J Biochem Tech (2018) Special Issue (2): 181-185
ISSN: 0974-2328

The Comparison of Placental Pathology between Small for Gestational Age (SGA) and Appropriate for Gestational Age (AGA Infants

Mojgan Barati, Mohammad Ali Afandy, Maryam Khanahmadloo*, Sara Masihi, Razieh Mohammad Jafari, Nastaran Ranjbari, Parvin Kheradmand, Nava Shirzadi

Received: 14 December 2017 / Received in revised form: 01 Jun 2018, Accepted: 08 June 2018, Published online: 05 September 2018

Abstract

Objective: Environmental damage to uterus or placenta can cause the fetus to deviate from its genetic program, causing complications such as intrauterine growth retardation (IUGR). SGA infants, defined as a weight below the 10th percentile for the gestational age. Risk of death in SGA infants is greater than AGA infants. The present study aimed to evaluate placental morphology in full-term SGA and AGA neonates. Methodology: This analytic case-control study was performed from 2016 to 2017 years, between Obstetrics and Gynecology and pathology departments of Ahvaz Imam Khomeini Hospital. Thirty placentas of SGA infants and 30 placenta of AGA infants were examined for pathologies. Results: In this study, 60 women and their neonates were included. Membranes insertion frequency in both groups was reported marginally. There was significant difference in placental weight ($p=0.001$) and FPR ($p<0.001$) in both groups. In addition, in Microscopic Examination of the placenta, villous infarction, decidual necrosis, villitis, chorioangiosis and perivillous fibrin deposition variables were found to be higher in SGA group than AGA group. Conclusion: The characteristics of placental insufficiency such as infarct, decidual necrosis, lower placental size, FPR, and perivillous fibrin deposition are more common in SGA term neonates than in AGA term neonates.

Keywords: Small for Gestational Age, Placental Pathology, Fetal Growth Restriction.

Introduction

Fetus intrauterine condition is important as a vital stage in growth and development. The placenta is functional center of maternal-fetal system which is responsible for respiration, secretion, endocrine and immunological function of fetus. For this reason, environmental damage to uterus or placenta can cause fetus to deviate from its genetic program, causing complications such as intrauterine (Oliveira

Mojgan Barati, Sara Masihi, Razieh Mohammad Jafari

Associate Professor, Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Mohammad Ali Afandy
Pathologist, Pathology Department, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Maryam Khanahmadloo*
Obstetrics and Gynecology resident, Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Nastaran Ranjbari
Associated Professor of Pathology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Parvin Kheradmand
Assistant Professor of Pathology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Nava Shirzadi
Fertility, Infertility and Perinatology Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

***Email:** maryam.khanahmadloo22@gmail.com

and et al., 2002) growth retardation (IUGR) (Oliveira and et al., 2002). Neonates can be divided into three groups based on birth weight: Infants with normal birthweight or appropriate for gestational age (AGA), infants with low birth weight or small for gestational age (SGA), and infants with high birthweight or large for gestational age (LGA). SGA infants, defined as a weight below the 10th percentile for the gestational age, and LGA infants, defined as birth weights greater than the 90th percentile, and the neonates weighting between the 10th and 90th percentile are AGA (Cunningham, 2014).

Risk of death in SGA infants is greater than AGA infants, but it should be kept in mind that SGA is not always a pathology, as 25% to 60% of SGAs are naturally small, and there is no evidence of metabolic abnormalities with growth retardation, but they will weight less than AGA infants in 2 years old (Cunningham, 2014; Barati and et al., 2016). SGA causes include maternal factors such as hypertension, chronic renal disease, advanced diabetes mellitus, cardiovascular or respiratory diseases, anemia, malnutrition, infection, alcohol consumption, smoking and narcotics, factors that involve placenta and uterus, such as decreased blood flow of uterus and placental, placental abruption, placental previa, infection of embryo surrounding tissues and factors related to the developing embryo such as multiple pregnancy, infection, congenital malformation and chromosomal anomalies (James-Todd and et al., 2014).

Several studies showed an association between SGA infant and various placental pathologies. In many studies, relationship between low placental weight and SGA infants has been revealed (Bjøro, 1981). Other studies have reported more chorioamnionitis in SGA infants (Williams and et al., 2000), and the association between SGA and socioeconomic factors, prolonged rupture of amniotic sac and infections (Bjøro, 1981; Bibbo and et al., 2012). The relationship between placental infarction and IUGR is fully described in literature (James-Todd and et al., 2014). In addition, some studies have shown relationship between placental infarction and perivillous fibrin deposition (Bjøro, 1981). Pathoanatomical findings suggest that chronic villitis, due to inflammatory processes at villus level, leads to a reduction in maternal-fetal exchange, the outcome of these processes leading to intrauterine malnutrition of the embryo, which, if continued, could result in IUGR (Knox & Fox, 1984; Labarrere & Althabe, 1987;Nordenvall & Sandstedt, 1990). Ischemic lesions are present in 43% of villous inflammation cases (Altshuler and et al., 1975).

The present study aimed to evaluate the placental morphology in full-term SGA and AGA neonates with using of macroscopic and microscopic finding of the placenta, membranes, and cord.

Methodology

This analytic case-control study was performed from 2016 to 2017 years, between Obstetrics and Gynecology and pathology departments of Ahvaz Imam Khomeini Hospital. Thirty SGA infants' placentas and 30 AGA infants' placentas were examined for pathologies. Gestational age determination was based on first trimester CRL (CRL> 10mm) (Lubchenco and et al., 1966; Lubchenco and et al., 1963). Exclusion criteria were losing of first-trimester CRL and precise gestational age, multiple congenital anomalies, and congenital infection diagnosed in prenatal period.

After enrolment, medical records of participants who gave informed consent including age, education, socioeconomic status, BMI, history of pregnancy, history of maternal diseases during pregnancy, chronic diseases before and during pregnancy, smoking, or alcohol during pregnancy, prenatal care, prenatal visits, and history of low birth weight infant were recorded. Neonates were also evaluated for gestational age and birth weight. The obtained placentas were macroscopic examined after removal of extra vessels and isolation of membrane. During the macroscopic examination cord length, cord insertion, cord vessels number, placental weight, Placental disk diameter and thickness and fetal placental index (Salafia and et al., 1976) were calculated. The histological microscopic examination were taken by an expert pathologist who didn't know the classification of the placentas. The current study approved by the Ethic committee of Ahvaz Jundishapur University of Medical Sciences with grant number of *IR.AJUMS.REC.1396.145* and written informed consent agreements obtained from all participants.

In this study, according to Beaudet et al. (Beaudet and et al., 2007), pathological characteristics were classified into seven types: 1) ischemic changes such as hemorrhagic endovasculitis (HEV), perivillous fibrin deposition, villous ischemia and hemorrhage, and chorangiosis; 2) villous infarction and decidual necrosis; 3) chronic villitis; 4) abnormal villous maturity (delayed, advanced, variable, and dysmaturity); 5) placental abruption; 6) meconium staining; and 7) others, such as villous edema, intervillous thrombosis, amnion nodosum, and congested villi.

Statistical Methods

Data analysis was performed using SPSS ver.23 (SPSS Inc. Chicago, USA). T-test, Mann-Whitney test, and chi-square test were used for analysis. For all cases, the significance level of p-values <0.05 was considered.

Results

In this study 60 women and their neonates were included. In the macroscopic examination, the highest frequency of cord insertion was central (insertion of the center on the placental surface) in the SGA and AGA groups with 13 (43.3%) and 14 (46.7%), respectively, and eccentric (insertion near the center on the placental surface) was next with 12 (40%) for both groups, and the lowest was velamentous in SGA and AGA groups with 1 (3.3%) and zero respectively, there was no significant difference between the two groups (0.005 <p). Membranes insertion frequency in both groups was reported marginally. There were significant difference in placental weight (p = 0.001) and the FPR (p <0.001) in SGA and AGA groups. (Table-1).

Table-1: Results of Gross Neonatal Pairs Survey in SGA and AGA Groups

Variable	SGA	AGA	Total	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Cord length	16.9 ± 8.4	18.9 ± 8.8	17.9 ± 8.6	0.36
No. of vessels	2.97 ± 0.2	3.0 ± 0.0	2.9 ± 0.2	0.32
The trimmed placental weight	443.6 ± 108.6	523.7 ± 71.6	483.7 ± 99.7	0.001
Placental disk diameter	17.8 ± 3.3	18.1 ± 2.7	17.9 ± 3.0	0.73
Placental disk thickness	2.7 ± 2.4	2.7 ± 0.5	2.7 ± 1.7	1
fetal placental weight ratio	5.3 ± 1.1	6.4 ± 0.6	5.9 ± 1.0	<0.001

In addition, in Microscopic Examination of placenta, Villas infarction, Decidual necrosis, Villitis, Chorioangiosis and Perivillous fibrin deposition variables were found to be higher in SGA group than AGA group. (Table-2)

Table-2: Microscopic examination of neonatal pairs in the SGA and AGA groups

Variable	SGA	AGA	total	p-value
	N (%)	N (%)	N (%)	
Villous infarction	(63.3) 19	(6.7) 2	(35.0) 21	<0.001
Decidual necrosis	(33.3) 10	(10.0) 3	(21.7) 13	0.028
Villitis	(43.3) 13	(6.7) 2	(25.0) 15	0.001
chorioangiosis	(6.7) 2	(3.3) 1	(5.0) 3	1
Perivillous fibrin deposition	(33.3) 10	(6.7) 2	(20.0) 12	0.01

In examining the history of maternal diseases, hypertension was 10% (0.10%) in SGA group, while in mothers of AGA group was zero percent. Diabetic mothers in both groups were equal (6.7%). History of SGA infant was only reported in 6 (20%) cases of SGA group. Minor thalassemia in the AGA group was 3 (10%), while in SGA group was only 1 (3. History of SGA infant difference was significant (p=0.024), But in the rest of maternal history, there were no significant difference between two groups (p> 0.05) (Table-3).

Table-3: Maternal pregnancy records in the SGA and AGA groups

Variable	SGA	AGA	p-value
	N (%)	N (%)	
IVF history	2 (6.7)	0 (0.0)	0.49
Preeclampsia	4 (13.3)	1 (3.3)	0.35
> 60 months from previous pregnancy	4 (13.3)	3 (10)	1
Previous SGA infant	6 (20)	0 (0.0)	0.024
low pre-pregnancy fruit consumption	1 (3.3)	0 (0.0)	1
Extreme daily exercise	1 (3.3)	0 (0.0)	1
Severe bleeding	0 (0.0)	1 (3.3)	0.67

The mean age of pregnancy was (37.3 ± 1.5 weeks) 260.9 ± 10.2 days for SGA group and (38.4 ± 0.7 weeks) 269.0 ± 4.8 days for AGA groups and both groups were matched. Also, BMI was (27.8 ± 5.2) for the SGA group and (25.1 ± 4.0) for the AGA group, the difference was statistically significant (p=0.026).The type of delivery in both groups was cesarean section. There was a significant difference in birth weight, abdominal circumference, and fetus weight in both SGA and AGA groups (p<0.001).

Discussion

This study showed that the characteristics of placental insufficiency such as infarct, decidual necrosis, lower placental size, fetal placental weight ratio, and perivillous fibrin deposition are more common in SGA term neonates than in AGA term neonates. In this survey, the pathologic examination of placenta in the small for gestational age (SGA) and appropriate for gestational age (AGA) infants

has been studied. Inappropriate placentation may leads to development of growth restriction and its consequence of placental insufficient and chronic ischemia which shown by placental histopathological lesions (Miller and et al., 2008; Baschat, 2010). The results of this study showed that there was significant difference between histopathologic findings (Villous infarction, decidual necrosis, villitis and Perivillous fibrin deposition) between SGA and AGA infants.

In macroscopic pathology examination of the placenta in the present study, there were significant differences in placental weight and FPR between SGA and AGA groups, which was consistent with the study of Biswas and Gosh (Biswas & Ghosh, 2008) studying the Gross morphological changes of placentas associated with intrauterine growth restriction of fetuses, 28 IUGR neonates and 22 normal neonates as control were enrolled In this case-control study and Gross morphology of placentas examined, which showed a significant decrease in weight, volume, and diameter in the placentas of IUGR neonates.

The largest study, which has only been included full-term infants, relates to Salafia et al. (Salafia and et al., 1992), which evaluates 128 placentas of IUGR term infants and their findings suggest that placental weight was lower, and chronic infarctions and villitis, vascular thrombosis, as well as Hemorrhagic endovasculitis were higher than AGA infants (179 cases), which was consistent with findings of this study. Parra-Saavedra et al. (Parra-Saavedra and et al., 2013) investigated placental findings in late-onset SGA births, their findings showed that late-onset SGA neonates with placental under perfusion lesions, including maternal and fetal malperfusion lesions, were at a greater risk of abnormal neurodevelopment at 2 years as compare to SGA neonates with placentas without such lesions. In our study, under perfusion lesions such as villous infarction, decidual necrosis, villitis and Perivillous fibrin deposition were significantly higher in SGA group.

Known risk factors for SGA include hypertension, vascular disease, age greater than 35 years, nulliparity, gestational diabetes, pre-eclampsia, smoking, and drug and alcohol consumption (Barati and et al., 2014). Similarly, the age of mothers over 30 years, chronic hypertension, diabetes mellitus, history of previous SGA, alcohol, and smoking, and pre-eclampsia were more common in mothers of SGA neonates, but other than history of previous SGA infant, the other risk factors were not significantly different between the SGA and AGA groups. In agreement with previous studies, severe SGA infants had worse adverse composite outcome with increased rate of phototherapy treatments and neonatal hypoglycemia episodes. Magnusson et al. (Magnusson and et al., 2004) suggested that the hypoglycemia is probably a result of an adaptation to a restricted placental size and transport capacity.

Fetal-placental factors leading to SGA include abnormal placentation and immune responses such as villitis and thrombotic diseases (Thorne and et al., 2014). Recent studies suggested that placental insufficiency due to superficial implantation. Remodeling of the spiral arterioles after the blastocyst implantation plays important role in successful placentation. The arteriolar transformation depth and the placental bed size are two main indicators of maternal blood sufficient flow to the placental, which needs approximately 100 arterioles in the myometrial and decidual segments. Defective deep placentation is not only associated with IUGR but also pre-eclampsia, placental abruption, spontaneous abortion and preterm labor, a spectrum of disorders characterized by placental insufficiency (Brosens and et al., 2014). The rate of placenta ischemia and villitis in our results were 63.3% and 43.3% respectively, which is in agreement with Thorne et al. (Thorne and et al., 2014) that reported an increase in ischemia and villitis (37.4% and 17.4%, respectively) in SGA infants.

Conclusion

This study showed that the characteristics of placental insufficiency such as infarct, decidual necrosis, lower placental size, fetal placental weight ratio, and perivillous fibrin deposition are more common in SGA term neonates than in AGA term neonates. Other features of placental perfusion deficiency, such as blood vessels count, disk diameter, disk thickness, as well as chorioangiosis, were not statistically significant between SGA and AGA groups, which is due to our inclusion criteria for term neonates, which supports the higher placental insufficiency prevalence in preterm infants.

Acknowledgments

The authors thank the patients and their families for their support, cooperation and patience. We would also like to thank the staff of the departments associated with care and management of the patients. This study was financially supported by Ahvaz University of Medical Sciences.

Conflict of Interest

The authors declare no conflict of interests.

References

Altshuler, G., Russell, P., & Ermocilla, R. (1975). The placental pathology of small-for-gestational age infants. *American Journal of Obstetrics & Gynecology*, *121*(3), 351-359.

Barati, M., Moramezi, F., Moramezi, H., Shirzadi, N., & Shirzadi, P. (2016). Evaluating the Prevalence of Small for Gestational Age and Its Associated Risk Factors. *Jentashapir Journal of Health Research*, *7*(3).

Barati, M., Shahbazian, N., Ahmadi, L., & Masihi, S. (2014). Diagnostic evaluation of uterine artery Doppler sonography for the prediction of adverse pregnancy outcomes. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*, *19*(6), 515.

Baschat, A. A. (2010). Fetal growth restriction–from observation to intervention. *Journal of perinatal medicine*, *38*(3), 239-246.

Beaudet, L., Karuri, S., Lau, J., Magee, F., Lee, S. K., & von Dadelszen, P. (2007). Placental pathology and clinical outcomes in a cohort of infants admitted to a neonatal intensive care unit. *Journal of Obstetrics and Gynaecology Canada*, *29*(4), 315-323.

Bibbo, M., Bron, C., Höpker, W. W., Kraehenbuhl, J. P., Ohlendorf, B., Olding, L., ... & Sordat, B. (2012). *Perinatal Pathology* (Vol. 66). Springer Science & Business Media.

Biswas, S., & Ghosh, S. K. (2008). Gross morphological changes of placentas associated with intrauterine growth restriction of fetuses: a case control study. *Early human development*, *84*(6), 357-362.

Bjøro, J. K. (1981). Gross pathology of the placenta in intrauterine growth retardation. In *Annales chirurgiae et gynaecologiae* (Vol. 70, No. 6, pp. 316-322).

Brosens, I., Pijnenborg, R., Vercruysse, L., & Romero, R. (2011). The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *American journal of obstetrics and gynecology*, *204*(3), 193-201.

Cunningham, F. G. (2014). Williams Obstetrics 24th edition McGraw-Hill Education.

James-Todd, T., Janevic, T., Brown, F. M., & Savitz, D. A. (2014). Race/Ethnicity, Educational Attainment, and Pregnancy Complications in N ew Y ork C ity Women with Pre-existing Diabetes. *Paediatric and perinatal epidemiology*, *28*(2), 157-165.

Knox, W. F., & Fox, H. (1984). Villitis of unknown aetiology: its incidence and significance in placentae from a British population. *Placenta*, *5*(5), 395-402.

Labarrere, C., & Althabe, O. (1987). Chronic villitis of unknown aetiology in recurrent intrauterine fetal growth retardation. *Placenta*, *8*(2), 167-173.

Lubchenco, L. O., Hansman, C., & Boyd, E. (1966). Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics*, *37*(3), 403-408.

Lubchenco, L. O., Hansman, C., Dressler, M., & Boyd, E. (1963). Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks of gestation. *Pediatrics*, *32*(5), 793-800.

Magnusson, A. L., Powell, T., Wennergren, M., & Jansson, T. (2004). Glucose metabolism in the human preterm and term placenta of IUGR fetuses. *Placenta*, *25*(4), 337-346.

Miller, J., Turan, S., & Baschat, A. A. (2008, August). Fetal growth restriction. In *Seminars in perinatology* (Vol. 32, No. 4, pp. 274-280). WB Saunders.

Nordenvall, M., & Sandstedt, B. (1990). Placental villitis and intrauterine growth retardation in a Swedish population. *APMIS*, *98*(1-6), 19-24.

Oliveira, L. H., Xavier, C. C., & Lana, A. (2002). Changes in placental morphology of small for gestational age newborns. *Jornal de pediatria*, *78*(5), 397-402.

Parra-Saavedra, M., Crovetto, F., Triunfo, S., Savchev, S., Peguero, A., Nadal, A., ... & Figueras, F. (2013). Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. *Placenta*, *34*(12), 1136-1141.

Salafia, C. M., Pezzullo, J. C., Minior, V. K., & Divon, M. Y. (1998). Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Placenta*, *19*(7), A24.

Salafia, C. M., Vintzileos, A. M., Silberman, L., Bantham, K. F., & Vogel, C. A. (1992). Placental pathology of idiopathic intrauterine growth retardation at term. *American journal of perinatology*, *9*(03), 179-184.

Thorne J, Downey P, Mooney EE. (2014). Placental pathology associated with small for gestational age infants. Irish medical journal. 107(8):249-250.

Thorne, J., Downey, P., & Mooney, E. E. (2014). Placental pathology in small for gestational age infants. *Irish medical journal*.

Williams, M. C., O'brien, W. F., Nelson, R. N., & Spellacy, W. N. (2000). Histologic chorioamnionitis is associated with fetal growth restriction in term and preterm infants. *American journal of obstetrics and gynecology*, *183*(5), 1094-1099.