Pregnancy outcomes in late-onset fetal growth restriction: a Delphi consensus-based approach

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Abstract

Objectives: *To assess pregnancy outcomes of late-onset fetal growth restriction based on Delphi consensus.*

Materials and methods: *A prospective study in 133 pregnant women with fetal growth restriction according to the Delphi consensus were investigated at the Obstetrics and Gynecology Center - Hue Central Hospital from May 2022 to June 2023.*

Results: *Late-onset fetal growth restriction rate as classified by the Delphi-consensus was 87.2%. Baseline characteristics included: average maternal age was 27.4 ± 5.5 (years); unemployment rate was 28.4%; underweight BMI was 41.4%; smoking (active/passive) was 31%; history of previous late-onset fetal growth restriction was 10.3%; hypertensive disorders of pregnancy was 24.1%; primigravida was 69.8%; abnormal amniotic fluid index was 31.9%; Doppler spectrum of umbilical artery with increased resistance was 13.8%, absent/reversed end-diastolic flow 6.9%; abnormal Doppler of the middle cerebral artery, abnormal ductus venosus, and abnormal cerebroplacental ratio in about 25% of cases. The abnormal non-stress CTG was 41.4%. Regarding pregnancy outcomes, average gestational age was 37.6 ± 1.9 (weeks); average weight was 2155.2 ± 321.8 (grams); cesarean section rate was 68.1%, particularly 43.0% due to late-onset fetal growth restriction; adverse perinatal outcomes were 40.5%. The value of ultrasound and non-stress CTG in predicting cesarean delivery and adverse perinatal outcomes had low sensitivity but high specificity.*

Conclusion: *Late-onset fetal growth restriction based on the Delphi consensus occurred at remarkably high rate. Although changes in arterial Doppler values have low sensitivity, the specificity is very high. The rate of adverse perinatal outcomes is notably high, emphasizing the need for early diagnosis for monitoring and determining the optimal intervention timing.*

Keywords: *Fetal growth restriction, Late-onset fetal growth restriction, Delphi consensus.*

1. INTRODUCTION

Fetal growth restriction (FGR) is a condition in which the fetus fails to attain full intrauterine growth and development due to impaired placental function, depending on race and gender [1], [2]. Fetal growth restriction is a pregnancy complication, affecting 5-10% of all pregnancies, including 30% of stillbirths, premature birth and postpartum asphyxia [3], [4]. The majority of cases of fetal growth restriction are reported in Asia, accounting for approximately 75% of all affected infants, followed by Africa continent and Latin America [5], [6]. In Vietnam, the rate of fetal growth restriction is recorded in the range of 5 - 10% [7], [8].

In clinical practice, it is difficult to identify fetal growth restriction because there is no gold standard for diagnosis. Some definitions use a biometric cutoff of the 10th percentile to diagnose fetal growth restriction [9]. This would include all small for gestational age (SGA) fetuses that are small in weight but physically healthy [9], [10]. Furthermore, there are some cases with weight greater than the 10th percentile but with reduced growth and altered arterial Doppler, increasing the risk of adverse perinatal outcomes [5], [6], [9].

In 2016, the multicenter experts panel on fetal growth restriction conducted a study based on the Delphi method, reaching a consensus on the definition of fetal growth restriction [1], [10]. Consensus was established on the basis of more stringent changes in biometric factors (weight percentiles), arterial Doppler (umbilical artery, middle cerebral artery, uterine artery, and ductus venosus). This helps to better diagnose and predict pregnancy outcomes in at-risk fetuses, while also supporting future research projects and assisting in the comparison of different studies [10]. According to the Delphi consensus, fetal growth restriction is divided into early-onset and late-onset based on gestational age of 32 weeks. Of these, late-onset fetal growth restriction accounts for up to 70% of cases. Although the clinical manifestations are milder than early-onset fetal growth restriction, they are associated with adverse pregnancy outcomes and the child's future development [2], [9], [10]. Early diagnosis of late-onset fetal growth restriction allows for appropriate management and better decision-making on the timing of pregnancy termination, thereby reducing the risk of intrauterine death or adverse third-trimester perinatal outcomes [10], [11], [12].

Currently, in Vietnam, there are not many studies using Delphi consensus in diagnosing and evaluating pregnancy outcomes in pregnant women with late-onset fetal growth restriction. Therefore, this study aims to assess pregnancy outcomes of late-onset growth restriction based on Delphi consensus.

2. MATERIALS AND METHODS

This prospective study was conducted on 133 women with singleton pregnancies from 32 weeks, diagnosed with fetal growth restriction according to Delphi consensus at the Obstetrics and Gynecology Center - Hue Central Hospital during the research period from May 2022 to June 2023.

The inclusion criteria: pregnant women from 32 weeks: 1) diagnosed fetal growth restriction based on the Delphi consensus, 2) singleton pregnancy, 3) no chromosomal abnormalities, 4) or congenital malformations.

The exclusion criteria: Stillbirth at the time of sample selection; congenital abnormalities, severe genetic abnormalities after birth; lost to follow-up.

The criteria and classification of early-onset and late-onset fetal growth retardation [10]:

- Early-onset fetal growth restriction: GA < 32 weeks, no congenital malformations: AC/EFW < 3rd percentile or loss of umbilical artery end-diastolic flow (UA-AEDF), or: 1) AC/EFW < 10th percentile combined with 2) UtA-PI > 95th percentile and/or 3) UA-PI > 95th percentile.

- Late-onset fetal growth restriction: GA ≥ 32 weeks, no congenital malformations: AC/EFW < 3rd percentile; or at least two of the following three criteria: 1) AC/EFW < 10th percentile; 2) AC/EFW through 2 quartiles on the growth chart; 3) CPR < 5th percentile or UA-PI > 95th percentile.

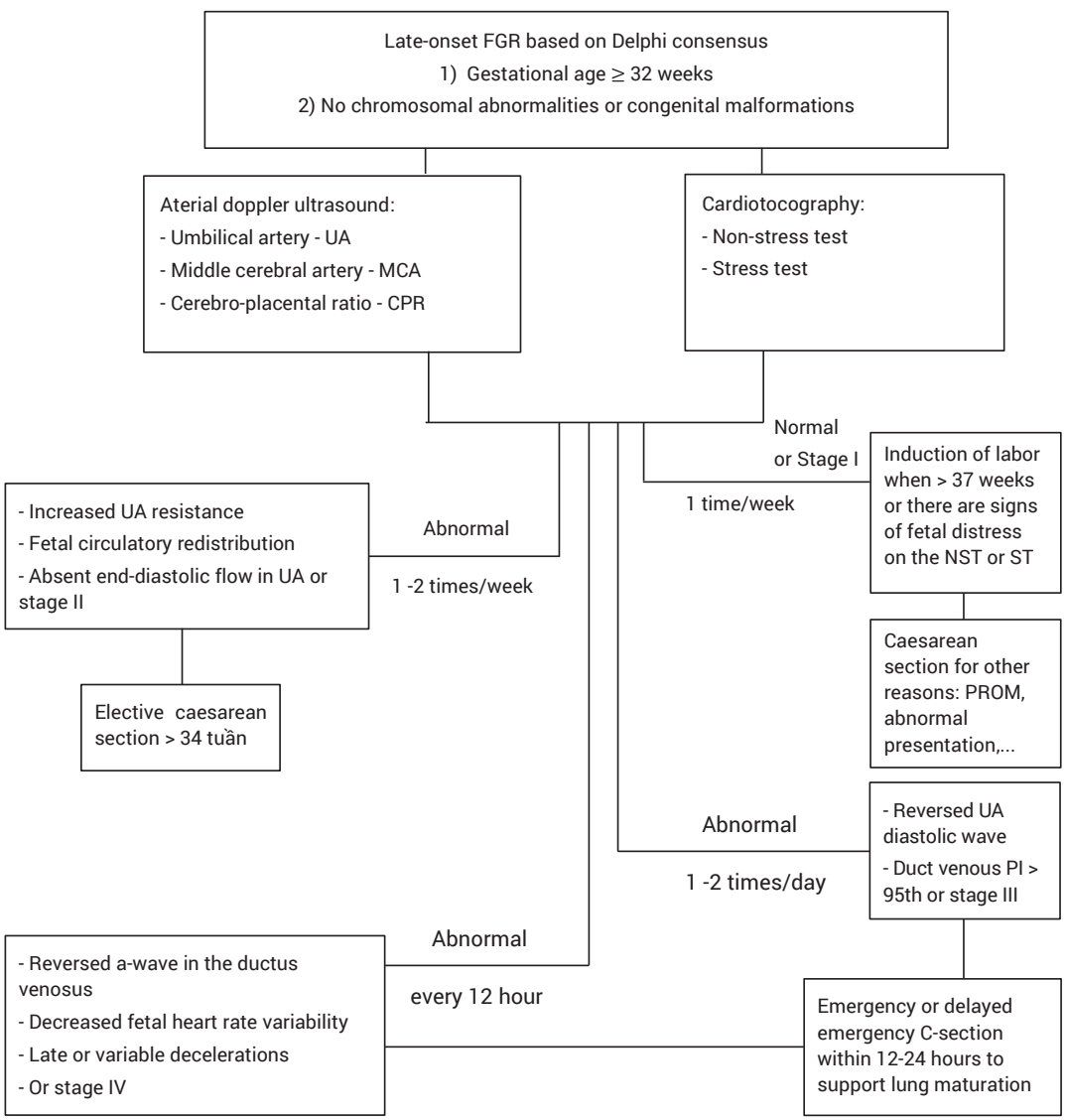

Figure 1. Flow chart for monitoring and managing late-onset FGR.

Study variables were collected as follows:

Step 1: Interview patients for baseline characteristics: Maternal age, geographical characteristics, ethnicity, occupation.

Step 2: Collect historical and medical history factors: PARA index, history of pregnancy with growth retardation, medical history during this pregnancy.

Step 3: Collect maternal characteristics: maternal height, BMI before pregnancy, active or passive smoking during pregnancy period, alcohol use during pregnancy, maternal weight at the time of admission (kg), maternal weight during pregnancy, fundal height (cm) and waist circumference (cm).

Step 4: Two-dimensional ultrasound, doppler ultrasound and fetal cardiotocography (CTG): Index values of two-dimensional ultrasound, doppler ultrasound and non-stress test.

Step 5: Record the management and pregnancy outcomes: week of pregnancy at the end of pregnancy, method of birth, status of the newborns after birth.

Data analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 22.0. Continuous variables were tested for normal distribution or not based on the Test for Normality (Kolmogorov-Smirnov). Categorical variables were compared with Chi-square with significance level α = 0.05. Errors and confounding factors were handled by 1) All patients received two-dimensional ultrasound and doppler ultrasound on the same ultrasound machine and were re-checked by the researcher; 2) The recorded values are the average value of three measurements on the same patient at the same time.

Research ethics

The study protocol has been approved by the Ethics Council in Biomedical Research, University of Medicine and Pharmacy, Hue University, approval number H2022/338. Patients were selected according to the indications, carefully explained and consented to participate in the study. All personal patient information was kept confidential. Diagnostic tests and treatments all brought benefits and did not harm the patient. Patients did not have to pay additional costs for the tests performed.

3. RESULTS

During the study period, we recorded 133 cases of fetal growth restriction according to the Delphi Consensus. Among them, there were 116 cases of late-onset fetal growth restriction, the rate of late-onset fetal growth restriction was 87.2%. The following results:

Table 1. Baseline characteristics of the study subjects

Characteristics	Late-onset FGR (n = 116)	Rate (%)
Maternal age (years) Mean (± SD)	27.4 ± 5.5	
Geography		
Urban	46	39.7
Rural	62	53.4
Mountain region	8	6.9
Unemployment	54	46.5
Kinh Ethnic	113	97.4
BMI before pregnancy		
Underweight	48	41.4
non-standardized weight gain	82	70
Weight gain during pregnancy (kg) Mean (± SD)	11.7 ± 4.4	
Height (mm) Mean (± SD)	154.8 ± 5.9	
Active and passive smoking	36	31.0
Using alcoholic beverages	3	2.6
FGR history	12	10.3
Hypertension, preeclampsia	28	24.1
Anemia	26	22.4
Primigravida	81	69.8
AC/EFW < 3rd	116	100.0

Unemployment (no stable job, housewife...); FGR: fetal growth restriction; Diagnosis with AC/EFW < 3rd (abdominal

circumference/estimated fetal weight less than 3rd percentile): according to one main criteria based on the Delphi Consensus.

Table 1 showed that the average age of women with late-onset FGR was 27.4 (± 5.5) years old, unemployed pregnant women accounted for 28.4%, the rate of hypertensive disorders in the study was 24.1%.

Table 2. Ultrasound and non-stress test characteristics

Characteristics	Late-onset FGR (n = 116)	Rate (%)
Abnormal amniotic fluid index	37	31.9
Abnormal placenta	2	1.7
Abnormal umbilical artery Doppler	24	20.7
PI-UA > 95th	30	25.9
PI-MCA < 5th	29	25.0
CPR < 5th	28	24.1
Non-reassuring non-stress test	48	41.4

Abnormal amniotic fluid includes oligohydramnios, polyhydramnios; Abnormal placenta includes abnormal location and placental morphology; UA: umbilical artery; PI-UA: umbilical artery pulsatility index; PI-MCA: middle cerebral artery pulsatility index; CPR: cerebro-placental ratio.

Table 2 showed that abnormal amniotic fluid index accounted for 31.9%, the rate of abnormal umbilical artery Doppler spectrum morphology was 20.7%.

Table 3. Pregnancy outcomes

Characteristics	Late-onset FGR (n=116)	Rate (%)
Caesarean section	79	**68.1**
FGR	34	**43.0**
End of pregnancy (week) Mean (± SD)	37.6 ± 1.9	
Adverse neonatal outcomes	47	40.5
Apgar score ≤ 7 at 1 min	46	39.7
Apgar score ≤ 7 at 5 min	13	11.2
Respiratory support	34	29.3
NICU admission	32	27.6
Preterm	37	31.9
Length of hospital stay > 7 days	23	19.8
Neonatal death, hemorrhage, convulsions	0	0.0
Neonatal gender		
Male	53	45.7
Female	63	54.3
Birthweight (gram) Mean (± SD)	2155.17 ± 321.77	
2000 - < 2500	80	65.5

NICU: neonatal intensive care unit; FGR: fetal growth restriction.

Table 3 showed that the rate of intervention by cesarean section was 68.1%, which the cause due to FGR was 43%. The average pregnancy termination week was 37.6 ± 1.9 (weeks). The rate of adverse neonatal outcomes was 40.5%. In particular, the proportion of newborns with Apgar score ≤ 7 at 1 minute was 39.7% and at 5 minutes was 11.2%; The proportion of newborns needing respiratory support was 29.3%; The rate of newborns with respiratory distress was 21.6%; The rate of infants admitted to NICU was 27.6%; The rate of preterm infants was 31.9%.

Table 4. Ultrasound and non-stress test values predicting birth method

Birth method	Vaginal delivery n = 37	Caesarean delivery n = 79	p-value
Abnormal umbilical artery Doppler, n (%)	2 (5.4)	22 (27.8)	< 0.05
PI-UA > 95th, n (%)	2 (5.4)	28 (35.4)	< 0.05
PI-MCA < 5th, n (%)	3 (8.1)	26 (32.9)	< 0.05
CPR < 5th, n (%)	1 (2.7)	27 (34.2)	< 0.05
Non-reassuring non-stress test, n (%)	3 (8.1)	45 (57.0)	< 0.05

UA: umbilical artery; PI-UA: umbilical artery pulsatility index; PI-MCA: middle cerebral artery pulsatility index; CPR: cerebro-placental ratio.

The rate of abnormal UA Doppler spectrum morphology was 20.7%, the predictive value for intervention by cesarean section was 27.8% (p < 0.05) (Table 4) and adverse neonatal outcomes were 38.3% (p < 0.05) (table 5). Abnormal umbilical artery pulsatility index (PI-UA > 95th) accounted for 25.9% and had a predictive value for intervention by cesarean section of 35.4% (p < 0.05) (Table 4) and adverse neonatal outcomes were 42.6% (p < 0.05) (table 5).

Table 5. Ultrasound and non-stress test values predicting neonatal outcomes

Neonatal outcomes	Normal n = 69	Adverse n = 47	p-value
Abnormal umbilical artery Doppler, n (%)	6 (8.7)	18 (38.3)	< 0.05
PI-UA > 95th, n (%)	10 (14.5)	20 (42.6)	< 0.05
PI-MCA < 5th, n (%)	9 (13.0)	20 (42.6)	< 0.05
CPR < 5th, n (%)	10 (14.5)	18 (38.3)	< 0.05
Non-reassuring non-stress test, n (%)	19 (27.5)	29 (61.7)	< 0.05

UA: umbilical artery; PI-UA: umbilical artery pulsatility index; PI-MCA: middle cerebral artery pulsatility index; CPR: cerebro-placental ratio.

Similar to the rate of abnormalities, the predictive value of intervention by cesarean section and adverse neonatal outcomes with abnormal middle cerebral artery pulsatility index (PI-MCA < 5th) were 25%, 32.9%, and 42.6%, respectively; with abnormal cerebro-placental ratio (CPR < 5th) were 24.1%, 34.2% and 38.3%, respectively; with non-reassuring non-stress test were 41.4%, 57% and 61.7%, respectively (p < 0.05) (table 4 and 5).

4. DISCUSSION

The rate of late-onset FGR in our study was 87.2%. This shows that the rate of late-onset FGR was quite common at the Obstetrics and Gynecology Center - Hue Central Hospital. However, this rate is similar to the result of Crovetto F. et al (2016) [13] studied on 9150 pregnancies, the rate of late-onset FGR among the total number of FGR was 87.2% (403/462). The result is similar to the research of some other authors with the finding that late-onset FGR accounts for about 70% of singleton pregnancies without birth defects

Regarding the clinical characteristics of late-onset FGR

The average age of pregnant women with late-onset FGR was 27.4 (± 5.5) years old, as shown in Table 1. The age group with the largest proportion was 20 - 29 years old (61.2%). This was also a popular reproductive age group in Vietnam. The majority of pregnant women were in rural areas (53.4%) and only 6.9% of those was in mountainous areas. Therefore, the majority of the patients were Kinh ethnic people, accounting for 97.4%. Unemployed pregnant women accounted for 28.4% and housewives accounted for 10.3%. In fact, low and unstable socio-economic condition is one of the factors contributing to FGR. According to research by Crovetto F. et al., 31.0% of women with late-onset FGR have low socioeconomic conditions compared to the group with normal development of 25.1% [13].

Regarding BMI and weight gain during pregnancy, up to 41.4% of pregnant women were underweight and up to 70% of pregnant women in the study group gained weight incorrectly. The average weight gain during pregnancy was 11.7 ± 4.4 (kg), lower than the recommended level as well as in the group of normal

pregnant women. The average height of FGR pregnant women in the study was 154.8 ± 5.9 (cm), of which the highest height was from 150 - 155 (cm). In the study of Feng Y. et al (2022) [14], the average height of pregnant women with late-onset FGR was 158.3 ± 4.9 (cm) compared to women with normal development of 160.3 ± 4.9 (cm). Low maternal weight and height are risk factors in FGR [14],[15]. In the study, the rate of FGR pregnant women smoking was 31%, most of which were passive smokers from relatives. According to research by Kovo M. et al (2012), pregnant women are considered to smoke cigarettes that affect fetal health when the number of cigarettes smoked daily is over ten cigarettes, the rate of pregnant women using cigarettes in this study was 15% [16]. The rate of pregnant women using alcoholic beverages during pregnancy in our study was very low at 2.6%.

Table 1 also showed that the rate of hypertensive disorders in the study was 24.1%. Preeclampsia is one of the most common diseases in pregnancy related to FGR. According to Chew L.C. et al (2023) [17], preeclampsia was a well-recognized cause of asymmetric FGR (EFW < 3rd percentile). The rate of anemic pregnant women in the study was 22.4%. 100% of pregnant women diagnosed with FGR have AC/EFW below the third percentile. 69.8% of pregnant women with FGR were pregnant for the first time. Previously, the research by Shah P.S. et al (2010) [18] showed that there was a significant decrease in the weight of newborns born to women giving birth for the first time compared to women giving birth for the second time (6 studies, 133533 participants, the difference was mean difference −282 g, 95% CI −483, −79 g, I2 = 100 %).

In addition, abnormal amniotic fluid index accounts for 31.9%, as shown in Table 2. This index is considered a factor predicting adverse perinatal outcomes, NICU admission and perinatal death according to authors Unterscheider J. et al (2013) [19].

Regarding pregnancy outcomes in cases of late-onset FGR

According to table 3, the average pregnancy termination week was 37.6 ± 1.9 (weeks). The rate of intervention by cesarean section was 68.1%, which the cause due to FGR was 43%, according to ISOUG practice guidelines on the management of late-onset fetal growth restriction [6]. Compared to other authors with the same pregnancy characteristics, the average gestational age of termination of pregnancy in the late-onset FGR by Yang Z. et al (2022) was 35.5 ± 1.5 (weeks) [20]; and by Feng Y. et al (2022) was similar to 35.9 ± 3.5 (weeks) [14]. According to research by Crovetto F. et al (2016), the cesarean section rate was 56.3% [13].

In our study, the criteria to evaluate neonatal outcomes included Apgar score at 1 minute and 5 minute, need for respiratory support, and preterm newborns requiring monitoring in the neonatal intensive care unit (NICU), prenatal/neonatal death, length of hospital stay more than 7 days. For cases with one of the following factors: Apgar score ≤ 7 at 1 and 5 minutes, need for respiratory support, preterm newborns, NICU admission, with a hospital stay of more than 7 days were all classified as adverse neonatal outcomes. In addition, we recorded no cases of stillbirth or infant death while being monitored at the hospital, as well as no cases of intraventricular hemorrhage and neonatal seizures.

The proportion of children with an Apgar score ≤ 7 at 5 minutes in the study by Crovetto F. et al (2016) [13] was 1.5%. In the study of Molina L.C.G et al (2020) [21], the Apgar score < 7 at 5 minutes was 9.1%; the rate of newborns admitted to NICU is 27.3%; no cases of respiratory failure, intraventricular hemorrhage, neonatal convulsions or neonatal death were recorded. Molina's research was similar to ours. According to research by Villalaín C. et al (2018) [22], the authors' characteristics of group G1 (EFW < 3rd percentile) were similar to our research group, showing Apgar score < 7 at 5 minutes was 2.7%; NICU admission with 2.7%, and no neonatal deaths. This author's adverse neonatal rate was much lower than our study because cases with abnormal arterial Doppler changes were not included.

Regarding birthweight, the average weight was 2155.2 ± 321.8 (gram). The majority of newborns had a weight in the range of 2000 - < 2500 grams, accounting for 65.5%, consistent with the average gestational age of 37.6 ± 1.9 (weeks). Compared to the study of author Yang Z. et al (2022) [20], the average birthweight was 2059.7 ± 232.4 (gram). Research by author Feng Y. et al (2022) [14], the average neonatal weight after birth was 2429.9 ± 509.6 (gr). It is clear that fetal and neonatal weight are important factors in determining cases of FGR.

The limitation of the study is the possibility of missing some cases of FGR with EFW > 3rd percentile and < 10th percentile with 1 of 2 contributing criteria. Future research direction is to select samples including cases with EFW < 10th percentile combined with growth chart monitoring and arterial doppler measurements to find cases of late-onset FGR.

5. CONCLUSION

Late-onset fetal growth restriction, as determined by the Delphi Consensus, is a condition which yielded a high hospitalization rate, demanding thorough consideration of risk factors, clinical and subclinical characteristics, and diagnostic criteria. By employing a multidimensional approach, healthcare providers can detect and intervene in cases of late-onset FGR, thereby diminishing the adverse neonatal outcomes associated with this condition, with a specific focus on reducing neonatal deaths.

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