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Dietary Protein Quality and Amino Acid Metabolism in Female Fertility: From Ovarian Function to Assisted Reproductive Technologies—A Narrative Review

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Abstract

Background: Infertility affects a substantial proportion of adults worldwide, and nutrition is increasingly recognized as a modifiable factor in female reproductive health. While the role of overall diet quality has been widely discussed, the specific contribution of dietary protein quality and amino acid metabolism remains insufficiently understood.

Aim: This review aimed to summarize current evidence on the relationship between dietary protein quality, amino acid metabolism, ovarian function, oocyte competence, embryo development, and outcomes of assisted reproductive technologies (ART).

Material and methods: A narrative review of epidemiological, clinical, metabolomic, and mechanistic studies was conducted. Particular attention was given to dietary protein sources, amino acid-dependent metabolic pathways, follicular-fluid amino acid profiles, female fertility outcomes, and ART-related endpoints.

Results: Current evidence suggests that protein source and overall dietary quality may be relevant to female fertility. Observational studies indicate that higher intake of plant-derived protein, fish, soy foods, and healthier dietary patterns may be associated with improved fertility or ART outcomes, although findings remain heterogeneous. Mechanistic studies support biologically plausible roles for amino acids in reproductive physiology through pathways involving one-carbon metabolism, nitric oxide synthesis, mTOR signaling, mitochondrial function, oxidative stress regulation, autophagy, and ferroptosis.

Conclusions: Available evidence supports a biologically plausible relationship between dietary protein quality, amino acid metabolism, and female reproductive health. However, direct evidence linking established protein quality indices with fertility or ART outcomes remains limited. Further prospective studies and randomized trials are needed.

Keywords: dietary protein quality; amino acids; female fertility; oocyte competence; assisted reproductive technology; reproductive nutrition.

1. Introduction

Infertility affects millions of people worldwide and represents an important public health concern. According to the World Health Organization, approximately one in six adults experiences infertility during their lifetime [1]. Although reproductive capacity is influenced by genetic, hormonal, environmental, and lifestyle factors, nutrition has emerged as an important modifiable determinant of female reproductive health [2-4].

Nutritional research in reproductive medicine has traditionally focused on dietary patterns, energy balance, and selected micronutrients. However, growing evidence suggests that dietary quality, including the quality and source of dietary protein, may also influence fertility

outcomes [2,4]. Proteins provide amino acids required for cellular function, while several amino acids also act as functional metabolites involved in metabolic regulation, nitric oxide synthesis, cellular signaling, and reproductive processes [5, 6].

Protein quality refers to the ability of dietary proteins to provide digestible and bioavailable amino acids in amounts sufficient to meet physiological requirements [7]. Several amino acids traditionally classified as non-essential may become conditionally essential under specific physiological or metabolic conditions and participate in processes beyond protein synthesis, including antioxidant defense, metabolic regulation, and reproductive function [5]. Therefore, the reproductive effects of dietary protein may depend not only on total protein intake but also on protein quality, amino acid profile, and the broader nutritional characteristics of protein-rich foods [3,4].

Amino acids are involved in follicular development, oocyte maturation, embryo development, and implantation. Human studies have linked amino acid turnover with oocyte developmental competence, while follicular-fluid analyses suggest that the ovarian microenvironment contains amino acid profiles relevant to oocyte quality and assisted reproduction [8, 9]. Amino acid transport systems are also important for preimplantation embryo development, blastocyst formation, and implantation potential [10].

Several amino acid-dependent pathways may contribute to reproductive outcomes. One-carbon metabolism is involved in methyl donor generation and epigenetic regulation during oocyte maturation and early embryonic development [11, 12]. Tryptophan-derived metabolites, including melatonin, may support antioxidant protection and ovarian function, whereas altered tryptophan metabolism has been observed in follicular fluid of women with diminished ovarian reserve [13, 14]. Arginine serves as a precursor for nitric oxide and may be relevant during the peri-implantation period [6, 15]. Altered branched-chain amino acid metabolism has also been associated with reproductive disorders such as polycystic ovary syndrome and premature ovarian insufficiency [16,17].

Epidemiological and clinical studies further suggest that protein source and dietary patterns may influence reproductive outcomes. Chavarro et al. reported that higher intake of plant-derived protein was associated with a lower risk of ovulatory infertility, whereas greater intake of animal protein was associated with increased risk [18]. Reviews indicate that healthier dietary patterns emphasizing seafood, poultry, whole grains, fruits, and vegetables may be

associated with improved female fertility and ART outcomes, although evidence from IVF populations remains heterogeneous [2, 19, 20].

Evidence from women undergoing assisted reproductive technologies (ART) also suggests that protein-rich foods and overall dietary patterns may influence treatment outcomes. Studies have reported associations between specific protein-rich foods, soy foods, healthier dietary patterns, and ART-related outcomes such as embryo yield, fertilization parameters, clinical pregnancy, and live birth rates [21-25]. In parallel, molecular studies linking mitochondrial dynamics, oocyte ferroptosis, proteomic regulation, oocyte competence, and early embryonic development provide biological plausibility for the importance of metabolic regulation in reproductive success [26-28].

Despite growing interest in reproductive nutrition, current evidence for women attempting conception remains focused largely on overall healthy dietary patterns, whereas the specific contribution of protein quality and amino acid composition remains insufficiently understood [2, 4, 20]. Therefore, this review aims to summarize current evidence regarding the relationship between dietary protein quality, amino acid metabolism, ovarian function, oocyte quality, embryo development, and ART outcomes, with particular attention to the biological mechanisms through which amino acids may influence female fertility and reproductive success.

Research Objective.

The objective of this review was to summarize current evidence regarding the relationship between dietary protein quality, amino acid metabolism, ovarian function, oocyte competence, embryo development, and outcomes of assisted reproductive technologies. Particular attention was given to the biological mechanisms through which amino acids may influence female fertility and reproductive success.

Research Problems.

This review addressed the following research problems:

1. How may dietary protein quality and protein source influence female reproductive health and fertility outcomes?
2. Which amino acid-dependent metabolic pathways are potentially involved in ovarian function, oocyte competence, embryo development, and implantation?

3. What evidence links protein-rich foods, dietary patterns, and amino acid availability with outcomes of assisted reproductive technologies?
4. What are the main limitations and knowledge gaps in current research on protein quality and female fertility?

Review Hypotheses.

This review was guided by the hypothesis that dietary protein quality and amino acid availability may influence female reproductive health through mechanisms involving metabolic regulation, oxidative stress responses, nitric oxide synthesis, one-carbon metabolism, mTOR signaling, mitochondrial function, autophagy, and ferroptosis. A secondary hypothesis was that protein source and the broader nutritional matrix of protein-rich foods may be more relevant to reproductive outcomes than total protein intake alone.

2. Research Materials and Methods

2.1. Participants

This study was designed as a narrative literature review and did not involve the recruitment of human participants, patients, or experimental subjects. Therefore, no participant characteristics, inclusion criteria for individuals, informed consent procedures, or ethical approval for human-subject research were required.

2.2. Procedure / Search Protocol / Measures

A targeted literature search was conducted to identify publications relevant to dietary protein quality, amino acid metabolism, female fertility, ovarian function, oocyte competence, embryo development, and assisted reproductive technology (ART) outcomes. Electronic databases, including PubMed/MEDLINE and Google Scholar, were searched using combinations of the following keywords: “dietary protein quality”, “protein intake”, “animal protein”, “plant protein”, “amino acids”, “female fertility”, “ovulatory infertility”, “oocyte competence”, “follicular fluid”, “embryo development”, “in vitro fertilization”, “assisted reproductive technology”, “one-carbon metabolism”, “tryptophan”, “arginine”, “branched-chain amino acids”, and “reproductive nutrition”.

The review included narrative reviews, systematic reviews, prospective cohort studies, clinical observational studies, metabolomic studies, and experimental studies relevant to female

reproductive physiology. Particular attention was given to studies evaluating dietary protein sources, amino acid-dependent metabolic pathways, follicular-fluid amino acid profiles, oocyte quality, embryo development, implantation, clinical pregnancy, live birth, and ART-related outcomes. Publications not related to female reproduction, fertility, ovarian function, amino acid metabolism, dietary protein quality, or reproductive nutrition were excluded.

2.3. Data Collection and Analysis

The collected literature was analyzed qualitatively. Evidence was organized thematically into sections addressing protein quality and female reproductive health, animal versus plant protein sources, amino acid metabolism and oocyte competence, amino acid availability during embryo development, amino acid-derived metabolic pathways, and clinical implications for fertility care and ART. Due to the narrative character of the review and heterogeneity of the included studies, no formal meta-analysis or quantitative synthesis was performed.

2.3.1. Statistical Software

No statistical software was used in this review, as the study did not involve original data collection, statistical testing, or meta-analysis. The findings were synthesized narratively based on the available epidemiological, clinical, metabolomic, and mechanistic literature.

2.3.2. Statistical Methods

No statistical analysis was performed because this article is a narrative review. The evidence was synthesized descriptively and interpreted qualitatively, with attention to study design, population characteristics, dietary exposures, reproductive outcomes, and methodological limitations of the included literature.

3. Literature Findings

3.1 Protein Quality and Female Reproductive Health

Protein quality is traditionally defined by the ability of dietary proteins to provide digestible indispensable amino acids in amounts sufficient to meet physiological requirements. Indices such as PDCAAS and DIAAS reflect differences in amino acid composition and digestibility between protein sources [7]. Although total protein intake is important for health, growing

evidence suggests that the quality and source of dietary protein may also influence female reproductive function [2, 4].

The biological effects of dietary protein depend not only on total intake but also on the availability of essential amino acids and bioactive amino acid derivatives. Several amino acids traditionally classified as non-essential, including arginine, glutamine, glycine, proline, serine, and cysteine, may become conditionally essential under increased metabolic demand and participate in cell signaling, antioxidant defense, metabolism, and reproductive function [5].

The concept of protein quality has evolved beyond the traditional classification of amino acids as essential or non-essential based mainly on growth and nitrogen balance. Hou et al. emphasized that several amino acids previously considered nutritionally non-essential, including arginine, glutamine, glycine, proline, serine, and cysteine, may become conditionally essential under increased metabolic demand. These amino acids perform functions beyond protein synthesis, including cell signaling, antioxidant defense, metabolic regulation, immune function, and reproductive physiology [5].

Although direct clinical studies examining protein quality indices and fertility outcomes remain limited, observational evidence suggests that dietary patterns rich in nutrient-dense protein sources may support reproductive health. In a comprehensive review, Gaskins and Chavarro reported that dietary patterns characterized by higher consumption of seafood, poultry, whole grains, fruits, and vegetables were generally associated with better fertility outcomes in women [2].

Additional epidemiological evidence supporting the importance of dietary protein source was provided by Chavarro et al., who reported that higher intake of animal protein was associated with an increased risk of ovulatory infertility, whereas greater consumption of plant-derived protein was associated with a lower risk. Substitution analyses further suggested that replacing a portion of energy intake from animal protein with plant protein may substantially reduce the risk of ovulatory infertility, highlighting the potential reproductive relevance of protein source in female fertility [18].

Similarly, Harak et al. highlighted that nutritional requirements change across the female life course and that adequate intake of protein, vitamins, minerals, omega-3 fatty acids, and other dietary components may support reproductive health and fertility. The authors also emphasized

that female fertility may benefit from dietary patterns rich in plant-based protein, dietary fiber, vitamins, and minerals [3].

Additional evidence comes from studies of women undergoing assisted reproductive technologies. In the prospective EARTH Study, Nassan et al. examined associations between preconception intake of meat and other protein-rich foods and outcomes of infertility treatment with ART. Greater fish consumption was associated with a higher probability of live birth, suggesting that the source of protein-rich foods may be relevant for reproductive outcomes beyond total protein intake alone [21].

Collectively, current evidence suggests that protein quality may influence female reproductive health through differences in amino acid composition, digestibility, and the broader nutritional profile of protein-rich foods. Although direct evidence linking established protein quality indices with fertility outcomes remains limited, available epidemiological and nutritional studies support the relevance of protein source and quality in reproductive health. Further research is needed to clarify the biological mechanisms underlying these associations and to inform evidence-based dietary recommendations for women seeking conception or undergoing fertility treatment.

3.2 Animal versus Plant Protein Sources and Female Fertility

Beyond total protein intake, the source of dietary protein may influence female reproductive health. Animal- and plant-derived proteins differ in amino acid composition, digestibility, accompanying micronutrients, fatty acid profile, and degree of processing, all of which may affect metabolic and reproductive pathways.

Epidemiological evidence suggests that higher intake of plant-derived protein may be associated with a lower risk of ovulatory infertility, whereas higher intake of animal protein may be less favorable in some populations [18]. This observation is consistent with broader evidence indicating that healthier dietary patterns, particularly those emphasizing seafood, poultry, whole grains, fruits, and vegetables, may be associated with better reproductive outcomes, although evidence from IVF/ART populations remains heterogeneous [2, 19, 20].

In women undergoing assisted reproductive technologies, protein-rich foods, soy foods, and overall dietary patterns have also been associated with treatment outcomes, including embryo yield, fertilization parameters, clinical pregnancy, and live birth rates [21-25]. Overall, current

evidence suggests that protein source may be relevant for fertility, although further studies are needed to determine whether these effects are mediated by amino acid composition, food matrix, degree of processing, or broader dietary quality. Detailed characteristics of the studies supporting these associations are summarized in Table 1.

Table 1. Summary of clinical and epidemiological studies investigating associations between dietary protein sources, dietary patterns, and female reproductive outcomes

Study	Study design / population	Exposure	Outcome assessed	Main findings
Chavarro et al., 2008	Prospective cohort; Nurses' Health Study	Animal versus plant protein intake	Ovulatory infertility	Higher intake of animal protein was associated with increased risk of ovulatory infertility, whereas higher intake of plant protein was associated with lower risk. Replacement of animal protein with plant protein was associated with reduced infertility risk.
Gaskins & Chavarro, 2018	Narrative review	Dietary patterns and protein sources	Female fertility	Healthier dietary patterns emphasizing seafood, poultry, whole grains, fruits, and vegetables were generally associated with better fertility outcomes.
Harak et al., 2025	Narrative review	Nutrition across female life stages	Reproductive health and fertility	Adequate intake of protein, vitamins, minerals, omega-3 fatty acids, and plant-based foods was described as supportive for female reproductive health.
Nassan et al., 2018	Prospective cohort; EARTH Study	Intake of meat and other protein-rich foods	ART outcomes	Greater fish consumption was associated with a higher probability of live birth after ART.
Vanegas et al., 2015	Prospective cohort; women undergoing ART	Soy food intake	Clinical pregnancy and live birth	Dietary soy intake was positively associated with the probability of live birth during ART treatment.
Gaskins et al., 2019	Prospective cohort; EARTH Study	Overall dietary patterns	Assisted reproduction outcomes	Greater adherence to healthier dietary patterns was associated with improved ART outcomes, including live birth.
Sun et al., 2019	Prospective cohort; women undergoing IVF	Mediterranean diet adherence	Embryo yield	Higher adherence to the Mediterranean diet was associated with improved embryo yield during IVF treatment.

Sanderman et al., 2022	Systematic review	Female dietary patterns	IVF outcomes	Healthier dietary patterns may be associated with improved IVF outcomes, although evidence remained heterogeneous.
Kellow et al., 2022	Systematic review	Preconception dietary patterns	Clinical pregnancy and live birth after ART	Some dietary patterns appeared promising for ART outcomes, but findings across studies were not fully consistent.
Wu et al., 2022	Prospective cohort	Preconception dietary patterns	IVF outcomes	Preconception dietary patterns were associated with IVF-related outcomes, including fertilization parameters and transferable embryos.
Budani & Tiboni, 2023	Narrative review	Nutrition and macronutrient quality	Female fertility and IVF outcomes	Nutrition, dietary quality, and macronutrient composition were described as modifiable factors potentially influencing fertility and IVF outcomes.

Abbreviations: ART, assisted reproductive technology; IVF, in vitro fertilization.

This table summarizes key clinical, epidemiological, and review studies evaluating associations between dietary protein sources, dietary patterns, and female reproductive outcomes, including ovulatory infertility and ART-related endpoints.

3.3 Protein Quality, Amino Acid Metabolism, and Oocyte Competence

Oocyte quality is one of the key determinants of female fertility and reproductive success. The developmental competence of an oocyte depends, in part, on the metabolic environment within the ovarian follicle, including the availability and utilization of amino acids. Human studies have demonstrated that amino acid turnover in oocytes is associated with developmental competence. Hemmings et al. reported that patterns of amino acid depletion and appearance differed according to oocyte maturation status and patient characteristics, indicating that amino acid metabolism may reflect oocyte developmental potential [8]. Similarly, follicular fluid analyses have shown that the ovarian microenvironment contains measurable amino acid profiles that may be altered in metabolic conditions relevant to assisted reproduction [9].

Amino acids contribute to ovarian function through multiple mechanisms, including regulation of mitochondrial metabolism, oxidative stress responses, and cellular signaling pathways [5, 26]. Mitochondrial dynamics are essential for oocyte quality, fertilization, and early embryo development [26]. Several amino acids also act as metabolic regulators rather than solely

substrates for protein synthesis, supporting antioxidant defense, cellular signaling, and metabolic homeostasis [5].

Recent experimental studies have identified specific amino acids involved in ovarian maintenance. Serine appears to support granulosa-cell survival by limiting ferroptosis and oxidative damage, thereby helping to preserve ovarian function and potentially contributing to ovarian reserve maintenance [29, 30]. In addition, alterations in tryptophan and its indole metabolites have been observed in the follicular fluid of women with diminished ovarian reserve, suggesting a potential role for amino acid-derived metabolites in ovarian aging [14].

Collectively, current evidence indicates that amino acid metabolism is closely associated with oocyte competence and ovarian health. Although direct clinical studies linking dietary protein quality with oocyte quality remain limited, available mechanistic and metabolomic data support the hypothesis that adequate amino acid availability may contribute to reproductive competence and female reproductive potential.

3.4 Protein Quality, Amino Acid Availability and Early Embryo Development

The developmental competence of the human embryo depends not only on successful fertilization but also on nutrient availability during the earliest stages of development. Among these nutrients, amino acids are particularly important because they serve as substrates for protein synthesis and regulators of metabolic and signaling pathways involved in preimplantation development.

Amino acid transport systems play a key role in early embryogenesis. Van Winkle described that these systems are dynamically regulated during preimplantation development and contribute to blastocyst formation, embryo viability, and implantation-related processes. This suggests that amino acid availability in the embryonic environment may influence developmental potential from the earliest stages after fertilization [10].

Human studies further support the relationship between amino acid metabolism and reproductive competence. Hemmings et al. demonstrated that amino acid turnover by human oocytes differs according to gamete developmental competence, patient characteristics, and gonadotrophin treatment, indicating that amino acid metabolism may reflect oocyte quality and contribute to subsequent embryo development [8].

Among individual amino acids, branched-chain amino acids, particularly leucine, are important metabolic regulators. Leucine activates the mTOR pathway, which is involved in protein synthesis, cell growth, autophagy, and energy metabolism. Experimental evidence identified a leucine–mTOR–autophagy axis in granulosa cells that contributes to ovulatory function and anovulation under circadian disruption [31]. Altered BCAA catabolism has also been linked to polycystic ovary syndrome, suggesting that amino acid metabolism may influence ovarian function through metabolic and endocrine pathways [16].

Nutrient-sensitive signaling pathways may also be relevant to embryo quality and pregnancy outcomes. In IVF populations, Li et al. reported that phosphorylated mTOR and its downstream target p-RPS6 in cumulus cells were associated with embryo quality and pregnancy outcome, supporting a link between mTOR-related signaling and reproductive competence [32].

Observational evidence from ART populations suggests that protein-rich foods may also influence reproductive outcomes. In the prospective EARTH Study, Nassan et al. found that greater fish consumption was associated with a higher probability of live birth, indicating that the source of protein-rich foods may be relevant beyond total protein intake alone [21].

Taken together, current evidence supports a biologically plausible link between amino acid availability, ovarian function, oocyte competence, embryo development, and ART outcomes. Although direct intervention studies remain limited, dietary protein source and amino acid availability may represent relevant areas for further investigation in reproductive nutrition.

3.5 Amino Acid-Derived Metabolic Pathways Supporting Oocyte and Embryo Development

The effects of dietary protein on female fertility may be mediated not only by total protein intake but also by specific amino acid-dependent metabolic pathways. Essential and conditionally essential amino acids participate in methyl donor generation, antioxidant defense, nitric oxide synthesis, nutrient sensing, mitochondrial metabolism, and ferroptosis regulation. These processes are relevant to folliculogenesis, oocyte maturation, embryo development, implantation, and ovarian reserve maintenance.The major amino acids and amino acid-dependent pathways involved in female reproductive physiology are summarized in Table 2.

Table 2. Major amino acids and metabolic pathways involved in female reproductive physiology

Amino acid	Major biological role	Reproductive relevance	Key references
Methionine	One-carbon metabolism and methyl donor generation	Oocyte maturation, embryo development, epigenetic regulation	Akamine et al., 2021; Ku et al., 2025
Tryptophan	Precursor for melatonin and indole metabolites	Antioxidant protection, ovarian function, oocyte quality	Ezzati et al., 2021; Liu et al., 2023
Arginine	Nitric oxide and polyamine synthesis	Vascular regulation, implantation-related processes, peri-implantation development	Wu et al., 2021; Wang et al., 2014
Leucine	Activation of mTOR signaling	Granulosa-cell function, autophagy regulation, ovulatory competence	He et al., 2026
Branched-chain amino acids (BCAAs)	Nutrient sensing and energy metabolism	PCOS-related metabolic dysfunction, premature ovarian insufficiency, granulosa-cell dysfunction	Mu et al., 2023; Guo et al., 2023
Serine	Redox regulation and ferroptosis control	Granulosa-cell survival, ovarian function, ovarian reserve maintenance	Gu et al., 2025; Gu et al., 2026

Abbreviations: BCAA, branched-chain amino acid; mTOR, mechanistic target of rapamycin; PCOS, polycystic ovary syndrome.

This table presents selected amino acids and amino acid-dependent pathways potentially involved in female reproductive physiology, with emphasis on oocyte maturation, embryo development, ovarian function, and implantation-related processes.

3.5.1 One-Carbon Metabolism and Epigenetic Regulation

One-carbon metabolism integrates folate- and methionine-dependent pathways that provide methyl groups required for DNA methylation and epigenetic regulation during oocyte maturation and early embryogenesis. Disruption of this pathway may compromise oocyte quality, fertilization, embryo development, and pregnancy outcomes, whereas adequate one-carbon metabolism may support reproductive competence [11, 12, 33].

3.5.2 Tryptophan Metabolism and Melatonin Production

Tryptophan is a precursor of melatonin, which contributes to antioxidant protection and mitochondrial homeostasis within the ovary. Since oxidative stress is an important contributor to reduced oocyte quality and ovarian aging, tryptophan-derived metabolites may influence reproductive competence. Altered tryptophan and indole metabolite profiles have been observed in follicular fluid of women with diminished ovarian reserve [13, 14].

3.5.3 Arginine, Nitric Oxide, and Ovarian Function

Arginine serves as the primary substrate for nitric oxide synthesis and is involved in vascular regulation, cellular signaling, and tissue remodeling. Nitric oxide may support follicular blood flow and implantation-related processes. Experimental evidence further indicates that arginine availability is important during the peri-implantation period [6, 15].

3.5.4 Branched-Chain Amino Acids and Nutrient Sensing

Branched-chain amino acids, particularly leucine, regulate cellular metabolism through nutrient-sensing pathways such as mTOR. Disruption of BCAA metabolism has been linked to reproductive disorders, including polycystic ovary syndrome and premature ovarian insufficiency. Experimental evidence also suggests that leucine-dependent mTOR signaling may influence granulosa-cell function, autophagy, and ovulatory competence [16, 17, 31].

The major mechanisms linking amino acid metabolism with female reproductive function are summarized in Table 3.

Table 3. Major mechanisms linking amino acid metabolism with female reproductive function

Mechanism	Key amino acids / metabolites	Biological effects	Reproductive relevance	Key references
One-carbon metabolism	Methionine, folate-dependent metabolites	Methyl donor generation, DNA methylation, epigenetic regulation	Oocyte maturation, embryo development, fecundability	Akamine et al., 2021; Ku et al., 2025
mTOR signaling and autophagy	Leucine, branched-chain amino acids (BCAAs)	Nutrient sensing, protein synthesis, autophagy regulation, energy metabolism	Ovulatory function, follicular development, PCOS-related metabolic dysfunction	He et al., 2026; Mu et al., 2023

Nitric oxide signaling	Arginine	Nitric oxide synthesis, vascular regulation, cellular signaling	Implantation-related processes, peri-implantation development	Wu et al., 2021; Wang et al., 2014
Antioxidant protection	Tryptophan-derived melatonin, serine	Oxidative stress regulation, mitochondrial protection, redox balance	Oocyte quality, ovarian function, diminished ovarian reserve	Ezzati et al., 2021; Liu et al., 2023; Gu et al., 2025; Gu et al., 2026
Ferroptosis regulation	Serine	Redox regulation, lipid peroxidation control, granulosa-cell survival	Ovarian function, ovarian reserve maintenance, protection against ovarian injury	Gu et al., 2025; Gu et al., 2026
Mitochondrial and proteomic regulation	Mitochondrial and proteomic pathways	Energy metabolism, mitochondrial dynamics, proteomic remodeling	Oocyte competence, embryo development, preimplantation viability	Yildirim & Seli, 2024; Zhang et al., 2024; Zhu et al., 2025

Abbreviations: BCAA, branched-chain amino acid; mTOR, mechanistic target of rapamycin; PCOS, polycystic ovary syndrome.

This table summarizes major biological mechanisms through which amino acid metabolism may influence female reproductive function, including epigenetic regulation, mTOR signaling, nitric oxide synthesis, antioxidant defense, ferroptosis regulation, and mitochondrial activity.

3.5.5 Implications for Reproductive Nutrition

Together, these findings indicate that amino acids influence female fertility through interconnected pathways involving epigenetic regulation, oxidative stress defense, vascular function, nutrient sensing, mitochondrial activity, and ferroptosis control. Therefore, reproductive nutrition should consider not only total protein intake but also the availability and balance of specific amino acids involved in ovarian and embryonic metabolism.

3.6 Clinical Implications for Fertility Care

The growing body of evidence linking nutrition with reproductive function has important implications for preconception counseling and fertility treatment. While current evidence has largely focused on overall dietary patterns and selected nutrients, emerging findings suggest that the quality and source of dietary protein may also be relevant to female reproductive outcomes [2, 3].

3.6.1 Beyond Total Protein Intake: The Importance of Protein Quality

Current evidence suggests that the reproductive effects of dietary protein may depend not only on total intake, but also on the source and quality of protein-rich foods. In women undergoing ART, higher fish consumption has been associated with a greater probability of live birth, suggesting that protein source may be relevant for reproductive outcomes [21].

Adequate nutritional status is also important for female reproductive health. Nutritional position statements emphasize that insufficient energy availability may adversely affect endocrine function, menstrual regularity, and reproductive health, particularly in physically active women [34].

Several amino acid-dependent pathways may explain the relevance of protein quality to reproductive physiology. One-carbon metabolism is associated with oocyte maturation, embryo quality, and pregnancy outcomes [11, 12]. Tryptophan-related metabolism and melatonin may contribute to ovarian reserve and antioxidant protection [13, 14], while arginine supports nitric oxide synthesis [6], and leucine-dependent mTOR signaling has been implicated in granulosa-cell function and ovulatory regulation [31]. Overall, fertility-oriented nutritional strategies should consider protein source, amino acid availability, and diet quality, although direct evidence linking formal protein quality indices with fertility outcomes remains limited.

3.6.2 Protein Sources and Reproductive Outcomes

The source of dietary protein may be relevant to female fertility. Observational evidence suggests that healthier dietary patterns emphasizing seafood, poultry, whole grains, fruits, and vegetables are associated with better fertility outcomes, although the role of specific protein sources requires further investigation [2].

Evidence from women undergoing assisted reproductive technology (ART) also supports the relevance of protein-rich foods. In the EARTH Study, greater fish consumption was associated with a higher probability of live birth after ART [21]. These findings are consistent with broader nutritional approaches emphasizing plant-based protein, dietary fiber, omega-3 fatty acids, vitamins, and minerals as supportive components of female reproductive health [3].

Findings from the Nurses' Health Study further suggest that protein source may influence ovulatory infertility risk. Higher intake of plant protein was associated with a lower risk of ovulatory infertility, whereas higher intake of animal protein was associated with increased risk.

Therefore, dietary counseling for women attempting conception may consider the balance between animal- and plant-derived protein sources as part of an overall fertility-supportive dietary pattern [18].

3.6.3 Potential Role of Amino Acid-Targeted Nutritional Interventions

Several amino acids have emerged as potential targets for future fertility-oriented nutritional research. Branched-chain amino acids, particularly leucine, may regulate ovarian function through mTOR-dependent pathways involved in granulosa-cell metabolism, autophagy, and ovulatory regulation [31]. Impaired BCAA catabolism has been implicated in polycystic ovary syndrome, whereas BCAA insufficiency has been linked to premature ovarian insufficiency through oxidative stress and impaired granulosa-cell function [16, 17].

Other amino acid-related pathways may also be relevant to reproductive physiology. One-carbon metabolism is associated with oocyte maturation, fertilization, embryo quality, and pregnancy outcomes [11]. Tryptophan metabolism may influence reproductive function through melatonin synthesis and antioxidant protection, while altered follicular-fluid tryptophan and indole metabolites have been observed in women with diminished ovarian reserve [13, 14]. Arginine-derived nitric oxide pathways may contribute to vascular regulation and reproductive tissue function [6].

Although these mechanisms are biologically plausible, clinical studies evaluating targeted amino acid supplementation specifically for female fertility remain limited.

3.7 Clinical Implications of Protein Quality for Assisted Reproductive Technologies

Assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), are widely used treatment options for infertility. Because ART outcomes are influenced by multiple biological and lifestyle-related factors, increasing attention has focused on nutritional status and dietary quality before and during fertility treatment.

Women undergoing IVF or other forms of ART may benefit from nutritional assessment before treatment. The ovarian follicular environment, including one-carbon metabolism, may influence oocyte maturation, fertilization, embryo quality, and pregnancy outcomes [11]. Observational evidence also suggests that preconception intake of protein-rich foods may be

associated with ART outcomes, with higher fish consumption linked to a greater probability of live birth [21].

Recent evidence suggests that dietary patterns may also be associated with ART outcomes. Systematic reviews have reported that healthier dietary patterns may be linked with improved IVF or ART outcomes, although heterogeneity between studies limits definitive conclusions [19, 20]. Among the patterns investigated, the Mediterranean diet has received particular attention. In a prospective cohort study, greater adherence to a Mediterranean dietary pattern was associated with improved embryo yield during IVF treatment [22]. These findings are consistent with broader evidence suggesting that healthy dietary patterns may support female fertility [2].

Protein source may also be relevant to reproductive outcomes. In the EARTH Study, Nassan et al. examined intake of meat and other protein-rich foods among women undergoing ART and found that greater fish consumption was associated with a higher probability of live birth [21]. Earlier epidemiological evidence also suggests that protein source may be relevant to female reproductive function, as higher plant protein intake was associated with lower risk of ovulatory infertility in the Nurses' Health Study [18].

Further evidence comes from studies of overall dietary patterns and specific protein-containing foods during fertility treatment. Higher adherence to a pro-fertility dietary pattern was associated with a greater probability of live birth among women undergoing ART [23]. Similarly, preconception dietary patterns were associated with IVF-related outcomes, including normally fertilized eggs and transferable embryos [24]. Soy food intake has also been positively associated with the probability of live birth during ART treatment [25].

Amino acid availability may further support early reproductive processes relevant to ART. Amino acid transport systems are important for preimplantation embryo development, blastocyst formation, and implantation-related processes [10]. In addition, amino acids may contribute to reproductive competence through cellular signaling, metabolic regulation, antioxidant defense, and nitric oxide synthesis [5, 6]. Amino acid turnover by human oocytes and follicular-fluid amino acid profiles have also been associated with developmental competence and metabolic conditions relevant to assisted reproduction [8, 9].

Overall, available evidence suggests that dietary quality, protein-rich food sources, and amino acid availability may be relevant to ART outcomes. However, most available data are

observational, and direct evidence linking established protein quality indices with IVF success remains limited. Further prospective studies and randomized controlled trials are needed before specific recommendations regarding optimal protein quality for women undergoing ART can be established [4].

4. Discussion

4.1. Interpretation of Current Evidence

This review summarizes current evidence suggesting that dietary protein quality and amino acid metabolism may be relevant to female reproductive health, ovarian function, oocyte competence, embryo development, and outcomes of assisted reproductive technologies (ART). Although the available literature remains heterogeneous, several consistent themes emerge. First, reproductive nutrition should not be limited to total energy intake or micronutrient status alone. Second, the source and quality of dietary protein may influence reproductive outcomes through both dietary pattern-related and amino acid-dependent mechanisms. Third, amino acids appear to participate in biological pathways essential for ovarian and embryonic development.

The available epidemiological and clinical evidence suggests that protein source may be more relevant than total protein intake alone. In prospective cohort studies, higher intake of plant-derived protein has been associated with a lower risk of ovulatory infertility, whereas higher intake of animal protein may be less favorable in some populations [18]. In ART populations, selected protein-rich foods, particularly fish, have been associated with a higher probability of live birth [21]. These observations are consistent with broader evidence suggesting that healthier dietary patterns, including Mediterranean-type and pro-fertility dietary patterns, may be associated with improved IVF or ART outcomes [2, 19, 20, 22, 23]. However, these associations should be interpreted cautiously, as most studies evaluate overall dietary patterns rather than protein quality as an isolated exposure.

Further evidence from fertility treatment populations supports the relevance of overall dietary quality and specific protein-containing foods. Preconception dietary patterns have been associated with IVF-related outcomes, including normally fertilized eggs and transferable embryos [24]. Soy food intake has also been positively associated with the probability of live birth during ART treatment [25]. These findings suggest that the reproductive relevance of protein-rich foods may depend not only on amino acid composition, but also on the broader

food matrix, processing level, accompanying micronutrients, fatty acids, fiber, and bioactive compounds.

4.2. Biological Plausibility and Mechanistic Pathways

The biological plausibility of a relationship between protein quality and reproductive outcomes is supported by mechanistic and metabolomic evidence. Amino acids are not only substrates for protein synthesis but also regulators of metabolic signaling, oxidative stress responses, nitric oxide synthesis, methylation reactions, and mitochondrial function [5, 6]. These processes are closely related to folliculogenesis, oocyte maturation, fertilization, embryo development, implantation, and ovarian reserve maintenance. Human studies demonstrating associations between amino acid turnover and oocyte developmental competence, as well as follicular-fluid amino acid profiles in women undergoing assisted reproduction, further suggest that amino acid metabolism may reflect the quality of the ovarian microenvironment [8, 9].

Several amino acid-dependent pathways appear particularly relevant. One-carbon metabolism may influence oocyte maturation, fertilization, embryo quality, and pregnancy outcomes through methyl donor availability and epigenetic regulation [11, 12]. Tryptophan-derived metabolites, including melatonin, may contribute to antioxidant protection and ovarian function, while altered tryptophan and indole metabolite profiles have been observed in follicular fluid of women with diminished ovarian reserve [13, 14]. Arginine-derived nitric oxide pathways may support vascular regulation and peri-implantation processes [6, 15]. In addition, branched-chain amino acid metabolism and leucine-dependent mTOR signaling have been linked to granulosa-cell function, ovulatory regulation, polycystic ovary syndrome, and premature ovarian insufficiency [16, 17, 31]. Serine-dependent regulation of ferroptosis may also be relevant to granulosa-cell survival and ovarian function [30].

4.3. Clinical Implications

From a clinical perspective, these findings suggest that dietary counseling for women attempting conception or undergoing ART should consider overall dietary quality, protein sources, and amino acid availability. Recommendations based solely on total protein quantity may be insufficient, as protein-rich foods differ in digestibility, amino acid profile, accompanying nutrients, and degree of processing. A fertility-supportive dietary approach may therefore favor nutrient-dense protein sources such as fish, legumes, nuts, soy foods, poultry, and minimally processed foods, while limiting highly processed protein sources. Nevertheless,

current evidence does not yet allow precise recommendations regarding optimal protein quality, amino acid intake, or supplementation strategies for improving fertility outcomes.

4.4. Limitations and Knowledge Gaps

Important limitations and knowledge gaps remain. Established protein quality indices, such as PDCAAS and DIAAS, are used to assess amino acid composition and digestibility of dietary proteins [7]. However, direct studies evaluating these indices in relation to female fertility, ovarian reserve, oocyte competence, embryo quality, or live birth rates remain lacking. Most available studies focus on total protein intake, animal versus plant protein, selected protein-rich foods, or overall dietary patterns. Therefore, it remains unclear whether differences in amino acid composition, digestibility, and bioavailability translate into measurable improvements in reproductive outcomes.

Another limitation is that much of the mechanistic evidence comes from experimental, animal, or cellular models. Pathways such as mTOR signaling, autophagy, oxidative stress regulation, mitochondrial dysfunction, and ferroptosis provide important biological insight, but translation to human fertility care requires caution [17, 30, 31]. In addition, observational studies may be affected by confounding from overall diet quality, socioeconomic status, lifestyle behaviors, body composition, infertility diagnosis, and ART protocols.

4.5. Future Research Directions

Future research should integrate detailed dietary assessment with reproductive biomarkers, follicular-fluid metabolomics, and clinically relevant fertility outcomes. Prospective cohort studies and randomized controlled trials are needed to determine whether improving dietary protein quality before conception or before ART can meaningfully influence ovarian response, oocyte competence, embryo development, implantation, pregnancy, and live birth. Research should also clarify whether women with specific reproductive or metabolic phenotypes, such as polycystic ovary syndrome, diminished ovarian reserve, premature ovarian insufficiency, or obesity-related infertility, may benefit from targeted dietary protein or amino acid-based interventions.

Advances in individualized and precision nutrition may provide useful frameworks for future reproductive nutrition research. Future studies should examine whether women with different reproductive, metabolic, or ovarian phenotypes respond differently to dietary protein patterns,

protein-rich food sources, or amino acid availability. However, such strategies require validation in well-designed human studies before they can be translated into clinical recommendations.

Overall, the findings of this review support the hypothesis that dietary protein quality may be an important but underexplored component of reproductive nutrition. While current evidence is insufficient to establish specific clinical guidelines, it highlights the need to move beyond total protein intake and to consider amino acid availability, protein source, food matrix, and metabolic context when evaluating the role of nutrition in female fertility and ART outcomes.

5. Conclusions

Female fertility depends on endocrine regulation, ovarian function, oocyte quality, embryo development, and maternal metabolic status. Although nutrition is increasingly recognized as an important modifiable factor in reproductive health, the specific role of dietary protein quality remains insufficiently understood.

Current evidence suggests that amino acids may influence reproductive physiology through pathways involving mTOR signaling, mitochondrial function, oxidative stress regulation, autophagy, ferroptosis, nitric oxide synthesis, and one-carbon metabolism. These mechanisms are relevant to folliculogenesis, oocyte maturation, fertilization, embryo development, implantation, and ovarian reserve maintenance.

Observational and clinical studies indicate that healthier dietary patterns and selected protein-rich foods, including fish, poultry, legumes, nuts, and minimally processed foods, may be associated with improved fertility and ART outcomes. However, most available studies evaluate overall dietary patterns rather than protein quality itself, making it difficult to determine the independent contribution of amino acid composition, digestibility, and food matrix to reproductive success.

Despite growing mechanistic evidence, important knowledge gaps remain. Direct studies evaluating established protein quality indices, such as PDCAAS and DIAAS, in relation to female fertility are lacking, and randomized trials assessing protein quality optimization before fertility treatment are needed.

Overall, available evidence supports a biologically plausible relationship between dietary protein quality, amino acid metabolism, and female reproductive health. Although current data

are insufficient to establish precise clinical recommendations, protein quality should be considered a promising component of reproductive nutrition and a relevant target for future fertility-supportive dietary interventions.

DISCLOSURE

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