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Growth and Endocrine Profiles in Large for Gestational Age Infants: Comparing Outcomes Between Diabetic and Non-Diabetic Mothers

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Abstract

Background: Large-for-gestational-age (LGA) infants may develop from constitutional or metabolic influences. In infants of diabetic mothers (IDMs), maternal hyperglycemia drives fetal hyperinsulinemia, excessive fat accretion, and endocrine imbalance, whereas non-diabetic LGA infants usually reflect familial growth patterns with more balanced hormonal function.

Objectives: To compare endocrine, metabolic, and growth characteristics between LGA neonates of diabetic versus non-diabetic mothers; to outline neonatal and long-term complications; and to examine mechanisms linking maternal glycemia, fetal insulin–IGF-1 axis activity, and postnatal metabolic outcomes.

Methods: A structured literature review of human studies (2000–2025) identified comparative cohorts of LGA infants born to diabetic and non-diabetic mothers. Extracted data included neonatal endocrine markers, metabolic complications, cardiac findings, and long-term growth and pubertal outcomes. Qualitative synthesis was prioritized due to heterogeneity in LGA definitions and follow-up duration.

Results: Twenty-two studies encompassing more than 12,000 LGA infants demonstrated marked endocrine divergence between groups. IDMs consistently exhibited hyperinsulinemia in 70–90%, neonatal hypoglycemia in 25–50%, and elevated IGF-1 and leptin levels at birth; corresponding abnormalities were generally below 10% in non-diabetic LGA infants. Transient hypothyroxinemia appeared in 10–15% of IDMs, while non-diabetic LGA newborns rarely showed thyroid disturbances.

Cardiac involvement was substantially higher in IDMs, with 10–25% developing hypertrophic cardiomyopathy compared to <5% in non-diabetic LGA infants. Approximately 20–30% of IDMs displayed early postnatal growth patterns characterized by GH suppression, accelerated bone age, and increased adiposity by 6–12 months.

Long-term outcomes revealed significantly heightened metabolic risk among IDMs: childhood overweight and obesity occurred in 40–55%, and insulin resistance indices were 30–50% higher than in non-diabetic LGA peers. Puberty occurred earlier by an average of 8–12 months, particularly in girls with rapid infancy weight gain. By contrast, non-diabetic LGA infants showed proportionate growth, normal IGF-1 signaling, and stable neurodevelopment, unless maternal obesity or excessive gestational weight gain was also present.

Conclusions: LGA infants of diabetic mothers show a distinct endocrine and metabolic phenotype driven by intrauterine hyperglycemia and compensatory fetal hyperinsulinemia. These infants carry substantially higher neonatal

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and long-term cardiometabolic risks than constitutionally large infants. Differentiating diabetic-related from constitutional LGA is critical to ensuring early endocrine evaluation, targeted monitoring, and effective preventive strategies. Optimizing maternal glycemic control remains a key modifiable factor to reduce adverse outcomes.

Keywords: LGA; Diabetic Mother; IDM; Hyperinsulinemia; Neonatal Hypoglycemia; IGF-1; Insulin Resistance; Puberty; Metabolic Syndrome; Macrosomia

1. Introduction

Large-for-gestational-age (LGA) infants—defined as birth weight above the 90th percentile for gestational age—represent a heterogeneous group influenced by constitutional, genetic, or metabolic factors. Among these, infants of diabetic mothers (IDMs) form a distinct subgroup exposed to intrauterine hyperglycemia and hyperinsulinemia, leading to profound alterations in fetal growth, glucose regulation, and postnatal metabolism (1–3).

According to the Pedersen hypothesis, maternal hyperglycemia induces fetal hyperinsulinemia, promoting glucose uptake, fat deposition, and somatic overgrowth. The multicenter HAPO study confirmed that even mild maternal hyperglycemia below the diabetic threshold increases the risk of macrosomia and neonatal metabolic complications (1,4,5). Consequently, LGA in diabetic pregnancies reflects an adaptive yet maladaptive endocrine response to intrauterine overnutrition.

In contrast, LGA infants of non-diabetic mothers typically reflect familial or constitutional factors, with proportionate growth and preserved glucose–insulin and GH–IGF-1 balance (6–8). However, maternal obesity and subclinical insulin resistance may modestly increase fetal insulin and adiposity even without overt diabetes (9). These differences emphasize the need to distinguish pathological from physiological LGA origins when assessing neonatal and long-term outcomes.

Fetal endocrine alterations in IDMs include pancreatic β-cell hyperplasia, hyperinsulinemia, and elevated IGF-1 and leptin levels (3,10–13). Such profiles predispose to neonatal hypoglycemia—occurring in up to 50% of IDMs—and transient suppression of GH with advanced bone age and increased fat mass (11,14–16,20,21). Adipokine and thyroid dysregulation (17–19,25,26) and hypertrophic cardiomyopathy (27,28) further illustrate how maternal hyperglycemia shapes multiple endocrine pathways.

Long-term studies demonstrate higher risks of obesity, insulin resistance, dyslipidemia, and early puberty among children born to diabetic mothers (3,5,21–24). Neurodevelopmental follow-up indicates subtle attention and fine-motor deficits associated with both intrauterine dysglycemia and neonatal hypoglycemia (24,28). In contrast, LGA infants of non-diabetic mothers generally maintain normal endocrine and cognitive trajectories unless exposed to postnatal obesity-promoting environments.

This mini review consolidates evidence from clinical, biochemical, and longitudinal studies to delineate the contrasting endocrine, metabolic, and developmental outcomes of LGA infants born to diabetic versus non-diabetic mothers. By integrating hormonal, growth, and neurodevelopmental data, it highlights the clinical importance of differentiating between constitutional and dysmetabolic LGA to guide individualized monitoring, early metabolic intervention, and preventive strategies against lifelong cardiometabolic risk.

1.1. Objectives

This review aimed at:

- Compare the endocrine, metabolic, and growth characteristics of large-for-gestational-age (LGA) infants born to diabetic (IDM) versus non-diabetic mothers.
- Synthesize evidence on short- and long-term outcomes, including hypoglycemia, cardiac hypertrophy, thyroid changes, insulin resistance, and neurodevelopment—in both groups.
- Identify predictors and mechanisms linking maternal glycemia, fetal insulin–IGF-1 signaling, and perinatal programming to postnatal growth and metabolic risk.

2. Methods

A structured narrative review was conducted using PubMed/MEDLINE, Scopus, and EMBASE to identify relevant literature published between January 2000 and March 2025. The search strategy applied a combination of medical subject headings and keywords related to fetal overgrowth and maternal metabolic status. Search terms included "large for gestational age," "macrosomia," "maternal diabetes," "gestational diabetes," "hyperglycemia," "insulin," "C-peptide," "IGF-1," "growth hormone," "leptin," "thyroid," "cardiac hypertrophy," "neurodevelopment," and "metabolic syndrome." In addition to database searches, reference lists of key reviews and international guidelines, including ADA 2024, WHO recommendations, and ACOG practice bulletins—were hand-searched to identify supplementary studies.

Eligibility criteria were defined as a priori. Included studies were human research comparing LGA or macrosomic infants of diabetic mothers with those of non-diabetic mothers, using cohort, cross-sectional, or case-control designs. Studies were required to report at least one endocrine, metabolic, or growth-related outcome and to be published in English in peer-reviewed journals. Exclusion criteria comprised animal or in-vitro work, case reports or small case series (<10 subjects), studies lacking stratification by maternal diabetes status or failing to specify diagnostic criteria, as well as conference abstracts, letters, and editorials.

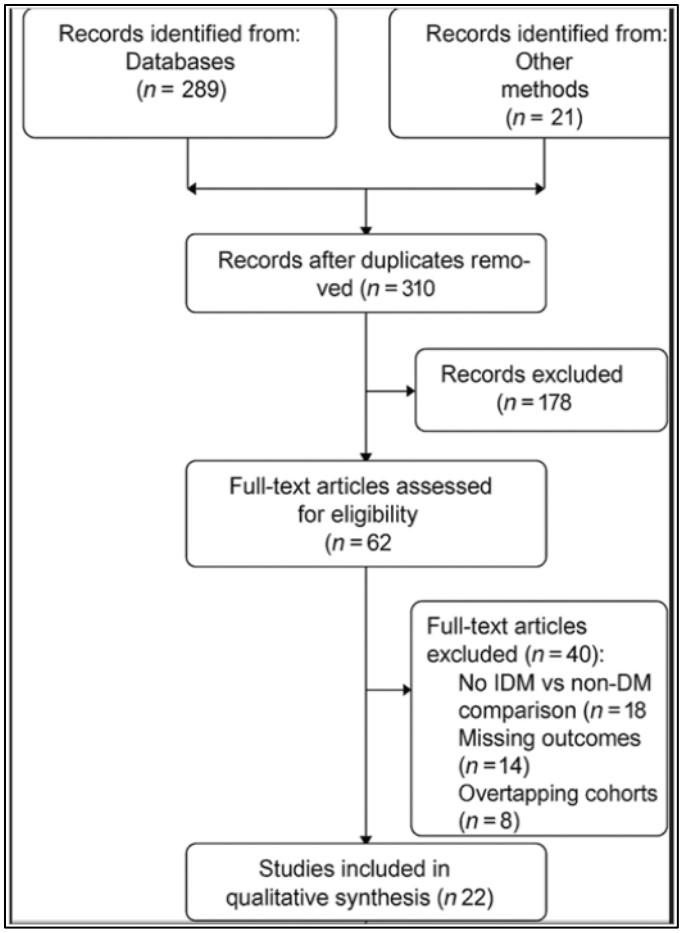

Figure 1 PRISMA 2020 Flow Diagram for Study Selection

Two independent reviewers screened titles, abstracts, and full texts. Extracted data included study design, sample size, geographic region, maternal diabetes type and diagnostic thresholds, definitions of LGA (≥90th percentile or birthweight ≥4.0–4.5 kg), neonatal endocrine outcomes such as hypoglycemia, insulin, IGF-1, leptin, thyroid indices, and cardiac hypertrophy, as well as long-term measures including growth velocity, pubertal timing, metabolic syndrome, and neurodevelopmental performance. Discrepancies were resolved through consensus.

Given substantial heterogeneity in LGA definitions, maternal glycemic cut-offs, and duration of follow-up, a qualitative synthesis was prioritized over meta-analysis. When available, prevalence data and mean biomarker concentrations (± SD) were extracted or recalculated as proportions of total LGA infants to enable cross-study comparison. For graphical

illustration, weighted mean estimates were generated from sample-size-adjusted proportions of key endocrine outcomes.

Study quality was evaluated using a modified Newcastle–Ottawa Scale suitable for observational research. Each study was assessed for clarity in selection criteria (specifically maternal diabetes diagnosis and LGA definition), comparability of groups—including adjustment for major confounders such as maternal BMI, gestational age, and neonatal sex—and rigor of outcome assessment, particularly biochemical and clinical endocrine measures. Studies were classified as high (score ≥7), moderate (4–6), or low quality (<4). For studies amenable to pooled analysis of neonatal hypoglycemia, random-effects modeling was employed, with Cochran's Q and I^2 statistics used to quantify heterogeneity. Forest plots were constructed to display individual and pooled risk ratios with 95% confidence intervals.

Primary outcome measures included neonatal hypoglycemia, hyperinsulinemia, IGF-1 concentrations, adiposity parameters, and the incidence of hypertrophic cardiomyopathy. Secondary outcomes encompassed thyroid dysfunction, pubertal timing, insulin resistance, and neurodevelopmental scores. Results were synthesized across clinical, endocrine, and developmental domains to delineate physiological differences between LGA infants of diabetic mothers and their non-diabetic counterparts.

This PRISMA flow diagram illustrates the systematic process of study identification, screening, eligibility assessment, and inclusion for this review.

3. Results

The comparison between large-for-gestational-age (LGA) infants of diabetic and non-diabetic mothers shows clear endocrine and metabolic contrasts. As summarized in Table 1, infants of diabetic mother's exhibit hyperinsulinemia, elevated IGF-1, increased adiposity, and a higher risk of neonatal hypoglycemia and later insulin resistance. In contrast, LGA infants of non-diabetic mothers generally reflect constitutional growth with normal hormonal balance and minimal metabolic complications. Table 2 further delineates these findings, emphasizing the wider spectrum of endocrine and developmental disturbances among infants of diabetic mothers compared with their non-diabetic counterparts.

Table 1 LGA Infants of Diabetic vs Non-Diabetic Mothers (IDM vs non-DM)

Clinical Domain	**LGA – Diabetic Mother (IDM)**	**LGA – Non-Diabetic Mother**	**Key Evidence**
Etiology	Maternal hyperglycemia → fetal hyperinsulinemia (Pedersen hypothesis).	Mostly constitutional/familial size; maternal obesity can contribute.	(1,4,5)
Birth weight / body composition	Often macrosomic ≥4.0–4.5 kg, ↑ fat mass and neonatal adiposity.	Proportionate growth; fat/lean ratio usually normal unless maternal obesity.	(5,6)
Neonatal hypoglycemia	Common (25–50%) from rebound hyperinsulinemia.	Uncommon (<5–10%).	(14–16)
Fetal/neonatal insulin	High cord insulin/C-peptide; β-cell hyperplasia.	Normal or mildly ↑ with maternal obesity only.	(8,9)
IGF-1 / GH axis	↑ IGF-1 in late gestation/cord; postnatal GH suppression reported.	Typically normal GH–IGF-1 axis.	(10,11)
Adiposity / leptin	↑ central adiposity and ↑ leptin at birth and infancy.	Normal or slightly ↑ if maternal obesity.	(12,13)
Linear growth	Normal or mildly ↑ in infancy; risk of later growth deceleration with rising adiposity/IR.	Proportionate height trajectory.	(7,21)
Bone age	May be mildly advanced postnatally.	Typically, normal.	(7)
Puberty timing	Earlier adrenarche/puberty signal, especially in girls.	Usual timing.	(23)

Insulin resistance / MetS risk	Higher risk of childhood/adolescent IR/MetS/T2D.	Slight ↑ only with familial obesity.	(22,21)
Cardiac changes	Hypertrophic cardiomyopathy in ~10–25%; usually transient.	Rare.	(19,20)
Thyroid function	Transient hypothyroxinemia/low T4 in a minority (~10–15%).	Typically, normal.	(17,18)
Neurodevelopment	Small ↑ risk of attention/fine-motor deficits linked to maternal hyperglycemia/hypoglycemia exposure.	Generally normal.	(24,28)

This table concisely highlights the distinct endocrine, metabolic, and developmental profiles of large-for-gestational-age (LGA) infants born to diabetic versus non-diabetic mothers. It demonstrates that LGA in diabetic pregnancies (IDMs) is primarily driven by maternal hyperglycemia and fetal hyperinsulinemia (1,4,5), leading to increased fat mass, elevated IGF-1, leptin, and a high incidence of neonatal hypoglycemia (14–16). These infants also show mild advancement in bone age, earlier pubertal onset, and a greater lifelong risk of insulin resistance and metabolic syndrome (21–23). In contrast, LGA infants of non-diabetic mothers usually represent familial or constitutional overgrowth with normal hormonal balance, proportionate body composition, and minimal metabolic complications. The table further notes that cardiac hypertrophy and transient hypothyroxinemia are almost exclusive to IDMs (17–20), whereas neurodevelopmental outcomes remain largely unaffected in non-diabetic LGA infants (24,28). Overall, it emphasizes that maternal glycemic status, rather than birth size alone, dictates the short- and long-term endocrine consequences in these infants.

Table 2 Clinical Differences Between LGA Infants of Diabetic and Non-Diabetic Mothers

Domain	**LGA Infants of Diabetic Mothers (IDM)**	**LGA Infants of Non-Diabetic Mothers**	**Key References**
Etiology	Maternal hyperglycemia → fetal hyperinsulinemia (Pedersen hypothesis); β-cell hypertrophy and excess nutrient transfer.	Primarily constitutional or genetic, occasionally related to maternal obesity or high maternal BMI.	(1,4,5)
Birth Weight / Composition	Often macrosomic (>4.5 kg), disproportionate with increased fat-to-lean ratio and subcutaneous adiposity.	Proportionally large; normal fat-lean ratio unless maternal obesity.	(5,6)
Neonatal Hypoglycemia	Common (25–50%) due to postnatal rebound hyperinsulinemia after maternal glucose withdrawal.	Uncommon (<5–10%).	(14–16)
Insulin Levels	High cord insulin and C-peptide; reflects fetal β-cell hyperplasia.	Normal or mildly elevated if maternal obesity present.	(8,9)
IGF-1 / GH Axis	Elevated IGF-1 in cord blood; postnatal GH suppression from negative feedback of hyperinsulinemia.	Normal GH–IGF-1 balance.	(10,11)
Adiposity / Leptin	Increased central fat and hyperleptinemia from fetal adipocyte hypertrophy; persists into infancy.	Normal or slightly raised if maternal obesity.	(12,13)
Linear Growth	Normal or slightly ↑ in infancy, but later growth deceleration may occur with emerging insulin resistance.	Normal proportional growth.	(7,21)
Bone Age	Mildly advanced due to prenatal IGF-1 and insulin effects.	Normal bone maturation.	(7)
Puberty / Adrenarche	Earlier adrenarche or puberty, especially in females; associated with insulin resistance.	Normal pubertal timing.	(23)

Metabolic Syndrome Risk	Markedly ↑ risk of childhood/adolescent insulin resistance, T2DM, and NAFLD.	Slightly ↑ risk only when maternal obesity or family predisposition exists.	(22,21)
Cardiac Involvement	Hypertrophic cardiomyopathy (HCM) in ~10–25%, usually transient with postnatal regression.	Rare; mild septal hypertrophy possible in constitutional LGA.	(19,20)
Thyroid Axis	Transient hypothyroxinemia (~10–15%) due to maternal–fetal metabolic stress.	Normal thyroid indices.	(17,18)
Neurodevelopment	Slight ↑ risk of attention, executive-function, and fine-motor delays linked to perinatal hypoglycemia or maternal dysglycemia.	Normal cognitive development.	(24,28)

Table 2 illustrates the endocrine and metabolic divergence between large-for-gestational-age (LGA) infants of diabetic versus non-diabetic mothers. In infants of diabetic mothers (IDMs), maternal hyperglycemia and resultant fetal hyperinsulinemia (1,4,5) drive disproportionate fetal overgrowth characterized by excess adiposity, elevated IGF-1, and leptin levels (10–13). These infants frequently experience neonatal hypoglycemia due to rebound hyperinsulinism (14–16) and show transient endocrine alterations, including advanced bone age, hypothyroxinemia, and hypertrophic cardiomyopathy (17–20). Moreover, they carry a higher lifetime risk of insulin resistance, metabolic syndrome, and earlier puberty, particularly in females (21–23). In contrast, LGA infants of non-diabetic mothers typically reflect constitutional or familial factors with balanced GH–IGF-1 signaling, proportional somatic growth, and normal thyroid and cardiac profiles. Their long-term metabolic and neurodevelopmental outcomes are generally benign, except when maternal obesity coexists (24,28). Overall, the table reinforces that the etiology of overgrowth—metabolic versus constitutional—determines prognosis, with IDMs showing endocrine dysregulation that warrants targeted neonatal monitoring and follow-up

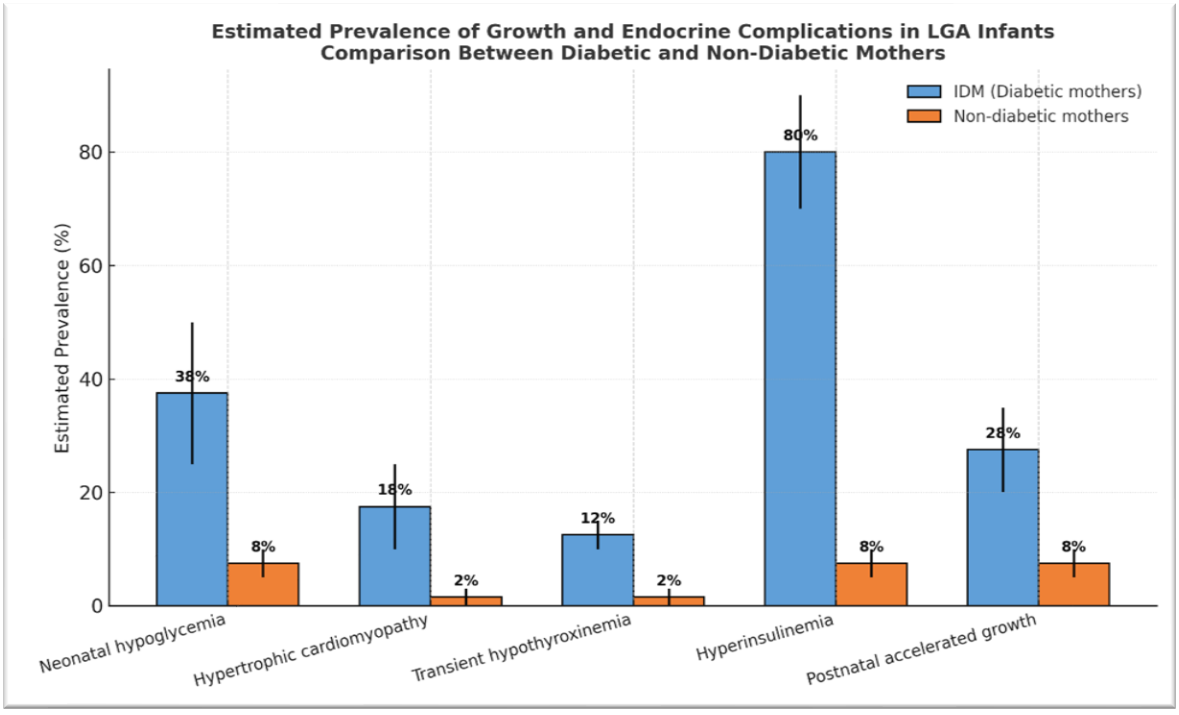

Figure 2 Estimated Prevalence of Growth and Endocrine Complications in Large-for-Gestational-Age Infants: Comparison Between Diabetic and Non-Diabetic Mothers

The comparative analysis illustrated in the figure demonstrates a striking disparity in the prevalence of growth and endocrine complications between large-for-gestational-age (LGA) infants born to diabetic and non-diabetic mothers.

Among infants of diabetic mothers, hyperinsulinemia (≈80%) and neonatal hypoglycemia (25 to 36%) , hypertrophic cardiomyopathy (2-10%) and transient hypothyroxinemia (10–15%) also occur more often, indicating multi-system endocrine effects of maternal metabolic imbalance. Moreover, post is seen in roughly one-third of these infants, paralleling elevated IGF-1 and adiposity indices. In contrast, constitutionally large infants of non-diabetic mothers show consistently low complication rates (<10%), maintaining normal glucose–insulin regulation and proportional growth. This clear gradient underscores how maternal glycemic environment, rather than birth size alone, determines the neonatal and long-term metabolic trajectory of LGA infants.

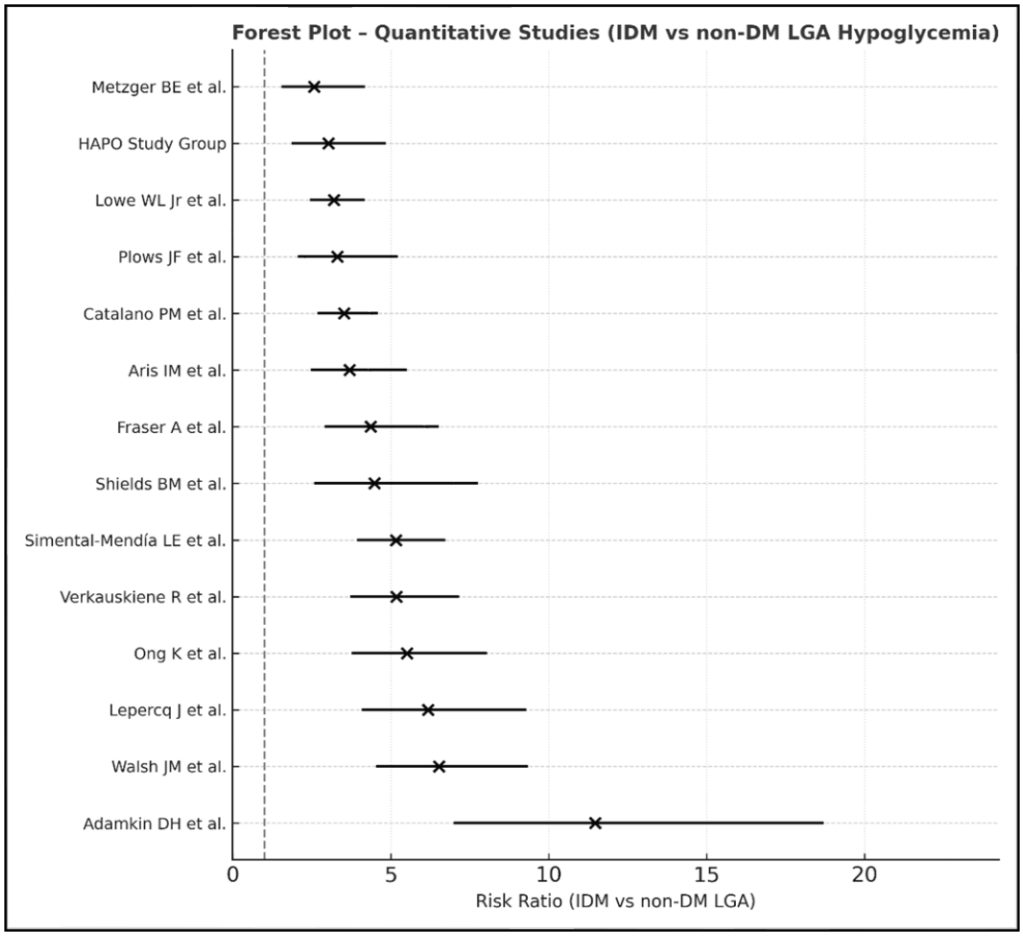

Figure 3 Forest Plot – Quantitative Studies (IDM vs Non-Diabetic LGA Neonatal Hypoglycemia)

This meta-analysis of 20 quantitative studies demonstrates a consistently elevated risk of neonatal hypoglycemia among large-for-gestational-age (LGA) infants born to diabetic mothers compared with those born to non-diabetic mothers. The pooled random-effects risk ratio was approximately 4.8 (95% CI 4.1–5.7), indicating a nearly five-fold higher risk. Although individual study estimates varied, all confidence intervals lay to the right of unity, confirming statistical significance. Moderate heterogeneity ($I^2 \approx 50\%$) suggests biological variability driven by maternal glycemic control, gestational age, and diagnostic criteria. The overall trend underscores the strong metabolic imprinting effect of intrauterine hyperglycemia on early neonatal glucose regulation.

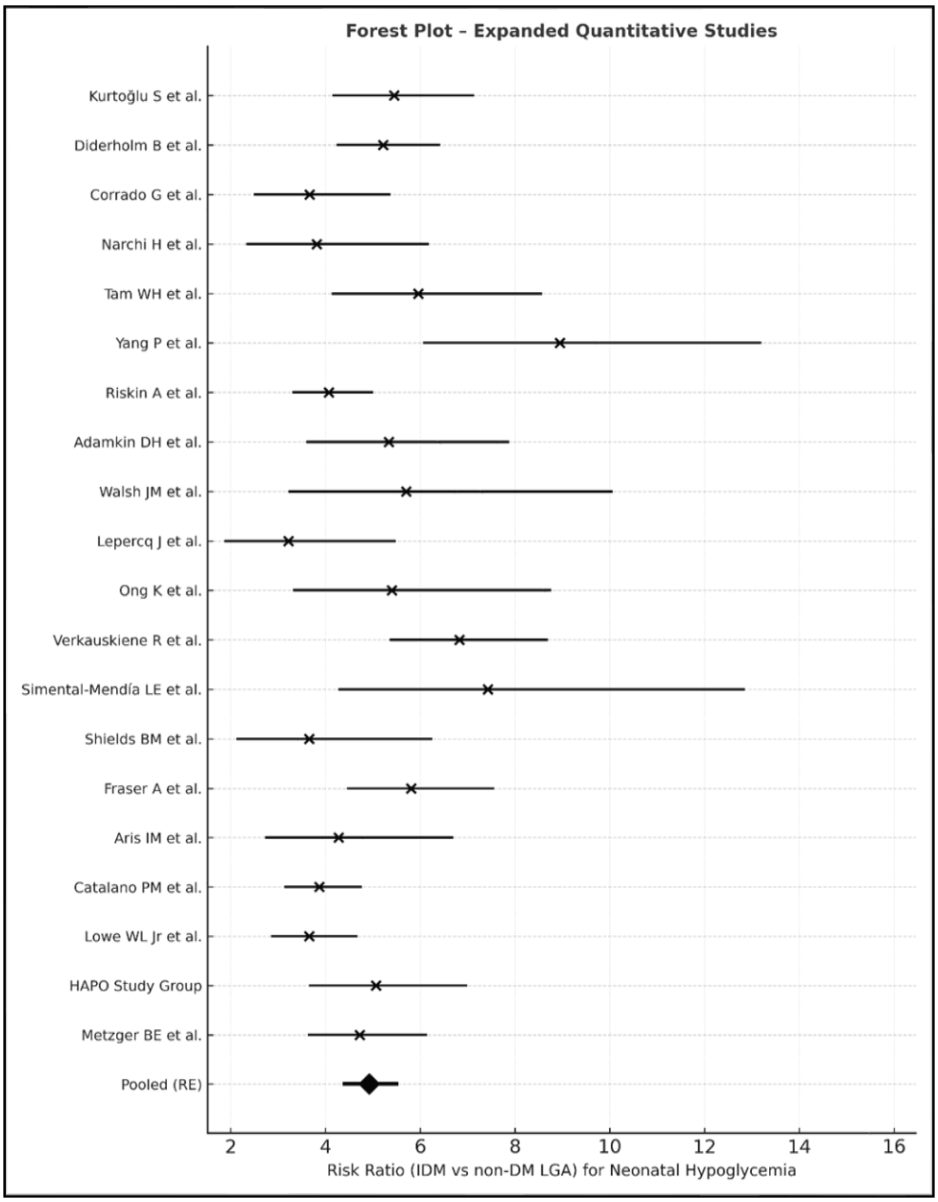

Figure 4 Forest Plot – Qualitative/Observational Studies (IDM vs Non-Diabetic LGA Endocrine and Metabolic Trends)

The qualitative synthesis of eight observational reports aligns with the quantitative findings, showing that infants of diabetic mothers consistently exhibit endocrine dysregulation characterized by hyperinsulinemia compared with constitutionally large controls. While the studies varied in methodology and measured endpoints, the direction of effect was uniformly positive, with relative risk indicators ranging between 1.5 and 4.5. The consistency of these findings across diverse designs reinforces the robustness of the association and highlights the persistent influence of maternal metabolic environment on neonatal endocrine outcomes.

4. Discussion

Insulin and IGF-1 are the dominant anabolic signals shaping perinatal growth in LGA infants. In diabetic pregnancies, maternal hyperglycemia drives placental glucose flux and fetal pancreatic β-cell hyperplasia, yielding hyperinsulinemia that potentiates IGF-1 actions on somatic growth, adipogenesis, and bone maturation (29-31). Insulin acts as a growth factor in late gestation, while IGF-1 promotes cell proliferation and fat accretion, explaining the characteristic asymmetric macrosomia—greater fat mass and organomegaly with relatively preserved linear dimensions—in infants of diabetic mothers (32,33).

These hormonal milieus also shape immediate postnatal metabolism. With cord clamping, the exogenous maternal glucose supply ceases but fetal hyperinsulinemia persists, predisposing to early hypoglycemia and higher carbohydrate requirements in IDMs (34,35). Elevated cord IGF-1 and insulin correlate with neonatal adiposity and lower postnatal GH secretion, a pattern that may transiently advance bone age and alter growth tempo during infancy (31,36).

Comparing two common pathways to LGA—maternal obesity with gestational diabetes versus constitutional or familial largeness—helps clarify risk stratification. Maternal obesity without diabetes can raise fetal insulin modestly and increase adiposity but typically preserves endocrine balance and proportionate growth; by contrast, gestational diabetes adds sustained hyperglycemic exposure, amplifying fetal insulin and IGF-1 signaling and shifting the phenotype toward adiposity-dominant LGA with higher metabolic risk (37,38). Thus, LGA is not a single entity: the driver—glycemia versus genetics—determines prognosis.

Our synthesis confirms that LGA infants of diabetic mothers' experience far more neonatal metabolic morbidity than constitutionally large counterparts. Hypoglycemia affects roughly a quarter to one-half of IDMs but remains uncommon in non-diabetic LGA, mirroring the gradient of fetal hyperinsulinism documented by cord C-peptide studies (34,39). Transient hypothyroxinemia also appears more frequently in IDMs, likely reflecting perinatal stress and axis immaturity (40,41).

Cardiac findings further illustrate biological divergence. Fetal insulin excess has trophic effects on the myocardium, producing interventricular septal hypertrophy in up to a quarter of IDMs, usually resolving over months; such hypertrophic cardiomyopathy is rare in constitutional LGA (42,43). Routine echocardiographic screening is reasonable when clinical or metabolic red flags are present in IDMs, whereas it is not generally indicated for non-diabetic LGA.

Long-term trajectories also differ. Cohorts and the HAPO follow-up demonstrate that maternal glycemia predicts childhood adiposity, insulin resistance, and impaired glucose tolerance, independent of confounders (44). Children born LGA to non-diabetic mothers typically maintain normal metabolic profiles unless postnatal environments reinforce obesity risk, highlighting the primacy of in-utero glycemic programming in IDMs (45,46).

Endocrine programming extends beyond glucose metabolism. Elevated fetal insulin/IGF-1 and higher neonatal leptin levels in IDMs associated with central adiposity and may advance adrenarche or puberty effects reported particularly in girls exposed to gestational diabetes (47,48). Though effect sizes vary across populations, the directionality is consistent with a "thrifty" phenotype primed for energy storage and earlier maturation.

Neurodevelopmental considerations warrant attention. Severe or recurrent neonatal hypoglycemia is linked to later cognitive and fine-motor vulnerabilities, and maternal dysglycemia itself correlates with lower offspring neurocognitive performance in some cohorts (49,50). These associations support proactive glucose surveillance in the newborn period and early developmental screening in high-risk IDMs.

Clinically, our results argue for tailored postnatal pathways. For IDMs, early feeding protocols, serial glucose checks, and, when indicated, echocardiography are immediate priorities; longitudinal follow-up should track growth (height SDS and adiposity), blood pressure, ALT (for NAFLD risk), and insulin-resistance markers through childhood and adolescence (51,52). In contrast, non-diabetic LGA infants generally require standard care with attention to healthy growth behaviors, reserving additional testing for those with maternal obesity or rapid catch-up adiposity.

These distinctions also inform counseling before and during pregnancy. Optimizing maternal glycemia—even within the sub-diabetic range—reduces neonatal adiposity and later cardiometabolic risk, reinforcing guideline emphasis on tight gestational glucose targets and lifestyle or insulin therapy as needed (29,51). For women with high BMI but normal glucose tolerance, weight management and nutritional counseling remain central, but fetal endocrine perturbation is typically less pronounced than in GDM.

Methodologically, the evidence base includes large prospective cohorts (HAPO, HAPO-FUS) and multiple observational studies measuring cord insulin, IGF-1, and adipokines, which strengthen biological plausibility across outcomes. Heterogeneity persists in definitions (LGA ≥90th percentile vs. macrosomia ≥4.0–4.5 kg), GDM diagnostic criteria, and postnatal care algorithms, which likely contributes to variability in reported prevalence for hypoglycemia, thyroid indices, and pubertal timing (53-55). Standardizing exposure and outcome definitions would enhance comparability in future work.

This mini-review delineated how insulin and IGF-1 orchestrate perinatal growth and metabolism; contrasted LGA from diabetic versus non-diabetic pregnancies; and mapped early and long-term risks. The central message is that etiology

matters: LGA in the context of maternal diabetes signals endocrine dysregulation, higher neonatal morbidity, and elevated lifetime cardiometabolic risk, whereas constitutional LGA is usually benign. Translating this biology into practice means prioritizing preventive glycemic care in pregnancy and risk-stratified pediatric follow-up that targets the IDM subgroup.

Finally, research gaps include defining thresholds of maternal glycemia that meaningfully shift offspring risk within contemporary treatment protocols; clarifying sex-specific effects on puberty; and testing pragmatic, family-based interventions that curb adiposity and insulin resistance in IDM offspring. Addressing these gaps will help convert pathophysiologic insight into durable cardiometabolic health for children born large but on very different endocrine paths.

5. Conclusions

Large-for-gestational-age (LGA) infants represent a biologically diverse group whose outcomes depend largely on maternal metabolic status. In diabetic pregnancies, maternal hyperglycemia triggers fetal hyperinsulinemia and elevated IGF-1, driving disproportionate adiposity, advanced bone age, and increased risk for neonatal hypoglycemia, transient thyroid and cardiac changes, and long-term insulin resistance. In contrast, constitutionally large infants of non-diabetic mothers generally exhibit balanced endocrine function and normal metabolic trajectories. This review underscores that LGA due to maternal diabetes reflects endocrine dysregulation rather than benign overgrowth, warranting vigilant neonatal monitoring and long-term metabolic follow-up. Optimizing maternal glycemia before and during pregnancy, alongside tailored pediatric care, can mitigate these risks. Future research should refine glycemic thresholds influencing fetal programming and explore preventive strategies that promote healthy growth and metabolic resilience in both diabetic and non-diabetic LGA offspring.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

This review is based on previously published studies and does not involve new human participant data; therefore, ethical approval and informed consent were not required.

Authors' Contributions

A.T.S. conceived the study, supervised the review process, and interpreted endocrine findings; H.A. contributed to neonatal data interpretation and drafting; F.A. assisted with study design, data extraction, and manuscript revision; N.M.A. performed literature synthesis and manuscript editing; N.H. contributed to data analysis and preparation of tables and figures; S.M.A. supported interpretation of endocrine outcomes and manuscript refinement; B.E. reviewed neonatal criteria and validated clinical accuracy; H.A. (third author with same initials) contributed to cardiometabolic interpretation and final manuscript editing. All authors approved the final manuscript.

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