



Molecular and Nutritional Modulation of Placental Physiology for Optimal Fetal Growth in Dairy Cattle

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Article History: 26-009 Received: 11 Dec 2025 Revised: 12 Jan 2026 Accepted: 17 Jan 2026 Published Online: 2026

Citation: Rehman MZ, Maalik A, Raza MA and Hanan A, 2026. Molecular and nutritional modulation of placental physiology for optimal fetal growth in dairy cattle. *Sci Soc Insights*, 5: 50-57. <https://doi.org/10.65822/j.sasi/2026.006>

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ABSTRACT

The bovine placenta is a dynamic and multifunctional organ that regulates nutrient transfer, endocrine regulation and fetal growth throughout the pregnancy. Its performance is mainly influenced by maternal nutrition, metabolic status and environmental stressors, which shape placental structure and function. This review illustrates recent molecular insights into the nutritional and physiological mechanisms that regulate nutrient transport systems, including glucose, amino acids and fatty acids, in response to maternal signals. Advancements in single-cell RNA sequencing and proteomics have revealed the specialized trophoblast subpopulations and signaling networks that govern angiogenesis, immune tolerance and metabolic adaptation. Furthermore, the roles of mTOR, oxidative stress pathways and fetal sex-specific gene expression patterns are explored to explain placental efficiency under varying gestational conditions. Translational perspectives emphasize targeted nutritional interventions, such as rumen bypass amino acids, omega-3 fatty acids and nanotechnology-based delivery systems as emerging strategies to optimize placental vascular function and fetal development. Collectively, this review highlights the potential of molecular nutritional approaches to enhance reproductive efficiency and promote sustainable dairy production.

Keywords: Bovine placenta, Nutrient transport, Molecular regulation, mTOR signaling, Fetal development, Placental efficiency

INTRODUCTION

The bovine placenta is a synepitheliochorial and cotyledonary organ specialized for facilitating nutrient, gaseous, and waste exchange between the dam and the fetus. The placenta also controls endocrine and immune signals that regulate fetal growth (Hayward et al., 2016). Its capacity to support fetal growth per unit of placental mass is a leading factor in birth weight, neonatal viability, and the dam's future lactation potential (Reynolds & Redmer, 2001). Unlike rodents or humans, the bovine placenta is cotyledonary with many discrete placentomes in which selective nutrient exchange occurs, posing specific regulatory challenges and adaptation mechanisms during pregnancy (Fowden et al., 2015). Emerging technologies using single-cell transcriptomics, proteomics, and bioinformatics are beginning to reveal the intricate molecular environment that dictates placental development. Key regulators, such as vascular endothelial growth factor (VEGF), promote angiogenesis to ensure proper fetal vascularization, and nutrient transporters, such as glucose (GLUT family) and amino acid transporters, ensure an adequate supply of nutrients according to fetal needs (Diniz et al., 2021; Wang et al., 2024).

Meanwhile, oxidative stress pathways and apoptotic signaling mechanisms ensure placental remodeling and integrity, often under the control of the maternal environment and nutritional inputs (Chen et al., 2025). Nutritional supplementation in late pregnancy is pivotal in modulating placental function. Antioxidants such as vitamin E and selenium improve vascular integrity and reduce oxidative damage, whereas energy and protein balance directly impact placental growth dynamics and the expression of nutrient transporters (Diniz et al., 2021). Environmental stress, like high ambient temperature, causes oxidative stress and inflammation, compromising the placental efficiency and fetal nutrient uptake (Chen et al., 2025)

Yet, intervention strategies combining molecular information with nutritional modulation are poorly developed, and there are gaps in linking molecular regulation with nutritional modulation in dairy cattle. Current evidence largely focuses on either angiogenic or metabolic aspects in isolation, with limited integrative models that explain how diet-

induced molecular adaptations influence placental efficiency across varying environmental and physiological conditions. There is a clear need to define the optimal combination of nutrients, the duration of supplementation and the systemic pathways through which nutrients can enhance angiogenesis, transporter expression and oxidative balance in the bovine. This review describes how specific molecular and nutritional regulation of bovine placental physiology can enhance placental efficiency, thereby maximizing fetal growth and subsequent dairy performance. The objectives are to clarify essential molecular mechanisms controlling nutrient transformation in the placenta, angiogenesis, and oxidative homeostasis; investigate the disruptive consequences of environmental and nutritional stressors on placental function; and assess nutritional approaches that might facilitate placental adaptation and resistance. Attending to these objectives will shed light on avenues to maximize placental physiology, ultimately benefiting calf health and dairy productivity.

The schematic illustrates the hierarchical organization of the bovine placenta, highlighting the maternal uterine components (caruncle and maternal blood vessels), fetal components (cotyledon, binucleate trophoblast cells, and fetal capillaries), and the maternal–fetal interface (Fig 1). This specialized synepitheliochorial arrangement facilitates efficient nutrient exchange, gas transfer, and waste removal while maintaining a distinct epithelial barrier between maternal and fetal circulations.

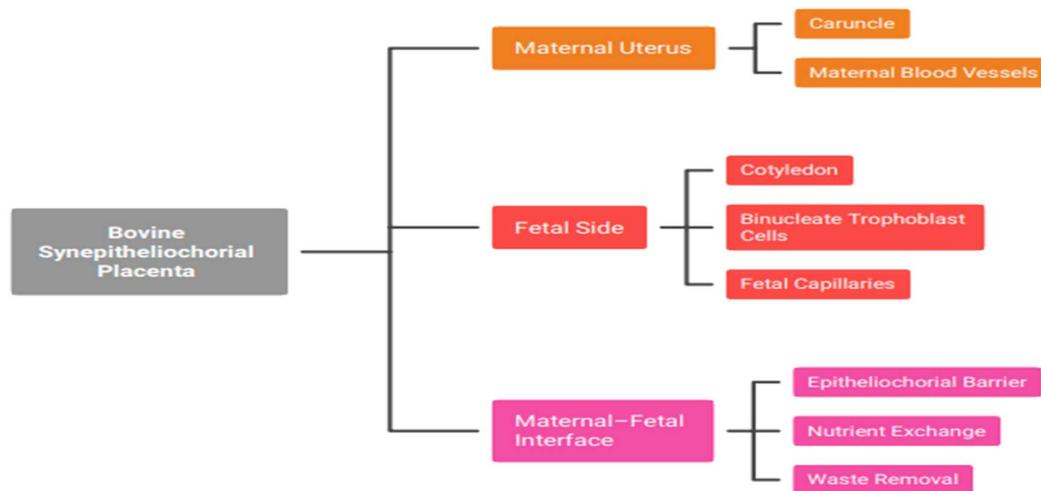


Fig. 1: Structural organization of the bovine synepitheliochorial placenta.

Early Placental Development and Nutritional Transition

The formation of the bovine placenta is the basic process of fetal development. It is a result of complex cell differentiation and of dynamic nutrient requirements that support embryonic and later fetal development. After 7 days post-conception, the bovine blastocyst forms while the outer trophoblast covering is differentiated into ruminant-specific specialized binucleate trophoblast cells (BNCs). These BNCs intermingle with maternal uterine epithelial cells to form the synepitheliochorial placental structure, which is very different from the hemochorial placenta in humans. This intermingling creates a unique maternal-fetal interface that is specialized for selective nutrient exchange and immunomodulation (Davenport et al., 2023; Wooding, 2022). During pre-implantation, from days 0 to 18 of pregnancy, the conceptus is nearly entirely reliant on histiotrophic nutrition; nutrients are obtained from uterine gland secretions rich in glycoproteins, lipids, amino acids, and growth factors. These nutrients provide vital substrates for cellular growth and trophoblast elongation.

Meanwhile, BNCs secrete pregnancy-specific glycoproteins and placental lactogens that modulate the uterine environment and maternal metabolic adaptation to pregnancy (Wooding, 2022). Amino acid supplementation, such as methionine during this period, has been shown to enhance conceptus growth by promoting protein synthesis and epigenetic control (Liu et al., 2021; Wooding, 2022). In this phase, anaerobic glycolysis constitutes the most preferred mechanism of energy metabolism.

During the 19th to 30th days, implantation starts remodeling of the endometrial surface by the trophoblast, facilitating the progressive establishment of fetal-maternal vascular contacts. This transition shifts nutrient delivery from the histiotrophic mode to a hemotrophic process (G. J. Burton & A. L. Fowden, 2015). This occurs due to vigorous angiogenesis, driven by elevated levels of vascular endothelial growth factor (VEGF) and insulin-like growth factor 2 (IGF-2) gene expression. This high level of VEGF and IGF-2 helps expand the placental vascular network and surface area for exchange (Sferruzzi-Perri et al., 2023). Trace mineral supplementation to the dam in early pregnancy enhances VEGF expression, placental vasculature development, and fetal nutrient delivery (Dávila Ruiz et al., 2024).

Mid-gestation (days 31–180) sustains this angiogenic growth and metabolic adaptation. The embryo shifts from glycolysis to oxidative phosphorylation for energy metabolism as oxygen availability increases with advancing

placental vascularization (Reynolds et al., 2023). Epigenetic changes, such as DNA methylation and histone modifications, strictly control genes that regulate blood vessel growth and nutrient transport during this stage. These changes enable the timely development of the placenta and functional adjustment. The dysregulation is associated with fetal growth restriction (FGR) and poor neonatal outcomes (Salmeri et al., 2022). Dietary interventions maximize mid-gestation energy and protein balance to enhance the expression of glucose (GLUT1 and GLUT3) and amino acids transporters, facilitating fetal nutrient uptake (Kang et al., 2022).

Late gestation (days 181–280) is a period of optimal fetal growth and placental efficiency of exchange, during which delivery of nutrients and oxygen relies mainly on maternal flow. The placenta, at its functional peak, has a higher nutrient demand to support continuous improvement in blood vessel development and transport functions. Antioxidant supplementation with vitamin E and selenium during this period is necessary to reduce oxidative stress markers and increase calf birth weights (Šmigoc et al., 2023). Furthermore, recommended dietary energy during late pregnancy increases placental nutrient transfer efficiency, supports fetal growth, and reduces the incidence of low birth weight due to metabolic stress.

Figure 2 illustrates key stages of placental development in dairy cattle from pre-implantation to late gestation, highlighting the transition from histiotrophic nutrition during early pregnancy to hemotrophic nutrient transfer during mid and late gestation. Progressive placental attachment, vascular development, and increasing nutrient transfer capacity support rapid fetal growth toward the end of pregnancy.

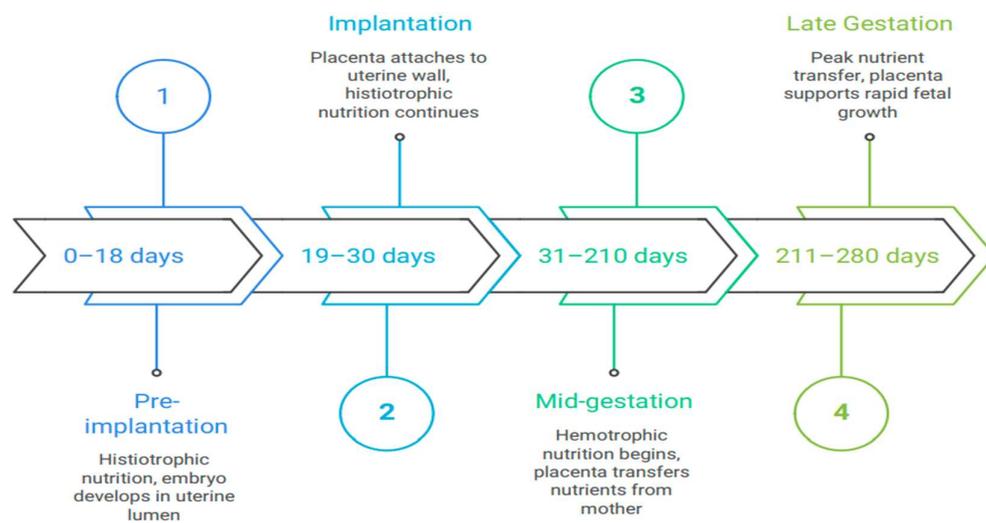


Fig. 2: Timeline of bovine placental development and dominant nutrient supply mechanisms across gestation.

As shown in Figure 3, the bovine placenta undergoes a coordinated progression of molecular and metabolic adaptations across gestation. Early in development (pre-implantation), VEGF and IGF-2 remain low, while glycolysis accounts for nearly 90% of total energy, underscoring the dominance of histiotrophic nutrition supported by uterine secretions. implantation (days 19-30), both VEGF and IGF-2 increase more than threefold, initiating vascular development and moderate activation of glucose transporters (GLUT1 and GLUT3). mid-gestation, oxidative phosphorylation becomes the primary metabolic pathway (65%), correlating with a significant rise in vascular density (75%) and nutrient transfer efficiency (80%). In late gestation, GLUT1 and GLUT3 reach 95% and 90% of maximal expression, respectively. while oxidative metabolism peaks at 80%, enabling optimal placental-fetal nutrient exchange. The data collectively demonstrate that molecular regulation of angiogenesis and metabolic transition emphasize placental maturation and efficiency in cattle (Graham J. Burton & Abigail L. Fowden, 2015) (Burton & Fowden, 2015; Šmigoc et al., 2023).

Table 1: Key Stages of Placental Development and Nutrient Supply in Dairy Cattle

Stage	Days post-Conception	Primary Nutrient Source	Key Features	Nutritional Considerations
Pre-implantation	0–18	Uterine secretions	Histiotrophic phase, conceptus elongation	Rumen-protected amino acids support epigenetic and protein synthesis
Implantation	19–30	Uterine glands & limited blood contact	BNC differentiation, early vascular remodeling	Maternal trace mineral (Se, Zn) supplementation improves angiogenesis
Mid-gestation	31–180	Maternal blood via cotyledons	Transition to hemotrophic nutrition, metabolic shift	Balanced energy-protein intake enhances nutrient transporter expression
Late gestation	181–280	Maternal circulation	Peak exchange efficiency, maximal fetal growth	Antioxidant supplementation reduces oxidative stress, supports growth

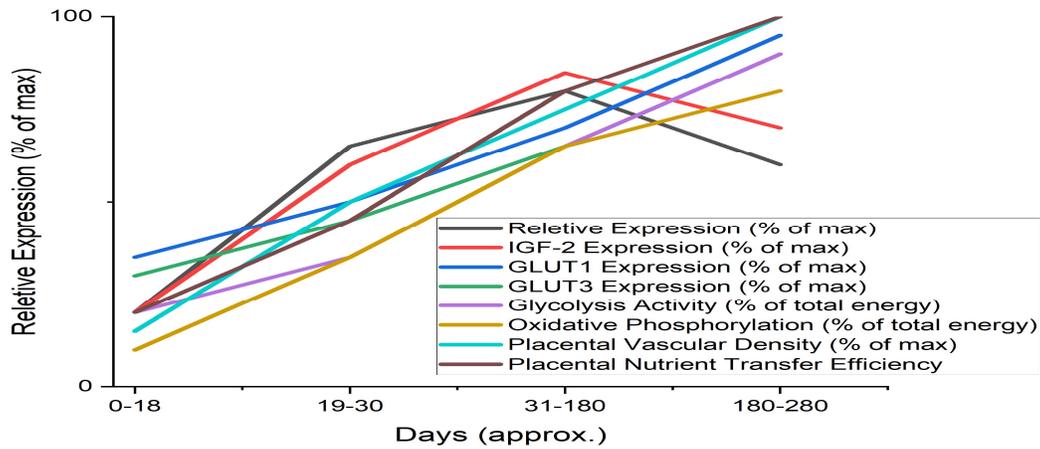


Fig. 3: Temporal expression of VEGF, mTOR, and nutrient transport activity during bovine gestation

Mechanisms and Regulation of Placental Nutrient Transport

Bovine placenta is a well-structured process for the transfer of nutrients. It relies on the large surface area of the cotyledonary villi, optimal maternal-fetal blood flow, trophoblast membrane density and certain transporter proteins. The transport mechanisms include simple diffusion, facilitated diffusion, active transport and receptor-mediated endocytosis. These mechanisms play important roles in providing sufficient substrates for growth to developing fetus (Luther et al., 2021). Nutrient exchange takes place via trophoblast and uterine epithelial layers, where binucleate cells form syncytial plaques. Syncytial plaques form a selectively permeable wall between maternal and fetal circulations, and transport nutrients via specific transport proteins (Wooding & Burton, 2008; Fowden et al., 2020). The main energy source of the fetus is glucose, which is transported primarily by facilitated diffusion via glucose transporters GLUT1 and GLUT3 on both maternal and fetal membranes. the cattle's placenta, GLUT1 expression increased under homeostatic conditions in late gestation to satisfy the excessive fetal demand for energy (Ferrell et al., 2020). Environmental stressors like maternal heat stress and metabolic diseases like ketosis inhibit GLUT1 and thereby impair glucose transport and fetal energy supply (Bionaz et al., 2022). The transport of amino acids is facilitated by sodium-dependent Systems A and ASC and sodium-independent System L transporters, which are essential for protein accretion in the fetus. Around 12–15 grams of amino acids per kilogram of fetal weight are required, thus, these transporters are vital (Rhoads et al., 2023). These transporter mechanisms are decreased when maternal protein is restricted, leading to adverse effects on fetal growth. On the other hand, supplementation of amino acids like methionine and arginine increase transporter expression and angiogenesis in the placenta, leading to increased nutrient transfer (Zhou et al., 2024). Leptin and mTOR signaling pathways describe the hormonal regulation of placental nutrient transport. These pathways link maternal metabolic status to fetal nutrient supply (Guadix et al., 2023). Lipids and fatty acids transported via passive diffusion and facilitated transport with the help of fatty acid transport proteins (FATP), CD36 and lipoprotein lipase (LPL). Docosahexaenoic Acid (DHA) and arachidonic acid are two of the most important long-chain PUFAs that significantly contribute to fetal membrane biogenesis and vascular development. Maternal obesity or excessive consumption of high-lipid diets disrupts these transporters, leading to abnormal fetal adiposity and affecting metabolic programming. (Marques et al., 2021). Mineral transport, such as iron transport via transferrin receptors and divalent metal transporter-1 (DMT1) through receptor-mediated endocytosis, is also an important factor. Dairy cows need 3–4 grams of iron per pregnancy for fetal hematopoiesis and placenta mitochondrial activity (Guerin et al., 2020). Zinc and copper are transported by maternal mineral-responsive membrane-bound metallothionein-regulated proteins, providing the trace elements essential for enzymatic and antioxidant activity in the fetus. Environmental stress, diet and metabolic illness can alter transporter expression and cause fetal development and postnatal health disruption. Knowledge of such mechanisms will guide nutritional and management practices to maximize placental nutrient transfer and enhance offspring productivity in dairy cattle.

Figure 4 illustrates how maternal nutrition activates mTOR signaling in the placenta, regulating key transporters for glucose, amino acids, and fatty acids across trophoblast layers to support fetal growth.

Table 2: Placental Nutrient Transport Mechanisms and Their Modulation by Maternal Conditions

Nutrient	Transport Mechanism	Major Transporters	Regulation / Maternal Influence
Glucose	Facilitated diffusion	GLUT1, GLUT3	Upregulated in late gestation; decreased in ketosis and heat stress
Amino acids	Active and facilitated	System A, ASC, System L (LAT1/2)	Enhanced by methionine and arginine; decreased in maternal protein restriction
Fatty acids	Diffusion and active	FATP, CD36, LPL	Increased in high-fat diets; dysregulated in negative energy balance
Iron	Receptor-mediated endocytosis	Transferrin receptor, DMT1	Sensitive to maternal iron and hepcidin levels

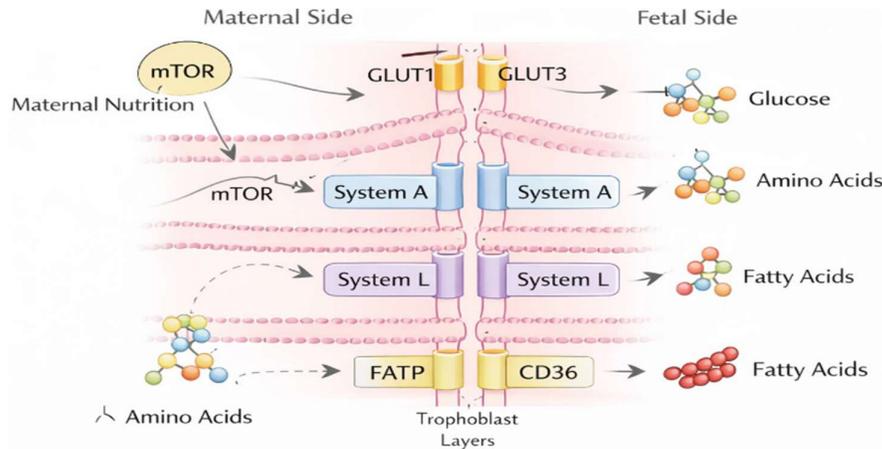


Fig. 4: TOR-regulated placental nutrient transport from mother to fetus.

Environmental and Maternal Modulation of Placental Efficiency

Placental function is highly sensitive to maternal nutritional status, metabolic health, and environmental conditions during the perinatal period (Kramer et al., 2023). Heat stress during the later stages of pregnancy is an important environmental stressor that compromises the placenta's function. Heat stress interferes with utero-placental blood flow and reduces villous density, thereby restricting the exchange surface area required for nutrient and oxygen delivery. Heat stress also reduces the expression of key angiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2). As a result, placental development and vascular remodeling decreased to support increased fetal demands during advanced pregnancy. Supplementation of antioxidants such as vitamin E, selenium, and rumen-protected methionine to heat-stressed dams has reduced oxidative damage, restored vascular function, and enhanced nutrient transport capacity in the placenta (Guo et al., 2022; Ramirez et al., 2024). Placental efficiency is also affected by maternal metabolic disorders. Obese and high body condition score (BCS) cows accumulate lipids in trophoblast cells of the placenta, which leads to mitochondrial dysfunction and oxidative stress. It also impairs fatty acid oxidation pathways and reduces placental metabolic potential (Fazio et al., 2022). This disruption of the metabolic environment increases the risk of offspring postnatal metabolic disease.

Meanwhile, dams in negative energy balance or in a nutrient-restricted environment exhibit placental downregulation of mechanistic target of rapamycin (mTOR) signaling pathways, leading to decreased levels of amino acid transporters and reduced nutrient delivery to the fetus (Gouvêa et al., 2024; Silva et al., 2022). These disruptions result in restricted growth and potentially compromised fetal health. Hence, maintaining proper metabolic balance through precise nutrition is essential for maintaining a healthy placenta and ensuring optimal fetal growth.

As shown in figure 5, placental efficiency markedly declines under environmental and nutritional stressors. Heat-stressed and nutrient-restricted cows exhibited a 20–30% reduction in placental efficiency compared with thermoneutral conditions, reflecting impaired angiogenesis and nutrient transport. Conversely, antioxidant and methionine supplementation restored efficiency beyond 110%, indicating improved vascular integrity and metabolic resilience. These results validate the text's discussion that placental performance is tightly coupled with maternal nutrition, oxidative balance and metabolic signaling (Flor-Aleman et al., 2023; Qu et al., 2022; Wawrzykowski et al., 2024).

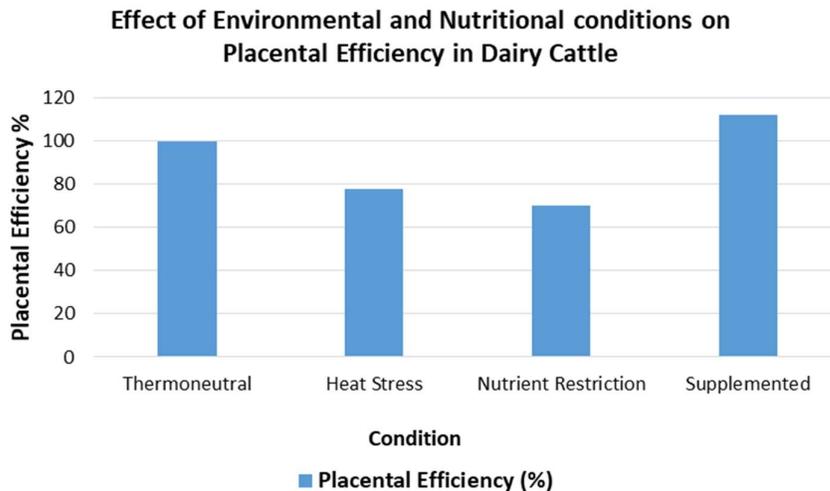


Fig. 5: Effect of environmental and nutritional conditions on placental efficiency in dairy cattle.

Molecular Advances and Translational Insights

Molecular technologies such as single-cell RNA sequencing (scRNA-seq) have transformed the understanding of bovine placental biology by defining distinct trophoblast subpopulations with specialized roles in nutrient transfer, angiogenesis and immune tolerance (Davenport et al., 2024). Transcriptome and proteome data integration highlights oxidative stress and mitochondrial dysfunction as signature features of placental insufficiency in at-risk pregnancies. These findings coincide with those in the human placenta and are further refined with unique cattle-specific refinements. Recent approaches leverage this molecular knowledge and employ targeted nutritional interventions, including supplementation with rumen bypass amino acids and omega-3 fatty acids. These supplementations facilitate mitochondrial energy production and boost transporter expression. In addition, nanotechnology-derived delivery systems, such as lipid nanoparticles for the encapsulation of trophoblast-targeted gene regulators, have the potential to enhance placental vascular perfusion and fetal development with fewer maternal side effects (Jiang et al., 2022; Shimada et al., 2024). These technologies highlight molecular-based nutrition and therapeutic interventions to enhance placental health in dairy cows.

Sex-Specific Placental Adaptations

Fetal sex significantly modulates placental gene expression and function. It also influences how dams and fetuses respond to maternal environmental conditions (Sedlmeier et al., 2021). Male fetuses usually express higher levels of growth-promoting genes such as insulin-like growth factor 2 (IGF-2) and exhibit greater abundance of nutrient transporters, which support rapid tissue development. However, this enhanced growth strategy reduced oxidative stress resilience and made male fetuses more vulnerable to adverse conditions such as malnutrition, hypoxia and heat stress. Female fetuses have a more conservative approach. They increase the activity of antioxidant enzymes, heat shock proteins and mitochondrial regulation, enhancing their capacity to survive environmental and metabolic stresses (Rokeby et al., 2023). These sex-based strategies influence not only fetal growth but also postnatal metabolic programming with long-term effects on feed efficiency and milk production capacity throughout the life.

Table 3: Impact of Fetal Sex on Placental Function and Offspring Outcomes

Fetal Sex	Key Adaptations	Sensitivity	Growth Outcome
Male	↑ Nutrient transporters, ↑ IGF-2 signaling	High vulnerability to nutrient and oxidative stress	Rapid growth but higher risk of fetal growth restriction (FGR)
Female	↑ Antioxidant enzymes, ↑ Heat shock protein expression	Greater resistance to oxidative and metabolic stress	Stable growth under adverse conditions

Future Directions

Future research needs to investigate spatial transcriptomics, advanced metabolomics, and high-resolution imaging modalities within a framework that enables the spatiotemporal nutrient delivery patterns during gestation. Identification and validation of reliable, non-invasive biomarkers, such as placenta-secreted microRNAs or exosomal proteins, may enable early detection of placental dysfunction, enabling timely interventions. In practical dairy production, precision feeding methods adjusted to gestational age and fetal sex may maximize placental function, calf vigor, and dam milk production. Furthermore, the application of machine learning and big data analysis to integrate multi-omics and phenotypic data will accelerate the development of tailored nutritional plans and management programs to maximize maternal-fetal Wellbeing.

Conclusion

The bovine placenta is an active metabolizing, multifunctional organ. It plays a central role in fetal development and maternal profitability. The expression of nutrient transporters, angiogenic remodeling and sensitivity to maternal environmental and metabolic signals mainly regulate its function. A Complete description of molecular and nutritional regulation of placental physiology provides a central platform for improved reproductive efficiency and sustainable dairy production. The subsections of genomics, personalized nutrition, real-time biomarker assessment and nanotechnologies will open avenues toward optimized maternal-fetal health and enhanced dairy cattle productivity.

DECLARATIONS

Funding: Any public, commercial, or non-profit funding agency did not support this study.

Conflicts of Interest: The authors declare no conflict of interest that could have influenced the work reported in this paper.

Data Availability: Data will be available from the corresponding author upon request.

Ethics Statement: Not Applicable

Authors' Contribution: Muhammad Zakria Rehman: Conceptualization, Investigation, Writing – original draft, Abdul Maalik, Muhammad Afzal Raza: Writing – review & editing. Abdul Hanan: Visualization, Writing – review & editing.

Generative AI Statements: The authors confirm that no generative artificial intelligence-based tools were employed for content generation or interpretation. All intellectual content, interpretations, and conclusions are the sole responsibility of the authors.

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