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Long-Term Maternal and Neonatal Outcomes Following Birth in Fetal Growth Restricted Pregnancies

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ABSTRACT

Background & Objective: This study aimed to assess maternal and neonatal outcomes in cases of Intrauterine Growth Restriction (IUGR). Understanding these outcomes is vital for early identification of potential adverse effects and facilitating prompt intervention and management.

Materials & Methods: This retrospective cohort study focused on mothers whose fetuses experienced IUGR at Imam Khomeini Hospital in Ahvaz, Iran, between March 2021 and 2022. Data on neurodevelopmental and clinical aspects were collected periodically up to 24 months' post-birth, encompassing various parameters such as infant age, gender, developmental and motor coordination disorders, neurodevelopmental status, medical and speech disorders, and maternal health during pregnancy.

Results: Over a one-year period, 80 breastfed infants were studied. At 6, 12, and 24 months after birth, 30% of children showed growth disorders. Boys had a slightly higher percentage of growth arrest (76.4% vs. 63.2%, P>0.05). Growth retardation was present in 13.16% of girls, compared to none of the boys. The most common medical outcomes were asthma and orthopedic disorders (5% each). Developmental disorders and motor disorders were the most common neurological and developmental outcomes, each affecting 11.25% of children. During pregnancy, 16.25% had gestational diabetes, 17.5% had hypertension, and 10% had hypothyroidism, which decreased to 6.25%, 11.25%, and 3.75%, respectively, after childbirth.

Conclusion: The present study indicates a significant prevalence of growth and developmental disorders, as well as medical outcomes such as asthma and orthopedic issues at the age of two in infants with IUGR. Mothers of these infants also faced significant postpartum issues, such as diabetes and hypertension.

Keywords: Fetal Growth Retardation, Growth Curves, Pregnancy Outcome, Mothers, Child

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Introduction

Fetal growth restriction (FGR) refers to a situation where a fetus fails to achieve its inherent growth potential, leading to an elevated risk of severe complications in both the short and long term (1). This condition is prevalent in 5-10 % of pregnancies, with placental insufficiency being the most common underlying cause (2). Due to the diverse underlying causes and presentations of FGR, and lacking a gold standard, the disorder could be aptly termed the placental insufficiency syndrome (3).

Small for Gestational Age (SGA) is frequently defined as infants whose birth weight falls below 10% of the community's average weight for that gestational age (4). Utilizing SGA in studies as a proxy for FGR is common, given the clear-cut threshold represented by the p10 cutoff. However, it is crucial to interpret the results cautiously, recognizing that there may be an underestimation of the actual effect (1).

Approximately 21% of neonatal deaths in Low- and Middle-Income Countries (LMICs) result from infants being small for their gestational age (5). SGA poses a public health concern, linked to increased neonatal and post-neonatal (29–365 days after birth) mortality (5, 6). SGA infants face higher risks of post-natal infections due to compromised immune function as peripheral T and B lymphocytes decrease at birth in SGA patients due to stress-induced erythropoiesis, although T lymphocyte numbers normalize later in childhood, their proliferative potential does not (7). In LMICs, SGA infants are 2.32 and 2.36 times more likely to experience stunting and wasting compared to those born with an adequate size for gestational age (8).

impact of SGA on growth and development can have long-term consequences, potentially leading to lower mental and cognitive performance in adulthood **(9)**. Hypoglycemia is common in SGA infants, and the risk of hypoglycemia increases with the severity of SGA due to reduced fat, protein, and glycogen stores. Infants born with SGA are at risk of long-term complications, including chronic kidney disease, coronary artery disease, high blood lipids, and high blood pressure **(10)**.

Intrauterine growth restriction (IUGR) represents a prevalent and intricate obstetric challenge, impacting around 10-15% of pregnant women **(11)**. IUGR increases the risk of intrapartum asphyxia, preterm delivery, and complications associated with prematurity, including respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis. Infants with IUGR are also prone to low Apgar scores, intubation, seizures, sepsis, neonatal death, other morbidities include polycythemia, hyperbilirubinemia, hypoglycemia, and hypothermia **(11, 12)**. Results of the systematic review study showed that mother's age (35%), body mass index (BMI) (25%), preterm childbirth, and diagnosis with a maternal chronic disease (25%) are the most common causes of low birth weight in Iran **(13)**.

The assessment of maternal and neonatal outcomes in cases of IUGR is crucial for identifying potential adverse outcomes and facilitating timely intervention and management. Moreover, healthcare providers can effectively counsel patients, addressing potential challenges, discussing treatment options, and emphasizing the importance of adherence to medical recommendations for optimal outcomes. Furthermore, they can proactively implement preventive measures to minimize the risks associated with IUGR, thereby enhancing overall maternal and neonatal well-being. Hence, this study was conducted to evaluate maternal and neonatal outcomes in patients affected by IUGR.

Methods

The present retrospective cohort study was conducted on mothers with fetuses affected by FGR who were hospitalized at Imam Khomeini Hospital affiliated to Ahvaz University of Medical Sciences, Ahvaz, Iran between March 2021 and 2022.

Exclusion criteria were pregnancies with appropriate neonatal weight for gestational age, fetal malformations or chromosomal abnormalities. Moreover, mothers who had a history of fetuses affected by FGR in their previous pregnancies were also excluded from the study. The definition of FGR has been defined according to diagnostics criteria established by Delphi procedure **(14)**.

After obtaining the ethical approval code of the Ahvaz University of Medical Sciences, in the first visit after obtaining the informed consent of the participants, qualified research personnel gathered neurodevelopmental and clinical information from birth until 24 months after birth (time intervals of: month 6, month 12, and month 24) through interview with mothers and assessing the medical records of the children and entered them into a researcher-made checklist. This information includes neonate age, gender, developmental and motor coordination disorder status, infant's life status, and in case of death includes time and cause of death, neurodevelopmental disorders (seizure, movement disorder, mental disorder, CP), orthopedic disorder (congenital hip dislocation, inguinal hernia), occurrence of medical disorder, speech disorder, hospitalization, IUGR stage in embryonic period, maternal health during pregnancy and child growth curve based on their age range. Postnatal growth failure was defined as either weight or length $<5^{th}$ percentile for age.

Continuous variables were characterized by presenting the mean ± standard deviation (SD), while categorical variables were presented using frequency and percentage. The normality distribution of the quantitative variables was evaluated through the Kolmogorov-Smirnov test. All analyses were performed using IBM SPSS software for Windows (version 22, SPSS Inc., Chicago, IL, USA), and statistical significance was set at a p-value less than 0.05.

Results

In this study, over a one-year period, a total of 80 breastfed infants were included in the study. 38 infants were girls (47.5%), and 42 infants were boys (52.5%). In terms of age, the mean age of mothers was 28.26 ± 5.29 years, ranging from 17 to 40 years. The mean gestational age at delivery time was 32.56 ± 1.39 week (32.67± 1.5 week in postnatal growth failure group vs. 32.29± 1.11 week in the normal group, P=0.55). Three cases of child mortality occurred during the specified period, two due to lung failure and one due to recurrent seizures. Among the examined children, 24 children (30%) exhibited growth disorders at 6, 12, and 24 months after birth. 6 (25%) of neonates in the postnatal growth failure group and 16 (29.63%) of infants in the normal groups were severe IUGR (P=0.675). The trend of weight changes in infants in both groups with growth disorders and normal growth from 6 months to 24 months is shown in Table 1. As observed, children with growth disorders show significantly less significant changes in all age ranges (P <0.001).

Table 1. Trend of weight changes in children with growth disorders and normal growth from 6 to 24 months

Weight	Postnatal growth failure group (N=14)	Normal group (N=66)	P.Value
Birth weight, kg	1.16 ± 0.35	1.91 ± 0.44	<0.001
Weight at month 6, kg	6.21 ± 0.81	8.57 ± 1.01	<0.001
Weight at month 12, kg	7.95 ± 0.74	10.09 ± 0.92	<0.001
Weight at month 24, kg	9.58 ± 0.80	11.37 ± 0.99	<0.001

As observed in Figure 1, the percentage of growth disorders in girls was 21.34% (13 individuals) compared to 19.26% (11 individuals) in boys (P=0.43). The percentage of growth arrest in boys was 76.4% (2 individuals) compared to 63.2% (1 individual) in girls (P>0.05). Growth retardation was reported in 13.16% (5 individuals) of girls, while none of the boys had growth retardation (P<0.001).

The distribution of the frequency of various medical outcomes from 6 to 24 months after birth is illustrated in Figure 2. The most common medical outcomes in infants were asthma and orthopedic disorders (5%), each affecting 4 individuals, while the least frequent medical condition was associated with gastrointestinal disorders, congenital heart failure, and hyperthyroidism, each occurring in one infant.

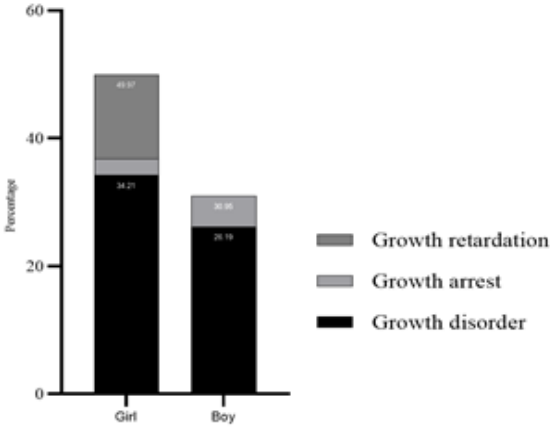


Figure 1. Comparison of growth disorders, growth retardation, and growth arrest by infant gender

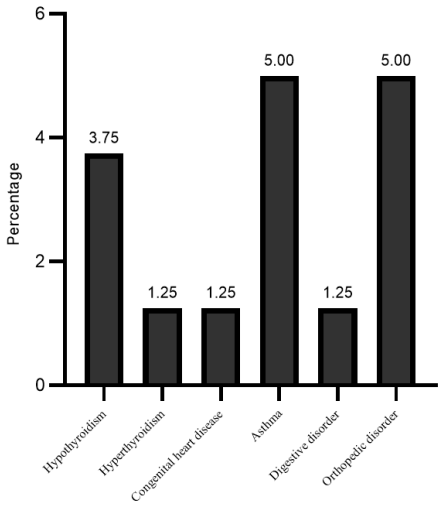


Figure 2. Proportion of various medical outcomes from 6 to 24 months after birth

The distribution of the frequency of various neurological and developmental outcomes from 6 to 24 months after birth is depicted in Figure 3. The most common neurological and developmental outcomes were developmental disorders and motor disorders, each affecting 11.25% of children. Seizures were reported in three children, and one child was reported to have cerebral palsy (CP).

In Figure 4, the ratio of pregnancy outcomes from 6 to 24 months after birth is shown, categorized as overall, improved, and continued postpartum outcomes. As observed, during pregnancy, there were 13 cases (16.25%) of gestational diabetes, 14 cases (17.5%) of hypertension, and 8 cases (10%) of hypothyroidism. However, after childbirth, these values had reduced to 6.25%, 11.25%, and 3.75%, respectively.

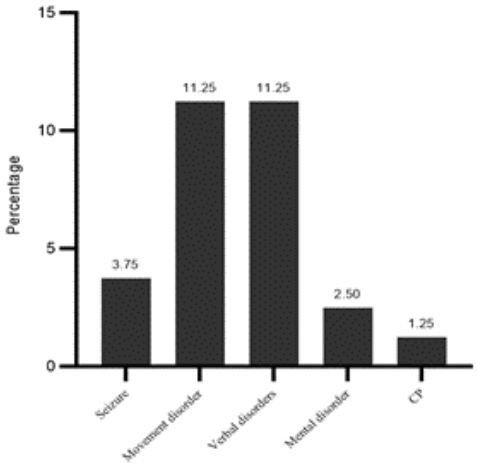


Figure 3. Proportion of various neurological and developmental outcomes from 6 to 24 months after birth

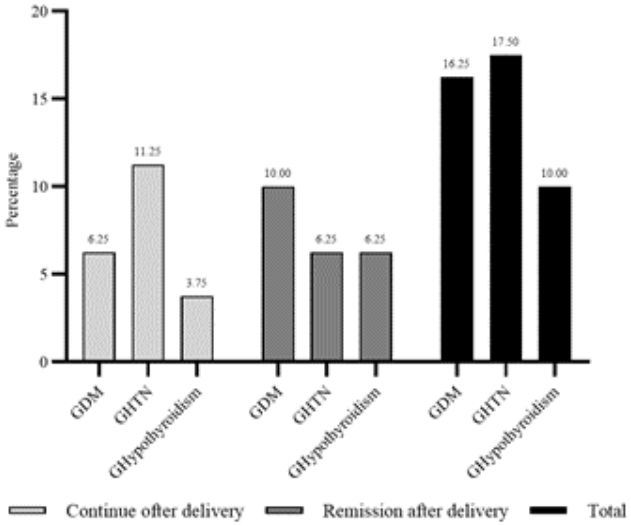


Figure 4. Proportion of pregnancy outcomes from 6 to 24 months after birth, categorized as overall, improved, and continued postpartum

Discussion

The aim of the present study is to investigate the maternal and fetal consequences of FGR in the 6 to 24 months period after birth. The findings of the study indicate that one-third of the children during the 6, 12, and 24 months after birth exhibited growth disorders. The average weight in the group with growth disorders was significantly lower than the normal group during the 6, 12, and 24 months. The prevalence of growth disorders and growth retardation was higher in girls than boys, while the frequency of growth arrest was higher in boys than girls. The most common medical outcomes in infants were asthma and orthopedic disorders (5%). The highest neurological and developmental outcomes were developmental and motor disorders (11.25%). Regarding maternal consequences, during pregnancy, there were 13 cases (16.25%) of gestational diabetes, 14 cases (17.5%) of hypertension, and 8 cases (10%) of hypothyroidism.

However, after childbirth, these values had reduced to 6.25%, 11.25%, and 3.75%, respectively.

The current study provides evidence on the impact of IUGR on the growth status and abnormal development of the brain in infants. Due to different diagnostic methods and varying inclusion and exclusion criteria concerning the relationship between IUGR, and Neurodevelopmental impairment, there are differences among studies **(15, 16)**. In preterm infants with IUGR and severe SGA, there is a reduction in total brain volume, particularly in the cerebral cortical gray matter, which correlates directly with head circumference **(17, 18)**.

Brain maturation and development are associated with retarded motor development skills in infants with severe SGA, leading to retarded motor development **(19)**. A study by Lin, et al. **(20)** investigated the effects of SGA on growth status and neurodevelopmental impairments at the age of two in very low birth weight (VLBW) infants with a gestational age of 24 to 32 weeks. Their growth status indicators, including weight, height, and head circumference, were below the 10th percentile. Their findings demonstrated that SGA increased the chances of birth weight (BW) < 10th percentile, body length (BL) < 10th percentile, and head circumference (HC) < 10th percentile by 25.2, 94.1, and 7.2 times, respectively. It could also elevate the risk of neurodevelopmental impairment by approximately 20%.

Another study by Pirhadi, et al. **(21)** revealed that SGA could increase the chance of developmental delays up to about 90.3 times. In the present study, the frequency of occurrence of movement and verbal disorders was higher than other neurological and developmental issues. Although evidence regarding the relationship between IUGR, and the risk of neurodevelopmental disorders like autism, which impacts the language and behavioral skills of children, was conflicting in terms of direction and strength of the relationship, a meta-analysis summarizing available evidence showed that SGA increased the risk of autism spectrum disorders by 17% **(22)**. An infant under the influence of IUGR constitutes a subset of SGA infants. In other words, SGA serves as a proxy for IUGR. In a study, IUGR infants had smaller growth size and body composition than appropriate for gestational age (AGA) children, but there was no significant difference between SGA and AGA infants **(23)**.

Previous studies suggest that there is no significant difference between IUGR in terms of psychological outcomes. For example, a study by Hartkopf, et al. **(24)** found that although infants with IUGR at the age of two had approximately 4.4 unit's lower mental development scores than infants with SGA, the difference between them was not statistically significant. However, it is important to note that while reduced fetal growth is usually natural, growth delay in IUGR has a pathological basis **(24)**.

In the present study, the most common medical outcome observed in the studied infants was asthma. The association between FGR with reduced pulmonary function and asthma has been demonstrated in previous studies **(25-27)**. However, some studies have also identified preterm birth, but not being small for gestational age, as a risk factor for asthma **(28)**. In the current study, asthma outcomes were examined at the age of two, while previous studies often investigated asthma as a later outcome in older ages. It should also be considered that asthma in mothers is a risk factor for the occurrence of SGA in infants **(29)**. In other words, one of the cognitive pathways could be that maternal asthma leads to asthma in children through the IUGR pathways.

Orthopedic disorders in infants were also observed in the present study, supporting the hypothesis that IUGR can have an impact on postnatal bone metabolism and skeletal growth, resulting in reduced bone mass, decreased mass and density, and lower Bone Mineral Density (BMD) **(30, 31)**. Regarding the occurrence of hypothyroidism in infants in line with the hypothesis of the effect of IUGR on thyroid function, it also indicates that hypothyroidism is a transient phenomenon **(32, 33)**. However, it is essential to note that evidence in this area is not yet conclusive and requires further investigation.

In the current study, 11% and 6% of mothers of infants still had hypertension and diabetes after childbirth, respectively. The association between preeclampsia and fetal growth restriction **(34)** and IUGR **(35, 36)** has been demonstrated in previous studies. Therefore, in women diagnosed with preeclampsia, ultrasound examination to assess serious growth restrictions should be considered. The cognitive and pathophysiological pathways of gestational diabetes on fetal growth are complex and multifaceted. Although gestational diabetes leads to macrosomia, it can also result in IUGR. One proposed mechanism for IUGR includes maternal microangiopathy (damage to small blood vessels), which is associated with long-term diabetes **(37)**.

Several limitations need attention in this study. The main limitation is the small sample size. Future studies with larger sample sizes should consider contributing factors such as the onset, duration, and severity of IUGR to obtain more accurate information about the impact of different types of IUGR. Additionally, in future studies, a comparison group such as those with AGA should be included for proper and valid judgments regarding the associations. Furthermore, longitudinal studies with longer durations, beyond two years, need to be conducted to make informed judgments about long-term outcomes.

Conclusion

In conclusion, the present study indicates a significant prevalence of growth and developmental

disorders, as well as medical outcomes such as asthma and orthopedic issues at the age of two in infants with IUGR. Mothers of these infants also faced significant postpartum issues, such as diabetes and hypertension. It is essential for the healthcare system to provide specialized care for IUGR infants to prevent later complications. Larger analytical studies with a longer follow-up period and a comparison group are also recommended.

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Conflict of Interest

The authors claimed no conflict of interest.

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