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ORIGINAL ARTICLE

Outcomes in patients with early-onset fetal growth restriction without fetal or genetic anomalies

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ABSTRACT

Objective: Early-onset fetal growth restriction is associated with poor pregnancy outcomes, but frequently is due to fetal structural or chromosomal abnormalities. The objective of this study was to determine outcomes in patients with early-onset fetal growth restriction without diagnosed fetal or genetic anomalies and to identify additional risk factors for poor outcomes in these patients.

Methods: This was retrospective cohort study of singleton pregnancies in women with early-onset growth restriction defined as a sonographic estimated fetal weight <10% diagnosed between 16–28 weeks' gestation. We excluded all women with a fetal structural or chromosomal abnormality diagnosed prenatally. Data on pregnancy characteristics and outcomes were collected and analyzed for estimated fetal weight <10% and ≤5%. A nested case-control study within the cohort of patients with ongoing pregnancies was then performed to identify risk factors associated with poor pregnancy outcome using chi-squared test.

Results: One hundred forty-two patients were identified who met inclusion and exclusion criteria and 20 patients were found to have fetal structural or chromosomal abnormalities. In the remaining 122 patients, the incidence of intrauterine fetal demise was 5.7% and there were high rates of preterm birth <37 weeks (20%), birth weight <10% (59.3%), and gestational hypertension (14.1%). Later gestational age at diagnosis and the presence of echogenic bowel and abnormal initial umbilical artery Dopplers were associated with poor pregnancy outcome (22.56 versus 20.86 weeks, $p = .046$), (17.4 versus 2.2%, OR 9.68, 95%CI 1.65–56.73), and (35.3 versus 0%, OR 4.46, 95%CI 2.65–7.50) respectively.

Conclusions: Patients with early-onset fetal growth restriction with no fetal structural or genetic abnormality have a high risk of poor pregnancy outcomes. Gestational age at diagnosis and certain ultrasound findings are associated with poor pregnancy outcome.

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Early-onset fetal growth restriction; umbilical artery dopplers; echogenic bowel

Introduction

Early-onset fetal growth restriction (FGR) can be associated with a number of adverse obstetrical conditions including fetal infection, aneuploidy, fetal anomalies, and placental dysfunction [1–3]. It is associated with a higher risk of intrauterine fetal demise and preterm delivery during the delivery and infants may suffer complications related to prematurity and perinatal asphyxia [4]. It is, however, often difficult to distinguish fetuses with growth restriction who are at risk for these complications from fetuses that are constitutionally small. Much of the early data available on early-onset FGR suggests a poor prognosis often due to fetal infection, aneuploidy, and fetal anomalies [2]. However, with first trimester aneuploidy screening and early anatomy ultrasounds, many of these patients are now screened out in the first trimester. Therefore, this prognostic data may not apply to a modern cohort of patients diagnosed with early-onset FGR.

Patients with early-onset FGR are usually offered a fetal evaluation that includes genetic testing, detailed anatomy scan with or without fetal echocardiogram, and testing for viral infections. For patients with a negative workup, the differential diagnosis is usually reduced to placental dysfunction or constitutionally small fetuses. These two etiologies have vastly different prognoses which make the counseling of patients difficult. Ultrasound evaluation for placental function including fetal Doppler studies and amniotic fluid volume have primarily been used to help guide delivery

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planning more so than to counsel patients regarding prognosis [3]. This is especially difficult for patients diagnosed <24-week gestation who may be considering termination of pregnancy.

There have been few studies evaluating this population of patients. The studies that have been published are often limited by small numbers of patients, and the applicability of these studies to patients is often difficult due to variations in definition of FGR and inclusion criteria [5–7]. The objective of this study was to determine outcomes in patients with early-onset FGR diagnosed between 16 0/7 and 28 0/7 weeks gestation without diagnosed fetal or genetic anomalies and to identify additional risk factors for poor outcomes in these patients.

Materials and methods

This study is a retrospective cohort study of singleton pregnancies with early-onset fetal growth restriction (FGR) at a single maternal-fetal medicine practice between 2011 and 2015. Biomedical Research Alliance of New York Institutional Review Board approval was obtained. Early-onset FGR was defined as an estimated fetal weight <10% using Hadlock criteria between 16 0/7 and 28 0/7 weeks gestation [8]. Estimated date of delivery was assigned by last menstrual period (LMP) with a consistent crown-rump length on ultrasound, crown-rump length if unsure LMP, or by intrauterine insemination date or embryo transfer date in patients who were conceived by assisted reproduction. Patients without a prior ultrasound to confirm the estimated date of delivery, an intrauterine fetal demise at the initial ultrasound diagnosing the FGR, or unavailable outcome data were excluded.

Patients routinely received a first trimester ultrasound for genetic screening for trisomy 21, 13 and 18 and/or to confirm the estimated date of delivery. Patients with early-onset FGR routinely received a detailed anatomical survey and were offered genetic screening and testing, fetal echocardiogram, and viral studies. Viral studies included cytomegalovirus, toxoplasmosis, and other indicated infections and were sent from maternal serum or amniotic fluid. Patients were followed with serial growth scans, approximately every 2 weeks, and fetal surveillance through biophysical profile and/or umbilical artery Doppler velocimetry. Abnormal umbilical artery Doppler velocimetry was defined as ≥95% starting at 19-week gestation, or absent or reverse flow at any gestation [9]. Internal guidelines were used to guide administration of antenatal steroids for fetal lung maturity and timing of delivery based on gestational age, severity of FGR, and results of fetal surveillance.

Baseline characteristics, fetal evaluation, and pregnancy outcomes were obtained from the computerized medical record or from the referring physician. Baseline characteristics evaluated were age and medical history, fetal evaluation included genetic screening and testing and ultrasound findings, and pregnancy outcomes included gestational age and birth weight at delivery [10].

Data were analyzed to report fetal evaluation and pregnancy outcomes in patients with early-onset FGR. A nested case-control study within the cohort of patients with an estimated fetal weight <10%, no known structural or genetic abnormality, and no elective termination of pregnancy was performed to identify risk factors associated with poor pregnancy outcome. The risk factors evaluated included maternal age, conception through *in vitro* fertilization, abnormal biochemical markers of aneuploidy, gestational age at initial diagnosis, oligohydramnios at initial diagnosis, echogenic bowel at initial diagnosis, and abnormal umbilical artery Doppler at initial diagnosis. Abnormal biochemical biomarkers of aneuploidy were defined as a low pregnancy associated plasma protein A (PAPP-A) ≤ 5% and/or an elevated maternal serum alpha fetoprotein (MSAFP) ≥ 2.0 MoM. For this case-control study, poor pregnancy outcome was defined as a subsequent intrauterine fetal demise or a preterm delivery <34 weeks. Chi-squared test or Student's *t* test was used as appropriate. Incidences and odds ratios were reported with a value of $p < .05$ used for significance.

Results

Two hundred twenty-five patients were identified. Twenty-four patients were excluded for having an intrauterine fetal demise at the initial ultrasound diagnosing the FGR, five patients were excluded for not having a confirmed estimated date of delivery, and 54 patients were excluded for unavailable outcome data. The remaining 142 patients met the inclusion criteria. Twenty patients were found to have a structural or genetic abnormality, 17 with a major structural anomaly, one with a genetic abnormality, and two with both a major structural abnormality and a genetic abnormality. No patient was found to have evidence of a fetal infection such as cytomegalovirus or toxoplasmosis.

There were 122 remaining patients with an estimated fetal weight <10%. Five patients (4.1%) underwent an elective termination of pregnancy. Table 1 shows the baseline characteristics of this population and Table 2 shows the pregnancy outcomes. Most patients were

Table 1. Baseline characteristics of patients with early-onset fetal growth restriction.

Baseline characteristic	EFW <10% ($n = 122$)	EFW ≤5% ($n = 35$)
Age, in years (mean, ±SD)	33.69 (±5.05)	34.01 (±4.91)
In vitro fertilization	20.5%	25.0%
Low PAPP-A ≤5%	26.8%	24.0%
Elevated AFP ≥2.0 MoM	18%	15%
Gestational age at diagnosis, in weeks (mean, ±SD)	21.11 (±3.63)	22.00 (±3.42)
Oligohydramnios[a]	0%	0%
Echogenic bowel[a]	7.4%	11.4%
Abnormal umbilical artery Dopplers[a]	13.8%	0%

[a]At initial scan with diagnosis of fetal growth restriction.
PAPP-A: pregnancy-associated plasma protein A; AFP: alpha-fetoprotein.

Table 2. Pregnancy outcomes in patients with early-onset fetal growth restriction.

Pregnancy outcomes	EFW <10% ($n = 122$)	EFW ≤5% ($n = 35$)
Subsequent intrauterine fetal demise	7 (5.7%)	2 (5.7%)
Elective termination of pregnancy	5 (4.1%)	1 (2.9%)
Pregnancy outcomes in patients with live deliveries		
Birth weight <10%	59.3%	68.8%
Birth weight <5%	40.7%	56.3%
Birth weight, in grams (mean, ±SD)	2470.76 (±470.76)	2259.84 (±259.84)
Preterm delivery <37-week gestation	20%	31.3%
Preterm delivery <34-week gestation	14.5%	15.6%
Preterm delivery <28-week gestation	2.7%	0%
Pregnancy-induced hypertension	14.1%	25.9%

Table 3. Characteristics and their association with poor pregnancy outcome in patients with early-onset fetal growth restriction.

Baseline characteristic	IUFD or PTD <34 weeks ($n = 23$)	No IUFD or PTD <34 weeks ($n = 94$)	*p* value or odds ratio (95%CI)
Age, in years (mean) (±2SD)	36.97 (±6.34)	32.71 (±4.38)	<.01
In vitro fertilization	55.56%	11.8%	9.38 (1.75–50.22)
Low PAPP-A ≤5%	58.33%	18.18%	6.30 (1.66–23.98)
Elevated AFP ≥2.0 MoM	57.14%	9.80%	12.27 (2.11–71.20)
Gestational age, in weeks (mean) (±2SD)[a]	22.56 (±3.64)	20.86 (±3.60)	.046
Oligohydramnios[a]	0%	0%	NA
Echogenic bowel[a]	17.4%	2.2%	9.68 (1.65–56.73)
Abnormal umbilical Artery Dopplers[a]	35.3%	0%	4.46 (2.65–7.50)

[a]At initial scan with diagnosis of fetal growth restriction.
IUFD: intrauterine fetal demise; PTD: preterm delivery; PAPP-A: pregnancy-associated plasma protein A; AFP: alpha-fetoprotein.

diagnosed at previable gestational ages with an average gestational age at diagnosis of 21.11 weeks. Of note, in the total cohort of patients with an estimated fetal weight <10%, the incidence of intrauterine fetal demise was 7/122 (5.7%) and there were high rates of preterm delivery <37-week gestation (20%), birth weight <10% (59.3%), and pregnancy-induced hypertension (14.1%).

A subgroup of 35 patients with an initial estimated fetal weight ≤5% were identified to evaluate pregnancy outcomes in patients with more severe FGR. In this cohort, one patient (2.9%) underwent an elective termination of pregnancy. Again, Table 1 shows the baseline characteristics of this population and Table 2 shows the pregnancy outcomes. In this cohort of patients with an estimated fetal weight ≤5%, the incidence of intrauterine fetal demise was 2/35 (5.7%), and the rate of preterm delivery <37-week gestation was 31.3%, birth weight <10% was 68.8%, and pregnancy-induced hypertension was 25.9%.

Table 3 shows the results of the nested case-control study of patients with early-onset FGR <10%, no fetal genetic or structural abnormalities, and no elective termination of pregnancy. Maternal factors associated with poor pregnancy outcome included age and pregnancy that was the result of *in vitro* fertilization. Abnormal markers of aneuploidy, specifically low PAPP-A (pregnancy-associated plasma protein A), and elevated AFP (alpha-fetoprotein) were also found to be associated with poor pregnancy outcome. Finally, ultrasound findings associated with poor pregnancy outcome include later gestational age, echogenic bowel, and abnormal umbilical artery Doppler at the time of diagnosis.

Discussion

In this study, we found that in patients with early-onset FGR, there is a high rate of preterm delivery, birth weight <10%, and pregnancy-induced hypertension.

However, we also found that 80.3% of patients with early-onset FGR delivered a live born infant after 34-week gestation which is often considered a favorable pregnancy outcome. Abnormal biochemical markers of aneuploidy and the ultrasound findings of later gestational age, echogenic bowel, and abnormal umbilical artery Dopplers at the initial scan were associated with poor pregnancy outcome. These findings may represent that once genetic and congenital anomalies are removed, findings suggestive of placental insufficiency are most likely to be associated with a poor prognosis. This information will be useful for counseling patients with early-onset FGR as far as prognosis.

There are few prior studies available that addressed similar populations. The most applicable study by Story et al. analyzed patients with an estimated fetal weight less than the third percentile prior to 24-week gestation [5]. They found higher rates of intrauterine fetal demise, preterm delivery, and pregnancy-induced hypertension which would be expected with analyzing more severe cases of FGR. However, they did not evaluate risk factors at the initial diagnosis which were associated with poor pregnancy outcome which is important for patients who are considering elective termination of pregnancy. A second study evaluated 36 pregnancies with an estimated fetal weight $<$501 g and absent or reverses end-diastolic flow velocity waveform in the umbilical artery. They found a much higher rate of intrauterine fetal demise and poor pregnancy outcome [6]. However, their data is difficult to compare as 501 g represents $>$99% at 18-week gestation and $<$1% at 29-week gestation (18–29 weeks was their gestational age range). The largest study evaluating patients with early-onset FGR, TRUFFLE, evaluated patients diagnosed between 26–32 weeks gestation and therefore their results are also difficult to compare with our study because of the later gestational age [7]. Three other studies specifically evaluated biochemical markers of aneuploidy, low PAPP-A, and elevated MSAFP, in patients with early-onset growth restriction and found similar findings that the combination of these markers and early-onset growth restriction are associated with poor outcomes [11–13]. The findings from these studies along with the findings from our study suggest that the commonly used estimated fetal weight $<$10% for intrauterine growth restriction especially without other markers of placental insufficiency may not have as poor of a prognosis as once suspected for patients in the second trimester.

The major strength of this study is that all patients were managed by a single maternal-fetal medicine practice. This allows that all patients were diagnosed using the same criteria and were managed similarly. The second major strength is that it is one of the few studies to evaluate ultrasound findings associated with poor pregnancy outcome in this population. This information is crucial for patients considering elective termination of pregnancy. One limitation of the study is that patients without outcome data were excluded and it is unknown if these patients may have had better or worse prognoses. However, patients without outcome data were found to have similar baseline maternal characteristics and ultrasound findings as patients with outcome data. The second limitation is that patients who declined invasive genetic testing but with fetuses and infants without documented anomalies were assumed to have normal karyotype. Using this method, fetuses with aneuploidy were unlikely to be included, but fetuses with microarray abnormalities may have been included. Similarly, infants diagnosed with viral infections after delivery may have been included. Finally, generalizability of this study may be limited to a population similar to ours and data on certain conditions such as maternal medical problems and demographics, prior poor obstetrical outcomes, and neonatal outcomes were only sporadically available and therefore not included in analysis.

Patients with a fetus diagnosed with early-onset FGR are faced with a broad spectrum of outcomes. Even after structural and genetic abnormalities have been excluded, the outcome ranges from a full term appropriate for gestational age infant to an intrauterine fetal demise or extremely preterm infant. This study adds to the prior studies that provide outcome data for patients with early-onset growth restriction which is useful for counseling patients. It also identifies easily available markers and ultrasound findings which may be associated with a poor prognosis which is useful for patients considering elective termination of pregnancy. Finally, it suggests that patients with fetuses with early-onset FGR have a high rate of gestational hypertension and should be closely monitored to allow for timely diagnosis.

Disclosure statement

The authors report no conflicts of interest.

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