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Postnatal growth and weight gain in term and near-term infants with severe neonatal hypoglycemia: A comparison between offspring of diabetic and non-diabetic mothers

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Abstract. *Objective:* This study aimed to evaluate postnatal growth patterns in infants with neonatal hypoglycemia, comparing infants of diabetic mothers (IDM) with infants of non-diabetic mothers (INDM) from birth to 3 years of age. *Methods:* We retrospectively analyzed the growth data of 79 IDM and 51 INDM infants who were treated for severe neonatal hypoglycemia at a single center. Anthropometric measurements, including weight-for-age Z score (WAZ), length-for-age Z score (LAZ), and weight-for-length Z score (WLZ), were collected at birth and at several intervals up to 36 months. *Results:* IDM were born at a higher gestational age and with better growth indices than INDM. During the first year, IDM had a progressive increase in WAZ, which stabilized thereafter, while INDM presented a significant catch-up in WAZ and LAZ, particularly in the first 18 months. After 2 months, IDM maintained higher WLZ scores than INDM. By 36 months, IDM had significantly higher WAZ and WLZ, suggesting a tendency towards increased weight relative to length. *Conclusion:* The growth patterns of infants with neonatal hypoglycemia are influenced by maternal diabetes status. While IDMs are at risk for increased adiposity, both groups show resilience in growth, underscoring the need for ongoing monitoring to support their growth needs. (www.actabiomedica.it)

Key words: Neonatal hypoglycemia, infants of diabetic mothers (IDM), infants of non-diabetic mothers (INDM), postnatal growth patterns, follow-up

Introduction

A transient reduction in blood glucose values immediately after birth is a common aspect of transitional metabolic adaptation in neonates. Typically, this resolves within the first few hours of life, with glucose levels gradually increasing to reach adult values (blood glucose > 70 mg/dL) within 72 to 96 hours (1). However, some neonates experience prolonged and severe hypoglycemia, often associated with specific risk factors (2). Understanding the long-term implications of this condition, particularly in terms of postnatal growth, is crucial, especially when comparing infants of diabetic mothers (IDM) to those of non-diabetic mothers (INDM).

Fetal growth is influenced by a combination of genetic and environmental factors, including maternal glycemia, which can impact birth weight and length (3). Infants born to mothers with gestational diabetes mellitus (GDM) are particularly susceptible to hyperinsulinism-related hypoglycemia. Those from well-controlled diabetic pregnancies generally show normal birth metrics, while those from poorly controlled diabetic pregnancies often present with

macrosomia (4,5). Conversely, impaired glucose control in early pregnancy can negatively affect placental development, leading to early fetal growth restriction and increased fetal adiposity later in pregnancy.

Although severe and persistently low glucose levels are known to adversely affect neurodevelopmental outcomes, the long-term significance of transient, asymptomatic neonatal hypoglycemia, including its impact on linear growth and weight gain during infancy and childhood, remains unclear (3-6). Several studies have examined the postnatal growth of IDM with varying results. For instance, Touger et al. (7) found that the offspring of diabetic mothers were heavier at birth but shorter at 1.5 years compared to the offspring of non-diabetic mothers, undergoing significant "catch down" in weight from birth to 1.5 years. Vohr et al. (8) and Hu et al. (9) reported associations between maternal GDM and increased risk of offspring being overweight or obese in early infancy [8,9]. In contrast, Guo et al. (10) observed no significant differences in height, weight, and body mass index (BMI) between IDM and a control group from 1 to 5 years of age.

This study aims to bridge the knowledge gap by comparing the postnatal linear growth and weight gain of IDM, particularly those with significant hypoglycemia, to that of INDM who experienced severe neonatal hypoglycemia due to prematurity or being small for gestational age (SGA). Such an investigation is essential to understand the complex interplay of maternal diabetes, neonatal hypoglycemia, and their combined effects on infant growth patterns.

Materials and methods

Anthropometric measures, including weight (Kg), length (cm), and weight-for-length Z scores, (WLZ) were collected at birth, 2, 4, 6, 12, 18, 24, and 36 months. The study involved data collection for 79 IDM and 51 NIDM. These neonates, admitted to the Neonatal Care Unit at Hamad General Hospital, Qatar, exhibited significant neonatal hypoglycemia, defined as a plasma glucose value of less than 20-25 mg/dL (1.1-1.4 mmol/L), requiring therapy intravenous (IV) glucose bolus followed by IV glucose infusion] for two days or more. Their anthropometric data were compared with those of NIDM who experienced hypoglycemia during the neonatal period, as well as with the World Health Organization (WHO) growth standards. The study received the Ethical Committee approval with the reference MRC-01-21-056 (March. 2021). A high level of confidentiality and privacy was assured as no names, or any other private information were included.

Statistical methods

Descriptive and comparative analyses were utilized in this study. Descriptive statistics, including means, standard deviations (SD), and standard error (SE), summarized the anthropometric data (weight, length, WLZ of IDM and INDM infants, providing an overview of the sample population's characteristics. Comparative analysis, using t-tests and ANOVA, assessed differences between the IDM and INDM groups, with a significance threshold set at P value: < 0.05.

Longitudinal data analysis techniques were employed to track and compare growth patterns over multiple time points (birth, 2, 4, 6, 12, 18, 24, and 36 months). Z-score analysis compared the two groups' infant growth measurements to WHO standards, aiding in understanding growth relative to a normative population. Figures were used to visually represent the growth trajectories and differences between the groups. The analysis likely included an evaluation of catch-up growth, especially in the context of WLZ, to evaluate over the time the infants' growth in comparison to expected norms.

Results

Infants of diabetic mothers (IDM, n = 79) were born with a gestational age (GA) of 37.3 ± 2.2 weeks and had WAZ of -0.8 ± 1.7, length-for-age Z scores (LAZ) of -0.6 ± 1.7, and weight-for-length Z scores (WLZ) of -0.96 ± 1.9. They were heavier and taller compared to infants of non-diabetic mothers (INDM) group. INDM had a GA of 36.7 ± 2.4 weeks, WAZ

of -2.2 ± 1, LAZ of -1.9 ± 2.4, and WLZ of -2.5 ± 1 (P:< 0.01).

IDM experienced a progressive gain in WAZ during the first 12 months, followed by stable WAZ during the second and third years. In contrast, INDM showed a progressive gain in WAZ from birth to 18 months, followed by an insignificant drop in WAZ at the 3rd year of age. WAZ gain during the first year was significantly higher in INDM compared to IDM. By 36 months of age, the WAZ was significantly higher in the IDM group (Figure 1).

IDM showed a progressive gain in LAZ from 2 months until 12 months (from -1 to -0.5), followed by stable LAZ (normal growth velocity) over the next 24 months. INDM exhibited a faster and more progressive gain in LAZ in the first 18 months (from -2 to -0.5), followed by stable LAZ. From 18 months onward, LAZ did not differ significantly between IDM and INDM (Figure 2).

At birth, IDM infants had better WLZ scores than NIDM infants. Both groups demonstrated catch-up growth in WLZ during the first 2 months, with NIDM infants showing a more significant and rapid gain. After 2 months and throughout the following 3 years, IDM infants consistently had higher WLZ scores compared to NIDM infants, indicating a generally higher WLZ (Figure 3).

Similar trajectories of LAZ by 18 months indicate that despite initial linear growth delays, these infants can catch-up during the first 18 months of life. This data provides valuable insights for healthcare providers in anticipating and supporting the growth needs of infants at risk due to maternal diabetes status. Optimizing early nutritional support based on recent recommendations to cope with catch up growth without inducing fast weight gain during the first few months can improve the long-term outcome of these infants.

Discussion

Neonatal hypoglycemia is a common metabolic condition in the neonatal period, generally reflecting the normal process of physiological glucose metabolism, and is transient in most cases. It predominantly occurs within the first 1–2 days post-birth, with a higher incidence in the initial 6–12 hours and is often asymptomatic. The condition affects 5–15% of normal newborns and approximately 50% of those at risk (11,12).

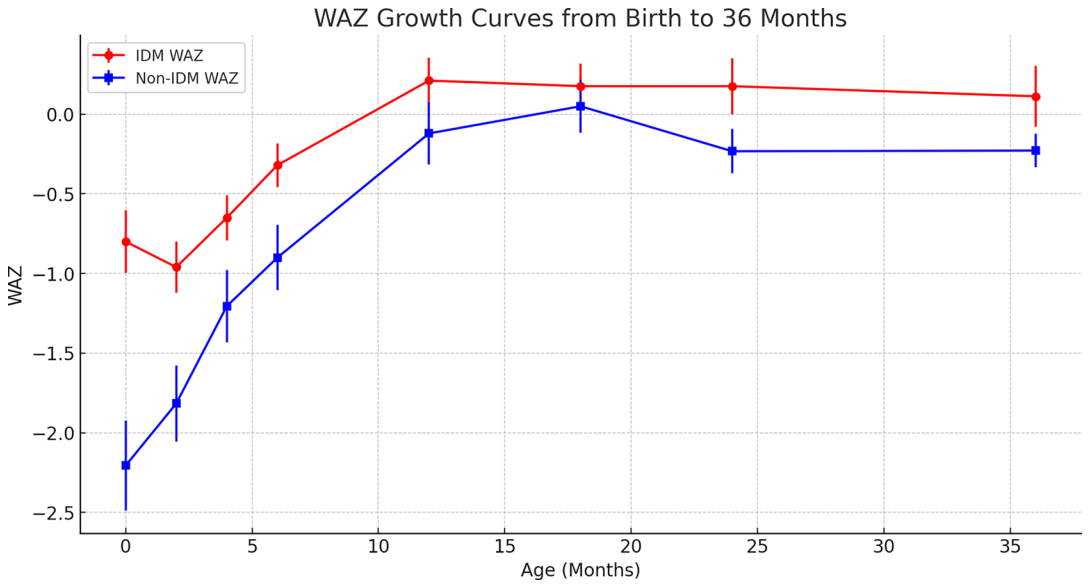

Figure 1. Weight standard deviation scores (SDS) (WAZ; Means ± SE) for infants with neonatal hypoglycemia: IDM (red curve) vs. NIDM (blue curve).

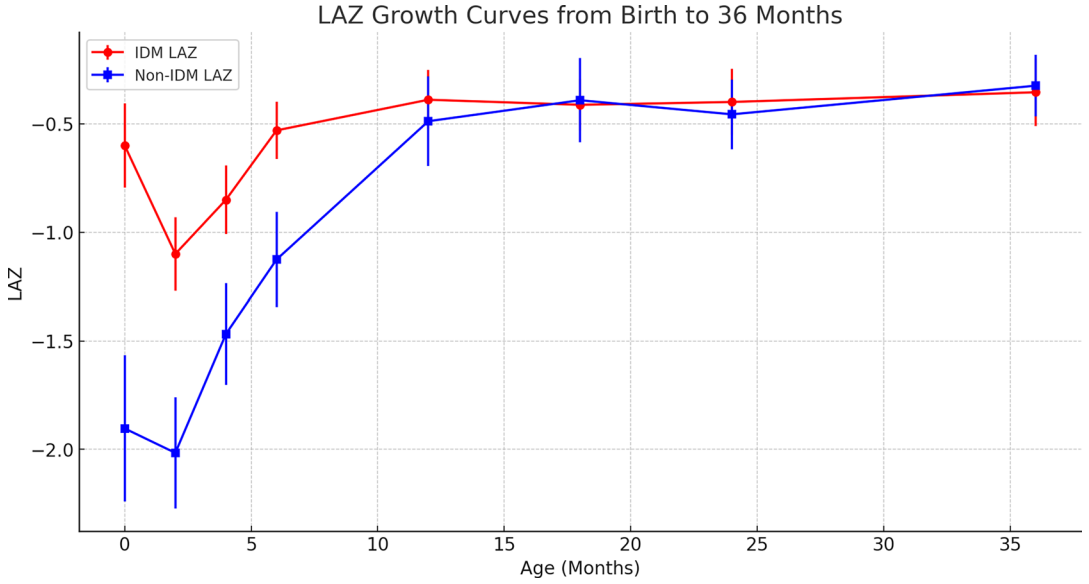

Figure 2. Length standard deviation scores (SDS) (LAZ; Means ± SE) for infants with neonatal hypoglycemia: IDM (red curve) vs. NIDM (blue curve).

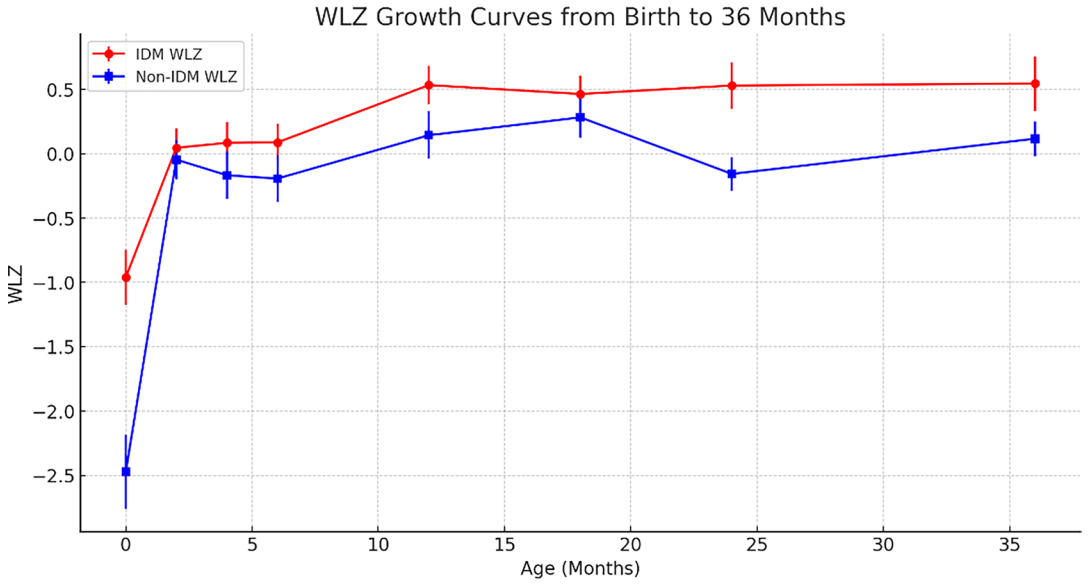

Figure 3. Weight-for-Length standard deviation score (SD) (WLZ; Means ± SE) for infants with neonatal hypoglycemia: IDM (red curve) vs. NIDM (blue curve).

There is growing evidence that abnormal maternal glucose metabolism from early pregnancy can adversely affect fetal growth, with fetuses of mothers with pre-GDM type 1 and type 2 diabetes being at risk for larger size at birth but also for delayed growth in early pregnancy (13). Impaired glucose control in early pregnancy may negatively impact placental development, leading to early fetal growth restriction and increased fetal adiposity later in pregnancy (14,15).

In addition, infants born SGA and preterm have decreased glycogen and fat stores, inappropriate release of insulin, and impaired counter regulatory hormones,

leading to increased risk of neonatal hypoglycemia (16,17). Extremely low blood glucose concentrations in neonates can cause apnea, irritability, lethargy, seizures, and brain damage; and prolonged or symptomatic hypoglycemia may correlate with long-term neurodevelopmental deficits (18-20).

We studied the growth of 2 groups of infants (79 IDM and 51 INDM) who experienced severe neonatal hypoglycemia that required treatment with IV dextrose. Comparing the growth pattern of our infants with other researchers, it was notable that infants with significant neonatal hypoglycemia who were IDM displayed a distinct growth pattern when compared to infants of INDM (12, 21). While IDM were born heavier and taller than the INDM group, essentially due to the intrauterine anabolic effects of insulin, INDM showed a greater catch-up in WAZ during the first 18 months and in LAZ during the first 12 months (22,23).

The progressive catch-up in LAZ was faster in INDM versus IDM during their first year of life. This faster linear growth appears to represent an adjustment of their lower LAZ at birth, due to intrauterine factors, to their genetic background postnatally. Being relatively taller at birth, the IDM babies experienced a slower adjustment to their genetic background. From the 12 months onwards, LAZ did not differ between the two groups and their growth in length was normal, but with no further catch-up (19, 24).

This suggests that while IDM are born with certain linear growth advantages, these do not persist. By the end of the 3rd year, WAZ and WLZ were significantly higher in IDM group vs INDM group reflecting a tendency to be heavier with age (18, 25,26). In agreement with our findings, Plagemann et al. (20) reported that IDM had higher frequencies of overweight and obesity during childhood. Martin et al. (21) found that adiposity was greater among children born to GDM mothers versus mothers with normal weight. In addition, Touger et al. (7) reported higher WAZ in IDM at 7 years of life compared to INDM. While Ornoy et al. (22) reported that in 57 born to women with well-controlled GDM, who had normal weight, weighed more and were taller than age and socio-economic status matched control children at 9–12 years. In other studies, school-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment (22-24).

Overall, our study contributes to the growing body of evidence indicating that IDM who experience significant hypoglycemia during early neonatal period can have different growth pattern compared to those who were INDM (mostly SGA). Significant faster catch-up growth occurs in SGA-INDM infants, particularly in the first year and a half of life versus IDM. The persistent higher WAZ and WLZ in the IDM group compared to the INDM group from 2 months onwards underscores the complexity of growth dynamics in the context of maternal diabetes. It appears that even severe hypoglycemia in neonatal period does not adversely affect the postnatal growth of IDM nor INDM.

Strength and limitation of the study

The strength of our study is its special focus on newborns with severe hypoglycemia and addressing an important clinical question about their long-term growth patterns. In addition, comparing IDM with INDM highlight the potential differences in growth patterns related to maternal diabetes.

The retrospective design may limit the accuracy and completeness of the data. In addition, there may be confounding variables that were not adequately controlled such as socioeconomic status, maternal health and placental factors that can influence infantile growth. In addition, longer term follow-up may be needed to fully understand the impact of neonatal hypoglycemia on growth during late childhood and puberty.

Ethics Approval: The study received ethical approval from the Research Center, Hamad Medical Center, with the reference MRC-01-21-056 (March. 2021).

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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