



Advancing the Future of Reproductive Technologies: The Formation of Gametes from Fibroblast-Derived Induced Pluripotent Stem Cells through in vitro Gametogenesis

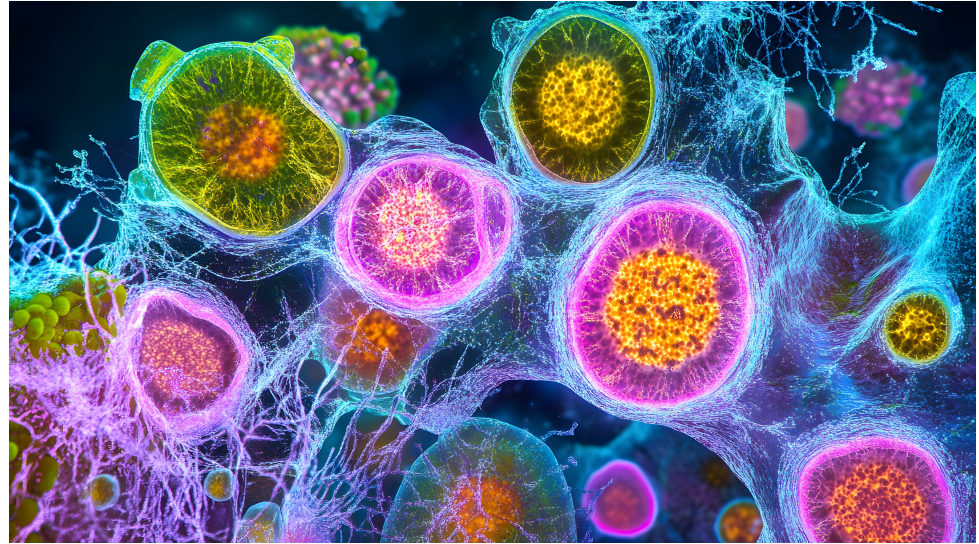
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Keywords:

Induced Pluripotent Stem Cells
In vitro Gametogenesis
Gametes
Infertility
Primordial Germ Cell-like Cells
Fibroblasts



Abstract

While Assisted Reproduction Technologies (ART) such as in vitro fertilization (IVF) are widely used as alternatives for people who cannot conceive offspring, many studies have shown the potential of using fibroblasts as an alternative to in vivo gametogenesis (IVG). Fibroblasts can be genetically reprogrammed into induced pluripotent stem cells (iPSCs), which can then further differentiate into primordial germ cell-like cells (PGCLCs), the possible precursors of functional gametes. This review examines differentiation pathways, ongoing clinical studies, ethical considerations, the development of test subjects, and future directions of using iPSCs. Therefore, this review evaluates the potential of using skin cells through IVG as a new method of reproductive technology.

Published June 30, 2026

Full Open Access

1. Introduction

Assisted reproductive services have been recognized and utilized as an alternative option for people who cannot undergo conception through *in vivo* gametogenesis. With the current advances in Assisted Reproduction Technology (ART), the range of fertility treatments has been expanded, reaching a wider global audience with increasing reported cases of treatment usage¹. ART, specifically *in vitro* gametogenesis, targets the various categories of people for its audience, including patients with infertility, cancer treatment recipients, and LGBTQ+ couples.

Currently, infertility is a significant problem present in the U.S., affecting millions of people, with common causes including ovulatory disorders (PCOS), endometriosis, and tubal damage in women². Data from the National Survey of Family Growth from 2015 to 2019 in the U.S., the estimated percentage of women with impaired fecundity was 13.4%, with the infertility rate of married women being approximately 8.5% and that of men between the ages of 15 and 49 being approximately 11.4% and 12.8% for men between the ages of 25-39.³ When comparing the trend of the data over time, the impaired fecundity and the infertility rate of married women both show a gradual increase³. Infertility is also a global issue outside of the U.S.⁴ The estimated worldwide infertility prevalence rate is 4-14%, with a consistent change over time.⁴ Also, the disparity in infertility rate internationally is present, as the infertility rate is estimated to be higher, especially in developing countries, than in developed countries, being 3.5-16.7% and 6.9-9.3%, respectively.⁴ Combined factors, such as lower accessibility for treatment, higher burdens of reproductive tract infections, and socio-demographic factors in developing countries, cause the difference in infertility rate between the two⁴.

ART is also a popular alternative candidate for LGBTQ+ couples.^{5,6} According to the data from the National Survey of Family Growth from 2017 to 2019 in the U.S., even though both rates of homosexual females and heterosexual females expressing desire for children are relatively similar, with approximately 48% and 51%, respectively, homosexual females were much less likely to get pregnant and much more likely to seek assisted

reproductive technology (31%), which was three times more than that of heterosexual female (10%). Their willingness towards adoption was comparable, being 7.0% vs 1.3%, respectively.⁷ ART provides the possibility of having children through *in vitro* gametogenesis to cancer treatment recipients and cancer survivors, as the treatment-induced gonadal failure (TIGF) is highly related to the infertility of the gonadotoxic cancer treatment recipients⁸. The chemotherapy drugs contain gonadotoxic agents, especially alkylating agents, and target both cancer cells and germ cells, spermatogonia and oocytes, in the gonads⁸. For female treatment recipients, chemotherapy may damage both growing and dormant follicles, causing premature ovarian insufficiency (POI) and loss of estrogen production and, therefore, infertility⁸. For male treatment recipients, chemotherapy may damage spermatogenic epithelium in the testes and thus spermatogonia, therefore causing infertility.⁸ In addition, the radiation from radiotherapy may cause infertility, as it can destroy the majority of oocytes and cause oligospermia, an insufficient amount of sperm, or even azoospermia, a complete absence of sperm⁹.

In this review, we examined the possibility of using skin cells as the precursor of *in vitro* gametogenesis. Skin cells are given as the potential solution for *in vitro* gametogenesis when derived into induced pluripotent cells and then primordial germ cell-like cells, mimicking the *in vivo* gametogenesis completely *in vitro*.^{11,14-27} When induced pluripotent stem cells (iPSCs) derived from skin cells are differentiated into primordial germ cell-like cells (PGCLCs), they can proceed to *in vitro* gametogenesis, enabling the controlled development of iPSCs into oocytes and spermatozoa.^{11,14-27} This process mimics natural gametogenesis, which marks a major step toward providing *in vitro* fertilization options for cancer survivors, LGBTQ+ individuals, and infertile individuals.¹⁰ We reviewed scientific articles detailing *in vitro* gametogenesis (IVG) and the process of reprogramming skin cells into functional gametes using induced pluripotent stem cells (iPSCs).

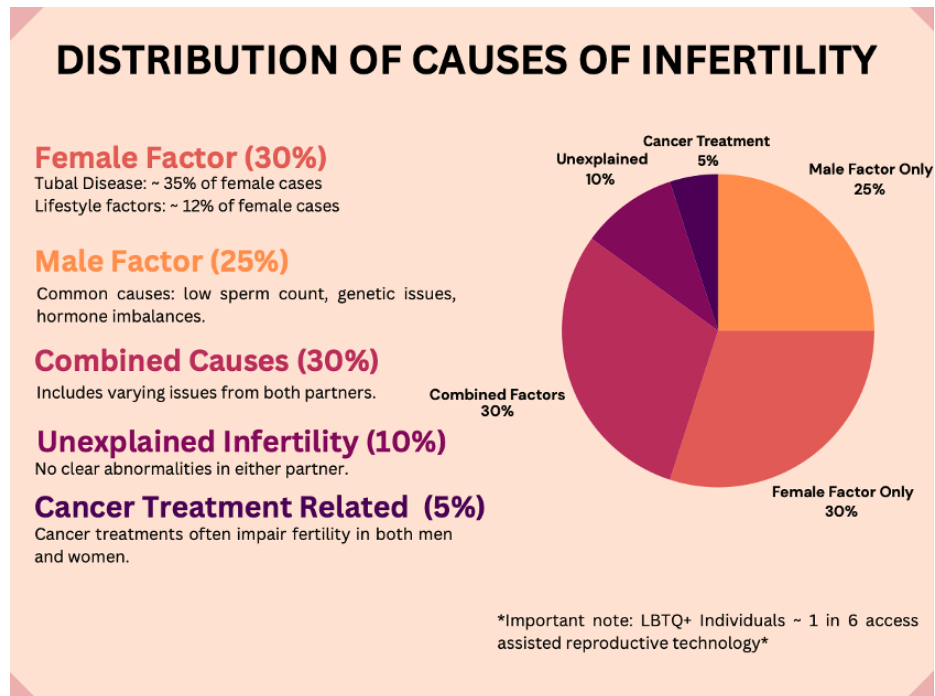


Figure 1. Distribution of Causes of Infertility

The pie chart illustrates the various infertility causes among affected individuals. Female factors and combined factors each account for 30% of cases, followed by male factors at 25%, unexplained infertility at 10%, and cancer treatment-related causes at 5%. Tubal disease in females contributes to approximately 35% of female-related infertility, while lifestyle factors account for 12% of cases. Male factor infertility commonly comes from low sperm count, genetic conditions, or hormonal imbalances. Combined causes involve issues from both partners. Unexplained infertility occurs when no clear abnormalities are identified with testing. Cancer treatments can impair fertility in both sexes and this number is variable. An important note: approximately 1 in 6 LGBTQ+ individuals access assisted reproductive technology. Created with [Canva.com](https://www.canva.com)

2. In Vitro Gametogenesis (IVG)

In vitro gametogenesis (IVG) is an emerging stem-cell-focused reproductive technique that holds large potential in the field of medicine ¹¹. This method involves generating functional ova or spermatozoa entirely outside of the human body by reprogramming somatic cells, such as skin cells, into induced pluripotent stem cells (iPSCs) ¹¹. These iPSCs are then guided through several stages in laboratory conditions to become primordial germ cell-like cells (PGCLCs), which, with certain signals, can become functional gametes ¹¹. The purpose of IVG is to mimic the natural in-body process of gametogenesis in vitro, which presents theoretical possibilities for same-sex couples, single parents by choice, and people who suffer from infertility to

bear genetically related children.¹² While IVG research remains experimental in the research space and has not yet reached clinical application in humans, the technology represents a significant step in the field of regenerative medicine.¹³

2.1 Differentiation Pathway

To generate gametes from fibroblasts, a type of skin cell, despite methodological differences in the details of protocols and underlying mechanisms among studies, they converge on a few steps for the possible mimicking of *in vivo* gametogenesis^{11,14-27}. The differentiation pathway of *in vitro* gametogenesis generally consists of two main steps: (1) the derivation of iPSCs from fibroblasts and (2) the differentiation of iPSCs into PGCLCs

^{11,14-27}.

For the collection of the fibroblasts, tail tips or embryos of the test subject, depending on which type of mammal the subject belongs to, were selected as the sampling location^{11,28}. From the data sources collected, most studies utilized mouse models, although other mammalian subjects, including dogs, geese, chickens, marmosets, and humans, were also present in more advanced studies^{11,14-27}. The collected fibroblast cells were then introduced to Yamanaka factors, which are known as Octamer 3/4 (Oct3/4), SRY-box containing gene 2 (Sox2), proto oncogene cytoplasmic Myc protein (c-Myc), and Krüppel-like factor 4 (Klf4), under the embryonic stem (ES) cell culture conditions to differentiate the fibroblast cells into iPSCs.^{20,25}

The Yamanaka factors are significant promoters in this derivation step of converting fibroblasts into iPSCs, as they signify a pluripotent, germline-ready cell population.³¹ The skin fibroblast is characterized as a type of somatic cell, which is a unipotent, non-reproductive cell that lacks pluripotency, a cell's ability to differentiate into different cell types³². Yamanaka factors are shown to be capable of reactivating the pluripotency networks of the somatic cells and therefore can "reprogram somatic cells into induced pluripotent stem cells."^{16, 33} This reactivation can then further lead to epigenetic remodeling, including DNA demethylation and chromatin reorganization, that reinstates a naive embryonic-like state.¹⁶ As

iPSCs are characterized as embryonic-like state cells that are differentiated and retain pluripotency, the reinstatement of an embryonic-like state through these transcription factors is significant.³⁴

Yamanaka factors are especially critical in maintaining epiblast-like pluripotency, which refers to having the "capacity to generate all somatic lineages of the embryo and the germline" and enabling responsiveness to PGC-inducing signals, such as bone morphogenetic protein 4 (BMP4) and WNT, which are necessary for the later steps in the differentiation process of *in vitro* gametogenesis.^{20, 31, 35} Among the four Yamanaka factors, Oct4 suppresses inappropriate WNT/ β -catenin-mediated mesoderm differentiation, preventing WNT signaling from becoming overactive, which could lead to ectopic mesodermal gene expression and primes cells to express the mesoderm regulator Brachyury by enabling Nodal/TdGF1 signaling.³⁶ Consequently, with the introduction of Yamanaka factors to the fibroblast, fibroblast cells are genetically reprogrammed and differentiate into iPSCs.

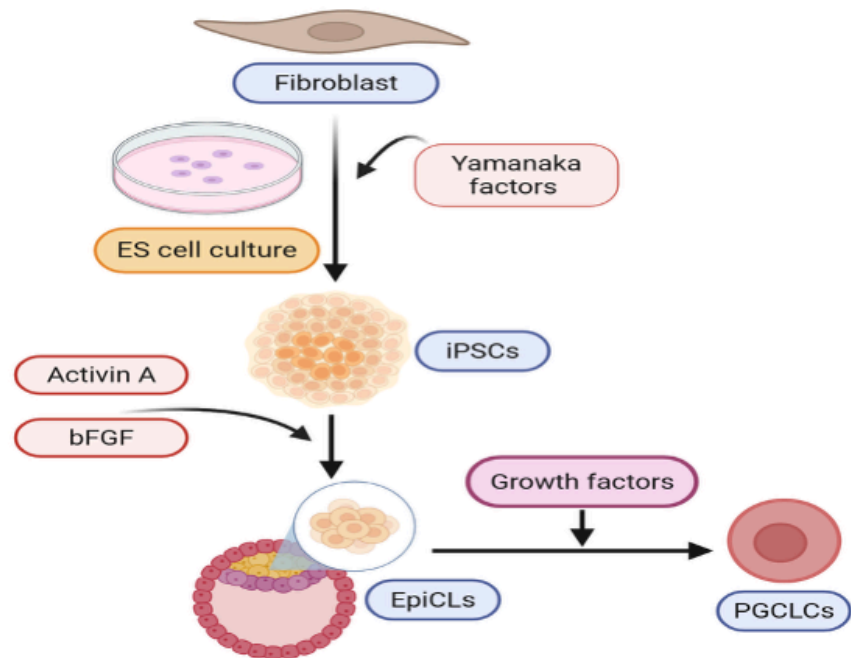


Figure 2: Overview of Differentiation Pathway from Fibroblast to PGCLC
The figure shows the simplified version of the differentiation pathway for generating PGCLCs from the fibroblast stem cells. The figure depicts the three significant steps of the path: first,

making iPSCs from fibroblasts using Yamanaka factors, then EpiCLs from iPSCs using Activin A and bFGF, and then finally PGCLCs from EpiCLCs using a different set of growth factors. Although the figure only represents the differentiation pathway as a three-step process, the mechanism varies for each study, incorporating more steps throughout the differentiation of PGCLCs. Created with BioRender. Rina, J. (2025) <https://BioRender.com/igqzkxc>

After fibroblasts are successfully reprogrammed into iPSCs with Yamanaka factors, they can then enter the second main stage of the differentiation pathway, from iPSCs to PGCLCs^{11, 21, 26, 37}. With the two growth factors, Activin A and basic Fibroblast Growth Factor (bFGF), iPSCs can first differentiate into epiblast-like stem cells (EpiCLs)^{17, 16, 28, 38, 39}. The introduction of the two growth factors is necessary for the progression of *in vitro* gametogenesis.

Activin A, a dimeric protein formed by two β A (INHBA) subunits, is a transforming growth factor-beta (TGF- β) superfamily of cytokines and growth factors and is critical in enhancing the formation of PGCLCs from iPSCs, regardless of the type of test subject^{28, 40}. For example, the exposure of Activin A to mouse skin-derived stem cells in both embryoid body-like aggregates stage (EBLSs) and co-culture stage maximizes PGCLC yield from the iPSCs through the SMAD3 signaling pathway⁴¹. Similarly, for the human subjects, the exposure of Activin A during derivation of human embryonic stem cells (hESCs) improves epiblast-like identity, which is crucial for PGCLC competency, and leads to more consistent and efficient PGCLC differentiation⁴².

Basic Fibroblast Growth Factor (bFGF), or FGF-2, is a family of heparin-binding growth factors, which is "a prototypical ligand among all the members and binds to all the receptor subtypes"⁴³. bFGF exposure is crucial for the *in vitro* proliferation, survival, and maintenance of germline competency in PGCs^{16, 17, 28, 39, 44}. For instance, in the study testing chicken PGCs, only the media that contained bFGF supported colony formation and the continuous proliferation of PGCs⁴⁴. When bFGF was removed from the culture, PGC proliferation was halted, and the rate of apoptosis, a type of cell death, significantly increased⁴⁴. The reintroduction of bFGF restored normal colony morphology and growth, thereby maintaining germline competency⁴⁴. Similarly, in goose PGCs, the *in vitro* propagation

required the continuous presence of bFGF, and the removal of bFGF completely halted the growth of PGCs.³⁹ Supplementing bFGF restored the exponential proliferation of PGCs, and bFGF also worked synergistically with BMP4 to maintain proper cell morphology and functional germline potential.³⁹

After the formation of the EpiCLs with the two growth factors, the EpiCLs can be aggregated with another set of growth factors (LIF, SCF, EGF, and BMP4) that are necessary to differentiate the EpiCLs into PGCLCs^{28, 38, 39}.

BMP4, Bone Morphogenetic Protein 4, is "a member of the TGF β superfamily of intercellular signaling proteins" and is necessary for the initiation of PGC formation²⁸. In the study evaluating the ability of BMP4, samples of homozygous BMP4 embryos, which were null mutants and thus are not affected by BMP4, lacked PGCs when analyzed by alkaline phosphatase (AP) staining and Oct4 expression analysis⁴⁵. In contrast, heterozygous BMP4 embryos, which are affected by the ability of BMP4, had a certain number of PGCs, depending on the dosage of BMP4⁴⁵. Moreover, BMP guides hPGCLCs toward gonadal fate, either as mitotic pro-spermatogonia or oogonia-like cells, suppresses MAPK/ERK signaling, which is linked to DNA demethylation, and facilitates DNA methylation by fostering both de novo and maintenance DNA methyltransferase activities, thereby supporting the *in vitro* gametogenesis process⁴⁶. Stem Cell Factor (SCF), Epidermal Growth Factor (EGF), and Leukemia Inhibitory Factor (LIF) are not necessary for the initiation of PGCLC differentiation, but they do promote the differentiation of PGCs into PGCLCs when used in conjunction with BMP4, which is a critical factor in the process.^{28, 39, 47, 48}

With the exposure of the four transcription factors, BMP4, LIF, SCF, and EGF, EpiCLS can differentiate into PGCLCs that resemble PGCs, which are primary undifferentiated embryonic stem cells and precursors of gametes (sperm and oocytes), and therefore progress towards further *in vitro* gametogenesis, including maturation of oocytes and spermatozoa⁴⁹

3. Evolution of Test Subjects

3.1 Mice

Mice have long served as the foundational model organism for IVG research, playing a central role in the discovery and refinement of the techniques required to convert somatic cells into fully functional gametes.⁵⁰ Nearly all phases of the IVG pathway, from the reprogramming of somatic cells into iPSCs to the generation of PGCLCs and ultimately to the derivation of viable sperm and oocytes, have been successfully demonstrated in mouse models.⁵⁰ This achievement places mice not only as key pieces to the future of the research but also as critical biological examples for validating the safety, reproducibility, and ethical guidelines necessary for potential translation to primates and humans.³⁸

One of the earliest influential research studies on IVG, called “Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors,” was conducted by Kazutoshi Takahashi and Shinya Yamanaka in 2006.⁵¹ In this landmark paper, adult mouse fibroblasts were reprogrammed into iPSCs by insertion of the Yamanaka factors, which could efficiently induce pluripotency, though, at the time, exact mechanisms were not fully understood.⁵¹ Ultimately, they discovered that the induced pluripotent stem cells created in their laboratory demonstrated many characteristics that were very similar to true embryonic stem cells such as the ability to proliferate extensively and express crucial stem cell genes such as OCT3/4, Nanog (though it was found to be nonessential for induction), E-Ras, Cripto, Dax1, Zfp296, and Fgf4.⁵¹ suggesting that the Yamanaka factors were required for successful reprogramming where removing any single gene greatly reduced the cells’ ability to become pluripotent.⁵¹ This approach was highly impactful as it provided an avenue that sidesteps the ethical issues tied to using real embryonic stem cells and opens the possibility of creating patient-specific stem cells from a fibroblast or tissue.⁵¹ Overall, this research marked a major turning point, proving that a small set of defined genes can dramatically change a cell’s fate and provide a powerful foundation for future medical advances.⁵¹ As well, it provided convincing evidence that differentiated somatic cells could revert to a pluripotent state without the use of embryonic stem cells, thus avoiding many of the ethical controversies and immunological problems associated with ESC-based research.⁵¹ Lastly, it showed that iPSCs generated through this method displayed the capacity to differentiate into a wide range of cell

types, including early germline precursor cells, making them essential for the beginning of IVG research.⁵¹

Further research in mice has solidified their role in advancing IVG. A recent study by Murakami et al. (2023) demonstrated the possibility of generating viable oocytes from male somatic cells, a finding that has significant implications for reproductive biology and potential same-sex reproduction²⁴. In this experiment, researchers began by converting fibroblasts from adult male mice into induced pluripotent stem cells²⁴. They then used advanced genetic techniques to remove the Y chromosome and create cells with two X chromosomes, as proper oocyte development requires an XX genetic makeup.²⁴ These genetically engineered cells were cultured under conditions promoting oocyte differentiation and remarkably matured into functional eggs.²⁴ Most importantly, the generated oocytes, once fertilized and implanted into surrogate females, were able to develop into healthy pups, although at a low efficiency rate of 7 pups from 630 embryo transfers.

²⁴ Nonetheless, this outcome represents a significant achievement, confirming that somatic cells from one sex can be reprogrammed and converted into gametes of the opposite sex through IVG²⁴.

As mentioned before, the entire IVG developmental pathway has now been mapped in mice, including the derivation of EpiLCs from iPSCs, specification into PGCLCs, and maturation into gametes using in vitro reconstitution of the gonadal setting.⁵⁴ Each of these stages has been validated in mice, establishing known reproducible findings that serve as a reference for researchers attempting similar processes in other species⁵⁴. These findings not only confirm the biological potential of IVG but also highlight the importance of mouse systems for testing the genetic and developmental potential of lab-derived gametes before any clinical applications can be considered.

Lastly, mouse-based IVG studies also act as a bridge toward expanding this technology to primates and ultimately to humans³⁸. Unlike humans, mice have reduced gestational durations, are highly fertile, and can be genetically modified with ease, making them ideal for quick experiment cycles.⁵⁵

Furthermore, many of their biological developmental processes originated before primates and rodents evolved into separate species and have remained

similar in both ever since, making mice a crucial intermediary model ⁵⁶. As such, findings from mouse IVG studies are increasingly aiding translational efforts in non-human primates, where more complex reproductive systems and ethical considerations begin to mimic those encountered in human contexts ³⁸. The leap from mice to primates is not merely procedural but strategic, giving researchers the ability to refine IVG protocols and long-term outcomes in organisms that are more biologically and evolutionarily relevant to humans.

3.2 Marmosets

Primates have also become an increasingly relevant organism for IVG research as the field moves beyond rodent models and into animals more anatomically and physiologically close to humans ³⁸. Small “New World” monkeys such as marmosets offer crucial advantages over mice not only because of their evolutionary proximity to humans but also due to their more comparable biology, developmental timing, and germline differentiation pathways. ⁵⁷ In addition, marmosets are valuable to researchers because their smaller size, rapid development, shorter pregnancies, and the natural blood chimerism between twin offspring offer unique features that facilitate efficient laboratory studies of reproductive and developmental processes ⁵⁷. With approximately 93% genetic sequence similarity to the human genome, marmosets serve as an accurate model for investigating primate-specific mechanisms that are often absent or overly simplified in rodent systems ^{38, 58}. Thus, these advantages not only strengthen their relevance in IVG research but also position marmosets as a critical bridge for translating preclinical discoveries into human biomedical applications.

Recent research has made significant progress in adapting current IVG techniques to the marmoset model. A memorable study by Seita et al. (2023) successfully generated marmoset primordial germ cell-like cells (cjPGCLCs) from somatic cell-derived induced pluripotent stem cells by growing the iPSCs on a feeder layer with suppressed WNT signaling, which allowed the researchers to influence the cells toward a specific germ cell fate ²⁶. Genetic analysis demonstrated that the resulting cjPGCLCs expressed hallmark markers and gene expression patterns similar to those of naturally occurring marmoset germ cells ²⁶. Furthermore, when these cjPGCLCs were

grown alongside mouse testicular cells, they exhibited features associated with the initial stages of maturation toward gametes, as evidenced by the activation of early gametogenic genes.²⁶ While full derivation of mature gametes has not yet been achieved in marmosets, these findings truly show the cells' capacity to respond to external signals and continue along the germline trajectory under the right conditions²⁶.

Perhaps most importantly, the molecular resemblance of these lab-grown cjPGCLCs to their *in vivo* equivalents, both in terms of critical germline markers and overall gene expression, indicates that the experiment was successful and the cells are following an authentic developmental path.²⁶ This progress not only validates the potential of IVG in a primate system but also marks a key step toward replicating complete functional gametogenesis in species more biologically similar to humans.

3.3 Humans

Lastly, research into the clinical and developmental potential of *in vitro* gametogenesis in humans has advanced significantly in recent years, building on many decades of foundational work in stem cell biology and regenerative medicine utilizing mice and small primate examples.³⁸ At the heart of this progress is the ability to reprogram adult somatic cells into human induced pluripotent stem cells, also known as hiPSCs, which serve as a platform for mimicking the earliest stages of human gamete development.^{60,61} This advancement has opened previously unprecedented avenues for studying germ cell differentiation and infertility treatment in a patient-specific and ethically grounded context.⁶¹

Although mouse models have proven significantly important for discovering early germline development pathways, key transcriptional factors strongly differ between mice and humans.⁶² For example, in mice, the transcription factor BLIMP1 (also known as Prdm1) plays a central role in primordial germ cell (PGC) specification.^{62, 63} In comparison, it has been shown that in humans, the specification of PGCs is critically dependent on SOX17, which functions as a master regulator initiating the germ cell program.²⁵ The importance of these differences is not just academic but carries important implications for biomedical research and its subsequent

translation of laboratory findings to clinical applications in humans.⁵² In more explanation, because the regulatory networks behind germline formation are distinct among species, conclusions drawn from mouse models cannot be directly extrapolated to humans without careful cross-checking.⁵² As a consequence, protocols developed to derive or manipulate germ cells based on mouse mechanisms may not be effective or could even prove misleading when applied to human cells.⁵² Thus, this critical difference in transcriptional regulation of germ cell fate between species has led to a growing body of human-specific research aimed at elucidating the molecular mechanisms underlying primordial germ cell development. For instance, recognizing the limitations of applying findings from mouse models, particularly since SOX17 does not play an equivalent role in mouse germline specification, recent studies have turned to *in vitro* stem cell models to experimentally validate these key regulatory pathways in human cells.²⁵ A crucial study by Irie et al. (2015) utilized a NANOS3-mCherry fluorescent marker to trace back the differentiation of human primordial germ-like cell-like cells (hPGCLCs) derived from human pluripotent stem cells.²⁵ Their findings confirmed that SOX17 serves as the principal initiator of the human germline gene expression system, while BLIMP1 functions downstream as a repressor to suppress the differentiation of hiPSCs to alternative somatic cell types, thereby confirming its commitment to the germline lineage.²⁵ This work provided direct functional evidence for the species-specific regulation of transcriptional control in human germ cell specification and demonstrated the utility of hPGCLC models for researching early germline pathways *in vitro*.²⁵

Building upon this research, another important study by Pandolfi et al. (2022) highlighted the potential of patient-specific IVG models.²⁷ Under this laboratory, researchers derived hiPSCs from dermal fibroblasts of monozygotic twin sister pairs, where in each set, one sister had normal ovarian function and the other was diagnosed with primary ovarian insufficiency (POI).²⁷ These fibroblasts were reprogrammed into hiPSCs using factors such as OCT4, SOX2, KLF4, cMYC, and ascorbic acid.²⁷ The resulting hiPSCs were then induced with Activin A, CHIR99021, and bFGF to form incipient mesoderm-like cells (iMeLCs), which were further

differentiated using BMP4, LIF, EGF, and Y-27632 into hPGCLCs²⁷. Interestingly, both sets of hiPSCs from the sisters exhibited similar competence in generating hPGCLCs, indicating that the initial specification of germline precursors was intact in both individuals²⁷. Thus, the findings of this study suggest that certain infertility disorders, such as POI, may not result from intrinsic problems as both twins' cells were equally capable of forming hPGCLCs²⁷. Instead, infertility may arise in the affected twin due to later disruptions in gametogenesis or from unequal allocation of germ cell precursors during early embryonic development rather than an inherent defect in the ability of their cells to form germ cells.²⁷ Overall, the study's findings support the idea that, at least for some forms of infertility, it is possible to generate hPGCLCs from a patient's own skin cells, offering promise for future fertility treatments²⁷.

Despite these promising developments, the full application of *in vitro* gametogenesis in humans remains in its beginning stages⁵⁴. While hPGCLCs can be reliably produced and validated, the subsequent maturation into fully functional oocytes or spermatozoa capable of fertilization is not fully possible⁵⁴.

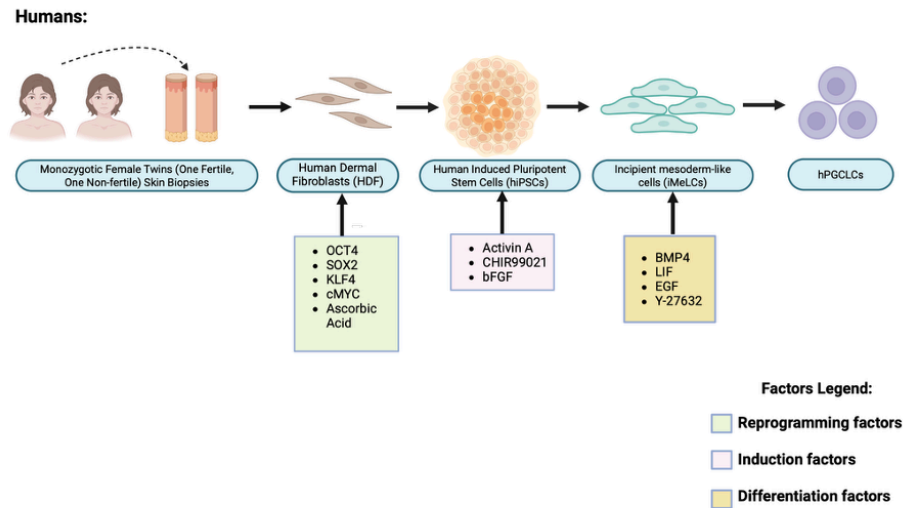
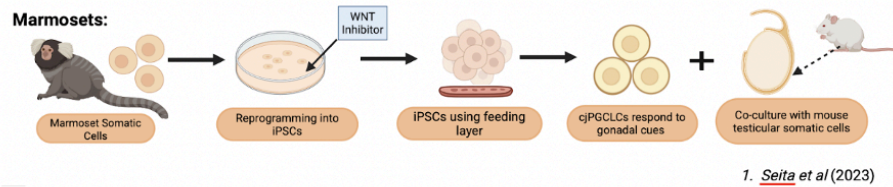
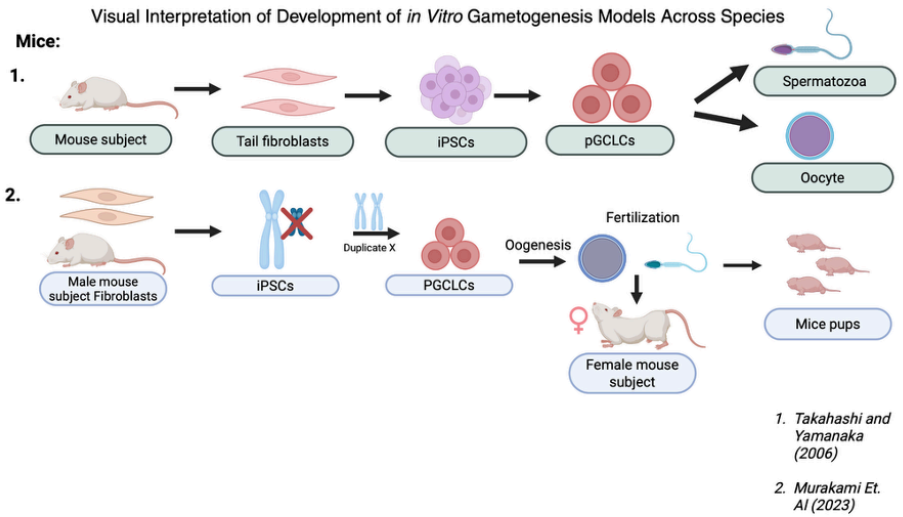


Figure 3. Comparative Overview of *In Vitro* Gametogenesis Models Across Mice, Marmosets, and Humans.

Different species have been studied for generating gametes from somatic cells via induced pluripotent stem cells. In mice, fibroblasts are reprogrammed into iPSCs and differentiated into primordial germ cell-like cells with the successful derivation of functional spermatozoa

and oocytes. Marmoset models use WNT-inhibited iPSC culture and co-culture with mouse testicular somatic cells to induce cjPGCLCs. Current human models remain incomplete, with PGCLCs created but have not yet reached final maturation into functional gametes. Created in BioRender. Barua, N. (2025) <https://BioRender.com/igqzkxc>

4. In Vitro Fertilization

Currently, the gold standard in assisted reproduction technology is *in vitro* fertilization (IVF), a common and widely used technique that involves collecting fully developed eggs and sperm, fertilizing them in a laboratory, and implanting the resulting embryo into the uterus.⁶⁴ To initiate the IVF process, it begins with ovarian stimulation, where hormones like FSH and LH are administered to the female patient to encourage the growth of multiple follicles in the ovaries.⁶⁵ Once the eggs have matured, they are thus retrieved from the ovaries, while sperm is collected either through ejaculation or directly from the testes via procedures like TESA, which involves aspirating a small sample of testicular tissue using a fine needle attached to a syringe, followed by immediate microscopic examination to detect moving sperm.^{65,66} These gametes are then fertilized *in vitro*, and the resulting embryos are kept and incubated for around 3 to 5 days, typically until the blastocyst stage, before one or more are transferred into the uterus.⁶⁷ Revolutionarily, IVF has enabled countless individuals and couples to conceive who otherwise might not have been able to due to infertility, advanced maternal age, genetic disease risks, or other personal circumstances.

⁶⁸

Despite its success, IVF is not without its limitations. The process is often physically invasive, hormonally demanding, and financially difficult to which these challenges are further exacerbated in cases involving patients with Turner syndrome, cancer survivors who have lost gonadal function, or individuals born without viable gametes, because they may have few or no functional eggs available for retrieval.⁶⁹ For these individuals, IVF is typically only possible through donor eggs or sperm.^{69, 70} However, donor-assisted IVF may not be a viable or acceptable option for everyone, due to personal, cultural, or ethical beliefs.⁷¹ IVF also has many biological limitations, including a high failure rate, as many embryo transfers do not result in pregnancy, due to genetic abnormalities in the embryo, which is especially seen in older patients.⁶⁸ For instance, data from the CDC show

that IVF live birth rates drop significantly with age, from 42.8% per cycle for women under 35 to 27.7% for women over 40.¹¹⁵

Other challenges, such as uterine contractions during transfer or immune rejection of the embryo, can also inhibit successful implantation ⁶⁸. In comparison of which factor causes more embryo failures, a research study by Fesahat et al. (2017) examined 97 younger women (37 years and under) and found that about 62.9% of embryos that appeared high-quality under microscope still carried chromosomal abnormalities, such as aneuploidies affecting chromosomes 13, 18, 21 along with sex chromosomes ¹¹⁶. These genetic defects were thus recognized as a leading cause of implantation failure and subsequent unsuccessful embryo transfers.¹¹⁶ Lastly, the cost of IVF in countries like the US can reach up to \$20,000–30,000 per cycle, when donor gametes are involved, thus making repeated cycles financially and emotionally burdensome for many patients.⁷²

With these challenges, the development of IVG is promising as it may one day help overcome some of the inherent limitations of IVF. For example, IVG could provide a solution for individuals who lack functional gametes and could significantly expand the ability of heterosexual individuals, LGBTQ+ individuals, or single parents to have biologically related children without relying on donors.¹¹ However, many cost, ethical, and regulatory obstacles remain before IVG can be considered a viable alternative to IVF in clinical settings.¹³

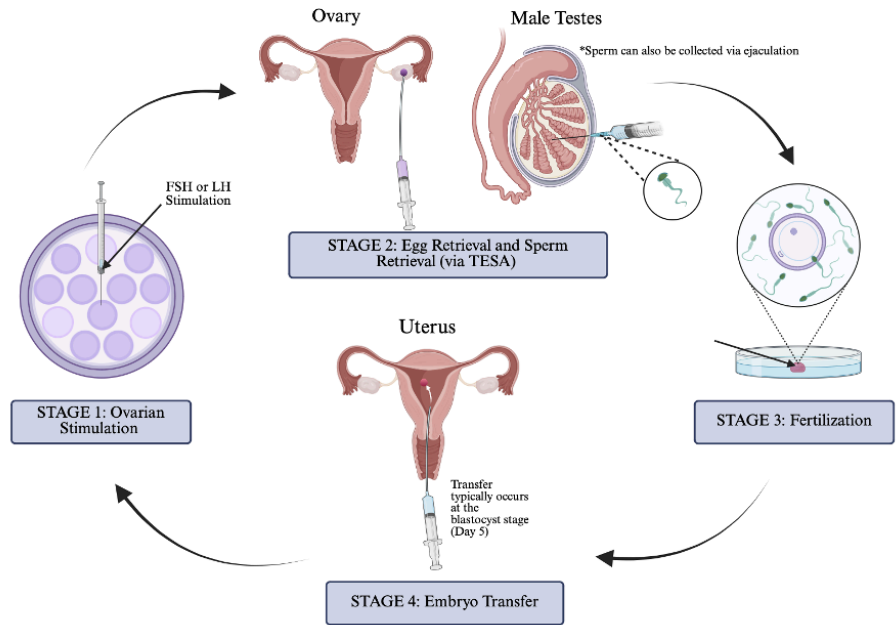


Figure 4: Overview of the In Vitro Fertilization (IVF) Process: From Ovarian Stimulation to Embryo Transfer.

Four main stages of the in vitro fertilization (IVF) process. The first stage involves ovarian stimulation, where hormones such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) are used. In the second stage, mature eggs are retrieved from the ovaries while sperm is collected either through ejaculation or by testicular sperm aspiration (TESA). The third stage is fertilization, where the retrieved eggs and sperm are combined in a laboratory setting to create embryos. In the fourth and final stage, one or more healthy embryos are transferred into the uterus, typically on day five after fertilization. Created in BioRender. Barua, N. (2025) <https://BioRender.com/qb3ocp1>

5. Ongoing Investigations and Clinical Trials

Recently, there have been investigations into different methods of infertility treatment for both men and women using machinery from IVG.

5.1 Female Infertility

Fertilo by Gameto is currently going through Phase III of clinical trials to determine if reproducing an environment that benefits the maturation of oocytes would increase the success rate of fertilization and oocyte maturation⁷⁴. In order to determine if Fertilo is truly successful and safe for future use, researchers are completing a randomized controlled trial: Fertilo versus Medicult In Vitro Maturation (IVM).⁷⁴ The overarching goal of the clinical trial is to evaluate the safety and efficacy of Fertilo for participants

ages 18-35. Fertilo was “designed to recreate an ovarian environment using young ovarian support cells (OSCs), maturing eggs through dynamic feedback during a ~1 day co-culture”.⁷⁵ From participants to cell culture, immature oocytes would be split into two exposures: 1) “cumulus oocyte complexes (COCs), or eggs surrounded by helper cells cultured in Fertilo for 30 hours” and 2) “cumulus oocyte complexes (COCs), or eggs surrounded by helper cells, cultured in Medicult IVM for 30 hours”.⁷⁴ The outcome measurement researchers would gather is the number of ongoing pregnancies at 12 weeks of gestation for each of the two exposures.

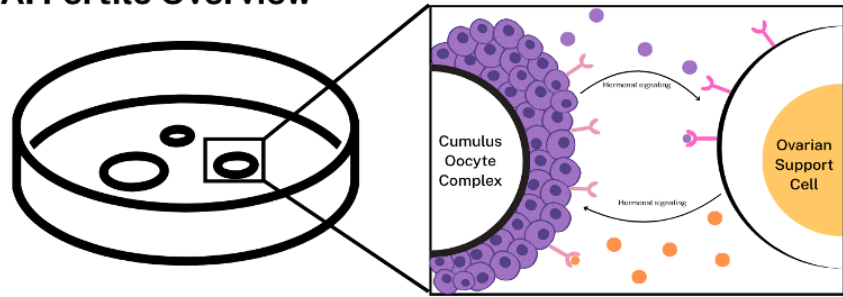
By utilizing these OSCs to co-culture the maturing eggs, it would induce hormonal signaling without additional doses of hormones, such as gonadotropin used in IVF treatments.⁷⁶ Injections of gonadotropin and other hormones to stimulate hormone signaling and growth factors are utilized in IVF treatments for approximately 14 days.

⁷⁴However, they are not completely successful, and women are not meeting their goals with these added hormones.⁷⁴ OSCs were derived from an engineered female iPSC line, and they were induced to behave like a human body’s granulosa cells, producing and responding to key hormones used in signaling. A previous study found that in order to begin generating human primordial germ cell-like cells (hPGCLCs) from human induced pluripotent stem cells (hiPSCs), two transcription factors must be used: NR5A1, RUNX1/2.⁷⁷ The resulting granulosa-like cells, when aggregated with hPGCLCs, support hPGCLC development (measured by DAZL expression) and could aid female reproductive health therapies.⁷⁷ The granulosa-like cells exhibited profiles resembling those of human fetal ovarian cells and replicate essential ovarian functions, including follicle formation and steroid hormone production.⁷⁷ To ensure the differentiation of hiPSCs, researchers had to ensure that OSCs expressed CD82, a marker associated with granulosa cell fate, indicating a successful differentiation.⁷⁶

IVM on its own does not reach the level of success that would be deemed viable to be used as a treatment for infertility. In another previous study related to Fertilo clinical trials, the researchers were able to ensure the OSC-IVM system significantly improved the rate of oocyte maturation in comparison to IVM.⁷⁸ From the OSC-IVM system, matured oocytes were

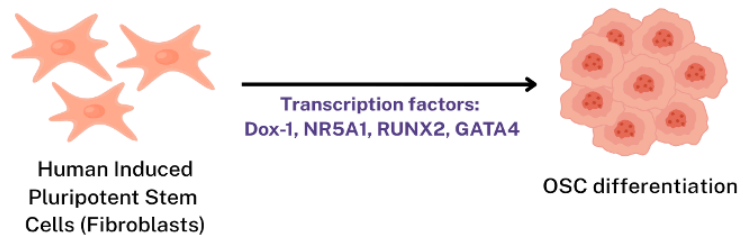
able “to achieve fertilization, to become embryos capable of cell divisions, and to form blastocysts”.⁷⁸ With a co-culture system, researchers utilized this method to recreate the ovarian microenvironment and support oocyte maturation in vitro. Before the transition to Phase III, the researchers determined “OSC-IVM significantly improved metaphase II maturation rates to around 68%, compared to 43–51% in controls”.⁷⁶ With this co-culture system between maturing eggs and OSCs, researchers were aiming to treat the eggs directly, allowing the yield of all healthy eggs that are ready for fertilization.⁷⁵ It also gives hope to the usage of Fertilo, an OSC-IVM treatment, rather than IVF, to reduce the side effects from systemic hormonal injections into the female human body.

A. Fertilo Overview

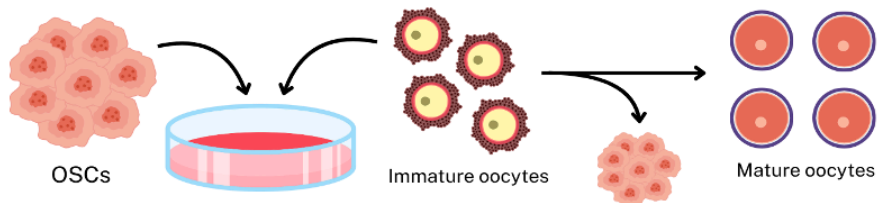


Instead of using hormonal injections as done in IVF treatment, Fertilo utilizes an alternative - ovarian support cells (OSCs) that provide hormonal signaling with the oocyte without any additional hormones added.

B. OSC Differentiation



C. OSC-IVM Co-culture System for Maturing Oocytes



Fertilo uses an OSC-IVM co-culture system. It was compared to traditional IVM treatment, results showing Fertilo having twice the success rate (44% versus 20%) of oocyte maturation.

Figure 5: Fertilo Methodology

The methodology for Fertilo contains the use of OSCs instead of hormonal injections (Figure 5A). The differentiation of OSCs must utilize certain transcription factors (Figure 5B). The overall co-culture system of Fertilo has allowed for higher rates of oocyte maturation in comparison to commercial IVF treatments available (Figure 5C). Created in Canva Nguyen, M. (2025)

5.2 Male Infertility

Researchers have taken a different approach to understanding the reason for male infertility, and ongoing clinical trials are focusing on the genetic aspect. Recently, “ A Study of Therapeutic Spermatogonial Differentiation for Infertile Men Via Testicular Organoid” has been recruiting participants to begin research into genetic markers associated with sterility and failed

spermatogenesis.⁷⁹ By comparing the genomic profiles of fertile (control) and sterile males, researchers will be able to map and delve into the genetic abnormalities associated with sterility and failed spermatogenesis. In order to do so, researchers will collect testicular and skin tissue samples from men, isolating spermatogonial stem cells to construct an ex vivo testis called “iTestis”.⁷⁹ Researchers would measure and compare the successful development of human spermatogonial stem cells (hSSCs) from testicular tissue samples and hiPSCs from skin samples. Both hSSCs and hiPSCs would express specific markers and can differentiate into spermatocytes and spermatids. Using hSSCs and hiPSCs, researchers would culture them with iTestis to determine if human spermatogenesis in vitro (iSperm) would be successful. iTestis is an organoid, a 3D structure resembling an organ (testes in this case), generated through single cells collected from a specific tissue. Previous research on testis organoids within neonatal mice was recorded to be the first to show full spermatogenesis to occur in vivo.⁸⁰ After eight weeks, analyses showed that these organoids formed seminiferous tubules containing spermatogonial stem cells (SSCs) and Sertoli cells, marked by PLZF, UCHL1, and SOX9. By ten weeks, the SSCs were actively proliferating and differentiating. At sixteen weeks, mature spermatids appeared in the organoid lumens⁸⁰. This research provided insight into how the ongoing clinical trial with iTestis is being utilized to study how genes regulate spermatogenesis and their contribution to sterility.

6. Biases in Articles

6.1 Technological Optimism

Despite its promise, IVG literature is marked by several notable biases. One prevalent issue is technological optimism, which is the tendency to believe that technological advances will inevitably lead to positive outcomes, often coupled with an underestimation of unresolved scientific and safety complexities⁸¹. In the context of IVG, this optimism is evident in the way many articles and reviews frame the technology as being on the cusp of revolutionizing reproductive medicine, even though most breakthroughs are confined to pre-clinical animal models and face many challenges.⁸² A prime example of such bias can be seen in the highly popular and widely cited paper

“Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors” by Takahashi et al. (2006), which is often noted as a foundational study for IVG somatic cell-derived iPSC research.²⁰ In this paper, the authors present their findings with a tone of excitement, suggesting that their work is a major step toward solving some of the most pressing challenges in regenerative medicine, such as immune rejection from tissue implantation and ethical concerns associated with embryonic stem cells.²⁰ In fact, the introduction of the paper points to the potential for iPSCs to address diseases like Parkinson’s disease, spinal cord injury, and diabetes, and proposes that generating pluripotent cells directly from a patient’s own somatic cells could sidestep many existing ethical and immunological barriers.²⁰ However, this forward-looking vision is somewhat misleading, as the actual research was limited to mouse models and accompanied by numerous unresolved issues, including low reprogramming efficiency, the risk of teratoma formation, and incomplete reprogramming of some cell lines.²⁰

As well, despite the author’s acknowledgment of the limitations of their experiment in later sections of the paper, the overall narrative still leans toward future clinical application.²⁰ The writing used, such as “However, we still do not know whether the four factors can generate pluripotent cells from human somatic cells. Use of c-Myc may not be suitable for clinical applications ... Nevertheless, the finding is an important step in controlling pluripotency, which may eventually allow the creation of pluripotent cells directly from somatic cells of patients,” hints at a subtle sense of progress inevitability.²⁰ This rhetorical pivot can be quite confusing to the reader, as on one hand, the authors clearly state that the technique is not ready for clinical use due to challenges like c-Myc’s inadequacy and the need for certain environments.²⁰ Yet on the other hand, they then frame the result as an important milestone, implying that the creation of patient-specific iPSCs is within reach due to their research.²⁰ This contrast sends a mixed message to the audience, suggesting caution while simultaneously promoting optimism, which may confuse many about the true distance between experimental findings and clinical implementation. It is important to note that this pattern is not unique to this study but is reflective of a broader trend in the literature, where the excitement surrounding new technologies

often overshadows the reality of scientific uncertainty, regulatory hurdles, and the need for rigorous testing.⁸³ As a result, both the scientific community and the public may develop unrealistic expectations about the timeline of IVG's clinical adoption, potentially influencing funding priorities and policy decisions in ways that are not fully grounded in the current state of the science.

6.2 Confirmation Bias

Closely related to technological optimism is the issue of confirmation bias, which refers to the tendency of researchers and authors to focus on data and results that support the promise of a new technology while insufficiently addressing contradictory evidence, limitations, or failures⁸⁴. This bias is not unfamiliar in the presentation of experimental results in IVG research, where successful outcomes are often highlighted and celebrated while setbacks, low efficiencies, and off results are relegated to supplementary sections. For example, in the study "Generation of functional oocytes from male mice in vitro" by Murakami et al. (2023), the researchers present a technological breakthrough in the generation of functional oocytes and live offspring from reprogramming male-derived mouse somatic cells into iPSCs, manipulating their sex chromosomes, and differentiating them into functional oocytes.²⁴ The paper's tone and structure place strong narrative emphasis on the achievement of successful fertilization, implantation, and birth of healthy, fertile offspring derived from these oocytes, reinforcing the sense of progress and possibility.²⁴ However, a closer examination of the study reveals that the efficiency of the process was extremely low, where only 7 live births resulted from 630 embryo transfers, translating to a success rate of just 1.1%.²⁴ This important limitation is acknowledged in the text but is not given the same prominence as the positive outcomes²⁴. Instead, it is buried in the results section and included in supplementary data, making it less visible to readers who may simply focus on the abstract and headline findings.

²⁴This notion is further supported in the journal article "Stem cell-derived gametes: what to expect when expecting their clinical introduction," as the authors claim that Murakami's technique to create XX cells was functional but limited in efficiency, yielding only a small number of successes and sparking substantial safety concerns, including the risk of aneuploidy due to a chemical missegregation agent

⁵³ Thus, the

original research study's selectivity in reporting of outcomes is an example of scientific "spin" as researchers will try to elevate the positive impact of this research while downplaying the negative or less important impact.⁸⁵ By emphasizing successes and glossing over failures or unsupportive data, the literature can create a distorted picture of the current state of the science, leading to overestimation of the readiness of IVG for clinical application. Furthermore, confirmation bias can influence not only the reporting of experimental results but also the interpretation of data and the framing of future research studies.⁸⁶ Some papers may cite only those works that support their hypotheses or desired outcomes, while ignoring or dismissing conflicting evidence.⁸⁶ These citation selection processes contribute to a self-reinforcing cycle in which the perceived promise of IVG is continually amplified, even with the rise of significant scientific, technical, and ethical complications. In the long run, such bias can hinder the field's progress by discouraging critical scrutiny and open discussion of the obstacles that must be overcome before IVG can become a safe and effective option for human reproduction.

6.3 Western-Centric Ethical Focus

Lastly, a third bias seen in the research on IVG concerns the dominance of Western-centric ethical perspectives. Much of the scholarly and policy writing on the subject is shaped by the legal, cultural, and philosophical concerns of Western societies, particularly those of the United States and Europe. This focus is evident in the way ethical arguments around IVG are often framed in terms of issues such as embryo destruction, germline modification, and the risk of eugenics, with reference to specific Western policies and bioethical principles.^{13, 110} For example, the *In Vitro-Derived Human Gametes as a Reproductive Technology: Scientific, Ethical, and Regulatory Implications: Proceedings of a Workshop of a 2023 workshop* novel on IVG devotes a considerable amount of attention to ethical concerns from US law and policy, such as the Dickey-Wicker Amendment, which restricts federal funding for research involving the destruction of human embryos.^{87, 110} The discussion is further shaped by bioethical issues that focus on individual autonomy, reproductive rights, and access to technology, values that are central to liberal Western societies.¹³ While the workshop does seem aware of a global presence as they include a brief

section on worldwide impact acknowledging that “medical ethics are based on the moral, religious, cultural, and philosophical ideals and principles of the society in which they are practiced,” and notes that different societies may have divergent views on the acceptability of IVG for various purposes (such as infertility treatment, disease prevention, or use by same-sex couples), these perspectives and their importance are treated as secondary to the main discussion.¹³ This Western-centric approach has several important implications. First, it risks marginalizing or overlooking the ethical and cultural norms of non-Western societies, where attitudes toward reproduction, family, and biotechnology may be significantly different.⁸⁸ For example, in some cultures, the creation of gametes outside the human body or the use of reproductive technologies by unmarried individuals or same-sex couples may be viewed as morally unacceptable, regardless of potential medical benefits.⁸⁹ By treating these perspectives as peripheral or as mere commentary, the literature fails to engage fully internationally with the global diversity of ethical practices. Finally, the lack of genuine engagement with non-Western perspectives can limit the richness and depth of ethical analysis in the field.⁹⁰ By broadening the conversation to include a wider range of cultural, religious, and philosophical viewpoints, researchers and policymakers can gain a more nuanced understanding of the potential benefits, risks, and social implications of IVG. This, in turn, can help ensure that the development and use of the technology are guided by principles that are responsive to the needs and values of diverse communities around the world.

In summary, the literature on IVG is shaped by several significant biases, such as technological optimism, confirmation bias, and a Western-centric ethical focus. These biases influence how the science is reported, how its promise and limitations are understood, and how ethical and policy debates are framed. Recognizing and critically examining these biases is essential for creating a more balanced and realistic conversation about the future of IVG and its place in society.

7. Ethical Limitations

7.1 Ethical Issues with IVG

In vitro gametogenesis (IVG) is gaining traction in biomedical research, offering promising possibilities for reproductive medicine, though significant ethical and regulatory challenges continue to limit its clinical application. Ethical concerns surrounding solo reproduction rise due to the risk of serious genetic defects and can be considered by some scientists as ethically unjustifiable due to the heightened risk of genetic abnormalities and lowering genetic diversity.⁹¹

Multiplex parenting involves creating a child from the genetic material of more than two individuals using IVG methods, which goes beyond the conventional two-parent model. Multiple genetic contributors can lead to complicated family structure and cause issues regarding parental rights and responsibilities.⁶¹ This issue further leads to the idea of genetic selection, better known as designer babies. IVG can possibly enable “preference-matched offspring.”⁹² Picking desirable genes is often considered morally and ethically problematic, as it aligns with the principles of eugenics. However, the potential of genetic selection does not necessarily render IVG morally unacceptable as a whole.

IVG could increase the risk of exploiting embryos without proper consent frameworks, since gametes created through IVG can be “generated from anybody’s cells,” making the establishment of clear consent protocols critical to safeguarding individual autonomy and reproductive rights.⁹¹

7.2 Conclusive and Inconclusive Results

In mice, researchers Mitinori Saitou and Katsuhiko Hayashi made significant progress by successfully producing functional sperm and egg cells using only induced pluripotent stem cells (iPSCs).¹³ After reprogramming mouse somatic cells into iPSCs, they were able to differentiate them into primordial germ cell-like cells (PGCLCs). When grafted into a living mouse, these PGCLCs developed into viable gametes after being mixed with embryonic gonadal tissue. The full reconstitution of gametogenesis from iPSCs in a mammalian model was demonstrated by the production of healthy, fertile offspring during fertilization using the lab-grown sperm and egg cells.¹³

However, applying these discoveries to humans has proven to be much more difficult. Even though human PGCLCs have been successfully produced in vitro from iPSCs, these cells have not yet developed into fully functional gametes.⁹³ The human germ cell maturation process is still unfinished and poorly understood, in contrast to that of mice. To date, no fully mature, functional human gametes have been produced, despite some progress, including the differentiation of human iPSCs into PGCLCs and meiotic haploid germ-like cells, especially sperm-like cells and early-stage oogonia.⁹⁴

Several challenges remain, including the completion of meiosis, full epigenetic reprogramming, maintenance of the genomic integrity, and the ability to support full maturation in vitro without relying on transplantation of gonadal tissue.^{93, 95} These obstacles highlight both the technical limitations and ethical challenges of applying in vitro gametogenesis in humans.

7.3 Global Ethical Concern

Globally, legal responses to in vitro gametogenesis (IVG) vary widely, reflecting differing ethical, cultural, and regulatory perspectives on artificial reproduction. In countries like Germany, IVG for reproductive purposes is strictly prohibited under national bioethics laws, such as Germany's Embryo Protection Act. This act strictly prohibits practices that would be necessary for in vitro gametogenesis. The Act forbids fertilizing an egg for any purpose other than achieving pregnancy in the woman from whom the egg was taken. These provisions mean that creating embryos in vitro, manipulating them outside the body, or gestating them in an artificial environment are all legally restricted. Because IVG involves generating gametes and embryos from stem cells and gestating them in non-traditional contexts, it would violate multiple sections of the ESchG, which is designed to tightly regulate and ethically constrain embryo use. As a result, IVG, even as a research endeavor, remains incompatible with the current German legal framework.⁹⁶

France's current bioethics legislation, the Law on Bioethics of August 2, 2021, bans the creation of embryos from lab-grown gametes. The law

forbids creating embryos for research and only permits work on embryos for the purposes of IVF, which is still controlled under strict regulations. Additionally, the French Public Health Code reinforces these restrictions by banning embryo genome editing, cloning, and any reproductive technique that might alter the genetic identity of future generations. As a result, IVG is effectively banned in France, as all stages necessary for its implementation are either directly prohibited or legally .⁹⁷

The United Kingdom also currently prohibits the use of IVG in reproduction under the Human Fertilisation and Embryology Act, though recent reports from the HFEA suggest growing pressure to regulate the technology more explicitly.⁹⁸

Japan and China permit IVG research but ban its clinical application, maintaining a clear line between experimental use and human reproduction.^{99, 100} The United States lacks a comprehensive federal ban, but the FDA strictly regulates any clinical application, and state-level laws and funding restrictions, such as the Dickey-Wicker Amendment, create additional barriers.¹⁰¹

7.4 Germline Editing

Any potential clinical use of gametes obtained from IVG raises the same exploitation issues that Malmqvist pointed out in the context of first-in-human germline gene-editing experiments. The transfer from laboratory approval to human use would expose participants and, consequently, their future offspring to irreversible reproductive threats without guaranteed therapeutic benefit, even if IVG procedures are able to produce morphologically normal oocytes and spermatozoa in vitro. This vulnerability is similar to Malmqvist's "exploitation problem." Therefore, before any clinical implementation can be ethically justified, IVG must meet strict preclinical standards that demonstrate consistent genomic imprinting, epigenetic fidelity, and functional competence in animal models in order to adhere to the ethical ideal of non-exploitation.¹⁰²

8. Future Directions/Discussion

8.1 Reproduction for Heterosexual Couples Suffering from Infertility

One of the most immediate and widely discussed clinical uses for IVG is in providing a new solution for infertility among heterosexual couples, particularly when one or both partners cannot produce functional gametes.⁹¹ Male individuals diagnosed with azoospermia, where no sperm are

present in the ejaculate, and female individuals with premature ovarian insufficiency, where ovarian activity ceases before the age of 40, represent key populations that could benefit from IVG-derived gametes.⁹¹ This also includes individuals who have lost reproductive capacity as a result of gonadotoxic cancer therapies, such as chemotherapy and radiation, which can irreversibly damage germline tissue.¹⁰³

Traditional assisted reproductive technologies such as IVF are often not viable for these patients where the standard approach relies on functional sperm and eggs, or alternatively, the use of donor gametes, a practice that raises complex ethical, cultural, and personal concerns for many couples.¹⁰⁴ For instance, some patients may find third-party gamete donation emotionally distressing or inconsistent with their desire for biological relatedness, while others particularly of certain races and ethnicities, may view it as contrary to societal expectations.^{59, 73} Thus, IVG introduces a radically new approach to this issue by enabling the derivation of autologous gametes from a patient's own somatic cells, such as skin fibroblasts.⁵³ The process would begin with the collection of somatic cells from each partner. These cells would then be reprogrammed into induced pluripotent stem cells using established techniques, such as utilizing transcription factors like OCT4, SOX2, KLF4, and c-MYC.¹⁰⁵ Once reprogrammed, the iPSCs would be guided along the germline differentiation pathway to form PGCLCs.¹¹ For the male partner, iPSCs would be differentiated into sperm-like cells, either through co-culture with testicular somatic cells or via *in vitro* mimicking of spermatogenesis.¹⁰⁶ For the female partner, iPSCs would be induced to form egg-like cells, often involving a more complex and hormonally regulated environment to support oocyte maturation.⁷⁸ Once both functional sperm and oocytes are generated *in vitro*, conventional assisted reproductive techniques would be

used to combine the gametes and create embryos though this application has only been tested in mice models.⁶² If clinically validated, this process would make it possible for infertile individuals to conceive without requiring donor material to which it has been reported that the ability to conceive a genetically related child offers profound psychological relief for many infertile couples, as existing literature has shown that infertility can lead to depression, anxiety, loss of identity, and relationship strain.⁹¹ Overall, for couples who are unable to pursue traditional ART or are unwilling to use donor gametes, IVG presents a potential future conception pathway for many heterosexual couples that is biologically, emotionally, and ethically aligned with their values. The creation of these gametes could significantly expand reproductive autonomy, particularly for those whose fertility loss was unexpected, unpreventable, or medically caused.⁶¹

8.2 Possibilities for Reproduction Equality with Same-Sex

Reproduction

IVG also holds substantial potential for same-sex couples who hope to have biologically related children. In traditional reproduction, two individuals of different sexes are required to produce biological offspring. However, same-sex couples, whether two males or two females, typically rely on egg or sperm donors and surrogates to become parents.^{13, 61} Although these options can result in loving and complete families, they often entail complex legal and emotional challenges where typically only one partner is genetically related to the child.⁹¹ With IVG, it may become possible for both partners in a homosexual couple to conceive a child by inducing iPSCs derived from their somatic cells into gametes of the opposite type¹⁰⁷. For instance, both partners could contribute genetically to an offspring by converting one partner's somatic cells into the opposite associated gamete, such as sperm from female-derived cells or oocytes from male-derived cells.¹⁰⁷ Though currently speculative, this application has been partially studied

in animal models. For example, Murakami et al. (2023) demonstrated that functional oocytes could be generated from male mouse somatic cells, resulting in the birth of healthy and fertile offspring²⁴. The efficiency was low, only 7 births out of 630 embryo transfers were successful, but the proof of principle is quite significant.²⁴ If translated to human systems, this development would allow for truly equal genetic parenthood among

same-sex couples, removing the need and challenges of third-party donation and aligning reproductive possibilities with values of inclusivity¹³ That said, transitioning this application to clinical use in humans remains a far-off goal. Technical challenges include the reprogramming of sex chromosomes and unknown effects on offspring health.⁴⁶ Ethical concerns, which will be discussed in detail, will also need to be navigated, particularly those related to germline modification and the societal reaction of manipulating aspects of natural human reproduction.¹⁰⁸

8.3 Solo-Reproduction

CloLastly, a third potential clinical application of IVG is solo-reproduction.¹⁰⁹ In this scenario, a single individual could theoretically produce both

gamete types from their own somatic cells, like skin cells, allowing for the creation of offspring without a genetic partner.¹⁰⁹ While this application remains highly theoretical and poses many ethical and genetic risks due to a lack of genetic diversity, it highlights the vast range of possibilities opened by IVG technologies.¹⁰⁹

8.4 Research Applications of IVG

Beyond clinical use, IVG serves as a powerful model for studying early human development and reproductive biology, as the controlled generation of PGCLCS and their maturation into gametes outside the body allows scientists to replicate aspects of human gametogenesis in laboratory settings.⁴⁷ A notable example of this is the construction of xenogeneic reconstituted ovaries (xrOvaries) in which human PGCLCS are combined with mouse somatic ovarian cells to recreate a typical ovarian environment, allowing for research into the early development of oogonia and their interactions with somatic ovarian cells.¹⁵ These systems can be further enhanced through organoid technologies and microfluidic platforms, which simulate *in vivo* conditions and allow for fine control of physical and chemical microenvironments.¹¹¹ IVG has also supported the creation of 3D stem cell-derived constructs such as embryoids, blastoids, and gastruloids.¹¹¹ These structures replicate specific milestones in human embryogenesis and serve as ethical alternatives to studying real embryos.¹¹¹ Researchers use them to investigate essential developmental events such as tissue organization, body axis formation, and germ layer specification, processes that are otherwise difficult to observe directly due to strict regulations.¹¹¹ Additionally, IVG has opened new doors for studying how germ cells undergo molecular and epigenetic changes.¹¹¹ Findings

from IVG-based studies have provided insight into crucial reprogramming events like the erasure of DNA methylation, the resetting of genomic imprints, and the reactivation of the X chromosome, all vital steps during early development.¹¹¹ Understanding these changes has merit not only for reproductive research but also for the broader field of regenerative medicine and stem cell biology. Lastly, another exciting area of application of IVG lies in pharmacological screening and environmental toxicology, where *in vitro models* of human germ cell development offer a non-invasive, ethically sound, and human-relevant platform for identifying compounds that disrupt meiosis or compromise gamete quality.²² When developed from patient-specific induced pluripotent stem cells, these models can even be tailored to assess individual risk for fertility issues related to toxic exposures.²² Coupling IVG with tools like CRISPR-Cas9 also enables the creation of

genetically defined infertility models, which can be used to test treatments or understand how specific mutations affect germ cell development.²²

8.5 Translational Avenues from Other Fields

Several techniques developed in other scientific fields hold promising potential for advancing IVG research by adapting proven research methodologies to fertility preservation and reproductive technologies. One notable example comes from wildlife conservation biology, where somatic cell cryopreservation has been successfully employed to safely hold genetic material from endangered species.¹¹² In a study by Katayama et al. (2022), avian fibroblasts were cryopreserved for periods ranging from eight to twelve years and later reprogrammed into functional iPSCs with retained viability and full reprogramming ability. This long-term preservation technique demonstrates the reliability and strength of cryopreservation techniques for maintaining somatic cells over extended years, thus ensuring that valuable genetic information can be effectively banked and utilized many years after initial collection.¹¹² Translating this approach to human fertility preservation, patients who face infertility risks due to aging, disease, or medical treatments could similarly “bank” somatic cells before undergoing fertility treatments.¹¹² This strategy would provide a crucial resource for future IVG applications, where stored somatic cells could successfully be reprogrammed and guided through gametogenesis *in vitro*, enabling the generation of functional gametes for reproduction.¹¹² The parallels between conservation biology and human IVG truly highlight how cross-disciplinary

techniques can transfer and accelerate the development of clinical fertility treatments.

In addition to somatic cell storage, another relevant area is the biobanking of testicular tissue containing spermatogonial stem cells (SSCs).¹¹³ In a study by Damyanova et al. (2024), researchers investigated the collection and cryopreservation of tissue from testicles with SSCs focusing on samples from pre-adolescent boys exposed to gonadotoxic therapies that pose a significant risk to their reproductive potential.¹¹³ Their research process involved isolating testicular tissue before the toxic treatments commenced, preserving the SSCs by cryopreservation, and then storing these tissues long-term for potential use in reproduction function recovery.¹¹³ As well, this paper examined how SSC techniques including cryopreservation of testicular tissue, laboratory expansion of stem cells and complete *in vitro* spermatogenesis can be adapted for both human fertility restoration and the conservation of endangered species.¹¹³ It emphasizes that while many of these methods were first developed in animal models and share conserved biological features across species, significant knowledge gaps are there for non-model organisms, like marsupials, meaning that species-specific research is essential to optimize the technologies for diverse ecological and medical applications.¹¹³ While the clinical application of *in vitro* spermatogenesis from SSCs remains largely conceptual at present, the preservation of these cells provides a foundation for fertility restoration techniques aligned closely with IVG goals.¹¹³ Cryopreserved SSCs offer the possibility of maturing sperm *in vitro* once the necessary technologies become clinically viable, potentially restoring reproductive potential for individuals who otherwise would face permanent infertility.¹¹³ Overall, these techniques from somatic cell cryopreservation and SSC biobanking illustrate the convergence of methodologies that could be adapted and optimized for human IVG research.¹¹³ By utilizing advances in cell storage and stem cell biology from different fields, the scope of IVG may expand beyond its current experimental boundaries toward practical applications, ultimately expanding reproductive options for patients worldwide.

8.6 Cost Implications of IVG

While there are not many projections on the potential numerical cost of IVG, In Vitro-Derived Human Gametes as a Reproductive Technology: Scientific, Ethical, and Regulatory Implications: Proceedings of a Workshop of a 2023 workshop novel, predicts that the new reproductive technology will initially cost more than *in vitro* fertilization, the most popular form of ART for infertility in patients, because “compared with other ART technologies, which were largely developed without considering the implications of commercialization, IVG has received initial investment and commercial interest, which may affect its ultimate cost.”¹¹⁷ This expectation theoretically makes sense, given that the concept of IVG has been discussed since 2006, and in recent years, start-up companies have emerged, such as Conception in 2018, which has secured approximately 20 million dollars through three rounds of private funding in 2021, with the aim of commercializing IVG for human medical applications.^{118, 119} Further supporting this projection, the workshop report indicates that business interests and funding models are likely to influence the eventual price, particularly as “supply and demand” from individuals seeking alternative infertility solutions could make the cost of IVG even more expensive.¹¹⁷ This could potentially lead to IVG becoming an exclusive option accessible only to wealthy patients, mimicking socioeconomic divides first seen in the early days of IVF.¹¹⁷ Therefore, if the introduction of IVG into clinical practice is similar to the pattern of IVF, it is likely that the treatment will remain high at first, making it mostly available only to those with high income.¹¹⁷ Interestingly, this wealth gap may contribute to persistently high prices for IVG because of perceived value tied to exclusivity where there is a “view [that] exists in some circles that ‘the most advanced technology regardless of cost is better’ ... this attitude may be based upon the perception that expensive resources are inherently valuable”¹¹⁷. This phenomenon of believing that technologies are better simply because they are new links back to a classic psychological bias called novelty bias, which has been documented before, notably in up-and-coming drug medical treatments^[120]. Overall, while IVG technology holds high promise for advancing fertility treatment, its projected costs, driven by a combination of early investment, market demand, and attitudes about technological novelty, raise concerns about financial accessibility¹¹⁷. Unless careful steps are taken, IVG may initially follow the trajectory of IVF, remaining out of reach for many

and potentially contributing to and deepening socioeconomic divides in access to reproductive healthcare ¹¹⁷. As IVG advances toward clinical use, addressing these economic and social barriers will be crucial to ensuring that its benefits are shared equitably.

9. Conclusion

In vitro gametogenesis serves as a promising solution for diverse infertility needs and particularly uses skin cell-derived induced pluripotent stem cells (iPSCs) to create these gametes and holds significant promise for overcoming infertility in a wide range of individuals, including cancer survivors, LGBTQ+ couples, and those with traditional infertility causes. Recent scientific advancements have brought IVG to the threshold of clinical reality. Although fully functional human gametes have yet to be matured entirely *in vitro*, the efficient differentiation pathway of induced pluripotent stem cells into primordial germ cell-like cells has made pivotal breakthroughs. However, in mouse models, IVG-derived gametes have been matured fully *in vitro* and have been fertilized to produce viable, healthy offspring. As a crucial proof of concept for the entire IVG perspective, alternative test subjects have led to the conclusion that IVG-derived gametes can fully mature *in vivo* and create offspring. Early-phase clinical trials are underway utilizing ovarian support cell (OSC) co-culture systems to assess the safety, efficacy, and potential to improve oocyte quality with fewer hormonal interventions than conventional IVF. ¹¹⁴

Regulations and ethical concerns must be taken into account in order to assess the technological advancements of IVG. IVG, being a fairly new reproductive advancement, raises questions around solo and multiplex reproduction, identity, exploitation, and equitable access. If the process of IVG is thoughtfully designed, these frameworks can also foster public trust and promote transparency. Current legislation surrounding IVG varies widely across the world, from strict bans on clinical usage to permissive research permissions. Heavily regulated guidelines and transparency are essential in preventing misuse and ensuring that IVG benefits are distributed justly across populations to prevent harm and create a supportive pathway for safe clinical translation of IVG. ¹³

In order to promote full gamete maturation in humans, future studies and clinical applications should concentrate on three-dimensional organoid systems and microenvironmental cues. Integrating IVG with gene editing tools and personalized medicine approaches holds promise for both treating fertility and for modeling human gametogenesis, embryogenesis, and toxicology in vitro. Such models have the potential to transform our knowledge of early developmental processes and facilitate the development of innovative infertility treatments⁶².

Ultimately, in vitro gametogenesis has the theoretical potential to transform reproductive medicine by expanding patient options beyond hormone-intensive IVF. In return, reducing side effects that may be treatment-related and addressing complex fertility challenges, which include genetic infertility, age-related oocyte decline, and treatment-induced infertility. In order to guarantee safety, effectiveness, and fair access, achieving these objectives will require ongoing interdisciplinary collaborations that bring together stem cell biologists, reproductive endocrinologists, bioengineers, ethicists, and regulators. Through this collective effort, in vitro gametogenesis stands to become not merely a marginal improvement but the foundational technology underpinning next-generation fertility care.

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