ORIGINAL RESEARCH

The role of gestational age and fetal weight in perinatal outcomes among intrauterine growth restricted preterm fetuses

Rubena Moisiu[1], Enkeleda Prifti[1], Alketa Hoxha[1], Enver Roshi[2], Eriola Pupi[1]

[1]University Hospital of Obstetrics-Gynecology "Koço Gliozheni", Tirana, Albania;
[2]Faculty of Public Health, University of Medicine, Tirana, Albania.

Corresponding author: Dr. Rubena Moisiu;
Address: University Hospital of Obstetrics-Gynecology "Koço Gliozheni", Boulevard "Bajram Curri",
Tirana, Albania;
Telephone: +355692026821; E-mail: rmoisiu@hotmail.com

Abstract

Aim: Our aim was to assess the role of gestational age and weight at delivery of intrauterine growth restricted (IUGR) preterm fetuses with placental dysfunction in order to help clinicians and parents for a better planning of the time of delivery.

Methods: A prospective observational study was conducted during 2010-2014 at the University Hospital of Obstetrics-Gynecology "Koço Gliozheni" in Tirana including pregnant women with a unique fetus, between 26.0wGA-36.6wGA, with intact membranes, with a fetal weight lower than the tenth percentile, and with at least one abnormal Arterial Doppler up to three days before delivery. After delivery, we collected data about adverse perinatal outcome as a composite outcome of perinatal mortality and severe morbidity: HIV (intraventricular hemorrhage), LP (periventricular leucomalacia), EN (necrotizing enterocolitis), BD (bronchopulmonary dysplasia), and sepsis.

Results: Our study included 91 cases. For all the subjects: Mean Gestational Age during diagnosis was 33±2.1wGA, Estimated Ultrasound Mean Fetal Weight was 1471±368g, Mean Gestational Age during delivery was 33.0±2.1wGA, and Mean Neonatal Weight was 1477±360g. Perinatal deaths were around 11%. Deaths and severe morbidity were significantly related to gestational age (LR: 1.18-2.82, P=0.001) and Fetal Weight (LR: 181-487, P=0.001). According to Kaplan-Meier analysis, for a gestational age below 31wGA, findings conferred a 31-fold increased risk of adverse perinatal outcome (HR=31.0, 95%CI=30.1-31.8, P<0.0001).

Conclusion: Perinatal outcome in preterm IUGR fetuses was significantly related to gestational age and weight at delivery in this study conducted in Tirana, the capital city of Albania.

Keywords: Arterial Doppler**,** IUGR, preterm.

Introduction

Intrauterine growth restriction (IUGR) is a major factor of perinatal morbidity and mortality. IUGR fetuses are identified with high resolution ultrasound machines, performing fetal weight and Doppler, in order to demonstrate placental dysfunction (1,2). The most important Doppler parameters, reaching general consensus for identification and managing hypotrophic fetuses, are Doppler of Umbilical and Cerebral Artery (3). These parameters will reflect further hypoxemia or acidemia of IUGR fetuses, signaling an intrauterine hostile environment, which will lead, in absence of intervention, in intrauterine fetal deaths. If IUGR fetuses are preterm, timing delivery is the most challenging process, from one side to avoid the complications from iatrogenic prematurity, and the other side avoiding complications of hypoxia and acidosis from placental dysfunction (4). Also, such deliveries must be organized according to the neonatal level of care. Gestational age and weight at delivery remain the most important prognostic factors in managing preterm IUGR fetuses (5-8). For the same gestational age, perinatal morbidity and mortality are in indirect relation with weight at delivery of the baby (9-12). According to GRIT study, fetuses delivered earlier, have a higher rate of complications of iatrogenic prematurity, as respiratory distress syndrome and neonatal mortality (5,13-15). Each day gained in utero increases survival 1-2% for fetuses more than 28wGA (Week Gestational Age), while after 34wGA, the impact of fetal weight decreases (6,16,17).

The aim of this study was to investigate the role of gestational age and weight at delivery in perinatal outcome among preterm IUGR fetuses in Albania.

Methods

This study recruited 91 singleton pregnancies, during August 2010 until December 2013, managed in University Hospital of Obstetrics-Gynecology "Koço Gliozheni", a tertiary level of care hospital. All eligible pregnancies were IUGR fetuses, defined as EFW less than 10th centile (18), between 26.0wGA and 37.0wGA. Dating of pregnancy was based in LMP, or ultrasound of CRL (19), or second trimester dating of BPD (20), HC (20), AC (21), FL (20).

Patients and their fetuses underwent a detailed anatomy on high resolution ultrasound. We included fetuses with criteria of normal anatomy, EFW lower than the 10th percentile, with at least one abnormal Arterial Doppler (Umbilical and/or Cerebral) up to three days before delivery: Pulsatility Index of UA >95th percentile (22), Absence of Diastolic Flow in UA (AEDF (intermittent), Reverse Flow in Umbilical Artery (REDF), MCAPI <5th percentile (23), ICP lower than the 5th percentile (24); delivery between 26wGA and 36.6wGA, normal neonatal evaluation, without clinical signs of chromosomal anomalies or genetic syndromes, intact chorionic membranes, without evidence of chorioamnionitis or signs of perinatal infection.

Ultrasound examinations were performed with: Medison SA 8000, Aloka alfa 10, with convex probe with high resolution, both with duplex Doppler and color flow maping, low filter (24Hz). All data and images were simultaneously transferred in software system ASTRAIA (13904-L001). Morphometric data were calculated upon reference curves according to gestational age in this system (20-24). Doppler examination of UA and MCA were according to guidelines (9,25). For calculation of the Pulsatility Index of Arteries, we used gestational age-specific reference curves for each artery (23,24). Intrapartum monitoring included also Non Stress test and Modified Biophysical Profile. All data had to be documented up to three days before delivery. All patients between 26.0wGA and 33.6wGA were administrated corticosteroids, if delivery was planned in one week.

From 2009, clinical protocol of managing these cases is based on mother's clinical situation and surveillance of fetal wellbeing through multivessel Doppler, information for fetal movements from the mother, NST and Modified Biophysical Profile. Each pregnancy was managed with intention to intervene

for non reassuring mother or fetal status, not influenced by the study.

For antenatal deaths, data were registered from the moment of the diagnosis until the moment of intrauterine fetal death. After delivery, among live fetuses, neonatal outcomes included the following parameters: GA, weight, centile according to WHO (13,14), gender, venous pH, BE, Apgar score in 1 and 5 minutes, admission to NICU. Adverse Perinatal Outcome was defined as a composite of intraventricular hemorrhagy, periventricular leukomalacia, hypoxic ischemic enchephalopaty, nechrotizing enterocolitis, bronchopulmonary dysplasia, sepsis and death (16,26). In cases of postanatal deaths, death was defined as neonatal death up to 28 day after delivery. Perinatal Death was defined as antenatal death (up to three days before delivery) and postnatal death (up to 28 days after delivery). Favourable Perinatal Outcome was defined as absence of Adverse Perinatal Outcome in neonates.

Results

All the statistical analyses including 91 pregnant women were done in SPSS, version 17.

During the surveillance period, four cases were excluded in utero, because of very early gestational age and pathological Arterial Doppler.

In the overall sample of the subjects: Mean Gestational Age during diagnosis was 32.9w GA±2.1; the Estimated Ultrasound Mean Fetal Weight was 1471±368g; the Mean Gestational Age during delivery was: 33.0±2.1wGA; and the Mean Neonatal Weight was: 1477±360g (Table 1).

Table 1. Clinical parameters in the overall sample and in subjects with adverse perinatal outcomes

Variable	All subjects (n=91)	Subjects with adverse perinatal outcome[*] (n=31)	P
Gestational age at entrance (weeks)	32.9±2.1	31.9±2.15	0.01
Estimated Fetal Weight (g)	1471±368	1280±394	0.01
Gestational age at delivery (weeks)	33.0±2.1	31.8±2.0	0.01
Fetal weight at delivery (g)	1477±360	1257±370	0.01

[*]Adverse perinatal outcome includes: Perinatal deaths and severe morbidity.

On the other hand, Mean Gestational Age with Perinatal Favorable Outcome was 33.7±1.8 wGA; Mean Neonatal Weight with Favorable Outcome was 1591±298g; Mean Gestational Age with Adverse Perinatal Outcome was 31.8±2.0 wGA; and Mean Neonatal Weight with Adverse Perinatal Outcome was 1257±370g (Table 2).

Table 2. Gestational age (weeks) and fetal weight (g) in relation to perinatal outcomes

Variable	Adverse perinatal outcome[*] (N=31)	Favourable perinatal outcome (N=60)	P
Weight at delivery (g)	1257±370	1591±298	0.001
Gestational age at delivery (weeks)	31.8±2.0	33.7±1.8	0.001

[*]Adverse perinatal outcomes include: perinatal deaths and severe morbidity.

Deaths and severe morbidity was significantly related to Gestational Age (LR 1.18 up to 2.82, P=0.001) and Fetal Weight (LR: 181-486.6, P=0.001).

According to Kaplan-Meier Analysis (not shown), for gestational age below 31wGA, findings conferred a 31-fold increased risk of adverse perinatal outcome (HR=31.0, 95%CI=30.1-31.8, P<0.0001).

Discussion

Our study recruited 91 singleton fetuses, between 28wGA up to 37 wGA, with diagnosis of IUGR and at least one pathological Arterial Umbilical or Cerebral Doppler. We recruited a representative sample including both aspects: early gestational age and placental dysfunction documented with pathological Arterial Doppler.

Our findings should be compared with data from other studies conducted in Europe and USA. In GRIT study (Growth Restriction Intervention Trial) conducted during 1996-2002 there were included 548 women with IUGR fetuses between 24wGA-36wGA (5), where was compared the perinatal outcome between early delivery (after maturation with corticosteroids up to 1 day), vs. delayed delivery up to five days after diagnosis. According to this report, the mean gestational age was 32 weeks, and mean neonatal weight in delayed delivery was 1400g, instead of 1200g in early delivery. In our study, mean gestational age was 33 weeks, and mean neonatal weight was 1480g. Overall neonatal mortality in GRIT study was about 8% in early delivery vs. 4% in delayed delivery, compared with our study at about 6%. Antenatal deaths in GRIT study were 0.7% in early delivery group vs. 3% in delayed delivery, compared with our study at 6%. Results of our study are relatively similar with delayed delivery group in GRIT study for entrance criteria and results of perinatal mortality. But, our babies were 1 wGA older and weighted 80g more at delivery.

In the study of Baschat et al., a multicentric study, authors included 604 IUGR fetuses less than 33wGA, with mean GA 29weeks (6). In this study, the authors report the importance of gestational age and weight at delivery like primary criteria in perinatal outcome. The authors reported an overall mortality 21.5%, while after 30wGA they reported a mortality of about 17%. In our study, we report a mortality of about 43% for the group of 28-29wGA, and a mortality of about 36% for the group of 30-31wGA. In the study of Baschat et al., the lower

cut-off of gestational age in relation to favourable perinatal outcome was 27wGA, while after 29wGA perinatal mortality was significantly better. In our study, we could demonstrate a sharp decline of adverse perinatal outcomes after 31-32wGA according to Kaplan Meier analysis.

TRUFFLE study, which represents the most updated results of tertiary level of care of NICU, reports data collected from 2005-2010 (8). This study included 503 women with gestational age up to 32 weeks of pregnancy. They report severe morbidity in 2/3 of the cases, with an overall mortality of 8%. Even in this study, gestational age and weight at delivery were the most important factors which determine perinatal outcome. This study provides data for cases with adverse perinatal outcome vs. favourable perinatal outcome with a mean weight of 867g vs. 1079g, and a mean gestational age of 29.4wGA vs. 31.2wGA. Our study reports data for adverse perinatal outcome vs. favourable perinatal outcome with a mean weight at delivery of 1257g vs. 1591g, and a mean gestational age of 31.8wGA vs.33.7wGA. TRUFFLE study reports more favorable findings than Baschat et al. study, such as the overall mortality less than 3% below 30wGA compared to 17% with Baschat study (6,8). But, besides these specific results, both studies agree with regard to adverse perinatal outcomes before 26-27wGA and concerning significant favorable outcomes after 30wGA.

In any case, our study and other studies conducted elsewhere have similar findings related to the importance of gestational age and weight at delivery as major determinants of perinatal outcomes. In our institution in Tirana, based on the current data, the gestational age for which we offer favorable perinatal outcome is 31-32wGA or more, and weight 1200g or more. Below 31wGA, this outcome is more obscure. Gestational age impact is a well-known fact. In NICU, small babies contribute in disproportionate way with adverse perinatal outcome (6,15). When we evaluate IUGR fetus with placental dysfunction, with Doppler, at preterm babies, gestational age impact is more important than cardio-vascular parameters

(6,8,23), which is confirmed also in our study. Furthermore, GRIT study suggests that fear of fetal deterioration is a bad guide for delivery before 33wGA (6). This makes it important to extremely avoid the effects of iatrogenic prematurity. Also, delayed delivery increased the risk of intrauterine death. In the GRIT study, babies aged two years who were enrolled at an immediate delivery instead of a delayed delivery, suffered 10% cerebral palsy vs. 0% in the delayed delivery. Hence, even in our study, especially before 34wGA, like in other studies, major determinants of perinatal outcomes are gestational age and weight at delivery. Classifying gestational ages in groups will help parents and doctors in Albania to manage more effectively these cases, before taking the decision and planning the time of delivery in IUGR preterm fetuses.

Conclusion

In IUGR preterm fetuses, gestational age and weight at delivery are major factors in perinatal outcomes. Surveillance of these pregnancies must integrate examinations, time of delivery according to gestational age and the level of NICU.

At our institution in Tirana, while planning the time of delivery for IUGR preterm fetuses, we consult couples for better chances of favorable perinatal outcomes, during 31 or more weeks of gestational age.

Conflicts of interest: None declared.

References

1. ACOG Practice Bulletin. Intrauterine Growth Restriction. Number 12,Washington, DC: ACOG; 2000.

2. Manning FA. Intrauterine growth retardation. In: Fetal Medicine. Principal and Practice. Norwalk, CT, Appleton & Lange; 1995:317.

3. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis and management. Am J Obstet Gynecol 2011;204:288-300.

4. Larkin JC, Hill LM, Speer PD, Simhan HN. Risk of morbid perinatal outcomes in small-for-gestational-age pregnancies: customized compared with conventional standards of fetal growth. Obstet Gynecol 2012;119:21-7.

5. GRIT study group. A randomized trial of timed delivery for the compromised preterm fetuses, short term outcomes and Bayesian interpretation. BJOG 2003;110:27-32.

6. Baschat AA, Cosmi E, Bilardo C, Wolf H, Berg C, Rigano S, et al. Predictors of Neonatal Outcome in Early Onset Placental Dysfunction. Obstet Gynecol 2007;109:253-62.

7. Bilardo CM, Wolf H, Stifter RH, Ville Y, Baez E, Visser GH, at al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol 2004;23:119-25.

8. Lees C, Marlow N, Arabin B, Bilardo C, Brezinka C, Derks JB, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction; cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42:400-8.

9. Berkley E. SMFM Clinical Guideline. Society for Maternal–Fetal Medicine Publication Committee. AJOG; 2012.

10. Leitner Y, Fattal-Valevski A, Geva R, Eshel R, Toledano-Alhadef H, Rotstein M, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: A longitudinal, 10-year prospective study. J Child Neurol 2007;22:580-7.

11. Tolsa CB, Zimine S, Warfield SK, Freschi M, Rossignol AS, Lazeyras F, et al. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res 2004;56:132-8.

12. Barker DJ, Osmond C. Infant mortality, child nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;327:1077-81.

13. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.

14. de Onis M, Garza C, Onyango AW, Rolland-Cachera MF. WHO growth standards for infants and young children. Arch Pediatr 2009;16:47-53.

15. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very low birth-weight neonates with intrauterine growth restriction. The Vermont Oxford network. Am J Obstet Gynecol 2000;182:198-206.

16. Untersheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Predictable progressive Doppler deterioration in IUGR; does it really exist? Am J Obstet Gynecol 2013;209:539-e1.

17. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. The Vermont Oxford network. Morbidity and Mortality among very low birthweight neonates with intrauterine growth restriction. Am J Obstet Gynecol 2000;182:198-206.

18. Morris RK, Say R, Robson SC, Kleijnen J, Khan KS. Systematic review and meta-analysis of middle cerebral artery Doppler to predict perinatal wellbeing. Eur J Obstet Gynecol Reprod Biol 2012;165:141-55.

19. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975;82:702-10.

20. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol 1994;4:34-48.

21. Créquat J, Duyme M, Brodaty G. Biometry 2000. Fetal growth charts by the French College of fetal ultrasonography and the Inserm U 155. Gynecol Obstet Fertil 2000;28:435-45.

22. Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. Early Hum Dev 1987;15:45-52.

23. Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenat Diagn 2007;27:1251-7.

24. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol 2003;21:124-7.

25. Veille JC, Hanson R, Tatum K. Longitudinal quantitation of middle cerebral artery blood flow in normal human fetuses. Am J Obstet Gynecol 1993;169:1393-8.

26. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004;191:481-7.