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Original article

Maternal and fetal risk factors affecting perinatal mortality in early and late fetal growth restriction

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ABSTRACT

Objective: To determine the factors which affect the perinatal deaths in early and late fetal growth restriction (FGR) fetuses using threshold of estimated fetal weight (EFW) < 5th percentile.
Materials and Methods: This retrospective study included singleton 271 FGR fetuses, defined as an EFW < 5th percentile. All fetuses considered as growth restrictions were confirmed by birth weight. Fetuses with multiple pregnancy, congenital malformation, chromosomal abnormality, and premature rupture of membrane were excluded. Samples were grouped in early and late FGR. Early FGR fetuses was classified as gestational age at birth ≤ 34 weeks and late FGR was classified as gestational age at birth > 34 weeks. Factors which affect the perinatal deaths were analyzed descriptively in early and late FGR. The perinatal mortality was calculated by adding the number of stillbirths and neonatal deaths.
Results: The study included 86 early and 185 late FGR fetuses, 31 resulted in perinatal deaths, 28 perinatal deaths were in early FGR, and three perinatal deaths were in late FGR. Perinatal deaths occurred more commonly in early FGR fetuses with an EFW < 3rd percentile. Prior stillbirth, preeclampsia, the degree of increasing vascular impedance of umbilical artery(UA) and uterine artery (UtA) showed significant correlation with perinatal death in early FGR. All three perinatal deaths in late FGR occurred in fetuses with EFW < 3rd percentile and severe oligohydramnios. Also, placental abruption and perinatal death was found significantly higher in increased vascular impedance of UtAs whatever the umbilical artery Doppler.
Conclusion: Only EFW < 3rd percentile and severe olgohydramnios seem to be contributing factors affecting perinatal death in late FGR in comparison with early FGR.

Introduction

Fetal growth restriction (FGR) is defined as failure of the genetic growth potential in the fetus and affects 7–10% of all pregnancies [1]. The main purpose of the management of fetal growth restriction is prediction and prevention of perinatal mortality. Recent reports have confirmed the largest contribution of FGR in the cause of perinatal mortality in nonanomalous fetuses [2]. The use of umbilical artery Doppler velocimetry is the only fetal monitoring associated with a decrease in perinatal mortality [3,4]. Also, abnormal Doppler velocimetry of uterine arteries is comparable with umbilical artery Doppler as a predictor of adverse outcomes in growth restricted fetuses [5–7]. In addition, uterine artery Doppler velocimetry has been shown to be able to identify FGR fetuses at increased risk for adverse perinatal outcomes even though the umbilical artery Doppler velocimetry was normal [7]. In accordance to current approaches on the natural history of growth restriction that differentiates as early-onset and late-onset forms [8]. Early-onset FGR is usually diagnosed with abnormal umbilical and uterine arteries Doppler and is frequently associated with preeclampsia [9]. Also, early-onset FGR is strongly correlated with perinatal death [10]. However, late-onset shows less change in umbilical and uterine arteries Doppler flow pattern, and has less association with preeclampsia [9]. Particularly at the early FGR stage, coexistence of preeclampsia may distort the natural history and fetal deterioration and mortality may occur unexpectedly.

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The diagnosis of fetal "smallness" is performed on the basis of an estimated fetal weight < 10^{th} percentile in spite of lack of sensitivity. But this classification identifies a subset of pregnancies at high risk of poorer perinatal outcome [11]. However, the threshold of EFW confirmed by birthweight was taken below the 5^{th} percentile to catch high risk FGR fetuses [8]. The aim of the present study is to determine factors which affect the perinatal mortalities in early and late FGR fetuses using the threshold of EFW below the 5^{th} percentile.

Materials and Methods

This retrospective study was performed at the Zeynep Kamil Gynecologic and Pediatric Training and Research Hospital, Istanbul, Turkey, between January 2009 and December 2012. The study was approved by the local ethics committee. This study included fetuses that had an antenatal diagnosis of FGR. Gestational age was determined by ensuring that the last menstrual period was confirmed by ultrasound examination as first-trimester crown–rump length. FGR was defined as an EFW < 5^{th} percentile based on sonographic measurements of the fetal head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) according to growth standards [12]. All fetuses considered as growth restriction were justified by birth weight. Fetuses with multiple pregnancy, congenital malformation, chromosomal abnormality, and premature rupture of membrane were excluded.

According to our hospital routine protocol; all FGR fetuses underwent serial sonographic evaluation twice weekly until birth but more frequently, even daily if deemed necessary. Sonographic assessments cover the following: fetal weight, amniotic fluid volume and uterine artery (UtA), and umbilical artery (UA) Doppler assessment. UA recordings were performed on a free floating cord loop in the absence of fetal breathing or movements. Abnormal UA Doppler assessment was defined as a pulsatility index (PI) > 95^{th} percentile [13], absent and reversed end-diastolic blood flow. The UA of FGR fetuses were evaluated according to UA blood flow characteristics (BFC) as follows: BFC 0, normal UA blood flow velocity waveform (PI $\leq$ 95^{th} percentile); BFC 1, forward diastolic blood flow with PI $\geq$ 95^{th} percentile; BFC 2, absent diastolic blood flow; and BFC 3, reversed diastolic blood flow. Doppler examination of the UtA was performed as bilaterally at the same time. Color Doppler was used to visualize the crossing of the uterine and external iliac arteries. UtA Doppler velocimetry was measured cranial of the vessel "crossing". The presence of a diastolic notch in the flow-profiles of the UA was noted qualitatively, and the PI was calculated from averaging the three waveforms of satisfactory quality. PI > 2 standard deviation (SD) was considered abnormal [14]. The blood flow waveform of the UtA was classified as UtA score (UtAS) according to Gudmundsson et al [15]. UtAS 0 indicated normal blood velocity waveform, PI $\leq$ 2 SD, and no notch present in either uterine arteries; UtAS 1 indicated PI > 2 SD or the presence of notch in one uterine artery; UtAS 2 indicated two abnormal parameters and notch or PI > 2 SD; UtAS 3 indicated three abnormal parameters; and UtAS 4 indicated PI > 2 SD and the presence of notch in both uterine arteries. Abnormal uterine artery Doppler was defined as UtAS 1–4.

Our sample was grouped as early and late FGR defined as an EFW < 5^{th} percentile. Early FGR fetuses was classified as gestational age at birth 34 weeks or less, late FGR was classified as gestational age at birth > 34 weeks. Corticosteroids to promote fetal lung maturation were administered to all early FGR fetuses. Comparisons of these groups were made to maternal demographics, baseline characteristics, sonographic findings, and pregnancy outcomes. The perinatal mortality was calculated by adding the number of stillbirths and neonatal deaths. Comparisons to maternal demographics, baseline characteristics, and sonographic findings were made between FGR fetuses that have perinatal mortalities and alive at hospital discharge.

Pregnancy-induced hypertension was defined as blood pressure $\geq$ 140/90. Preeclampsia was defined as blood pressure $\geq$ 140/90 mmHg in the presence of proteinuria as $\geq$300 mg/dl on a 24-hour collection of urine. Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome was defined as alanine aminotransferase > 70 IU/L with platelets < 100×10^9/L and with evidence of hemolysis from blood or lactate dehydrogenase (LDH) > 600 U/L.

The decision for time and mode of delivery was made by senior obstetricians based on gestational age, none or poor fetal growth in repeated sonography every 3–4 weeks, absent or reversed end-diastolic flow in the umbilical artery, nonreassuring fetal tracing, oligohydraamnios, and maternal and obstetrical indications necessitate delivery, for example, severe eclampsia or placental abruption. Placental abruption was defined as a vaginal bleeding and/or uterine tenderness and nonreassuring fetal status leading to an emergency delivery, and an evidence of retroplacental bleeding or clot of postdelivery examination of the placenta.

Statistical analysis was performed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as numeric (%) or mean ± standard deviation (SD) values, as appropriate. Kolmogorov–Smirnov tests were performed for the distribution of continuous data. Statistical analyses were performed by Student *t* test for normal distribution data and Mann–Whitney *U* test for abnormal distribution data. Chi-square and Fisher's exact tests were used for comparison of categorical variables. Statistical significance was set at $p \leq 0.05$.

Results

The study included 271 FGR fetuses. Of these, 86 (31.7%) FGR fetuses were early FGR. The maternal demographic characteristics, obstetric histories, and perinatal clinical characteristics are shown in Table 1. The mean gestational age at delivery was 35.43 ± 3.81 weeks and the mean ultrasound estimated gestational age at delivery was 31.07 ± 3.49 weeks. The mean birth weight was 1812.75 ± 634.75 g. Preeclampsia occurred in 95 of the 271 (35.1%). The rate of cesarean delivery was 75.2%. Nine fetuses (3.3%) died during the follow up. The number of newborns admitted to neonatal intensive care unit (NICU) was 138 (52.7%). A total of 22 newborns died in the neonatal period. The perinatal mortality rate was 11.4%.

Table 2 shows the comparison of maternal demographic characteristics, obstetric histories, and perinatal clinical characteristics between the early and late FGR groups. The early FGR group had a significantly higher maternal age and gravidity. Obstetric history of prior preeclampsia and prior FGR, preeclampsia, and placental abruption in the current pregnancy were found significantly higher in the early FGR group. Amniotic fluid index was significantly lower in the early FGR group. The rate of cesarean delivery was higher in the early FGR group. Perinatal death rate in the early FGR group and late FGR group were found to be 32.6% and 1.6%, respectively. Abnormal UA and UtA Doppler were significantly higher in the early FGR group.

When compared to perinatal mortalities and live newborns at hospital discharge (Table 3), the mean gestational age at delivery and the mean ultrasound estimated gestational age at delivery were significantly lower in perinatal mortalities. Also, the mean birth weight was significantly lower in perinatal mortalities. Prior stillbirth, preeclampsia, and placental abruptions were found significantly higher in women that had perinatal death. The degree of increasing vascular impedance of UtA showed significant correlation with perinatal death. Also, the degree of abnormality of