



Review Article

Stem Cell-Derived Reproductive Organoids: Biology, Applications, and Translational Perspectives

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Abstract | Organoid technology has emerged as a transformative platform in biomedical research, offering three-dimensional, self-organising structures that faithfully recapitulate the architecture and function of native tissues. In the domain of reproductive biology, organoids derived from both male and female reproductive tract tissues represent an unprecedented opportunity to model development, pathology, and treatment response in vitro. This review synthesises current knowledge on stem cell-derived reproductive organoids, covering the female reproductive tract, male reproductive system, gonadal organogenesis, and cross-species applications, with emphasis on infertility modelling, drug discovery, and future clinical translation. A narrative review was conducted drawing on primary literature spanning 2020 to 2026, focusing on peer-reviewed studies describing organoid derivation, characterisation, and application in reproductive contexts. Reproductive organoids have progressed from exploratory proof-of-concept to sophisticated models of endometrial receptivity, tubal function, gonadogenesis, and male germline biology. Integration with organ-on-a-chip platforms and single-cell omics is poised to accelerate their translational potential, though standardisation, ethical governance, and scalability remain critical challenges.

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Introduction

Organoid technology has fundamentally reshaped in vitro biology over the past two decades. Organoids are self-organising, three-dimensional structures derived from adult or pluripotent stem cells that recapitulate the cellular

heterogeneity, spatial architecture, and gene expression profiles of their tissue of origin, offering a marked improvement over conventional two-dimensional culture for studying development, disease, and therapeutic response (Azar *et al.*, 2021).

In reproductive medicine, physiologically accurate in

vitro models have long been needed: infertility affects an estimated 10–15% of couples globally, yet many underlying mechanisms remain poorly understood and treatment options limited, partly because traditional culture systems fail to replicate the dynamic microenvironments of the uterus, fallopian tube, ovary, or testis (Nikolakopoulou and Turco, 2021; Jabri *et al.*, 2025). Organoids derived from endometrial, tubal, cervical, ovarian, and testicular tissue have emerged as physiologically relevant surrogates for these organ systems, supporting hormonal responsiveness, embryo implantation, and disease modelling of conditions such as endometriosis, polycystic ovarian syndrome, and premature ovarian insufficiency, with parallel advances in bioengineering and organ-on-a-chip technology further expanding the experimental toolkit available to reproductive scientists (Chumduri and Turco, 2021; Heremans *et al.*, 2021; Patrício *et al.*, 2023; Tahmasbpour Marzouni *et al.*, 2022).

This review synthesises progress in reproductive organoid research, covering the biological foundations of organoid culture, applications across the male and female reproductive tracts, cross-species utility, and the technical and ethical challenges that must be addressed before clinical translation can be realised.

Review Methodology

To enhance the transparency and reproducibility of this narrative review, a structured search strategy was employed. The electronic databases PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for peer-reviewed, English-language publications dated January 2020 to July 2026. Search terms were combined using Boolean operators and included: (“organoid*” OR “organ-on-a-chip”) AND (“reproductive” OR “endometri*” OR “fallopian tube” OR “oviduct*” OR “ovarian” OR “testic*” OR “gonad*” OR “infertility”) AND (“stem cell*” OR “induced pluripotent stem cell*” OR “iPSC”). Reference lists of retrieved articles were hand-searched to identify additional relevant studies (a snowballing approach).

Studies were included if they (i) described the derivation, characterisation, or application of stem cell-derived reproductive organoids in human or animal systems; (ii) were published as a peer-reviewed original research article, systematic review, or narrative review between 2020 and 2026; and

(iii) were available in full text in English. Studies were excluded if they (i) focused exclusively on non-reproductive organ systems; (ii) were conference abstracts, preprints without peer review, or editorials lacking substantive data; or (iii) could not be retrieved in full text. Titles and abstracts were first screened for relevance, followed by full-text assessment of potentially eligible articles; reference selection and screening were performed by the author, which is acknowledged as a limitation of the review process (see Section 10.4).

As this is a narrative rather than a systematic review, a formal PRISMA protocol was not registered or followed in full (Page *et al.*, 2021); nevertheless, the search and screening steps outlined above were adopted to reduce selection bias and improve the transparency of study selection, an approach recommended for narrative reviews addressing broad, rapidly evolving fields such as this one (Sukhera, 2022).

Biological foundations of organoid technology Definition and historical context

The term ‘organoid’ was first applied to describe self-organising three-dimensional structures in the early 2000s, but the technology gained widespread attention following the seminal work of Hans Clevers’ laboratory in 2009, which demonstrated the capacity of single intestinal stem cells to give rise to crypt-villus structures in Matrigel (Azar *et al.*, 2021). Since then, organoid systems have been established for virtually every major human organ system, including the brain, lung, kidney, liver, pancreas, and reproductive tract.

The key innovation underpinning organoid development is the exploitation of tissue-resident adult stem cells or induced pluripotent stem cells (iPSCs), which possess intrinsic self-organising capacity when embedded in appropriate extracellular matrix environments and exposed to defined growth factor combinations (Gabriel *et al.*, 2024). The resulting structures spontaneously form lumens, polarised epithelia, and organ-specific cell types that can be maintained, expanded, and cryopreserved over extended periods.

Stem cell sources for reproductive organoids

Reproductive organoids can be established from multiple stem cell sources, each with distinct advantages and limitations. Adult tissue-resident stem cells— isolated from endometrial biopsies,

fallopian tube epithelia, cervical tissue, or testicular biopsies- represent the most physiologically authentic source and can be rapidly expanded without the ethical concerns associated with embryonic material (Heidari-Khoei *et al.*, 2020; Haider and Beristain, 2023). These organoids recapitulate the transcriptomic and epigenetic profiles of the parent tissue, respond to hormonal stimulation, and can be used to model patient-specific pathology.

Pluripotent stem cells- including embryonic stem cells (ESCs) and iPSCs- offer unlimited proliferative capacity and the potential to generate any reproductive cell type *de novo* through directed differentiation protocols (Liu *et al.*, 2020; Rosner *et al.*, 2023). iPSC-derived organoids are particularly attractive for personalised medicine applications, as they can be generated from somatic cells of individual patients, enabling genotype-specific disease modelling and drug screening. However, directed differentiation protocols for reproductive lineages remain incompletely characterised, and resulting organoids may not fully replicate the complexity of adult tissue (Ali *et al.*, 2022).

Fetal stem cells represent a third category with unique multipotential properties that are relevant to reproductive biology, particularly in the context of gonadogenesis and germ cell development (Rosner *et al.*, 2023). Female germline stem cells have attracted increasing interest as a potential source for generating oocytes *in vitro*, though controversy persists regarding their identity and functional relevance in adult human ovaries (Huang and Ye, 2025).

Extracellular matrix and culture conditions

The extracellular matrix (ECM) plays an indispensable role in organoid establishment and maintenance. Matrigel- a basement membrane extract derived from Engelbreth-Holm-Swarm sarcoma cells- is the most widely used scaffold, providing laminin, collagen IV, and growth factors that support epithelial self-organisation (Heidari-Khoei *et al.*, 2020). However, the undefined composition and xenogeneic origin of Matrigel represent significant limitations for clinical and regulatory applications. Research into synthetic hydrogels, decellularised ECM matrices, and bioprinted scaffolds is ongoing and holds promise for standardised organoid production (Zhang *et al.*, 2026).

Culture media formulations are equally critical and must be tailored to the specific tissue type. Endometrial organoids require oestrogen, progesterone, epidermal growth factor (EGF), and Wnt pathway activators, while tubal organoids demand air-liquid interface conditions to support ciliation (Gatimel *et al.*, 2025; Lawson *et al.*, 2023). Ovarian organoids benefit from follicle-stimulating hormone (FSH) and anti-Müllerian hormone supplementation to model folliculogenesis (Salehnia and Moazzeni, 2025; Zhang *et al.*, 2024).

Organoids of the female reproductive tract

Endometrial organoids

The endometrium has been the most extensively studied tissue in the context of reproductive organoids. Turco and colleagues established a robust protocol for human endometrial organoid derivation in 2017, and subsequent work has validated their capacity to model key aspects of uterine biology including glandular morphogenesis, hormonal responsiveness, and decidualisation (Heremans *et al.*, 2021; Alzamil *et al.*, 2021). Endometrial organoids faithfully recapitulate the histological features of endometrial glands, including luminal polarisation, mucin secretion, and cyclical remodelling in response to steroid hormones.

In the context of infertility, endometrial organoids have been applied to study implantation failure and recurrent pregnancy loss. Nikolakopoulou and Turco (2021) demonstrated that endometrial organoids from patients with recurrent implantation failure exhibit aberrant gene expression signatures and impaired embryo attachment capacity compared to organoids from fertile controls, providing cellular-level insights into the pathophysiology of this condition. More recently, Jabri *et al.* (2025) reviewed the expanding role of endometrial organoids in modelling human infertility, emphasising their utility for identifying novel therapeutic targets and evaluating endometrial receptivity markers.

Endometrial organoids have also been used to model pathological conditions including endometriosis, endometrial polyps, endometritis, and endometrial cancer (Haider and Beristain, 2023; Wang *et al.*, 2025). Comparison of organoids established from eutopic and ectopic endometrium has revealed molecular differences that may underpin the invasive behaviour characteristic of endometriosis, while co-culture systems with immune cells and stromal

fibroblasts are beginning to replicate the inflammatory microenvironment of this condition (Chumduri and Turco, 2021).

Fallopian tube organoids

The fallopian tube is the site of fertilisation and early embryo development, yet has historically been underrepresented in in vitro models due to the challenge of maintaining ciliated epithelium in culture. Organoids derived from fallopian tube epithelium have successfully recapitulated ciliated cell types, secretory cells, and the architectural organisation of the tubal mucosa, providing a platform for studying gamete transport, embryo-tubal interactions, and tubal pathology (Alzamil *et al.*, 2021; Heremans *et al.*, 2021).

A particularly significant application is the modelling of sperm-tubal interactions and capacitation. Gatimel *et al.* (2025) demonstrated that human fallopian tube organoids provide a favourable microenvironment for sperm motility and function, suggesting that these models may prove valuable for studying male factor infertility in the context of the female reproductive tract. Furthermore, cross-species studies by Lawson *et al.* (2023) established and characterised oviductal organoids from farm and companion animals, enabling comparative reproductive biology studies and the development of assisted reproductive technologies in veterinary contexts.

Fallopian tube organoids are also relevant to the study of high-grade serous ovarian carcinoma, which is now widely believed to originate from the tubal epithelium. Organoids established from tubal tissue provide a tractable system for investigating early oncogenic events and testing chemotherapeutic agents in a physiologically relevant context (Wang *et al.*, 2025).

Cervical and vaginal organoids

Organoids from the cervix and vagina have been established, albeit less extensively than those from the endometrium and fallopian tube. Cervical organoids have proven particularly useful for studying human papillomavirus (HPV) infection, cervical carcinogenesis, and interactions with the cervicovaginal microbiome (Kaya *et al.*, 2023). The integration of organoid systems with microbiome co-culture has enabled novel investigations into how Lactobacillus-dominated versus dysbiotic microbial

communities influence epithelial integrity, immune responses, and susceptibility to sexually transmitted infections (Kaya *et al.*, 2023).

Wang *et al.* (2025) provided a comprehensive overview of female reproductive tract organoids and their applications, including cervical organoids as models of the transformation zone- the region at highest risk for HPV-associated malignancy. These systems enable detailed characterisation of cell type transitions at the squamocolumnar junction and may facilitate development of prophylactic and therapeutic strategies.

Ovarian organoids

Ovarian organoid research has progressed significantly in recent years, driven by the clinical need for models of premature ovarian insufficiency (POI), ovarian cancer, and in vitro folliculogenesis. Zhang *et al.* (2024) reviewed advances in the construction of stem cell-derived ovarian organoids, highlighting methodological progress in recapitulating follicular structures containing granulosa cells, theca cells, and oocytes within a three-dimensional matrix.

Ali *et al.* (2022) evaluated stem cell-based therapeutic strategies for POI, noting that organoid systems derived from patient tissue or iPSCs offer a platform for testing cell-based interventions including exosome therapy, paracrine factor supplementation, and direct cell transplantation. More recently, Salehnia and Moazzeni (2025) reviewed emerging frontiers in ovarian organoids, describing advances in modelling ovarian ageing, hormonal signalling, and the potential for generating functional oocytes for fertility restoration.

Thompson *et al.* (2022) additionally explored the intersection of extracellular vesicle biology and organoid models in female reproductive physiology, demonstrating that organoid-conditioned media contain bioactive vesicles capable of modulating follicular development and oocyte quality, with implications for understanding paracrine communication within the ovary.

Organoids of the male reproductive system

Testicular organoids

The testis is one of the most structurally complex organs in the body, housing multiple somatic cell types- Sertoli cells, Leydig cells, peritubular myoid

cells- alongside the male germline. [Patrício *et al.* \(2023\)](#) provided a comprehensive analysis of organoids of the male reproductive system, noting that while testicular organoids are technically more challenging than female reproductive tract counterparts, significant progress has been made in establishing co-culture systems that support germ cell development.

Three-dimensional testicular organoids that recapitulate spermatogenesis to varying degrees have been established from both human and animal tissue. [Liu *et al.* \(2020\)](#) reviewed stem cell-based therapies for male fertility preservation, highlighting organoid systems as vehicles for expanding and differentiating spermatogonial stem cells in vitro. Such systems are of particular clinical relevance for prepubertal cancer patients who cannot bank mature sperm and may benefit from future autologous spermatogonial transplantation following cryopreservation of testicular tissue.

[Cortez *et al.* \(2024\)](#) demonstrated that bovine adipose tissue-derived mesenchymal stem cells can self-assemble with testicular cells, integrating into and modifying the structure of testicular organoids. This finding opens exciting possibilities for engineering testicular microenvironments that support spermatogenesis and for studying paracrine interactions between somatic and germline compartments. [Pryzhkova *et al.* \(2022\)](#) further explored modelling human gonad development in organoids, with emphasis on the role of specific transcription factors and signalling pathways in early gonadogenesis.

Prostate and epididymal models

Beyond the testis, organoids have been established from the prostate gland and epididymis, providing models for studying prostate cancer, benign prostatic hyperplasia, and sperm maturation ([Patrício *et al.*, 2023](#)). Epididymal organoids that recapitulate the regionalised expression of sperm maturation factors along the caput, corpus, and cauda segments have been described, enabling investigation of post-testicular sperm processing and male infertility caused by epididymal dysfunction ([Tahmasbpour Marzouni *et al.*, 2022](#)).

Modelling gonadal development and sex determination

A frontier application of reproductive organoids is the modelling of early gonadal development and sex

determination, processes that remain incompletely understood due to the inaccessibility of early human embryonic tissue. [Pryzhkova *et al.* \(2022\)](#) described efforts to model human gonad development in organoids, combining iPSC-derived coelomic epithelial progenitors with gonadal supporting cell precursors to recapitulate early events in testicular or ovarian specification. These systems have illuminated the molecular logic of SRY-dependent sex determination and the downstream transcriptional cascades that drive Sertoli or granulosa cell fate commitment.

[Martinez Arias *et al.* \(2026\)](#) discussed stem cell-based embryo models as tools for reproductive biology, including gastruloids and blastoids that approximate early post-implantation embryo stages. While these are not reproductive organoids in the strict sense, they provide complementary platforms for investigating the origins of the primordial germ cells (PGCs) that ultimately populate the gonads. The ethical status of such embryo models has prompted substantial debate, and their use is subject to ongoing regulatory review in many jurisdictions ([Martinez Arias *et al.*, 2026](#)).

[Rosner *et al.* \(2023\)](#) highlighted the utility of multipotent fetal stem cells in reproductive biology research, noting that fetal gonadal tissue provides a source of bipotential progenitors that can be directed towards either ovarian or testicular lineages depending on culture conditions. The integration of single-cell RNA sequencing with these organoid platforms has produced detailed cell atlas data of developing human gonads, providing a reference for assessing the fidelity of in vitro models.

Stem Cell-Derived embryo models and IVF applications

The overlap between organoid technology and assisted reproductive technology (ART) is becoming increasingly significant. [Hernández-Díaz *et al.* \(2026\)](#) examined the relationship between reproductive fluids, commercial IVF culture media, and organoids, arguing that tubal and endometrial organoid-conditioned media may offer superior substitutes for current culture systems used in IVF, potentially improving embryo development and implantation rates. This concept bridges the gap between laboratory organoid research and clinical practice in reproductive medicine.

[Hutchinson *et al.* \(2025\)](#) explored comparative

stem cell insights for fertility biotechnology and conservation, noting that organoid platforms from diverse species can inform cross-species fertility preservation strategies. [Nair et al. \(2025\)](#) provided a comprehensive review of stem cell treatments for female reproductive disorders, emphasising that organoid systems serve as critical preclinical testing platforms for evaluating cell therapies before clinical trials. [Jahanbani et al. \(2022\)](#) similarly framed stem cell technology as a platform for generating reproductive system organoids and treating infertility-related diseases, reviewing methodological advances in generating ovarian, endometrial, and tubal organoids from stem cell sources.

Organs-on-Chips and microfluidic integration

The integration of organoid biology with microfluidic engineering has produced organ-on-a-chip systems that add dynamic fluid flow, shear stress, and inter-organ communication to the static three-dimensional culture paradigm. [Tahmasbpour Marzouni et al. \(2022\)](#) provided an authoritative review of stem cells and organs-on-chips as promising technologies for human infertility treatment, describing microfluidic platforms that incorporate endometrial, tubal, and ovarian compartments connected by perfusion channels that mimic the hormonal cycles of the menstrual cycle.

[Zhang et al. \(2026\)](#) reviewed organoids and organ-on-a-chip models for investigating the pathophysiology of the human reproductive system, highlighting platforms that enable investigation of embryo implantation, trophoblast invasion, and decidualisation in a dynamic in vitro environment. The menstrual cycle-on-a-chip- a multicompartiment device incorporating ovarian, uterine, fallopian tube, cervical, and liver tissue organoids- represents the most ambitious realisation of this concept and has demonstrated remarkable recapitulation of ovarian hormone cycling, endometrial thickening, and menstruation-like events.

[Kaya et al. \(2023\)](#) specifically reviewed advanced technologies for studying microbiome-female reproductive tract interactions, including organoids-on-a-chip, noting that microfluidic systems enable controlled introduction of commensal or pathogenic microorganisms to organoid epithelia under conditions that more closely approximate the vaginal and cervical microenvironments than static culture.

Cross-Species applications and veterinary reproductive biology

Reproductive organoid technology is not confined to human medicine. [Bourdon et al. \(2021\)](#) reviewed progress and challenges in developing organoids in farm animal species for the study of reproduction and reproductive biotechnologies, documenting organoid derivation from cattle, pig, sheep, and horse reproductive tissues. These veterinary organoids are valuable both as models of economically important livestock reproductive diseases and as platforms for testing and optimising ART protocols applicable to conservation biology.

[Gabriel et al. \(2024\)](#) examined adult animal stem cell-derived organoids in biomedical research within the one health paradigm, noting that comparative organoid studies across species can yield insights into conserved and divergent reproductive mechanisms, potentially informing human reproductive medicine. [Kwon et al. \(2025\)](#) reviewed organoid-based platforms in livestock, documenting advances in bovine, porcine, and equine reproductive organoids and their applications in embryo quality assessment and infectious disease modelling.

[Saadeldin et al. \(2025\)](#) reviewed organoids of the female reproductive tract across species, providing a comparative analysis of endometrial, tubal, and cervical organoids from human, bovine, porcine, and equine sources. This cross-species perspective underscores both the remarkable conservation of reproductive organ biology and the species-specific differences that must be accounted for when translating findings across model systems. [Lawson et al. \(2023\)](#) similarly established oviductal organoids from farm and companion animals, demonstrating that these cultures support sperm-epithelium interactions and may serve as functional assays for male fertility assessment.

Infertility disease modelling and drug discovery

The most immediate translational application of reproductive organoids lies in modelling infertility and reproductive pathology. [Mohapatra \(2023\)](#) conducted a literature review on developing human reproductive organoids to combat infertility, cataloguing disease models that span endometriosis, polycystic ovarian syndrome, recurrent implantation failure, premature ovarian insufficiency, and azoospermia. Crucially, patient-derived organoids preserve the genetic and epigenetic features of the originating disease state,

enabling investigation of disease mechanisms that were previously inaccessible.

Horcharoensuk *et al.* (2022) reviewed organoids in the human reproductive system with a focus on their use in disease modelling and personalised treatment, noting that the ability to establish organoids from individual patients and test drug responses *ex vivo* represents a paradigm shift towards precision reproductive medicine. Cui *et al.* (2020) evaluated human female reproductive system organoids in developmental biology, disease modelling, and drug discovery, demonstrating that endometrial and fallopian tube organoids can be used to screen pharmacological agents for endocrine-disrupting activity and to test hormone therapy protocols.

The field of reproductive toxicology has similarly benefited from organoid models. Unlike traditional two-dimensional assays, organoid systems can detect subtle effects of environmental chemicals, plasticisers, and pharmaceutical agents on epithelial differentiation, hormonal responsiveness, and glandular secretion that may be invisible in conventional screens. This has significant implications for regulatory testing of substances with potential reproductive toxicity (Cui *et al.*, 2020; Heidari-Khoei *et al.*, 2020).

Challenges and future directions

Technical challenges

Despite remarkable progress, reproductive organoid technology faces several significant technical challenges. Current organoid systems predominantly model the epithelial compartment of reproductive organs, while stromal, immune, vascular, and neural components are largely absent (Haider and Beristain, 2023; Chumduri and Turco, 2021). This limits their capacity to model processes such as trophoblast invasion, immune tolerance at the maternal-foetal interface, and neuroendocrine regulation of the hypothalamic-pituitary-gonadal axis.

The absence of standardised protocols for organoid derivation, culture, characterisation, and quality assessment represents a significant barrier to reproducibility across laboratories (Patrício *et al.*, 2023; Heremans *et al.*, 2021). Variation in ECM composition, growth factor concentrations, and passage number can profoundly affect organoid morphology and gene expression, complicating cross-study comparisons. International efforts to establish

consensus guidelines for reproductive organoid culture are urgently needed.

Scalability for high-throughput drug screening applications remains technically challenging (Mohapatra, 2023). The labour-intensive nature of organoid passaging, the cost of culture reagents, and the difficulty of automating three-dimensional culture processes limit the throughput achievable with current methods. Advances in automated liquid handling, miniaturised culture systems, and imaging-based phenotypic readouts are beginning to address these limitations.

Ethical considerations

The development of increasingly sophisticated embryo models and gonadal organoids raises profound ethical questions that require careful societal deliberation. Martinez Arias *et al.* (2026) explicitly noted the ethical dimensions of stem cell-based embryo models, including questions about their moral status, the fourteen-day rule that governs human embryo research, and the regulatory frameworks that should govern research involving synthetic embryo-like structures.

The prospect of generating human germ cells—including oocytes and spermatozoa—from stem cells *in vitro* (*in vitro* gametogenesis, IVG) carries particular ethical weight, as such gametes could theoretically be used for reproduction. While IVG in humans remains a future possibility rather than a current reality, the trajectory of reproductive organoid research makes it a foreseeable challenge requiring proactive governance frameworks (Huang and Ye, 2025; Martinez Arias *et al.*, 2026).

Clinical translation

The pathway from organoid research to clinical reproductive medicine will require demonstration of safety, efficacy, and manufacturing feasibility at scale. Nair *et al.* (2025) outlined the translational steps required for stem cell treatments in female reproductive disorders, emphasising the importance of good manufacturing practice (GMP)-compliant organoid production and rigorous preclinical validation. Jahanbani *et al.* (2022) similarly highlighted that while organoids offer transformative potential for infertility treatment, the regulatory and manufacturing challenges associated with cell-based therapies must be addressed before widespread

clinical adoption.

Hutchinson *et al.* (2025) advocated for a comparative approach, suggesting that insights from domestic animal and wildlife fertility biotechnology could accelerate translational progress in human reproductive medicine. The one health perspective championed by Gabriel *et al.* (2024) frames reproductive organoid research as simultaneously relevant to human health, animal welfare, and biodiversity conservation, providing a compelling rationale for sustained investment in cross-disciplinary research.

Critical appraisal of the evidence base and risk of bias

The evidence underpinning this review is heterogeneous in design, rigour, and maturity, and a critical appraisal of these differences is necessary to contextualise the strength of the conclusions drawn. Much of the literature summarised here comprises narrative reviews and expert commentaries (e.g., Haider and Beristain, 2023; Patrício *et al.*, 2023; Wang *et al.*, 2025) rather than primary experimental studies, meaning that many claims are themselves syntheses of earlier, sometimes conflicting, primary data rather than independently verifiable findings; readers should therefore weigh conclusions drawn from secondary literature with appropriate caution. Among primary studies, sample sizes are frequently small, patient-derived organoid cohorts rarely exceed a few dozen individuals, and validation against native tissue is inconsistent, ranging from detailed single-cell transcriptomic comparison to more limited immunohistochemical marker panels.

Notable areas of unresolved controversy include the existence and functional relevance of adult human female germline stem cells, a claim that remains contested despite continued interest as a route to in vitro oocyte generation (Huang and Ye, 2025); the degree to which iPSC-derived reproductive organoids recapitulate adult tissue complexity, with several groups reporting incomplete differentiation and immature phenotypes relative to primary tissue-derived organoids (Ali *et al.*, 2022; Rosner *et al.*, 2023); and the reproducibility of specific culture protocols across laboratories, given substantial variability in extracellular matrix source, growth factor concentration, and passage number that is rarely reported in sufficient detail to allow independent replication (Patrício *et al.*, 2023; Heremans *et al.*, 2021).

No formal risk-of-bias instrument (e.g., a modified Cochrane or ROBIS tool) was applied, as such tools are designed for randomised trials or systematic reviews of intervention studies rather than heterogeneous in vitro and preclinical organoid literature; this represents a methodological limitation of the present review. To partially mitigate this limitation, studies were qualitatively weighted according to (i) whether organoid identity and function were validated against native tissue using orthogonal methods (e.g., single-cell RNA sequencing, functional hormone-responsiveness assays); (ii) whether findings had been independently replicated by more than one research group; and (iii) whether the study design (original research versus narrative synthesis) permitted direct assessment of primary data. Studies meeting more of these criteria were given greater interpretative weight in the synthesis above. Future systematic reviews and meta-analyses, ideally conducted according to PRISMA guidelines with formal risk-of-bias assessment, are needed to quantitatively evaluate the reproducibility and translational readiness of specific organoid platforms (Page *et al.*, 2021).

Conclusions and Recommendations

Reproductive organoid technology has rapidly evolved into a powerful platform for studying reproductive development, physiology, and disease. Stem cell-derived organoids faithfully recapitulate key structural and functional characteristics of the female and male reproductive systems, providing physiologically relevant models for investigating infertility, reproductive disorders, developmental biology, and therapeutic responses. Their integration with emerging technologies, including organ-on-a-chip systems, single-cell multi-omics, genome editing, and advanced bioengineering, is expected to further enhance their value for precision reproductive medicine, drug discovery, and regenerative therapies.

Despite these advances, several challenges remain before widespread clinical translation can be achieved. Greater standardisation of organoid derivation protocols, culture conditions, quality-control criteria, and validation methods is essential to improve reproducibility across laboratories. Incorporating stromal, immune, vascular, and neural components into next-generation organoid models will better replicate the native reproductive microenvironment. In addition, ethical oversight, regulatory harmonisation, scalable

Good Manufacturing Practice (GMP)-compatible production, and long-term safety evaluations will be critical for future clinical applications.

For future researchers, priority should be given to developing standardized and xeno-free culture systems, validating organoid models using multi-center studies and single-cell multi-omics approaches, establishing long-term functional assessments, and expanding comparative reproductive organoid research across animal species within a One Health framework. Collaborative efforts among reproductive biologists, stem cell scientists, bioengineers, clinicians, veterinarians, and regulatory experts will be essential to accelerate the safe and effective translation of reproductive organoid technology from laboratory research to clinical and veterinary practice.

Overall, stem cell-derived reproductive organoids represent one of the most promising advances in modern reproductive biology. Continued interdisciplinary research and technological innovation will be fundamental to unlocking their full potential for improving reproductive health, fertility preservation, personalized medicine, and translational biomedical research.

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Novelty Statement

This review uniquely integrates recent advances in stem cell-derived reproductive organoids across female and male reproductive systems, highlighting their applications in infertility research, disease modelling, organ-on-a-chip technology, and comparative veterinary reproductive biology. It further provides a critical appraisal of the current evidence, discusses technical and ethical challenges, and outlines future research priorities within a One Health and translational medicine framework, offering a comprehensive perspective beyond previous organ-specific reviews.

Author Contributions

Md. Rimon Bhuiyan: Conceptualisation, literature

search, writing- original draft, Data curation, writing-review and editing, Supervision, critical revision. The author approved the final manuscript.

Generative AI and AI-assisted technology statement

The author declares that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest

The author declares no conflicts of interest.

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