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Research Article

Deciphering the Molecular Messages of Extracellular Vesicles: A New Paradigm for the Diagnosis of Male and Female Infertility

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ABSTRACT

Infertility represents one of the most significant silent public health crises today [1,2]. Progressive alterations in seminal parameters [3,4], declining ovarian reserve [5] and an earlier onset of menopause [6] are shaping a scenario of accelerated reproductive decline globally [7,8]. Extracellular vesicles (EV) nanoscale membrane-bound particles secreted by virtually all cell types—carry molecular cargo including proteins, non-coding RNAs, lipids, and metabolites that directly reflect the physiological state of their cell of origin [9,10]. This systematic review synthesizes scientific evidence published between 2020 and 2025 regarding the utility of EV as diagnostic and prognostic biomarkers in male and female infertility [11-13]. Ultimately, these findings point toward a new paradigm of precision reproductive medicine based on interpreting each patient's individual molecular profile [14,15].

KEYWORDS

Extracellular vesicles, Exosomes, Male infertility, Female infertility, Biomarkers, Ovarian reserve, Seminal parameters, Precision medicine, MiRNA, Proteomics.

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Introduction

The Global Reproductive Crisis

Over recent decades, global demographics have undergone a transformation without precedent in recorded human history [1]. Fertility rates have continuously declined across virtually every continent, pushing numerous developed and developing nations below the generational replacement threshold of 2.1 children per woman [1,7]. Far from being a simple statistical trend, this phenomenon constitutes a major public health emergency with widespread implications for demographic structures, economic sustainability, and global healthcare systems [7,8].

Demographic projections elaborated by the United Nations Population Division in its World Population Prospects 2024 report highlight the extent of this shift [7]. By the year 2050, the global population of children under age 5 is estimated to be approximately 650 million, while the population over age 85 is projected to reach 450 million [7]. By 2080, projections point

toward an unprecedented demographic inversion where adults over age 85 could outnumber children under age 5 for the first time in recorded history, reaching an estimated 530 million compared to 490 million, respectively (Figure 1) [7,8].

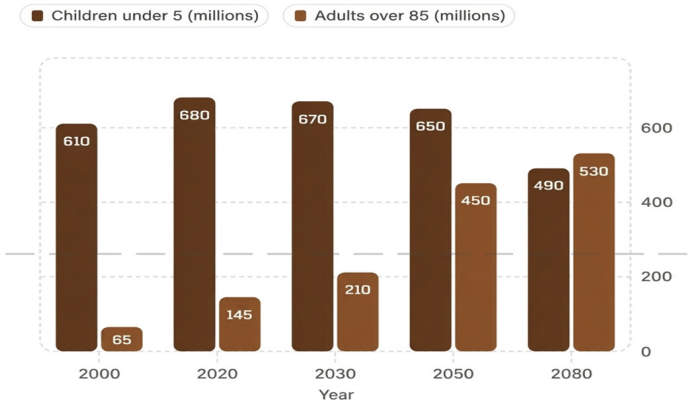

Figure 1: Global population projections for children under 5 versus adults over 85 (2000–2080). Source: UN World Population Prospects 2024 [7]; GBD 2021 Demographics Collaborators [8].

While social, cultural, and economic factors contribute significantly to this decline, biological and medical causes of infertility play an increasingly central role [2,16]. Data from the World Health Organization indicates that approximately 17.5% of the adult population worldwide experiences infertility at some point in their lives, affecting roughly 1 in 6 people across all income levels and geographic regions [2]. Within this global context, the development of precise, personalized, and prognostically powerful diagnostic tools is urgent [13,14]. Extracellular vesicles have emerged as silent molecular carriers of reproductive cell function, offering a path forward for precision reproductive medicine [9,15].

Demographic Projections: The Pyramidal Inversion

Data from the United Nations and the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease study illustrate a profound structural shift [7,8]. In the year 2000, children under age 5 outnumbered adults over age 85 by a ratio of more than 9 to 1 [7]. By 2080, this relationship is projected to completely reverse, creating an inverted population pyramid that presents unprecedented social and medical challenges [7,8]. This demographic crossing directly impacts reproductive healthcare [1,2]. As birth rates drop, each individual pregnancy acquires greater biological, social, and economic value. Consequently, enhancing success rates in assisted reproduction techniques (ART) is becoming a defining clinical priority [17,18]. Strategic investment in diagnostic innovations, such as EV-based biomarkers, fits into this broader demographic imperative [13,14].

Decline of Reproductive Parameters: Epidemiological Evidence

The reduction in human reproductive capacity extends beyond decision-making around delayed parenthood [1,16]. Robust scientific evidence demonstrates that fundamental biological parameters in both men and women are undergoing accelerated deterioration due to complex environmental, epigenetic, and metabolic factors [16,19,20].

Decline in Male Seminal Quality

A landmark meta-analysis analyzed data from over 57,000 men across 53 countries over a 40-year period, documenting a 62.3% decline in sperm concentration between 1973 and 2018, with an accelerated rate of decline observed after 1990 [3]. In parallel, World Health Organization reference standards for semen parameters have been adjusted downward over time [4]. For example, the normality threshold for sperm concentration was lowered from 20 million/mL in 1999 to 15 million/mL in 2010, and updated to 16 million/mL with adjusted percentiles in the 2021 sixth edition manual [4]. These shifting thresholds reflect a broader population-level trend toward compromised seminal parameters driven by occupational exposures, lifestyle factors, and endocrine disruption Figure 2 [16,19].

Ovarian Reserve and Premature Menopause

In female reproductive health, measures of ovarian reserve—such as anti-Müllerian hormone (AMH) levels and antral follicle count (AFC)—demonstrate declining trends among young women globally [5]. Studies indicate that up to 10% to 15% of women under age 35 present ovarian reserve parameters indicative of a poor response to controlled ovarian stimulation [17]. Additionally, the average age of natural menopause shows a downward shift in populations with higher exposure to chronic oxidative stress, adverse nutritional conditions, and endocrine disruptors [6,20]. Premature ovarian insufficiency (POI), defined as loss of normal ovarian function before age 40, currently affects 1% to 2% of women of reproductive age [6].

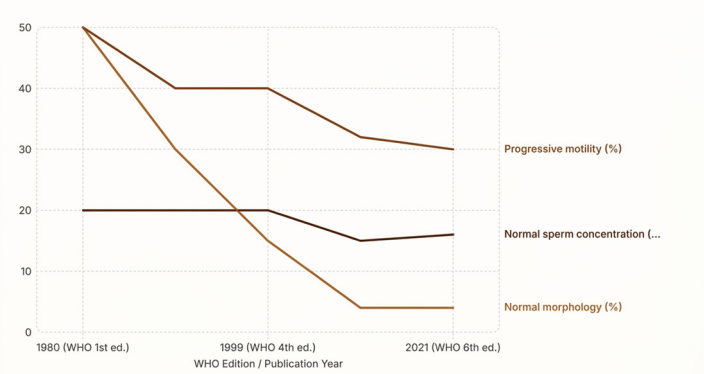

Figure 2: Evolution of WHO reference values for semen analysis across successive editions of the WHO Laboratory Manual. The progressive reduction of normality thresholds mirrors the population-level decline in male reproductive parameters. Source: WHO Laboratory Manual for Examination and Processing of Human Semen, 1st–6th editions [4].

Ovarian Reserve Trends and Temporal Evolution of Menopause

Comparative analyses between historical and contemporary cohorts demonstrate a downward shift in ovarian reserve curves across reproductive age groups [5,17]. This indicates that reduced ovarian reserve cannot be attributed solely to delayed childbearing [5]. Cumulative exposure to environmental contaminants such as bisphenol A (BPA), phthalates, and organochlorine pesticides, alongside chronic oxidative stress, altered gut microbiota, and transgenerational epigenetic changes, significantly modulates follicular health [20,21].

Because chronological age alone is an incomplete predictor of biological ovarian reserve, individualized molecular assessment is becoming necessary [17,22]. For instance, registry data from Europe and North America shows that POI prevalence has increased from approximately 0.8% to 1.9% over the past two decades [6]. Evaluating extracellular vesicles provides a novel means to study the cellular and pathogenic pathways underlying these conditions Figure 3 [9,23].

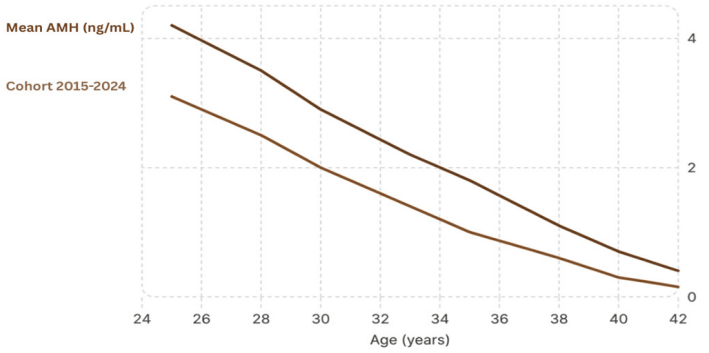

Figure 3: Comparison of mean AMH levels by age group between historical and contemporary cohorts. A downward shift of the ovarian reserve curve is observed across all age groups in the current cohort. Data adapted from Birch Petersen et al. and La Marca et al. [5,17].

Paradigm Shifts in Infertility Diagnosis

Historically, infertility diagnostics relied primarily on counting and physical observation, such as conventional semen analyses and transvaginal ultrasonography [4,24]. Modern reproductive medicine recognizes that infertility is not a simple binary state (fertile versus infertile), but rather a spectrum of biological dysfunctions with high molecular heterogeneity [22,24].

Patients presenting with similar clinical manifestations—such as severe oligozoospermia or poor ovarian response—may possess distinct underlying molecular pathologies [11,12]. This heterogeneity helps explain why standardized treatment protocols can produce varied outcomes among clinically similar patients [17,18]. Understanding these differences forms the rationale behind utilizing extracellular vesicles for precision diagnostics [13,14].

Extracellular Vesicles: Biology and Classification

Extracellular vesicles are membrane-bound lipid particles released by cells under normal and pathological conditions [9,10]. According to the International Society for Extracellular Vesicles (ISEV) consensus guidelines (MISEV2023), EV are classified into three primary subtypes based on their biogenesis, size, and biological properties [9]:

- **Exosomes (30–150 nm):** Formed within the late endosomal compartment via multivesicular bodies [10]. Enriched in tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70), and microRNAs (miRNAs) [9,10]. They mediate intercellular communication and modulate recipient cell function via cargo transfer [25].
- **Microvesicles (100–1000 nm):** Formed by direct outward budding of the plasma membrane [25]. Their biogenesis involves phospholipid rearrangement and actomyosin activity [25]. They carry membrane proteins, growth factors, and messenger RNAs, participating in the regulation of local microenvironments [9,25].
- **Apoptotic Bodies (500–5000 nm):** Released during programmed cell death [26]. They contain cell fragments, organelles, and nuclear material [26]. Their presence in reproductive biofluids often reflects cellular stress, inflammation, or structural damage within tissue microenvironments [26,27].

Methodological advances over the last five years—including size-exclusion chromatography (SEC), nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and high-throughput omics platforms—have significantly improved the isolation and characterization of EV from reproductive fluids [28,29].

Extracellular Vesicles in Male Infertility: The Male Secretome

Seminal plasma contains high concentrations of EV secreted along the male reproductive tract [11,30]. Prostasomes, the primary EV produced by the prostate, contain over 900 distinct proteins involved in metabolic regulation, membrane fusion, and immunomodulation that protect spermatozoa within the female reproductive tract [11,31].

Comparative proteomic and transcriptomic analyses show that the miRNA and protein profiles of seminal EV differ significantly between fertile and infertile individuals, exhibiting specific molecular signatures in conditions such as oligozoospermia, asthenozoospermia, and teratozoospermia [30,32]. Additionally, epididymal EV (epididymosomes) transfer proteins essential for sperm maturation, capacitation, the acrosome reaction, and sperm-oocyte interaction [31,33]. Analyzing epididymosomal cargo provides a potential diagnostic tool for cases of idiopathic male infertility where standard semen parameters appear normal (Table 1) [33,34].

Extracellular Vesicles in Female Infertility

Intercellular communication mediated by EV is equally vital to

Table 1: Diagnostic and Prognostic Applications of Seminal Extracellular Vesicles in Reproductive Medicine.

Diagnostic & Prognostic Applications of Seminal EV	Clinical Relevance & Evidence
Molecular Subtyping	miRNA profiling in seminal EV achieves high diagnostic sensitivity (>85%) for subtyping oligozoospermia beyond conventional parameters [32].
Epigenetic Assessment	EV-transmitted histone modifications and DNA methylation patterns correlate with embryonic implantation rates and early development [31,33].
ICSI Outcome Prediction	Seminal EV molecular signatures offer higher predictive accuracy for ICSI outcomes than traditional isolated semen metrics [34].
Detection of Subclinical Inflammation	Enrichment of specific miRNAs (e.g., miR-122) and cytokines (e.g., IL-6) identifies silent male tract inflammation missed by standard cultures [27].

female reproductive physiology, influencing follicular development, endometrial receptivity, and maternal-embryonic interaction [23].

Follicular Fluid EV

Human follicular fluid contains EV secreted by granulosa cells, theca cells, and the oocyte [12,23]. Studies published between 2020 and 2025 have cataloged over 1,500 proteins and 200 miRNAs within follicular EV, demonstrating measurable differences between follicles producing competent oocytes and those with lower developmental potential [12]. For example, expression levels of miR-335 in granulosa-derived EV positively correlate with fertilization rates and blastocyst formation in IVF cycles [35]. Similarly, miR-21 levels in follicular EV associate with improved endometrial receptivity and implantation outcomes [36].

Endometrial EV and Uterine Receptivity

During the window of implantation, the endometrium secretes EV into the uterine cavity [37]. The molecular composition of these endometrial exosomes changes throughout the menstrual cycle and shows distinct alterations in individuals with recurrent implantation failure (RIF), endometriosis, or premature ovarian insufficiency [37,38]. During the late secretory phase, endometrial EV transfer functional proteins and miRNAs to the blastocyst trophectoderm, regulating genes associated with adhesion and invasion [39]. In patients with endometriosis, peritoneal fluid EV exhibit altered miRNA and protein profiles enriched for pro-angiogenic and inflammatory markers [38].

The Molecular Cargo of EV: Precision Reproductive Diagnostics

Multi-omic characterization of EV cargo—encompassing transcriptomics, proteomics, metabolomics, and lipidomics—provides a high-resolution snapshot of cellular physiological status [13,14]. Integrating multi-omic EV profiles with computational tools enables the generation of patient-specific molecular signatures that map to outcomes such as fertilization success, embryo quality, implantation, and live birth rates [14,18].

Core Clinical Applications of EV Technology in Reproductive Medicine

Extracellular vesicle (EV) technology holds significant core clinical applications across both diagnostic and therapeutic realms in reproductive medicine.

In terms of diagnostic potential, EV technology enables the identification of underlying molecular subtypes of idiopathic infertility [11,33], as well as a precise evaluation of real sperm fertilizing capacity beyond what traditional morphology alone can offer [31,34]. Additionally, it provides enhanced monitoring of the biological ovarian reserve compared to serum anti-Müllerian hormone (AMH) measurement alone [5,12] and offers a non-invasive risk assessment tool for recurrent implantation failure [37,39].

From a therapeutic perspective, EV present several promising avenues. Mesenchymal stem cell EV (MSC-EV) can be utilized to support tissue repair in premature ovarian insufficiency [40], while functional sperm EV can be applied to enhance overall fertilization capacity [31]. Furthermore, EV technology facilitates the targeted delivery of therapeutic cargo or growth factors to modulate the endometrial environment or optimize preimplantation embryos [38,40].

Systematic Review Methodology

This review was conducted in accordance with PRISMA 2020 guidelines [9,13]. A comprehensive search was executed across PubMed/MEDLINE, EMBASE, Scopus, Web of Science, and the Cochrane Library for literature published from January 2020 to March 2025.

Search strategies combined terms such as “extracellular vesicles”, “exosomes”, “male infertility”, “female infertility”, “seminal plasma”, “follicular fluid”, “endometrial receptivity”, “ovarian reserve”, “biomarkers”, “precision medicine”, “miRNA”, and “proteomics”.

Selection Criteria

- **Inclusion Criteria:** Original research articles, meta-analyses, and systematic reviews published between January 2020 and March 2025 in JCR Q1/Q2 journals; studies evaluating human reproductive EV; studies featuring verified control groups and adequate sample sizes; full text available in English or Spanish [9,13,18].
- **Exclusion Criteria:** Exclusively animal studies without human correlation; studies published before January 2020; conference abstracts without full text; studies assessed as having a high risk of bias using Cochrane RoB 2.0 tools; research unrelated to fertility or reproductive biology.

Discussion: Towards Precision Reproductive Medicine

The results of this systematic review converge on a fundamental paradigm shift in the understanding and treatment of infertility: the move from a standardized population model to an individualized molecular model, based on the interpretation of each patient's unique biological message [13,18].

For decades, reproductive medicine has operated under the implicit assumption of a universal "normal" reproductive biology, from which pathology thresholds are defined and treatment protocols applicable to all patients are designed. WHO semen analysis reference values, standardized ovarian stimulation protocols, and morphological embryo selection criteria are expressions of this population-based logic. However, the evidence accumulated in the last five years demonstrates that this approach is inherently limited because it ignores the extraordinary molecular heterogeneity that exists among individuals with the same clinical presentation [14].

Extracellular vesicles offer precisely what the classical model cannot: non-invasive access to the actual molecular state of reproductive cells in their native microenvironment. Analysis of the microRNA, protein, and long non-coding RNA cargo of extracellular vesicles (EV) from follicular fluid, seminal plasma, or uterine fluid allows for the identification of specific molecular perturbations that determine reproductive failure in each individual patient. This information not only has diagnostic value but also guides molecularly targeted therapeutic interventions: modulation of specific signaling pathways, correction of nutritional or metabolic deficiencies with documented molecular impact, or even EV therapies designed to restore impaired intercellular communication [15,40].

A central aspect of this new perspective is the recognition that environmental, cultural, nutritional, and psychosocial factors do not act identically in all individuals but rather modulate reproductive biology through epigenetic mechanisms that are uniquely expressed in the molecular profile of each patient's EV. Exposure to endocrine disruptors, chronic stress, altered microbiota, and dietary patterns leave specific molecular footprints on gallbladder cargo, which can be identified, quantified, and potentially reversed with personalized interventions [20,21].

Conclusions

The new era of reproductive medicine cannot continue analyzing the individual through the lens of population statistics. The message is in the cell, and the cell transmits it through its vesicles.

This systematic review permits the extraction of the following principal conclusions:

Documented Global Reproductive Crisis

The decline in male and female reproductive parameters, the earlier onset of menopause, and the deterioration of ovarian reserve configure a global biological reproductive crisis that transcends sociodemographic factors and demands a response from molecular biology. The demographic inversion projected for 2080 underlines the urgency of this challenge [3-7].

EV as the New Diagnostic Standard

Extracellular vesicles from reproductive fluids represent the diagnostic tool with the greatest transformative potential for reproductive medicine in the coming decade. Their multi-omics cargo surpasses in informational capacity any previous individual biomarker, including serum AMH, conventional semenology, and morphological embryo grading systems [13,28,29].

EV-Based Therapeutic Individualization

Analysis of the molecular profile of EV enables the design of precise, personalized therapeutic interventions aimed at correcting the specific molecular perturbations of each patient, transcending the model of universally applied standardized protocols and moving toward truly individualized reproductive care [14,15,18].

Integration of Environmental and Epigenetic Context

Understanding how environmental, cultural, and metabolic factors are expressed in the vesicular profile of each individual is the foundation of 21st-century precision reproductive medicine. We must not generalize across populations: each patient carries in their vesicles the molecular map of their own fertility. The future of reproductive medicine lies in reading that map with precision, empathy, and individualized therapeutic intent [20,21,40].

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