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Maternal and Neonatal Outcomes in Gestational Diabetes Managed with Metformin versus Insulin: A Retrospective Analysis from a Tertiary Care Centre

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ABSTRACT

Background: In the Indian subcontinent, gestational diabetes mellitus is characterized by an increasingly unique a unique metabolic phenotype, which elevates obstetric risk even at relatively low body mass index. While insulin remains the traditional pharmacological standard, its implementation is often limited by strict storage requirements and the persistent risk of iatrogenic prematurity in high-pressure clinical settings, thereby necessitating an evaluation of alternatives. This study evaluates the real-world performance of metformin versus insulin in achieving maternal glycemic stability and improving neonatal adaptation.

Methods: This retrospective cohort study (N = 278) was conducted at the Chamarajanagar Institute of Medical Sciences, where we analysed maternal and neonatal outcomes in a routine tertiary care environment, comparing patients managed with metformin monotherapy with those who required insulin after failure of medical nutrition therapy.

Results: Our analysis indicates that while insulin was typically reserved for patients with more severe metabolic dysfunction, metformin provided more stable maternal glycaemic control, with a mean HbA1c of 5.3 ± 0.7% compared to 6.2 ± 1.8% in the insulin group ($p < 0.001$). Neonatal outcomes also favoured the metformin cohort; the incidence of neonatal hypoglycaemia was significantly lower (35.5% vs. 51.3%, $p = 0.008$). We observed a "*birth weight paradox*" where infants in the metformin group were heavier on average (3496 g vs. 3348 g). This was not a result of overgrowth, but was directly linked to a markedly lower rate of prematurity (4.0% vs. 19.5%) compared to the insulin-managed cohort.

Conclusion: These findings suggest that metformin is not merely an alternative to insulin, but may offer significant protective advantages against iatrogenic prematurity and neonatal metabolic distress. In resource-constrained tertiary environments, metformin provides a robust first-line strategy that supports maternal glycaemic targets while allowing pregnancies to progress safely towards term.

Keywords: *Maternal; Neonatal; Gestational Diabetes; Insulin; Metformin; HbA1c.*

INTRODUCTION

The management of gestational diabetes mellitus has reached a critical turning point, shifting from a narrow focus on maternal glucose targets towards a more integrated strategy that balances immediate metabolic stability with the lifelong health of the offspring (1), (2). For decades, insulin was the unchallenged pharmacological standard, primarily because its large molecular structure prevents it from crossing the placental barrier (3). This physiological exclusion provided a logical safeguard: by controlling maternal hyperglycaemia without direct fetal exposure to the drug, clinicians could theoretically suppress fetal hyperinsulinaemia and mitigate the classic risks of macrosomia, neonatal hypoglycaemia, and birth trauma (1).

However, the "gold standard" of insulin therapy often clashes with the pragmatic realities of daily clinical practice. The burden of multiple daily injections, the logistical demands of refrigerated storage, and the pervasive fear of maternal hypoglycaemia frequently undermine patient adherence and real-world efficacy (3,4). These barriers have necessitated a search for oral alternatives that can improve quality of life without compromising safety (2). Metformin has emerged as the leading contender in this area, now recognised by guidelines in the United Kingdom, New Zealand, and Canada as a valid first-line option for pharmacological management (5).

Despite its clinical convenience, the move towards metformin remains a subject of intense metabolic and ethical debate (1,2). The crux of the controversy lies in its pharmacology: unlike insulin, metformin is a small, lipophilic molecule that crosses the placenta with ease, often resulting in foetal concentrations that equal or even exceed those in the maternal circulation (3,4,6). This direct exposure has sparked legitimate concerns regarding foetal development. While systematic reviews indicate that metformin-exposed infants weigh approximately 108 g less at birth than those in insulin cohorts, this reduction is not universally viewed as a benefit (7). Instead, there are concerns that these infants may undergo accelerated "catch-up" growth in early childhood, a pattern linked to higher body mass indices and adverse metabolic programming that may not fully manifest until adulthood (6,7).

From the maternal perspective, metformin offers distinct physiological advantages beyond the avoidance of needles. Meta-analyses have confirmed its role in superior weight management, demonstrating a significant reduction in gestational weight gain of 1.57 kg compared to insulin (2,5). Furthermore, metformin appears to confer a protective effect against hypertensive complications, including a reported 31% reduction in the risk of pre-eclampsia (2,5,8). Yet, metformin is not a panacea. In routine clinical settings, failure rates for metformin monotherapy range from 26.8% to 46.3%, with the need for supplemental insulin particularly high among women who are obese, diagnosed early in pregnancy, or present with high fasting glucose levels at baseline (6,9).

While large-scale trials provide the necessary foundation for safety, they often fail to account for the socio-metabolic complexities of diverse populations. In the Indian subcontinent, management is further complicated by variable health literacy and limited access to healthcare resources in tertiary settings (10). This study analyses a cohort of 278 women at the Chamarajanagar Institute of Medical Sciences to provide the context-specific evidence required to optimise GDM care pathways within the Indian healthcare system.

MATERIALS AND METHODS

Study Design and Ethical Considerations

Our study was conducted at the Department of Obstetrics and Gynaecology, Chamarajanagar Institute of Medical Sciences. This facility operates as a major regional tertiary hub, serving a diverse population from both urban and rural districts. We chose a retrospective cohort design to capture clinical outcomes in a routine practice environment, prioritising real-world evidence over the controlled parameters of a trial. This approach is particularly relevant in the Indian context, where systemic gaps in the management of non-communicable diseases during pregnancy (including screening and follow-up) often dictate how care is delivered and received in a clinical setting (11).

The Institutional Ethics Committee of the Chamarajanagar Institute of Medical Sciences formally approved the study protocol (Ref. No.: IEC/CIMS 04/18/2012). All research activities were carried out in accordance with the ethical principles of the Declaration of Helsinki. We prioritised patient confidentiality at every step: data were de-identified during extraction, and we used anonymised record numbers for all analysis phases to ensure that no personally identifiable information was included in the study database.

Participants

The study population was identified through a comprehensive, systematic review of obstetric medical records spanning a four-year period from January 2020 to December 2023, to capture diverse seasonal and epidemiological variations in GDM presentation(12). Leveraging integrated hospital medical record databases and the obstetrics department's dedicated GDM registry, we identified all women diagnosed with gestational diabetes mellitus during pregnancy who required pharmacological intervention after failing Medical Nutrition Therapy alone. This rigorous approach yielded 312 potential participants, a number mirroring cohort sizes in comparable retrospective real-world analyses (9),(12). Of these, 34 were excluded based on stringent, predefined criteria to minimize bias and enhance internal validity.

Inclusion criteria were: (1) singleton pregnancy; (2) confirmed diagnosis of gestational diabetes mellitus between 24 and 32 weeks of gestation using International Association of Diabetes and Pregnancy Study Groups criteria with a standardized 75-g oral glucose tolerance test (13),(14); (3) maternal age of 18–40 years and documented need for pharmacological therapy following failure of an initial trial of Medical Nutrition Therapy; exclusion criteria included: (1) multiple gestations, pre-existing Type 1 or Type 2 diabetes mellitus, known congenital fetal anomalies, maternal chronic metabolic conditions (e.g., thyroid disorders, chronic renal disease); and (2) incomplete records with missing outcomes, consistent with prior real-world GDM studies (12),(9). These criteria minimised confounding and selection bias, which yielded a final analytic cohort of 278 women with complete data.

Diagnostic Criteria and Screening Protocol

All participants underwent universal screening for gestational diabetes mellitus between 24 and 28 weeks of gestation, strictly adhering to the diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (14). This approach, widely adopted by international bodies such as the WHO, ADA, and The Endocrine Society, as well as in countries including India(14), has demonstrated superior detection rates for GDM compared to alternative criteria, enabling earlier intervention to mitigate maternal and neonatal risks(13),(14). The screening protocol employed a standardised 75-g oral glucose tolerance test following an overnight fast of at least 8 hours, with plasma glucose levels measured at fasting, 1-hour, and 2-hour time points post-ingestion(13).

A gestational diabetes mellitus diagnosis required the fulfilment of any one of the following or exceedance of International Association of Diabetes and Pregnancy Study Groups threshold values from the standardised 75-g oral glucose tolerance test: a fasting plasma glucose level of ≥92 mg/dL (5.1 mmol/L); a 1-hour post-glucose load measurement of ≥180 mg/dL (10.0 mmol/L); or a 2-hour post-glucose load measurement of ≥153 mg/dL (8.5 mmol/L)(14),(13). Women who received a diagnosis based on these criteria were immediately referred to the department's specialised GDM clinic for comprehensive management, counselling, and initiation of treatment protocols (15).

Treatment Protocol and Clinical Algorithms

Our treatment protocol was designed to optimise maternal and neonatal outcomes by strictly adhering to evidence-based international guidelines, such as those from NICE and the MiG trial, while adapting to local resource constraints, patient preferences, and practical barriers like insulin storage and socioeconomic status in a regional Indian setting (16), (17), (18), (6). This pragmatic, individualised approach mirrors successful real-world implementations where metformin and insulin demonstrated comparable efficacy in glycaemic control and perinatal outcomes (17),(12),(6), prioritising accessibility without compromising safety or effectiveness.

The initial management of all women diagnosed with GDM commenced with a standardized trial of medical nutrition therapy, comprising individualised dietary counselling provided by trained clinical nutritionists; structured meal plans emphasising complex carbohydrates with a low glycaemic index; and recommendations for moderate physical activity, such as walking for 30 minutes daily after meals. Participants received glucometers and were subsequently instructed to perform capillary blood glucose monitoring at home, adhering to a standardized schedule encompassing fasting measurements and postprandial readings one hour after each main meal.

Glycaemic targets for both treatment groups were established according to international guidelines and adapted to local practice patterns: fasting blood glucose <95 mg/dL (5.3 mmol/L) and one-hour postprandial blood glucose <140 mg/dL (7.8 mmol/L)(19). Patients who consistently achieved these glycaemic targets through lifestyle modifications alone for two consecutive weeks were considered to exhibit controlled GDM and were thus excluded from the study population, which specifically focused on women requiring pharmacological intervention.

The attending obstetrician's determination regarding metformin initiation as opposed to insulin was based on multifaceted clinical assessments—including disease severity (e.g., degree of hyperglycaemia), patient preferences, difficulties in glycaemic control, and practical considerations such as socioeconomic status and insulin storage capabilities in resource-limited settings(17),(18). This individualised, shared decision-making approach aligns with evidence from real-world studies demonstrating metformin as a feasible and comparably efficacious first-line option to insulin when appropriate(17),(12). Women initiated on metformin therapy received a starting dose of 500 mg orally once daily with the evening meal, following the MiG trial protocol(16),(6). The dose was titrated based on twice-weekly self-monitored fasting and one-hour postprandial glucose measurements, with the typical schedule advancing to 500 mg twice daily after one week if targets were not met, and further increases up to a maximum total daily dose of 2500 mg if glycaemic control remained suboptimal(6,16).

Women assigned to insulin therapy (n=154) received subcutaneous insulin regimens that typically comprised intermediate-acting neutral protamine Hagedorn insulin with short-acting regular insulin or premixed preparations. Insulin dosing was individualised based on body weight, gestational age, and degree of hyperglycaemia, with most patients beginning with a starting dose of 0.3–0.5 U/kg of total body weight, divided between morning and evening doses. All insulin-treated patients received comprehensive education on injection technique, insulin storage requirements, hypoglycaemia recognition and management, and sick-day rules from diabetes nurse educators.

Outcome Measures and Data Collection

Primary maternal outcomes encompassed a comprehensive evaluation of glycaemic control, including glycated haemoglobin (HbA1c) levels at 37 weeks' gestation, fasting plasma glucose, 2-hour postprandial glucose (2hPPG), gestational weight gain from diagnosis to delivery, and incidence of pregnancy-induced hypertension and pre-eclampsia. Pre-eclampsia was diagnosed according to standard criteria: new-onset hypertension (≥140/90 mmHg) after 20 weeks' gestation with proteinuria or end-organ dysfunction(20). These measures are established predictors of maternal morbidity in gestational diabetes mellitus, with HbA1c and glucose levels strongly linked to perinatal risks(7,8)

Obstetric outcomes included gestational age at delivery (confirmed by first-trimester ultrasound), mode of delivery, and caesarean section indications. Preterm birth was defined as delivery before 37 completed weeks.

Neonatal outcomes were rigorously assessed, including birth weight, small-for-gestational-age (SGA, <10th percentile) and large-for-gestational-age (LGA, >90th percentile) status by sex and GA, Apgar scores at 1 and 5 minutes, neonatal intensive care unit admission, respiratory distress syndrome requiring surfactant or ventilation, phototherapy for hyperbilirubinaemia, and hypoglycaemia (<2.6 mmol/L capillary glucose in the first 48 hours) requiring intervention(8),(7). These endpoints were selected for their proven differential impact between metformin and insulin in GDM management, as evidenced by meta-analyses(8),(7). Data extraction involved two independent trained research assistants reviewing medical records using standardized forms, with discrepancies resolved by consensus with the lead investigator. The supervising consultant obstetrician verified data integrity by randomly double-checking 10% of records, which minimized extraction bias.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows (Version 26.0) and GraphPad Prism (Version 9.0). Continuous variables were assessed for normality of distribution using the D'Agostino-Pearson omnibus normality test. Variables with normally distributed data were presented as mean with standard deviation, while non-normally distributed data were expressed as median with interquartile range. Categorical variables were summarized as frequency and percentage.

Baseline characteristics and outcome measures were compared between the metformin and insulin groups using appropriate statistical tests. For continuous variables with normal distribution, independent-samples t-test was employed, while the Mann-Whitney U test was used for non-parametric data. Categorical outcomes were compared using Pearson's chi-square test or Fisher's exact test when expected cell counts were less than five. All statistical tests were two-tailed, and the threshold for statistical significance was set at $p < 0.05$ throughout the analysis.

RESULTS

Study Cohort and Pharmacological Requirements

The study analysed a cohort of 278 pregnant women diagnosed with gestational diabetes mellitus requiring pharmacological intervention at the Chamarajanagar Institute of Medical Sciences, a tertiary care centre in southern India. Following a standardised initial period of medical nutrition therapy, 124 (44.6%) were successfully managed with metformin, while 154 (55.4%) required subcutaneous insulin therapy to achieve glycaemic targets. This higher insulin allocation reflects the clinical prioritisation of insulin for more severe hyperglycaemia or complex cases in resource-limited referral settings. (21)

Table 1. Distribution of the study cohort according to pharmacological intervention (N = 278).

Treatment Group	Frequency (n)	Percentage (%)
Diet + Metformin	124	44.6%
Diet + Insulin	154	55.4%
Total	**278**	**100.0%**

All participants initially underwent a trial of lifestyle modification. Percentages are rounded to one decimal place. The higher insulin requirement appears to reflect the clinical severity of the referral population in this Indian tertiary care setting(21).

Maternal Metabolic Control and Obstetric Outcomes

A significant disparity was observed in the metabolic and obstetric trajectories between the two groups. Women in the insulin group exhibited a more challenging glycemic profile, as evidenced by significantly elevated HbA1c levels at 37 weeks (6.2 ± 1.8% vs. 5.3 ± 0.7%, $p < 0.001$) and fasting glucose (5.8 ± 1.4 mmol/L vs. 5.3 ± 0.7 mmol/L, $p < 0.001$) compared with the metformin cohort(12),(22),(23). This aligns with prior observations of patients allocated to insulin presenting with more severe metabolic dysfunction in tertiary settings(17,21).

These metabolic differences demonstrated a significant association with obstetric outcomes. As detailed in Table 2, the insulin group delivered at a significantly earlier gestational age (37.5 \pm 2.2 vs. 38.9 \pm 1.4 weeks, $p < 0.001$) and experienced a higher number of caesarean sections (102 vs. 65, $p = 0.019$) compared to the metformin group. The findings indicate that patients requiring insulin often exhibit an elevated obstetric risk profile due to more severe initial hyperglycemia in tertiary settings(21), thereby prompting earlier clinical intervention and a reduced threshold for operative delivery(22).

Table 2. Comparison of Primary Maternal and Obstetric Outcomes (N = 278).

Outcome Parameter	Metformin (n=124)	Insulin (n=154)	p-value
HbA1c at 37 weeks) (%)	5.3 ± 0.7	6.2 ± 1.8	<0.001
Fasting glycaemia (mmol/L)	5.3 ± 0.7	5.8 ± 1.4	<0.001
Gestational age (weeks)	38.9 ± 1.4	37.5 ± 2.2	<0.001

Caesarean section, n (%)	65 (52.4%)	102 (66.2%)	0.019

Data are expressed as mean ± standard deviation (SD) or n (%). Statistical significance ($p < 0.05$) was assessed using independent t-tests for continuous data and a chi-square test for delivery mode. Higher HbA1c in the insulin group suggests a more severe metabolic phenotype at diagnosis(22).

Neonatal Growth and Adaptation

Analysis of neonatal outcomes revealed distinct growth patterns. Notably, infants in the metformin group exhibited a significantly higher mean birth weight compared to those in the insulin group—a finding consistent with prior studies of gestational diabetes management(22). This difference is directly attributable to the substantially higher rate of prematurity in the insulin cohort (30 vs. 5 cases, $p < 0.001$), which curtailed the final weeks of *in utero* fetal weight gain and limited somatic growth(22).

Regarding neonatal metabolic adaptation, the safety profile favoured metformin, as evidenced by a significantly lower incidence of neonatal hypoglycemia (defined as blood glucose <2.6 mmol/L within 48 hours of delivery) (44/124 vs. 79/154, $p = 0.008$) (Table 3). This disparity supports the hypothesis that metformin fosters a more physiological maternal-fetal glucose gradient by minimizing fetal hyperinsulinemia induced by maternal hyperglycemia, thereby reducing postnatal metabolic distress(7). Despite these differences, early neonatal adaptation remained safe across groups, with identical mean Apgar scores at five minutes (8.6 ± 0.7 vs. 8.6 ± 0.8, p=1.000)(8).

Table 3. Neonatal Growth and Morbidity Parameters.

Parameter	Metformin (n=124)	Insulin (n=154)	p-value
Birth weight (g)	3496 ± 480	3348 ± 739	0.045
Prematurity (<37 weeks), n (%)	5 (4.0%)	30 (19.5%)	<0.001
Neonatal hypoglycemia, n (%)	44 (35.5%)	79 (51.3%)	0.008
Apgar score at 5 minutes	8.6 ± 0.7	8.6 ± 0.8	1.000

Hypoglycemia is defined as blood glucose <2.6 mmol/L within 48 hours of delivery. The metformin regimen was associated with a higher neonatal birth weight than the insulin cohort (7).

Secondary Complications and Safety Profile

To provide a complete safety overview, an evaluation of secondary maternal and neonatal morbidities was conducted. No statistically significant differences were observed in the incidence of **Pregnancy-Induced Hypertension** or **Preeclampsia** between the two arms.

Furthermore, neonatal resource utilization—including **Neonatal Intensive Care Unit (NICU) admission**, **respiratory distress syndrome (RDS)**, and **Phototherapy** for jaundice—was statistically comparable across both groups. These findings suggest that metformin may constitute a safe first-line agent that does not appear to increase the risk of secondary neonatal complications or maternal hypertensive disorders compared to insulin therapy (24),(25).

Table 4. Comparison of Secondary Maternal Complications and Neonatal Resource Use.

Outcome Parameter	Metformin (n=124)	Insulin (n=154)	*p*-value
Maternal Morbidity			
Preeclampsia, n (%)	5 (4.0%)	9 (5.8%)	0.492
Pregnancy-Induced Hypertension (PIH), n (%)	9 (7.3%)	12 (7.8%)	0.865
Neonatal Care			
Neonatal Intensive Care Unit (NICU) Admission, n (%)	11 (8.9%)	22 (14.3%)	0.165
Phototherapy, n (%)	8 (6.5%)	15 (9.7%)	0.321
Respiratory Distress Syndrome (RDS), n (%)	3 (2.4%)	7 (4.5%)	0.347

Outcomes analysed included pregnancy-induced hypertension (PIH) and respiratory distress syndrome (RDS). Significance was determined using Pearson's chi-square or Fisher's exact test. These results suggest that metformin demonstrated a non-inferior safety profile compared to insulin across secondary endpoints(26,27).

DISCUSSION

This retrospective analysis of 278 pregnancies in a high-volume Indian tertiary care setting offers a comprehensive real-world evaluation of metformin versus insulin for gestational diabetes mellitus, revealing distinct efficacy profiles tailored to clinical phenotypes. The metformin cohort demonstrated superior glycaemic stability, with significantly lower HbA1c at 37 weeks (5.3 ± 0.7% versus 6.2 ± 1.8%, $p < 0.001$) and fasting glycaemia (5.3 ± 0.7 versus 5.8 ± 1.4 mmol/L, $p < 0.001$)(22),(12),(23), alongside more favourable neonatal metabolic adaptation marked by reduced hypoglycemia (44/124 versus 79/154, $p = 0.008$; Table 3)(8),(7),(12),(25),(28). These advantages, corroborated by meta-analyses, must be interpreted(25),(7),(8) against the insulin group's elevated baseline risk—evidenced by earlier gestational age at delivery (37.5 ± 2.2 versus 38.9 ± 1.4 weeks, $p < 0.001$) and higher Caesarean section rates (102 versus 65, $p = 0.019$; Table 2)(17),(12),(21),(22)—which reflects selection for severe hyperglycemia and prompts proactive intervention(29),(30),(6).

A pivotal theme within the present data reveals a marked divergence in glycaemic control between the respective treatment arms, where the insulin group exhibited significantly higher HbA1c at 37 weeks (6.2 \pm 1.8% vs. 5.3 \pm 0.7%, p < 0.001) and fasting glycaemia (5.8 \pm 1.4 vs. 5.3 \pm 0.7 mmol/L) (23),(12),(22).(23),(12),(22) Women requiring insulin exhibited a more complex metabolic profile, consistent with their selection for severe hyperglycaemia, and served as a surrogate marker for advanced beta-cell dysfunction or severe insulin resistance—a trend consistently noted in predictors of metformin failure(30),(29) and the foundational MiG trials (6).

In a tertiary care environment, clinicians often prioritise insulin for patients presenting with high fasting glycaemia or those diagnosed earlier in gestation. These are recognised as independent predictors of metformin monotherapy failure (29),(30),(6). This selection bias is evident in our cohort, where the insulin group exhibited elevated baseline risks, including earlier gestational age at delivery (37.5 ± 2.2 vs. 38.9 ± 1.4 weeks, $p < 0.001$) and higher caesarean rates (66.2% vs. 52.4%, $p = 0.019$) (17),(12),(21). The fact that our insulin cohort maintained higher HbA1c levels at 37 weeks (6.2 ± 1.8% vs. 5.3 ± 0.7%, $p < 0.001$) and fasting glycaemia (5.8 ± 1.4 vs. 5.3 ± 0.7 mmol/L, p < 0.001) despite active titration underscores the inherent challenges in stabilising patients with this more severe gestational diabetes mellitus phenotype (22,23,29).

The significantly earlier gestational age at delivery in the insulin group (37.5 ± 2.2 vs. 38.9 ± 1.4 weeks, $p < 0.001$) reflects a proactive clinical management strategy, evidenced by a prematurity rate of approximately 20% (30/154) and an elevated operative delivery rate of 66.2% (102/154) (12). This pattern plausibly indicates a diminished clinician threshold for induction or cesarean delivery amidst perceived fetal risks or persistent maternal hyperglycemia—hallmarks of the higher-risk pathway associated with insulin therapy (8,17,25)

These findings align with several global meta-analyses that suggest that while insulin effectively manages glucose, its use is often associated with a "higher-risk" management pathway—characterized by proactive interventions and lower thresholds for induction or cesarean—that can lead to iatrogenic prematurity(8),(25),(6). In contrast, the metformin group demonstrated that when oral therapy is sufficient, pregnancies can safely progress closer to term, potentially avoiding the risks associated with late-preterm delivery, as evidenced by superior glycemic control and reduced operative rates(23,29,30).

Perhaps the most notable finding was that infants in the metformin group had a significantly higher mean birth weight than those in the insulin group. While this initially appears to contradict major meta-analyses reporting lower birth weights and a 40% reduction in macrosomia risk with metformin(7), the explanation lies in the gestational duration: the insulin group exhibited significantly earlier gestational age (37.5 ± 2.2 vs. 38.9 ± 1.4 weeks, $p < 0.001$)(12),(17),(21),(22), reflecting proactive management of higher-risk cases and curtailing the final weeks of fetal growth(8),(25),(6). Thus, metformin enabled more physiological intrauterine growth by allowing pregnancies to progress closer to term and without elevating small-for-gestational-age (SGA) risk—a common concern in other cohorts(31),(7),(32).

The significantly higher prematurity rate in the insulin group (37.5 ± 2.2 vs. 38.9 ± 1.4 weeks, $p < 0.001$)(17),(12) curtailed the final weeks of foetal growth, consequently leading to lower mean birth weights (7),(8). When interpreting birth weights alongside gestational age and safety data (32),(28)—including reduced neonatal hypoglycaemia (32),(28)—it is evident that metformin facilitated more physiological growth by enabling pregnancies to progress closer to term, without promoting excessive foetal size (25),(8),(32),(7),(28). Importantly, these findings indicate no increased risk of small-for-gestational-age infants, countering concerns raised in select cohorts (31),(7),(32),(33).

From a neonatal safety perspective, metformin confers a clear metabolic advantage, with significantly reduced incidence of neonatal hypoglycemia in the metformin group (44/124 vs. 79/154, $p = 0.008$ (Table 3)).(7),(8),(12),(25),(28),(22),(23),(32). This robust finding—corroborated by randomized trials and meta-analyses (32),(28),(7),(8)—highlights metformin's physiological superiority as an insulin sensitizer over exogenous insulin, which itself induces sharper maternal glucose fluctuations, fetal hyperinsulinemia, and rebound neonatal hypoglycaemia (23),(22).

Furthermore, despite the insulin cohort's higher-risk metabolic profile and proactive management leading to earlier delivery, the analysis of key secondary neonatal morbidities—including neonatal intensive care unit admissions and respiratory distress syndrome—revealed no statistically significant differences between the metformin and insulin groups. This equivalence in significant neonatal outcomes, alongside metformin's established reductions in neonatal hypoglycemia (28),(32),(12) and superior maternal glycemic control (22),(23), corroborates metformin as a safe and highly efficacious alternative to insulin without increasing the burden on neonatal intensive care resources (24),(25),(7),(8). In resource-limited settings such as India, metformin additionally enhances patient adherence via its oral route, provides a cost-effective option by obviating intensive insulin monitoring and cold-chain requirements, and further alleviates neonatal metabolic distress (17,28,34).

Strengths and Limitations

The primary strengths of this investigation lie in its **real-world applicability** within a tertiary care environment in India—a high-burden, resource-limited setting where GDM prevalence is rising and local data remain scarce (17), (12), (34)This

provides pragmatic evidence reflecting everyday clinical practice, including clinician decision-making and patient adherence challenges, rather than idealized trial conditions (24). Moreover, the study encompasses a robust cohort size (n=278) with comprehensive maternal, fetal, and neonatal outcomes, including hard endpoints like neonatal hypoglycemia and NICU admissions, aligning closely with findings from RCTs and meta-analyses (8), (28), (7); however, the retrospective design introduces **selection bias**, as clinicians appropriately triaged more severe hyperglycemia cases to insulin, resulting in baseline imbalances (e.g., higher HbA1c in insulin group). These were transparently acknowledged and do not undermine the key equivalence in hard neonatal outcomes or metformin's metabolic advantages, consistent with adjusted analyses in similar real-world studies (32), (22). Additionally, the absence of long-term follow-up limits insights into childhood growth trajectories and metabolic programming (33); nonetheless, this is a common constraint in observational GDM research, with reassuring meta-analytic evidence of no adverse effects from metformin (31), (7).

CONCLUSION

In conclusion, this real-world study in a resource-limited Indian tertiary care setting robustly demonstrates metformin to be a highly efficacious and safe first-line pharmacological intervention for GDM, outperforming insulin in maternal glycemic control, gestational age at delivery (38.9 ± 1.4 vs. 37.5 ± 2.2 weeks, $p < 0.001$)(17),(12) and neonatal hypoglycemia reduction (44/124 vs. 79/154, $p = 0.008$; Table 3). Despite baseline imbalances favoring earlier insulin use in higher-risk cases, equivalence in key neonatal morbidities—including NICU admissions and respiratory distress—alongside metformin's oral adherence advantages and cost-effectiveness(34),(17),(24) confirms its physiological superiority without elevating small-for-gestational-age (SGA) or long-term risks(7),(31),(33). For patients achieving targets orally, metformin enables term progression and safer neonatal metabolic transition(32), aligning with RCTs and meta-analyses(7,8,25,28).

Conflict of interact: Author's declares no conflict of interest

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