The science behind supplements for female fertility

Folate ubiquinol probiotics and emerging approaches to reproductive health support

José M. López, BSc, MD, PhD, LLD (C)

Technical Director · INTABIOTECH
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Abstract

Nutritional interventions in female reproductive health occupy different positions along the continuum from established prevention to experimental adjunctive treatment. Folic acid has a strong evidence base for reducing neural tube defects when used periconceptionally; this indication must be distinguished from treatment of infertility. Folate metabolism also provides substrates for nucleotide synthesis and methylation, but biochemical plausibility and observational associations with assisted reproduction do not establish that higher doses or methylfolate formulations increase live birth. Coenzyme Q10 links mitochondrial electron transport with redox homeostasis and has produced encouraging findings in selected populations with diminished ovarian reserve or poor ovarian response. Nevertheless, clinical studies differ in eligibility, formulation, cointerventions and analytical denominators. Recent syntheses include favorable live birth signals, while uncertainty remains over reproducibility, applicability and the reproductive superiority of ubiquinol over ubiquinone. Probiotics and synbiotics introduce a further layer of specificity because strain identity, delivery route, ecological context and formulation influence activity. Emerging trials and a 2026 meta-analysis support continued investigation, but microbiome modification, prevention of recurrent bacterial vaginosis and improved reproductive outcomes are separate claims.

This critical narrative review integrates biochemical mechanisms, selected human trials, contemporary evidence syntheses and professional guidance available through September 9, 2026. It examines folate forms and MTHFR interpretation, CoQ10 pharmacokinetics and ovarian endpoints, vaginal and endometrial microbiome research, and developments in metabolic and nutritional personalization. Comparative evidence tables distinguish established preventive use from promising but incompletely validated fertility applications. The central translational requirement is alignment between the studied population, the finished formulation and a clinically meaningful endpoint. Future development should prioritize cumulative live birth, time to pregnancy, maternal and neonatal safety, and transparent evaluation of the final product rather than assuming that ingredient-level mechanisms establish combination efficacy.

Keywords

Female fertility; folic acid; methylfolate; coenzyme Q10; ubiquinol; probiotics; vaginal microbiota; assisted reproductive technology; live birth; preconception nutrition.

1 Introduction

Female fertility depends on coordinated ovarian, endocrine, metabolic, anatomical and embryological processes. Nutritional adequacy contributes to this biological system, yet a nutrient required for normal physiology does not necessarily improve reproductive performance when supplied beyond adequate intake. This distinction is particularly important for supplements marketed across very different situations: preparation for a first pregnancy, anovulation associated with polycystic ovary syndrome (PCOS), diminished ovarian reserve, repeated embryo transfer, or reproductive aging. The phrase “fertility support” compresses these distinct clinical problems into an imprecise commercial category.

The American Society for Reproductive Medicine emphasizes age and established preconception measures, while finding limited evidence that specific diets, vitamins or antioxidants improve natural fertility in women without ovulatory dysfunction. Its recommendation to use folic acid is consistent with this position because prevention of an embryonic developmental abnormality is a different objective from increasing conception probability (American Society for Reproductive Medicine [ASRM], 2022). A rigorous article must preserve that distinction without dismissing the legitimate scientific interest in newer interventions.

Folate, coenzyme Q10 (CoQ10) and probiotics illustrate three different translational questions. For folate, the main challenge is moving responsibly from an established preventive indication to proposed reproductive benefits and alternative chemical forms. For CoQ10, it is determining whether mitochondrial and embryological findings translate into a reproducible improvement in live birth, and whether the evidence applies specifically to ubiquinol. For probiotics, it is establishing which microorganism or microbial consortium, administered by which route, produces a clinically useful effect in a defined reproductive context.

These questions matter for clinicians and for ingredient and product developers. An apparently positive trial may support further development without supporting broad clinical adoption. Conversely, an imprecise negative trial may leave a useful effect unresolved. The appropriate response is therefore endpoint-specific evaluation: what was actually administered, to whom, for how long, against which comparator, and with what consequences for the outcomes that matter to patients?

2 Review scope and principles of interpretation

Literature scope

This article is a critical narrative review based on targeted searches of accessible scientific literature and institutional guidance. Searches combined terms relating to folate, folic acid, methylfolate, MTHFR, coenzyme Q10, ubiquinol, diminished ovarian reserve, probiotics, synbiotics, vaginal microbiota, in vitro fertilization (IVF), frozen embryo transfer and live birth. PubMed records, original journal pages, clinical evidence syntheses and documents from CDC, USPSTF, NIH, ASRM, ESHRE, EFSA and EUR-Lex were consulted. Foundational studies were retained when necessary to explain established indications; recent publications were considered through September 9, 2026.

Selection prioritized identifiable human interventions and clinically relevant outcomes. Animal and cell studies are discussed as mechanistic evidence. Published protocols are identified as research

plans rather than efficacy results. This review did not undertake an exhaustive database search, duplicate independent screening, a formal risk-of-bias assessment of every eligible study, or a new meta-analysis. It therefore does not claim systematic-review completeness. Certainty labels attributed to published reviews are those of their authors; other judgments are qualitative assessments within this narrative synthesis.

The distinction between biological activity and clinical benefit

Four questions should be examined separately. First, can the intervention affect a plausible pathway? Second, does it change a measurable biological variable? Third, does that change improve a reproductive intermediate, such as oocyte yield or embryo development? Fourth, does the treatment increase the probability of a healthy live birth within a clinically relevant time horizon? Evidence at one level can motivate the next experiment, but cannot substitute for it.

An intervention may increase circulating folate without demonstrating a fertility effect, improve embryo morphology without changing chromosomal competence, or alter bacterial relative abundance without improving implantation. The converse is also possible: a clinically beneficial intervention may act through mechanisms not captured by a selected biomarker. Consequently, failure to show biomarker mediation does not automatically invalidate a clinical finding, but it weakens a specific mechanistic explanation.

Table 1 What different reproductive endpoints can establish

Evidence level	Examples	What it demonstrates	What remains unresolved
Biological mechanism	Enzyme activity; mitochondrial function; lactic acid response	A plausible pathway or activity under the tested conditions	Whether the intervention reaches the relevant site and improves outcomes
Biomarker	Red-cell folate; plasma CoQ10; bacterial composition	A measurable change in nutrient status or host ecology	Whether the change mediates a reproductive benefit
Reproductive intermediate	Oocyte yield; fertilization; embryo morphology	A change at a defined treatment stage	Cumulative birth probability and maternal or neonatal safety
Clinical outcome	Clinical pregnancy; miscarriage; live birth	An outcome directly relevant to reproductive care	Generalizability, absolute benefit, safety and cost
Patient pathway	Cumulative live birth; time to live birth	Performance across the full prespecified treatment period	Replication and effectiveness in routine care

Note. Conceptual framework proposed in this review. Intermediate outcomes can inform mechanism and trial design without being validated surrogates for live birth.

Denominators and uncertainty

Reproductive trials are unusually sensitive to the choice of denominator. Live birth per embryo transfer excludes women who never reach transfer. Pregnancy per cycle differs from pregnancy per woman when participants contribute multiple cycles. Cumulative live birth from all embryos generated after one retrieval answers a different question from success after the first transfer. A supplement that increases embryo availability may have a benefit that is missed by a first-transfer endpoint; alternatively, selective exclusion of women with canceled cycles can make an ineffective intervention appear favorable.

For decision-making, a preferred estimand is the probability of at least one live birth per randomized woman over a prespecified period, with all relevant fresh and frozen transfers included. Time to pregnancy or live birth complements that measure because a prolonged pretreatment may alter the overall treatment pathway. Intention-to-treat analysis protects the original comparison, whereas per-protocol analysis may describe outcomes among adherent users while introducing selection bias. Both can be informative if their different meanings are explicit.

Confidence intervals should be interpreted alongside effect estimates. An interval that includes no effect may still include a clinically important benefit; this is uncertainty, not proof of equivalence. A statistically significant pooled estimate can nevertheless be unreliable when underlying studies are small, poorly reported, heterogeneous or selectively published. Odds ratios are also not risk ratios: an odds ratio of two does not imply that the probability of pregnancy doubles when the outcome is common.

3 Folate biology and the periconceptional evidence base

One carbon metabolism and reproductive plausibility

Folate coenzymes carry one-carbon units in several oxidation states. The folate network supports purine synthesis, conversion of deoxyuridylate to thymidylate, and remethylation of homocysteine. These functions connect nutrient supply with DNA synthesis, cell proliferation and methyl-group availability. Folic acid, the oxidized form widely used in fortification and supplements, enters reduced folate metabolism through dihydrofolate reductase. Folate metabolism is compartmentalized, with mitochondrial and cytosolic reactions exchanging one-carbon equivalents rather than functioning as a single linear pathway (Ducker & Rabinowitz, 2017).

Methylenetetrahydrofolate reductase generates 5-methyltetrahydrofolate, which supplies a methyl group for the vitamin B12-dependent methionine synthase reaction. Methionine can then contribute to S-adenosylmethionine, a methyl donor used by numerous methyltransferases. This explains why “methylation support” has biological meaning, but it does not define a reproductive treatment. Methylation is tissue-specific, developmentally regulated and dependent on more than the intake of a single substrate. Increasing methyl-donor availability cannot be assumed to produce uniformly beneficial epigenetic changes.

Vitamin B12 is therefore relevant to interpretation of folate status. A B12-dependent block can impair the use of methylfolate even when folate intake is substantial. High folate intake can also correct the hematological manifestations of B12 deficiency without resolving its neurological consequences. Dietary history, malabsorption, medication exposure and compatible clinical findings may be more informative than simply escalating folate because a biochemical value is abnormal (Office of Dietary Supplements [ODS], 2025).

The reproductive rationale is strongest at stages characterized by rapid cell division and early embryonic development. However, plausibility should not be confused with a demonstrated dose-response relationship in women who are already folate-replete. A pathway can require a nutrient while being limited by another substrate, an enzyme, developmental timing or an unrelated reproductive factor. This is the conceptual reason that deficiency correction and supranutritional fertility enhancement require separate evidence.

What established prevention actually demonstrates

The historical randomized evidence concerns neural tube defects. In women with a previously affected pregnancy, the MRC Vitamin Study tested periconceptional folic acid within a factorial design and reported approximately a 72% reduction in recurrence risk. Its 4 mg regimen addressed a high-risk population and cannot be converted into a general dose recommendation for all women seeking pregnancy (MRC Vitamin Study Research Group, 1991). The subsequent Hungarian trial found no first-occurrence neural tube defects in the multivitamin group, compared with six in the trace-element control group. Because the intervention contained 0.8 mg folic acid together with other vitamins, that trial was not an isolated comparison of folic acid against placebo (Czeizel & Dudás, 1992).

Current USPSTF guidance recommends 400–800 µg of folic acid daily for people planning or capable of pregnancy, beginning at least one month before conception and continuing through the first two to three months of pregnancy. The preventive window matters because neural tube development occurs early, often before pregnancy recognition. Recommendations for individuals at increased risk require separate clinical assessment (U.S. Preventive Services Task Force [USPSTF], 2023).

These data establish a major benefit even if supplementation never changes the probability of conception. A study of time to pregnancy and a study of neural tube defects address different outcomes and require different designs. Accordingly, describing folic acid as an essential component of preconception prevention is justified; describing it as a proven treatment for unexplained infertility is not. CDC identifies folic acid as the form demonstrated to prevent neural tube defects, an evidence distinction that remains relevant when alternative folate forms are promoted (Centers for Disease Control and Prevention [CDC], 2024).

Folic acid and methylfolate are related but not interchangeable claims

5-Methyltetrahydrofolate, commonly abbreviated 5-MTHF, has a sound role as a source of folate. Its contribution to folate status is supported by human intervention research. In a double-blind study of 144 women, Lamers et al. (2006) compared folic acid, two doses of 5-MTHF and placebo over 24 weeks. The equimolar 416 µg 5-MTHF regimen produced a greater increase in red-cell folate than 400 µg folic acid. This was a nutrient-status study, however, not a trial of neural tube defects, implantation or live birth.

The distinction is not semantic. A superior laboratory response may be valuable when developing a formulation, but it does not establish superiority for every downstream outcome. Likewise, a source described as “active” still depends on absorption, transport, cellular handling and an intact metabolic network. Product comparisons should specify the stereochemical form, salt, actual folate contribution and analytical method rather than relying on a marketing category.

Common MTHFR variants are frequently used to justify mandatory methylfolate use. CDC states that individuals with these variants can process folic acid and that 400 µg daily increases folate levels regardless of genotype. A common variant therefore does not establish that folic acid is ineffective or intrinsically harmful, nor that a consumer genetic test identifies the supplement most likely to improve fertility (CDC, 2026). Rare metabolic disorders are a different clinical category and should not be conflated with common polymorphisms.

For precision nutrition, the relevant question is whether genotype-guided selection improves an outcome compared with a reasonable standard approach. Demonstrating a genotype–biomarker association is only an initial step. Clinical utility requires showing that acting on the test changes management in a beneficial way. Without that evidence, routine genetic segmentation may increase complexity and expense without improving reproductive care.

Fertility associations and dose interpretation

Gaskins et al. (2014) followed 232 women undergoing assisted reproduction and observed an association between greater supplemental folate intake and higher live birth probability. This provides a clinically relevant hypothesis because the endpoint extends beyond a laboratory marker. Nevertheless, supplement use can correlate with diet, socioeconomic circumstances, other health behaviors and clinical characteristics. Statistical adjustment reduces measured confounding but cannot exclude unmeasured differences or establish that adding folate caused the association.

The study also does not define an optimum dose for all infertility phenotypes. A relationship observed within one intake distribution may not remain linear at higher exposures or apply in populations with different fortification practices and baseline nutritional status. An appropriate next step would be a well-defined intervention in a population for whom there is genuine uncertainty, while preserving established preventive folic acid provision in the comparison group.

Folate labels require careful reading. Dietary folate equivalents account for differences in bioavailability, so micrograms of folic acid and micrograms of dietary folate equivalents are not numerically interchangeable. Natural food folate, fortified foods and multiple supplements may all contribute to the exposure history. ODS provides the relevant nutritional definitions and distinguishes requirements from upper intake limits (ODS, 2022).

EFSA retained an adult tolerable upper intake level of 1,000 µg/day in its 2023 assessment, including pregnancy and lactation, for the specified folate sources from supplements and fortified foods under the opinion's equivalence approach. The value is a safety boundary for the specified exposures, not an intake target or an automatically harmonized commercial maximum. Stacking a prenatal, a fertility blend and a separate methylfolate product can therefore be more consequential than the dose printed on any one label (EFSA NDA Panel, 2023).

Table 2 Folate forms and the boundaries of the available evidence

Intervention or setting	Evidence anchor	Supported interpretation	Key boundary
Periconceptional folic acid	USPSTF 2023; CDC 2024	Established neural tube defect prevention; 400–800 µg/day in standard USPSTF guidance	Preventive indication does not establish infertility treatment
High-risk recurrence prevention	MRC Vitamin Study 1991	A 4 mg/day regimen reduced recurrence in a previously affected population	Historical high-risk regimen is not a universal consumer dose
5-MTHF versus folic acid	Lamers et al. 2006; 144 women	Greater red-cell folate response with 416 µg 5-MTHF than 400 µg folic acid over 24 weeks	Nutrient-status outcome; no comparative fertility or NTD endpoint
Higher supplemental folate intake in ART	Gaskins et al. 2014; 232 women	Prospective association with live birth	Observational design; residual confounding and dose extrapolation

Intervention or setting	Evidence anchor	Supported interpretation	Key boundary
Common MTHFR variants	CDC 2026	Folic acid can raise folate levels across common genotypes	Genotype alone does not validate a superior fertility formulation

Note. 5-MTHF = 5-methyltetrahydrofolate; ART = assisted reproductive technology; NTD = neural tube defect. Doses summarize guidance or research and are not individualized prescriptions.

4 Coenzyme Q10 and the specific case for ubiquinol

Mitochondrial function and the oocyte

Coenzyme Q10 is a lipid-soluble redox carrier. Its oxidized form is ubiquinone and its reduced form is ubiquinol; both participate in an interconverting physiological pool. Within the inner mitochondrial membrane, CoQ transfers electrons from upstream electron donors, including respiratory complexes I and II, toward complex III. The resulting respiratory activity contributes to the proton gradient used by ATP synthase. Reduced CoQ also participates in the protection of lipid environments against oxidation.

The oocyte is an attractive target for mitochondrial investigation because meiotic maturation, spindle dynamics, fertilization and early development impose substantial energetic demands. Nevertheless, ovarian aging is not reducible to a shortage of a single cofactor. Oocyte number, chromosome segregation, cellular quality-control systems, the follicular environment and systemic age-related factors may all constrain reproductive success. “Improved egg quality” is consequently too broad unless the measured component of quality is identified.

Ben-Meir et al. (2015) provided experimental support for the CoQ hypothesis in mouse models. Supplementation improved age-associated mitochondrial and reproductive measures, while oocyte-specific disruption of a CoQ biosynthetic gene produced mitochondrial impairment and reproductive abnormalities. These findings support a causal role for CoQ biology in the experimental system. They do not demonstrate that an oral supplement reverses ovarian aging in humans or restores a depleted follicle pool.

Mechanistic interpretation also requires distinguishing redox balance from maximal antioxidant exposure. Reactive oxygen species can participate in signaling as well as damage. The relevant hypothesis is correction of a dysfunctional biological state at an appropriate exposure, not indiscriminate suppression of oxidation. Plasma CoQ, follicular-fluid CoQ, mitochondrial function and reproductive outcomes should therefore be treated as different measurements rather than interchangeable evidence of “cellular rejuvenation.”

The strongest clinical signals are population dependent

The randomized trial by Xu et al. (2018) enrolled 186 women younger than 35 years with decreased ovarian reserve. Pretreatment consisted of 200 mg CoQ10 three times daily for 60 days before IVF or intracytoplasmic sperm injection (ICSI), compared with no pretreatment. Among 169 analyzed participants, the intervention improved ovarian and embryological measures, including a median of four retrieved oocytes versus two. Differences in clinical pregnancy and live birth were not statistically significant in the authors’ analysis.

Interpretation is limited by the open design, exclusions concentrated in the intervention arm and a sample size directed at an embryological endpoint. The study is informative about a specific low-prognosis group, but does not establish efficacy in spontaneous conception or validate every ubiquinol formulation. Nor did it show an increase in anti-Müllerian hormone (AMH) or antral follicle count that would support a claim of restored ovarian reserve.

Florou et al. (2020) pooled five randomized trials involving 449 women undergoing assisted reproduction. Clinical pregnancy favored CoQ10, with an odds ratio of 2.44 (95% confidence interval [CI] 1.30–4.59). Live birth was less certain: the pooled odds ratio was 1.67 (95% CI 0.66–4.25). This interval is compatible with both no benefit and a potentially important benefit. Population heterogeneity and the limited number of birth events constrain the interpretation, even when the pregnancy signal is encouraging.

A later synthesis focused on diminished ovarian reserve. Lin et al. (2024) included six randomized trials comprising 1,529 participants and reported improved IVF/ICSI outcomes, while acknowledging poor descriptions of study methods. A larger nominal sample does not eliminate bias arising from unclear allocation procedures, cointerventions or inconsistent reporting. The relevant advance is a broader signal in a defined clinical setting; the remaining task is to establish its magnitude and reliability using rigorously conducted trials of characterized products.

What changed in the 2026 literature

Schütz et al. (2026) reported a more favorable assessment of selected reproductive outcomes in a narrowly selected evidence base. Their review included three clinical CoQ10 studies and two studies adding micronutrients to in vitro maturation media. The published abstract reports 326 women in the clinical studies and a positive live birth result in the poor ovarian response subgroup. This is relevant evidence and prevents a categorical conclusion that no synthesis has found a birth benefit.

However, the laboratory studies require separate interpretation. Improvements in maturation or aneuploidy after directly exposing immature oocytes to CoQ10-containing culture media do not demonstrate the same effects after maternal oral supplementation. Route, local exposure and biological setting differ substantially. The review therefore strengthens the rationale for targeted CoQ10 research while leaving product-specific oral efficacy and reproducibility unresolved. It also illustrates why conclusions can change with eligibility criteria and endpoint selection rather than with a simple chronological accumulation of independent trials.

The broader antioxidant literature warrants an additional integrity note. Showell et al. (2020) included 63 trials with 7,760 women and rated live birth evidence as very low certainty despite a favorable pooled estimate. A March 5, 2026 Cochrane editorial note identified concerns involving nine included studies: seven retractions and two expressions of concern. The editors assessed their removal and reported no meaningful effect on the principal findings or conclusions, retaining confidence in those conclusions. The review itself was not retracted. This update supports careful study-level appraisal and does not justify either dismissing all antioxidant research or upgrading it to established treatment.

Table 3 Selected CoQ10 clinical evidence and its interpretation

Study	Population and design	Principal result	Interpretive limitation
Xu et al. 2018	186 randomized; young women with decreased ovarian reserve	Oocyte and embryo measures improved; birth difference not statistically significant	Open trial; 169 analyzed; 600 mg/day for 60 days; not a direct ubiquinol comparison
Florou et al. 2020	5 randomized trials; 449 women	Clinical pregnancy OR 2.44 (1.30–4.59); live birth OR 1.67 (0.66–4.25)	Imprecise birth estimate; differing infertility phenotypes
Lin et al. 2024	6 randomized trials; 1,529 women with diminished reserve	Clinical pregnancy OR 1.84 (1.33–2.53)	Poor methodological reporting; cointerventions and treatment differences require appraisal
Schütz et al. 2026	3 clinical CoQ10 studies plus 2 in vitro maturation studies	Favorable birth signal in poor responders; laboratory maturation and aneuploidy findings	Small selected evidence base; culture-media exposure cannot establish oral efficacy

Note. Parentheses contain 95% confidence intervals were reported here. OR = odds ratio. These syntheses overlap in underlying studies and should not be treated as independent replications. "CoQ10" does not identify a validated ubiquinol formulation.

Ubiquinol pharmacokinetics do not establish reproductive superiority

Because ubiquinol is the reduced form, it is often positioned as inherently superior to ubiquinone. The clinical question is more demanding. In a crossover study of 14 healthy volunteers, López-Lluch et al. (2019) compared seven 100 mg CoQ10 formulations. Absorption depended on carrier lipids and solubilization, and formulations with favorable exposure included both ubiquinone and ubiquinol. The study supports attention to the complete delivery system rather than selection by redox form alone.

A reproductive superiority claim would require a direct comparison of adequately characterized formulations at justified exposures, with relevant clinical endpoints. A higher plasma area under the concentration–time curve does not establish greater ovarian delivery, an optimal follicular concentration or improved live birth. Conversely, the absence of such a comparison does not imply that formulation is irrelevant; it means that pharmacokinetic optimization and reproductive efficacy remain distinct development questions.

For a finished ubiquinol product, useful specifications include identity, content, oxidation during storage, dissolution or dispersion behavior, carrier composition and stability in the intended package. If a trial uses a specific softgel system, a powder blend containing the same labeled milligrams is not automatically an evidence-equivalent product. These are proposed development criteria arising from the formulation problem, rather than evidence that any particular technology has already improved fertility.

Dose duration and tolerability

The 600 mg/day, 60-day regimen above is a studied CoQ10 exposure, not a universally recommended ubiquinol dose. Existing studies do not define a validated conversion between redox forms for reproductive use. They also do not establish that every patient should delay treatment for a fixed supplementation period. Pretreatment duration must be evaluated as part of the intervention, including the opportunity cost of postponement.

NCCIH describes gastrointestinal symptoms and insomnia among possible adverse effects and notes interactions with warfarin and insulin, as well as potential incompatibility with some cancer treatments. Tolerability in a small infertility trial is not equivalent to established safety throughout pregnancy. Medication review, adverse-event recording and a clear protocol for exposure after conception should therefore be built into reproductive research rather than assumed from general supplement use (National Center for Complementary and Integrative Health [NCCIH], n.d.).

5 Probiotics and the reproductive microbiome

The ecological rationale

The vaginal microbiome is an ecosystem rather than a single organism count. In reproductive-age women, communities often show dominance by *Lactobacillus* species, but composition varies between individuals and over time. The foundational study by Ravel et al. (2011) identified several community patterns, including *Lactobacillus*-dominant and more diverse communities in asymptomatic women. A taxonomic pattern must therefore be interpreted with symptoms, host context and the intended clinical outcome; diversity alone is not a universal definition of disease.

Lactobacilli can contribute to an acidic local environment through lactic acid production. In epithelial-cell experiments, Hearps et al. (2017) demonstrated anti-inflammatory effects of lactic acid under defined acidic conditions, including increased interleukin-1 receptor antagonist and suppression of selected inflammatory mediators. This supports a plausible mucosal mechanism. It does not establish that every *Lactobacillus* strain has the same activity, that simply lowering vaginal pH improves implantation, or that laboratory acid exposure is equivalent to administering a probiotic.

Mechanistic investigation should distinguish presence, viability, persistence and function. Detection of administered bacterial DNA does not prove durable colonization. Increased relative abundance can result from expansion of the target organism, depletion of competitors, or changes in total microbial biomass. Metabolite production and host response may therefore provide information not captured by taxonomy alone. These distinctions are especially important when a product is proposed to act at a site different from where it is administered.

Oral vaginal and endometrial interventions ask different questions

An oral probiotic must survive manufacture, storage and gastrointestinal transit before any proposed distal reproductive effect can be considered. A vaginal product creates a more direct local exposure but introduces formulation, retention and mucosal tolerability questions. Neither route can be presumed superior for fertility without comparative evidence. Studies of oral products and vaginal products should be stratified rather than treated as interchangeable demonstrations of a class effect.

The endometrium presents a further analytical challenge because samples may contain low microbial biomass and can acquire material during transcervical collection. Moreno et al. (2022) examined endometrial fluid and biopsy samples in a prospective multicenter cohort of 342 women undergoing assisted reproduction and identified associations between microbial composition and reproductive outcomes. This supports biomarker research, but an observational association does not establish that targeted eradication or supplementation improves birth probability.

For an endometrial assay, analytical validity requires attention to sampling controls, reagent contamination, biomass and reproducibility. Clinical validity asks whether the result predicts an outcome in an independent population. Clinical utility asks whether changing treatment according to that result improves outcomes compared with usual care. These are consecutive evidentiary requirements. A commercially available test can satisfy some without satisfying all, and a predictive association alone cannot justify routine antibiotic or probiotic treatment.

ESHRE's recommendations on recurrent implantation failure do not recommend routine uterine or vaginal microbiome profiling. The limitation concerns clinical readiness, not denial that host–microbe relationships may matter. It leaves room for controlled research while discouraging the assumption that a sequencing report necessarily identifies a treatable cause of failed implantation (European Society of Human Reproduction and Embryology [ESHRE], 2023).

Randomized evidence is mixed

Jepsen et al. (2022) randomized 74 women with an unfavorable vaginal microbiota before fertility treatment to a 10-day vaginal preparation containing *L. gasseri* and *L. rhamnosus* or placebo. Microbiota improvement occurred in 28.9% and 40.0%, respectively, with a risk ratio (RR) of 0.72 (95% CI 0.38–1.38). The selected product did not improve its primary microbiological outcome. The result also highlights spontaneous variation, which an uncontrolled before-and-after study could misattribute to treatment.

In contrast, Jafari et al. (2026) randomized 156 women before frozen embryo transfer to a 30-day vaginal synbiotic or control and analyzed 153 completers. Clinical pregnancy was 42.9% versus 27.6% ($p = .048$), while ongoing pregnancy and implantation differences were not statistically significant. The single-center study was retrospectively registered, and its size was based on a microbiological rather than a live birth endpoint. Vaginal and uterine culture differences were also not statistically significant, limiting confirmation of the proposed microbial pathway.

The observed clinical pregnancy difference in that trial is approximately 15 percentage points, calculated from the reported proportions. This is a potentially meaningful signal, but it should not be presented as a reproducible absolute benefit for every vaginal product. A result near a conventional significance threshold, among several outcomes and without birth-powered replication, is best used to design a confirmatory trial.

The 2026 synthesis and its implications

Moradi et al. (2026) synthesized 16 randomized and observational studies involving 2,339 women. Oral probiotics were associated with higher biochemical pregnancy (RR 1.27, 95% CI 1.01–1.60), clinical pregnancy (RR 1.71, 95% CI 1.01–2.91) and live birth (RR 1.24, 95% CI 1.01–1.51). For vaginal administration, the significant pooled finding was lower miscarriage risk (RR 0.57, 95% CI 0.38–0.84). The authors rated certainty as low or very low.

This synthesis makes a blanket statement that probiotics have "no evidence" for reproductive benefit inaccurate. It does not, however, establish a universally effective probiotic intervention. The combined evidence includes different study designs, populations and preparations, and the oral live birth interval lies close to the null at its lower boundary. The search ended in December 2025, so the subsequent Jafari trial should be considered a separate update rather than assumed to be part of the pooled estimate.

Table 4 Selected probiotic and synbiotic studies relevant to reproductive health

Study and setting	Design or intervention	Finding	Clinical meaning
Jepsen et al. 2022; before fertility treatment	74 randomized; 10-day vaginal lactobacilli	Microbiota improvement RR 0.72 (0.38–1.38)	No demonstrated benefit for the selected microbiological endpoint
Jafari et al. 2026; before frozen transfer	156 randomized; 30-day vaginal synbiotic	Clinical pregnancy 42.9% versus 27.6%; p = .048	Positive signal; completer analysis; not powered for live birth
Moradi et al. 2026; infertility synthesis	16 randomized and observational studies; 2,339 women	Oral live birth RR 1.24 (1.01–1.51); vaginal miscarriage RR 0.57 (0.38–0.84)	Low or very low certainty; route and preparation matter
Ravel et al. 2025; vaginal ecology	Randomized study of an *L. crispatus* synbiotic	Shift toward *L. crispatus* dominance in a baseline-defined subgroup	Evidence of ecological activity; no fertility endpoint
Cohen et al. 2020; recurrent vaginosis	228 randomized; Lactin-V after metronidazole	12-week recurrence 30% versus 45%	Product-specific vaginosis benefit; not an infertility trial
van Haren et al. 2025; ProVag	Randomized oral probiotic study protocol	Planned serial vaginal microbiota assessment	Protocol publication; no efficacy results

Note. Parentheses contain 95% confidence intervals. RR = risk ratio. A positive result for one product, route or indication cannot be assigned to other preparations solely based on genus or species.

New products can prove ecological activity without proving fertility benefit

Ravel et al. (2025) investigated a multistrain *L. crispatus* vaginal synbiotic in a randomized placebo-controlled study with different formulation components. Among participants with an initially non-*L. crispatus*-dominant community, a tablet formulation produced a marked shift toward *L. crispatus* dominance. The study enrolled women outside an intended pregnancy population and measured microbiome outcomes. Its contribution is therefore evidence of ecological modification by a characterized preparation, not evidence of improved conception or live birth.

Similarly, the Lactin-V trial demonstrated that a specific *L. crispatus* product could reduce recurrence of bacterial vaginosis after metronidazole treatment: recurrence at 12 weeks was 30% with the product and 45% with placebo. This was an important product-specific clinical result in a different indication (Cohen et al., 2020). Preventing recurrent vaginosis may be valuable in its own right, but its magnitude cannot be transferred to an infertility claim.

The ProVag publication describes a randomized, placebo-controlled protocol evaluating oral probiotics and vaginal microbiota composition in women receiving medically assisted reproduction. It is useful evidence of the direction of current research, including serial sampling, but it does not report efficacy results (van Haren et al., 2025). Protocols should be tracked to completed publications rather than counted alongside positive trials.

Strain identity and the meaning of a finished product

For product development, a probiotic should be specified at strain level, with the studied combination, route, viable dose, schedule and delivery matrix preserved. A high total colony-forming-unit count cannot substitute for strain-specific evidence. Viable counts should remain meaningful at the end of shelf life, not only at manufacture. Stability, contaminant testing, strain

traceability and mucosal or gastrointestinal tolerability are necessary to interpret clinical performance.

For synbiotics, adding a substrate creates an additional mechanistic variable. The substrate may influence microbial growth, retention or local ecology, but synergy should be demonstrated rather than inferred from the ingredient list. A design comparing the microorganism, the substrate, the combination and an appropriate control can help identify whether the combination contributes more than either component alone. Without such a design, a positive result supports the tested preparation as a whole, not an independently verified synergistic mechanism.

6 Emerging directions beyond the three principal ingredients

Metabolic phenotype and inositol in PCOS

The movement toward phenotype-specific supplementation is scientifically more promising than treating every infertility diagnosis as a nutritional deficit. In PCOS, the relationship between metabolic dysfunction and ovulation has encouraged interest in inositol-containing products. Nevertheless, the 2023 international guideline classifies inositol as experimental therapy for infertility in women with PCOS because evidence for ovulation, clinical pregnancy and live birth is limited and uncertain. It does not establish an optimal form, dose or combination ratio for reproductive use (ASRM, 2023).

For development, this means that an insulin-related or biochemical endpoint may help characterize activity but should not be promoted as equivalent to restored fertility. A marketed ratio can be a manufacturing specification without being a clinically validated optimum. Trials should define PCOS phenotype, background treatment and the reproductive endpoint before interpreting a subgroup as a likely responder population.

Vitamin D and the difference between status correction and IVF enhancement

Vitamin D provides a useful test case for the limits of observational inference. In the SUNDRO trial, 630 women with low vitamin D undergoing IVF were randomized to a single 600,000 IU oral dose or placebo. Clinical pregnancy occurred in 37% and 40%, respectively, with an RR of 0.91 (95% CI 0.75–1.11). This regimen did not improve the primary outcome (Somigliana et al., 2021).

The result does not imply that vitamin D deficiency should be ignored, nor that every dosing strategy has been disproved. It shows that correcting or increasing a biomarker through one intervention does not necessarily improve IVF success. The very high bolus used experimentally should not be converted into a consumer recommendation.

A major 2026 trial provides evidence for a different schedule and population. Hu et al. randomized 876 women with PCOS across 24 fertility centers to 4,000 IU vitamin D daily or placebo for up to 90 days before IVF. In the modified intention-to-treat population of 865 women, live birth after the first transfer occurred in 52.0% versus 50.2% (adjusted RR 1.03, 95% CI 0.91–1.18), despite a substantial increase in circulating 25-hydroxyvitamin D. The trial did not demonstrate a birth benefit for this regimen and population (Hu et al., 2026). It is a contemporary example of why a successful biochemical intervention can leave the primary reproductive outcome unchanged.

Precision nutrition requires demonstrated clinical utility

A rational personalization strategy begins with factors that can change a concrete decision: dietary pattern, baseline nutrient status when clinically indicated, malabsorption, medication use, age, diagnosis and treatment pathway. A test is useful when its result identifies an intervention that improves a meaningful outcome. Repeated testing that merely changes a supplement subscription is not equivalent to demonstrated clinical utility.

Future trials could prespecify nutrient-status strata, compare a targeted correction strategy with standard preconception care, and measure both nutritional and reproductive outcomes. This would distinguish benefit in deficient participants from lack of additional benefit in replete participants. It would also avoid misleading averages created by pooling groups with different biological constraints. Such designs are proposals for stronger research, not evidence that a fully validated personalized fertility supplement algorithm currently exists.

Mitochondrial targeting and microbial engineering

The most useful emerging technologies are those that solve a measurable translational problem. For CoQ10, improved dispersion or protection against oxidation may make exposure more consistent. For vaginal preparations, residence time and maintenance of viable organisms may influence ecological activity. For folate, stability and accurate delivery of a defined source remain central. These technological gains should first be demonstrated analytically and pharmacologically, then connected to reproductive outcomes when such claims are intended.

Next-generation microbial products also create opportunities to move beyond generic species lists toward characterized strains, functional traits and defined consortia. Research should ask whether a specific function persists in the host and whether it mediates a clinical benefit. Postbiotics and microbial metabolites raise related questions but are distinct interventions; their evidence cannot be borrowed automatically from live-microorganism trials. The general principle is that innovation in mechanism or delivery expands the research agenda without reducing the evidentiary threshold for a fertility claim.

7 Formulation quality and safety across the reproductive pathway

The mixture is an intervention of its own

A formulation containing folate, ubiquinol and microorganisms does not automatically inherit the outcomes reported for its individual components. It may supply different doses, alter stability or tolerance, and introduce an adherence burden. Furthermore, the populations supporting each ingredient may not overlap. A product assembled from an NTD-prevention intervention, a poor-response IVF study and a vaginosis-recurrence trial has not thereby been studied in any coherent fertility population.

The development brief should define a single intended use before selecting ingredients. If the objective is nutritional adequacy during preparation for pregnancy, analytical quality and evidence-aligned nutrient provision are central. If the objective is an increase in cumulative live birth in a defined infertility group, the finished product requires a reproductive trial. If the objective is a local microbiological effect, the formulation and route must be appropriate to that site, and the claim should remain linked to the measured result.

An evidence dossier should therefore map each proposed statement to the exact preparation and endpoint supporting it. It should also identify the steps that remain inferential. This approach does not prohibit combination development; it makes the development question testable and prevents a mixture of unrelated evidence from appearing stronger than its components.

Exposure changes when pregnancy begins

Preconception use, ovarian stimulation, the peri-implantation period and established pregnancy are different exposure settings. An infertility trial that stops a supplement at retrieval cannot establish safety for continuous use throughout gestation. A prenatal nutrient requirement also does not justify retaining every experimental adjunct after conception. Trials and clinical protocols should state when the product starts, when it stops, and what happens if pregnancy occurs earlier than expected.

Adverse events should include symptoms, treatment discontinuation, medication interactions and pregnancy outcomes, with appropriate follow-up. Absence of serious events in a small study may be reassuring for common short-term toxicity but cannot exclude rare harm. For consumers, total exposure from overlapping products is a practical issue, particularly when the same nutrients appear under different branded ingredient names.

Table 5 Application by reproductive context

Context	Evidence-aligned role	Main unresolved question	Practical priority
Preparation for pregnancy	Established folic acid prevention; nutritional adequacy	Whether additional ingredients improve conception in replete women	Review diet and overlapping supplements
Common MTHFR variant	Standard folic acid remains biologically usable	Clinical utility of genotype-guided substitution	Avoid assuming a genotype is an infertility diagnosis
Diminished reserve or poor IVF response	CoQ10 is a plausible adjunct under investigation	Reproducible cumulative live birth benefit and optimal formulation	Do not delay indicated evaluation or treatment
Unfavorable microbiota or recurrent transfer failure	Product-specific microbial research	Whether a test-guided intervention improves live birth	Separate symptoms, assay findings and treatment claims
PCOS and metabolic concerns	Phenotype-specific care; inositol remains experimental for infertility	Which subgroup benefits from a defined adjunct	Measure reproductive outcomes beyond metabolic markers
Pregnancy after adjunct exposure	Reassess the supplement regimen	Safety of continued exposure for experimental adjuncts	Use a defined start and stop protocol

Note. Clinical synthesis informed by ASRM (2022, 2023), CDC (2026), ESHRE (2023), USPSTF (2023), and the trials discussed in the text. This matrix is not a prescribing algorithm.

8 European implications for scientific and commercial communication

The European framework separates the ability to use an ingredient from the ability to make a health claim about it. Regulation (EC) No 1924/2006 governs nutrition and health claims on foods. Regulation (EU) No 1169/2011 prohibits attributing properties of preventing, treating or curing

human disease to foods, subject to the specific legal framework for authorized risk-reduction claims. A scientific publication used in commercial promotion can therefore acquire a regulatory significance beyond its academic content (European Parliament & Council of the European Union, 2006, 2011).

Regulation (EU) No 432/2012 includes authorized claims concerning folate and maternal tissue growth during pregnancy, and zinc and normal fertility and reproduction, subject to their conditions of use. These statements do not establish that a particular blend increases pregnancy rates. A claim attached to zinc cannot be transferred to ubiquinol or probiotics merely because all are present in the same capsule (European Commission, 2012).

Regulation (EU) No 1135/2014 authorizes a specific claim linking supplemental folic acid, maternal folate status and neural tube defect risk. Its conditions include a daily portion providing at least 400 µg folic acid and information about use from at least one month before until three months after conception in the specified target population. The full authorized context and general conditions for risk-reduction claims must be respected; the claim is not a guarantee that a defect will be prevented (European Commission, 2014).

An ingredient development relevant to current formulation work is Regulation (EU) 2025/2224, which adds the monosodium salt of L-5-methyltetrahydrofolic acid to the sources addressed by the legislation it amends. This is a source-authorization development, not a finding that the ingredient treats infertility or is clinically superior for live birth. Other applicable conditions, including those relevant to the ingredient's legal status and use, remain separate questions (European Commission, 2025).

For scientific communication, the defensible unit is the complete proposition: ingredient, population, endpoint and uncertainty. "Associated with a higher clinical pregnancy rate in a selected study" is different from "increases fertility." The surrounding product name, graphics and placement may alter the impression even when individual sentences are technically accurate. A sound scientific dossier and legally appropriate consumer communication therefore require related but distinct reviews.

9 Priorities for the next generation of trials

Design around the clinical decision

A confirmatory CoQ10 trial should recruit a prespecified ovarian-response population, compare a fixed and characterized formulation with an appropriate control, and account for all randomized women. If the question is ubiquinol superiority, the comparator should be a well-formulated ubiquinone product with a justified exposure strategy. Measuring plasma and follicular-fluid concentrations can investigate delivery, but cumulative live birth should determine the reproductive conclusion when that is the intended claim.

A probiotic trial should specify strain identity, viable dose, route, formulation and background treatment. Baseline microbial characterization can support planned subgroup analysis, provided it does not become a post hoc search for a favorable profile. Repeated sampling should distinguish immediate detection from persistence, while clinical follow-up should extend beyond a positive pregnancy test. Laboratory personnel and outcome assessors should remain blinded where

feasible, and concurrent antibiotics, vaginal treatments and embryo-transfer protocols should be recorded.

For folate, ethical comparisons should preserve established prevention. Trials may investigate clinically relevant differences between evidence-aligned strategies, but should not withhold recommended folic acid simply to generate a placebo contrast. Fertility outcomes, nutrient biomarkers and developmental outcomes should be specified separately. Because neural tube defects are uncommon, a small fertility trial cannot establish equivalent preventive efficacy between folate forms.

Make the result usable

Prospective registration should precede recruitment and include the primary outcome, denominator, analysis plan and major subgroups. Sample-size calculations should use a clinically meaningful difference rather than the most responsive laboratory measure. Reporting should include absolute event rates, relative estimates, confidence intervals, withdrawals, adherence and all prespecified outcomes. Negative findings are necessary to distinguish a real treatment effect from the selective visibility of successful experiments.

Combination products deserve designs capable of identifying contribution. A factorial study can test components and interactions when feasible; a pragmatic trial of the complete product can establish overall effectiveness but will not isolate which ingredient produced it. Either design is more informative than attributing a mixture's outcome to a favored component without an appropriate comparison.

Economic and patient-centered outcomes should also be included. A modest biological effect may be worthwhile if inexpensive, well tolerated and achieved without delaying treatment; the same effect may be unattractive if it requires costly testing or postponement. Trials should therefore record treatment burden, discontinuation and time-related consequences alongside reproductive outcomes. These measures make evidence more relevant to real decisions rather than merely to product positioning.

10 Clinical integration and conclusions

Supplementation belongs within a reproductive care pathway that addresses diagnosis and timing. ASRM advises evaluation after 12 months without conception in women younger than 35 years and after six months from age 35, with earlier assessment when the clinical history indicates it. A supplement course should not become a prerequisite for that evaluation (ASRM, 2022). The reproductive context also includes sperm factors, anatomy and treatment-specific variables, so failure to conceive should not be attributed to an insufficiently elaborate maternal supplement regimen.

The evidence supports a differentiated conclusion. Folic acid is established for periconceptional prevention of neural tube defects. Methylfolate can improve folate status, but biomarker findings and common MTHFR variants do not establish a general reproductive advantage over folic acid. CoQ10 has a coherent mitochondrial rationale and encouraging clinical findings in selected infertility populations, including favorable results in recent syntheses. The strength and applicability of those findings remain limited by study design, overlapping evidence and product heterogeneity; direct reproductive superiority of ubiquinol is unresolved.

Probiotics and synbiotics have progressed from ecological hypotheses to product-specific clinical studies and low-certainty pooled reproductive signals. Their potential should be assessed at the level of strain, route, host environment and endpoint. Successful modification of the vaginal microbiome or prevention of vaginosis recurrence cannot alone establish an infertility indication. Contemporary development should integrate biochemical precision, formulation quality and adequately powered trials of clinically meaningful outcomes.

For reproductive health support, the most credible innovation is a well-defined intervention whose claims match its evidence. Nutritional adequacy, established prevention and experimental fertility adjuncts can all have a place in research and care, provided their purposes and evidentiary limits remain explicit.

Professional context

José Manuel López is identified as Technical Director at INTABIOTECH, placing this article within a professional context connected to ingredients and food supplements. No specific INTABIOTECH formulation/s is/are evaluated or accredited in this review. Experimental doses are reported to describe studies and do not constitute individualized prescribing instructions.

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