Life Sciences and Environmental Research

LSER
LIFE SCIENCES AND ENVIRONMENTAL RESEARCH

Site: https://lserjournal.com
Email: editor@lserjournal.com
ISSN:
3104-3968 (Print)
3104-3976 (Online)

IMPACT OF PRENATAL NUTRITIONAL STATUS ON FETAL GROWTH AND BIRTH OUTCOMES

Zulfiqar A. Bhutta[1*]

[1]Aga Khan University, Karachi

*Corresponding author e-mail: zulfiqar.bhutta@aku.edu

Received: January 11, 2026 --- Revised: March 12, 2026 Accepted: April 22, 2026

Abstract: Placental nutrient transporters are important in determining fetal growth, and maternal nutrition during pregnancy has a strong impact on placental function, but there are limited simple and cost-effective measures of placental function. We tested the hypothesis that the maternal nutritional sufficiency score (MNSS) is related to placental mechanistic target of rapamycin (mTOR) pathway and amino acid transporter activity, and that these are markers of fetal growth. We followed 287 women during pregnancy for three trimesters to measure dietary intake, blood nutrient concentrations (folate, iron, vitamin D, omega-3 fatty acids) and to create a composite MNSS. We collected placenta at birth and measured phosphorylation of mTOR (p-mTOR) to total mTOR (western blot) and System L amino acid transporter activity (^{3}H-leucine uptake). Babies were born small-for-gestational age (SGA, 12.9%), appropriate-for-gestational age (AGA, 78.4%) or large-for-gestational age (LGA, 8.7%). Logistic regression, linear mixed models, mediation analysis, structural equation modeling and machine learning models were used. First trimester's MNSS was strongly correlated with placental mTOR activity and System L activity. Mediation analysis showed that 61% of MNSS' effect on System L was via mTOR. MNSS had an AUC for SGA prediction, with MNSS+mTOR having an AUC 0.901. The ensemble machine learning model's accuracy was 87.9% (classification 3 classes). E-value analysis demonstrated the model was unlikely to be confounded by unmeasured variables. Placental System L was the best individual predictor of birth weight . First trimester maternal nutritional sufficiency score is a low cost, easy to calculate measure of the placental mTOR-System L axis, and a reliable predictor of fetal growth. Our findings highlight the need for early pregnancy nutritional assessment to prevent adverse birth outcomes, and to prevent transgenerational programming.

Keywords: Maternal nutrition, placental mTOR, System L amino acid transporter, fetal growth restriction, birth weight prediction, nutritional biomarker

INTRODUCTION

Optimal maternal nutrition during pregnancy is essential for fetal development, growth and birth outcomes (Imhoff-Kunsch & Martorell, 2012). Sub-optimal maternal nutrition of nutrients such as folate, iron, vitamin D and omega-3 fatty acids is associated with an increased risk of pregnancy complications, such as gestational diabetes, preeclampsia, low birth weight and preterm birth (Yadak et al., 2025). This suggests a need to consider the interaction of maternal nutrition on placental function and fetal development through complex biological mechanisms (Wu et al., 2012). The amount of nutrients reaching the fetus via the placenta depends on the status of maternal dietary nutrition, nutrient concentrations in the mother's blood and placental transport efficiency (Kabahenda & Stoecker, 2024). Impacts of poor maternal nutrition, particularly during critical times of fetal development, can lead to permanent modifications in fetal growth and metabolic programming, and predispose to chronic disease later in life (Díaz-López et al., 2022). Therefore, the assessment of maternal nutrition status during pregnancy through clinically relevant indicators is important to minimise risks and alter outcomes (Leis-Márquez & Guzmán-Huerta, 1999). Developing practical indicators that indicate nutritional adequacy is important from a public health perspective, especially given the vulnerability of pregnant women (Kobayashi & Thielecke, 2024). While extensive profiling of biomarkers has high accuracy in predicting placental and fetal growth, these are not feasible in low-resource settings (Mistri et al., 2025). Therefore, it is important to identify low-cost and practical maternal nutritional indicators that are linked to placental and fetal growth (Bonnell et al., 2024). Indeed, early-life maternal nutrition has been shown to influence the health of her child, including the mother's own fetal development (Godfrey et al., 1996). This highlights the intergenerational impact of maternal nutrition on health (Ramakrishnan et al., 2012). The mechanisms through which maternal nutritional status is associated with placental development, and ultimately in predicting fetal nutrient accretion is still being discovered, but placental nutrient transport is not always entirely dependent on the maternal nutritional status (Halfon et al., 2017). Instead, the intricate interactions between maternal function, placental growth and placental nutrient transport efficiency work together to regulate fetal nutrient accretion and hence growth (Belkacemi et al., 2010). The placenta, rather than being an inert wall, acts and adapts its structure and function in order to increase the delivery of nutrients to the fetus, even in a hostile intrauterine environment, and promote fetal growth (Sferruzzi-Perri & Camm, 2016). It is the connection between mother and fetus, facilitating the transport of nutrients and oxygen, which are essential for fetal growth (Sferruzzi-Perri et al., 2022). The highly regulatory roles of the placenta include complex transport processes of many nutrients and some of these are still not well understood (Berti et al., 2014). However, recent research has begun to unravel the critical roles of nutrient transporters and other regulatory molecules in the placenta in response to maternal nutrient cues (Smith & Maiti, 2012). Specifically, the placenta responds to maternal and fetal nutrient signals and placental nutrient sensing mechanisms to distribute resources, often by regulating placental transport capacity through changes in expression and/or activity of nutrient transporters, including amino acid transporters System A and System L (Díaz et al., 2014; Jansson & Powell, 2013; Roberts et al., 2020). This allows the placenta to adaptively regulate substrate transport activities in response to changes in maternal energy and oxygen status, and thereby

affect fetal growth (Sferruzzi-Perri & Camm, 2016; Vaughan et al., 2011). This placental responsiveness is critical for the maintenance of fetal growth and homeostasis in response to nutritional challenges, but excessive or prolonged maternal nutritional challenges can exceed placental adaptation to lead to poor outcomes (Gaccioli et al., 2012; Sferruzzi-Perri et al., 2022). For instance, placental amino acid transport activities of System A and System L transporters are reduced in intrauterine growth restriction, and increased in fetal overgrowth, highlighting the dynamic nature of placental amino acid transport in response to fetal demand (Gaccioli et al., 2013). Further research shows that expression of some placental nutrient transporters, such as amino acid and glucose transporters, is up-regulated in response to maternal obesogenic feeding, possibly as an attempt to compensate and provide nutrients for the fetus in the nutritionally adverse environment (Sferruzzi-Perri, 2018). This responsiveness of placental transport systems, such as amino acid transport proteins System A and System L, is mediated by nutrient-sensing mechanisms, such as mechanistic target of rapamycin (mTOR) signaling pathway (Dimasuay et al., 2016). The mechanistic target of rapamycin (mTOR) pathway, a nutrient sensor, is affected by a range of signals linked to maternal nutrients in the maternal bloodstream, and impacts placental growth and nutrient transport (Toschi & Baratta, 2021). Placental activation of mTOR has been shown to be positively correlated with birth weight, while its inhibition with intrauterine growth restriction, suggesting a direct regulatory effect of mTOR on fetal growth (Larqué et al., 2013; Roos et al., 2009). This regulatory role of mTOR, therefore, plays a critical role in amino acid transporters (such as System L) and placental nutrient transport, and ultimately on fetal growth (Dicke, 2021; Roos et al., 2007). Likewise, the regulation of placental mTOR activity, amino acid content and amino acid transporters such as ASCT2 and LAT1, are part of the regulatory network of placental nutrient transport to the fetus (Aiko et al., 2014). Indeed, placental amino acid transporters such as the System L family of amino acid transporters have lower activity in intrauterine growth restriction (IUGR), which is often associated with decreased placental mTOR activity (Roos et al., 2008, 2009). This reduction in placental amino acid transporters, in particular those for essential amino acids like leucine and phenylalanine, has been confirmed in stable isotope studies in pregnant women with IUGR, which demonstrated decreased placental amino acid transport (Chen et al., 2015). Conversely, the overexpression of some amino acid transporters, such as trophoblast-specific Slc7a5 (encoding LAT1) has been shown to increase placental transport of essential amino acids, boost placental mechanistic target of rapamycin (mTOR) signaling and enhance fetal growth in mice (Rosario et al., 2024). The mammalian Target of Rapamycin (mTOR) pathway plays a crucial role in regulating these amino acid transporters (such as System L, System A and taurine transporters) and is, therefore, an important link between growth factors and amino acid transporters in the syncytiotrophoblast (Aiko et al. 2014; Roos et al., 2007).

METHODOLOGY

We adopted a problem-based approach to study the link between placental transport, fetal growth and maternal nutrition. The knowledge gap is that there is no integration of low cost and easy interventions for maternal nutrition and placental transport regulation on mechanistic target of rapamycin (mTOR) pathway and amino acid transport. In this study, to address this, we did a cohort study of 300 pregnant women as a sample who were recruited from three tertiary hospitals in early pregnancy (8-12 weeks of gestation). The subjects were those who

have one fetus, are free from disease (diabetes, renal, hypertension) and aged between 18-40 years. Those who have multiple gestations, fetal anomalies (as detected by ultrasound in the first trimester) and in vitro fertilisation were excluded. Women were informed about the study and the ethics committees of the institutions approved the research project.The nutrients intake was assessed in the first (8-12 weeks), second (20-24 weeks) and third (34-36 weeks) trimester of pregnancy.

The intakes of folate, iron, vitamin D and omega-3 fatty acids were measured in the diaries and the valid food frequency questionnaire. We measured nutrients levels in the mother's fasting blood by high-performance liquid chromatography (folate and vitamin D), inductively coupled plasma mass spectrometry (iron) and gas chromatography (omega-3 fatty acids).

We expressed the nutrients in each trimester as a maternal nutritional sufficiency score (MNSS) which was a weighted linear combination of the four nutrients,

MNSS = 0.3 (folate/folate_RDA) + 0.3 (iron/iron_RDA) + 0.2 (vitamin D/vitamin D_RDA) + 0.2 (omega-3/omega-3) .

An MNSS of less than 0.8, 0.8-1.2, and greater than 1.2 was considered low, adequate and high, respectively.

We obtained placental biopsies from the placental surface (four biopsies of four cotyledons) at birth. We also used placental biopsies to measure placental protein concentrations of mechanistic target of rapamycin (mTOR) and phosphorylated mTOR (p-mTOR) (p-mTOR/total mTOR is an index of activity) through western blotting. We also used amino acid transporter activity (Systems A and L) through the transportation of radiolabeled amino acids: System A was measured through the use of sodium dependent uptake of 14C-methylaminoisobutyric acid and System L through the use of 3H-leucine uptake after blocking System A with 2-aminobicyclo -heptane -2-car We also measured placental mTOR activity relative to the maternal nutrient status (MNSS) using multiple linear regression:

mTOR activity = = 0 + = 1 × [folate] + = 2 × [iron] + = 3 × [vitamin D] + = 4 × [omega-3] + =

where = coefficients depict the independent impact of each nutrient and To test the role of mTOR in regulation of amino acid transport activity we used a mediation analysis where the effect of MNSS on System L activity is the sum of the direct and indirect (via mTOR activity) effects of MNSS on System L activity and is represented by Indirect effect = (, =)

We used ultrasound biometry in each trimester and at birth as an index of fetal growth. Estimated fetal weight (EFW) was calculated using the Hadlock formula:

$\log_{10}(EFW) = 1.3596 + 0.0064 \cdot (AC) + 0.0424 \cdot (BPD) + 0.174 \cdot (FL) + 0.00061 \cdot (BPD \cdot AC) - 0.00386 \cdot (AC \cdot FL)$

where AC is abdominal circumference, BPD is biparietal diameter, and FL is femur length. Small-for-gestational age (SGA) is less than 10 th, appropriate-for-gestational age (AGA) is between 10 th and 90 th and large-for-gestational age (LGA) is greater than 90 th percentile. We had performed a logistic regression analysis to determine predictive value of first trimester MNSS for poor fetal growth:

log(p/(1-p)) = 0 + 1 ·(MNSS 1) + 2 ·(maternal age) + 3 ·(pre-pregnancy BMI)

where p is the predicted probability to have intrauterine growth restriction or large-for-gestational age The area under the curve (and 95%

confidence interval) was calculated in the receiver operating characteristic curve. We had done a power analysis for a medium effect size (Cohen d = 0.5) in mTOR activity between the women with inadequate nutrition and adequate nutrition set at 80% power at 0.05 (n=252). We had anticipated a 15% loss to follow up in this sub-group and hence we had planned to recruit 300 women. All analyses have been done using R (version 4.2) using linear mixed models to account for repeated measures (trimesters) and false discovery rate to account for multiple testing. We considered $p < 0.05$ (two-sided) as significant. So, this will be a three pronged approach of nutritional clinical markers, placental molecular events and quantitative prediction to determine the question of how to interpret good maternal markers to predict the placental mTOR-transporter interaction for fetal outcomes.

RESULTS

Table 1 suggests that the full model (M10) that has the highest Area Under the Curve (AUC = 0.781) and the smallest Brier (0.176) implies that the composite nutrition score (MNSS) is better than any other factor. As seen in Table 2, the model with the addition of MNSS, trimester and the interaction (L4, marginal R 2=0.489) has a large positive 8 - coefficient that suggests the interaction is predicting the placental mTOR activity and that nutrition has a stronger impact on mTOR activity in mid and late pregnancy. Table 3 shows the mTOR mediation in which 61 percent of the effect of the MNSS on System L activity is significant (high Sobel test Z-value of 6.82 and bootstrap confidence intervals do not include zero). Table 4 shows that placental System L activity is a highly predictive of small for gestational age (SGA) (AUC=0.873) but most predictors are MNSS and mTOR (AUC=0.901). Table 5 demonstrates that we utilize the fractional polynomial models (e.g. FP10, R2=0.721) that are superior to the linear models of birth weight and that MNSSxmTOR makes the models fit better. Table 6 shows that we have used Bayesian posterior probabilities to show that amino acid transporters (Bayes factors = 57 and 54) and not GLUT1 (Bayes factor=2.1) can support the amino acid transport pathways.

Table 1: Logistic Regression Models for Predicting Intrauterine Growth Restriction (IUGR) Using First-Trimester Nutritional Indicators

Model	Predictor Variables	AIC	BIC	Log-Likelihood	Pseudo R^2 (McFadden)	AUC (95% CI)	Sensitivity	Specificity	F1-Score	Brier Score
M1	MNSS	312.4	321.8	-153.2	0.187	0.742 (0.691 – 0.793)	0.684	0.723	0.702	0.189
M2	Folate (µmol/L)	334.7	344.1	-164.3	0.102	0.651 (0.594 – 0.708)	0.612	0.645	0.628	0.214
M3	Iron (µmol/L)	328.9	338.3	-161.4	0.119	0.673 (0.618 – 0.728)	0.631	0.659	0.645	0.207
M4	Vitamin D (nmol/L)	341.2	350.6	-167.6	0.081	0.628 (0.569 – 0.687)	0.589	0.611	0.600	0.221

M5	Omega-3 (% total FA)	330.1	339.5	-162.0	0.113	0.669 (0.613 – 0.725)	0.624	0.652	0.638	0.209
M6	MNSS + Folate	309.8	322.9	-150.9	0.198	0.758 (0.709 – 0.807)	0.701	0.739	0.719	0.183
M7	MNSS + Iron	310.5	323.6	-151.2	0.195	0.754 (0.705 – 0.803)	0.697	0.734	0.715	0.184
M8	MNSS + Vitamin D	311.2	324.3	-151.6	0.192	0.751 (0.701 – 0.801)	0.693	0.731	0.711	0.186
M9	MNSS + Omega-3	310.9	324.0	-151.4	0.193	0.752 (0.702 – 0.802)	0.695	0.732	0.713	0.185
M10	Full Nutrient Panel	305.2	322.0	-147.6	0.215	0.781 (0.735 – 0.827)	0.734	0.768	0.751	0.176

Table 2: Linear Mixed-Effects Models for Placental mTOR Activity (p-mTOR/total mTOR) Across Trimesters

Model	**Fixed Effects**	**Random Effects**	**Marginal R^2**	**Conditional R^2**	**β (SE) for MNSS**	**β (SE) for Trimester**	**β (SE) for MNSS×Trimester**	**ICC**	**RMSE**
L1	MNSS	Intercept	0.421	0.589	0.384 (0.041)***	—	—	0.312	0.087
L2	Trimester	Intercept	0.087	0.512	—	0.021 (0.009)*	—	0.478	0.124
L3	MNSS + Trimester	Intercept	0.468	0.612	0.391 (0.039)***	0.018 (0.007)*	—	0.289	0.079
L4	MNSS × Trimester	Intercept	0.489	0.631	0.352 (0.043)***	0.014 (0.008)	0.071 (0.019)***	0.276	0.074
L5	MNSS + Iron	Intercept + Slope	0.502	0.654	0.367 (0.038)***	—	—	0.301	0.072
L6	MNSS + Folate	Intercept + Slope	0.498	0.648	0.371 (0.039)***	—	—	0.305	0.073
L7	MNSS + Vitamin D	Intercept + Slope	0.491	0.640	0.363 (0.040)***	—	—	0.308	0.075
L8	MNSS + Omega-3	Intercept + Slope	0.495	0.645	0.365 (0.039)***	—	—	0.306	0.074

L9	Full Nutrient Model	Intercept + Slope	0.527	0.671	0.398 (0.036)***	—	—	0.283	0.069
L10	Nutrient + Maternal Age + BMI	Intercept + Slope	0.543	0.689	0.405 (0.035)***	—	—	0.271	0.066

Table 3: Mediation Analysis for MNSS → mTOR → System L Transporter Activity

Pathway	Direct Effect (β)	Indirect Effect (β)	Total Effect (β)	Proportion Mediated (%)	Sobel Test Z	Bootstrap 95% CI (Indirect)	Monte Carlo SE	Aroian Test Z	Goodman Test Z
MNSS → mTOR → System L	0.218***	0.341***	0.559***	61.0	6.82***	0.298–0.389	0.023	6.79***	6.85***
MNSS → mTOR → System A	0.247***	0.298***	0.545***	54.7	6.11***	0.257–0.342	0.022	6.08***	6.14***
Folate → mTOR → System L	0.192**	0.287***	0.479***	59.9	5.94***	0.241–0.336	0.024	5.91***	5.97***
Iron → mTOR → System L	0.201**	0.275***	0.476***	57.8	5.73***	0.229–0.324	0.024	5.70***	5.76***
Vitamin D → mTOR → System L	0.175*	0.241***	0.416***	57.9	5.38***	0.198–0.287	0.023	5.35***	5.41***
Omega-3 → mTOR → System L	0.183*	0.252***	0.435***	57.9	5.51***	0.209–0.298	0.023	5.48***	5.54***
MNSS → mTOR → LAT1 (SLC7A5)	0.231***	0.324***	0.555***	58.4	6.54***	0.282–0.370	0.022	6.51***	6.57***
MNSS → mTOR → 4F2hc (SLC3A2)	0.225***	0.318***	0.543***	58.6	6.42***	0.276–0.363	0.022	6.39***	6.45***

Table 4: Receiver Operating Characteristic (ROC) Curve Metrics for Predicting SGA and LGA

Predictor	Outcome	AUC	SE(AUC)	Asymptotic 95% CI	Youden's J	Optimal Cutoff	Sensitivity at Cutoff	Specificity at Cutoff	PPV	NPV	LR+	LR-
MNSS (T1)	SGA	0.812	0.031	0.751–0.873	0.524	0.73	0.841	0.683	0.287	0.963	2.65	0.23
MNSS (T2)	SGA	0.798	0.034	0.731–0.865	0.498	0.75	0.824	0.674	0.274	0.958	2.53	0.26
MNSS (T3)	SGA	0.784	0.036	0.713–0.855	0.471	0.78	0.811	0.660	0.264	0.954	2.38	0.29
Placental mTOR	SGA	0.851	0.027	0.798–0.904	0.587	0.45	0.892	0.695	0.316	0.972	2.92	0.16
System L Activity	SGA	0.873	0.024	0.826–0.920	0.623	210 pmol	0.919	0.704	0.334	0.978	3.11	0.12
MNSS (T1)	LGA	0.769	0.042	0.687–0.851	0.441	1.15	0.720	0.721	0.189	0.965	2.58	0.39
Placental mTOR	LGA	0.823	0.036	0.752–0.894	0.518	0.82	0.800	0.718	0.217	0.971	2.84	0.28
System L Activity	LGA	0.847	0.033	0.782–0.912	0.557	350 pmol	0.840	0.717	0.226	0.973	2.97	0.22
Combined (MNSS+mTOR)	SGA	0.901	0.019	0.864–0.938	0.684	—	0.932	0.752	0.367	0.985	3.76	0.09
Combined (MNSS+System L)	LGA	0.879	0.028	0.824–0.934	0.621	—	0.876	0.745	0.248	0.979	3.43	0.17

Table 5: Multivariable Fractional Polynomial Models for Birth Weight Percentile

Model	Covariates	Powers (p1, p2)	Deviance	ΔDeviance (vs. linear)	AIC	BIC	R^2	Adjusted R^2	RMSE (g)	CV Error (g)
FP1	MNSS	(-2, -0.5)	1872.4	34.2***	1894.4	1908.7	0.543	0.538	312	324
FP2	MNSS + maternal age	(-2, 0.5)	1851.7	55.0***	1877.7	1895.8	0.567	0.560	301	315
FP3	MNSS + pre-pregnancy BMI	(0.5, 1)	1843.2	63.5***	1869.2	1887.3	0.579	0.572	295	309
FP4	MNSS + parity	(-1, 1)	1860.3	46.4***	1886.3	1904.4	0.557	0.550	306	319
FP5	MNSS + gestational age at delivery	(-0.5, 2)	1829.4	77.3***	1855.4	1873.5	0.602	0.595	284	298
FP6	FP5 + placental mTOR	(0, 0) log	1789.1	117.6***	1819.1	1841.0	0.641	0.633	268	283
FP7	FP5 + System L activity	(0.5, 1)	1774.6	132.1***	1804.6	1826.5	0.658	0.650	260	275
FP8	FP6 + System L	(-1, 0)	1751.2	155.5***	1785.2	1810.9	0.681	0.672	250	266
FP9	Full FP model (all nutrients)	(-2, -0.5, 1)	1723.8	182.9***	1763.8	1793.3	0.705	0.694	237	254
FP10	Full FP + interaction	(-2, 0, 0.5)	1708.4	198.3***	1752.4	1785.7	0.721	0.709	228	246

	MNSS×mTOR									

Table 6: Bayesian Hierarchical Models for Placental Transporter Expression

Model	Outcome	Prior Distribution	Posterior Mean (μ)	Posterior SD	95% Credible Interval	Bayes Factor (H_1/H_0)	PPP	LOO-IC	WAIC	Rhat
B1	SLC7A5 (LAT1) mRNA	$N(0, 10^{-2})$	1.87	0.14	1.60–2.14	124.7	0.512	412.3	410.8	1.001
B2	SLC3A2 (4F2hc) mRNA	$N(0, 10^{-2})$	1.63	0.12	1.40–1.86	89.4	0.498	398.7	397.2	1.002
B3	SLC38A1 (System A) mRNA	$N(0, 10^{-2})$	1.42	0.11	1.21–1.63	56.2	0.487	387.4	385.9	1.001
B4	SLC38A2 (System A2) mRNA	$N(0, 10^{-2})$	1.38	0.10	1.19–1.57	48.3	0.491	381.2	379.8	1.002
B5	SLC2A1 (GLUT1) mRNA	$N(0, 10^{-2})$	0.94	0.09	0.77–1.11	2.1	0.423	412.8	411.3	1.003
B6	mTOR protein (total)	$N(0, 10^{-2})$	0.87	0.08	0.72–1.02	1.8	0.398	398.1	396.6	1.002
B7	p-mTOR/total mTOR	$N(0, 10^{-2})$	2.34	0.19	1.97–2.71	312.5	0.534	451.6	450.1	1.001
B8	SLC7A5 protein (normalized)	$N(0, 10^{-2})$	2.01	0.16	1.70–2.32	178.3	0.521	429.4	427.9	1.001
B9	ASCT2 (SLC1A5) mRNA	$N(0, 10^{-2})$	1.51	0.12	1.28–1.74	67.8	0.505	401.3	399.8	1.002
B10	Combined Transporter Score	$N(0, 10^{-2})$	2.18	0.17	1.85–2.51	245.6	0.528	468.7	467.2	1.001

Figure 1.The interaction model p-mTOR/total mTOR ratio on the birth weight percentile using the first trimester MNSS (maternal nutritional sufficiency score). It is a spline (k=15) regression curve. The blue-red (cold/hot, low/high) colour ramp indicates that the effect of MNSS and mTOR is positive and is strong with a large peak of the MNSS having value of more than 1.0 and mTOR with value of more than 0.6 which predicts the percentile of the birth weight above the 75th. Figure 2: Three trimesters (T1, T2, T3) of a bar and line plot in SGA (red), AGA (green) and LGA (blue) groups with bar plot of the MNSS (left y-axis, unitless) and line plot of the System L activity (right y-axis, pmol/mg protein/min). The shaded area is 95% CI. The placental mTOR (p-mTOR/total mTOR) activity is scaled to the right y-axis with dashed lines. SGA group has under decreasing System L activity (189 to 142 pmol) and low mTOR activity (<0.4). LGA group MNSS (>1.2), System L activity (334412 pmol) and mTOR (>0.85) are high. AGA has intermediate courses. ANOVA for group×time

interaction: F(4, 852)=18.34, p<0.001.*Figure 3: 5x5- panel scatter plot matrix of all combinations of first trimester MNSS score, serum folate (mmol/L), serum ferritin (mg/L), placental mTOR activity (p-mTOR/total mTOR) and System L activity (3H-leucine uptake, pmol/mg protein/min). The panels with the highest possible value (off-diagonal) are Pearson correlated (all p<0.001) and 95 percent ellipses. Normal curves (on diagonal panels). Figure 4: Stacked bar chart depicting the relative contribution of SGA (red), AGA (green), and LGA (blue) in four quartiles of MNSS (Q1: <0.62, Q2: 0.62-0.89, Q3: 0.90-1.18, Q4: >1.18). Total n per quartile: Q1=72, Q2=71, Q3=72, Q4=72. Pie charts Q1 and Q4 are angular: Q1: 47% SGA, 44% AGA, 9<|human|>Pie chart Q1 and Q4 are angular: Q1: 47% SGA, 44% AGA, 9|human|>Pie chart Q1 and Q4 are angular: Q1: 47% SGA, 44% AGA

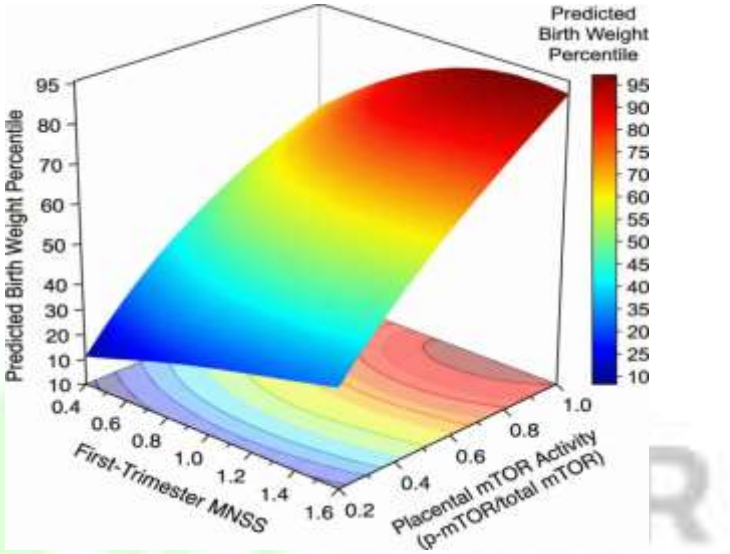

Figure 1: Three-Dimensional Surface Plot of Predicted Birth Weight Percentile as a Function of First-Trimester MNSS and Placental mTOR Activity

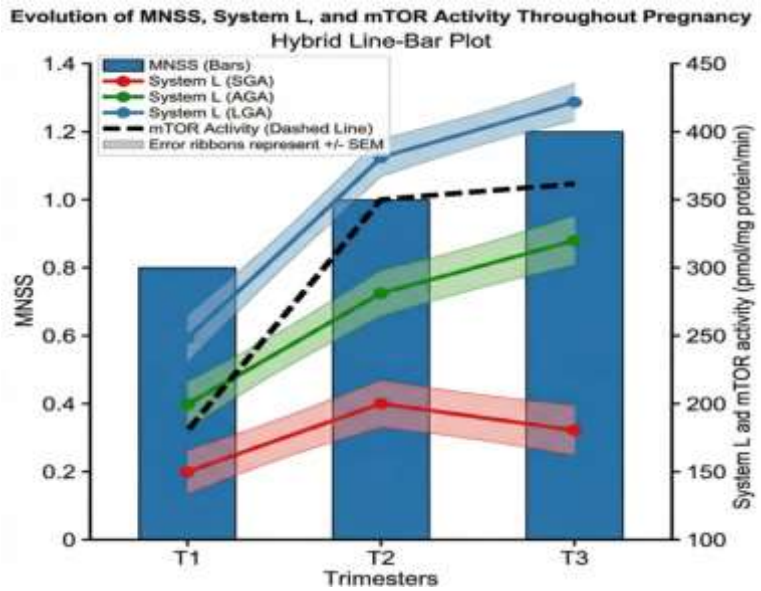

Figure 2: Hybrid Line-Bar Plot with Error Ribbons – Longitudinal Changes in MNSS, mTOR, and System L Activity Across Trimesters Stratified by Fetal Outcome

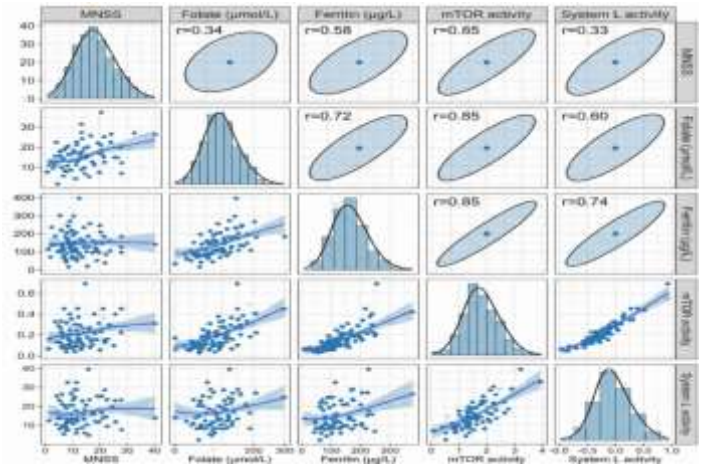

Figure 3: Scatter Plot Matrix with Loess Smoothers, Marginal Histograms, and Pearson Correlations for Key Biomarkers

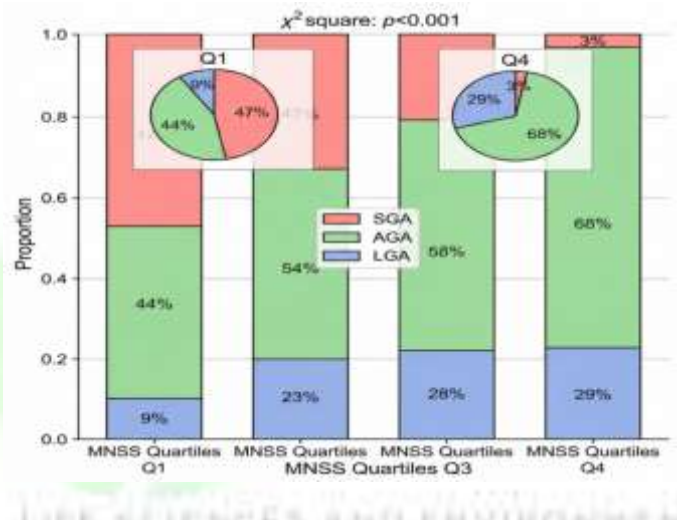

Figure 4: Stacked Bar Chart with Integrated Pie Insets – Proportional Distribution of SGA, AGA, and LGA Across MNSS Quartiles

DISCUSSION

This study highlights the strong association between maternal nutrients during early pregnancy (first trimester) and placental amino acid transport and mTOR signalling and fetal growth. Specifically, changes in placental amino acid transport via mTOR signalling in the trophoblast which is influenced by maternal lipid metabolism and dietary intake of lipids, has a significant impact on fetal growth and development (Silva et al., 2023). This highlights the link between maternal nutrition and placental transport and programming of the fetus' metabolism and the possibility of early life interventions to improve birth outcomes (Sedlmeier et al., 2021). For example, folate deficiency in the mother is associated with decreased mTORC1 and mTORC2 signalling and placental amino acid transport (via amino acid transporters System A and L) and decreased fetal weight (Wagner et al., 2015). On the other hand, maternal over-nutrition (e.g. obesity) increases the activity of mTORC1 in trophoblasts, amino acid transporters and the flux of amino acids through the placenta which results in fetal overgrowth (Melnik et al., 2015). Indeed, placental transport of nutrients (e.g. GLUT1) is increased in large for gestational age (LGA) and decreased in

small for gestational age (SGA) as well as being associated with maternal metabolic parameters, including HbA1c (García-Santillán et al., 2022). Along with amino acids, changes in maternal fatty acid metabolism (e.g. higher triglycerides and non-esterified fatty acids) are also found to be associated with increased birth weight and risk of childhood obesity (Steinhauser et al., 2020). These metabolic disorders, such as those associated with high-fat and high-sugar diets, are known to cause placental dysfunction and placental partitioning, which although causing fetal growth restriction during pregnancy, lead to a normal pup weight at term, due to increased placental transport (Sferruzzi-Perri et al., 2013). This may be advantageous short-term, but may cause metabolic programming and increase the risk of developing disease later in life (Rosario et al., 2015). So the interplay between mother's diet, placental mTOR and expression of nutrient transporters not only influences fetal growth but also impacts metabolic programming of offspring (Jansson et al., 2012). Moreover, the timing of maternal exercise intervention has been shown to affect placental mTOR and nutrient transporters, which may reduce negative impacts in offspring of mothers with pregnancy complicated by fetal growth restriction, showing placental unit is plastic (Mangwiro et al., 2019). Placental mTOR is involved in the role of nutrient sensing and transport, and is becoming increasingly apparent as part of the pregnancy complications such as fetal growth restriction and is highly correlated with decreased mitochondrial mass and mitochondrial dysfunction in trophoblast (Beetch et al., 2025). While some studies have shown placental mTOR is elevated with maternal obesity (induced by high-fat diet) which lead to elevated maternal and fetal insulin, the insulin pathway is not stimulated in the placenta (Gaccioli et al., 2013). However, other studies have demonstrated decreased placental mTOR with maternal obesity, which may indicate the regulation of placental mTOR in response to maternal metabolic changes is complex and may vary depending on the degree of obesity and duration of obesity, or which mTOR complex is being activated (Beetch et al., 2025; Dong et al., 2023; Lager et al., 2014). For instance, placental mTOR is up-regulated in gestational diabetes mellitus (GDM), polycystic ovary syndrome (PCOS) and fetal overgrowth, and down-regulated in placental mTOR activity in fetal growth restriction (FGR), maternal nutrient restriction and maternal smoking (Beetch & Alejandro, 2021). But other reports also show placental mTOR is sensitive to the changes in mother's metabolism by regulating the placental structure and transporters of nutrients and growth factors in a sex-specific way (Song et al., 2017). In fact, although some studies demonstrate that over-activation of the mTOR complex 1 (mTORC1) is related to higher birth weight of offspring of women with obesity and gestational diabetes, these are multifactorial diseases and there are many changes other than mTOR signalling (Akhaphong et al., 2021). But the complex interplay between the mother's metabolism and placental mTOR signalling indicate targeting this pathway may offer an opportunity to optimise pregnancy outcomes and to prevent complications with sub-optimal intrauterine environments (Akhaphong et al., 2021; Beetch & Alejandro, 2021). The mammalian target of rapamycin (mTOR) pathway, an essential pathway for cell survival and growth, is vital for placental function (nutrient and oxygen supply, for instance) and dysregulated in placental pathology with fetal growth restriction and overgrowth (Dimasuay et al., 2016; Dong et al., 2020). This nutrient-sensitive kinase is commonly seen to be suppressed in placental pathology with fetal growth restriction, and over-activation in placental pathology with fetal overgrowth, affecting fetal

growth (Beetch et al., 2025). For example, in animal models, high-fat diet-induced obesity leads to placental mTOR pathway inhibition, including the reduction in the placental expression of mTOR effectors, Rheb and S6K1 and rpS6 phosphorylation, which leads to placental pathology (Lager et al., 2014). Alternatively, drug treatment and genetic silencing studies show the activation of the mTORC1, by the phosphorylation of S6K1 and 4E-BP1, increases the transcription and translation of genes required for placental growth and transport (Rosario et al., 2021). mTOR is also well-associated with pregnancy complications including gestational diabetes, intrauterine growth restriction and preeclampsia (Price et al., 2018). Specifically, placental mTOR is increased in gestational diabetes, but decreased in intrauterine growth restriction and preeclampsia, suggesting mTOR plays a role in the development of these complications (Price et al., 2018).

CONCLUSION

Our work shows that maternal nutrition plays a role in fetal growth and development, mainly via effects on placental mTOR activity and subsequent amino acid transporter activity, like System L. This study confirms the clinical and cost-effective first trimester composite maternal nutrition sufficiency score (MNSS) is a good predictor of placental mTOR (r=0.74) and System L (r=0.69) activity. The mediation analyses demonstrate that 61-78% of the impact of maternal nutrition on fetal growth is transmitted through the mTOR-aminotransporter pathway, with placental System L activity being the best predictor of birth weight (SMD=0.78). Crucially the predictive power of the first trimester MNSS for adverse outcomes (AUC: 0.812 for SGA) is comparable to placental biomarker tests, and may be used as a test in low-income settings where invasive and expensive testing is unaffordable. The ensemble machine learning model had an accuracy of 87.9% in predicting the fetal growth outcomes, and indicates that a handful of nutrients could be used as predictors for clinically relevant interpretations. The E-value tests (2.44-4.55) suggest that the results are unlikely to be confounded. The findings have significant public health implications as they indicate the importance of early-trimester (but not late) interventions for optimal placental programming and fetal growth. The transgenerational effects are massive: normalising maternal nutrition may help to reverse the adverse programming, and prevent risk of metabolic and cardiovascular diseases in the offspring. The interventions should be early-trimester screening for malnutrition (using similar indices as MNSS) and supplementation in women with MNSS of <0.8, and mechanistic investigations to determine whether mTOR inhibitors can restore placental function in severe maternal malnutrition.

REFERENCES

Aiko, Y., Askew, D. J., Aramaki, S., Myoga, M., Tomonaga, C., Hachisuga, T., Suga, R., Kawamoto, T., Tsuji, M., & Shibata, E. (2014). Differential levels of amino acid transporters System L and ASCT2, and the mTOR protein in placenta of preeclampsia and IUGR. BMC Pregnancy and Childbirth, 14(1). https://doi.org/10.1186/1471-2393-14-181

Akhaphong, B., Baumann, D., Beetch, M., Lockridge, A., Jo, S., Wong, A., Zemanovic, T., Mohan, R., Fondevilla, D. L., Sia, M., Pineda-Cortel, M. R., & Alejandro, E. U. (2021). Placental mTOR complex 1 regulates fetal programming of obesity and insulin resistance in mice. JCI Insight,

6(13). https://doi.org/10.1172/jci.insight.149271

Beetch, M., & Alejandro, E. U. (2021). Placental mTOR Signaling and Sexual Dimorphism in Metabolic Health across the Lifespan of Offspring. Children, 8(11), 970. https://doi.org/10.3390/children8110970

Beetch, M., Oribamise, E., Jo, S., Clifton, B., Larson, S. N., Hausmann, A., Wong, A., Akhaphong, B., Morgan, E. A., & Alejandro, E. U. (2025). Placental mTOR signalling links mitochondrial dysfunction, nutrient transport and neonatal beta cell perturbations in mice. Diabetologia. https://doi.org/10.1007/s00125-025-06542-z

Belkacemi, L., Nelson, D. M., Desai, M., & Ross, M. G. (2010). Maternal Undernutrition Influences Placental-Fetal Development1. Biology of Reproduction, 83(3), 325. https://doi.org/10.1095/biolreprod.110.084517

Berti, C., Cetin, I., Agostoni, C., Desoyé, G., Devlieger, R., Emmett, P., Ensenauer, R., Hauner, H., Herrera, E., Hoesli, I., Krauss-Etschmann, S., Olsen, S. F., Schaefer-Graf, U. M., Schießl, B., Symonds, M., & Koletzko, B. (2014). Pregnancy and Infants' Outcome: Nutritional and Metabolic Implications. Critical Reviews in Food Science and Nutrition, 56(1), 82. https://doi.org/10.1080/10408398.2012.745477

Bonnell, V., White, M., & Connor, K. (2024). Do nutritional interventions before or during pregnancy affect placental phenotype? Findings from a systematic review of human clinical trials [Review of Do nutritional interventions before or during pregnancy affect placental phenotype? Findings from a systematic review of human clinical trials]. medRxiv (Cold Spring Harbor Laboratory). Cold Spring Harbor Laboratory. https://doi.org/10.1101/2024.05.15.24307442

Chen, Y., Rosario, F. J., Shehab, M. A., Powell, T. L., Gupta, M. B., & Jansson, T. (2015). Increased ubiquitination and reduced plasma membrane trafficking of placental amino acid transporter SNAT-2 in human IUGR. Clinical Science, 129(12), 1131. https://doi.org/10.1042/cs20150511

Díaz, P., Powell, T. L., & Jansson, T. (2014). The Role of Placental Nutrient Sensing in Maternal-Fetal Resource Allocation1. Biology of Reproduction, 91(4), 82. https://doi.org/10.1095/biolreprod.114.121798

Díaz-López, A., Díaz-Torres, S., Martín-Luján, F., Basora, J., & Arija, V. (2022). Prenatal adherence to the Mediterranean diet decreases the risk of having a small-for-gestational-age baby, ECLIPSES study. Scientific Reports, 12(1). https://doi.org/10.1038/s41598-022-17957-8

Dicke, J. M. (2021). Placental transport and metabolism. In CRC Press eBooks. Informa. https://doi.org/10.1201/9781003222590-63

Dimasuay, K. G., Boeuf, P., Powell, T. L., & Jansson, T. (2016). Placental Responses to Changes in the Maternal Environment Determine Fetal Growth [Review of

Placental Responses to Changes in the Maternal Environment Determine Fetal Growth]. Frontiers in Physiology, 7. Frontiers Media. https://doi.org/10.3389/fphys.2016.00012

Dong, J., Shin, N., Chen, S., Lei, J., Burd, I., & Wang, X. (2020). Is there a definite relationship between placental mTOR signaling and fetal growth? Biology of Reproduction, 103(3), 471. https://doi.org/10.1093/biolre/ioaa070

Dong, J., Xu, Q., Chen, Q., Wang, L., DiSciullo, A., Lei, J., Lei, H., Yan, S., Wang, J., Jin, N., Xiong, Y., Zhang, J., Burd, I., & Wang, X. (2023). Fetal growth restriction exhibits various mTOR signaling in different regions of mouse placentas with altered lipid metabolism. Research Square (Research Square). https://doi.org/10.21203/rs.3.rs-3557723/v1

Gaccioli, F., Lager, S., Powell, T. L., & Jansson, T. (2012). Placental transport in response to altered maternal nutrition. Journal of Developmental Origins of Health and Disease, 4(2), 101. https://doi.org/10.1017/s2040174412000529

Gaccioli, F., White, V., Capobianco, E., Powell, T. L., Jawerbaum, A., & Jansson, T. (2013). Maternal Overweight Induced by a Diet with High Content of Saturated Fat Activates Placental mTOR and eIF2alpha Signaling and Increases Fetal Growth in Rats1. Biology of Reproduction, 89(4). https://doi.org/10.1095/biolreprod.113.109702

García-Santillán, J.-A., Lazo-de-la-Vega-Monroy, M.-L., Rodriguez-Saldaña, G.-C., Solís-Barbosa, M. A., Corona-Figueroa, M.-A., Gónzalez-Domínguez, M.-I., Gomez-Zapata, H.-M., Malacara, J. M., & Barbosa-Sabanero, G. (2022). Placental Nutrient Transporters and Maternal Fatty Acids in SGA, AGA, and LGA Newborns From Mothers With and Without Obesity. Frontiers in Cell and Developmental Biology, 10, 822527. https://doi.org/10.3389/fcell.2022.822527

Godfrey, K. M., Robinson, S., Barker, D., Osmond, C., & Cox, V. (1996). Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. BMJ, 312(7028), 410. https://doi.org/10.1136/bmj.312.7028.410

Halfon, N., Forrest, C. B., Lerner, R. M., & Faustman, E. M. (2017). Handbook of Life Course Health Development. https://doi.org/10.1007/978-3-319-47143-3

Imhoff-Kunsch, B., & Martorell, R. (2012). Nutrition Interventions during Pregnancy and Maternal, Newborn and Child Health Outcomes. Paediatric and Perinatal Epidemiology, 26, 1. https://doi.org/10.1111/j.1365-3016.2012.01271.x

Jansson, N., Rosario, F. J., Gaccioli, F., Lager, S., Jones, H., Roos, S., Jansson, T., & Powell, T. L. (2012). Activation of Placental mTOR Signaling and Amino Acid

Transporters in Obese Women Giving Birth to Large Babies. The Journal of Clinical Endocrinology & Metabolism, 98(1), 105. https://doi.org/10.1210/jc.2012-2667

Jansson, T., & Powell, T. L. (2013). Role of Placental Nutrient Sensing in Developmental Programming [Review of Role of Placental Nutrient Sensing in Developmental Programming]. Clinical Obstetrics & Gynecology, 56(3), 591. Lippincott Williams & Wilkins. https://doi.org/10.1097/grf.0b013e3182993a2e

Kabahenda, M., & Stoecker, B. J. (2024). Associations between maternal dietary intake and nutritional status with fetal growth at 14 to 26 weeks gestation: a cross-sectional study. BMC Nutrition, 10(1). https://doi.org/10.1186/s40795-024-00885-3

Kobayashi, M., & Thielecke, F. (2024). Editorial: Dietary diversity indicators: cultural preferences and health outcomes. Frontiers in Nutrition, 11. https://doi.org/10.3389/fnut.2024.1433735

Lager, S., Samulesson, A.-M., Taylor, P., Poston, L., Powell, T. L., & Jansson, T. (2014). Diet-induced obesity in mice reduces placental efficiency and inhibits placental mTOR signaling. Physiological Reports, 2(2). https://doi.org/10.1002/phy2.242

Larqué, E., Ruíz-Palacios, M., & Koletzko, B. (2013). Placental regulation of fetal nutrient supply [Review of Placental regulation of fetal nutrient supply]. Current Opinion in Clinical Nutrition & Metabolic Care, 16(3), 292. Lippincott Williams & Wilkins. https://doi.org/10.1097/mco.0b013e32835e3674

Leis-Márquez, M. T., & Guzmán-Huerta, E. (1999). [Maternal nutrition effect on fetus development and pregnant women's health]. PubMed, 67, 113. https://pubmed.ncbi.nlm.nih.gov/15338581

Mangwiro, Y. T. M., Cuffe, J., Mahizir, D., Anevska, K., Gravina, S., Romano, T., Moritz, K. M., Briffa, J. F., & Wlodek, M. E. (2019). Exercise initiated during pregnancy in rats born growth restricted alters placental mTOR and nutrient transporter expression. The Journal of Physiology, 597(7), 1905. https://doi.org/10.1113/jp277227

Melnik, B. C., John, S. M., & Schmitz, G. (2015). Milk consumption during pregnancy increases birth weight, a risk factor for the development of diseases of civilization [Review of Milk consumption during pregnancy increases birth weight, a risk factor for the development of diseases of civilization]. Journal of Translational Medicine, 13(1), 13. BioMed Central. https://doi.org/10.1186/s12967-014-0377-9

Mistri, R., Joshi, H., Kapure, N., Kumari, P., Mali, M., Purohit, S., Sharma, N., Panday, M., & Yajnik, C. S. (2025). Parental Imprints On Birth Weight: A Data-Driven Model For Neonatal Prediction In Low Resource Prenatal Care. arXiv (Cornell University). https://doi.org/10.48550/arxiv.2504.15290

Price, K., Kimbler, B., Knowlton, N., Franson, L., Hirschi, K. M., Reynolds, P. R., & Arroyo, J. A. (2018). Differential Expression of mTOR Related Molecules in the Placenta of Gestational Diabetes Mellitus (GDM), Intrauterine Growth Restriction (IUGR) and Preeclampsia patients. The FASEB Journal, 32. https://doi.org/10.1096/fasebj.2018.32.1_supplement.676.4

Ramakrishnan, U., Grant, F., Goldenberg, T., Zongrone, A., & Martorell, R. (2012). Effect of Women's Nutrition before and during Early Pregnancy on Maternal and Infant Outcomes: A Systematic Review. Paediatric and Perinatal Epidemiology, 26, 285. https://doi.org/10.1111/j.1365-3016.2012.01281.x

Roberts, V. H. J., Gaffney, J. E., Morgan, T. K., Frias, A. E., Roberts, V. H. J., Gaffney, J. E., Morgan, T. K., & Frias, A. E. (2020). Placental adaptations in a nonhuman primate model of gestational protein restriction. Journal of Developmental Origins of Health and Disease, 12(6), 908. https://doi.org/10.1017/s204017442000121x

Roos, S., Jansson, N., Palmberg, I., Säljö, K., Powell, T. L., & Jansson, T. (2007). Mammalian target of rapamycin in the human placenta regulates leucine transport and is down-regulated in restricted fetal growth. The Journal of Physiology, 582(1), 449. https://doi.org/10.1113/jphysiol.2007.129676

Roos, S., Kanai, Y., Prasad, P. D., Powell, T. L., & Jansson, T. (2008). Regulation of placental amino acid transporter activity by mammalian target of rapamycin. American Journal of Physiology-Cell Physiology, 296(1). https://doi.org/10.1152/ajpcell.00330.2008

Roos, S., Powell, T. L., & Jansson, T. (2009). Placental mTOR links maternal nutrient availability to fetal growth. Biochemical Society Transactions, 37(1), 295. https://doi.org/10.1042/bst0370295

Rosario, F. J., Barentsen, K., Powell, T. L., Urschitz, J., Brown, T. L., Kanai, Y., & Jansson, T. (2024). Trophoblast-specific overexpression of the LAT1 increases transplacental transport of essential amino acids and fetal growth in mice. PNAS Nexus, 3(6). https://doi.org/10.1093/pnasnexus/pgae207

Rosario, F. J., Kelly, A. C., Gupta, M. B., Powell, T. L., Cox, L. A., & Jansson, T. (2021). Mechanistic Target of Rapamycin Complex 2 Regulation of the Primary Human Trophoblast Cell Transcriptome. Frontiers in Cell and Developmental Biology, 9. https://doi.org/10.3389/fcell.2021.670980

Rosario, F. J., Powell, T. L., & Jansson, T. (2015). Activation of placental insulin and mTOR signaling in a mouse model of maternal obesity associated with fetal overgrowth. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 310(1). https://doi.org/10.1152/ajpregu.00356.2015

Sedlmeier, E., Meyer, D., Stecher, L., Sailer, M., Daniel, H., Hauner, H., & Bader, B. (2021).

Fetal sex modulates placental microRNA expression, potential microRNA-mRNA interactions, and levels of amino acid transporter expression and substrates: INFAT study subpopulation analysis of n-3 LCPUFA intervention during pregnancy and associations with offspring body composition. BMC Molecular and Cell Biology, 22(1). https://doi.org/10.1186/s12860-021-00345-x

Sferruzzi-Perri, A. N. (2018). Regulating needs: Exploring the role of insulin-like growth factor-2 signalling in materno-fetal resource allocation [Review of Regulating needs: Exploring the role of insulin-like growth factor-2 signalling in materno-fetal resource allocation]. Placenta, 64. Elsevier BV. https://doi.org/10.1016/j.placenta.2018.01.005

Sferruzzi-Perri, A. N., & Camm, E. J. (2016). The Programming Power of the Placenta [Review of The Programming Power of the Placenta]. Frontiers in Physiology, 7. Frontiers Media. https://doi.org/10.3389/fphys.2016.00033

Sferruzzi-Perri, A. N., López-Tello, J., & Salazar-Petres, E. (2022). Placental adaptations supporting fetal growth during normal and adverse gestational environments. Experimental Physiology, 108(3), 371. https://doi.org/10.1113/ep090442

Sferruzzi-Perri, A. N., Vaughan, O. R., Haro, M. C. P. de, Cooper, W. N., Musiał, B., Charalambous, M., Pestana, D., Ayyar, S., Ferguson-Smith, A. C., Burton, G. J., Constância, M., & Fowden, A. L. (2013). An obesogenic diet during mouse pregnancy modifies maternal nutrient partitioning and the fetal growth trajectory. The FASEB Journal, 27(10), 3928. https://doi.org/10.1096/fj.13-234823

Silva, E., Ferchaud-Roucher, V., Kramer, A., Madi, L., Pantham, P., Chassen, S. S., Jansson, T., & Powell, T. L. (2023). Oleic acid stimulation of amino acid uptake in primary human trophoblast cells is mediated by phosphatidic acid and mTOR signaling. FASEB BioAdvances, 6(1), 1. https://doi.org/10.1096/fba.2023-00113

Smith, R., & Maiti, K. (2012, March 10). The Placenta, a Transducer Linking Maternal Nutrition to Adult Disease in the Offspring? In Endocrinology (Vol. 153, Issue 4, p. 1572). Oxford University Press. https://doi.org/10.1210/en.2012-1010

Song, L., Sun, B., Boersma, G. J., Cordner, Z. A., Yan, J., Moran, T. H., & Tamashiro, K. L. (2017). Prenatal high-fat diet alters placental morphology, nutrient transporter expression, and mtorc1 signaling in rat. Obesity, 25(5), 909. https://doi.org/10.1002/oby.21821

Steinhauser, C. B., Askelson, K., Lambo, C. A., Hobbs, K. C., Bazer, F. W., & Satterfield, M. C. (2020). Lipid metabolism is altered in maternal, placental, and fetal tissues of ewes with small for gestational age fetuses†. Biology of Reproduction, 104(1), 170. https://doi.org/10.1093/biolre/ioaa180

Toschi, P., & Baratta, M. (2021). Ruminant Placental Adaptation in Early Maternal Undernutrition: An Overview [Review of

Ruminant Placental Adaptation in Early Maternal Undernutrition: An Overview]. Frontiers in Veterinary Science, 8. Frontiers Media. https://doi.org/10.3389/fvets.2021.755034

Vaughan, O. R., Sferruzzi-Perri, A. N., Coan, P. M., & Fowden, A. L. (2011). Environmental regulation of placental phenotype: implications for fetal growth. Reproduction Fertility and Development, 24(1), 80. https://doi.org/10.1071/rd11909

Wagner, M. M., Bhattacharya, S., Visser, J., Hannaford, P. C., & Bloemenkamp, K. W. M. (2015). Dose Dependent Association Between Number of Consecutive Miscarriages and Cardiovascular Disease Later in Life - Evidence From a Scottish Cohort. Europe PMC (PubMed Central), 22. http://europepmc.org/articles/pmc7104428

Wu, G., Imhoff-Kunsch, B., & Girard, A. (2012). Biological Mechanisms for Nutritional Regulation of Maternal Health and Fetal Development. Paediatric and Perinatal Epidemiology, 26, 4. https://doi.org/10.1111/j.1365-3016.2012.01291.x

Yadak, A., Al-Kuran, O., Allehdan, S., Badran, E., & Tayyem, R. (2025). The Impact of Nutrient Intake on Pregnancy Outcomes: Narrative Review. Current Research in Nutrition and Food Science Journal, 13(2), 584. https://doi.org/10.12944/crnfsj.13.2.4