EDFs are at a substantially increased risk for perinatal mortality (23). We have observed higher incidences of UA absent/reversed EDF and elevated PI/absent a wave in DV in pregnancies with perinatal mortality than survivors. In the regression model including Doppler parameters of UA absent/reversed EDF, increased DV PI and absent/reversed a wave in DV revealed ORs of 2.57, 6.97, 4.51 and 8.75 respectively for perinatal mortality in our EO-FGR group. Cardiotocography, Doppler examination and biophysical profiles are fetal surveillance methods used in the management of EO-FGR. TRUFFLE trial showed a better outcome by the integrated use of both DV and computerized cardiotocography short-term variation (cCTG-STV) in the management of EO-FGR (18). The authors of the TRUFFLE study emphasized that before 32 weeks of gestation, delaying delivery until there is an absent DV a-wave, abnormalities in cCTG-STV or recurrent decelerations in fetal heart rate is likely to be safe and possibly associated with a more favorable 2-year outcome in EO-FGR (6). As cCTG was not available, the role of this method was not addressed; however, loss of variability and recurrent decelerations in CTG were indications for delivery in our study group. Optimal delivery timing is a challenge in the management of pregnancies with EO-FGR. Gestational age, maternal conditions, CTG and Doppler results should be taken together in the decision making. Our data confirm that UA reversed EDF and absent a wave in DV are highly associated with perinatal mortality.

No perinatal mortality was observed in our LO-FGR group; however, a composite adverse outcome was found in 20% of pregnancies. Adverse neonatal outcomes have been reported in pregnancies with LO-FGR (5, 24). Many recent studies have demonstrated that low CPR is related with a higher rate of cesarean delivery, low Apgar score, neonatal unit admission, and neonatal complications (25, 26). Low CPR reflects a brain sparing affect as a result of cerebrovascular dilation due to hypoxia and such LO-FGR fetuses are more suspectable to delivery complications. We have also observed higher incidence of low CPR in fetuses with the composite adverse outcome than normal outcome. Although the number of LO-FGR pregnancies are limited in our study group, our data supports the role of CPR in the management of LO-FGR pregnancies.

## CONCLUSION

EO- and LO-FGR groups pose different perinatal and obstetric outcomes. Optimal timing of delivery is still the main challenge in management of early severe FGR. Birth weight and gestational age at delivery are the most important variables for perinatal outcome. UA reversed EDF and absent DV a wave are highly associated with perinatal mortality. In LO-FGR, CPR <5$^{th}$ percentile is related with a higher risk of delivery complications and may play a role in the management of such pregnancies.

**Ethics Committee Approval:** This study was approved by the Institutional Ethical Review Board of Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine (Date: 15.12.2020, No: 160381)

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**Author Contributions:** Conception/Design of Study- R.M., V.A., D.K.; Data Acquisition- R.M., V.A., İ.B.O.; Data Analysis/Interpretation- R.M., V.A., D.K.; Drafting Manuscript- R.M., V.A., İ.B.O.; Critical Revision of Manuscript- R.M., V.A., D.K., İ.B.O.; Approval and Accountability- R.M., V.A., D.K., İ.B.O.

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