Effect of Allostatic Load on Adverse Pregnancy Outcomes of Women (Postprint)

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Abstract

Literature; pregnancy outcome information was obtained by reviewing the hospital electronic medical record system. Multivariate Logistic regression analysis was used to explore the effect of AL on adverse pregnancy outcomes in women in late pregnancy. Results: A total of 354 women in late pregnancy with an average age of (29.3$±$4.1) years and upper quartile of AL total score of 3 were included in this study. The upper quartile of the total AL score of the study subjects was used as the high-risk threshold, and they were divided into low-level AL (AL <3) and high-level AL (AL ≥ 3) according to their AL scores. High AL pregnant women accounted for 32.8% (116/354) and low AL pregnant women accounted for 67.2% (238/354). The prevalence of adverse pregnancy outcomes was 15.5% (55/354), including 9.9% (35/354) of macrosomia, followed by preterm birth (5.4%, 19/354) and low birth weight (2.3%, 8/354). The incidence of adverse pregnancy outcomes was higher in women in late pregnancy with high AL (26.7%, 31/116) than in women in late pregnancy with low AL (10.1%, 24/238) (P<0.05); the incidence of preterm birth (10.3%, 12/116) and delivery of macrosomia (15.5%, 18/116) was higher in women in late pregnancy with high AL than in women in late pregnancy with low AL (2.9%, 7/238; 7.1%, 17/238) (P<0.05). Multivariate Logistic regression analysis showed that women in late pregnancy with high AL had a 2.465-fold increased risk of adverse pregnancy outcomes compared to women in late pregnancy with low AL [95% CI (1.315, 4.622), P<0.05]. High AL level was a risk factor for preterm birth [OR=4.832, 95% CI (1.545, 15.114)] and delivery of macrosomia [OR=2.868, 95% CI (1.392, 5.909)] in women in late pregnancy compared to low AL level (P<0.05). Conclusion: High level of AL in women in late pregnancy increases the risk of adverse pregnancy outcomes, especially the risk of preterm birth and delivery of macrosomia. Attention to AL in women during pregnancy should be enhanced to provide a theoretical basis for preventing adverse pregnancy outcomes.

Full Text

Preamble

Effect of Allostatic Load on Adverse Pregnancy Outcomes of Women in Late Pregnancy

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Abstract

Background: The incidence of adverse pregnancy outcomes has remained high in recent years, posing a serious threat to maternal and neonatal life and health. Chronic stress is known to be a risk factor for adverse pregnancy outcomes, while the relationship between allostatic load (AL)—a composite physiological index of chronic stress—and adverse pregnancy outcomes has not been clarified.

Objective: To explore the effect of AL on adverse pregnancy outcomes in women in late pregnancy.

Methods: Women in late pregnancy who met the study requirements were recruited using convenience sampling from November 2021 to November 2022 at the obstetrics outpatient clinics of the 901 Hospital, Joint Logistic Support Force of the Chinese People's Liberation Army, and Jin'an Maternal and Child Health Care Hospital. Basic information including general and obstetric data were collected through questionnaires, biological indicators were collected through physical examination and laboratory tests, and AL scores were calculated by referring to AL-related literature. Pregnancy outcome information was obtained by reviewing the hospital electronic medical record system. Multivariate logistic regression analysis was used to explore the effect of AL on adverse pregnancy outcomes in women in late pregnancy.

Results: A total of 354 women in late pregnancy with an average age of (29.3 $\pm$ 4.1) years were included. The upper quartile of the total AL score was 3, which was used as the high-risk threshold. Participants were divided into low-level AL (AL $<$ 3) and high-level AL (AL $\geq$ 3) groups. High AL pregnant women accounted for 32.8% (116/354) and low AL pregnant women accounted for 67.2% (238/354). The prevalence of adverse pregnancy outcomes was 15.5% (55/354), including macrosomia at 9.9% (35/354), followed by preterm birth at

5.4% (19/354) and low birth weight at 2.3% (8/354). The incidence of adverse pregnancy outcomes was higher in women with high AL (26.7%, 31/116) than in those with low AL (10.1%, 24/238) ($P < 0.05$). The incidence of preterm birth (10.3%, 12/116) and delivery of macrosomia (15.5%, 18/116) was higher in women with high AL compared to those with low AL (2.9%, 7/238 and 7.1%, 17/238 respectively) ($P < 0.05$). Multivariate logistic regression analysis showed that women with high AL had a 2.465-fold increased risk of adverse pregnancy outcomes compared to women with low AL [OR = 2.465, 95% CI (1.315, 4.622), $P < 0.05$]. High AL level was a risk factor for preterm birth [OR = 4.832, 95% CI (1.545, 15.114)] and delivery of macrosomia [OR = 2.868, 95% CI (1.392, 5.909)] in women in late pregnancy compared to low AL level ($P < 0.05$).

Conclusion: High levels of AL in women in late pregnancy increase the risk of adverse pregnancy outcomes, especially the risk of preterm birth and delivery of macrosomia. Attention to AL in women during pregnancy should be enhanced to provide a theoretical basis for preventing adverse pregnancy outcomes.

Keywords: Pregnancy trimester, third; Allostatic load; Chronic stress; Adverse pregnancy outcome; Root cause analysis

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Maternal and infant health is a top priority for national health, and adverse pregnancy outcomes are an important cause of harm to maternal and infant health. Adverse pregnancy outcomes mainly refer to a series of pregnancy complications and abnormal birth outcomes occurring during pregnancy that jeopardize the health of the mother and fetus, such as preterm delivery, low birth mass, macrosomia, preeclampsia, and birth defects. Adverse pregnancy outcomes not only increase maternal and neonatal mortality but also lead to neurodevelopmental problems in children (e.g., low IQ and cerebral palsy) and increase the risk of obesity and diabetes mellitus in offspring during adulthood. China has a large delivery base, and data from the National Health Commission show that in 2021, the number of hospitalized live births in China reached 10,515,000. The occurrence of adverse pregnancy outcomes reduces the quality of births, hinders the development of eugenics, and imposes a huge economic burden on families and society. Numerous factors influence adverse pregnancy outcomes, and chronic psychosocial stress has been identified as a risk factor. Allostatic load (AL) is a measure of chronic physiological stress, reflecting the accumulated wear and tear of the body' s physiological systems under chronic stress. Currently, there are few foreign studies on AL and adverse pregnancy outcomes, and these studies show large differences in results, while relevant studies in China remain scarce. The level of AL in late pregnancy represents the level of chronic stress accumulated by pregnant women throughout the gestation period. Therefore, the present study analyzes whether the level of AL in late pregnancy is a risk factor for adverse pregnancy outcomes and provides a reference for strengthening pregnancy risk assessment and reducing the occurrence of adverse pregnancy outcomes.

1. Objects and Methods

1.1 Study Subjects

A prospective study design was adopted, and convenience sampling was used to select women in late pregnancy who were enrolled at the Department of Obstetrics and Gynecology, 901 Hospital, Joint Logistic Support Force of the Chinese People' s Liberation Army, from November 2021 to November 2022, as study subjects. Inclusion criteria were: (1) natural conception, singleton; (2) 30-34 weeks of gestation; (3) clear thinking and normal expression; (4) informed consent. Exclusion criteria were: (1) previous severe psychiatric and psychological disorders; (2) underlying diseases such as heart disease, hypertension, diabetes, or hepatitis before pregnancy. Additional exclusion criteria included: (1) incomplete questionnaire completion; (2) inability to follow up pregnancy outcomes. This study was reviewed by the Ethics Committee of Anhui Medical University (Ethics Approval Number: s20210076).

1.2.1 Baseline Survey

1.2.1.1 Questionnaire Survey Method: The questionnaire collected: (1) General information including age, occupation, education level, annual per capita household income, history of COVID-19 vaccination, and smoking and drinking during pregnancy (ever smoking was considered smoking, and drinking >15 g/d was considered drinking); (2) Obstetric information including number of deliveries, history of spontaneous abortion, and history of obstetric and gynecological surgery (including history of cesarean section, laparoscopic surgery, and hysteroscopic surgery); (3) Depression in late pregnancy assessed using the Edinburgh Postnatal Depression Scale (EPDS). The EPDS consists of 3 dimensions and 10 items, with higher scores indicating more severe depression. In this study, we used a score of 9 as the critical value recommended in the literature, and a score of $ $9 was considered indicative of late-pregnancy depression. All investigators received uniform and strict training before the survey. The questionnaire survey was conducted after obtaining informed consent from study participants and explaining precautions for questionnaire completion. The completeness of questionnaires and key information were checked promptly at the end of each survey.

1.2.1.2 Physical Examination: Measurements included: (1) Height and body mass measured by an all-in-one height and body mass machine, with readings accurate to 1 cm and 0.1 kg respectively; (2) BMI calculated according to height and body mass; (3) Waist circumference measured by a tape measure taken along the level of the navel around the abdomen, with readings accurate to 0.1 cm; (4) Blood pressure measured by an electronic sphygmomanometer.

1.2.1.3 Laboratory Examination: Fasting was performed after 22:00 one day before delivery, and fasting blood was collected at the hospital laboratory before 10:00 the next day (subjects fasted for at least 8 hours). All measurements were performed by laboratory staff. Ultrasensitive C-reactive protein, fasting

blood glucose, high-density lipoprotein, and total cholesterol were measured using Beckman Coulter AU5800 and Hitachi 7600-020 automatic biochemical analyzers.

1.2.2 Follow-up of Pregnancy Outcomes

Pregnancy outcomes were obtained by reviewing the hospital' s electronic medical record system. Delivery information included delivery gestational week, mode of delivery, and maternal health status. Newborn information included newborn birth mass, gender, length, and health status. Adverse pregnancy outcomes included preterm labor, low birth mass, and macrosomia. The primary study outcomes were adverse pregnancy outcomes (occurrence of preterm labor, low birth mass, and macrosomia).

1.2.3 AL Evaluation

Currently, there is no uniform gold standard for AL evaluation methods. Based on relevant literature on AL, the following biomarkers were selected as evaluation indexes of AL in women in late pregnancy: BMI, systolic blood pressure, diastolic blood pressure, waist circumference, total cholesterol, high-density lipoprotein, fasting blood glucose, and ultra-sensitive C-reactive protein. These 8 indicators represent physiological changes in the cardiovascular system, metabolic system, and immune system under chronic stress. The AL scoring method used the high-risk quartile method, in which the lower quartile of the HDL indicator was considered high-risk, and the upper quartile of the remaining indicators was considered high-risk. Biomarker scores in the high-risk quartile were counted as 1, otherwise 0. Finally, the scores of each biomarker were summed to obtain the total score, i.e., the AL score, with a total score ranging from 0-8. Higher scores indicated higher health risk.

1.3 Statistical Methods

Data were double-checked and analyzed using SPSS 22.0 software. Measurement data conforming to normal distribution were expressed as mean ± standard deviation. Categorical data were expressed as frequency and percentage. The chi-square test and Fisher' s exact test were used for comparisons between groups. To prevent omission of important independent variables, the level of statistical significance for two-sided tests was relaxed to $\alpha = 0.10$. Variables that were statistically significant in univariate analyses were included in multivariate logistic regression analyses. Statistically significant differences were considered at $P < 0.05$.

2. Results

2.1 Baseline Data of the Study Population

A total of 354 women in late pregnancy with a mean age of (29.3 ± 4.1) years were included. The upper quartile of the total AL score was 3, which was used as the high-risk threshold. Participants were categorized according to their AL scores into low-level AL (AL < 3) and high-level AL (AL ≥ 3). The percentage of pregnant women with high-level AL was 32.8% (116/354) and with low-level AL was 67.2% (238/354). The average gestational week of delivery for the 354 study subjects was (38.9 ± 1.3) weeks. The mode of delivery included cesarean section and vaginal delivery, with 137 (38.7%) cesarean sections and 217 (61.3%) vaginal deliveries. The incidence of adverse pregnancy outcomes was 15.5% (55/354), with macrosomia at 9.9% (35/354), followed by preterm labor at 5.4% (19/354) and low birth mass at 2.3% (8/354).

2.2 Comparison of the Incidence of Adverse Pregnancy Outcomes Among Women with Different Characteristics in Late Pregnancy

The differences in the incidence of adverse pregnancy outcomes among women with different ages, history of spontaneous abortion, and gestational diabetes were statistically significant ($P < 0.10$). The differences in the incidence of preterm labor among women with different levels of AL in late pregnancy were statistically significant ($P < 0.10$). There were statistically significant differences in the incidence of low-birth-mass infants among women with different levels of gestational anemia ($P < 0.10$). There were statistically significant differences in the incidence of macrosomia among women with different levels of gestational diabetes ($P < 0.10$), as shown in Table 1 .

Note: The table data in the original manuscript appears to be corrupted and incomplete.

2.3 Comparison of Adverse Pregnancy Outcomes Among Women with Different Levels of AL

The incidence of adverse pregnancy outcomes among women with high levels of AL was higher than that of women with low levels of AL, and the difference was statistically significant ($P < 0.05$). The incidence of preterm labor and the rate of delivery of macrosomia among women with high levels of AL were higher than those of women with low levels of AL, and the differences were statistically significant ($P < 0.05$). There was no statistically significant difference in the incidence of low birth mass among women with different levels of AL in late pregnancy ($P > 0.05$), as shown in Table 2 .

Table 2. Comparison of Adverse Pregnancy Outcomes in Late Pregnant Women with Different AL Levels

Classification	Cases	Preterm labor	Low birth mass	Macrosomia	Adverse pregnancy outcomes
Low-level AL	238	7 (2.9%)	3 (1.3%)	17 (7.1%)	24 (10.1%)
High-level AL	116	12 (10.3%)	5 (4.3%)	18 (15.5%)	31 (26.7%)
^{2} value		<0.001			

2.4 Multivariate Logistic Regression Analysis of AL and Adverse Pregnancy Outcomes

2.4.1 Multivariate Logistic Regression Analysis of Adverse Pregnancy Outcomes in Women in Late Gestation: Using adverse pregnancy outcome in the third trimester as the dependent variable (assignment: none = 0, occurrence = 1), AL level (assignment: low-level AL = 0, high-level AL = 1) and statistically significant variables from univariate analysis including age (assigned: <35 years = 0, $ $35 years = 1), history of spontaneous abortion (assignment: no = 0, yes = 1), and gestational diabetes (assigned: no = 0, with = 1) were included as independent variables. Third trimester depression (assigned: no = 0, have = 1) was also included as an independent variable. Multivariate logistic regression analysis showed that high levels of AL are a risk factor for adverse pregnancy outcomes in women in the third trimester, as shown in Table 3 .

Table 3. Multivariate Logistic Regression Analysis of Influencing Factors for Adverse Pregnancy Outcomes in Late Pregnant Women

Variable	Wald ^{2} value	P value	OR value	95% CI
Age (with reference to <35 years)				(0.852, 4.102)
History of spontaneous abortion (with none as a reference)				(0.804, 3.451)
Gestational diabetes mellitus (with none as a reference)				(0.898, 3.147)

Variable	Wald ^{2} value	P value	OR value	95% CI
Depression in late pregnancy (with none as a reference)				(0.804, 3.096)
AL level (with low-level AL as a reference)				(1.315, 4.622)
High-level AL				

2.4.2 Multivariate Logistic Regression Analysis of AL and Three Adverse Pregnancy Outcomes: Multivariate logistic regression analysis was performed with preterm labor, low birth mass, and macrosomia as dependent variables (assigned values: not occurring = 0, occurring = 1), with AL as the independent variable and adjusting for some variables. The results showed that high levels of AL were a risk factor for preterm labor and delivery of macrosomia in women in late pregnancy compared with low levels of AL ($P < 0.05$), as shown in Table 4 .

Table 4. Multivariate Logistic Regression Analysis of the Association Between AL and Adverse Pregnancy Outcomes

Type of adverse pregnancy outcome	Dependent Variable	^{2} value	P value	OR value	95% CI
Preterm labor[a]	High-level AL				(1.545, 15.114)
Low birth massb	High-level AL				(0.234, 8.840)
Macrosomiac	High-level AL				(1.392, 5.909)

Note: a indicates adjustment for age, education level, occupation, family income per capita, history of abortion, anemia during pregnancy, and gestational diabetes mellitus; b indicates adjustment for preterm birth and anemia during pregnancy; and c indicates adjustment for gestational age at delivery and gestational diabetes mellitus.

3. Discussion

With continuous changes in fertility policy, China's population development has entered a critical turning period. Eugenics and promoting long-term balanced population development have become the focus of maternal and child health care, but the occurrence of adverse pregnancy outcomes has seriously impeded this process. Chronic stress is known to be one of the risk factors for adverse pregnancy outcomes. In this study, we used AL as a measure of stress during pregnancy to investigate the effect of AL on adverse pregnancy outcomes in women in late pregnancy, with a view to reducing the incidence of adverse pregnancy outcomes and promoting the health of mothers and infants.

3.1 Incidence of Adverse Pregnancy Outcomes

A total of 354 women in late pregnancy were included in this study, and the incidence rate of adverse pregnancy outcomes was 15.5%, which was lower than the 19.77% reported in the study by Wang Dan and the 21.6% in the study by Yang Xiaowu. This difference may be mainly due to the fact that the target population of this investigation was women in late pregnancy, and the types of adverse pregnancy outcomes did not include early miscarriage. The incidence of macrosomia in this study was 9.9%, slightly higher than the 8.7% incidence reported in another study, which may be related to improved material living standards and overnutrition during pregnancy. Preterm labor is a global public health problem and a major cause of neonatal mortality. According to data reported by the World Health Organization, about 15 million preterm babies are born globally each year, with a prevalence rate of 10%, and this rate is still increasing. A research team in China used data from the National Maternal Event Surveillance System to reveal that the overall preterm birth rate in China rose from 5.9% in 2012 to 6.4% in 2018, indicating that preterm birth remains a problem that cannot be ignored. Low birth mass often occurs in conjunction with preterm labor, which is not only one of the leading causes of infant mortality but also carries a higher risk of developmental delay in childhood and long-term stunting. The incidence of low birth mass in China has increased from 2.64% in 2015 to 3.7% in 2021, showing a rising trend year by year. The incidence of adverse pregnancy outcomes is high and harmful, reducing the quality of the birth population and hindering the development of eugenics. With the implementation of the three-child policy, the group of high-risk pregnant women will continue to expand in the future, greatly increasing the risk of adverse pregnancy outcomes. Therefore, it is crucial to pay attention to risk assessment for adverse pregnancy outcomes to provide a scientific basis for preventing their occurrence.

3.2 AL and Adverse Pregnancy Outcomes

In this study, 116 pregnant women had high levels of AL among the 354 women in late pregnancy, accounting for 32.8%. Univariate analysis showed that the incidence of adverse pregnancy outcomes in women with high levels of AL was

significantly higher than that in women with low levels of AL. Multivariate logistic regression analysis showed that AL was a risk factor for preterm labor and macrosomia, and that high levels of AL increased the risk of adverse pregnancy outcomes. These findings were consistent with the results of a study by Lueth et al. The occurrence of adverse pregnancy outcomes is the result of a combination of risk factors, but the pathophysiologic mechanisms leading to these outcomes remain uncertain, and cumulative stress may be an influential factor. Pregnancy is a stressful process, and pregnant women face different stressors at different times during pregnancy, experiencing varying stress loads. Women in late pregnancy not only suffer from stress accumulated in early and mid-pregnancy but also face stress associated with late pregnancy, and the level of late-gestational AL represents the level of chronic stress that accumulates throughout the gestation period. In addition, the physiological load of pregnant women increases continuously during pregnancy and reaches its peak in late pregnancy, so the physiological and psychological loads of women in late pregnancy are at a high level. When the accumulated load exceeds the body' s ability to cope, it causes dysfunction of several physiological systems and results in high levels of AL.

Since conception and pregnancy require a complex series of neurological, endocrine, immune, and metabolic changes to maintain them, the course of pregnancy may be altered when these physiological systems become dysfunctional. The present study found that high levels of AL in late pregnancy increase the risk of preterm labor. The etiology and pathogenesis of preterm labor are complex, and it has been shown that maternal stress and stress-related reactions during pregnancy increase the overall risk of preterm labor. Stress activates the maternal inflammatory system, which increases the level of inflammatory system stress, leading to high levels of AL in the body. Inflammatory markers also suppress the immune system response, increasing susceptibility to adverse pregnancy outcomes, which may ultimately induce preterm labor. Studies have shown that adverse stress during pregnancy increases the risk of preterm labor and low birth mass, and there is a significant association between elevated AL and shorter gestation. A secondary analysis of a multicenter randomized clinical trial found that increased AL scores were associated with an increased probability of preterm labor and low birth mass. In addition, stress in women during pregnancy may affect physiologic stress, risk of preterm labor, and birth outcomes over multiple generations, and factors determining the risk of preterm labor may be passed on to offspring through the maternal line, including cumulative stress.

The results of this study suggest that high levels of AL in women in late pregnancy are a risk factor for the development of macrosomia, with the risk of macrosomia in women with high levels of AL being 2.868 times higher than in those with low levels of AL. The occurrence of macrosomia is closely related to maternal blood glucose and lipid levels, which depend on the regulation of various physiological systems of the body, especially the metabolic system. AL contains a number of physiological indicators of the metabolic system and can reflect the physiological function of the metabolic system in a more comprehen-

sive manner. With the rapid development of the economy and rising concern for nutrition during pregnancy, macrosomia will remain a serious problem in the coming years. Close attention should be paid to fetal growth and development during pregnancy, and interventions such as personalized dietary guidance and exercise plans should be formulated for pregnant women to alleviate physiological and psychological stress through the provision of professional guidance and to achieve early detection and early prevention.

In conclusion, the results of this study show that high levels of AL in women in late pregnancy increase the risk of preterm labor and macrosomia. AL, as a comprehensive physiological indicator of chronic stress, is able to assess the functional response to chronic stress in a more comprehensive way. High levels of AL in women in late pregnancy reflect the dysfunction of multiple physiological systems caused by the cumulative stress load during pregnancy. The process of pregnancy to labor requires a series of normal physiological activities to maintain, and therefore, when the level of AL is elevated, the dysfunction of multiple physiological systems may affect the process of pregnancy and lead to the occurrence of adverse pregnancy outcomes. However, only three types of adverse pregnancy outcomes were included in this study. In the future, more large-sample, prospective cohort studies should be conducted to include as many types of adverse pregnancy outcomes as possible, to further investigate the association between AL and adverse pregnancy outcomes in pregnant women and the potential mechanisms.

Authors' Contributions: Minghuan Wang and Dehui Yuan were responsible for recruiting study participants and data collection, managing and analyzing the data. Minghuan Wang wrote the paper. Min Yu and Yougang Wang were responsible for organizing the site and coordinating the project. Qiaozhi Yu, Fangfang Yang, and Liu Zhang were involved in data collection. Yuhong Li was responsible for the overall design of the study, organizing the project, quality control, and proofreading the article.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.