Original Article

Maternal and neonatal outcome in fetuses weighing less than the first centile

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ABSTRACT

Introduction: This study aims to investigate the maternal and neonatal outcomes in fetuses with a weight below the first centile.
Materials and Methods: This retrospective epidemiological study examined 62 mothers with fetuses weighing below the first centile who participated in Imam Khomeini Hospital in Ahvaz, Iran, between March 2020 and February 2021. Data related to maternal and neonatal demographic variables, pregnancy outcomes, and neonatal complications were collected and analyzed from the patient's medical records.
Results: In this study most participants were primiparous (61.28%). The observed prenatal complications included hypertensive disorders of pregnancy (22.58%), gestational diabetes (17.74%), placental abruption (11.29%), anemia (8.06%), oligohydramnios (19.35%), fetal anomalies (4.84%), and stillbirth (4.84%). Abnormal Doppler findings were observed in 42.85% of mothers, and preterm birth was observed in 72.58%. Neonatal outcomes included respiratory distress syndrome (42.37%), hypoglycemia (37.29%), hypothermia (32.20%), hyperbilirubinemia (30.51%), meconium aspiration syndrome (28.81%), hypocalcemia (27.12%), polycythemia (25.42%), thrombocytopenia (11.86%), anemia (8.47%), sepsis (6.78%), fetal anomalies (8.47%), and neonatal death (11.86%). An Apgar score of ≤7 at 5 minutes after birth was observed in 13.56% of neonates, and the neonatal admission rate to the NICU was 84.75%.
Conclusions: The results of this study revealed that fetuses with birth weights below the first centile could result in multiple perinatal complications. Therefore, monitoring and prenatal care are essential to reduce IUGR and perinatal complications in these neonates. Timely recognition of the status of very low birth weight fetuses and screening for associated complications and interventions can help prevent the occurrence of neonatal complications.

Keywords: Prenatal outcomes, fetal growth restriction, neonatal outcomes, small for gestational age

Introduction

Identifying intrauterine growth-restricted (IUGR) infants is one of the biggest challenges in modern perinatology. Fetal growth restriction (FGR) occurs when the fetus does not achieve the desired biological growth due to placental insufficiency. FGR can occur in the early to late stages of pregnancy (1-3). FGR occurs in every 1 in 10 pregnancies, and this rate reaches 20% in developed countries (4). FGR is associated with 12% mortality in the fetal period and 8% in the neonatal period (5). About 60% of cases of FGR are idiopathic and multifactorial, while in 40% of cases, there is a specific etiology, such as underlying maternal diseases, chromosomal abnormalities, fetal malformations, and infectious diseases (6).

FGR is associated with an increase in stillbirth, morbidity (7, 8), and neonatal and childhood mortality (9). Individuals with FGR also experience neurological and somatic complications in the perinatal period and long-term health consequences such as an increased risk of neurodevelopmental disorders, cognitive impairment (10), and cardiovascular and endocrine disorders in adulthood (4, 11-13).

Due to the lack of a gold standard for identifying growth restriction in newborns, Small for gestational age (SGA) is used as a screening tool. SGA is typically used for infants with a birth weight below the 10th centile (4, 14). There is no international consensus on which birth weight chart can best identify infant growth restriction (15, 16). FGR is a pathological condition in which the fetus is confronted with oxygen and nutrient limitations (17), and although most cases of FGR are SGA at birth, some demographic factors such as maternal age, parity, race, and body mass index (BMI) may be associated with birth weight (18). Therefore, SGA does not necessarily indicate a pathological condition, as up to 70% of small fetuses are healthy,

have reached their full potential for intrauterine growth, and are not at high risk of adverse perinatal outcomes and mortality (19). Based on the definition of SGA, healthy small infants may be subjected to unnecessary interventions (20), and small infants may be diagnosed as SGA, while FGR may not be diagnosed in fetuses with an estimated fetal weight greater than the 10th centile (1).

FGR is a functional pair pathology relevant primarily to smaller sizes. However, given the limited availability of routine clinical performance evaluation criteria for pairs, diagnosing FGR in extensive studies is often challenging. Consequently, SGA is often used as an essential parameter for FGR diagnosis (20, 21). Although FGR is commonly associated with severe adverse outcomes in preterm infants, most neonates born with a birth weight below the 10th centile are structurally small but healthy, whereas a considerable proportion of fetuses with pair failure have a birth weight above the 10th centile (22). (Sheibani and colleague in a historical cohort study on 8460 cosecutive pregnant women recruited for chromosomal abnormalities screening within the first trimester at fertility infertility and perinatology research center in ahvaz joundishapor university of medical sciences between april 2014 and april 2015 showed that measuring the serum level of MOM PAPP-A during the first trimester can be a valuable marker for predicting adverse outcomes of pregnancy such as SGA PE and abortion. The best cutoff value for this marker to predict the outcome is 0.3 in pregnant Iranian women(23

Therefore, using birth weight charts to demonstrate the risk of severe adverse outcomes in preterm infants has no theoretical basis (16, 23).

A study reported weak clinical application of charts to identify weak adverse outcomes in preterm infants, without unit cut-offs, to distinguish between low- and high-risk adverse outcomes (24). Although birth weight charts and reference curves have been extensively examined and compared, little attention has been paid to the thresholds used to define FGR (23, 24), and studies on severe adverse outcomes of preterm infants are limited, particularly in terms of the weight percentile in relation to FGR. Although various studies have shown that very low birth weight (VLBW) fetuses are at risk for adverse perinatal and neonatal outcomes and pose a risk to the mother, these outcomes have been investigated primarily in fetuses with FGR associated with gestational age at birth. In addition, most studies have examined babies with a birth weight less than the 10th centile, and adverse outcomes in infants with a weight less than the first centile have not been investigated separately. Therefore, this study aimed to investigate maternal and neonatal outcomes and consequences in fetuses with a weight less than the first centile.

Materials and Methods:

The present study investigated the maternal and neonatal outcomes in fetuses with a birth weight of less than the first centile.

This study extracted data from the IMAN system from 62 mothers with babies weighing less than the first centile at Imam Khomeini Hospital. Maternal characteristics, including maternal age, weight, height, and BMI at the beginning of pregnancy, parity, delivery method, screening results, Doppler, and maternal complications during delivery, were collected and recorded through a questionnaire. Additionally, neonatal characteristics, complications, and maternal status were evaluated up to 28 days after delivery. Finally, the collected data were subjected to statistical analysis. The inclusion criteria for the study were fetuses with a weight below the first centile, singleton pregnancies, and complete information available in medical records, including baseline characteristics and maternal and neonatal outcomes. Exclusion criteria included twin or multiple pregnancies and incomplete information available in the patient's medical records.

The gestational age was determined based on the crown-rump length (CRL) measurement on the initial ultrasound (before week 12 of pregnancy). The fetal weight was calculated using the Hadlock formula (HC-AC-FL) based on biparietal diameter, head circumference (HC), abdominal circumference (AC), and femur length (FL) measurements (25). The fetal weight centile was estimated by ultrasound based on WHO criteria (26). Pregnancy complications, including gestational diabetes mellitus (GDM), hypertensive pregnancy disorders (including gestational hypertension, chronic hypertension, pre-eclampsia, and eclampsia), maternal anemia, oligohydramnios, IUGR, stillbirth, and reasons for termination of pregnancy were investigated and recorded. GDM was defined according to WHO criteria as any degree of glucose intolerance first recognized during pregnancy (at any time during pregnancy) (27). Pregnancy-induced hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after week 20 of pregnancy in women without previous hypertension, confirmed by at least two blood pressure measurements taken at an interval of 4-6 hours. Pre-eclampsia was defined as pregnancy-induced hypertension accompanied by end-organ damage (28). HELLP syndrome was defined as hemolysis, elevated liver enzymes, and low platelets (<150,000/μL) (28).

IUGR was defined based on the estimated fetal weight in ultrasound evaluation when the fetal weight was below the tenth centile compared to gestational age, accompanied by evidence of pathophysiology, especially abnormal Doppler (29). Fetal demise and placental abruption were diagnosed by assessing patient symptoms, including bleeding and pain, ultrasound evaluation, and fetal monitoring. Stillbirth was diagnosed based on ultrasound results or delivery of a dead fetus after 20 weeks of gestation (30).

Perinatal outcomes included an Apgar score of less than or equal to 7 at 5 minutes after birth, Arterial Blood Gas (ABG) on admission to NICU, neonatal anomalies, neonatal status at NICU discharge, length of NICU stay, and other major short-term neonatal complications such as respiratory distress syndrome (RDS), sepsis, meconium aspiration syndrome (MAS), hypothermia (body temperature less than 36.5 °C),

hypoglycemia (blood glucose <70 mg/dL), hypocalcemia (total serum calcium level <8 mg/dL in term infants or <7 mg/dL in preterm infants), thrombocytopenia (platelet count less than 150 × 109/L), polycythemia (central venous hematocrit ≥65% or hemoglobin level above 22 g/dL) (24, 56), and hyperbilirubinemia (total bilirubin >15 mg/dL). The sex of the neonate and birth weight were also recorded. Diagnosing neonatal complications such as RDS and neonatal infections was based on clinical and laboratory findings, chest radiographs, blood cultures, and white blood cell counts. Mortality within the first 28 days after birth was defined as neonatal mortality.

Statical analysis:

Quantitative variables were described using mean ± SD. The qualitative variables were characterized using frequency and percentage. For qualitative variables, frequency and percentage were used to depict the characteristics of the data. The normality of the data was verified using the Kolmogorov-Smirnov test, and the homogeneity of variances was assessed using Levene's test. The independent samples t-test and the chi-square test were employed to compare the quantitative and qualitative variables between the two groups. Statistical analyzes were performed using SPSS software version 22 (SPSS Inc., Chicago, IL, USA). The significance level for all tests was set at 0.05.

Results:

Maternal Characteristics and outcomes:

This study examined 62 pregnant women with a fetal weight below the first centile. The mothers' mean age, weight, and BMI were 30.28±5.71 years, 71.25±13.62 kilograms, and 27.76±4.45, respectively. Most mothers were housewives (n=46, 74.19%) and nulliparous (n=38, 61.28%). A history of abortion was present in 12.90% (n=8) of the mothers. In terms of gravida, 38 mothers (61.28%) were gravida 1, 17 mothers (27.42%) were gravida 2 to 3, and 9 mothers (11.29%) were gravida four or more. None of the mothers in this study had achieved pregnancy by in vitro fertilization (IVF). Furthermore, the mean gestational age at delivery was 35.17 ± 5.211 weeks (29-41 weeks). (Table 1).

Table 1. The primary characteristics of the investigated mothers

Maternal characteristics	Variables	Results
Age (year) (Mean ± SD)	-	30.28 ± 5.71
Weight (kg) (Mean ± SD)	-	71.25 ± 13.62
BMI (Kg/m^2) (Mean ± SD)	-	27.76 ± 4.45
Gestational age at delivery (Mean ± SD)	-	35.17 ± 5.21
Mother's occupation n (%)	Housewife	46 (74.19)
	Employee	7 (11.29)
	Student	3 (3.84)
	Freelance job	6 (9.68)
Gravida n (%)	1	38 (61.28)
	2-3	17 (27.42)
	≥4	9 (11.29)
Parity n (%)	Nulliparous	38 (61.28)
	Multiparous	24 (38.71)
History of abortion n (%)	-	8 (12.90)
IVF n (%)	-	0 (0)

In this study, the prevalence of hypertensive disorders in pregnancy was observed in 22.58% (n=14) of pregnant mothers with a fetal weight less than the first centile, including 16.13% (n=10) of pre-eclampsia (7 cases of severe pre-eclampsia), 4.84% (n=3) of HELLP syndrome, and 1.61% (n=1) of gestational hypertension (Table 2).

In this study, all mothers were diagnosed with IUGR (100%, n=62). Moreover, the IUGR stage at the delivery time was mainly stage II (n=52, 83.87%). Other adverse pregnancy outcomes included gestational diabetes mellitus in 17.74% (n=11), placental abruption in 11.29% (n=7), anemia in 8.06% (n=5), and oligohydramnios in 19.35% (n=12) of pregnant mothers. Fetal anomalies and stillbirth were also observed in 3 cases each (4.84%) (Table 2).

In this study, Doppler ultrasonography was performed in only 35 of the studied mothers at 20 weeks of gestation, and abnormal uterine artery (UA) Doppler indices were observed in 15 (42.85%) cases. Additionally, there were no cases of maternal mortality in the studied mothers. Additionally, the delivery method was the cesarean section in 82.26% of the mothers (n=51) and vaginal delivery in 17.74% (n=11). Preterm delivery (before 37 weeks) was observed in 45 cases (72.58%) and term delivery in 17 cases (27.42%). After 28 days postpartum, hypertension was observed in 4 cases (6.45%), heart failure in 2 cases (3.23%), and anemia in 3 cases (4.84%) of the studied mothers (Table 2).

Table 2. Examining the frequency of pregnancy complications in the investigated mothers

Pregnancy complications	Variables	N (%)
Hypertensive disorders	Total	14 (22.58)
	Pre-eclampsia	10 (16.13)
	HELLP syndrome	3 (4.84)
	Gestational hypertension	1 (1.61)
Gestational diabetes mellitus	-	11 (17.74)
Placental abruption	-	7 (11.29)
Anemia	-	5 (8.06)
Oligohydramnios	-	12 (19.35)
IUGR stage at the time of delivery	Stage I	10 (16.13)
	Stage II	52 (83.87)
Doppler ultrasonography	abnormal uterine artery	15 (42.85)
Fetal anomalies	-	3 (4.84)
Stillbirth	-	3 (4.84)
Method of delivery	Cesarean section	51 (82.26)
	Vaginal delivery	11 (17.74)
Time of delivery	Preterm	45 (72.58)
	Term	17 (27.42)
Condition of mothers 28 days after delivery	Hypertension	4 (6.45)
	Heart failure	2 (3.23)
	Kidney failure	0 (0)
	Anemia	3 (4.84)

Neonatal characteristics and outcomes:

The mean birth weight of neonates was 1464.70 ± 407.30 grams (850-2560 grams). The distribution of birth weight below the first centile is presented in Figure 1. The gender distribution of the fetuses revealed that the cohort consisted of 29 female neonates (46.77%) and 33 male neonates (53.23%). Eight neonates (13.56%) had an Apgar score ≤ 7 at 5 minutes post-birth. The ABG test was performed on 47 neonates. The mean PCO2 was 31.75 ± 8.26 mmHg, and the mean HCO3 was 19.7 ± 3.21 mEq/L. Moreover, among the 47 neonates with ABG results, three neonates (6.38%) had a pH < 7.25, and 18 neonates (38.30%) had low PO2 (Table 3).

Table 3. The primary characteristics of babies with a weight below the first centile

Infant Characteristics	Variables	Results
Sex (n=62) n (%)	Female	29 (46.77)
	Male	33 (53.23)
Birth weight (grams) (Mean ± SD)	-	1464.70 ± 407.30
Apgar score ≤ 7 at 5 minutes n (%)	-	8 (13.56)
ABG (n=47)	pH < 7.25	3(6.38)
	PCO_2, mmHg (Mean ± SD)	31.75 ± 8.26
	HCO_3, mEq/liter (Mean ± SD)	19.7 ± 3.21
	Low PO_2*	18 (38.30)

* Less than 45 mmHg in preterm babies and less than 50 mmHg in term babies

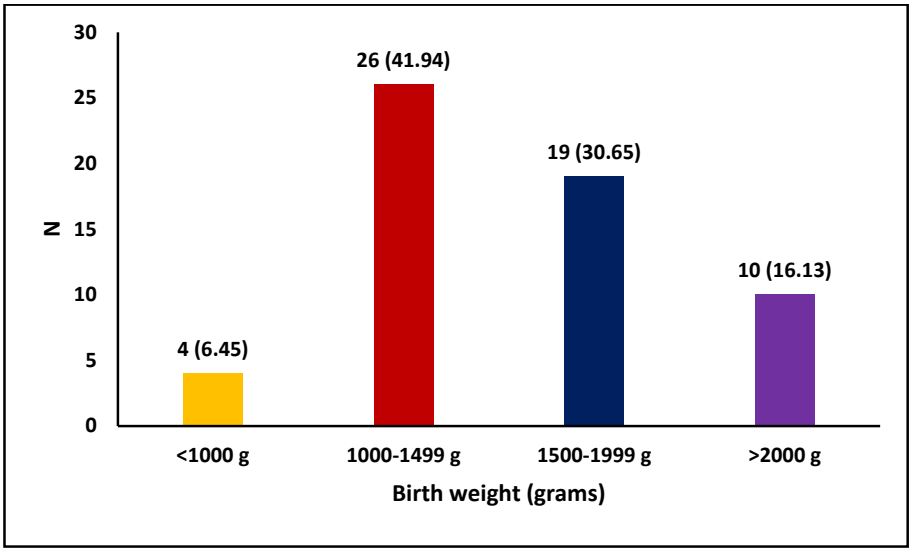

Figure 1. Frequency distribution of birth weight with weight below the first centile

The overall hospitalization rate of neonates in the NICU was 84.75% (n=50). Additionally, the mean stay in the NICU was 14.6 ± 33.33 days (4-56 days). Respiratory distress syndrome (RDS) was observed in 42.37% (n=25) of the neonates with a weight less than the first centile. Moreover, 38.98% (n=23) of the neonates required positive airway pressure (CPAP), and 45.76% (n=27) needed ventilatory assistance (Table 4).

The outcomes of neonates with weight less than the first centile included hypoglycemia in 37.29% (n=22), hypothermia in 32.20% (n=19), hyperbilirubinemia in 30.51% (n=18), MAS in 28.81% (n=17), hypocalcemia in 27.12% (n=16), polycythemia in 25.42% (n=15), thrombocytopenia in 11.86% (n=7), anemia in 8.47% (n=5), and neonatal sepsis in 6.78% (n=4). Finally, the rate of neonatal anomalies detected in the NICU was 8.47% (n=5), and the neonatal mortality rate was 11.86% (n=7) (Table 4).

Table 4. Outcomes of infants with weight below the first centile

Infant complications	Variables	N (%)
hospitalization in the NICU	-	50 (84.75)
Baby's condition during hospitalization	Respiratory distress syndrome (RDS)	25 (42.37)
	needed Ventilatory assistance	27 (45.76)
	required positive airway pressure (CRAP)	23 (38.98)
Negative neonatal outcomes	Sepsis	4 (6.78)
	meconium aspiration	17 (28.81)
	Hypoglycemia	22 (37.29)
	Hypocalcaemia	16 (27.12)
	Hyperbilirubinemia	18 (30.51)
	Hypothermia	19 (32.20)
	Polycythemia	15 (25.42)
	Thrombocytopenia	7 (11.86)
	Anemia	5 (8.47)
neonatal anomalies	Heart disease	4 (6.76)
	Hypospadias	1 (1.69)
neonatal mortality	-	7 (11.86)

In the present study, no significant differences were observed in the incidence of adverse neonatal outcomes based on neonatal gender (P > 0.05). Women with hypertensive disorders during pregnancy, including pre-eclampsia, were more likely to have infants with lower birth weight compared to women without hypertension (P < 0.0001) (Table 5).

Table 5. Comparison of the birth weight based on the mother's hypertensive disorders during pregnancy

Variable	Hypertension during pregnancy (n=14)	without gestational hypertension (n=48)	P-value*
Birthweight (gr)	1321.16 ± 329.37	1608.23 ± 485.23	<0.0001

* Independent sample t-test

Discussion:

Changes in intrauterine growth can increase the risk of adverse perinatal outcomes. Therefore, proper and timely identification of this disorder is crucial (31, 32). The present study showed a high prevalence of adverse perinatal outcomes in infants with a birth weight below the first centile. Specifically, the prevalence of hypertensive disorders during pregnancy was 22.58% (n=14) in pregnant women with fetuses weighing less than the first centile, including 1 case of pregnancy-induced hypertension, 10 cases of pre-eclampsia, and 3 cases of HELLP syndrome. Furthermore, gestational diabetes mellitus was observed in 11 cases (17.74%), placental abruption in 7 cases (11.29%), anemia in 5 cases (8.06%), and oligohydramnios in 12 cases (19.35%). Fetal anomalies were observed in 3 cases (4.84%), and most deliveries were cesarean section (82.26%). Abnormal Doppler was observed in 42.85% of the studied mothers. Preterm delivery (before 37 weeks) was observed in 45 cases (72.58%). Perinatal death was observed in 10 cases, including three stillbirths (4.84%) and seven neonatal deaths (11.86%).

The study findings demonstrate restricted intrauterine growth in all studied mothers, indicating that fetal weight below the first centile increases the risk of IUGR and other adverse neonatal outcomes. Furthermore, preterm birth and its associated complications are highly probable in these infants, as many of the human fetal systems and organs are immature before the 37th week of gestation. Premature delivery challenges infant survival outside the uterine environment, mainly due to respiratory problems (33).

The adverse outcomes of neonates born with a birth weight below the first centile include RDS with an incidence of 42.37% (n=25), hypoglycemia in 37.29% (n=22), hypothermia in 32.20% (n=19), hyperbilirubinemia in 30.51% (n=18), MAS in 28.81% (n=17), hypocalcemia in 27.12% (n=16), polycythemia in 25.42% (n=15), thrombocytopenia in 11.86% (n=7), anemia in 8.47% (n=5), neonatal sepsis in 6.78% (n=4), and an Apgar score of ≤ 7 at 5 minutes after birth in 13.56% (n=8) of the cases. The hospitalization rate in the NICU was 84.75% (n=50), with 38.98% (n=23) of neonates requiring CPAP and 45.76% (n=27) requiring Ventilatory assistance. The rate of neonatal anomalies discovered in the NICU was 8.47% (n=5), and the rate of neonatal mortality was 11.86% (n=7).

Infants with SGA infants have a significantly higher incidence of morbidity and mortality and risk developing long-term complications throughout their life (34). In the current study, hypoglycemia and hyperbilirubinemia were among the most common complications observed in preterm infants with a birth weight below the first centile. SGA infants may face low liver glycogen stores, high glucose utilization from disease stress, and/or unstable glucose metabolism, leading to hypoglycemia. Therefore, despite the possibility of hypoglycemia being resolved as the infant grows, precise monitoring of the infant's blood glucose levels is crucial to prevent complications resulting from hypoglycemia. SGA fetuses are also at risk of exposure to a relatively hypoxic environment, which may lead to compensatory erythropoiesis and/or acidosis, ultimately resulting in hyperbilirubinemia (35, 36). In addition, the high demand for infant hospitalization for extended periods is also related to the severity of their morbidity, as reported in other studies.

Infants with IUGR and SGA are also at a high risk of developing polycythemia, as reported in other studies (37). Giri et al. also reported a three-fold increase in the risk of polycythemia in infants with SGA compared to those with average weight (37). Polycythemia, defined as venous hematocrit > 65%, occurs as a response to intrauterine hypoxia. Polycythemia leads to alterations in blood flow in some organs, which can lead to severe complications (38).

In Tsai et al. (39) and Gidi et al. (37) studies, the most common adverse outcome of neonatal SGA was RDS (45.8% and 38.5%, respectively). Findings regarding the effect of IUGR and SGA on RDS are conflicting (37, 40). In some studies, the risk of RDS in SGA neonates was not significantly different from that of neonates with appropriate weight for gestational age (37, 41). This difference in neonatal outcomes in SGA infants may be due to differences in the timing of fetal distress, the severity of FGR, and the degree of cardiovascular adaptation (42).

In the current study, the sex distribution of 62 infants was examined, and it was found that the male infants were slightly more frequent than the female infants (53.23% and 46.77%, respectively). This finding is consistent with the results of the Joiya study, which reported a higher frequency of male infants among those classified as SGA (56.1%) (43). Similarly, a higher frequency of male infants was also observed in the Dey et al. study, which investigated 200 infants with SGA (57%) (44).

Consistent with previous studies (45, 46), the present study found that most women with fetuses weighing less than the first centile at birth were primiparous. In the study by Kozuki et al., nulliparity was also identified as an 80-fold increased risk factor for delivering an SGA infant (47).

In the study by Lubrano et al., it was observed that primiparous mothers had a higher prevalence of fetuses with FGR and SGA (72.5% and 63%, respectively). These infants had higher rates of cesarean delivery (72% and 18%), NICU admission (64% and 11%), jaundice (38.6% and 6.4%), anemia (28% and 0%), hypoglycemia (13% and 9.7%), RDS (42% and 1.6%), need for assisted ventilation (46% and 2.3%), sepsis (8.3% and 0%), and fetal death (0.8% and 0%). Furthermore, acidosis (pH less than 7.1 and increased lactate) was observed in 0.8% and 4.8% of cases, respectively (48).

Joiya et al. study revealed that most mothers with infants suffering from SGA were primiparous, accounting for 61.1% of the cases, with a prevalence of anemia and hypertension of 48.8% and 61.8%, respectively. The most frequent neonatal complications observed were perinatal asphyxia (63.7%), MAS (51%), polycythemia (47.1%), thrombocytopenia (41.4%), hypothermia (37.6%), hypocalcemia (32.5%), and hypoglycemia (24.2%). Furthermore, this study identified maternal hypertension, primiparity, short interpregnancy interval, and anemia as risk factors for the development of SGA (43).

In a study by Liu et al., maternal risk factors for neonates with SGA were reported to include pregnancy-related hypertension (21%), placental abruption (8.8%), abnormal amniotic fluid (31.5%), and anemia (4.9%). In comparison, adverse neonatal outcomes included asphyxia (22.6%), congenital malformations (14.36%), hypoglycemia (21.5%), hypoxic-ischemic encephalopathy (25.4%), RDS (16.1%), pneumonia (38.1%), hyperbilirubinemia (36.3%), and sepsis (2.7%) (49). In a study by Dey et al., the most common neonatal complications for SGA neonates included perinatal asphyxia (65.5%), sepsis (54%), jaundice (42.0%), hypothermia (31%), and hypoglycemia (25%) (44).

In the Kamphof et al. study, severe adverse outcomes in neonates with SGA were more common in the group with a birth weight below the third centile than those below the 5th and 10th centiles. The most common adverse outcomes were asphyxia, sepsis, respiratory disorders, the need for Ventilatory assistance, and perinatal death (24). Other studies have also reported hypertensive disorders in pregnancy and pre-eclampsia as risk factors for FGR (50). In the Afaya study, adverse outcomes in LBW neonates (birth weight less than 2500 grams) included hypertensive disorders in pregnancy (12.4%), pre-eclampsia (22.4%), PROM (the premature rupture of membranes) (87.1%), gestational age less than 37 weeks (29.5%), and an Apgar score of less than seven at 5 minutes (24.1%) (51). The Mitao study also reported a significant association between low Apgar scores 5 minutes after birth and low birth weight (LBW) neonates (52).

In the study by Desta et al., neonates with LBW were found to have an increased risk of adverse outcomes, including preterm birth (72.9%), antenatal anemia (18.6%), low Apgar score (42%), NICU admission (22.6%), and neonatal death (19.3%). Maternal risk factors included hypertensive disorders during pregnancy (37.1%) and a history of miscarriage (20.9%), while pregnancy complications were observed in 65.7% of mothers, and the stillbirth rate was 35.4% (33).

In Ramos et al.'s study, neonatal outcomes were investigated in pregnancies with FGR (fetal weight below the 10th centile), demonstrating hypertensive disorders, including chronic hypertension in 10.9%, pre-eclampsia in 9%, and gestational hypertension in 7.3% of pregnant women. The study observed adverse health outcomes in newborns, including an Apgar score of less than seven at 5 minutes in 11.1% of cases, RDS in 24.1%, transient tachypnea of the newborn (TTN) in 11.1%, need for ventilatory assistance in 17%, and hypoglycemia in 35.2%. Half of the newborns were also admitted to the neonatal intensive care unit (NICU) (53).

In Gidi et al.'s study, neonatal outcomes of SGA infants were evaluated, and the results showed that hypoglycemia (28.6%), hyperbilirubinemia (29.34%), asphyxia (7.18%), polycythemia (6.43%), RDS (38.5%), sepsis (43.3%), and mortality (7.6%) were the most common complications. Furthermore, 84.4% of the infants were hospitalized for a prolonged period (more than 21 days). Pregnancy complications were observed in 43.4% of cases, including hypertensive disorders during pregnancy (37). Boghossian's study reported that SGA infants are at increased risk for preterm birth and RDS (54). Furthermore, in Tsai et al.'s study, 62.5% of mothers with SGA infants were primiparous, and the most common adverse neonatal outcomes were respiratory distress syndrome (45.8%), intraventricular hemorrhage (IVH) (41.3%), and neonatal death (21.3%). Additionally, SGA infants have been reported to have an increased risk of morbidity and mortality associated with VLBW infants (39). In the study by Chaudhary et al., adverse pregnancy outcomes in infants with SGA included hypertensive disorders during pregnancy (14.5%), gestational diabetes (10.0%), oligohydramnios (43.7%), and anemia (56.3%) (55). Another study reported a high incidence of hypothermia, hypoglycemia, and the need for NICU hospitalization and oxygen therapy in SGA infants, even after excluding perinatal complications such as pregnancy-induced hypertension and IUGR (45).

The present study revealed a higher incidence of certain neonatal complications than in previous studies, attributable to the lower birth weight of the study infants (less than the first centile weight) and the existence of IUGR in all studied mothers. However, the lack of separate examination of maternal and neonatal outcomes in infants weighing less than the first centile precludes accurate comparison of the findings with those of other studies. Consequently, the higher prevalence of neonatal complications in this study should be interpreted with caution and needs further investigation in future studies focusing on infants with extremely low birth weight.

It is well established that newborns with LBW at any gestational age are associated with an increased risk of morbidity and mortality. However, the threshold at which this risk increases significantly is unclear (56). Asher and McLean suggested that fetal growth standards should be based on the mean weight for gestational age, thus limiting infants who are small for gestational age (SGA) to the 3rd centile weight at birth rather than the 10th centile (57). Furthermore, in a population-based study by McIntire et al. (1999), the most significant complications were reported in infants <3rd centile weight. Specifically, intrapartum uterine resuscitation grade 3 or 4 occurred in 3.2% of infants, respiratory distress requiring ventilation in 22.5%, and neonatal death in 6.9% of infants with birth weight <3rd centile. Additionally, these complications were more than twice as high in infants with weight <3rd centile compared to other infants (56). In the study by Jain et al., neonates with a birth weight below the third centile were at high risk of adverse outcomes,

including hypoglycemia (14.3%), MAS (5%), pulmonary hemorrhage (1.9%), polycythemia (9.3%), jaundice requiring treatment (55.4%), RDS (3.3%), TTN (9.1%), and in-hospital mortality (3.5%). Furthermore, adverse outcomes in neonates with severe SGA (birth weight below the third centile) were more than twice as high as those of neonates with moderate SGA (birth weight between the 3rd and 10th centiles) (58). Furthermore, Ludvigsson et al. demonstrated in a population-based study in Sweden that SGA, particularly severe SGA (birth weight below the third centile), is associated with an increased risk of infant mortality, with the highest estimated risk for death due to infection and neurological disease (59). These results indicate that neonates with severe SGA (birth weight below the 3rd centile) should be closely monitored to mitigate the high risk of neonatal complications.

In the study conducted by Madden et al., the negative consequences of neonatal SGA were examined in two groups of term infants with birth weights less than the fifth centile and between the 5th and 10th centiles. The findings revealed perinatal mortality, including stillbirth and neonatal death, perinatal morbidity comprising severe acidosis at birth, Apgar scores less than three at 5 minutes postpartum, and RDS and NICU hospitalization were significantly higher in the two studied groups. Moreover, all severe neonatal complications were significantly more frequent in the group with a birth weight less than the fifth centile compared to the group with a birth weight between the 5th and 10th centiles. Only stillbirth did not differ significantly between the two groups. Additionally, nulliparity was higher in the two studied groups (62.8% and 57.6%, respectively) (60). Furthermore, the study by Desta et al. revealed a significant correlation between perinatal outcomes and birth weight in infants with LBW, where neonates with lower birth weight had a higher probability of neonatal complications, hospitalization at the NICU, low Apgar scores, and mortality (33).

In the current study, a higher incidence of hypertensive disorders in pregnancy, specifically pre-eclampsia, was observed in neonates with a birth weight below the first centile. Furthermore, women with hypertensive disorders in pregnancy, including pre-eclampsia, exhibited a significant association with lower birth weight neonates compared to normotensive controls.

The causes and pathogenesis of SGA have not been fully identified, and the identified risk factors have varied in different studies. In previous studies, pregnancy-induced hypertension has been recognized as an essential risk factor for SGA, negatively affecting uterine fetal growth and development (49, 61). Evidence confirms that high blood pressure caused by pregnancy leads to trophoblastic invasion into spiral arteries that provide nutrients to the fetus, resulting in reduced blood supply (62, 63). This reduction in uteroplacental blood flow leads to a decrease in oxygen and nutrient supply to the fetus, resulting in a decrease in fetal weight compared to gestational age (SGA), preterm birth, and IUGR, predisposing the infant to low birth weight (62).

Gidi et al. (37) and Boghossian et al. (54) reported that hypertensive disorders in pregnancy could lead to SGA. Also, in Desta et al. study, hypertensive disorders in pregnancy were associated with the birth of LBW infants (33). In a population-based cohort study of 16,936 pregnant women in China, the birth weight of infants in mothers with hypertensive disorders in pregnancy (pregnancy-induced hypertension and pre-eclampsia) was significantly lower than that of mothers without hypertension (64). In another study by de los Reyes et al., the prevalence of hypertensive disorders in pregnancy with SGA infants was 21.3%, and low maternal weight, malnutrition, and increased uterine artery Doppler indices were identified as risk factors for SGA. The study also reported a high prevalence of hypertensive disorders (21.3%) during pregnancy with SGA infants, and hypertensive disorders during pregnancy were identified as one of the risk factors for giving birth to infants with SGA (65). Previous investigations have established a significant correlation between hypertensive disorders during gestation and the delivery of neonates with LBW (52, 66). This association suggests that hypertension results in impaired uteroplacental function.

In the current investigation, the pH levels of most infants were within the normal range, which indicates the suitability and timeliness of the delivery method (48). Additionally, ABG outcomes at birth indicated that infants weighing less than the first centile had reduced bicarbonate (acidosis) and arterial blood oxygen levels (hypoxemia) due to secondary fetal growth limitation. Hypoxia causes anaerobic glycolysis, leading to lactic acid production. Since secondary FGR is linked to incomplete vascular growth and uteroplacental blood flow deficiency, it results in a decline in fetal access to oxygen and nutrients, ultimately reducing growth (67). Neonates with SGA are at a high risk of IUGR, and IUGR under hypoxic conditions causes acidosis (68). Hypoxia also results in cardiovascular and metabolic adaptations in fetuses that lower the metabolic rate, and due to the limited availability of oxygen, there is a decrease in glucose utilization relative to transferred glucose (69). These circumstances increase the likelihood of fetal cardiovascular and metabolic disorders in the intrauterine milieu (70, 71).

Although the small fetal size does not necessarily indicate pathology, it places the fetus at increased risk of adverse outcomes. FGR warrants clinical management (72), but diagnosing fetuses with SGA remains challenging, with no gold standard. Although standard charts are recommended to detect changes in fetal growth, their performance is poor in predicting short-term adverse outcomes for at-risk SGA neonates (73).

Overall, adverse neonatal outcomes associated with prematurity and growth restriction are consistent with the findings of other studies, which indicate that gestational age and birth weight plays a crucial role in reducing adverse neonatal complications (48).

The reason for some differences in results and the prevalence of adverse outcomes can be attributed to differences in the characteristics of the study sample, differences in methodology, definitions, and cut-offs for various parameters, as well as differences in the socio-economic level of individuals. Moreover,

variations in the findings could be attributed to dissimilarities in the attributes of the research sample since ethnicity has also been identified as a risk factor for SGA (74).

Additionally, differences in the occurrence of neonatal outcomes may be due to the multifactorial nature of these outcomes, the cause of SGA and the severity of FGR, the duration of in-utero hypoxia, and differences in other maternal risk factors and the characteristics of the study population. Maternal age during delivery may also affect physiological changes and adaptation to the extrauterine environment (37). Furthermore, the target population in the present study consisted of fetuses with a birth weight below the first centile, while most studies were conducted on infants with SGA (birth weight below the 10th centile), and a small number were also conducted on infants with severe SGA (birth weight below the third centile). Additionally, some studies were only conducted on term SGA infants, while our study had a high percentage of preterm deliveries. Therefore, more longitudinal studies are recommended, and standard definitions for various outcomes are considered.

The present study faced several limitations that should be considered. First, the data were collected retrospectively, increasing the possibility of bias in the results. Additionally, the study was limited to a single healthcare center, and the generalization of the results to the entire population of pregnant women and neonates should be made with caution. Furthermore, due to the retrospective nature of this study, it was not possible to investigate the impact of some factors related to SGA birth, such as maternal education level, smoking and alcohol consumption by the mother, maternal dietary habits during pregnancy, use of iron and folic acid supplements, and maternal mental health. In addition, this study did not assess the impact of perinatal health care, gestational weight gain, and primary neonatal mortality. The small sample size was another limitation of this study. Conducting further studies with larger sample sizes and in a multicenter setting could lead to better results.

Conclusions:

The present study revealed a high incidence of adverse maternal and neonatal outcomes in fetuses with a birth weight less than the first centile. The most frequent maternal adverse outcomes observed were hypertensive disorders during pregnancy, while the most common perinatal complications included RDS, hypothermia, and hyperbilirubinemia. Additionally, a high rate of preterm births and NICU admissions were observed. Furthermore, the majority of the studied mothers were nulliparous. Therefore, prompt recognition of LBW fetuses, a high index of suspicion, screening for complications associated with this condition, and timely intervention can prevent neonatal complications. Based on the study findings, it is recommended to conduct regional assessments to determine the incidence and risk factors of neonates with a birth weight below the first centile. These results can be valuable for physicians, healthcare professionals, and health policymakers in managing and implementing the necessary measures to mitigate the health risks of both the mother and the neonates.

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Conflicts of Interest:

The authors report that this study has no competing or conflict of interest.

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Ethics statement:

This study was carried out after obtaining a research license from the Research Council and the approval of the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.HGOLESTAN.REC.1401.052). In all stages of this research, the Helsinki Declaration on ethical research and principles of patient confidentiality were considered.

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