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Partner-specific biological interactions in human reproduction

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The World Health Organization estimates that 17.5% of adults' worldwide experience infertility during their lifetime, while approximately 15%–30% of couples undergoing infertility evaluation receive a diagnosis of unexplained infertility. Current diagnostic approaches predominantly assess female and male reproductive factors separately, although successful conception, implantation, and placentation depend on continuous biological interactions between the partners. This review aims to critically evaluate the concept of couple biocompatibility as a pair-dependent component of human reproduction and explore its potential as a framework for future precision reproductive medicine. We distinguish individual reproductive factors and interaction modifiers from genuine partner-specific effects, including differential sperm responses to female reproductive tract secretions, maternal immune adaptation to paternal antigens, and maternal KIR–paternal/fetal HLA-C interactions. We further classify candidate biomarkers as partner-specific, partner-interaction, or downstream reproductive outcome biomarkers and evaluate their current clinical maturity. No core partner-specific or partner-interaction assay currently qualifies as a validated, guideline-supported test of general couple biocompatibility. However, integration of defined-pair functional assays with multi-omics, extracellular-vesicle profiling, advanced reproductive models, and computational approaches may provide a foundation for future couple-specific diagnostic platforms. Rather than replacing established infertility assessment, couple biocompatibility could extend it toward precision reproductive medicine in which reproductive potential is evaluated not only at the level of each individual, but also at the level of the biological pair.

KEYWORDS
couple biocompatibility, diagnostics, endometrium, infertility, partner-specific, precision medicine, spermatozoa

1 Introduction

Current evidence indicates that reproductive outcomes depend not only on each partner's reproductive competence but also on the biological interactions that occur throughout conception, implantation, and placentation. Understanding these interactions offers an opportunity to extend reproductive assessment beyond the evaluation of each partner separately toward an integrated, couple-specific approach.

Although their clinical translation requires further validation, partner-specific interactions may provide an important foundation for the development of precision reproductive medicine and personalized conception strategies.

The World Health Organization (WHO) estimates that 17.5% of adults worldwide, approximately one in six people, experience infertility during their lifetime (World Health Organization, 2023). Conventional infertility evaluation focuses on abnormalities within either partner, including endocrine dysfunction, impaired gametogenesis, tubal pathology, uterine abnormalities, genetic disorders, and semen-quality defects. Assisted reproductive technology (ART) may address some identified barriers, but routine investigations remain centered on the partners separately (Carson and Kallen, 2021; Penzias et al., 2021; Schlegel et al., 2021).

Approximately 15%–30% of couples undergoing infertility evaluation receive a diagnosis of unexplained infertility (uIF) after standard assessment identifies no explanatory ovulatory, tubal, uterine, or conventional semen abnormality. The reported proportion varies with the diagnostic definition, completeness of the work-up, referral setting, population, and study period; the 15%–30% range used throughout this review reflects contemporary reviews and guidelines (Ray et al., 2012; Gelbaya et al., 2014; Guideline Group on Unexplained Infertility et al., 2023; Raperport et al., 2024). This residual category may contain occult individual abnormalities or interaction-dependent mechanisms, but the diagnosis itself is not evidence of couple biocompatibility.

Human reproduction is inherently interaction-dependent (Massimiani et al., 2019; Vallet-Buisan et al., 2023). After ejaculation, sperm encounter a selective female environment that regulates survival, migration, capacitation, and fertilization, while implantation and placentation require embryo–maternal signaling. These processes involve female reproductive tract secretions, seminal plasma (SP), immune pathways, genetic combinations, cellular interactions, and conceptus–maternal crosstalk. Variation in these processes may influence specified reproductive endpoints, but interaction dependence must be demonstrated rather than inferred from an abnormality in one compartment (Kanannejad, 2025; Sakkas et al., 2015; Schjenken and Robertson, 2020; Kekäläinen, 2021; Chan and Robertson, 2025).

In this review, couple biocompatibility refers to the extent to which the reproductive effect of a gamete, secretion, antigen, genotype, or cellular signal from one partner depends on the biological characteristics of the other partner or of the conceptus generated by that pair. A phenomenon is considered partner-specific when its effect cannot be inferred adequately from either partner alone, for example, when the same sperm sample responds differently to reproductive tract fluids from different women, or when risk is associated with a defined maternal–paternal/fetal genotype combination. Couple biocompatibility is therefore a dynamic and stage-specific biological process that reflects the unique reproductive interactions between two partners across conception, implantation, and placentation (Figure 1; Rath et al., 2008; Kekäläinen, 2021; Miller, 2024; Daupagne et al., 2025).

To distinguish this construct from general infertility, we organize biological evidence into three levels. Individual reproductive factors, such as polycystic ovary syndrome (PCOS), tubal occlusion, oligoasthenoteratozoospermia (OAT), varicocele, sperm DNA fragmentation (SDF), or an isolated endometrial abnormality, affect one partner and are not themselves evidence of couple biocompatibility. Interaction modifiers, including inflammation, oxidative stress, SP composition, and the maternal immune or endometrial milieu, may alter the setting in which partners interact but do not establish a pair-specific effect unless tested across defined combinations. Genuine partner-specific interactions occur when an outcome depends on the particular male–female or maternal–paternal/fetal combination (Hiby et al., 2004; Robertson, 2005; Shen et al., 2023; Wasilewska et al., 2023; Druart, 2012). This biological-factor framework is distinct from the biomarker taxonomy used in Section 6.

Despite growing interest in these mechanisms, current knowledge remains fragmented across multiple disciplines. Existing reviews commonly focus on isolated aspects of reproductive compatibility, including reproductive immunology, sperm function, endometrial receptivity, or genetic matching, without integrating these findings into a unified conceptual framework (Schjenken and Robertson, 2020; Kekäläinen, 2021; Mahé et al., 2021; Bui et al., 2022).

Accordingly, this review first separates conventional individual causes of infertility from interaction modifiers and direct partner-specific effects. It then evaluates the strongest genetic, immunological, biochemical, and cellular examples of pair dependence and reviews proposed tests according to the construct they measure and their level of clinical validation. Conventional reproductive disorders are discussed only insofar as they constrain or alter the context in which partner-specific interactions occur.

The three levels classify the available evidence rather than permanently classifying a diagnosis or molecule. An interaction modifier should be considered partner-specific only when a cross-pair, crossover, or factorial design demonstrates dependence on the particular biological combination.

Couple-level assessment does not necessarily measure couple biocompatibility. Carrier screening, parental karyotyping, and related genetic investigations may estimate inherited reproductive risk for a couple without measuring a functional interaction between partners. These adjacent applications are therefore distinguished from the core partner-specific construct.

The biomarker classification used in this review is independent of the biological-factor framework. A partner-specific biomarker is a paired characteristic defined by the particular couple, a partner-interaction biomarker is a functional readout produced by directly combining material from the defined partners; and a downstream reproductive outcome biomarker is measured in one partner, one compartment, or an embryo without demonstrating pair dependence. These categories prevent one-partner measurements from being relabeled as partner-specific diagnostics.

Clinical phenotypes are considered separately within this framework, as partner-specific interactions may operate at different stages of the reproductive process. uIF is a diagnosis of exclusion after standard assessment identifies no explanatory ovulatory, tubal, uterine, or conventional semen abnormality. Recurrent implantation failure (RIF) is an ART-specific phenotype characterized by repeated failure to achieve

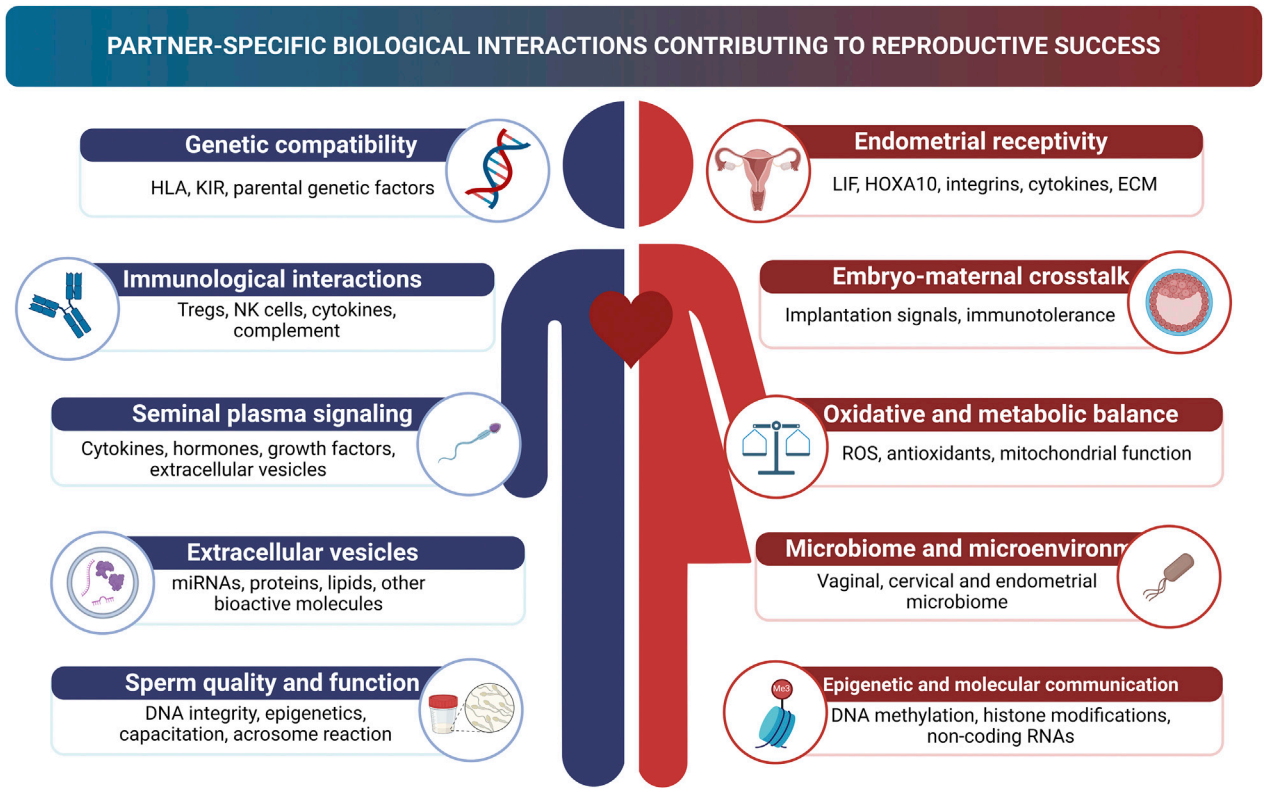


FIGURE 1
Partner-specific biological interactions contributing to reproductive success. Image created using BioRender.

implantation following embryo transfer, whereas recurrent pregnancy loss (RPL) concerns pregnancy losses occurring after conception. Accordingly, when ART is unsuccessful, the specific stage and reproductive endpoint should be defined rather than broadly described as "repeated ART failure." Distinguishing these phenotypes is essential for identifying where partner-specific biological interactions may contribute to reproductive outcomes and for developing future phenotype-specific, couple-oriented approaches to reproductive assessment.

2 Epidemiology and prevalence of infertility

Infertility is a major global public health concern with significant medical, psychological, and socioeconomic consequences. The World Health Organization (WHO) defines infertility as the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Increasing recognition of both female and male factors has highlighted infertility as a complex and multifactorial condition requiring comprehensive evaluation and management (Mascarenhas et al., 2012; Cox et al., 2022).

WHO estimates that 17.5% of adults worldwide, approximately one in six people, experience infertility during their lifetime (World Health Organization, 2023). This is a person-based lifetime-prevalence estimate and should not be presented as though it were a per-couple or point-period estimate. Population studies using different denominators and observation periods may yield different values (Centers for Disease Control and Prevention, 2021; Cox et al., 2022).

Infertility is classified as primary or secondary according to reproductive history (Vander Borght and Wyns, 2018). Primary infertility refers to couples who have never achieved a pregnancy, whereas secondary infertility describes failure to conceive following at least one prior pregnancy (Giudice and Kao, 2004; Vander Borght and Wyns, 2018). Approximately 15%–30% of couples undergoing infertility evaluation receive a diagnosis of uIF (Gelbaya et al., 2014; Guideline Group on Unexplained Infertility et al., 2023). Variation across reports reflects differences in diagnostic definitions, work-up completeness, referral setting, population, and study period. The residual category may include occult individual abnormalities and interaction-dependent mechanisms. However, uIF is not itself evidence of couple biocompatibility.

These observations provide a rationale for investigating couple biocompatibility as an additional dimension of reproductive assessment. Improved understanding of partner-specific genetic, immunological, biochemical, and cellular interactions may help explain a proportion of currently uIF cases and contribute to the development of more precise diagnostic approaches (Figure 2).

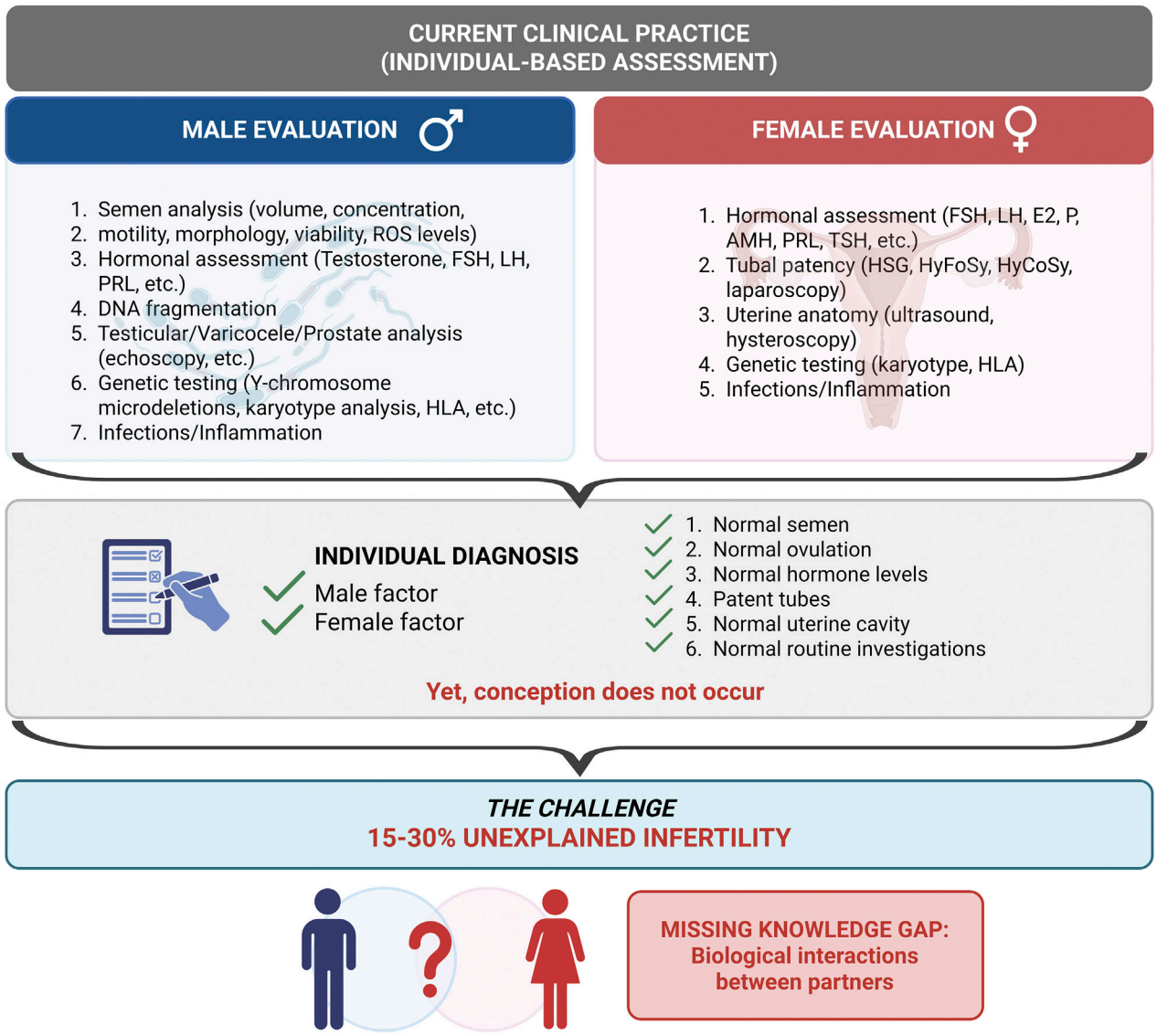


FIGURE 2
Major causes of couple infertility, conventional and advanced diagnostics with a link to a current gap of knowledge of unexplained infertility. Image created using BioRender.

3 Conventional diagnostic approaches in infertility evaluation

Conventional diagnostic approaches form the foundation of infertility evaluation by enabling systematic assessment of female, male, and couple-related factors. These methods integrate hormonal, functional, and anatomical investigations to identify the most common causes of infertility and guide individualized management strategies. However, they primarily evaluate male and female partners separately and provide limited insight into the biological interactions that may influence reproductive compatibility.

3.1 Female partner assessment

A detailed hormonal profile helps identify ovulatory disorders, diminished ovarian reserve, and endocrine dysfunction. First-line assessment may include follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, anti-Müllerian hormone (AMH), prolactin (PRL), and thyroid-stimulating hormone (TSH), interpreted according to the clinical question (Penzias et al., 2021; Bosch et al., 2021; Oduwole et al., 2021; Polyzos et al., 2022; Gleicher et al., 2010; Seckin et al., 2012; Demir et al., 2022; Erden et al., 2022; Mustafa and Mousa, 2022; Nida, 2022; Sharma et al., 2023; Zhao et al., 2023; Orok et al., 2024).

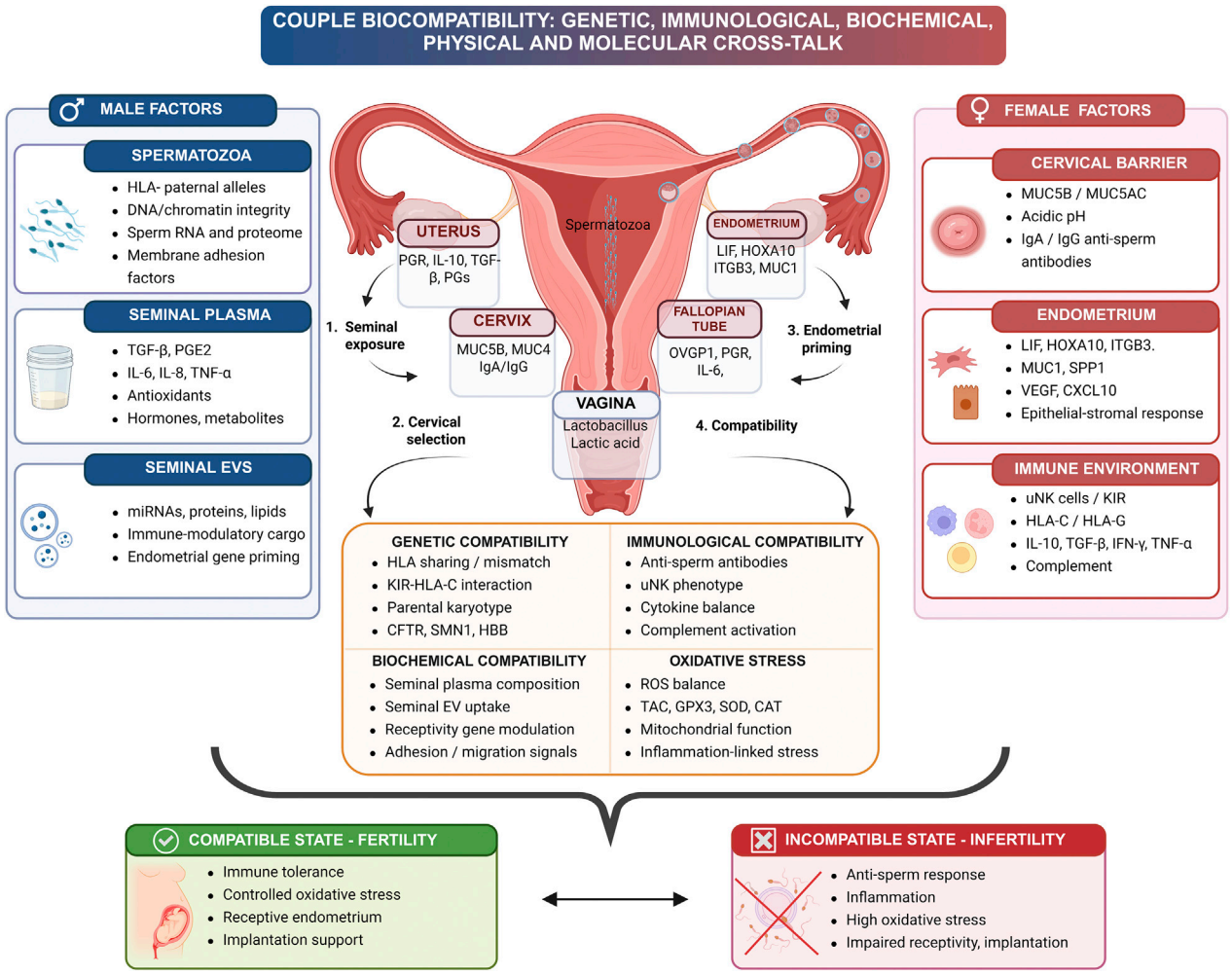


FIGURE 3
Representation of a concept of couple biocompatibility with potential factors affecting conception. Image created using BioRender.

Assessment of ovulation and ovarian reserve commonly combines hormonal testing with ultrasound evaluation. AMH correlates with the number of growing follicles and reflects ovarian reserve, although it is primarily a marker of oocyte quantity rather than quality and does not reliably predict natural fecundability or live birth (Iliodromiti et al., 2015; Moolhuijsen and Visser, 2020; Russell et al., 2022; Cedars, 2022; Volovsky and Seifer, 2024).

Evaluation of tubal patency and uterine anatomy is a core component of infertility assessment. Common modalities include hysterosalpingography (HSG), hysterosalpingo-foam sonography (HyFoSy), hysterosalpingo-contrast sonography (HyCoSy), and laparoscopy with or without hysteroscopy (Varlas et al., 2021; Grigoriadis et al., 2024; Nguyen et al., 2024; Groszmann and Benacerraf, 2016). Laparoscopy permits direct assessment and treatment of selected pelvic pathology, whereas HSG, HyCoSy, and HyFoSy are less invasive first-line approaches for tubal patency and uterine-cavity assessment (Fatum et al., 2002; Saunders et al., 2011; Mayrhofer et al., 2022; van Welie et al., 2022; Tsakos et al., 2023; Kamphuis et al., 2024; Soares et al., 2000; Roma Dalfó et al., 2004; Saravelos et al., 2008).

3.2 Male partner assessment

Semen analysis is the standard first-line laboratory test in the evaluation of male infertility, assessing semen volume, sperm concentration, motility, morphology, and vitality (Björndahl, 2023).

It remains the cornerstone of male factor infertility evaluation and provides clinically useful information regarding reproductive potential (Verón et al., 2018; Stavros et al., 2024). Nevertheless, normal semen parameters do not guarantee fertility, and abnormal findings do not imply sterility, as conventional semen analysis correlates only imperfectly with both natural conception and assisted reproductive technology outcomes (Wang and Swerdloff, 2014; Verón et al., 2018; Stavros et al., 2024).

When routine semen analysis is normal or inconclusive, selected sperm-function tests may provide additional information. SDF has been associated with reduced natural conception, some poorer ART outcomes, and miscarriage, while oxidative stress can contribute to

sperm DNA damage (Tremellen, 2008; Vaughan et al., 2020; Minhas et al., 2021; Stavros et al., 2024; Moazamian et al., 2025). Sperm penetration, zona binding, acrosome reaction, and capacitation assays remain specialized or research tools and do not demonstrate partner specificity unless defined female material is used (Oehninger et al., 2014; Pachetti et al., 2020).

3.3 Couple assessment

Current infertility evaluation also includes assessment of couple-related factors, particularly coital frequency and timing relative to ovulation. Clinical guidelines recommend intercourse every 2–3 days during the fertile window when expectant management is pursued (Guideline Group on Unexplained Infertility et al., 2023; Costello et al., 2024; Evans-Hoeker et al., 2013). Monitoring cervical mucus characteristics and urinary LH may assist with intercourse timing (Evans-Hoeker et al., 2013).

Historically, the post-coital test (PCT) was used to evaluate sperm–cervical-mucus interaction, it is no longer recommended because of poor reproducibility, limited clinical utility, and lack of predictive value for spontaneous conception (Practice Committee of the American Society for Reproductive Medicine, 2015; Penzias et al., 2021; Eggert-Kruse et al., 1995).

Despite substantial advances in infertility diagnostics, these investigations largely evaluate partners independently and provide limited information regarding biological interactions occurring between them.

4 Concept of couple biocompatibility and partner-specific interactions

The central unit of analysis in couple biocompatibility is the reproductive pair rather than either partner considered independently. Direct evidence requires either a functional response compared across defined male–female combinations or a biological or statistical effect attributable to a maternal-by-paternal/fetal combination after accounting for each partner's contribution. Currently, the coexistence of abnormalities in two partners, or the fact that both partners are tested, is insufficient to establish biocompatibility (Figure 3; Kekäläinen, 2021; Fitzpatrick et al., 2020).

Within this framework, the clearest examples arise at three interfaces. Female reproductive tract secretions can elicit different functional responses from sperm from different men; seminal plasma and paternal antigens engage the maternal immune system; and maternal KIR receptors interact with paternal/fetal HLA-C at the maternal-fetal interface (Robertson, 2005; Fitzpatrick et al., 2020; Piekarska et al., 2021; Piekarska et al., 2022; Shen et al., 2023; Bromfield, 2014). These observations establish biological plausibility, but they do not show that paired molecular profiles can diagnose infertility, predict live birth, or guide treatment. We therefore distinguish mechanistic evidence, clinical association, and demonstrated clinical utility throughout this review.

Studies are identified throughout as human clinical, human observational, human *ex vivo*/*in vitro*, animal *in vivo*/*in vitro*, computational/*in silico*, or preclinical-platform evidence. Animal and computational studies support biological plausibility only and are not treated as evidence of diagnostic performance or clinical utility.

4.1 The biological interaction between spermatozoa, seminal plasma, and the female reproductive tract

Comparative mammalian evidence indicates that only a small fraction of deposited sperm reaches the oviduct and approaches the oocyte (Eisenbach and Giojalas, 2006). This attrition reflects selection involving sperm, SP, and the female reproductive tract (FRT); quantitative extrapolation from nonhuman models should be interpreted cautiously.

The FRT contains coordinated biological checkpoints. Cervical mucus, uterine clearance, the uterotubal junction (UTJ), oviductal epithelial binding, and chemotactic or physical guidance can influence sperm progression. Much of the detailed checkpoint biology derives from comparative mammalian research, whereas human cross-pair studies provide the most direct evidence relevant to this review (Kölle, 2022; Soto-Heras et al., 2023; Miller, 2024; Eisenbach, 2025). Further molecular detail is summarized in Supplementary Table S1.

Oxidative stress is relevant to sperm function but is an interaction modifier rather than a partner-specific mechanism. Reactive oxygen species (ROS) generated by leukocytes or sperm can damage sperm DNA and membranes, and smoking can increase seminal leukocytes and oxidative stress while reducing antioxidant capacity (Dutta et al., 2019; Tremellen, 2008; Ribeiro et al., 2021). These changes may alter sperm performance in the FRT, but an oxidative-stress result from one partner does not establish couple-specific incompatibility.

Evidence for pair specificity is strongest when the response of the same sperm sample varies across female-derived environments. Such cross-pair effects have been reported for sperm chemoattraction or viability in follicular fluid and cervical mucus (Fitzpatrick et al., 2020). By contrast, interindividual variation in cervical mucus, uterine immune activity, or oviductal fluid alone should be described as a potential modifier until a male-by-female interaction is demonstrated.

4.2 Immunological, genetic, and biochemical compatibility aspects

4.2.1 Immunological compatibility

At the immunological level, compatibility between partners is created by the capacity of male SP to prime the female immune environment for tolerance toward paternal antigens, and by the absence of antibody-mediated immune responses that impair sperm function (Schjenken and Robertson, 2020; Silva et al., 2021; Gupta et al., 2022).

SP delivers cytokines and signaling factors, including transforming growth factor beta (TGF-β), prostaglandins, and granulocyte–macrophage colony-stimulating factor (GM-CSF), that can condition epithelial and dendritic-cell responses and promote regulatory T cells (Tregs) directed toward paternal alloantigens. Human mechanistic studies support seminal-fluid

signaling, while a mouse mating and uterine epithelial-cell study showed sperm-induced changes in uterine immune parameters (Robertson, 2005; Robertson et al., 2013; Schjenken and Robertson, 2020; Schjenken et al., 2021). Human observational studies have examined Treg profiles separately in uIF, RPL, and later placentation disorders. These phenotypes should not be pooled, and none of these observations provides a standardized diagnostic or treatment-selection biomarker.

Antisperm antibodies (ASAs) illustrate the boundary between an individual factor and a relational mechanism. Sperm-bound ASA may reflect immune responses or disruption within the male reproductive tract, whereas antibodies in the female reproductive tract can impair sperm–mucus and sperm–oocyte interactions (Silva et al., 2021; Gupta et al., 2022). Routine ASA assays do not establish that a response is specific to one particular pairing. ASA-related infertility is therefore classified here as an immunological interaction modifier unless partner specificity is directly shown.

4.2.2 Genetic compatibility

HLA-related reproductive mechanisms encompass two distinct questions: partner HLA sharing, for which clinical associations remain inconsistent, and maternal KIR recognition of fetal trophoblast HLA-C, which has a stronger biological basis but has not yielded a validated clinical test.

At the gamete level, experimental studies have reported associations between partner HLA dissimilarity and sperm performance in follicular fluid or cervical mucus, consistent with possible post-copulatory immunogenetic selection (Magris et al., 2021). These findings support pairing-dependent biological responses but do not establish a clinically useful HLA compatibility rule or prediction of pregnancy or live birth.

At placentation, maternal KIR receptors interact with trophoblast HLA-C, including a paternally inherited allele, and may modulate uterine natural killer (NK)-cell signaling. Foundational human studies chiefly concern placentation-related outcomes, particularly pre-eclampsia and recurrent pregnancy loss; they should not be extrapolated to uIF or recurrent implantation failure without phenotype-specific evidence (Hiby et al., 2004; Piekarska et al., 2021; Wasilewska et al., 2023). This is a strong conceptual example of pair dependence, but population-dependent associations do not establish deterministic causation, predictive utility, or benefit from genotype-guided treatment.

4.2.3 Biochemical compatibility

Female reproductive tract secretions contain chemoattractants, including progesterone and C-C motif chemokine ligand 20 (CCL20), that can influence sperm function (Oren-Benaroya et al., 2008; Duan et al., 2020). In a human cross-pair experiment, Fitzpatrick et al. (2020) found that follicular fluid differentially attracted sperm according to the male–female combination, independently of standard semen-quality measures. This defined-pair design demonstrates a partner interaction; it does not yet provide a clinical prediction rule.

Female hormones and exposure to seminal plasma influence oviductal fluid and the sperm reservoir (Kölle, 2022). These observations establish a biologically interactive environment, but partner specificity should be claimed only where responses have been compared across defined male–female combinations. Follicular-fluid cross-pair studies therefore provide more direct evidence of couple biocompatibility than general descriptions of oviductal physiology.

4.3 Influence on sperm survival, migration, and implantation potential

The following stages illustrate where individual prerequisites and relational mechanisms meet. Evidence that a factor affects sperm survival within the female reproductive tract, migration toward the oocyte, or embryo implantation is not sufficient to classify it as partner-specific; the relevant outcome must depend on the biological pairing.

4.3.1 Sperm survival

Sperm survival within the female reproductive tract is actively regulated. Cervical mucus, uterine immune activity, and oviductal epithelial binding can influence sperm passage and viability (Menge et al., 1982; Schjenken and Robertson, 2020; Kölle, 2022). These processes create opportunities for partner-dependent effects, but pair specificity should be inferred only from studies that compare defined sperm–female environment combinations.

4.3.2 Sperm migration

Sperm migration through the female reproductive tract involves thermotaxis, rheotaxis, and chemotaxis (Eisenbach, 2025). The clearest pair-dependent evidence concerns chemotaxis: Fitzpatrick et al. (2020) found that human follicular fluid attracted sperm differently according to the male–female combination, independently of conventional semen measures. Computational models further show how sperm properties and tract conditions can interact, but modeling alone does not demonstrate a clinical cross-pair effect (Diemer et al., 2021).

4.3.3 Implantation potential

Implantation potential refers to the capacity of a fertilised embryo to successfully attach to and invade the endometrial lining, initiating early gestational development (Norwitz et al., 2001). Successful implantation depends on endometrial receptivity, maternal immune tolerance, adequate placentation, and coordinated molecular communication between maternal and paternal factors.

SP can alter endometrial gene expression and immune signaling. Factors including TGF-β, prostaglandins, interleukin-1 (IL-1), and tumor necrosis factor alpha (TNF-α) have been implicated in Treg and implantation-related pathways (Mayoral Andrade et al., 2020; Schjenken and Robertson, 2020; Shen et al., 2023). A randomized human *in-vivo* study reported endometrial transcriptomic changes after vaginal SP exposure (Catalini et al., 2024). These mechanistic findings support cross-partner signaling but do not establish a clinically predictive assay.

Maternal immune adaptation also involves regulatory T cells and uterine NK-cell signaling. Because fetal trophoblast HLA-C

includes a paternally inherited allele, maternal KIR–fetal HLA-C signaling represents a genuine partner- and embryo-specific interaction (Hiby et al., 2004; Robertson et al., 2013). Nevertheless, reported associations involving maternal KIR AA and fetal HLA-C2 are population-dependent and currently do not support routine genotyping or immunomodulatory treatment.

Sperm DNA integrity is an important paternal determinant of early embryonic development. Oxidative stress, environmental exposures, and defective chromatin packaging can compromise the paternal genome and may exceed the oocyte's repair capacity (Esteves et al., 2021; Zou et al., 2026). Within the present framework, SDF remains an individual sperm factor or interaction modifier unless variation in its effect is shown to depend on the female partner in a defined pairwise design.

Overall, implantation involves individual prerequisites, such as endometrial receptivity and embryo genomic competence, as well as relational mechanisms, such as maternal responses to paternal antigens and maternal KIR–fetal HLA-C signaling. Only the latter are core examples of couple biocompatibility; the former may constrain or modify those interactions.

More information regarding molecular factors in human reproduction can be found in Supplementary Table S1, provided as a supplementary document.

5 Conventional reproductive disorders and their relationship to partner-specific interactions

5.1 Female factors as individual causes and interaction modifiers

PCOS, luteal-phase dysfunction, endometriosis, and tubal disease are established female reproductive factors, but they are not inherently partner-specific. PCOS primarily impairs ovulation and may alter endometrial or decidual function, whereas luteal dysfunction may produce a suboptimal window of implantation (Carson and Kallen, 2021; Gonnella et al., 2024; Matsuyama et al., 2024). These conditions can change the environment encountered by sperm or embryos, but their presence alone should not be described as couple incompatibility.

Endometriosis may alter pelvic anatomy, inflammation, oxidative stress, and endometrial receptivity, whereas tubal disease principally compromises gamete transport; severe bilateral disease may prevent gamete interaction altogether (Shi et al., 2025; Carson and Kallen, 2021; Didziokaite et al., 2023; Gonnella et al., 2024). Where reproductive anatomy remains functional, disease-associated changes may plausibly modify gamete or embryo responses, but direct male-by-female interaction data are limited. We therefore treat these disorders as individual causes or contextual modifiers rather than evidence of partner-specific biocompatibility.

5.2 Male factors as individual causes and interaction modifiers

Male factor infertility accounts for approximately 40%–50% of infertility cases and primarily results from impairments in sperm production, function, or transport (Agarwal et al., 2021; Minhas et al., 2021; Stavros et al., 2024). Its etiology is heterogeneous and often multifactorial, with a substantial proportion of cases remaining idiopathic (Agarwal et al., 2021; Stavros et al., 2024).

OAT and varicocele are individual male-factor diagnoses. OAT reduces the number and functional competence of sperm entering the female reproductive tract, and varicocele may impair semen quality; neither diagnosis demonstrates that reproductive success varies according to the female partner (Colpi et al., 2018; Jensen et al., 2017; Minhas et al., 2021). Their relevance to this review is limited to how they constrain the male biological input available for subsequent partner interactions.

Elevated SDF has been associated with impaired embryo development, implantation, and miscarriage risk, including in some men with otherwise normal semen analyses (Minhas et al., 2021; Stavros et al., 2024; Zurera-Egea et al., 2025). Nevertheless, SDF remains an individual sperm characteristic unless a study demonstrates a differential effect across oocytes or female reproductive environments. OAT, varicocele, and SDF are therefore classified as individual factors or interaction modifiers rather than direct evidence of couple biocompatibility.

5.3 Immunological factors and relational responses

Immunological infertility spans both individual and relational mechanisms. Autoimmune disease, antiphospholipid antibodies, male ASA, chronic genital inflammation, and isolated changes in NK cells or cytokines are primarily individual immune abnormalities or nonspecific markers (Robertson et al., 2018; Yang et al., 2022; Fijak et al., 2018; Dutta et al., 2021). They may impair fertility or modify the reproductive environment, but they do not demonstrate pair-specific incompatibility without evidence that their effect depends on the partner.

Relational immune mechanisms arise when female tissues respond to male-derived antigens or when maternal receptors encounter paternal/fetal ligands. Seminal plasma and sperm can prime maternal responses to paternal antigens, while maternal KIR–fetal HLA-C signaling can influence trophoblast invasion and placentation (Hiby et al., 2004; Robertson et al., 2013; Schjenken and Robertson, 2020). These mechanisms fit the proposed concept more directly because the relevant biological signal is defined by the combination of partners.

ASAs occupy an intermediate category: they can disrupt sperm motility, mucus penetration, zona binding, and fertilization, but many arise from an individual male immune response and standard assays rarely establish partner specificity (Graczykowski et al., 1998; Fijak et al., 2018; Leathersich and Hart, 2022). They are therefore treated as interaction modifiers unless a pair-specific response is demonstrated.

5.4 Unexplained infertility as a context for interaction hypotheses

Unexplained infertility is diagnosed when standard evaluation identifies no explanatory ovulatory, tubal, uterine, or conventional semen abnormality; approximately 15%–30% of couples undergoing infertility evaluation receive this diagnosis (Carson and Kallen, 2021; Guideline Group on Unexplained Infertility et al., 2023). The

TABLE 1 **Conceptual classification, evidence maturity, and clinical status of proposed partner-specific, partner-interaction, downstream outcome, and adjacent reproductive tests.**

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
Paired HLA sharing or dissimilarity	Partner-specific biomarker: paired genotype relationship	Principally RPL; smaller separate RIF literature	Human observational cohorts and meta-analyses; inconsistent and population-dependent	Clinically available but not guideline-recommended	Routine partner HLA determination is not recommended	Pair-defined but without validated prediction or treatment selection (Meuleman et al., 2015, Hsiao et al., 2022, Bender Atik et al., 2023)
Maternal KIR–paternal/fetal HLA-C	Partner-specific biomarker: receptor–ligand genotype combination	Placentation disorders and RPL; smaller RIF cohorts	Human mechanistic and observational evidence; population heterogeneity; fetal allele may be inferred	Clinically available but not guideline-recommended	Unsuitable for routine diagnostic or therapeutic use	Strong conceptual interaction, but no validated clinical utility (Hiby et al., 2004, Moffett et al., 2016, Bender Atik et al., 2023)
Cross-pair sperm response to follicular fluid or cervical mucus	Partner-interaction biomarker when the same sperm sample is tested across defined female samples	Mechanistic studies relevant to uIF hypotheses	Small human *ex vivo* studies of chemotaxis, viability, or motility; no prospective live-birth validation	Research/ experimental test	No routine clinical recommendation	Core example of pair-dependent reproductive biology and a promising model for developing functional couple-specific assays; analytical standardization and prospective outcome validation are required. (Fitzpatrick et al., 2020)
Partner-derived seminal-plasma exposure with maternal response readout	Partner-interaction biomarker only when material from the defined male partner is used	Implantation-related mechanistic research	Human mechanistic/ transcriptomic studies plus animal causal models	Research/ experimental test	No routine clinical recommendation	Defined-partner exposure models may enable functional assessment of paternal–maternal immune communication; isolated maternal cytokine or Treg measurements alone do not demonstrate pair specificity. (Robertson et al., 2013, Catalini et al., 2024)
Post-coital test	Partner-interaction readout in the couple context	Historical infertility and uIF evaluation	Human studies and randomized evidence show poor reproducibility and no outcome benefit	Clinically available but not guideline-recommended	Not recommended in routine infertility or uIF evaluation	Direct in concept but clinically obsolete (Oei et al., 1998, Penzias et al., 2021, Guideline Group on Unexplained Infertility et al., 2023)

(*Continued*)

TABLE 1 Continued

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
In-vitro sperm–cervical-mucus penetration or cross test	Partner-interaction readout only when defined partners are paired	Historical infertility evaluation	Human *in-vitro* studies; heterogeneous methods and limited predictive value	Research/ experimental test	Not recommended routinely	Donor or pooled mucus tests are sperm-function assays, not pair-specific biomarkers (Ola et al., 2003)
Defined-pair sperm–endometrium co-culture	Partner-interaction biomarker	Pre-implantation mechanistic research	Human *in-vitro* and animal co-culture studies; no standardized clinical endpoint	Research/ experimental test	No routine clinical recommendation	Defined-pair co-culture provides a promising experimental platform for identifying individualized sperm–endometrial responses; clinical translation will require standardized partner-derived models and validated reproductive endpoints. (Ajdary et al., 2020, Murdica et al., 2020)
Sperm penetration, zona binding, acrosome reaction, and capacitation assays	Usually a downstream male-function biomarker; interaction only with defined female material	Selected male-factor or fertilization research	Human laboratory studies; methods and thresholds vary	Research/ experimental test	Not recommended as routine compatibility testing	Functional information does not by itself demonstrate pair dependence (Oehninger et al., 2014)
IZUMO1–JUNO, HSPA2, and SPACA3 assays	Fertilization-interaction mechanism; not a validated biomarker	Molecular fertilization research	Bovine, mouse, human-sperm/ hamster-oocyte, *in silico*, and early human donor-sperm studies	Preclinical/ mechanistic approach	No clinical recommendation	No validated pregnancy or live-birth prediction (Hamze et al., 2020, Stepanenko et al., 2022, Cots-Rodríguez et al., 2026)
Direct and indirect antisperm-antibody assays	Downstream individual immune marker or interaction modifier	Selected male-factor evaluation; not routine uIF testing	Human clinical associations; heterogeneous assays and thresholds	Clinically available but not guideline-recommended	Not recommended in the initial male or routine uIF evaluation; selected use only if management may change	A positive result is not a general compatibility diagnosis (Brannigan et al., 2024, Guideline Group on Unexplained Infertility et al., 2023)
SDF assays: TUNEL, SCSA, SCD, or Comet	Downstream male outcome biomarker	Selected male-factor and otherwise unexplained RPL contexts	Human clinical associations; assay and threshold heterogeneity; no pair-specific effect	Clinically available but not guideline-recommended	Not routine in uIF with normal semen; may be considered selectively in RPL, with unproven treatment benefit	Not evidence of partner incompatibility (Stavros et al., 2024, Practice Committee of the American Society for Reproductive Medicine, 2026b)

(*Continued*)

TABLE 1 Continued

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
Seminal ROS or oxidative-stress assays	Downstream male-compartment biomarker	Male-factor research and selected clinical settings	Human association studies; heterogeneous platforms and thresholds	Clinically available but not guideline-recommended	No recommendation as a compatibility test	Oxidative stress may modify interaction conditions but is not pair-defined (Dutta et al., 2019)
Peripheral NK-cell number or phenotype	Downstream maternal immune biomarker	Separate RPL and RIF studies	Small heterogeneous human observational studies; not a proxy for uterine NK cells	Clinically available but not guideline-recommended	Not recommended in RPL or RIF	Cell number, phenotype, and cytotoxicity are distinct measurements (Bender Atik et al., 2023, ESHRE Working Group on Recurrent Implantation Failure et al., 2023)
Peripheral NK-cell cytotoxicity	Downstream maternal immune-function biomarker	Mainly RPL cohorts	Human observational studies with inconsistent prognostic findings; stress-sensitive	Clinically available but not guideline-recommended	Not recommended in RPL or RIF	Not interchangeable with NK-cell number or uterine measurements (Hadinedoushan et al., 2007, Katano et al., 2013)
Uterine/endometrial NK-cell abundance or phenotype	Downstream maternal tissue biomarker	Separate RPL and RIF studies	Cycle- and assay-dependent human observational studies; inconsistent prediction	Clinically available but not guideline-recommended	Not recommended in RPL or RIF	Not partner-specific unless a defined ligand interaction is measured (Tuckerman et al., 2007)
Peripheral cytokine profiles	Downstream maternal systemic biomarker	RPL, RIF, or mixed cohorts	Small heterogeneous observational studies; no standardized thresholds	Clinically available but not guideline-recommended	Not recommended in clinical RPL or RIF assessment	Peripheral concentrations do not represent the uterine compartment (Makhseed et al., 2001, Kwak-Kim et al., 2003)
Endometrial or uterine-fluid cytokine profiles	Downstream female-compartment biomarker unless a defined paired exposure is used	Exploratory RIF studies	Small human observational studies; timing and platform heterogeneity	Research/ experimental test	Not recommended routinely	Local and peripheral cytokines must not be pooled (Lédée-Bataille et al., 2004)
Complement C3/ C4 or activation markers	Downstream maternal immune biomarker	RPL, antiphospholipid-positive cohorts, and adverse pregnancy outcomes	Human association studies plus mechanistic models; not an infertility-compatibility test	Clinically available but not guideline-recommended	No routine standalone role in infertility or compatibility testing	Established laboratory assays for other indications do not establish reproductive utility (Nalli et al., 2021)
Isolated Treg abundance or phenotype	Downstream maternal immune biomarker	Mechanistic and small observational reproductive studies	Human observational and animal mechanistic evidence; no standardized assay or threshold	Research/ experimental test	No routine recommendation	Not partner-specific unless antigen-specific pair dependence is demonstrated (Robertson et al., 2018)

(*Continued*)

TABLE 1 Continued

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
Antiphospholipid-antibody testing	Adjacent antiphospholipid syndrome (APS) investigation outside the compatibility taxonomy	RPL	Validated clinical evidence for a defined phenotype	Guideline-supported test	Recommended within the evidence-based RPL work-up	A clinically relevant comparator, not evidence for broader immune-compatibility panels (Bender Atik et al., 2023, Practice Committee of the American Society for Reproductive Medicine, 2026b)
ERA and other endometrial transcriptomic panels	Downstream female outcome biomarker	Implantation timing and RIF-related use	Human observational and trial evidence; limited reproducibility and no clear routine live-birth benefit	Clinically available but not guideline-recommended	Not recommended routinely as an add-on or compatibility test	Measures an endometrial compartment, not a partner interaction (ESHRE Add-ons Working Group et al., 2023)
Uterine-fluid extracellular-vesicle, miRNA, mRNA, or proteomic panels	Downstream female-compartment biomarker	Implantation and receptivity research	Human exploratory multi-omics studies; no validated thresholds or outcome utility	Research/ experimental test	No routine recommendation	These approaches offer minimally invasive access to molecular features of the reproductive environment and could contribute to future multi-parametric couple assessment; pair specificity requires demonstration of a defined partner-dependent response (Giacomini et al., 2021, Apostolov et al., 2025)
Semen or isolated seminal-plasma omics panels	Downstream male-compartment biomarker	Male fertility and ART-outcome research	Human discovery studies and systematic reviews; limited external validation	Research/ experimental test	No routine compatibility recommendation	Seminal-plasma multi-omics may characterize the male molecular input into couple-level reproductive interactions and could contribute to integrated pair-specific models when linked to a defined female-partner response (Llavanera et al., 2022, van den Berg et al., 2024)

(*Continued*)

TABLE 1 Continued

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
AI embryo assessment or time-lapse scores	Downstream embryo/ outcome model	Embryo prioritization and ART outcome prediction	Predominantly retrospective human datasets; limited randomized evidence and transportability concerns	Clinically available but not guideline-recommended	Not guideline-supported as a compatibility test or for widespread outcome-improving use	Predicted outcome is not proof of a partner mechanism (Practice Committee of the American Society for Reproductive Medicine, 2026a)
Integrated multi-omics or AI prediction models	Downstream reproductive outcome model unless an interaction term is prospectively tested	Specified ART endpoints	Computational or retrospective modeling; limited external and prospective validation	Research/ experimental test	No routine recommendation	Integration of molecular, cellular, clinical, and partner-interaction data represents a promising route toward multidimensional couple-specific prediction models. Future models should incorporate explicit partner-interaction terms and validate distinct reproductive endpoints prospectively
CFTR and expanded carrier screening	Adjacent pair-level inherited-risk test outside the compatibility taxonomy	Preconception or pregnancy carrier assessment	Established analytical and clinical validity for defined Mendelian risks	Guideline-supported test	Supported for defined preconception/ pregnancy indications with counseling	Pair-level inherited risk, not a functional compatibility assay (American College of Obstetricians and Gynecologists Committee on Genetics, 2017, Deignan et al., 2023)
Parental karyotyping	Adjacent individual/ couple inherited-risk test outside the compatibility taxonomy	Risk-assessed RPL and selected infertility indications	Established cytogenetic test with indication-specific yield	Established clinical test	Guideline-supported only for defined indications after risk assessment	Does not measure biological interaction between partners (Bender Atik et al., 2023)
PGT-M	Embryo/inherited-risk test outside the compatibility taxonomy	Defined monogenic disease risk	Established clinical laboratory method for a specified familial variant	Guideline-supported test	Supported for defined monogenic indications with counseling	Not a euploidy or compatibility test (Practice Committee and Genetic Counseling Professional Group of the ASRM, 2023)
PGT-SR	Embryo/inherited-risk test outside the compatibility taxonomy	Parental structural chromosomal rearrangement	Established indication-specific laboratory method	Established clinical test	Indication-specific use with genetic counseling	May not distinguish a normal embryo from a balanced carrier, depending on method

(*Continued*)

TABLE 1 Continued

Test or approach	Measurement and biomarker category	Phenotype or indication	Evidence basis/model	Clinical status	Current clinical position	Interpretation and translational potential
PGT-A	Downstream embryo chromosomal-status test	Embryo prioritization in IVF	Established laboratory method; benefit varies by population and endpoint	Established clinical test	Not recommended as universal IVF screening	Assesses sampled embryo chromosomal status, not partner compatibility (Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2024)
Generic organoid, assembloid, microfluidic, or organ-on-chip models	Experimental platform rather than a biomarker	Mechanistic reproductive research	Human or nonhuman *in-vitro* bioengineering and device-development studies	Preclinical/ mechanistic approach	No clinical recommendation	Pair-specific only if defined partners and prespecified functional outcomes are used
Computational sperm-migration or systems-biology models	Model rather than a biomarker	Mechanistic or ART-outcome research	In-silico simulation or retrospective prediction	Preclinical/ mechanistic approach	No clinical recommendation	Useful for hypothesis generation; not evidence of diagnostic performance (Diemer et al., 2021)

Conceptual classification and clinical status are independent. "Clinically available" does not imply analytical validity, clinical validity, or clinical utility. Guideline support applies only to the phenotype and indication stated. Routine infertility, uIF, RIF, RPL, and ART-outcome prediction are not interchangeable indications.

residual category may contain occult individual abnormalities or interaction-dependent mechanisms, but uIF is not evidence of couple biocompatibility.

Couple biocompatibility is most plausibly investigated in unexplained infertility when studies test a defined cross-partner mechanism, such as differential sperm responses to a woman's reproductive tract secretions or a maternal KIR–paternal/fetal HLA-C combination. Isolated SDF, endometrial receptivity, or immune-marker abnormalities should remain classified as individual factors or modifiers unless a pair-specific interaction is demonstrated.

Future studies should use crossover or factorial designs that separate male and female main effects from a true male-by-female interaction and should evaluate clinically meaningful outcomes, including live birth.

6 Clinical status and conceptual classification of proposed tests and assays

To avoid equating biological plausibility with clinical utility, each method is classified independently by what it measures and by its clinical status. A partner-specific biomarker is a paired variable defined by the particular reproductive combination, such as partner HLA sharing or a maternal KIR–paternal/fetal HLA-C combination. A partner-interaction biomarker is a functional readout generated by directly combining biological material from defined partners, such as the response of sperm to follicular fluid from the female partner. A downstream reproductive outcome biomarker is measured in one partner, one compartment, or an embryo and is associated with an endpoint without demonstrating pair dependence. SDF, isolated endometrial transcriptomics, immune profiles, fluid-derived omics markers, and AI embryo scores fall into this third category unless a true interaction design is used. Carrier screening, parental karyotyping, PGT-M, PGT-SR, PGT-A, and antiphospholipid-antibody testing are adjacent indication-specific tests outside the compatibility-biomarker taxonomy.

Clinical status is assigned separately as established clinical test, guideline-supported test, clinically available but not guideline-recommended, research/experimental test, or preclinical/mechanistic approach. Guideline support applies only to the stated indication and phenotype. Clinical availability does not establish analytical validity, clinical validity, or clinical utility, and no current partner-specific or partner-interaction assay is validated for routine diagnosis of general couple biocompatibility. Table 1 applies both axes to every proposed method.

6.1 Couple-defined genetic markers and adjacent inherited-risk tests

6.1.1 Partner HLA sharing and phenotype-specific associations in RPL and RIF

Partner HLA sharing has principally been investigated in recurrent pregnancy loss (RPL), with a smaller and separate retrospective literature in recurrent implantation failure (RIF). RPL concerns loss after conception, whereas RIF is an ART-specific non-implantation phenotype. Associations in either group do not constitute evidence for uIF. HLA-sharing results vary by locus, population, study design, and phenotype, and HLA dissimilarity should not be described as required for implantation.

Paired HLA-DQA1/DQB1 typing is a partner-specific biomarker that is clinically available in some specialist settings but not guideline-recommended. RPL-focused studies and meta-analyses report inconsistent, population-dependent associations (Meuleman et al., 2015; Hsiao et al., 2022). Shetty et al. (2024) included separate RPL and RIF groups, but its retrospective allele-frequency findings do not establish cross-phenotype prediction or treatment-selection utility. The European Society of Human Reproduction and Embryology (ESHRE) does not recommend routine HLA determination, apart from a narrow possible explanatory or prognostic role for specified maternal HLA class II alleles in Scandinavian women with secondary RPL after the birth of a boy; this exception does not support general partner HLA matching (Bender Atik et al., 2023).

6.1.2 KIR–HLA-C interactions between mother and embryo

Maternal KIR and paternal HLA-C genotyping is a partner-specific genotype biomarker that is clinically available in some settings but not guideline-recommended. It estimates a potential maternal KIR–fetal HLA-C interaction but does not always identify the allele inherited by an embryo when the father is heterozygous. The evidence supports mechanism and association, not a validated diagnostic or treatment-selection test (Piekarska et al., 2021; Piekarska et al., 2022; Bos and Colucci, 2024).

Extravillous trophoblast expresses maternal and paternal HLA-C allotypes recognized by maternal KIR receptors (Hiby et al., 2010). Most foundational studies concern placentation-related outcomes, particularly pre-eclampsia and RPL. These findings should not be extrapolated to uIF or RIF without phenotype-specific evidence. Associations involving maternal KIR AA and fetal HLA-C2 are population-dependent, incompletely replicated, and do not establish causal placental impairment (Hiby et al., 2004; 2010; 2014).

Small retrospective studies have explored HLA-C-based donor selection or granulocyte colony-stimulating factor (G-CSF) treatment in selected KIR/HLA-C groups (Cozzolino et al., 2024; Seles et al., 2024). These studies demonstrate feasibility but not clinical utility. The lack of prospective randomized validation, population-dependent allele frequencies, and a validated treatment-selection threshold precludes using KIR/HLA-C results to select donors or immunomodulatory treatment in routine care.

KIR and HLA-C frequencies differ substantially among populations, and reported associations have not been uniformly replicated (Moffett and Shreeve, 2023). Current ESHRE guidance does not recommend routine KIR/HLA genotyping and considers KIR/HLA-C typing unsuitable for diagnostic or therapeutic use at present (Moffett et al., 2016; Bender Atik et al., 2023).

6.1.3 CFTR, chromosomal translocations, and expanded carrier screening

Cystic fibrosis transmembrane conductance regulator (CFTR) carrier screening and expanded carrier screening are adjacent inherited-risk tests rather than compatibility biomarkers. Current American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) guidance support CFTR carrier screening in preconception or pregnancy care, with partner testing when one carrier is identified (American College of Obstetricians and Gynecologists Committee on Genetics, 2017; Deignan et al., 2023). When both partners carry pathogenic variants in the same autosomal-recessive condition, counseling may include preimplantation genetic testing for monogenic conditions (PGT-M), donor gametes, or prenatal diagnosis. These established, indication-specific applications estimate inherited risk and do not validate a functional biocompatibility construct.

Expanded carrier screening (ECS) can assess both partners across many autosomal-recessive and X-linked conditions and can identify at-risk couples who would not be detected by targeted screening alone. Sequential or parallel couple testing is increasingly used in preconception and *in-vitro* fertilization (IVF) settings, although implementation varies. ECS is an inherited-risk assessment with indication-specific counseling implications, not a functional compatibility test (Gregg et al., 2021; Capalbo et al., 2021; 2024; Wang et al., 2023b).

Chromosomal translocations are an established reproductive-risk category: although balanced in one partner, they can generate unbalanced gametes and embryos, with risk varying by the rearrangement and cytogenetic features (Scriven et al., 2001; Bender Atik et al., 2023). In RPL, parental karyotyping should be considered after individual risk assessment. When a balanced rearrangement is identified, preimplantation genetic testing for structural rearrangements (PGT-SR) can identify embryos predicted not to carry an unbalanced product; depending on the method, it may not distinguish a chromosomally normal embryo from a balanced carrier. An improvement in cumulative live birth over expectant management has not been consistently demonstrated (Ikuma et al., 2015; Li et al., 2022; Shetty et al., 2022).

6.2 Immunological measurements: clinical tests and experimental biomarkers

6.2.1 Antisperm antibodies in semen, serum, or cervical mucus

The best-established clinical effect of ASA is impaired sperm-cervical-mucus interaction. Human studies linked sperm-bound or cervical-mucus ASA with impaired mucus penetration and

TABLE 2 Immune mechanisms, candidate biomarkers, phenotype-specific evidence, and clinical recommendations.

Measurement	Biological role and compartment	Evidence model and phenotype	Biomarker relation	Clinical status	Current recommendation and interpretation	Key references
Seminal-plasma/paternal-antigen response	Female epithelial, dendritic-cell, cytokine, or Treg response after exposure	Human mechanistic studies plus animal causal models; no validated prognostic threshold	Partner interaction only with a defined male partner's material	Research/experimental test	Promising model of partner-specific immune communication when the response is measured after exposure to material from the defined male partner; isolated cytokine or Treg measurements are not pair-specific	Robertson et al. (2013); Catalini et al. (2024)
Maternal KIR–paternal/fetal HLA-C	Maternal uterine NK-cell recognition of trophoblast ligand	Human observational RPL and placentation studies; smaller RIF cohorts	Genuine pair-defined genotype interaction	Clinically available but not guideline-recommended	One of the clearest biological examples of pair-defined immunogenetic interaction; current evidence does not yet support routine diagnostic or treatment selection	Hiby et al. (2004); Moffett et al. (2016) Bender Atik et al. (2023)
Peripheral NK-cell number or phenotype	Systemic innate-immune state measured by blood flow cytometry	Heterogeneous RPL and RIF associations; no validated threshold	Downstream maternal biomarker	Clinically available but not guideline-recommended	Not recommended; not a proxy for uterine NK cells or cytotoxicity	Bender Atik et al. (2023); ESHRE Working Group on Recurrent Implantation Failure et al. (2023)
Peripheral NK-cell cytotoxicity	Systemic effector function; stress-sensitive functional assay	Observational RPL evidence with inconsistent prognosis	Downstream maternal biomarker	Clinically available but not guideline-recommended	Not recommended in RPL or RIF.	Hadinedoushan et al. (2007); Katano et al. (2013)
Uterine/endometrial NK-cell abundance or phenotype	Local tissue remodeling, vascular adaptation, and trophoblast interaction	Cycle- and assay-dependent RPL/RIF studies; inconsistent prediction	Downstream maternal biomarker unless a defined ligand interaction is measured	Clinically available but not guideline-recommended	Not recommended; cell number and phenotype are distinct from blood measurements	Tuckerman et al. (2007)
Peripheral cytokines	Systemic inflammatory milieu in serum or plasma	Small heterogeneous RPL, RIF, or mixed cohorts	Downstream maternal biomarker	Clinically available but not guideline-recommended	Not recommended; no standardized prognostic or treatment-selection threshold	Makhseed et al. (2001); Kwak-Kim et al. (2003)
Endometrial or uterine-fluid cytokines	Local implantation-related signaling	Exploratory RIF studies; timing and platform heterogeneity	Downstream female biomarker unless a paired exposure assay is used	Research/experimental test	Research only; do not pool with peripheral cytokine results	Lédée-Bataille et al. (2004)
Treg frequency, phenotype, or function	Immune tolerance to paternal antigens in blood or endometrium	Mechanistic and small observational human studies plus animal evidence	Downstream maternal biomarker unless antigen-specific pair dependence is shown	Research/experimental test	No standardized assay or clinical threshold; research only	Robertson et al. (2018)

(*Continued*)

TABLE 2 Continued

Measurement	Biological role and compartment	Evidence model and phenotype	Biomarker relation	Clinical status	Current recommendation and interpretation	Key references
Complement components or activation products	Innate defense, inflammation, and tissue remodeling	Associations mainly in RPL, APS, and adverse pregnancy outcomes	Downstream maternal/systemic biomarker	Clinically available but not guideline-recommended	No routine standalone role in infertility or compatibility assessment	Nalli et al. (2021)
Antiphospholipid antibodies	APS-related thrombotic and placental pathology	Validated indication-specific RPL evidence	Adjacent APS investigation, not a compatibility biomarker	Guideline-supported test	Recommended in the evidence-based RPL work-up; does not validate broader immune panels	Bender Atik et al. (2023); Practice Committee of the American Society for Reproductive Medicine (2026b)

Antiphospholipid-antibody testing is included as a clinically relevant comparator. It is an established, indication-specific RPL, investigation, not evidence of partner-specific immune compatibility.

subsequent fertility but did not establish a general pair-specific compatibility marker (Kremer and Jager, 1992; Menge et al., 1982).

Cervical-mucus ASA appear uncommon but may be clinically relevant in selected cases. In a prospective study of 192 patients with long-standing infertility, Eggert-Kruse et al. (1993) found an incidence below 2%; all ASA-positive women had a negative PCT, and no pregnancy occurred during more than 12 months of follow-up among women with a positive indirect mixed antiglobulin reaction (MAR) test. This small study supports a selected association, not routine screening or partner-specific diagnosis.

The WHO sixth semen manual lists ASA assessment among extended semen examinations and describes indirect immunobead testing for sperm-free fluids (World Health Organization, 2021). ESHRE does not recommend ASA testing in semen when semen analysis is normal, serum ASA testing in either partner, or the PCT in uIF. The American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) guideline likewise advises against ASA testing in the initial male evaluation (Schlegel et al., 2021; Brannigan et al., 2024; Guideline Group on Unexplained Infertility et al., 2023).

Direct mixed antiglobulin reaction (MAR) or immunobead tests and indirect serum or cervical-mucus assays are individual immune measurements or interaction modifiers, not partner-specific biomarkers. They are clinically available but not guideline-recommended for routine infertility or uIF evaluation; selected use may be considered when marked sperm agglutination or suspected obstruction means the result could change management (Gupta et al., 2022).

6.2.2 Immune mechanisms and candidate biomarkers: NK cells, cytokines, tregs, complement activation

Reproductive immunology encompasses analytically distinct measurements. Peripheral-blood NK-cell abundance, peripheral NK-cell cytotoxicity, uterine or endometrial NK-cell abundance and phenotype, circulating cytokines, local endometrial cytokines, Treg measurements, and complement components sample different compartments and functions. They must not be treated as interchangeable indicators of immune compatibility. Except for a defined maternal response to paternal antigen or a maternal receptor–paternal/fetal ligand combination, these are maternal immune-state or downstream compartment biomarkers rather than partner-specific biomarkers.

Peripheral NK-cell assays measure circulating cell number, phenotype, or cytotoxicity; uterine or endometrial assays evaluate tissue-resident cells, usually by immunohistochemistry or flow cytometry. Peripheral and uterine NK cells differ in phenotype and function, their measured abundance does not correlate reliably, and uterine NK-cell abundance varies with cycle timing. Cell number, phenotype, and cytotoxicity are distinct measurements and should not be used as proxies for one another.

Evidence is phenotype-specific and inconsistent. In RPL cohorts, Hadinedoushan et al. (2007) reported increased peripheral NK cytotoxicity and IL-2, whereas Katano et al. (2013) found that elevated peripheral NK activity did not independently predict subsequent miscarriage. Tuckerman et al. (2007) found that peri-implantation uterine NK-cell counts did not predict subsequent pregnancy outcome in women with recurrent miscarriage. These findings concern RPL and do not establish biomarkers for uIF or RIF; peripheral NK measurements may also reflect stress-related mobilization (Shakhar et al., 2006).

Current phenotype-specific guidance reflects this uncertainty. ESHRE does not recommend peripheral or uterine NK-cell testing in RPL or RIF, and ASRM emphasizes that immune tests and interventions in ART are limited by weak, heterogeneous evidence (Penzias et al., 2018; Bender Atik et al., 2023; ESHRE Working Group on Recurrent Implantation Failure et al., 2023). Parallel recommendations do not imply that the phenotypes or assays are biologically equivalent.

Peripheral cytokine concentrations and local endometrial cytokine expression are distinct. Small observational studies in RPL reported systemic inflammatory profiles (Makhseed et al., 2001), mixed cohorts included both recurrent loss and multiple failed implantations after IVF (Kwak-Kim et al., 2003), and local

uterine cytokine studies addressed ART-defined RIF (Guo et al., 2022; Lédée-Bataille et al., 2004). These results should not be pooled across phenotype or specimen type. No cytokine profile has a standardized threshold or validated prognostic or treatment-selection utility.

Tregs have a biologically plausible role in tolerance to paternal antigens, but Treg frequency or phenotype in blood or endometrium is not itself partner-specific, and no standardized clinical assay or threshold has been validated. Complement activation is a separate innate-immune pathway. Serum C3, C4, and activation products have mainly been studied in RPL, adverse pregnancy outcomes, and antiphospholipid-positive populations; complement profiling is not a routine infertility or compatibility test (Girardi et al., 2006; Chighizola et al., 2020; Nalli et al., 2021).

Antiphospholipid-antibody testing is a distinct, guideline-supported investigation in the evidence-based RPL work-up and should not be presented as validation of broader reproductive-immunology panels. By contrast, NK-cell assays, cytokine profiles, isolated Treg measurements, and complement panels lack validated routine utility for uIF, RIF, or RPL compatibility assessment (Sugiura-Ogasawara et al., 2006; Bender Atik et al., 2023; Practice Committee of the American Society for Reproductive Medicine, 2026b). Table 2 separates biological role, biomarker evidence, clinical status, and recommendation for each immune measurement.

6.3 Molecular and cellular assays: interaction models and outcome markers

6.3.1 Interaction assays between sperm and endometrial or cervical cells

The historical PCT and *in-vitro* sperm–cervical-mucus penetration or cross tests should be separated. The PCT measures a couple-context interaction *in vivo*, whereas laboratory penetration or cross tests may compare defined or donor mucus. Either may yield a partner-interaction readout only when biological material from the defined partners is paired. Despite early human studies, poor reproducibility and limited prediction prevent their use as validated compatibility tests (Moghissi, 1976; Eggert-Kruse et al., 1993; Ola et al., 2003).

However, the clinical usefulness of cervical interaction assays proved limited. A randomized trial showed that routine use of the post-coital test increased additional testing and treatment without improving pregnancy rates (Oei et al., 1998). Consistently, ASRM states that the post-coital test is no longer recommended because it is subjective, poorly reproducible, inconvenient, rarely changes management, and does not predict inability to conceive (Penzias et al., 2021). ESHRE likewise recommends that the post-coital test should not be used in couples with unexplained infertility (Guideline Group on Unexplained Infertility et al., 2023).

6.3.2 *In vitro* Co-culture systems to evaluate endometrial receptivity and sperm response

Co-culture systems are partner-interaction assays only when sperm and female tissue or secretions from the defined partners are paired. Human studies using endometrial cells, pooled samples, donor material, generic cell lines, or organoids can clarify mechanism but remain preclinical or experimental models rather than partner-specific diagnostics (Kim and Lee, 2026; Fusi et al., 1994; Guerin et al., 1997).

Human *in-vitro* studies show that endometrial-cell-derived extracellular vesicles (EVs) can be taken up by sperm and alter capacitation-associated signaling (Franchi et al., 2016; Murdica et al., 2020). By contrast, sperm-induced changes in endometrial receptivity genes, including LIF, LIFR, MUC1, VEGF, and homeobox A10 (HOXA10), were demonstrated in a mouse co-culture model (Ajdary et al., 2020). The latter supports biological plausibility but is not evidence of a human diagnostic biomarker. However, these approaches remain largely experimental. Limited standardization, small study populations, and lack of clinical validation currently restrict their application to research settings rather than routine fertility assessment.

6.3.3 Proteomic and transcriptomic outcome markers and interaction readouts

Endometrial receptivity arrays and other endometrial transcriptomic panels are downstream female outcome biomarkers, not partner-specific tests. They are clinically available but not guideline-recommended for routine add-on use because reproducibility and evidence of improved live birth remain inadequate (Díaz-Gimeno et al., 2011; Cozzolino et al., 2022; Arian et al., 2023; ESHRE Working Group on Recurrent Implantation Failure et al., 2023; ESHRE Add-ons Working Group et al., 2023). Isolated seminal-plasma omics are downstream male-compartment biomarkers, and uterine-fluid omics are downstream female-compartment biomarkers. A molecular response becomes a partner-interaction biomarker only when defined partner material is used in a paired exposure design.

Transcriptomic studies provide biological insight, but analytical reproducibility remains limited. A systematic review of 74 endometrial studies found inconsistently reported differentially expressed genes (Walker et al., 2023), and a 2024 RNA-sequencing study found no distinct endometrial profile separating implantation failure from success, although displacement of the window of implantation (WOI) remained possible (Bui et al., 2024). Earlier work identified expression differences between women with uIF and fertile controls, supporting endometrial biology without establishing a partner-specific or clinically validated marker (Altmäe et al., 2010).

A human endometrial epithelial-organoid study found that SP exposure altered receptivity-associated, immune, and hormone-response pathways; because the experiment did not establish clinical outcome prediction, it is an experimental interaction model rather than a validated test (van den Berg et al., 2025). Uterine-fluid extracellular-vesicle messenger RNA (mRNA), microRNA (miRNA), and surface-proteomic profiles are a separate, single-compartment downstream biomarker approach with potential as a liquid biopsy of endometrial state (Giacomini et al., 2021; Apostolov et al., 2025). These two evidence types should not be conflated.

Proteomic and transcriptomic studies provide valuable mechanistic information about endometrial state and male–

female molecular signaling. However, no combined partner assay has been standardized or prospectively validated, and current transcriptomic receptivity panels should not be used as first-line couple-biocompatibility tests (Aplin and Stevens, 2022; ESHRE Working Group on Recurrent Implantation Failure et al., 2023).

6.3.4 Molecular fertilization mechanisms and experimental functional assays

Sperm–oocyte recognition, sperm–cervical-mucus interaction, zona binding, capacitation, and gamete-fusion signaling are biologically important, but most proposed readouts are sperm-function or preclinical mechanistic assays rather than clinical compatibility tests. A partner interaction is demonstrated only when material from the defined pair is combined and the pair-dependent effect is analyzed (Hull et al., 1984; Ola et al., 2003; Nakano et al., 2015; Achinger et al., 2025).

IZUMO1–JUNO binding is essential for gamete fusion, while sperm–zona interactions involve proteins including heat shock protein family A member 2 (HSPA2) and sperm acrosome associated 3 (SPACA3) (Jean et al., 2019; Pacak et al., 2023; Leung et al., 2023). The cited functional assays span different evidence models: Hamze et al. (2020) developed JUNO-coated beads for bovine sperm; Stepanenko et al. (2022) combined *in silico* docking with mouse IVF and a human-sperm/hamster-oocyte penetration assay; and Cots-Rodríguez et al. (2026) evaluated a human-sperm JUNO-bead assay in donor samples without validating pregnancy or live-birth prediction. These are preclinical or early translational approaches, not validated clinical compatibility tests.

Historically, sperm–cervical mucus interaction tests and post-coital testing were used to evaluate functional compatibility between spermatozoa and the female reproductive tract. However, poor reproducibility, limited predictive value, and lack of impact on clinical management have led to their abandonment in contemporary fertility practice (Hull et al., 1984; Eamer et al., 2015).

At present, biochemical compatibility markers contribute primarily to understanding fertilization mechanisms rather than serving as validated diagnostic tools. Further development of functional assays capable of assessing real-time interactions between spermatozoa, oocytes, and female reproductive tissues may provide future opportunities for compatibility-based fertility testing.

7 Management strategies and assisted reproductive technologies

Assisted reproductive technologies (ART) are central to contemporary fertility care when natural conception is impeded by established physiological barriers or gamete dysfunction They range from intrauterine insemination (IUI) to advanced micromanipulation procedures like intracytoplasmic sperm injection (ICSI). Current ART procedures are not, however, validated as diagnostic or corrective interventions for a general couple-biocompatibility deficit.

7.1 Personalized medicine in infertility

Genetic, molecular, and computational methods may improve stratification and treatment planning in selected ART settings. Their value depends on the clinical question and level of validation; availability or predictive performance alone should not be interpreted as evidence that a couple-specific mechanism has been identified.

7.1.1 Genetic and molecular profiling

Preimplantation genetic testing comprises distinct tests with different indications. PGT-M is an established, guideline-supported test for a defined monogenic risk, and PGT-SR is an established indication-specific test when a parent carries a structural rearrangement. Preimplantation genetic testing for aneuploidy (PGT-A) assesses chromosomal status in sampled embryo-biopsy material and is clinically established but is not recommended as universal IVF screening and is not a compatibility test. Its value depends on the population, endpoint, and testing strategy (Practice Committee and Genetic Counseling Professional Group of the American Society for Reproductive Medicine, 2023; Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2024).

7.1.2 Artificial intelligence and big data integration

Artificial intelligence (AI) systems are being investigated for embryo morphology, developmental kinetics, laboratory workflow, and prediction of specified ART outcomes. Most evidence is retrospective and algorithm performance may not transport across clinics, populations, imaging systems, or laboratory protocols. AI embryo scores are downstream embryo or outcome models, not partner-specific diagnostics, and association-level prediction should not be described as evidence that a couple-specific mechanism has been identified (Mrugacz et al., 2026; Mina et al., 2025; Wu et al., 2025).

The 2026 ASRM committee opinion emphasizes limited randomized evidence that AI improves clinically meaningful IVF outcomes and recommends prospective validation, transparent reporting, bias assessment, and human oversight before widespread adoption (Practice Committee of the American Society for Reproductive Medicine, 2026a). AI availability or workflow integration therefore does not establish guideline-supported compatibility testing.

8 Future directions and emerging technologies

Bioengineering, advanced cellular models, and systems biology are expanding opportunities to investigate gamete interactions, endometrial responses, and partner-specific reproductive mechanisms (Figure 4). Together with multi-omics and computational approaches, these technologies may provide the foundation for future couple-specific diagnostic platforms. Their clinical translation will require analytical standardization,

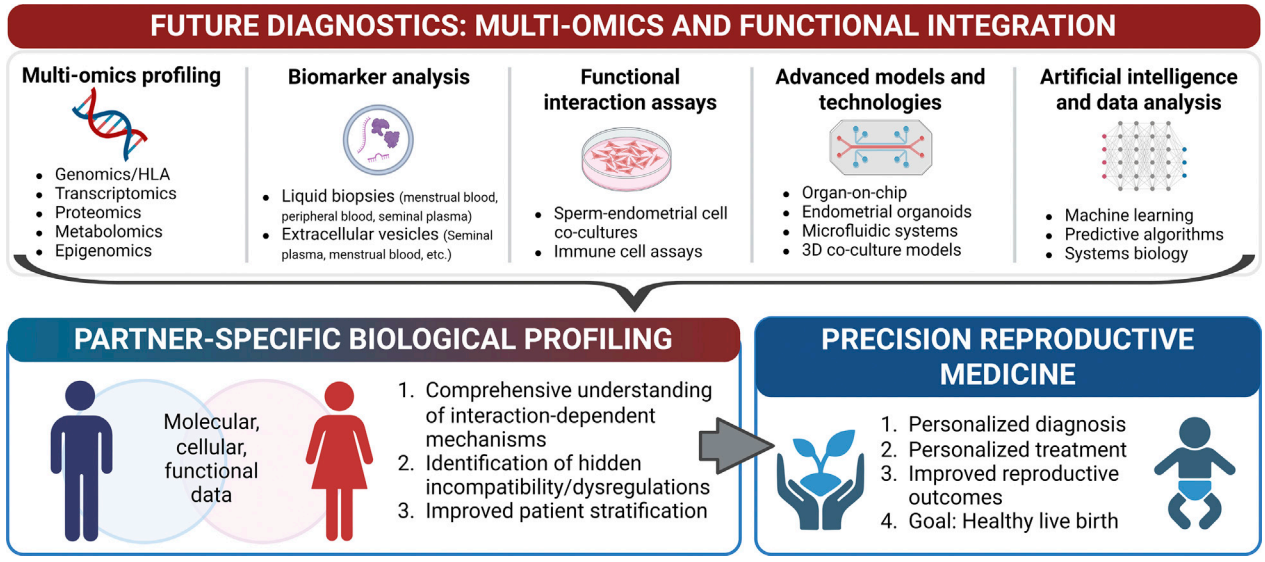


FIGURE 4
Future diagnostics and partner-specific biological profiling for a succesfull live birth. Image created using BioRender.

prospective validation, and demonstration of meaningful improvement in reproductive assessment and patient care.

8.1 Lab-on-chip and microfluidic systems for gamete interaction studies

Microfluidic and organ-on-chip platforms reproduce selected aspects of reproductive physiology under controlled flows, gradients, and cell–cell signaling conditions (Lee et al., 2025; Young and Huh, 2021; Yan et al., 2023; Deng et al., 2024; Ak et al., 2025). Current studies are *in-vitro* bioengineering or device-development studies and should be classified as preclinical or early translational. Clinical diagnostic use would require standardized defined-pair protocols and prospective association with prespecified outcomes such as fertilization, implantation, or live birth.

8.2 3D endometrial organoid and co-culture models

Three-dimensional endometrial organoids reproduce selected hormone responses and secretory features, and co-culture can model aspects of maternal–embryonic communication (Jabri et al., 2025). Saadeldin et al. (2024) is a veterinary/nonhuman organoid review; these and related human platforms remain preclinical models. Reproducibility, representation of *in-vivo* complexity, use of defined partner material, and prospective prediction of specified clinical outcomes require validation.

8.3 Non-invasive biomarkers from blood, uterine fluid, or semen

Oxidative-stress markers, microRNAs, cell-free DNA, isolated seminal-plasma biomarkers, uterine-fluid extracellular vesicles, and proteomic or metabolomic panels characterize one partner or one compartment. They are downstream reproductive outcome biomarkers rather than partner-specific diagnostics unless a defined cross-partner response is tested. Reported associations with gamete quality, implantation, or ART outcomes require external validation and standardized thresholds before clinical use (Farzizadeh et al., 2026; Volovsky and Seifer, 2024; Llavanera et al., 2022; Voros et al., 2025).

8.4 Integration of systems biology and personalized diagnostics

Systems biology, multi-omics, and AI can integrate clinical and molecular variables, but most current models are computational, retrospective, or exploratory. They should be evaluated against prespecified, stage-specific endpoints such as fertilization, blastocyst formation, implantation, clinical pregnancy, pregnancy loss, and live birth; the umbrella phrase “IVF failure” obscures biologically distinct outcomes. A model becomes evidence of partner interaction only if male and female main effects are separated from a prospectively validated interaction term (Siristatidis et al., 2021; de Santiago and Polanski, 2022; Sengupta et al., 2024).

These technologies may improve mechanistic research and preclinical modeling. Together, these technologies provide an opportunity to move from isolated biomarker assessment toward integrated reproductive profiling in which molecular, cellular, functional, and clinical characteristics of both partners are evaluated within the context of the biological pair. Prospective validation of such approaches against stage-specific reproductive outcomes will be essential for their translation into precision reproductive medicine.

9 Limitations and current challenges

Mechanistic and observational findings support the biological plausibility of partner-specific reproductive effects, but substantial challenges remain before related approaches can be integrated into routine fertility care. Most proposed markers have been investigated in relatively small cohorts, retrospective studies, or highly selected populations, while large prospective studies evaluating clinically meaningful outcomes such as live birth remain limited. Consequently, the predictive value and clinical utility of many proposed biomarkers have not been firmly established.

A further challenge is the inconsistency of findings across studies. Associations reported for HLA sharing, KIR–HLA-C interactions, cytokine profiles, NK-cell activity, endometrial receptivity markers, and SP-mediated immune responses have not always been replicated in independent cohorts. Differences in study design, patient selection criteria, laboratory methodologies, and outcome definitions contribute substantially to this variability and complicate interpretation of the available evidence.

Ethnic and population-specific variation represents another important limitation. The frequency of HLA alleles, KIR haplotypes, immune phenotypes, and other genetic factors differs considerably among populations. As a result, compatibility associations identified in one ethnic group may not be directly transferable to another, limiting the generalizability of many currently available studies.

Standardization also remains a major obstacle. Many proposed compatibility tests, including NK-cell assays, cytokine profiling, transcriptomic analyses, extracellular vesicle characterization, and sperm–endometrium interaction models, lack standardized protocols, validated reference ranges, and reproducible laboratory methodologies. This hampers comparison between studies and restricts widespread clinical implementation.

Importantly, many reported associations remain correlative rather than causal. Although disturbances in genetic, immunological, biochemical, and molecular interactions have been linked to infertility, implantation failure, recurrent pregnancy loss, and adverse pregnancy outcomes, direct evidence demonstrating that these factors independently cause reproductive failure remains limited. Infertility itself is a multifactorial condition, making it difficult to disentangle compatibility-related mechanisms from other biological and environmental influences.

Most methods discussed in this review do not directly measure a partner interaction. HLA sharing and KIR–HLA-C analyses are pair-defined markers; cross-pair sperm–fluid and defined-pair cellular assays are experimental interaction readouts; and SDF, endometrial receptivity, NK-cell measurements, cytokines, complement, isolated seminal-plasma or uterine-fluid profiles, and AI embryo scores are downstream single-compartment or embryo biomarkers. Current guidance does not support routine immune, receptivity, or genotype-based compatibility panels. Carrier screening, parental karyotyping, indication-specific PGT-M and PGT-SR, and antiphospholipid-antibody testing have separate roles and should not be relabeled as tests of couple biocompatibility.

Taken together, current evidence supports the biological relevance of couple biocompatibility, but significant scientific, methodological, and clinical challenges remain. Future studies should prioritize large multicenter prospective cohorts, standardized testing methodologies, validation across diverse populations, and evaluation of clinically meaningful reproductive outcomes before compatibility-based diagnostics can be incorporated into routine reproductive medicine.

10 Clinical and research contexts for couple biocompatibility

In uIF, the relevant research question is whether a pair-dependent mechanism explains failure to conceive after a normal standard assessment, as no compatibility assay is recommended routinely. RIF is an ART-specific phenotype and should be evaluated according to RIF guidance; NK-cell, cytokine, KIR/HLA-C, and commercial receptivity tests should not be assembled into a general compatibility panel. RPL has a separate evidence-based work-up: antiphospholipid-antibody testing and selected parental karyotyping have indication-specific roles, whereas HLA, KIR/HLA-C, NK-cell, cytokine, and complement panels are not routine compatibility tests. “Repeated ART failure” should be avoided unless the failed stage and endpoint: fertilization, transferable-embryo formation, implantation, biochemical pregnancy, clinical pregnancy, or pregnancy loss—are specified.

11 Conclusion

Human reproduction depends not only on the reproductive competence of two individuals but also on the biological interactions that emerge when they form a reproductive pair. Couple biocompatibility provides a framework for studying this currently underexplored level of reproductive biology. The strongest evidence comes from defined pair-dependent interactions, including differential sperm responses to female reproductive tract secretions, maternal adaptation to paternal antigens, and maternal KIR–paternal/fetal HLA-C interactions. Although no core partner-specific or partner-interaction assay currently qualifies as a guideline-supported clinical compatibility test, this should define the starting point for translational development. Future integration of pair-specific functional assays with multi-omics, extracellular-vesicle profiling, advanced reproductive models, and computational analysis may enable reproductive assessment to move beyond parallel evaluation of two individuals toward biologically integrated evaluation of the couple. With rigorous prospective validation against clinically meaningful outcomes, couple biocompatibility could therefore become an important component of precision reproductive medicine and provide a foundation for personalized approaches to conception.

Author contributions

KG: Investigation, Validation, Visualization, Writing – original draft. GD: Investigation, Writing – original draft.

GV: Investigation, Methodology, Writing – original draft. GK: Investigation, Methodology, Writing – original draft. PB: Investigation, Writing – original draft. IL: Investigation, Writing – original draft. RV: Investigation, Methodology, Writing – original draft. JP: Investigation, Methodology, Writing – original draft. AK: Investigation, Writing – original draft. EB: Investigation, Writing – original draft, Writing – review and editing. IU: Conceptualization, Funding acquisition, Writing – original draft, Writing – review and editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this manuscript, the authors used artificial intelligence tools solely to assist with language editing and grammar refinement of the final manuscript draft. All scientific interpretation, critical evaluation of the literature, conclusions, figures, and final manuscript content were independently reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the work.

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Supplementary material

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Glossary

ACMG	American College of Medical Genetics and Genomics
ACOG	American College of Obstetricians and Gynecologists
AMH	Anti-Müllerian Hormone
APS	Antiphospholipid Syndrome
ART	Assisted Reproductive Technology
ASA	Antisperm Antibody
ASRM	American Society for Reproductive Medicine
AUA	American Urological Association
CCL20	C-C Motif Chemokine Ligand 20
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
DFI	DNA Fragmentation Index
DNA	Deoxyribonucleic Acid
ECS	Expanded Carrier Screening
ERA	Endometrial Receptivity Analysis
ESHRE	European Society of Human Reproduction and Embryology
EV	Extracellular Vesicle
FSH	Follicle-Stimulating Hormone
HLA	Human Leukocyte Antigen
HOXA	Homeobox A
HSG	Hysterosalpingography
HSPA2	Heat Shock Protein Family A Member 2
HyCoSy	Hysterosalpingo-Contrast Sonography
HyFoSy	Hysterosalpingo-Foam Sonography
ICSI	Intracytoplasmic Sperm Injection
IL	Interleukin
IVF	*In Vitro* Fertilization
IZUMO1	Izumo Sperm-Egg Fusion Protein 1
JUNO	Folate Receptor 4 (Oocyte Receptor for IZUMO1)
KIR	Killer-cell Immunoglobulin-like Receptor
LH	Luteinizing Hormone
LIF	Leukemia Inhibitory Factor
LIFR	Leukemia Inhibitory Factor Receptor
MAR	Mixed Antiglobulin Reaction
miRNA	MicroRNA
mRNA	Messenger RNA
MSC	Mesenchymal Stromal Cell
MUC1	Mucin 1
MUC6	Mucin 6
NK	Natural Killer
OAT	Oligoasthenoteratozoospermia
PCOS	Polycystic Ovary Syndrome
PCT	Post-Coital Test
PGT-A	Preimplantation Genetic Testing for Aneuploidy
PGT-M	Preimplantation Genetic Testing for Monogenic Conditions
PGT-SR	Preimplantation Genetic Testing for Structural Rearrangements
PRL	Prolactin
RIF	Recurrent Implantation Failure
ROS	Reactive Oxygen Species
RPL	Recurrent Pregnancy Loss
RNA	Ribonucleic Acid
SP	Seminal Plasma
SPACA3	Sperm Acrosome Associated 3
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumor Necrosis Factor Alpha
Treg	Regulatory T Cell
TSH	Thyroid-Stimulating Hormone
uIF	Unexplained Infertility
UTJ	Uterotubal Junction
uNK	Uterine Natural Killer Cell
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WIN-Test	Window Implantation Test
WOI	Window of Implantation
ZP	Zona Pellucida