e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com

International Journal of Pharmaceutical Quality Assurance 2026; 17(9); 305-311

Original Research Article

Assessment of the Fasting Glucose-to-Insulin Ratio as a Screening Marker of Insulin Resistance in Prepubertal Girls with Premature Adrenarche

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Received: 17-08-2026 / Revised: 10-09-2026 / Accepted: 24-09-2026

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Conflict of interest: Nil

Abstract:

Background: Premature adrenarches are increasingly recognized as an early indicator of metabolic abnormalities, particularly insulin resistance. The fasting glucose-to-insulin (G: I) ratio has emerged as a simple and inexpensive surrogate marker for identifying insulin resistance in pediatric populations.

Aim: To assess the fasting glucose-to-insulin ratio as a screening marker of insulin resistance in prepubertal girls with premature adrenarche.

Methodology: A retrospective observational study was conducted over three months in the Department of Biochemistry at Netaji Subhas Medical College and Hospital in Bihta, Patna, Bihar, India. Medical records of 115 prepubertal girls aged 4–9 years with premature adrenarche were reviewed. Demographic, anthropometric, clinical, biochemical, and hormonal data were collected. The fasting G:I ratio was calculated using fasting glucose and insulin values, and statistical analysis was performed using SPSS version 26.0.

Results: Nearly half of the participants had a fasting G:I ratio suggestive of insulin resistance. Girls with lower G:I ratios exhibited significantly higher fasting insulin levels, body mass index, and triglyceride concentrations, along with lower HDL cholesterol levels, indicating an adverse metabolic profile.

Conclusion: The fasting glucose-to-insulin ratio is a practical, inexpensive, and useful screening marker for early identification of insulin resistance in prepubertal girls with premature adrenarche.

Keywords: Premature Adrenarche, Insulin Resistance, Fasting Glucose-To-Insulin Ratio, Fasting Insulin, Prepubertal Girls, Screening Marker.

DOI: 10.25258/ijpqa.17.9.46

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Introduction

Insulin resistance (IR) is a metabolic state in which the peripheral tissues of the body have a lowered response to insulin, both internally and externally produced, leading to decreased use of glucose and an increase in insulin levels. It is a key factor in the pathogenesis of type 2 diabetes mellitus (T2DM); obesity; metabolic syndrome; cardiovascular diseases; and some endocrine diseases. While insulin resistance is traditionally considered an adult disease, there is growing evidence that it can manifest during childhood and adolescence, especially in children with obesity, endocrine dysfunction and/or family history of metabolic diseases. Thus, it is critical to identify insulin resistance in children and young people early to avoid future metabolic and cardiovascular problems by implementing timely lifestyle and therapeutic interventions [1].

The evaluation of insulin sensitivity has come a long way in the last few decades. The hyper insulinemic-euglycemic clamp method is regarded as the gold standard for assessing insulin sensitivity as it is the only method that directly quantifies insulin-mediated glucose disposal. The commonly used intravenous glucose tolerance test (IVGTT), which measures insulin sensitivity after intravenous injection of glucose, similarly yields reliable estimates of insulin sensitivity by mathematical modelling, the frequently sampled intravenous glucose tolerance test (FSIVGTT). Both methods are, however, technically difficult, costly and cumbersome and are not

suited to large epidemiological studies or routine clinical use. They are too complex to use in resource poor environments, where simpler, cheaper, and more easily reproducible screening tools are needed [2].

The fasting glucose to insulin (G: I) ratio is one of the many surrogate indices that have been proposed to assess insulin resistance and is a viable and cost-effective index. The ratio is derived from the fasting plasma glucose and fasting serum insulin levels, which are commonly measured in clinical laboratories. A lower fasting glucose / insulin ratio suggests a lower insulin sensitivity and higher insulin resistance [3]. The G:I fasting ratio is contrasted with the more sophisticated dynamic test, which only needs a single fasting blood sample and can be used in out-patient screening, large population-based studies and routine clinical evaluation.

A strong correlation has been shown in several investigations between fasting G:I ratio and insulin sensitivity, as evaluated by other reference methods, making this ratio useful as a screening tool for insulin sensitivity. Insulin resistance has emerged as an area of growing interest in one paediatric disorder, premature adrenarche (PA). The definition of premature adrenarches is the early development of adrenal androgen secretion before the age of 8 years in girls, resulting in the appearance of pubic hair, axillary hair, body odor, oily skin, mild acne, without any signs of central puberty. While early development of adrenarche was once thought to be a normal developmental process, there has been increasing evidence that it could be an initial stage of metabolic dysfunction and not just an isolated endocrine event [4].

Various studies have demonstrated an elevation of fasting insulin, reduction in insulin sensitivity, obesity, dyslipidemia and prevalence of acanthosis nigricans in children with premature adrenarches when compared with age matched with healthy children. Insulin-resistance seems to be a key factor in the pathogenesis of premature adrenarches. Hyperinsulinemia can indirectly or directly increase the production of adrenal androgens by increasing the sensitivity of the adrenal glands to ACTH. In the past, there have been reports that around 50% of prepubertal girls with premature adrenarches show insulin resistance on the FSIVGTT. Moreover, it has been reported that insulin sensitivity is inversely proportional to the level of androgens, meaning that girls with higher insulin resistance have higher level of androgens as well. The results indicate that metabolic abnormalities may play a major role in the endocrine dysfunction which has been described in premature adrenarche [5]. The effects of premature adrenarche on metabolism are not limited to childhood.

The results of long-term follow-up studies have shown that girls with premature adrenarche are at a higher risk for obesity, impaired glucose tolerance, metabolic syndrome, polycystic ovary syndrome (PCOS), and type 2 diabetes mellitus during adolescence and early adulthood. Hyperandrogenism, ovulatory dysfunction and insulin resistance are hallmarks of polycystic ovarian syndrome, a common endocrine disorder among reproductive-age women [6]. Legro et al. showed that the fasting glucose-to-insulin ratio had a strong correlation with insulin sensitivity assessed by FSIVGTT in women with PCOS and suggested that a fasting G:I ratio < the cutoff was a good surrogate for identifying women with insulin resistance, with a high sensitivity and specificity.

The findings suggest that simple biochemical markers might be useful for early detection of insulin resistance in high-risk children and their families. The fasting glucose-to-insulin ratio is an appealing screening tool, given that both glucose and insulin can be readily measured and assessed in the laboratory and is inexpensive, especially in developing countries where advanced metabolic testing may not be readily available. Insulin resistance and type 2 diabetes are emerging as a serious problem in India owing to the urbanization, sedentary lifestyle and the changing eating patterns in children [7].

Children with endocrine disorders like premature adrenarche may thus be a particularly vulnerable population that should be screened metabolically early. Although the prevalence of metabolic disorders in children is increasing, little information is available on the use of fasting glucose/insulin ratio as a screening tool in prepubertal girls of eastern Indian who suffer from premature adrenarche. Nutritional counselling, physical activity, weight management and periodic metabolic monitoring are preventive strategies that may be implemented to prevent development of hyperglycemia and the associated negative consequences if insulin resistance is detected early. Fasting glucose to insulin ratio could be a simple screening test that could help clinicians identify kids who have a higher metabolic risk without costly and invasive procedures. This strategy could have a positive impact on the long-term consequences of obesity in two ways: providing early intervention and minimizing the burden of metabolic syndrome, Type 2 Diabetes Mellitus, and cardiovascular disease in the future [8].

Insulin resistance is becoming a common problem of children with premature adrenarche and the need for convenient, accurate, and affordable screening tools, the present study was conducted to evaluate the fasting glucose to insulin ratio as a screening tool for insulin resistance in prepubertal girls with premature adrenarche, in a tertiary care hospital in Bihta, Patna, Bihar, India. The results from this study will offer region-specific proof of the clinical value of

the FPGR and will help integrate the FPGR into the early identification of children who may be at risk for future metabolic complications, thus promoting better screening and preventive health care practices.

Methodology

Study Design: This retrospective observational study was conducted to assess the fasting glucose-to-insulin (G: I) ratio as a screening marker of insulin resistance among prepubertal girls with premature adrenarches. The study involved the retrospective review of hospital records of eligible patients who had undergone clinical, biochemical, and hormonal evaluation during the study period.

Study Area: The study was carried out in the Department of Biochemistry in collaboration with the Department of Pediatrics at Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India.

Study Duration: The study was conducted over a period of 3 months.

Sample Size: A total of 115 prepubertal girls diagnosed with premature adrenarche were included in the study based on the availability of complete clinical, anthropometric, hormonal, and biochemical records.

Sample Population: The study population comprised prepubertal girls aged 4–9 years diagnosed with premature adrenarche who attended the pediatric endocrine outpatient department of the tertiary care hospital. Premature adrenarche was defined as the appearance of Tanner stage II–III pubic hair before the age of 8 years without evidence of central puberty. Patients who had undergone fasting blood glucose, fasting serum insulin, hormonal investigations, and other relevant laboratory assessments were included for analysis.

Data Collection: Data were collected retrospectively from hospital medical records, laboratory registers, and electronic medical records using a structured data collection form. Information regarding demographic characteristics, age, anthropometric measurements (height, weight, and body mass index), family history of type 2 diabetes mellitus, clinical findings, Tanner staging, fasting blood glucose, fasting serum insulin, fasting glucose-to-insulin ratio, hormonal profile, and lipid profile were extracted. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Obesity was defined according to age- and sex-specific BMI values above the 95th percentile. The fasting glucose-to-insulin ratio was calculated using fasting plasma glucose and fasting serum insulin values obtained after an overnight fast of 10–12 hours.

Inclusion Criteria

- Prepubertal girls aged 4–9 years.
- Presence of Tanner stage II–III pubic hair before 8 years of age consistent with premature adrenarche.
- Girls with documented fasting blood glucose and fasting serum insulin values.
- Availability of complete clinical, biochemical, hormonal, and anthropometric records.
- Patients evaluated during the study period with confirmed diagnosis of premature adrenarche.

Exclusion Criteria

- Girls with evidence of breast development or central precocious puberty.
- Patients with congenital adrenal hyperplasia or other enzymatic defects of adrenal steroidogenesis.
- Patients with known endocrine disorders, diabetes mellitus, chronic systemic illness, or malignancy.
- Patients receiving medications known to affect glucose metabolism or insulin secretion.
- Incomplete medical records or missing biochemical investigations.

Study Procedure: Following the medical records of eligible prepubertal girls diagnosed with premature adrenarche were reviewed retrospectively. Clinical information, including age, anthropometric measurements, Tanner staging, body mass index (BMI), and family history of type 2 diabetes mellitus, was extracted from hospital records. Laboratory data comprising fasting plasma glucose and fasting serum insulin levels obtained after an overnight fast of 10–12 hours were collected, and the fasting glucose-to-insulin (G:I) ratio was calculated by dividing fasting plasma glucose (mg/dL) by fasting serum insulin (μU/mL), with lower ratios considered indicative of reduced insulin sensitivity. Where available, hormonal parameters including cortisol, dehydroepiandrosterone (DHEA), androstenedione, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), insulin-like growth factor-binding protein-1 (IGFBP-1), and lipid profile were also reviewed. The collected anthropometric, biochemical, and hormonal parameters were subsequently analyzed to determine their association with the fasting glucose-to-insulin ratio and insulin resistance among the study participants.

Statistical Analysis: The collected data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. The association between fasting glucose-to-insulin ratio and biochemical as well as anthropometric variables was assessed using Spearman's correlation coefficient. Comparisons between study groups were performed using the student's

independent t-test for continuous variables and the Chi-square test for categorical variables, wherever appropriate. Multiple linear regression analysis was performed to identify independent predictors of insulin resistance. A p-value <0.05 was considered statistically significant throughout the study".

Result

Table 1 presents the demographic and anthropometric characteristics of the study participants. A total of 115 prepubertal girls with premature adrenarches were included in the study. Most participants belonged to the 6–7 years age group, followed by 8–9 years and 4–5 years. Nearly half of the participants had a normal body mass index, while approximately one-quarter each were overweight and obese. A positive family history of type 2 diabetes mellitus was present in a considerable proportion of participants. The mean age and BMI indicated that the study population mainly consisted of young prepubertal girls with varying nutritional status.

Table 1: Demographic and Anthropometric Characteristics of Study Participants (N = 115)

Variable	Frequency (n)	Percentage (%)
Age Group (Years)		
4–5	24	20.9
6–7	52	45.2
8–9	39	33.9
BMI Category		
Normal Weight	53	46.1
Overweight	31	27
Obese	31	27
Family History of Type 2 Diabetes Mellitus		
Present	49	42.6
Absent	66	57.4

Table 2 shows the clinical characteristics of the study participants. Tanner stage II pubic hair was the most common clinical presentation, followed by Tanner stage III. Body odor was the most frequently observed associated clinical feature, while oily skin, acanthosis nigricans, and mild acne were observed in varying proportions. The presence of acanthosis nigricans in nearly one-third of participants suggests the coexistence of metabolic abnormalities associated with insulin resistance in a subset of girls with premature adrenarche.

Table 2: Clinical Characteristics of Prepubertal Girls with Premature Adrenarche (N = 115)

Clinical Characteristic	Frequency (n)	Percentage (%)
Tanner Stage II Public Hair	72	62.6
Tanner Stage III Public Hair	43	37.4
Body Odor	68	59.1
Oily Skin	44	38.3
Mild Acne	29	25.2
Acanthosis Nigricans	36	31.3

Table 3 summarizes the biochemical profile of the study participants. The mean fasting blood glucose level remained within the normal reference range, whereas the mean fasting serum insulin level was relatively elevated. The average fasting glucose-to-insulin ratio was close to the proposed screening cut-off for insulin resistance. Lipid profile analysis demonstrated mildly elevated triglyceride levels, while total cholesterol, LDL cholesterol, and HDL cholesterol remained largely within acceptable limits. These findings indicate that biochemical alterations related to insulin resistance may occur even in the presence of normal fasting glucose levels.

Table 3: Biochemical Profile of Study Participants (N = 115)

Parameter	Mean ± SD	Reference Range
Fasting Blood Glucose (mg/dL)	90.8 ± 8.5	70–99
Fasting Serum Insulin (µU/mL)	15.7 ± 6.3	2–15
Fasting Glucose-to-Insulin Ratio	7.1 ± 2.2	>7 Normal
Total Cholesterol (mg/dL)	168.4 ± 26.7	<170
Triglycerides (mg/dL)	112.5 ± 34.6	<150
HDL Cholesterol (mg/dL)	43.2 ± 7.8	>40
LDL Cholesterol (mg/dL)	101.8 ± 23.4	<110

Table 4 depicts the distribution of participants according to the fasting glucose-to-insulin ratio. Approximately half of the girls had a fasting glucose-to-insulin ratio below the screening cut-off, suggesting possible insulin resistance, whereas the remaining participants had values consistent with relatively preserved insulin sensitivity. These findings indicate that a substantial proportion of prepubertal girls with premature adrenarche may already exhibit evidence of insulin resistance.

Table 4: Distribution of Fasting Glucose-to-Insulin Ratio (N = 115)

G:I Ratio Category	Frequency (n)	Percentage (%)
<7 (Suggestive of Insulin Resistance)	57	49.6
≥7 (Normal Insulin Sensitivity)	58	50.4

Table 5 compares biochemical and anthropometric parameters between girls with a fasting glucose-to-insulin ratio below and above the screening cut-off. Participants with a lower fasting glucose-to-insulin ratio demonstrated significantly higher fasting serum insulin levels, body mass index, and triglyceride concentrations, along with significantly lower HDL cholesterol levels. Fasting blood glucose also showed a modest but statistically significant difference between the two groups. These observations suggest that a reduced fasting glucose-to-insulin ratio is associated with an adverse metabolic profile and may serve as a useful indicator of insulin resistance.

Table 5: Comparison of Biochemical Parameters According to Fasting Glucose-to-Insulin Ratio

Parameter	G:I Ratio <7 (n=57) Mean ± SD	G:I Ratio ≥7 (n=58) Mean ± SD	p-value
Fasting Blood Glucose (mg/dL)	92.4 ± 8.8	89.2 ± 7.9	0.042
Fasting Serum Insulin (µU/mL)	20.4 ± 5.3	11.1 ± 2.8	<0.001
BMI (kg/m²)	21.2 ± 3.1	17.0 ± 2.1	<0.001
Triglycerides (mg/dL)	124.8 ± 33.5	100.5 ± 28.6	0.001
HDL Cholesterol (mg/dL)	40.2 ± 6.9	46.1 ± 7.2	<0.001

Table 6 presents the correlation between the fasting glucose-to-insulin ratio and selected metabolic variables. The fasting glucose-to-insulin ratio showed a strong negative correlation with fasting serum insulin and body mass index, indicating that increasing insulin levels and obesity were associated with lower ratio values. A moderate negative correlation was observed with triglyceride levels, while a positive correlation was found with HDL cholesterol. Fasting blood glucose demonstrated only a weak negative correlation with the ratio. Overall, these findings support the utility of the fasting glucose-to-insulin ratio as a simple screening marker for identifying insulin resistance and associated metabolic abnormalities in prepubertal girls with premature adrenarche.

Table 6: Correlation of Fasting Glucose-to-Insulin Ratio with Selected Variables (N = 115)

Variable	Spearman Correlation (r)	p-value
BMI	-0.512	<0.001
Fasting Serum Insulin	-0.746	<0.001
Fasting Blood Glucose	-0.184	0.048
Triglycerides	-0.338	<0.001
HDL Cholesterol	0.297	0.002

Discussion

A retrospective study was conducted to evaluate the usefulness of fasting glucose to insulin ratio (G: I) as a screening tool for insulin resistance in 115 prepubertal girls with premature adrenarche attending a tertiary care hospital at Bihta, Patna, Bihar. The G:I ratio in near fasting state was low (nearly half of the participants had a G:I ratio below the proposed screening cut-off) indicating a high prevalence of insulin resistance among this population. Furthermore, the insulin levels in girls with lower G:I ratio were significantly higher, and had higher BMI, higher triglycerides, and lower HDL cholesterol levels, further confirming the relationship between low insulin sensitivity and adverse metabolic" changes [9].

Most of the study participants in the present study were in the 6–7 years age range, a range that corresponds to natural age of presentation for premature adrenarche. In a second study, Utriainen et al. (2015) reported that the most common age of onset for premature adrenarche is 5-8 years, and that affected children have clinical signs of adrenal androgen excess before they reach true puberty. Similarly, Ibáñez et al. (2000) reported that most cases of PMA are diagnosed in the early school-age years and is one of the earliest endocrine changes associated with

later onset of metabolic dysfunction [10]. These observations are consistent with our results indicating that most of the diagnoses of premature adrenarches occur during the middle prepubertal years.

The current study found that about 49.6% of the girls had a FGIR lower than the screening threshold, indicative of insulin resistance. This is very similar to Silfen et. al. (2002) who reported insulin resistance in about 50% of prepubertal girls with premature adrenarches when they used the frequently sampled intravenous glucose tolerance test (FSIVGTT). Likewise, Ibáñez et al. (2000) found that, insulin sensitivity was significantly decreased in girls with exaggerated adrenarche relative to healthy controls, highlighting the early development of insulin resistance in childhood and its link to elevated adrenarche levels [11]. Our results corroborate previous reports, further supporting the presence of early metabolic impairment in a large number of children with premature adrenarches.

We found in our study that girls with a lower fasting G:I ratio had significantly higher fasting serum insulin levels than those with normal G:I ratios with fasting glucose levels in the normal physiological range. Similar results were reported by Legro et al. (1998) who noted that fasting insulin was a good indicator of decreased insulin sensitivity in women with polycystic ovary syndrome (PCOS) and that fasting G: I was correlated well with insulin sensitivity calculated by the FSIVGTT. In the present study they used a higher cut-off point of less than 4.5 for their G:I ratio, which was similar to the previous pediatric studies, while their study proposed a G:I ratio of <4.5 as the optimal screening cut-off for obese adult women with PCOS. The variation in these cut-off values may be due to the difference in insulin secretion between prepubertal children and adult women [12].

In the current study, BMI was strongly negatively correlated with the fasting glucose/insulin ratio, suggesting that the overweight and obese girls were more likely to have insulin resistance. A similar finding was also reported by Silfen et al. (2002), who showed that insulin-resistant girls with premature adrenarches had significantly higher levels of BMI and fasting insulin than girls with preserved insulin sensitivity. Similarly, Reinehr (2013) found childhood obesity to be one of the most powerful risk factors for insulin resistance and the onset of type 2 diabetes mellitus, regardless of fasting glucose levels. In keeping with this hypothesis, it was found that a high level of excess adiposity greatly contributed to poor insulin sensitivity in childhood [13]. Girls with low fasting G:I ratios also had significant abnormalities of the lipid parameters in the present study. Girls with insulin resistance had significantly higher triglyceride levels and lower HDL cholesterol levels than insulin sensitive girls.

The same metabolic abnormalities have been reported by Silfen et al. (2002) who found that insulin-resistant girls with premature adrenarche had lower HDL cholesterol and other metabolic syndrome features. In addition, Utriainen et al. (2015) found that dyslipidemia was also common in children with premature adrenarches with insulin resistance and may be a precursor to later development of cardiometabolic disease. These findings suggest that abnormalities in lipid metabolism start early in childhood, and that they are related to the progression of insulin resistance [14]. The present study found high negative correlation between fasting G:I ratio and fasting insulin level with BMI and triglycerides showing significant inverse correlation with the ratio. Legro et al., (1998) reported that the fasting G:I ratio correlated more with insulin sensitivity than fasting insulin alone, thus making it a viable and convenient surrogate marker for insulin resistance.

Moreover, Bergman et al. (1985) showed that insulin sensitivity assessed by the FSIVGTT is strongly linked with the physiological insulin action and is one of the most valuable reference tests to validate surrogate measures of insulin sensitivity. The current results thus corroborate the clinical relevance of the simple and cost-effective fasting G:I ratio for screening purposes [15]. The available evidence indicates that early onset of adrenarche is not just a normal developmental phase but can be a precursor to polycystic ovary syndrome (PCOS) and metabolic syndrome. Ibáñez et al. (2009) reported that there is a higher risk of hyperandrogenism, insulin resistance, impaired glucose tolerance, and PCOS in girls with early adrenarche. Similarly, Dunaif et al. (1989) showed that insulin resistance is a primary metabolic defect involved in hyperandrogenism and ovarian dysfunction in women with PCOS. The metabolic phenotype described in the present study, such as obesity, hyperinsulinemia, dyslipidemia and lower fasting G:I ratio, are thus in agreement with the early metabolic phenotype associated with later endocrine diseases [16].

The results of this study suggest that fasting glucose-to-insulin ratio is a clinically relevant, inexpensive and practical screening tool to detect insulin resistance in prepubertal girls with premature adrenarches. Simultaneous evaluation of fasting insulin and the calculation of the G:I ratio may help identify children at risk earlier, due to the fact that fasting glucose level may not be elevated in the early stages of insulin resistance. Early diagnosis would allow for timely lifestyle modification, nutritional counselling, weight management and longterm metabolic monitoring which would help to decrease future risk of type 2 diabetes mellitus, metabolic syndrome and polycystic ovary syndrome.

Conclusion

The present retrospective study showed that a significant percentage of prepubertal girls with premature adrenarche had characteristics of insulin resistance -- a low fasting glucose to insulin ratio. The metabolic profile of girls with lower glucose-to-insulin ratios was unfavorable, including higher fasting insulin, higher BMI, higher triglycerides and lower HDL cholesterol, without a difference in fasting blood glucose levels. The results suggest that the fasting glucose to insulin ratio is a simple, inexpensive and clinically useful screening index for early detection of insulin resistance in this high-risk paediatric population. Fasting glucose and insulin should be regularly checked and can help identify children who are at an early stage of developing metabolic problems such as obesity, type 2 diabetes mellitus, metabolic syndrome and polycystic ovary syndrome. This readily available marker can help identify early signs and symptoms of illness, promote timely lifestyle changes, regular metabolic surveillance, and timely preventive measures, thereby enhancing the likelihood of improved health outcomes. However, larger prospective multicenter studies with long-term follow-up are warranted to confirm these results and to confirm the diagnostic value of the FGR in a wide variety of pediatric populations.

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