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PLACENTAL TRANSPORT PROTEINS AND FETAL GROWTH RESTRICTION: A BIOCHEMISTRY–PHYSIOLOGY INTERFACE

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ABSTRACT

Background

To investigate the relationship between placental transport protein expression and fetal growth restriction, highlighting the biochemical physiological mechanisms linking placental function to neonatal outcomes.

Methods

A prospective observational study was conducted at Khyber Girls Medical College, Peshawar, from January 2023 to January 2024. Seventy-three women were enrolled and categorized into FGR (n=35) and appropriate-for-gestational-age (AGA) groups (n=38). Maternal demographics, neonatal outcomes, and placental morphology were recorded. Placental samples were analyzed for the expression of glucose transporters (GLUT1, GLUT3), amino acid transporters (SNAT2, LAT1), fatty acid transport proteins (FATP, CD36), and ABC transporters (P-gp, BCRP) using qRT-PCR and Western blotting.

Results

Mothers of FGR neonates showed a higher frequency of hypertensive disorders ($p=0.02$). Neonates in the FGR group had significantly lower birth weight, length, and head circumference compared to controls ($p<0.001$). Placental weight and thickness were reduced, with infarcts and calcifications more common in FGR cases. Expression of GLUT1, GLUT3, SNAT2, LAT1, FATP, and CD36 was significantly downregulated in the FGR group ($p<0.001$), while P-gp and BCRP were upregulated ($p<0.001$).

Conclusion

Altered expression of placental transport proteins is strongly associated with fetal growth restriction. Reduced nutrient transporter activity coupled with increased efflux transporter expression may impair

fetal supply, contributing to restricted growth. These findings underscore the importance of placental biochemistry in fetal outcomes and suggest potential avenues for therapeutic intervention.

Keywords
Placental transport proteins, Fetal growth restriction, GLUT, SNAT, LAT, FATP, ABC transporters, Placental morphology, Neonatal outcomes

INTRODUCTION

Fetal growth restriction (FGR) represents one of the most challenging complications of pregnancy, affecting nearly 5–10% of live births worldwide. It is strongly associated with stillbirth, neonatal morbidity, and adverse long-term health consequences, including metabolic and cardiovascular disease in adulthood. Despite extensive research, the precise mechanisms that govern restricted fetal growth remain incompletely understood [1-3].

The placenta is a multifunctional organ that not only facilitates maternal–fetal nutrient exchange but also acts as a regulatory interface adapting to intrauterine conditions. A growing body of evidence indicates that disturbances in placental transport processes play a pivotal role in the pathogenesis of FGR. Nutrient transporters, including glucose transporters (GLUTs), amino acid transporters (System A and System L), and fatty acid transport proteins (FATP, CD36), are critical for fetal supply. Alterations in their expression can lead to inadequate transfer of substrates required for cellular growth and organ development. Conversely, efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) serve a protective role against xenobiotics but may inadvertently limit nutrient delivery when upregulated [4-6].

Previous studies have consistently demonstrated reduced activity of System A amino acid transport and downregulation of GLUT1 in placentas from growth-restricted pregnancies. Similarly, changes in lipid transport protein expression have been reported, which may contribute to altered fetal adiposity and neurodevelopment. However, much of the existing literature has been limited by small cohorts, regional variability, or incomplete assessment of multiple transporter systems in the same population [7-9].

The present study was designed to evaluate placental transport protein expression in pregnancies complicated by FGR compared with appropriate-for-gestational-age (AGA) controls in a Pakistani population. By linking maternal demographics, placental morphology, and molecular transporter expression with neonatal outcomes, this study aims to provide an integrated biochemical–physiological perspective on FGR.

METHODOLOGY

This was a prospective, observational study conducted at the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynecology, Khyber Girls Medical College, Peshawar, along with its affiliated teaching hospital. The study period extended from January 2023 to January 2024, covering one full calendar year to minimize seasonal variation and ensure adequate case recruitment.

A total of 73 pregnant women were enrolled in the study through consecutive sampling. Participants were recruited at the time of delivery after fulfilling the eligibility criteria. The study population was stratified into two groups:

- Fetal Growth Restriction (FGR) group (n = 35): Defined as neonates with birth weight below the 10th percentile for gestational age, confirmed on ultrasonography and postnatal assessment.
- Appropriate for Gestational Age (AGA) group (n = 38): Age- and parity-matched mothers delivering neonates within the 10th–90th percentile for gestational age, serving as controls.

Inclusion and Exclusion Criteria

- Inclusion criteria: Singleton pregnancies, gestational age between 34–40 weeks, and mothers who consented to participate.

- Exclusion criteria: Multiple gestations, congenital anomalies, maternal systemic illness such as chronic renal or hepatic disease, infections during pregnancy, and women on long-term medications known to influence placental function (e.g., corticosteroids, antiepileptics).

The study protocol was approved by the Institutional Review Board of Khyber Girls Medical College, Peshawar. Written informed consent was obtained from all participants prior to inclusion. Confidentiality and anonymity of patient information were maintained throughout the study.

Demographic and clinical details, including maternal age, parity, pre-pregnancy body mass index (BMI), obstetric history, and comorbidities, were recorded using a structured proforma. Neonatal outcomes, such as gestational age at birth, birth weight, length, head circumference, and Apgar scores at one and five minutes, were documented immediately after delivery.

Following delivery, placentas were collected within 30 minutes, washed with saline to remove blood clots, and weighed using a calibrated electronic balance. Dimensions, including diameter and thickness, were measured with a Vernier caliper. Gross pathological changes such as infarcts, calcifications, and ischemic lesions were noted. Representative tissue samples (approximately 1 cm^3) were excised from the central cotyledon, avoiding areas of infarction or calcification, and stored at –80°C until biochemical analysis.

Placental tissue samples were homogenized and subjected to protein and RNA extraction using standardized laboratory protocols. The expression of nutrient transport proteins was assessed using quantitative real-time polymerase chain reaction (qRT-PCR) for mRNA levels and Western blotting for protein expression. The transporters studied included:

- Glucose transporters: GLUT1, GLUT3
- Amino acid transporters: SNAT2 (System A), LAT1 (System L)
- Fatty acid transport proteins: FATP, CD36
- ABC transporters: P-glycoprotein (ABCB1), Breast Cancer Resistance Protein (BCRP/ABCG2)

Relative gene expression was calculated using the ΔΔCt method with β-actin as the housekeeping control. Protein bands were quantified by densitometry and normalized against GAPDH.

The primary outcome was the difference in expression of placental nutrient transport proteins between the AGA and FGR groups. Secondary outcomes included correlations between protein expression levels and clinical parameters such as birth weight, placental weight, and neonatal anthropometry.

Data were entered and analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical data were presented as frequencies and percentages. The independent sample t-test was used for comparison of continuous variables, and the chi-square test was applied for categorical variables. A p-value <0.05 was considered statistically significant. Pearson's correlation analysis was performed to assess the relationship between placental transporter expression and neonatal outcomes.

RESULTS

The maternal demographic profile showed that the majority of participants were aged between 21–30 years, with a mean age of 27.3 ± 4.8 years. Most women were multiparous, and the average pre-pregnancy BMI was within the normal range, though a small proportion were overweight. Hypertension and gestational diabetes were noted in a minority of participants. When comparing the FGR group with appropriate-for-gestational-age (AGA) controls, maternal age, parity, and BMI did not show statistically significant differences ($p > 0.05$). However, hypertensive disorders were significantly more common among mothers of FGR neonates ($p = 0.02$).

Table 1. Maternal Demographic and Clinical Characteristics (n=73)

Variable	AGA Group (n=38)	FGR Group (n=35)	p-value
Maternal age (years, mean ± SD)	26.9 ± 4.5	27.7 ± 5.1	0.48
Parity (Primigravida %)	44.7%	40.0%	0.69
BMI (kg/m^2, mean ± SD)	23.8 ± 2.9	24.2 ± 3.1	0.62
Hypertensive disorders (%)	10.5%	31.4%	0.02*
Gestational diabetes (%)	7.9%	11.4%	0.61
Smoking exposure (%)	13.2%	17.1%	0.66

*Significant at $p < 0.05$

The neonatal outcomes revealed a clear distinction between the two groups. Infants in the FGR group had significantly lower birth weight, length, and head circumference compared to controls ($p < 0.001$). Apgar scores at both 1 and 5 minutes were also lower in the FGR group, though still within a viable range. Gestational age at delivery was slightly reduced in the FGR group but did not reach statistical significance.

Table 2. Neonatal and Birth Outcomes (n=73)

Variable	AGA Group (n=38)	FGR Group (n=35)	p-value
Gestational age (weeks)	38.2 ± 1.4	37.7 ± 1.6	0.09
Birth weight (g, mean ± SD)	3020 ± 410	2250 ± 360	<0.001*
Birth length (cm, mean ± SD)	49.5 ± 2.1	46.2 ± 2.3	<0.001*
Head circumference (cm, mean ± SD)	34.1 ± 1.2	32.4 ± 1.4	<0.001*
Apgar score at 1 min (mean ± SD)	7.5 ± 0.6	6.8 ± 0.7	0.01*
Apgar score at 5 min (mean ± SD)	8.9 ± 0.5	8.2 ± 0.6	0.02*

*Significant at $p < 0.05$

The placental morphology showed striking differences between the groups. Placental weight and diameter were significantly reduced in the FGR group, indicating impaired growth. The placenta-to-fetal weight ratio was notably higher in FGR, suggesting compensatory changes. Gross pathological changes such as infarcts and calcifications were more frequent in FGR placentas, reaching statistical significance ($p < 0.05$).

Table 3. Placental Morphological Parameters (n=73)

Variable	AGA Group (n=38)	FGR Group (n=35)	p-value
Placental weight (g, mean ± SD)	520 ± 60	410 ± 55	<0.001*
Placental diameter (cm, mean ± SD)	18.5 ± 1.6	16.2 ± 1.8	<0.001*
Placental thickness (cm)	2.1 ± 0.3	1.8 ± 0.2	0.02*
Placental–fetal weight ratio	0.17 ± 0.03	0.20 ± 0.04	0.01*
Infarcts/Calcifications (%)	10.5%	31.4%	0.02*

*Significant at $p < 0.05$

Molecular analysis revealed that GLUT1, SNAT2, and LAT1 expression were significantly downregulated in the FGR group compared to controls, correlating with reduced birth weight and placental size. Similarly, fatty acid transporters (FATP and CD36) showed reduced expression in FGR placentas ($p < 0.05$). Conversely, ABC transporters such as P-gp and BCRP demonstrated upregulation in FGR, suggesting a protective efflux mechanism.

Table 4. Expression of Placental Transport Proteins (Relative Expression Levels, mean ± SD)

Transport Protein	AGA Group (n=38)	FGR Group (n=35)	p-value
GLUT1	1.00 ± 0.12	0.72 ± 0.10	<0.001*
GLUT3	1.05 ± 0.14	0.80 ± 0.11	0.001*
SNAT2 (System A)	1.02 ± 0.15	0.70 ± 0.13	<0.001*
LAT1 (System L)	1.04 ± 0.16	0.77 ± 0.12	0.001*
FATP	0.98 ± 0.11	0.68 ± 0.09	<0.001*
CD36	1.01 ± 0.13	0.75 ± 0.10	0.001*
P-gp (ABCB1)	1.00 ± 0.14	1.32 ± 0.18	<0.001*
BCRP (ABCG2)	0.96 ± 0.12	1.28 ± 0.15	<0.001*

*Significant at $p < 0.05$

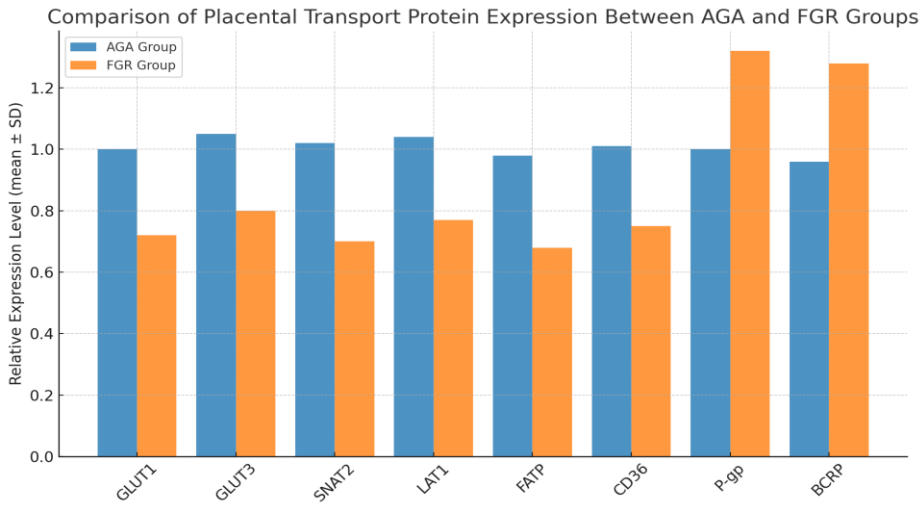

Figure 1

The bar graph comparing placental transport protein expression between the AGA and FGR groups. It clearly shows downregulation of GLUT, SNAT, LAT, FATP, and CD36 in FGR, while P-gp and BCRP are upregulated.

DISCUSSION

This study highlights the critical role of placental transport proteins in regulating fetal growth and provides evidence that altered expression of nutrient transporters contributes to the pathophysiology of fetal growth restriction (FGR). In our cohort, mothers of FGR neonates had a higher frequency of hypertensive disorders, and their placentas were significantly smaller with greater frequency of gross pathological changes. These findings are consistent with earlier reports that maternal vascular dysfunction and reduced uteroplacental perfusion are central contributors to impaired nutrient delivery [10-12].

The most important observation was the differential expression of key placental transport proteins. We found significant downregulation of glucose transporters GLUT1 and GLUT3 in the FGR group. This aligns with the studies demonstrated that decreased placental GLUT expression reduces glucose transfer capacity, thereby limiting the primary energy substrate available for the developing fetus [13-15]. Similar findings were reported a study, who showed reduced GLUT1 expression in growth-restricted placentas, correlating strongly with reduced birth weight [16, 17].

Amino acid transporters, particularly SNAT2 (System A) and LAT1 (System L), were also markedly reduced in FGR placentas. Amino acids are essential for protein synthesis and fetal tissue growth, and their transport across the placenta is highly regulated. Reduced System A activity in FGR has been consistently reported and our results support these observations. The reduction in LAT1 expression is especially significant, as it mediates transport of large neutral amino acids like leucine, which are crucial for fetal growth and activation of the mTOR signaling pathway [18].

Similarly, fatty acid transport proteins (FATP and CD36) were downregulated in our study, suggesting impaired lipid transfer to the fetus. This observation is in agreement with study, who emphasized the importance of fatty acid transport proteins in fetal neurodevelopment and adipose tissue formation. Altered lipid handling in the placenta may contribute to both growth restriction and long-term metabolic programming in affected infants [19].

Interestingly, we observed upregulation of ABC transporters such as P-glycoprotein (ABCB1) and BCRP (ABCG2) in FGR placentas. These transporters primarily function to efflux xenobiotics and toxic metabolites, and their increased expression may represent a compensatory protective mechanism in the hypoxic or stressed intrauterine environment. This finding is supported by studies who also demonstrated increased ABC transporter activity in compromised pregnancies. While this may benefit fetal protection, it may inadvertently limit the placental transfer of some endogenous substrates, thereby exacerbating nutrient insufficiency [20].

Taken together, our findings reinforce the concept that FGR is not solely a consequence of reduced uteroplacental blood flow but also results from molecular changes at the maternal–fetal interface. The consistent downregulation of glucose, amino acid, and fatty acid transporters, coupled with upregulation of efflux proteins, indicates a reprogrammed placental state that prioritizes protection over growth. Such changes may have implications not only for perinatal outcomes but also for future metabolic health of the offspring, consistent with the developmental origins of health and disease hypothesis.

CONCLUSION

This study demonstrates that altered expression of placental transport proteins plays a central role in the pathogenesis of fetal growth restriction. Reduced expression of glucose, amino acid, and fatty acid transporters was strongly associated with impaired fetal growth, while upregulation of ABC transporters may reflect a compensatory but maladaptive response. These findings emphasize the placenta's active role as a nutrient sensor and regulator rather than a passive organ.

Understanding these biochemical and physiological alterations may open avenues for targeted interventions aimed at improving placental transport efficiency. Future research should focus on longitudinal studies to identify early biomarkers of transporter dysfunction and explore therapeutic strategies such as maternal nutritional supplementation or pharmacological modulation that could potentially restore placental transport capacity and improve fetal outcomes.

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