Original Article

Premature birth and insulin resistance in infancy: A prospective cohort study

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ABSTRACT

Objective: This study was done to determine the role of prematurity and other variables to predict insulin sensitivity in infancy. **Subjects and Methods:** In this prospective study, 36 preterm appropriate for gestational age (AGA), 11 preterm small for gestational age (SGA), and 17 term SGA included as study cohort and 36 term AGA as control cohort. Detailed anthropometry assessment was performed at birth, 3, 6, and 9 months and at 9 months, fasting plasma glucose and serum insulin was done. Insulin resistance was determined by using homeostasis model assessment version 2. **Results:** It is found that preterm AGA (mean difference 0.617, 95% confidence interval [CI]; 0.43–0.80, $P = 0.0001$), preterm SGA (mean difference 0.764, 95% CI; 0.44–1.09, $P = 0.0001$), and term AGA (mean difference 0.725, 95% CI; 0.49–0.96, $P = 0.0001$) group had significantly higher insulin resistance than control. There was no significant difference in between preterm SGA and preterm AGA (mean difference 0.147 95% CI; −0.13–0.42, $P = 0.927$). In multiple regression models, SGA status ($\beta = 0.505$) was more significant predictor of insulin resistance index than gestational age ($\beta = -0.481$), weight-for-length ($\beta = 0.315$), and ponderal index ($\beta = -0.194$). **Conclusion:** Preterm birth is a risk factor for the future development of insulin resistance which may develop as early as infancy.

Key words: Homeostasis model assessment, insulin resistance index, ponderal index, preterm, small for gestational age

Introduction

Low birth weight (LBW) is associated with an increased risk for a number of conditions arising in adulthood, such as type 2 diabetes, dyslipidemia, coronary artery disease, essential hypertension, and cerebrovascular accidents.[1,2] Insulin resistance (i.e., reduced insulin sensitivity) is a well-established, early metabolic abnormality in the pathogenesis of these conditions.[3-6]

It has been proposed that a reduced insulin sensitivity in LBW subjects results from the adaptation to adverse *in utero* conditions during a critical period of development.[2]

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However, it is well known that LBW newborns are also exposed to postnatal stress, which is reflected in higher neonatal morbidity and mortality.[7,8] This has led to the hypothesis that postnatal stress may as well contribute to the metabolic modifications in LBW children, independently of the adequacy of their birth weight to gestational age. If early postnatal stress plays a role in long-term metabolic modifications, prematurity may be an important confounding factor.[7,8] Most previous studies linking LBW to the propensity toward disease in adulthood have focused on those who were small for gestational age (SGA) and born at term. Only few studies demonstrate the association of prematurity with a tendency to disease in letter adulthood but data's are still conflicting, and further evidence is still required to establish a definitive role. Moreover, it has been recognized that reduced insulin sensitivity, a hallmark in

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most LBW-related conditions may be present as early as the 1st year of life.[9,10] Hence, we planned a prospective cohort study to elaborate insulin sensitivity in infants who were LBW and born prematurely.

In addition, it has been suggested that besides *in utero* stress and postnatal stress, other independent variables such as ponderal index (PI), birth weight, catch-up growth for weight and length, and current weight and length may also contribute in insulin sensitivity. Our second aim, therefore, was to determine the role of other variables to predict insulin sensitivity in infancy.

Subjects and Methods

The present study was a prospective (cohort) study, conducted in Umaid Hospital and Dr. S. N. Medical College, Jodhpur, over a period of 12 months. Sample size was calculated at power 80%, confidence interval (CI) 95%, four independent variables and assuming expected multiple regression coefficient 0.4 as observed in a previous study titled as, "Determinants of insulin sensitivity and secretion in very-low-birth weight children" Bazaes *et al*. 2004. The resulting value of sample size came out to be 68. In the beginning phase of the study, total 150 neonates born in this tertiary care center were enrolled to compensate loss during follow-up. Those with a birth weight at par or above the 10th percentile were defined as being appropriate for gestational age (AGA), and those with a birth weight below 10th percentile as being SGA. Neonates born 28–36 weeks of gestational age were defined as preterm. The study population was divided into four strata (preterm AGA, preterm SGA, term AGA, and term SGA) according to their gestational age and their birth weight for gestation thereafter sampling was done by stratified random sampling method. The study cohort was formed by 50 preterm AGA and control was formed by 50 term AGA neonates. Another cohort of 50 SGA neonates (25 preterm SGA and 25 term SGA) was also included. This group was added for the sake of comparison and in order to determine other variables to predict insulin sensitivity in infancy. During follow-up (till 9 months of the age) numbers of participating infants were decreased, 15 were excluded (8 preterm AGA, 1 term AGA, 5 preterm SGA, and 1 term SGA) and 35 did not come in follow-up (6 preterm AGA, 13 term AGA, 9 preterm SGA, and 7 term SGA). Finally, 100 infants (36 preterm AGA, 36 term AGA, 11 preterm SGA, and 17 term SGA) were gone through anthropometric and hormonal evaluation, with adequate sample size.

Exclusion criteria included neonates of diabetic mother and those having first degree relative with type-2 diabetes mellitus, chronic illness, or medical therapy known to influence insulin sensitivity, chromosomal syndromes, congenital anomalies, congenital infections and sick neonates (intracranial hemorrhage, perinatal asphyxia, pyomeningitis, necrotizing enterocolitis), neonates requiring positive pressure ventilation, and vasopressors.

Approval for the study was obtained from the Dr. S. N. Medical College Institutional Research Review Board. Written informed consent was obtained from the parents or guardians. The nature, purpose, and possible risks of the study were explained to the parents in detail before consent was obtained.

Complete history including family history and antenatal, natal, and postnatal history was taken in all subjects. General physical examination and systemic examination was done, and accurate assessment of gestational age was done by using the expanded New Ballard Score.[11] Detailed anthropometry (length, weight, PI, head circumference, chest circumference, and weight-for-length) was performed according to the World Health Organization (WHO) Guidelines[12] by a trained pediatrician. Birth weight, length, and head circumference were converted into standard deviation scores (SDS) (Z = [observed value − mean value]/SD) according to the WHO reference to allow comparison of subjects with different gestational ages, chronological ages, and sexes.[13,14] The weight-for-length index was used to provide an age-adjusted evaluation of relative obesity.[15,16] Routine blood investigation and fasting blood sugar level of all neonates (after 2–4 h fasting) were performed.

Conventionally, all subjects below the age of 1 year are considered as infants. However, the upper age cutoff for the enrolled subjects was limited to 9 months instead of 12 months in this study to avoid biases arising out of the transition to childhood from infancy during the last few months. The reason behind not using 6 months of age as cut off is because by that age, the term neonates may not be exposed to complementary feed, whereas preterm neonates would have received both breastfeeding and complementary feeding (corrected age of 6 months for prematurity).

Both cohorts and controls were followed at corrected age of 3 months, 6 months, and 9 months. All infants were on exclusive breastfeed for 5.56 ± 0.84 months (preterm AGA 5.47 ± 0.78, preterm SGA 5.60 ± 0.85, term AGA 5.60 ± 0.85, term SGA 5.79 ± 0.84, $P \geq 0.05$, range 4–7 months) and then started complementary feed according to the Indian Academy of Pediatrics guideline. On each follow-up, anthropometry assessment was performed.

At the age of 9 months (5 ml), blood sample was obtained for fasting plasma glucose and serum insulin (SI) level (after 2–4 h fasting). Glucose was estimated by glucose oxidase-peroxidase aminophenazone-phenol method using the commercially available kit (Human mBH, Weisbaden, Germany). SI was estimated by immunoradiometric assay using commercial kits (DPC Inc., Los Angeles, USA). The intra- and inter-assay coefficients of variation for the insulin were 5.2 and 7.3%, respectively; sensitivity was 1.2 μU/ml and specificity was 80%. Insulin resistance was determined using Homeostasis Model Assessment Version 2 (HOMA-2 calculator available at http://www.dtu.ox.ac.uk/homa). For calculation of HOMA-2, glucose values were converted to mg/dl and insulin levels to μU/ml.

Statistical methods

Differences in demographic characteristics and clinical measures between control and premature groups were investigated by means of analysis of variance for continuous variables and the Chi-square test for proportions. Differences in neonatal characteristics were evaluated with the use of Fisher's exact test for proportions and the Mann–Whitney U-test for continuous variables. General linear model (ANCOVA) was used to investigate differences in glucose-regulation variables among the four groups of subjects. The four groups, divided according to their gestational age (preterm vs. term) and weight for gestation (AGA vs. SGA), were included as factor, whereas PI and weight-for-length at 9 months (wfl) were included as covariance in this model. The specific hypotheses tested were the difference in insulin sensitivity between appropriate- and small-for-gestational-age subjects within the premature groups and the difference in insulin sensitivity between the premature groups and the term group. Further analysis was performed by multiple regression models using log insulin resistance index (IRI) as depended variable and gestational age, PI, weight-for-length, and SGA status as independent variables. The data on fasting SI and HOMA IRI were logarithmically transformed to meet the assumptions of normality. All analysis was carried out by using the SPSS Version 20.0 statistical package (SPSS, Inc., Chicago, USA).

Results

Out of hundred subjects, 36 preterm AGA, 11 preterm SGA, and 17 term SGA, as study cohorts and 36 term AGA, as control cohort, were enrolled in this study. Baseline characteristics of these groups are summarized in Table 1. As it was expected, gestational age, weight (SD score), length (SD score), head circumference (SD score), and weight-for-length index were significantly different among the groups. Preterm SGA babies were smaller (length SDS) (P = 0.013) and thinner than preterm AGA (P = 0.001 *post hoc* test). Data about neonatal characteristics were summarized in Table 2,

Table 1: Baseline characteristics of the study subjects*

Characteristic	Premature AGA (*n*=36)	Premature SGA (*n*=11)	Term control (*n*=36)	Term SGA (*n*=17)	*P*†
Neonatal					
Gestational age (weeks)	31.72±2.53	34.90±1.04	38.27±0.70	38.05±0.55	0.001
Male, *n* (%)	22 (61.11)	10 (90.90)	19 (52.77)	7 (41.17)	0.06
LSCS, *n* (%)	9 (25)	2 (18.18)	7 (19.44)	3 (17.64)	0.90
Weights (g)	1653±350	1523±250	2988±241	2178±188	0.001
Weights (Z-score)	−0.10±0.86	−2.26±0.75	−0.37±0.48	−2.21±0.59	0.001
Length (cm)	41.48±2.40	44.15±2.15	48.27±1.38	46.32±1.82	0.001
Length (Z-score)	0.10±1.09	−0.65±0.87	−0.41±0.57	−1.10±0.84	0.001
Head circumference (cm)	29.86±1.67	29.57±1.48	34.31±0.73	33.20±1.51	0.001
Head circumference (Z-Score)	0.72±1.10	−1.48±0.79	0.26±0.52	−0.36±1.06	0.001
Ponderal index (g × 100/cm^3)	2.310±0.369	1.767±0.225	2.663±0.248	2.205±0.287	0.001
Fasting blood sugar (mg/dl)	64.61±8.67	64.81±9.73	69.13±10.93	64.82±10.51	0.214
Nine months					
Weights (g)	7.060±0.413	7.603±0.349	8.075±0.513	8.085±0.300	0.001
Weights (Z-score)	−1.82±0.71	−1.37±0.50	−0.56±0.65	−0.46±0.58	0.001
Length (cm)	64.38±2.47	66.95±2.64	68.85±1.15	68.12±1.26	0.001
Length (Z-score)	−2.98±1.14	−2.14±1.33	−0.98±0.62	−1.20±0.77	0.001
Head circumference (cm)	41.26±1.47	42.43±1.66	44.29±0.66	43.17±1.10	0.001
Head circumference (Z-Score)	−2.52±1.21	−1.96±1.38	−0.135±0.60	−0.89±1.06	0.001
Weight-for-length Z-score	0.041±1.01	−0.048±1.22	0.05±0.78	0.36±0.60	0.585
Weight catch-up (g)	5405±470	6080±477	5086±542	5907±345	0.001
Weight catch-up (Z-score)	−1.72±1.23	0.88±0.86	−0.18±0.82	1.75±0.71	0.001
Length catch-up (cm)	22.91±2.11	22.80±3.0	20.58±1.29	21.80±1.45	0.001
Length catch-up (Z-score)	−3.09±1.73	−1.49±1.27	−0.57±0.69	−0.11±0.57	0.001

*Plus and minus values are means±SD. †ANOVA was used for continuous variables, and the Chi-square test was used for proportions. LSCS: Lower segment cesarean section, AGA: Appropriate for gestational age, SGA: Small for gestational age, ANOVA: Analysis of variance

and no significant difference was observed in maternal characteristics and oxygen requirement, antibiotic days, and days until full oral feeding established. Glucose regulation variables were summarized in Table 3. IRI (median 1.80, interquartile range 3.90 [0.53–4.39], skewness 1.60 [Rt skewed], kurtosis 2.42, mean 2.95, and SD 3.20) and SI (median 8.80, interquartile range 17.55 [2.62–20.16], skewness 1.67 [Rt skewed], kurtosis 2.94, mean 13.49, SD 14.29) had abnormal distribution and converted to Log 10 value to normalize the distribution [Figure 1]. Generalized linear model (ANCOVA) was constructed to adjust gestational age, weight for gestation, PI, and weight-for-length (R^2 = 0.76, adjusted R^2 = 0.75; means 75% variability explained by this model). Change in R^2 value for these factors show that gestational age, birth weight, and weight-for-length were good predictors for IRI (P = 0.0001) as compared to PI (P = 0.002). Pairwise contrast shows that (adjustment for multiple comparisons by Bonferroni), both preterm AGA (mean difference 0.617, 95% CI; 0.43–0.80, P = 0.0001) and preterm SGA (mean difference 0.764, 95% CI; 0.44–1.09, P = 0.0001) groups had significantly higher insulin resistance than term AGA group. Similarly, infants who had been born term SGA had significantly higher insulin resistance than term AGA (mean difference 0.725, 95% CI; 0.49–0.96, P = 0.0001). No significant difference was found in between preterm SGA group and preterm AGA group (mean difference 0.147 95% CI; −0.13–0.42, P = 0.927). It was noticed that when we combine both preterm cohort, insulin resistance gets increased by 5.2% but not become significantly higher (mean difference −0.076, 95% CI; −0.26–0.11, P = 0.95) than term SGA.

Further analysis was done by using multiple regression models summarized in Table 4. IRI at 9 months was found negatively correlated with gestational age (ρ = −0.42, P = 0.001), birth weight Z-score (ρ = −0.35, P = 0.001), PI (ρ = −0.61, P = 0.001), length at 9 months (Z-score) (ρ = −0.413, P = 0.001) and catch-up growth for length (ρ = −0.311, P = 0.002) and positively correlated with SGA status (ρ =0.511, P = 0.001), weight-for-length (ρ = 0.393, P = 0.001), and catch-up growth for weight (ρ = 0.198, P = 0.048).

Multiple regression models were constructed using sequential method including gestational age, PI, weight-for-length as continuous variables, and type according to weight for gestation (AGA vs. SGA) as categorical variables. Minimum variables which predict the largest amount of

Table 2: Maternal and neonatal characteristics in two groups of premature neonates

Characteristics	Premature AGA (*n*=36)	Premature SGA (*n*=11)	*P*†
Maternal, *n* (%)			
Preeclampsia	5 (13.88)	3 (27.27)	0.30
PROM	4 (11.11)	2 (18.18)	0.53
Antenatal glucocorticoids	5	2	0.72
Neonatal			
Inhaled oxygen therapy required, *n* (%)	21 (58.33)	5 (45.45)	0.45
Duration of inhaled oxygen therapy (days)	2.33±2.87	1.8±2.44	0.61
Duration of antibiotics therapy (days)	2.86±3.66	2.45±2.50	0.25
Duration until full oral feed established (days)	3.25±2.33	2.09±2.46	0.26

†Fisher's exact test was used for proportions, and the Mann-Whitney U-test was used for continuous variables. PROM: Premature rupture of membranes

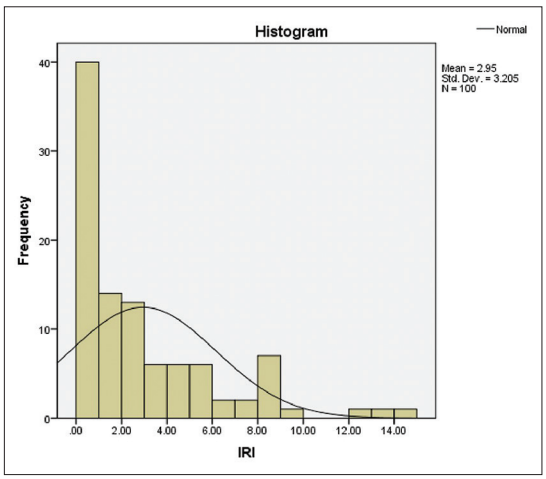

Figure 1: Right skewed distribution of insulin resistance index

Table 3: Indicator of glucose homeostasis*

Characteristic	Premature AGA (*n*=36)	Premature SGA (*n*=11)	Term control (*n*=36)	Term SGA (*n*=17)
Fasting glucose (mg/dl)	90.63±7.72	88.81±14.47	78.50±8.29	87.94±9.00
SI (μU/ml)	14.88±12.26	26.89±13.75	3.1±2.96	23.78±17.77
	10.89 (6.62-22.65)	32.72 (9.30-38.69)	2.36 (1.56-2.89)	19.56 (10.88-34.73)
Log_{10} SI	1.04±0.35	1.33±0.34	1.39±0.27	1.26±0.34
IRI	3.33±2.83	6.12±3.39	0.59±0.57	5.05±3.71
	2.39 (1.42-4.88)	8.07 (1.84-8.70)	0.43 (0.23-0.62)	4.15 (2.32-7.07)
Log_{10} IRI	0.38±0.35†	0.66±0.39‡	−0.32±0.28	0.59#

*Plus and minus values are means±SD. Q_1-Q_3 values are median and 25-75 interquartile range. *P* values were derived from general linear model using univariate analysis of covariance; gestational age, weight for gestation, ponderal index, weight-for-length index were controlled for in this analysis. †*P*=0.001 for the comparison with term controls, ‡*P*=0.001 for the comparison with term controls, #*P*=0.001 for the comparison with term controls. IRI: Insulin resistance index, SD: Standard deviation, AGA: Appropriate for gestational age, SGA: Small for gestational age, SI: Serum insulin

Table 4: Sequential multiple regression analysis for identifying influence of perinatal stress and anthropometric variables on insulin resistance index (dependent variable)

Model	Adjusted R^2	Unstandardized coefficients		Standardized coefficients	95.0% CI for *B*		Partial correlation	*P*
		B	SE	*β*	Lower bound	Upper bound		
1. Constant		2.595	0.493		1.616	3.573		0.000
Gestational age	0.188	−0.068	0.014	−0.443	−0.095	−0.040	−0.443	0.000
2. Constant		3.282	0.425		2.439	4.125		0.000
Gestational age	0.434	−0.042	0.012	−0.275	−0.066	−0.018	−0.330	0.001
PI		−0.677	0.103	−0.527	−0.881	−0.474	−0.557	0.000
3. Constant		3.128	0.377		2.380	3.876		0.000
Gestational age	0.557	−0.039	0.011	−0.254	−0.060	−0.017	−0.345	0.001
PI		−0.666	0.091	−0.518	−0.847	−0.486	−0.600	0.000
wfl9		0.206	0.039	0.355	0.129	0.284	0.475	0.000
4. Constant		3.213	0.309		2.599	3.826		0.000
Gestational age	0.702	−0.073	0.010	−0.481	−0.094	−0.053	−0.596	0.000
PI		−0.250	0.096	−0.194	−0.440	−0.059	−0.258	0.011
wfl9		0.183	0.032	0.315	0.119	0.247	0.504	0.000
Type[a]		0.586	0.085	0.505	0.418	0.754	0.579	0.000

PI: Ponderal index, Wfl9: Weight-for-length at 9 months, Type: Type according to weight for gestation dependent variable - Log IRI, R^2=0.196 for model 1, ΔR^2=0.249 for model 2, ΔR^2=0.125 for model 3, ΔR^2=0.144 for model 4. [a]Coded 0 for AGA and 1 for SGA. AGA: Appropriate for gestational age, SGA: Small for gestational age, SD: Standard deviation, IRI: Insulin resistance index, CI: Confidence interval

variability (birth weight and length have collinearity with PI and weight and length at 9 months have collinearity with weight-for-length) were included in this model to validate and stabilize the model. Model 1 contains gestational age. Subsequently, PI, weight-for-length, and type according to weight for gestation were added in model 2, 3, and 4, respectively. As a measure of "goodness of fit," adjusted R^2 was increased in each model from 0.188 in model 1 to 0.702 in model 4, which indicates 70% of variability, now explained by model 4 (Significant R^2 changes in each step $P = 0.001$) [Table 4].

Substituting the variables and the unstandardized coefficients from the Table 4, the equation for model was as follows:

$$\text{Log IRI} = 3.213 - (0.173 \times \text{Gestational age}) - (0.25 \times \text{PI}) + (0.183 \times \text{weight-for-length}) + (0.586 \times \text{type})$$

Because AGA is coded zero, the final term in the equation was removed for AGA. The term "type" indicates that after adjusting for gestational age, PI, and weight-for-length at 9 months, SGA babies were 0.586 more IRI than AGA. In effect, this means that y-intercept was 3.799 for SGA (i.e., 3.213 + 0.586) and 3.213 for AGA. Thus, the lines for AGA and SGA were parallel, but AGA had a lower y-axis intercept [Figure 2].

Standardized coefficients indicated the relative importance of each variable in comparable standardized units (z-scores) to predict IRI. Type according to weight for gestational age with a standardized β coefficient of 0.505 was a more significant predictor of IRI than gestational age

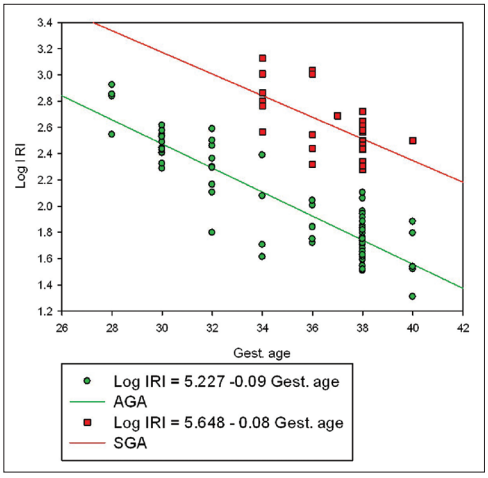

Figure 2: Scatter plot for insulin resistance index on gestational age with regression line (appropriate for gestational age vs. small for gestational age)

(β = −0.481), weight-for-length (β = 0.315), and PI (β = −0.194). As with an *R*-value, the negative sign was an indication of the direction of effect only [Table 4].

The partial correlation was the unique contribution of gestational age (−0.596), PI (−0.258), weight-for-length (0.504), and type (0.579) to predicting IRI after the effect of other three factor was removed and was an estimate of the relative importance of each predictive variable in isolation from other factors [Table 4].

Model was validated for stability, precision, and reliability by testing for collinearity, interaction, and residuals. There was no collinearity (significant relationship between explanatory variables) in between variables (correlation coefficient ρ < 0.7, variance inflation factor (VIF) <4, and

tolerance >0.2). Interactions (multiplicative rather than additive relationship between two explanatory variables) were tested by including the interaction term (gestational age × type, PI × type, and gestational age × type × PI) in model, which shows no significant increase in adjusted R^2 ($P > 0.05$). Similarly, when IRI plotted against gestational age, no significant difference between slope of regression line of AGA and SGA babies were present ($P > 0.05$) [Figure 2], which further favor in no interaction between gestational age and type according to weight for gestation. Standard residuals (distances between each data point and the value predicted by the regression equation) showed normal distribution (mean <0.00001, SD = 0.98) indicates equal spread of variance over the length of regression model, and the model was homoscedastic [Figure 3].

Alternative regression model was constructed to determine role of catch-up growth in insulin resistance. In this model, gestational age, catch-up for weight, and type according to weight for gestation sequentially added (adjusted $R^2 = 71.9\%$ mean 71.9% variability explained by this model). Catch-up growth ($\beta = 0.714$) is a significant predictor of insulin resistance independent of gestational age and SGA status. Weight-for-length and PI were not included in this model because of collinearity of catch-up growth with PI and weight-for-length at 9 months (VIF >4, tolerance <0.2, condition index in collinearity diagnostics >30). In collinearity, diagnostics condition index were 35.97, 41.70, and 57.73 for weight catch-up, weight-for-length at 9 months, and PI, respectively.

Substituting the variables and the unstandardized coefficients, the equation for this model was as follows:

$$\text{Log IRI} = 5.621 - (0.153 \times \text{gestational age}) + (0.234 \times \text{weight catch-up at 9 months}) + (0.320 \times \text{type})$$

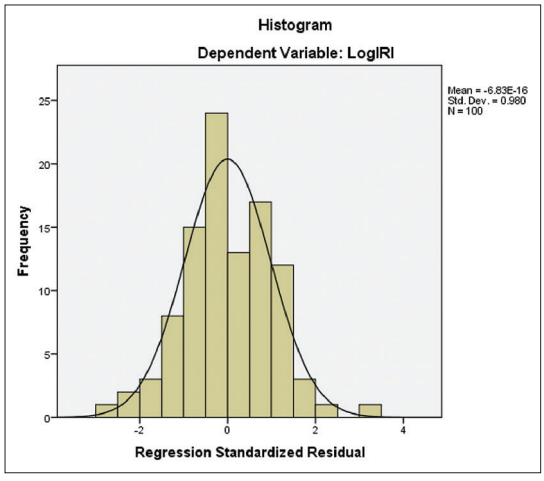

Figure 3: Normal distribution of regression standardized residuals

Discussion

Prematurity is associated with increased insulin resistance in childhood[17-20] and adolescence.[21-24] By adulthood, the data are conflicting, with some studies demonstrating that fat mass is the major determinant of IS with no effect of gestation[25-27] whereas others identify a persisting effect of preterm birth.[28,29] The present study demonstrates the association of prematurity with insulin resistance in infancy after adjusting for significant covariables. These findings provide additional evidence that preterm birth may be a risk factor for the future development of the insulin resistance and type-2 diabetes, and the insulin resistance may develop as early as infancy. We fill a gap in the knowledge, regarding insulin resistance in preterm born babies in 1st year of life which was unexplored till date.

Our secondary outcome is the effect of other variables on insulin sensitivity in infancy. A particular strength of our study is that we also include term SGA cohort in our study for comparison and explore relative importance of each variables to predict the insulin resistance in infants. The present study explores that SGA status is the most significant predictor of insulin resistance followed by gestational age, weight-for-length, and PI in the descending order. Most of the studies reveals that in preterm born babies, SGA status exerts no effect on insulin sensitivity in childhood,[17-20,23,30] adolescence,[23] and adulthood.[26,31] Contrary to this, Gray *et al*.,[8] Bazaes *et al*.,[32] and Reinehr *et al*.,[24] respectively, found that SGA preterm born babies have reduced insulin sensitivity in neonatal, childhood, and adolescence. Gray used a milk tolerance test (MTT) and showed that SGA preterm neonates had higher post-MTT insulin levels. Reinehr study included both preterm and term SGA born subjects thus insulin resistance might be due to confounding effect of term gestation. Bazaes *et al*. used both HOMA modeling and intravenous glucose tolerance test and found reduced insulin sensitivity in SGA babies by using HOMA model but not after stimulated insulin release. However in term SGA born babies' insulin resistance in infancy,[9,10] childhood,[33-35] adolescent,[36,37] and adulthood[38,39] is well established. With concurrence to most of the studies, we also report that SGA status exerts no impact on insulin sensitivity in preterm born babies, but its impact during infancy is a matter of special mention here.

In multiple regression analysis, SGA born infants have higher insulin resistance (0.586 more IRI) than AGA born infants irrespective of their gestational age, PI, and current weight-for-length. This difference is insignificant in preterm babies and become significant with increasing gestational

age in term babies [Figure 2]. Furthermore, combination of both preterm cohorts does not result in significantly higher insulin resistance than term SGA. These results indicate antenatal stress prior to the third trimester does not contribute in metabolic derangement, and critical window for the same is present in third trimester. Similarly, Hofman *et al*.[20] also reported that third trimester is critical window period for metabolic imprinting, but there also remains a debate because studies in animals and humans have suggested several critical periods from the periconceptual period to later pregnancy.[40,41] Additional studies would require confirming the importance of this period and may provide further insight into the role of this critical period in the third trimester.

Lower PI (thinness) at birth associated with insulin resistance in adulthood.[42-45] Contrary to this, Whincup *et al*.[46] results show that LBW but not PI is associated with insulin resistance in childhood. Our results also demonstrate that low PI (thinness at birth) is associated with higher insulin resistance with special concern to infancy. PI is a continuum with proportionality in SGA fetuses and depends on the duration of intrauterine insult and the extent of its effects on weight and length before delivery.[47] Relatively brief duration intrauterine insult which affects more on weight than length results in lower PI (asymmetrical intrauterine growth restriction [IUGR]), and therefore higher insulin resistance. These results further favor that critical window period for metabolic derangement in LBW babies may present in third trimester in which maximum fetus weight growth occurs.

Insulin is an important growth factor during infancy, and insulin secretion could be relevant for fat deposition and weight gained shortly after birth. IUGR followed by catch-up growth for weight in infancy[9,10,37,38,48] and early childhood[34,35,38,49,50] may be a sequence that led to high basal metabolic index (BMI),[10,35,39] obesity, and fat mass,[17,34,38,49] and therefore insulin resistance in infancy,[37,48] childhood,[33-35,38,49] adolescent,[37] and adulthood.[38,39,51]

Similarly, prematurity followed by postnatal catch-up growth for weight in infancy[17,19,21,27,52] and early childhood[19] may be a sequence that led to high BMI,[22,31,32] obesity, fat mass,[17,25-27,52] and therefore insulin resistance in childhood,[17,19,32] adolescent,[21,22] and adulthood.[17,25-27,31]

In present study, we examine early changes in body composition by using weight-for-length, which provides a more accurate measure of adiposity (BMI for >2 years) than weight alone.[15,16] Our study indicates that higher weight-for-length is associated with higher insulin resistance in infancy, and thus, it indicates an association of adiposity with insulin resistance as early as the 1st year of life. Collinearity between catch-up growth for weight and weight-for-length indicate that excess adiposity is superimposed on normal growth related adiposity during catch-up growth. Concomitant to this, converging evidence suggests that catch-up growth in preterm[53] and small for gestation[54] is intimately linked with a disproportionately faster rate to gain body fat rather than lean tissue, that is, to a preferential acceleration of fat recovery or "catch-up fat."

Therefore, we create a hypothesis that catch-up growth for weight in infancy and early childhood and the higher BMI and obesity in letter childhood, adolescence, and adulthood are the same spectrum phenomenon in different window periods of life after exposure to environmental factors such as high energy intake or low physical activity and may be a result of metabolic imprinting after inutero stress or postnatal stress.

The current study has several methodological strengths. First, it is one of the few to implement a prospective, longitudinal design to investigate the link between prematurity and insulin resistance as early as infancy. Second, this study examines early changes in body composition using weight-for-length, which provides a more accurate measure of adiposity than weight alone. Third, regression model is tested for stability, collinearity, and interaction between various variables and finally, this study also includes full-term SGA infants, and thus can identify the relative importance of various variables to determine insulin sensitivity in infancy.

Our cohort did have better clinical outcomes than the total cohort of surviving children who had been born prematurely since we excluded subjects with major or moderate disability. On the basis of these neonatal characteristics and on the better developmental outcome of our cohort, we do not believe that a selection bias has occurred that influenced our findings.

Finally, we have drawn equation to estimate IRI by using gestational age, PI, SGA status, and current weight-for-length. By using weight-for-length which is age-independent variable, we can monitor insulin resistance during follow-up in both preterm and SGA babies. Identification of these infants may help to focus preventive measures aimed at controlling the current epidemic of obesity and its complications, but we should be cautious while making recommendations for nutrition till we have evidence available from randomized control trial.

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Conflicts of interest

There are no conflicts of interest.

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