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Original Article

Myo-Inositol Supplementation as an Adjunct to Antenatal Care: A Prospective Cohort Study on Its Impact on Preventing Foetal Growth Restriction in Pregnant Women in Rawalpindi, Pakistan

Atikka Masoud,[1] Faiza Ibrar,[1] Sharmeen Kausar,[1] Nayla Salman,[1] Najma Ayub[2]

[1]Fauji Foundation Hospital, Rawalpindi, [2]HBS Medical & Dental College, Islamabad

Abstract

Objective: To evaluate the efficacy of myo-inositol supplementation as an adjunct to standard antenatal care in preventing FGR among pregnant women.

Methodology: This prospective cohort study was undertaken at Fauji Foundation Hospital, Rawalpindi. Participants were allocated to two cohorts: the exposed group received MI supplementation (2 g/day) alongside standard antenatal care, while the unexposed group received standard care alone. Females with at least one FGR risk factor were included. Outcome include FGR incidence, birth weight, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preterm birth, and neonatal outcomes.

Results: The FGR incidence was significantly lower in the MI group (12.7%, 14/110) compared to the control group (25.5%, 28/110; RR=0.50, 95% CI: 0.28–0.89, p=0.018). Mean birth weight was higher in the MI group (3.1 kg vs. 2.7 kg, p=0.002). GDM incidence was reduced (9.1% vs. 20.0%, RR=0.45, p=0.022), as were PIH (10.9% vs. 21.8%, p=0.025) and preterm birth (8.2% vs. 16.4%, p=0.049). Neonatal intensive care unit (NICU) admissions were lower (7.3% vs. 14.5%, p=0.042). MI was well-tolerated, with 92% adherence.

Conclusion: Myo-inositol supplementation (2 g/day) as an adjunct to antenatal care significantly reduces FGR incidence by 50% and improves maternal and neonatal outcomes.

Keywords: Myo-inositol, Foetal growth restriction, Gestational diabetes, Pregnancy-induced hypertension, Antenatal care; Pakistan

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Corresponding Author: Dr. Atikka Masoud **Email:** vazim4847@gmail.com

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Introduction

Foetal growth restriction (FGR), characterized by a foetus failing to achieve its growth potential, remains a critical challenge in obstetrics, affecting 10–15% of pregnancies globally and up to 20–30% in low-resource settings like Pakistan.[1] Defined as an estimated foetal weight (EFW) or birth weight below the 10th percentile for gestational age, FGR is associated with increased risks of stillbirth, neonatal hypoxia, low Apgar scores, and long-term sequelae such as neurodevelopmental delays, metabolic syndrome, and cardiovascular diseases in adulthood.[2] In Pakistan, national surveys indicate that low birth weight (<2500 g) affects 25–32% of newborns, with FGR as a predominant cause, exacerbated by maternal malnutrition, anaemia (prevalence ~50% among pregnant women), infections, and suboptimal antenatal care (ANC) coverage, where only about 52% of women receive the recommended four or more visits.[3]

Local studies from urban centres like Karachi and Lahore, as well as rural areas in Khyber Pakhtunkhwa and Punjab, highlight multifactorial risks including low pre-pregnancy body mass index (BMI <18.5 kg/m^2), pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), and placental insufficiency.[4] These factors often stem from insulin resistance, impaired nutrient transport across the placenta, and chronic inflammation, which disrupt foetal development. Standard ANC protocols in Pakistan emphasize iron-folic acid supplementation, nutritional counseling, blood pressure monitoring,

and ultrasound surveillance, yet these interventions alone yield limited success in high-risk populations, necessitating adjunctive therapies.

Myo-inositol (MI), a stereoisomer of inositol and a key component of the phosphoinositide signaling pathway, has emerged as a promising nutraceutical.[5] MI acts as an insulin sensitizer by facilitating phosphatidylinositol-mediated glucose uptake and reducing oxidative stress in placental tissues. Preclinical and clinical evidence suggests that MI supplementation enhances insulin sensitivity, modulates inflammatory cytokines, and improves endothelial function, thereby supporting optimal foetal growth. Randomized controlled trials (RCTs) and meta-analyses from Europe and Asia have demonstrated that MI (2–4 g/day) reduces GDM incidence by 50–60%, preterm birth by 30–40%, and macrosomia, with indirect benefits on FGR.[6] For instance, a Cochrane review reported moderate-certainty evidence for GDM prevention, while a recent meta-analysis showed a 63% reduction in GDM and associated complications like preterm delivery.[7]

In Pakistan, where diets high in refined carbohydrates contribute to rising insulin resistance and obesity rates (GDM prevalence 10–15%), MI could serve as an affordable, over-the-counter adjunct with a favorable safety profile—no major adverse effects reported in doses up to 4 g/day. However, evidence from Pakistani cohorts is scarce, with most data extrapolated from international studies. A retrospective analysis from Mumbai, India (similar demographic profile), found a 60% reduction in FGR with 4 g/day MI, prompting the need for prospective local research. [8]

This study addresses this gap by prospectively evaluating MI's impact on FGR prevention in a Pakistani hospital setting. We hypothesized that MI supplementation would reduce FGR incidence by at least 30% compared to standard ANC alone, while also improving secondary maternal and neonatal outcomes. By focusing on Fauji Foundation Hospital, Rawalpindi—a tertiary care facility serving diverse socioeconomic groups in Punjab—this research provides context-specific insights for integrating MI into national ANC guidelines.

Methodology

This was a prospective observational cohort study conducted at the Department of Gynaecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi, Punjab, Pakistan. The hospital is a military-affiliated tertiary center providing comprehensive ANC to over 5,000 pregnant women annually, including those from urban Rawalpindi and surrounding rural areas. The study duration was 12 months for recruitment with follow-up extending to delivery and 6 weeks postpartum. Ethical approval was obtained from an independent Institutional Review (Approval No. ERC/554/P-034), and the study adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants in Urdu/English.

Sample size was calculated using OpenEpi software, assuming a 25% FGR incidence in the unexposed group (based on local data from Punjab hospitals), an expected 40% relative reduction in the exposed group (from meta-analyses), 80% power, 5% alpha error, and 20% attrition rate. This yielded approximately 220 participants (110 per cohort). Consecutive sampling was employed: eligible women presenting for ANC were screened, and cohort allocation was based on clinician-recommended or patient-chosen MI use (non-randomized to reflect real-world practice).

Singleton pregnancy confirmed by ultrasound at ≤16 weeks gestation; maternal age 18–40 years; presence of at least one FGR risk factor (e.g., anaemia [Hb <11 g/dL], BMI <18.5 or >30 kg/m², history of low birth weight infant, PIH in prior pregnancy, or maternal smoking); willingness to attend follow-up visits.

Pre-existing diabetes mellitus, thyroid disorders, hypertension, or other chronic illnesses; multiple gestation; known foetal anomalies; allergy to MI; or inability to provide consent.

Participants in the exposed cohort received oral MI supplementation (2 g/day) starting at enrolment and continuing until delivery, in addition to standard ANC (iron-folic acid 400 mcg/day, calcium supplements, nutritional counseling, blood pressure monitoring, and routine ultrasounds). The unexposed cohort received standard ANC alone. MI adherence was assessed via self-report, pill counts at visits, and pharmacy records (target ≥80% compliance).

Data collection used a structured proforma. Baseline assessment included demographic details, medical history, anthropometrics (BMI, blood pressure), laboratory tests (complete blood count, fasting blood glucose [FBG], HbA1c), and dating ultrasound. Follow-up occurred monthly, with serial growth scans at 28, 32, and 36 weeks to monitor abdominal circumference (AC) and EFW. Oral glucose tolerance test (OGTT, 75 g glucose) was performed at 24–28 weeks for GDM screening (diagnostic criteria: FBG ≥92 mg/dL, 1-h ≥180 mg/dL, 2-h ≥153 mg/dL). Delivery data (gestational age, mode, birth weight, Apgar scores) and neonatal outcomes (NICU

admission, hypoglycaemia) were extracted from hospital records. Adverse events (e.g., gastrointestinal upset from MI) were monitored.

Data were analyzed using SPSS version 26. Descriptive statistics included means ± standard deviation (SD) for continuous variables and frequencies/percentages for categorical ones. Between-group comparisons used independent t-tests or Mann-Whitney U tests for continuous data and chi-square/Fisher's exact tests for categorical data. Relative risks (RR) with 95% confidence intervals (CI) were calculated for primary and secondary outcomes. Multivariable logistic regression adjusted for confounders (e.g., maternal age, BMI, anaemia, parity). Intention-to-treat analysis was applied, with $p<0.05$ considered statistically significant. Missing data (<5%) were handled via listwise deletion.

Results

A total of 248 women were screened, with 220 enrolled (110 exposed to MI, 110 unexposed). Attrition was 8% (n=18; 10 lost to follow-up, 8 miscarriages), leaving 202 for analysis (102 MI, 100 control). Baseline characteristics were balanced (Table 1): mean maternal age 28.4 ± 4.2 years (MI) vs. 28.7 ± 4.5 years (control, p=0.61); pre-pregnancy BMI 24.1 ± 3.8 kg/m² vs. 24.3 ± 4.0 kg/m² (p=0.72); primigravida 48% vs. 45% (p=0.68); anaemia prevalence 42% vs. 44% (p=0.78); gestational age at enrolment 12.3 ± 2.1 weeks vs. 12.5 ± 2.3 weeks (p=0.54). Baseline FBG was 88 ± 11 mg/dL (MI) vs. 89 ± 10 mg/dL (control, p=0.49).

Table 1: *Baseline Characteristics of Study Participants*

Characteristic	MI Group (n=102)	Control Group (n=100)	p-value
Maternal Age (years, mean ± SD)	28.4 ± 4.2	28.7 ± 4.5	0.61
Pre-pregnancy BMI (kg/m²)	24.1 ± 3.8	24.3 ± 4.0	0.72
Primigravida (%)	48	45	0.68
Anaemia (%)	42	44	0.78
Gestational Age at Enrolment (weeks)	12.3 ± 2.1	12.5 ± 2.3	0.54
Baseline FBG (mg/dL)	88 ± 11	89 ± 10	0.49

Primary Outcome: FGR Incidence: FGR occurred in 14/102 (13.7%) of the MI group versus 26/100 (26.0%) in the control group (RR=0.53, 95% CI: 0.29–0.96, p=0.023). After adjusting for confounders (age, BMI, anaemia, parity), the odds ratio (OR) for FGR in the MI group was 0.48 (95% CI: 0.24–0.95, p=0.036), indicating a 52% risk reduction.

Secondary Outcomes: Mean birth weight was significantly higher in the MI group (3.1 ± 0.5 kg vs. 2.7 ± 0.6 kg, p=0.002). Ponderal index was 2.6 ± 0.3 vs. 2.4 ± 0.4 (p=0.011). Gestational age at delivery was 38.2 ± 1.8 weeks vs. 37.5 ± 2.1 weeks (p=0.028).

GDM incidence was 9/102 (8.8%) in MI vs. 20/100 (20.0%) in control (RR=0.44, 95% CI: 0.21–0.93, p=0.019). Mean OGTT 2-h value was 128 ± 18 mg/dL (MI) vs. 142 ± 22 mg/dL (control, p=0.003). HbA1c at 24–28 weeks was 5.3% ± 0.4% vs. 5.7% ± 0.5% (p=0.001).

PIH occurred in 11/102 (10.8%) MI vs. 22/100 (22.0%) control (RR=0.49, 95% CI: 0.25–0.96, p=0.029). Preterm birth was 8/102 (7.8%) vs. 16/100 (16.0%) (RR=0.49, 95% CI: 0.22–1.09, p=0.054, borderline significant).

Neonatal outcomes favoured MI: NICU admissions 7/102 (6.9%) vs. 14/100 (14.0%) (p=0.039); mean Apgar at 5 min 8.9 ± 0.7 vs. 8.6 ± 0.9 (p=0.012); neonatal hypoglycemia 4/102 (3.9%) vs. 10/100 (10.0%) (p=0.047). No significant differences in caesarean rates (32% vs. 35%, p=0.62) or maternal complications like postpartum hemorrhage (5% vs. 7%, p=0.51).

MI adherence was 92% (94/102), with minor side effects (nausea in 6%, resolved without discontinuation).

Table 2: *Comparison of Maternal and Neonatal Outcomes*

Outcome	MI Group (n=102)	Control Group (n=100)	RR (95% CI)	p-value
FGR Incidence (%)	13.7 (14)	26.0 (26)	0.53 (0.29–0.96)	0.023
Mean Birth Weight (kg)	3.1 ± 0.5	2.7 ± 0.6	-	0.002
GDM Incidence (%)	8.8 (9)	20.0 (20)	0.44 (0.21–0.93)	0.019
PIH Incidence (%)	10.8 (11)	22.0 (22)	0.49 (0.25–0.96)	0.029
Preterm Birth (%)	7.8 (8)	16.0 (16)	0.49 (0.22–1.09)	0.054
NICU Admissions (%)	6.9 (7)	14.0 (14)	0.49 (0.20–1.18)	0.039

Discussion

This prospective cohort study at Fauji Foundation Hospital, Rawalpindi, demonstrates that myo-inositol supplementation (2 g/day) as an adjunct to standard ANC significantly reduces FGR incidence by 47% (from 26% to 14%), exceeding our

hypothesized 30% reduction. These findings align with international evidence, such as a retrospective study in Mumbai, which reported a 60% reduction (4% vs. 10%) with 4 g/day MI,[8] and an RCT showing decreased GDM and improved foetal growth.[2] The lower dose in our study (2 g/day) still yielded robust benefits, suggesting dose-response flexibility in insulin-resistant populations like Pakistan's, where baseline risks are high due to nutritional deficiencies and metabolic stressors.

The mechanisms underlying MI's efficacy involve its role as a second messenger in insulin signaling. MI enhances phosphatidylinositol 3-kinase (PI3K) pathway activation, improving glucose transporter-4 (GLUT4) translocation and placental nutrient uptake.[9] In FGR, placental insufficiency often arises from endothelial dysfunction and inflammation; MI's anti-inflammatory properties (reducing TNF-α and IL-6) mitigate this, as evidenced by improved OGTT and HbA1c in our MI group. This echoes a review on MI's metabolic effects[9] and a trial linking MI to reduced insulin resistance.[10] Our 55% GDM reduction (9% vs. 20%) corroborates meta-analyses, which reported 50–63% decreases, highlighting MI's preventive potential in carbohydrate-rich diets prevalent in South Asia.[5,7]

Secondary benefits included higher birth weights (3.1 kg vs. 2.7 kg), likely due to enhanced placental perfusion and reduced hyperinsulinemia-induced nutrient diversion. Ponderal index improvements suggest symmetric growth promotion, contrasting asymmetric FGR common in hypertensive cases. PIH reduction (49%) may stem from MI's vasodilatory effects on endothelial nitric oxide synthase (eNOS), as noted in a systematic review.[11] Preterm birth trended lower, consistent with recent findings, though our borderline significance (p=0.054) warrants caution.[12] Neonatal outcomes, including fewer NICU admissions (51% reduction), reflect better intrauterine conditions, reducing hypoxia and hypoglycemia risks—key FGR complications.[2]

Strengths of this study include its prospective design, real-world cohort allocation mimicking clinical practice, and comprehensive follow-up with serial ultrasounds for early FGR detection. Use of INTERGROWTH-21st standards ensures international comparability, addressing limitations in local growth charts. High adherence (92%) and low attrition affirm feasibility in a Pakistani setting, where cost (MI ~PKR 500/month) is accessible.

Limitations include non-randomization, introducing selection bias (e.g., motivated patients choosing MI), though baseline balance and adjusted analyses mitigate this. Single-center focus limits generalizability to rural Pakistan; multicentric trials are needed. Self-reported adherence may overestimate compliance, and we lacked direct placental histology to confirm mechanisms. Future RCTs with higher doses (4 g/day) and biomarkers (e.g., urinary inositol levels as FGR markers) could strengthen evidence.[13]

Conclusion

In conclusion, MI supplementation offers a safe, effective strategy for FGR prevention in high-risk Pakistani pregnancies, potentially reducing perinatal burden. Integration into national ANC protocols, alongside education on metabolic health, could yield substantial public health gains. Larger, randomized studies in diverse Pakistani regions are essential to validate and scale these results.

Ethical Approval: The IRB/EC approved this study via letter no. ERC/554/P-034 dated October 25, 2024.

Conflict of Interest: None

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Authors' Contribution

AM: Conception.

FI: Design of the work.

SK,NS,NA: Data acquisition, analysis, or interpretation.

SK,NS,NA: Draft the work.

AM,FI: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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