

Analysis of perinatal risk factors for small-for-gestational-age and appropriate-for-gestational-age late-term infants

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Abstract. To investigate the potential risk factors for small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) late-term infants, 100 cases of single full-term SGA infants delivered in the Department of Obstetrics, The First Affiliated Hospital of Chongqing Medical University in 2017 were enrolled as the SGA group. A total of 100 healthy AGA who were born at the same time with the same gestational age were randomly included as the control group. The perinatal and postpartum adverse conditions of the two groups were recorded, and Apgar tests were performed on all newborns at 1 min (T1), 5 min (T2) and 10 min (T3) after birth. A follow-up survey was conducted in all patients at 6 and 12 months of age. At the second follow-up, the development quotient of the children was measured using the Gesell Developmental Schedule, and the perinatal risk factors of SGA were analyzed. The incidence of intrauterine distress, respiratory distress syndrome and infectious disease in the SGA group was significantly higher compared with that in the AGA group ($P<0.05$). The Apgar scores at T1, T2 and T3 were significantly lower in the SGA group compared with the AGA group ($P<0.05$). The Apgar score at T1 was lower compared with that at T2 in the SGA group ($P<0.05$), and the Apgar score at T2 was lower compared with that at T3 ($P<0.05$). The length of hospital stay in the SGA group was significantly longer compared with that in the AGA group ($P<0.05$). The development quotient at the 6 and 12th month in the SGA group was significantly lower compared with that in the AGA group ($P<0.05$). Logistic regression analysis showed that there was no correlation between SGA and maternal age, regardless of firstborn status, neonatal sex, mode of delivery and living environment. SGA was significantly associated with umbilical cord abnormalities, maternal pregnancy-induced hypertension, gestational diabetes, pregnancy infection and intrauterine distress ($P<0.05$).

An abnormal umbilical cord, maternal pregnancy-induced hypertension, gestational diabetes, infection during pregnancy and intrauterine distress are all perinatal risk factors for SGA. Effective interventions are needed in clinical assessment to prevent the occurrence of SGA.

Introduction

Small-for-gestational-age (SGA) infants are 10th-percentile infants that weigh less than the average birth weight of a child of the same age (1). SGA can be divided into two types: Uniform and non-uniform, based on the weight of the newborn and the length/head circumference ratio (2). SGA infants not only show a significantly higher perinatal mortality than normal newborns, but also show a high probability of cognitive dysfunction and decreased learning ability at school age and in adulthood (3). In addition, SGA infants are more likely to suffer from diseases during growth to adulthood due to deficiencies in innate immunity, and their final height is also likely to be significantly lower than that of their peers by two standard deviations (4). According to statistics, SGA accounts for 3-6% of all newborns worldwide (5). In countries with a large population and fast population growth, such as China and India, the incidence of SGA is as high as 10% (6). SGA has a certain degree of influence on the intelligence, physical fitness and neurodevelopment of newborns. Typically, the developmental capacity of all aspects of SGA infants is significantly lower than that of appropriate-for-gestational-age (AGA) infants (7). Some data also indicate that SGA may decrease blood sugar, blood pressure and lipid regulation, which will increase the risk of immune or metabolic diseases (8). Approximately 80% of SGA newborns develop such diseases after delivery, and the current prevalence is still on the rise (9,10). Moreover, SGA has a significantly higher risk of death compared with AGA (11).

Currently, maternal hypertension during pregnancy, multiple pregnancies and oligoamnios are considered as the main causes of SGA in late preterm infants (12). Several studies have indicated that the pathological changes associated with hypertension during pregnancy, which include spasm of systemic arterioles of the umbilical cord blood tube, which directly affects the blood exchange between fetus and mother, can cause insufficient blood supply to the fetus. Insufficient blood supply seriously affects fetal growth and development, thereby leading to the occurrence of SGA (13). It is clinically

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recommended to intervene in pregnant women during the perinatal period to prevent the occurrence of SGA (14). However, current B-ultrasound methods cannot accurately distinguish whether or not the fetus in the maternal uterus will be SGA (15). Therefore, if relevant risk factors of SGA babies are found as predictors, this could aid medical staff in assessing the possibility of pregnant women giving birth to SGA infants. In addition, relevant intervention measures may be carried out to prevent the occurrence or reduce the risk of SGA. The present study aimed to summarize the perinatal risk factors for SGA and provide an effective reference and guidance for clinics.

Materials and methods

Ethics approval and patient consent. The current study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. The parents of all subjects gave their signed informed consent.

Study subjects. In total, 100 cases of single term full-term SGA delivered in the Department of Obstetrics were collected as subjects and regarded as the SGA group between May 2017 to May 2018, comprising 64 males and 36 females. A total of 100 healthy AGA patients who were born at the same time with the same gestational age were randomly included as the control group, comprising 68 males and 32 females.

The inclusion criteria for study subjects were as follows: Full-term neonates, whose gestational age was 37-42 weeks (260-293 days) with a body weight of >2.5 kg and body length of >47 cm; the diagnosis of SGA and AGA met the reference standard of birth weight for newborns of different gestational ages published in 2015 (16). The exclusion criteria for study subjects were as follows: Multiple pregnancies; neonates with abnormal chromosomes or structure; neonates with congenital malformations or inherited metabolic diseases; neonates with a birth weight exceeding the 90th percentile of average gestational age; uterine malformations; placenta previa; family history of genetic disease; neonates with fetal growth restriction according to prenatal B-ultrasound; pregnant women who were transferred; and pregnant women with mental illnesses.

Outcomes measurement. Perinatal and postpartum adverse conditions such as respiratory distress syndrome and infection in the two groups were recorded. Based on the Apgar scoring criteria (17), Apgar tests were performed on all newborns at 1 min (T1), 5 min (T2) and 10 min (T3) after birth. The differences between the two groups of newborns were compared and the hospital stays of the two groups were measured. All patients underwent a 1-year follow-up survey. The follow-up included hospital review and follow-up visits, which were performed at 6 and 12 months. The length and weight of the child were recorded. During the second follow-up, the development quotient (DQ) of the children was measured using Gesell Developmental Schedules (18). A DQ <85 indicated that the child has physical damage; a DQ <65 indicated that the child showed severe growth retardation. Logistic regression analysis was used to study the maternal clinical situation and risk factors of SGA.

Statistical analysis. The data were analyzed and processed using SPSS 24.0 statistical software (IBM Corp.). The count data, such as the percentage of pregnant women, are expressed in terms of (%), and the χ^2 test was used for comparison between groups. Measurement data such as age are expressed in the form of the mean \pm standard deviation, and Student's t-test was used for comparison between groups. Repeated measures ANOVA and Bonferroni's post hoc test were used for comparison between multiple time points. Logistic regression analysis was used for risk factor analysis. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Baseline data. Maternal and newborn data for the two groups were compared. No significant difference was found between the two groups in terms of white blood cell count, red blood cell count, platelet count, maternal age, maternal weight, gestational week, delivery mode, living environment, neonatal gender, first delivery status, maternal pregnancy-induced hypertension and gestational diabetes (Table I), indicating that the two groups were comparable.

Comparison of adverse conditions between the SGA and AGA groups. No significant difference was found in the incidence of neonatal pneumonia between the SGA and AGA groups. In the SGA group, 13% (13 cases) of neonates had intrauterine distress, which was significantly higher compared with the AGA group (4%, 4 cases; $P = 0.023$). In the SGA group, 10% (10 cases) of neonates developed respiratory distress syndrome, which was significantly higher compared with the AGA group (2.00%, 2 cases; $P = 0.017$). In the SGA group, 8% (8 cases) of neonates developed infectious disease, while no cases in the AGA group developed infectious disease. The difference between the two groups was found to be statistically significant ($P = 0.004$; Table II).

Comparison of Apgar score and hospital stay. The Apgar scores of T1, T2 and T3 in the SGA group were 5.24 ± 1.24 , 6.17 ± 1.05 and 6.84 ± 0.87 , respectively. The Apgar scores of T1, T2 and T3 in the AGA group were 7.66 ± 1.22 , 8.72 ± 0.63 and 8.89 ± 0.54 , respectively. The comparison of Apgar scores at T1, T2, and T3 between the two groups indicated that the SGA group scores were significantly lower compared with the AGA group ($P < 0.05$). No significant difference was found in the Apgar score of the AGA group between scores calculated at T2 and T3, while the Apgar score at T1 was lower compared with the T2 and T3 scores ($P < 0.05$). In the SGA group, the Apgar score at T1 was lower compared with the T2 score ($P < 0.05$), and the Apgar score at T2 was lower compared with the T3 score ($P < 0.05$). The length of hospital stay of the SGA group was 4.05 ± 1.27 days, which was significantly longer compared with the AGA group (2.86 ± 1.04 days; $P < 0.05$) (Figs. 1 and 2).

Comparison of prognosis. The follow-up success rate was 100%. The body length and body weight at the 6th month of the SGA group were measured to be 62.33 ± 2.34 cm and 7.28 ± 0.34 kg, respectively, which was significantly lower compared with AGA group measurements (67.25 ± 1.06 cm and 8.07 ± 0.12 kg; $P < 0.05$). At the 12th month, the SGA group body length and body weight

Table I. Comparisons of clinical data.

Parameter	SGA group (n=100)	AGA group (n=100)	χ^2 or t	P-value
WBC, $\times 10^9$	16.24 \pm 2.25	16.58 \pm 2.51	1.009	0.314
Maternal WBC, $\times 10^9$	7.63 \pm 1.01	7.52 \pm 1.35	0.652	0.515
RBC, $\times 10^9$	4.27 \pm 1.12	4.05 \pm 1.34	1.260	0.209
Maternal RBC, $\times 10^{12}$	4.05 \pm 1.36	4.12 \pm 1.07	0.405	0.686
PLT, $\times 10^{12}$	269.53 \pm 40.59	262.16 \pm 42.88	1.248	0.213
Maternal PLT, $\times 10^9$	187.54 \pm 62.15	179.33 \pm 59.42	0.955	0.341
Maternal age, years	24.86 \pm 3.22	25.04 \pm 3.50	0.379	0.706
Maternal weight, kg	62.13 \pm 5.87	61.94 \pm 6.16	0.223	0.824
Gestational week	42.86 \pm 2.58	42.33 \pm 2.04	1.611	0.109
Mode of delivery (%)			0.188	0.664
Vaginal birth	62 (62.00)	59 (59.00)		
Caesarean section	38 (38.00)	41 (41.00)		
Living environment (%)			0.362	0.548
Urban	69 (69.00)	65 (65.00)		
Country	31 (31.00)	35 (35.00)		
Neonatal sex (%)			0.357	0.551
Male	64 (64.00)	68 (68.00)		
Female	36 (36.00)	32 (32.00)		
Number of births (%)			0.829	0.363
First birth	79 (79.00)	84 (84.00)		
Two or more births	21 (21.00)	16 (16.00)		
Pregnancy-induced hypertension (%)			0.307	0.579
Yes	8 (8.00)	6 (6.00)		
No	92 (92.00)	94 (94.00)		
Gestational diabetes (%)			0.053	0.818
Yes	11 (11.00)	10 (10.00)		
No	89 (89.00)	90 (90.00)		

SGA, small-for-gestational-age; AGA, appropriate-for-gestational-age; WBC, white blood cells; RBC, red blood cells; PLT, platelets.

Table II. Comparison of adverse conditions between the two newborn groups.

Condition	SGA group (n=100)	AGA group (n=100)	χ^2	P-value
Fetal intrauterine distress (%)	13 (13.00)	4 (4.00)	5.207	0.023
Respiratory distress syndrome (%)	10 (10.00)	2 (2.00)	5.674	0.017
Neonatal pneumonia (%)	6 (6.00)	2 (2.00)	2.083	0.149
Infectious disease (%)	8 (8.00)	0 (0.00)	8.333	0.004

SGA, small-for-gestational-age; AGA, appropriate-for-gestational-age.

were measured to be at 70.24 \pm 2.38 cm and 8.62 \pm 0.42 kg, respectively. This was also significantly lower compared with AGA group measurements (74.86 \pm 0.95 cm and 9.08 \pm 0.24 kg; $P < 0.05$). The body length and body weight at the 12th month significantly increased ($P < 0.05$) compared with the measurements at the 6th month. The DQ of the SGA group was 72.62 \pm 2.87, which was significantly lower compared with that of the AGA group (88.36 \pm 3.87; $P < 0.05$) (Figs. 3-5).

Analysis of SGA-related risk factors. Logistic regression analysis showed that there was no correlation between SGA and maternal age, regardless of first child status, neonatal sex, mode of delivery and living environment. SGA was significantly associated with umbilical cord abnormalities, maternal pregnancy-induced hypertension, gestational diabetes, pregnancy infection and intrauterine distress ($P < 0.05$); therefore, these are risk factors for SGA (OR>1; Table III).

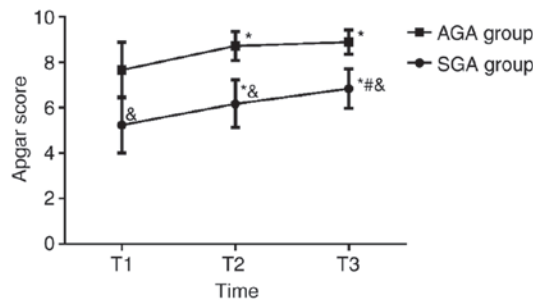


Figure 1. Comparison of Apgar scores between the two groups. The SGA group showed significantly lower Apgar scores compared with the AGA group. *P<0.05 vs. respective T1; #P<0.05 vs. respective T2; &P<0.05 vs. AGA group. SGA, small-for-gestational-age; AGA, appropriate-for-gestational-age. T1, 1 min; T2, 5 min; T3, 10 min.

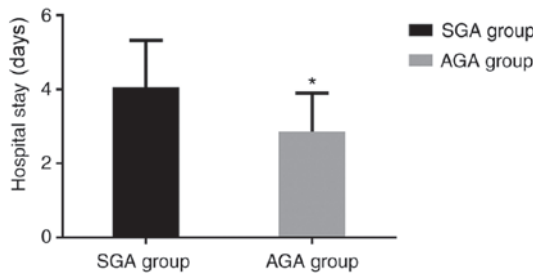


Figure 2. Comparison of hospital stays between the two groups. The SGA group exhibited significantly longer length of hospital stay compared with the AGA group. *P<0.05 vs. SGA group. SGA, smaller-for-gestational-age; AGA, appropriate-for-gestational-age.

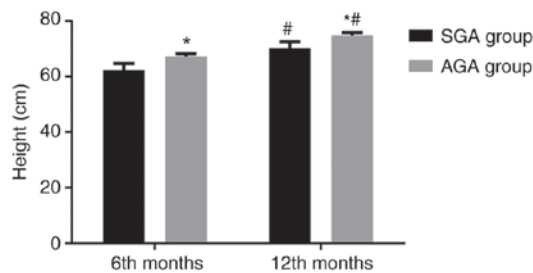


Figure 3. Comparison of body lengths between the two groups. The body length at the 6th month was significantly lower compared with body length at the 12th month in the SGA group. At the 12th month in the SGA group, the body length was also significantly lower compared with that in the AGA group. *P<0.05 vs. respective SGA group; #P<0.05 vs. respective 6th month. SGA, smaller-for-gestational-age; AGA, appropriate-for-gestational-age.

Discussion

SGA is presently one of the key factors that threaten the healthy growth of newborns (19,20). The clinical prevention of SGA is currently advocated to pregnant women in the perinatal period. However, the only current testing available is mainly the B-ultrasound method (21), and this method is still unable to correctly diagnose whether or not the fetus will develop SGA (22,23). Therefore, clinical research is constantly looking for effective means to distinguish the occurrence of SGA in newborns. However, to the best of our knowledge, no breakthrough research results have been obtained. Therefore, summarizing the risk factors that may affect SGA through

Table III. Logistic regression analysis of SGA risk factors.

Risk factor	OR	95% CI	P-value
Umbilical cord abnormality	2.29	1.36-3.82	0.002
Maternal age	0.93	0.65-1.33	0.698
Number of births	1.09	0.66-1.81	0.736
Neonatal sex	0.83	0.25-2.66	0.752
Pregnancy-induced hypertension	1.36	1.04-1.77	0.024
Living environment	1.08	0.79-1.47	0.648
Fetal intrauterine distress	1.80	1.31-2.47	<0.001
Pregnancy infection	1.59	1.07-2.37	0.022
Mode of delivery	1.05	0.84-1.31	0.660

OR, odds ratio; CI, confidence interval.

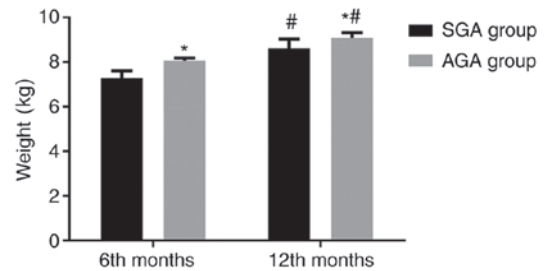


Figure 4. Comparison of weights between the two groups. The body weight at the 6th month was significantly lower compared with body weight at the 12th month of the SGA group. At the 12th month in the SGA group, the body weight was also significantly lower compared with that in the AGA group. *P<0.05 vs. respective SGA group; #P<0.05 vs. respective 6th month. SGA, smaller-for-gestational-age; AGA, appropriate-for-gestational-age.

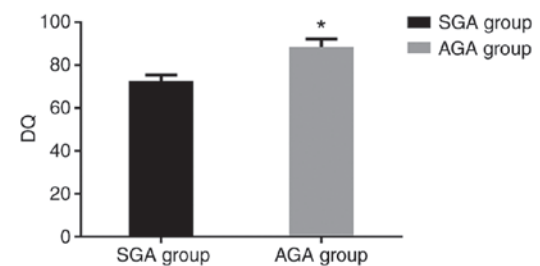


Figure 5. Comparison of the DQ index between two groups. The DQ of the SGA group was significantly lower compared with that of the AGA group. *P<0.05 vs. SGA group. DQ, development quotient; SGA, smaller-for-gestational-age; AGA, appropriate-for-gestational-age.

representative clinical data is the most traditional and the most effective way. A review of relevant literature found that articles on the study of SGA risk factors were generally outdated and because the hospital conditions at that time were quite different from modern conditions, it is not suitable for clinical guidance (24-26). Therefore, the present study aimed to summarize the influencing factors affecting SGA through the study of infants with SGA and AGA admitted to the Department of Obstetrics, The First Affiliated Hospital of Chongqing Medical University in 2017. Advanced statistical software and a random experimental design were used to ensure that the experimental

results were more authentic and reliable, and possible high-risk events were analyzed in detail in the present study for clinical reference.

The results of this experiment showed that the risk of intrauterine distress, respiratory distress syndrome and infectious diseases in the SGA group was significantly higher than that in the AGA group, suggesting that SGA can increase the risk of neonatal disease. Studies have shown that SGA has an impact on the normal development of neonatal body function (27,28),

The significant increase in the incidence of SGA in this study also confirms the view that SGA will affect the normal development of neonatal body function. The pathogenesis of SGA mainly includes maternal umbilical blood vessels spasms and systemic small arterial spasms, which affects blood exchange between the fetus and the mother (29). This causes insufficient blood supply to the fetus and affects fetal growth and development, leading to SGA (30). Therefore, SGA causes incomplete development of organ function, due to insufficient blood supply in the maternal uterus. Furthermore, the immune capacity of the fetus may be relatively low, hence the risk of disease greatly increased after birth (31). No significant difference was found in the incidence of neonatal pneumonia between the two groups, although this may be due to the small number of subjects. The SGA group demonstrated lower Apgar scores and a longer hospital stay compared with the AGA group. Other reasons are speculated to be consistent with the above points. Due to the decreased oxygen saturation of the mother, the fetal tissue is hypoxic, causing dyspnea, and this is consistent with the results of Kiely *et al* (32), who demonstrated that children with SGA have lower Apgar scores than children with AGA.

The prognosis of the two groups of newborns was further compared. The growth and development of the SGA group was significantly lower compared with the AGA group. This suggested that SGA has a great negative impact on the healthy growth of newborns, and should be paid more attention in the clinic. It is necessary to conduct a careful and complete prenatal examination in pregnant women to prevent the occurrence of SGA. Logistic regression analysis showed that umbilical cord abnormalities, maternal pregnancy-induced hypertension, gestational diabetes, pregnancy infection and intrauterine distress were all risk factors for SGA.

Khalil *et al* (33) found that the older the mother, the higher the likelihood of SGA in the newborn. However, no difference was observed with respect to maternal age in the present study. Moreover, the research subjects of Khalil *et al* were mostly Caucasian, and the present study focused on Asians. Regional and race differences may also be one of the reasons for the difference in results. The sample size in future studies will be enlarged for subsequent analysis and verification.

This study analyzed the risk factors of SGA by comparing the differences in the growth and development, as well as the risk of diseases between SGA and AGA newborns. However, due to limited experimental conditions, there are still some limitations. For example, the number of subjects in the study is too small to perform a larger statistical analysis. Moreover, the risk factors may be influenced by other variables such as ethnicity, region and living habits. However, since the limitations of this study are relatively high, this may have resulted in some accidental error data. Future studies could be conducted with several hospitals to expand the sample size of the study

and obtain more comprehensive and representative case data for analysis. In addition, the pathogenesis of SGA has not been completely defined, and a possible correlation between fetal anthropometric data, usually registered during prenatal medical check-ups, and the aforementioned pregnancy risk factors was not analyzed herein, which will be studied in future research.

In summary, an abnormal umbilical cord, maternal pregnancy-induced hypertension, gestational diabetes, infection during pregnancy and intrauterine distress are all perinatal risk factors of SGA. Effective interventions are needed in the clinic to prevent the occurrence of SGA.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JC conceived and designed the research and interpreted the results of the experiments. JL contributed to the design of the study and the interpretation of experimental results. XT performed experiments, analyzed data and drafted the initial manuscript. JL and XT approved the final version of manuscript. JC edited and revised the manuscript.

Ethics approval and consent to participate

The current study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. The parents of all subjects gave their signed informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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