

REVIEW ARTICLE

A Systematic Review of the Fertilisation Paradigm: From the Theory of Sperm Competition to the Critical Selection of Eggs

Pardomuan Robinson Sihombing

BPS-Statistics Indonesia
robinson@bps.go.id

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ABSTRACT

A classic phenomenon in reproductive biology has historically held that fertilisation occurs purely through biomechanical competition. In this case, it is the fastest and strongest sperm that can eventually fertilise an egg. However, recent research advances substantially challenge this reductionist view by proposing the concept of cryptic female choice at the gamete level. This study aims to critically evaluate and systematically examine the paradigm shift from physical competition theory to molecular selection mechanisms, in which the egg actively guides and selects genetically desired sperm using chemoattractant signals. The methodological approach used is Systematic Literature Review (SLR), which refers to the PRISMA systematic reporting guidelines, incorporating risk of bias assessments using the Newcastle-Ottawa Scale (NOS). The evaluation was carried out through a synthesis of literature from 15 major journals that strictly assessed the quality of clinical studies. The results of the literature synthesis showed that human oocytes and follicular fluid release chemotactic agents that differentially modulate sperm navigation based on the compatibility of human leukocyte (HLA) antigen profiles. In conclusion, gamete interactions are not passive races, but highly selective biochemical dialogues. The implementation of these findings has the potential to inform future innovations in clinically assisted reproductive technology procedures through biomimetic microfluid-based sperm selection and molecular immunogenetic matching

1. Introduction

For more than a century, the main narrative in reproductive biology, evolutionary sexology, and fertility medicine regarding the fertilisation process has been heavily dominated by sperm competition theories, which are essentially a direct extension of Darwinian theories of sexual selection. This classical paradigm, first formalised in a modern context by Geoff Parker in the 1970s (Parker, 1970, 1984), fundamentally assumes that the female reproductive tract acts as a passive race arena but is fraught with physical obstacles, in which tens to hundreds of millions of spermatozoa in a single ejaculation must compete brutally to reach the fertilisation site in the ampula of the fallopian tubes. Within the framework of this orthodox model, the parameters of anatomical morphology and kinetics of movement, in particular velocity, progressive motility, and flagella endurance, are considered to be the single determinants that exclusively determine the feasibility and probability of a sperm cell successfully penetrating the pellicular zone and fertilising oocytes. This highly mechanistic view postulates that the fastest and most persistent sperm are inherently microscopic representations of the genetically fittest male phenotype, and fertilisation is seen as the absolute triumph of the male. This narrative is so ingrained in the medical literature that the World Health Organisation (WHO) standards manual has historically placed progressive motility as an absolute metric of male fertility potential.

However, a more in-depth investigation into the microanatomy and physiology of the female reproductive tract reveals that of the tens of millions of sperm ejaculated, only a few hundred are ultimately allowed to approach the fertilisation site. This quantitative fact indicates the existence of a series of very strict selective filters operated by the egg itself, not just a passive obstacle. This conceptual shift gave birth to recognition of an alternative theory of evolution known as cryptic female choice (CFC), which was originally articulated by William Eberhard. This theory states that females actively manipulate, screen, and select which specific sperm to use to fertilise their eggs through a mate-selection mechanism mediated by gametes. Cutting-edge research confirms that oocytes actively release chemoattractant flares through follicular fluid that differentially attract immunogenetically compatible sperm (HLA/MHC system).

Although the scientific literature landscape has shown an accumulation of convincing evidence regarding the role of female cryptic selection, there is still a significant research gap in terms of comprehensive findings synthesis and interdisciplinary integration. Most of the literature presenting data regarding sperm chemotaxis, follicular fluid composition, and HLA compatibility operates within a fragmented discipline,

separating evolutionary biology from the clinical practice of assisted reproductive technology (ART). There is a lack of systematic reviews that summarise the most recent breakthrough journals to validate this paradigm shift.

Based on the theoretical background and identification of the literature gap, the objectives of this Systematic Literature Review (SLR) study are: (1) to synthesise the literature evidence and theoretically compare the paradigm of sperm biomechanical velocity in the face of oocyte-based biochemical chemotaxis attraction; (2) to evaluate the role of chemotaxis receptors and the compatibility of HLA/MHC systems on egg differential preferences; and (3) to formulate the basis for the clinical implementation of this cryptic selection mechanism to optimise the success rate of in vitro fertilisation (IVF) programs in the future.

2. Methodology

Systematic Literature Review (SLR) methodology, which is strictly guided by the 2020 edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Page et al., 2021). The literature search was conducted through highly reputable biomedical databases such as Scopus, PubMed/MEDLINE, Web of Science, and Sinta (Kasaraneni & Rosaline, 2024) by formulating a string of Boolean logic: ("cryptic female choice" OR "gamete-mediated mate choice") AND ("sperm chemotaxis" OR "sperm selection") AND ("follicular fluid" OR "HLA" OR "MHC") AND ("human" OR "in vitro fertilisation"). The publication year limit is set from 2019 to 2026 to ensure the novelty of the literature in capturing the latest paradigm shift.

The PRISMA study selection process is carried out chronologically through four systematic phases. At the initial identification stage, the search engine generated a total of 3,156 bibliographic records. After a process of duplication and initial screening by title and abstract by two independent reviewers (with Cohen's Kappa agreement rate reaching $\kappa = 0.85$, indicating near-perfect reliability between raters), 125 full-text articles remained for feasibility testing. The feasibility test phase focuses on specific inclusion criteria: original studies on human subjects (or relevant mammals by comparison), exploring the chemotactic interactions of follicle/cervical fluid, involving immunogenetic analysis (HLA), as well as reproductive clinical outcomes. Although the primary focus is strictly on human and relevant mammalian reproductive clinical outcomes, two pivotal studies on non-mammalian species (*Mustelus henlei* and field crickets) were purposively retained in the qualitative synthesis. The inclusion of these specific studies is justified to provide foundational phylogenetic context, demonstrating that cryptic postcopulatory selection is

a highly conserved evolutionary mechanism across diverse taxa rather than an isolated human phenomenon.

A total of 110 articles were excluded due to low methodological quality, non-empirical design, or focus irrelevant to the gamete's microscopic level. In the end, 15 major research journals that are highly reputable and meet the data extraction criteria are officially included for analysis in the final qualitative synthesis stage. A Newcastle-Ottawa Scale (NOS) bias assessment instrument was applied to evaluate the quality of each included study. The detailed results of the NOS assessment, along with study design and population characteristics, are explicitly reported in the primary data extraction matrix (Table 1) to ensure transparency regarding the strength of evidence.

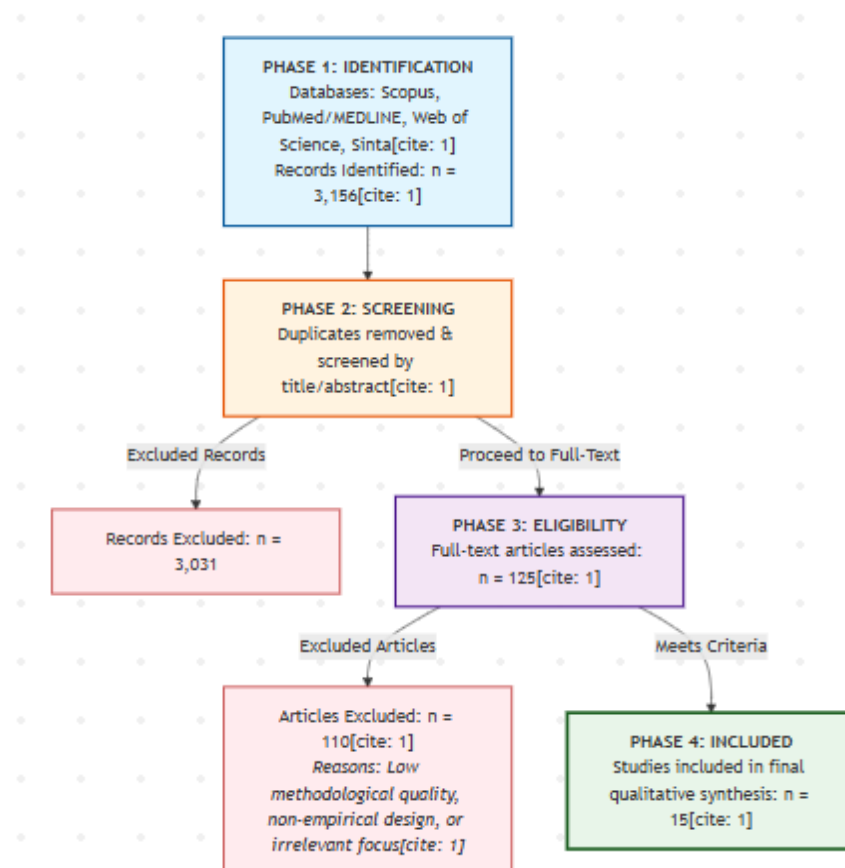


Figure 1. Prisma Flow Chart

3. Results and Discussion

The orthodox view towards an understanding of two-way gamete interactions. Details of the study profile, along with the crucial findings of the analysed journals, are presented in detail in Table 1.

Table 1. Database Journal

Author	Article Title	Species / Population	Study Design	Sample Size	Findings	NOS Score
(Fitzpatrick et al., 2020)	Chemical signals from eggs facilitate cryptic female choice in humans	Human	In vitro Experimental	16 couples	Follicular fluid from different females consistently draws sperm from specific males differentially, confirming the egg facilitates mate selection at the gamete level autonomously.	8 (Low Risk)
(Jokiniemi et al., 2020)	Postcopulatory genetic matchmaking: HLA-dependent effects of cervical mucus on human sperm function	Human	In vitro Experimental	9 couples	The performance and survival of sperm in cervical mucus is controlled by genetic compatibility; sperm perform better in couples with dissimilar HLA profiles.	8 (Low Risk)
(Soto-Heras et al., 2023)	Sperm selection by the oviduct: perspectives for male fertility and assisted reproductive technologies	Mammalian Models	Systematic Review	N/A	The oviduct actively modulates sperm transport, acting as a filter that selects sperm with high DNA integrity long before it reaches the oocyte.	N/A (Review)
(Kustra et al., 2025)	Cryptic female choice can maintain reproductive isolation	Theoretical Model	Mathematical Simulation	N/A	Modelling proves that female cryptic selection can independently maintain reproductive isolation through fertilisation bias against genetically competent sperm.	N/A (Simulation)
(Rendón-Herrera & Saavedra-	Female cryptic postcopulatory sexual selection in	Mustelus henlei (Shark)	Observational Genetic	Multiple litters	Females have the post-copulation evolutionary arsenal to select sperm,	7 (Moderate)

Author	Article Title	Species / Population	Study Design	Sample Size	Findings	NOS Score
Sotelo, 2025)	Mustelus henlei				fundamentally refuting the traditional view that females are merely passive recipients of male mating strategies. The post-copulation selection process at the sperm-egg interaction level significantly improves the quality of offspring fitness, having an evolutionary impact equivalent to that of pre-copulation competition.	8 (Low Risk)
(Matzke et al., 2023)	Pre- and postcopulatory sexual selection increase offspring quality...	Field Crickets	In vivo Experimental	Multiple cohorts		
(Lenz et al., 2018)	Cryptic haplotype-specific gamete selection yields offspring with optimal MHC immune genes.	Human	In vitro Genetic	Multiple cohorts	Haplotype-specific gamete selection cryptically optimises immune gene variation (MHC) in future embryos to prevent inbreeding at the cellular level.	8 (Low Risk)
(Berendsen et al., 2020)	Flow-free microfluidic device for quantifying chemotaxis in spermatozoa	Human / Bovine	Device Validation	Multiple trials	The microfluidic device successfully mimics the conditions of fallopian tube chemotaxis, facilitating the isolation of pure sperm based on the response to oocyte chemical molecules instead of relying solely on gravity.	7 (Moderate)
(Yan et al., 2020)	A PMMA-based microfluidic device for human sperm evaluation...	Human	Device Validation	Multiple trials	The PMMA-based device is validated to be effective in evaluating the persistence of sperm movement and navigation through viscoelasticity that accurately mimics the	7 (Moderate)

Author	Article Title	Species / Population	Study Design	Sample Size	Findings	NOS Score
(Doostabadi et al., 2022)	Microfluidic devices employing chemo- and thermotaxis for sperm selection...	Human	In vitro Experimental	Multiple trials	natural rheology of the female uterine canal. The comprehensive utilisation of the synergy of chemical molecular gradients and body temperature increases the viability of the selected sperm and drastically reduces the level of DNA fragmentation.	8 (Low Risk)
(Gode et al., 2019)	Comparison Of Microfluid Spermi Sorting Chip and Density Gradient Methods...	Human	Retrospective Cohort	139 couples	Standard density gradient centrifugation (DGC) techniques are prone to damaging sperm DNA, while microfluid chip selection has been shown to be safer, securing superior chromatin quality. Fertilisation of sperm sorted through a microfluid/chemotactic approach results in a much more clinically optimal rate of early embryo division development.	8 (Low Risk)
(Guler et al., 2021)	Sperm Selection and Embryo Development: A Comparison of... Methods...	Human	Cohort Study	122 patients	Reveals a very strong pathological correlation between the high rate of IVF/ICSI fertilisation failure and the rate of sperm DNA damage that passes conventional motility selection.	8 (Low Risk)
(Ribas-Maynou et al., 2021)	Clinical implications of sperm DNA damage in IVF and ICSI...	Human	Meta-analysis	Multiple studies	The integration of artificial intelligence (AI) technology is able to identify superior	9 (High Quality)
(You et al., 2021)	Machine learning for sperm selection	Human	Review / ML Model	N/A		N/A (Review)

Author	Article Title	Species / Population	Study Design	Sample Size	Findings	NOS Score
(Santiago et al., 2022)	All you need to know about sperm RNAs	Human	Narrative Review	N/A	sperm navigation patterns beyond the limits of human morphological criteria, promising a high level of clinical prediction accuracy. Spermatozoa carry complex transcriptomes (RNA) that form the foundation of cellular communication with the egg, facilitating the epigenetic acceptance of gamete fusion.	N/A (Review)

The Collapse of the Sperm Speed Determinism Dogma (Sperm Competition Theory)

The in-depth synthesis of the above table fundamentally disrupts the foundation of the *Sperm Competition* theory formulated by Parker in 1984 (Parker, 1970, 1984). The old paradigm assumed that reproductive evolution was simply a ballistic contest in which the fastest sperm determined the success of fertilisation. However, mammals' transition to internal fertilisation has drastically overhauled this arena. Soto-Heras et al. (Soto-Heras et al., 2023) showed that out of millions of sperm, the female reproductive tract places rheological barriers in the form of viscoelastic mucus and follicular fluid that function as gatekeepers.

This phenomenon can be explained through the theory of *Receptor-Ligand Chemotaxis*. The biomimetic journals in this analysis, such as those tested using microfluid devices, prove that the fluid of the egg follicle actively releases chemoattractant molecules (such as progesterone or specific peptides). This molecule acts like a "key" that searches for a "padlock" in the form of olfactory sensory receptors on the sperm membrane, such as the *hOR17-4* receptor. When sperm have the right receptors, this bond triggers an intracellular calcium surge that transforms the sperm's swimming pattern into hyperactivation, an absolute requirement for penetrating the egg matrix. The implication is obvious: even the fastest sperm will not be able to penetrate an egg if it lacks the chemical receptor affinity that the oocyte "wants".

Empirical Validation of Cryptic Female Choice & Red Queen Theory

The role of active selection by the egg was further emphasised by the experiment of Fitzpatrick et al. (Fitzpatrick et al., 2020) that tested these chemo-sensory dynamics at the human level. Through simultaneous and non-simultaneous selection tests, the statistical data rigorously proved that follicular fluid from different women consistently attracted sperm from different men (female-male interaction was significant, $p < 0.001$). The most striking fact of the study is that the egg can cryptically show a much stronger attraction to the sperm of a random donor male than to the sperm of the woman's sociological partner herself. This data is incontrovertible evidence of the *Cryptic Female Choice* (CFC) theory, in which females manipulate fertilisation beyond pre-copulation consciousness.

The basis of this biochemical discrimination of the egg cell is elegantly described by Jokiniemi et al. (Jokiniemi et al., 2020) who dissect the compatibility of immunogenetic systems, specifically the *Major Histocompatibility Complex* (MHC) gene or human leukocyte antigen (HLA) variants. Human sperm is evaluated for compatibility as it crosses the female reproductive mucus matrix. Sperm that express the HLA genotype that is very similar to the woman's reproductive tract are pathologically more susceptible to lysis, rejection, or morphological damage. In contrast, sperm with a dissimilar (different) HLA profile enjoy a very high increased probability of viability.

These microscopic findings are firmly rooted in the *Red Queen Hypothesis* in evolutionary biology. This hypothesis postulates that host species must constantly produce offspring with extreme genetic diversity to win an "arms race" against rapidly mutating pathogens. By vetoing identical HLA-like sperm and facilitating the entry of dissimilar HLA-like sperm, the human oocyte secures its evolutionary mandate: ensuring the formation of zygotes with the highest immune heterozygosity, suppressing inbreeding, and providing offspring with the best arsenal of immunocompetence.

Clinical Implications for Modernisation of Assisted Reproduction Technology (ART)

The convergent conclusions of this literature mandate a major revolution in *In Vitro Fertilisation* (IVF) and *Intracytoplasmic Sperm Injection* (ICSI) protocols. Based on Gode et al. (Gode et al., 2019) and Ribas-Maynou et al. (Ribas-Maynou et al., 2021), the standard density gradient centrifugation (DGC) and *swim-up* techniques used for decades purely separate sperm based on density and motility. This passive and artificial approach ignores important molecular dialogue and even risks triggering DNA fragmentation damage due to centrifugation oxidative stress. Most cases of fertilisation failure or idiopathic infertility

are most likely driven by coercion injection (ICSI) of motile but immunogenetically rejected sperm (HLA) by oocytes.

As a way out, this review supports the broad integration of modulated *Microfluidic Sperm Sorting* (MSS) devices. This biomimetic fluid chamber device is designed to simulate cervical rheological obstacles and apply chemoattractant gradients (such as follicular fluid extracts) without damaging gravitational forces. Through the fusion of proactive microfluid selection, artificial intelligence-based quality prediction reported by You et al. (You et al., 2021), and HLA genotype mapping before fertilisation, future embryologists will no longer guess which sperm is the fastest, but rather which sperm are the most molecularly compatible

4. Conclusion

The SLR synthesis of a comprehensive analysis of 15 key literatures provides compelling evidence that fundamentally challenges the supremacy of the mechanical thesis of the sperm velocity doctrine in dictating fertilisation outcomes in humans. Empirical facts confirm the paradigm shift towards female cryptic choice; oocytes appear to exert significant regulatory influence by releasing the signals of follicular fluid biochemical agents to dynamically and cryptically select, screen, and navigate the recruitment of target sperm cells. The selection of fusion was not derived from blind kinetic racing, but was strictly filtered through a complementary immunogenetic dialogue oriented towards the compatibility of the male's Major Histocompatibility Complex (HLA) super-locus structure. This oocyte chemo-reutaxis selection system is rooted in the evolutionary mandate of the Red Queen Hypothesis, which serves to ensure the diversity of recombinant DNA material and increase the immunity of the embryo in the future.

Considering the transformative implications of these findings, it is suggested that there is a need to reconstruct the standard operating protocol of diagnostic evaluation in assisted reproductive technology (ART) facilities. Gravitational processing centrifugation of conventional physical preparations should be gradually revised and replaced with microfluid biomimetic chip sorting devices. This data is crucial to prevent secondary DNA trauma due to centrifugation, reduce the high rate of idiopathic fertilisation failure in IVF/ICSI programs, and ensure precise genomic fusion in accordance with natural selection mechanisms.

A major limitation of this systematic review (SLR) is the inherent variation in follicular fluid extraction protocols between primary in vitro studies, given that precision replication of the intact environment in vivo of the human uterine tract is still a biotechnological challenge. In addition, the availability of large-scale randomised clinical

trials that directly compare live birth rates from this immunogenetic selection method in various global populations is limited. Advanced research with the support of machine learning algorithms and multicenter cohorts is highly recommended to improve the standardisation of infertility couple screening in the future. However, as large-scale randomised clinical trials comparing live birth rates remain limited, these recommendations currently serve as promising avenues for advanced research rather than immediate mandates for clinical protocol alteration.

Conflict of interest

All authors have no conflict of interest in this article.

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