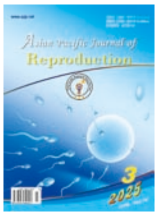

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A narrative review of spermbots in assisted reproduction: Integrating AI for enhanced fertility outcomes and future innovations

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ABSTRACT

Sperm-structure-integrating nanodecorated microrobots have shown promise in medicine delivery and infertility treatment. A variety of spermbots use cutting-edge nanomaterials and 3D printing technology to enhance their functioning, such as biomimetic sperms and flagellate microorganisms. The success rates of assisted reproductive technology techniques like *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) may increase as a result of these developments. Furthermore, the incorporation of artificial intelligence (AI) into spermbots has the potential to optimize reproductive therapies by reducing inherited illnesses through genetic screening and editing. However, before the widespread implementation of spermbots in clinical practice, several critical aspects must be addressed. Thorough investigations into biocompatibility, ethical considerations, and long-term safety are necessary to ensure that these technologies are safe and effective for *in vivo* applications.

KEYWORDS: Spermbots; Micro robotics; Artificial intelligence (AI); Assisted reproductive technology (ART); Intracytoplasmic sperm injection (ICSI); Male infertility

1. Introduction

Infertility is estimated to impact 8%–12% of couples worldwide, and in about 50% of cases, a male factor is either the primary or contributory issue[1]. The World Health Organisation (WHO) defines male infertility as a man's inability to conceive a fertile female throughout a minimum of one year of consistent, unprotected intercourse. About 20% of cases are the only result of the male, while another 30% to 40% of cases of infertility have the male as a contributing component[2]. Features of male infertility are typically defined as abnormal semen parameters observed during semen assessment or abnormal physiological results during sexual or ejaculatory processes. The most prevalent anomalies found in semen are teratozoospermia (less than 4% typical forms), asthenozoospermia (less than 42% motile), oligospermia (low volume, less than 1.5 mL) and oligozoospermia (less than 15 million spermatozoa/mL). When sperm motility is less than 40% (severe asthenozoospermia) or when sperm are incapable of moving, male infertility is classified as clinically severe. According to a new retrospective study and meta-analysis, environmental exposure and adverse lifestyle decisions have been contributing to a sharp decline in human sperm quality over the past few decades[3].

According to the American Centres for Disease Control (CDC), assisted reproductive technologies (ART) comprise any fertility-related procedures that involve the manipulation of eggs or embryos. Intrauterine inseminations and other similar procedures that involve the manipulation of only sperm are not covered by this definition. The criteria also do not include treatments where ovarian stimulation is carried out without a strategy for egg retrieval. Variations in ART practice outcomes are a defining feature. Standardising ART practice globally and enhancing outcomes could be facilitated by reaching an international consensus on

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the definition of ART success that takes perinatal outcomes into consideration[4].

A biohybrid microrobot powered by sperm cells is called a "spermbot". A mature mammalian sperm's structure is composed of three separate sections: the head, midpiece and tail. In particular, haploid chromosomes—the paternal genetic components necessary for zygote formation—are found in the head region. The tight encirclement of the axoneme by the mitochondrial sheath forms the midpiece region. It is so believed that the midpiece generates the energy required to drive sperm movement. Lastly, the cilium, the fundamental building block that powers sperm motility, is specialised in the tail or flagella region[5]. The so-called "spermbot" offers us with an innovative chance for developing fascinating ART applications. Significant advancements have been made in the design and optimisation of several spermbots, or sperm-like nanorobots, throughout the last ten years. Potential uses of spermbots can be divided into two categories: medication delivery and infertility therapy. However, the application of these nanorobots in clinical practice is behind, particularly in the realm of ART.

2. Methodology

This narrative review employed a systematic literature analysis approach selecting publications from 2014 to 2024, utilizing scientific databases including Scopus, PubMed and Google Scholar. The search strategy used key terms such as "spermbot," "microrobotics," "assisted reproductive technology," "biohybrid robots," and "artificial intelligence in reproduction," combined using Boolean operators. Studies were selected based on predefined inclusion criteria: peer-reviewed articles, clinical trials, systematic reviews, and technological reports specifically addressing spermbot development, applications in ART, or related artificial intelligence (AI) integration. The methodology involved a three-stage screening process: initial title and abstract review, full-text assessment, and quality evaluation. Data extraction focused on five primary domains: spermbot design and architecture, navigation mechanisms, integration with ART procedures, safety and biocompatibility assessments, and future technological developments. Special emphasis was placed on studies demonstrating practical applications or clinical potential, with particular attention to those incorporating AI elements or advanced control systems. The analysis included both qualitative synthesis of technological developments and quantitative assessment of performance metrics where available.

3. Fundamental biology and spermbot architecture

Sperm is designed to spread paternal genes by leveraging this maternal investment: it is often extremely motile and streamlined for speed and efficiency in the fertilisation process. Sperm competition is strong, and the vast majority fail in their mission: only a few of the billions of sperm discharged during a human male's reproductive life successfully fertilise an egg[6,7].

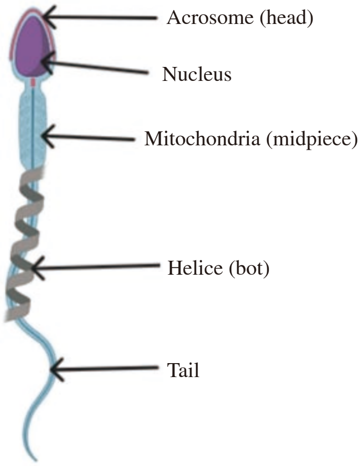

Figure 1. Microhelice sperm structure.

Typically, sperm are "stripped-down" cells that lack cytoplasmic structures like ribosomes, endoplasmic reticulum, or the Golgi apparatus, which are superfluous for the process of transferring DNA to the egg. Instead, they are armed with a powerful flagellum to drive them across an aqueous medium. On the other hand, sperm have a large number of mitochondria that are positioned so that they can stimulate the flagellum most effectively[8].

A spermbot's hybrid design combines a biological sperm cell with particular nanodecorations. In order to produce spermbots, five fundamental types of nano-components have been produced thus far: the complex nanocarrier, the rice grain-shaped (or spindle-type) nanoparticle, the microtube, the microhelice, and the tetrapod microtube (Figure 1).

One-to-one paired spermbots are made using the first three categories of nanocomponents. Conical microtubes that can catch sperm heads in their hollow cavities are created by rolling functional nanomembranes on photoresist. Complex nano components can now be directly constructed thanks to the advancement of nanoscale three-dimensional (3D) printing technology. Multiple sperms can be carried by a recently developed complicated magnetic microcarrier, which can also be produced using two-photon lithography. One-to-many nano components of this kind could be utilised to regulate the dosage of delivered cargos, like tailored medications[5].

There are many different kinds of sperm mimics, which are useful for both developing functioning nanobots and understanding how sperm motility is regulated. Here, we characterise these sperm mimics as nanobots that resemble sperm and divide them into two subcategories: biomimetic sperms and flagellate microorganisms.

To simulate sperm motility, various artificial sperm types have been developed. Iron oxide nanoparticles for the head and polystyrene for the tail are combined to create the most basic form of a biomimetic sperm. This delicate microrobotic sperm is more than 300 μm long and swims at a speed of 100 μm/s. The three

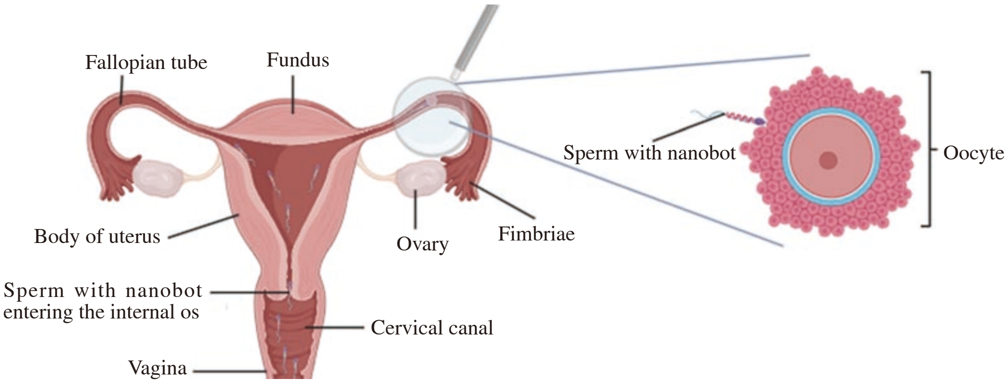

Figure 2. Mechanism of spermbot in assisting fertilisation.

stages of spermbot's intended uses are likewise rapidly developing. Initially, research solely looked at controlling sperm mobility remotely. Subsequent research tests validated spermbots' capacity to load drugs. Meanwhile, 3D ovarian cancer cells also confirm the biocompatibility and therapy impact. Multipurpose spermbot was created using a 4D printed microcarrier. This innovative microcarrier has the ability to regulate sperm capacitation and sperm-dependent cumulus cell disintegration in addition to delivering numerous sperm[9].

4. Spermbot locomotion and control mechanism

The spermatozoon can be remotely guided *via* bodily fluids and acts as a biocompatible driving power for the microtube[10]. If the spermbot is used to deliver a medication, the medication may be placed onto the exterior surface of the microtube. pH or temperature change may cause the medication to release by altering the drug's attachment to and unloading from the microtube surface (Figure 2). The most obvious promise of this system, aside from medicine delivery, is the development of novel ART, since the magnetic microtube allows us to remotely transfer a single sperm cell to a chosen area[11] .

Spermbots can swim in extremely viscous environments at low Reynolds numbers and are physiologically compliant. When compared to alternative binding processes like surface functionalisation or the insertion of nanoparticles, the purely mechanical capture action within the microtube does not change the cell[12]. Temperature adjustments can be used to modify the speed and duration of this sperm-driven microtube[13]. The magnetic transmitter with minimal external magnetic fields is made possible by the microtube's magnetic layer being integrated within it. The spermbots should, ideally, be removed without the need for future surgery, be completely degraded or recovered in their natural habitat. Either local pH and temperature changes or the action of particular enzymes like collagenase and matrix metalloproteinase (MMPs), which are found in the body, could facilitate the degradation process. Therefore, while designing a medical microrobot, selecting the appropriate material composition including biocompatibility and biodegradability is essential. Its adaptability and capacity to change shape enable them to actively overcome biological barriers and gain minimally invasive access to anatomical regions that are difficult to reach. Depending on the mechanical characteristics of the geometrical design, magnetisation of the magnetic material, magnetisation profile inside the robot body, applied external magnetic field, and viscosity of the biological fluid, they also undergo multimodal locomotion and induce versatile shape deformations[14].

5. Spermbot and ART

Sperm-like microrobot motion is primarily driven by a piezoelectric mechanism acting as a micro-actuator to generate nano-position movement. The nonlinear behaviour of piezoelectric materials, which can lower manipulation precision or potentially cause system instability, has made the control system for piezoelectric actuators a popular topic in recent years. The issue of the nonlinear response of the Uchino piezoelectric actuator has been resolved by the application of mathematical modelling and control techniques[15]. By guiding the chosen sperm cells to the oocyte position in the natural environment within the human body, spermbots aim to circumvent the evacuation of the egg from the body and *in vitro* fertilisation (IVF). This is the concept underlying the implementation of alternative assisted reproduction technologies. Since the oocytes and spermatozoa will be maintained in their typical microenvironment during fertilisation, the goal of spermbot technology is to increase the rate of pregnancy. The artificial stressors that gametes and embryos encounter in the *in vitro* environment are the reason behind the low success rate of IVF, and research has revealed that the quality of embryos created *in vitro* is inferior to that of their *in vivo* counterparts[16].

These spermbots are acting in ART, helping to solve a number of key challenges with fertility treatments. They help enhance sperm

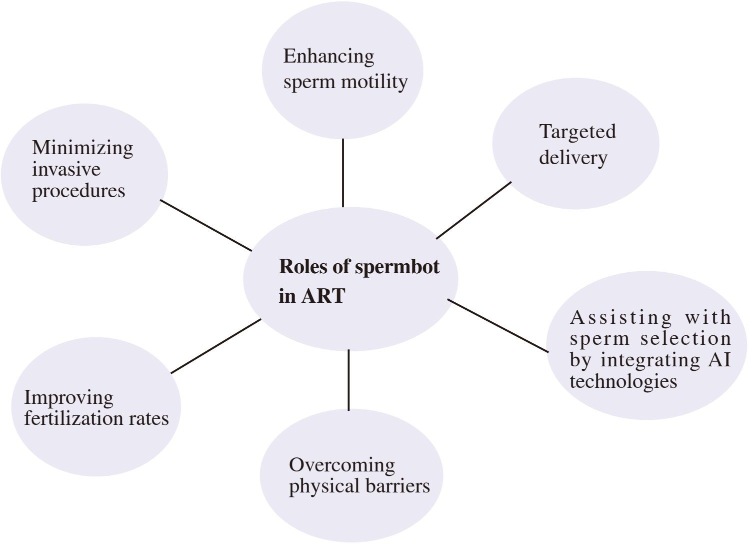

Figure 3. Various roles of spermbot in assisted reproductive technology (ART). AI: artificial intelligence.

motility, a very important constituent in successful fertilization, as poor motility significantly impairs fertilization. They also help in the active delivery of the gametes by swimming them directly up to the egg, enhancing the effectiveness of fertilization. This novelty decreases the resort to more intrusive techniques, such as IVF, since it allows sperm to overcome physical barriers of the human reproductive system. Also, when combined with AI, spermbots support the selection of the most viable sperm and improve overall fertilization rates. In this way, they reduce the physical and emotional stress associated with invasive methods of ART, hence, offering a more efficacious and less intrusive treatment of infertility (Figure 3).

The spermbot is made up of a magnetic microtube that serves as an envelope for the cell and does not impede sperm activity, making it possible to track the cell *in vivo*[17]. Therefore, the spermbot may potentially be used as a research tool to investigate the spermatozoa's natural routes within the body. The spermbot may be useful for investigating where spermatozoa are held back in the female reproductive canal, where they run into difficulties, and how long they stay at particular stages. In the end, this method will aid in improving our comprehension of the causes of various cases of infertility.

6. Biological safety consideration and ethical implications

Complex nanomaterials found in spermbots' nano components may be the source of biocompatibility issues. Certain designs have the ability to use magnetic force to carefully remove nano components, such the magnetic microhelix. The fact that this procedure simply disassembles the spermbots and does not entirely remove the nanocomponents could make it more difficult to use spermbots *in vivo*. Therefore, the creation of biodegradable nanoparticles may present a way to create an environment free from contamination[18].

The development of an *in vitro* sperm control and imaging system is comparatively simple. Before being implemented in *in vivo* settings, the efficacy and safety of the remote control and image monitor should be assessed and confirmed. In addition, it is commonly known that a variety of intricate ethical and legal issues have arisen in tandem with the use of ART[4]. Because spermbot bypasses the stages of natural selection in the female reproductive system, it encounters difficulties. Therefore, it cannot be overstated that ethical and legal considerations should always come before technical advancement, even in cases where spermbot technologies are ready and useful for clinical practice.

Handling spermbots should be a minimally invasive or noninvasive process overall. Because of this, the platforms for imaging and controlling must be more accustomed to the human body. Finally, additional care must be taken with assisted reproduction to prevent long-term consequences on the embryo because fertilisation is merely the start of a new life. For the purpose of providing a secure environment for the development of the succeeding embryo, the nano components of spermbots should be entirely eliminated or broken down. Avoiding the introduction of extra micro pollutants is also crucial for the treatment of disorders related to the reproductive tract. The main drawback of spermbots is the introduction of nano components, which could provide an unknown harm to the health of the developing fetus and the recipient female. Therefore, the process of converting spermbots into *in vivo* applications for assisted fertilisation will take time[19].

7. Emerging technologies and future directions

Spermbots are anticipated to be evaluated and approved for *in vitro* clinical use in the near future. In particular, spermbots can function as complementary or improved instruments for the *in vitro* aided fertilisation procedures that are currently in use such as IVF and intracytoplasmic sperm injection (ICSI).

Automated, intelligent, and precise ART will enter a new era with the combination of *in vitro* technologies, spermbots, and AI tools. Developing spermbots that have been drug-loaded to treat gynaecologic illnesses or tumors that have arisen in the female reproductive system *in vivo*. The sperm components should be modified to lose their capacity to fertilise, or sperm-like microbots can be used to create the spermbots. In order to deliver drugs, these spermbots should also be engineered to be site-specific. Thorough evaluation and validation are necessary for the safety and removal of nano components. Reaching the objective of converting spermbots into *in vivo* assisted fertilisation is the last phase. The most promising approach, when looking at the spermbot designs that are currently on the scene, is the recently created multifunctional spermbots that are based on 4D-printed microcarriers. These microcarriers are specifically made to be stimuli-responsive to the environment of the female reproductive canal. At this time, however, *in vivo* validation of the microcarriers' safety as well as that of the accompanying regulating and imaging systems is also necessary[20].

Spermbots, microscopic robotic instruments that can direct and move sperm, have the potential to completely transform reproductive therapies. They could raise the success rates of ART by making sure that sperm reach the egg more effectively. Technological developments in spermbots may make it possible to incorporate editing and genetic screening features. This could lessen the chance of inherited disorders by detecting and fixing genetic flaws in sperm before fertilisation. Sperm behaviour, motilityand interactions with the egg could be studied in greater depth with the use of spermbots. This may result in novel perspectives on human reproduction and the creation of innovative fertility remedies. They might also be applied in diagnostics to more precisely evaluate the health and functionality of sperm[5]. The expensive cost of these technologies may restrict their availability, and substantial *in vivo* validation is necessary to ensure their safety and efficacy. Present imaging and navigation technologies may lack the accuracy required for targeted medication administration and real-time manipulation of the reproductive tract.

8. Conclusions

Although spermbots have great potential to revolutionize ART and enhance reproductive health, their successful application will depend on ongoing study, cautious evaluation of the ethical and safety consequences, and technological developments. The optimization of spermbots for *in vivo* applications, including the improvement of drug-loaded systems and site-specific targeting mechanisms, should be the main emphasis of future research. AI could improve spermbot performance even more by allowing for more accurate control and sophisticated genetic screening to reduce hereditary disorder. Spermbots may provide previously unheard-of insights into the behavior of sperm and their interactions with eggs as the area develops, resulting in creative solutions for problems with fertility and furthering our knowledge of human reproduction. These cutting-edge instruments could determine the future of reproductive medicine and usher in a new era of accuracy and efficacy in assisted reproduction.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

Neeraj Vishwakarma contributed to the conception or design of the work, drafting of the work, approval of the final version of the manuscript, and agreed on all aspects of the work. Nancy Nair contributed to the literature review, revision of the manuscript for important intellectual content, approval of the final version of the manuscript, and agreed to all aspects of the work. Charu Pareek contributed to the literature review, revision of the manuscript for important intellectual content, offering a lot of feedback and revision to make it rich in intellectual content, approval of the final version of the manuscript, and agreed to all aspects of the work. Namrata Choudhary made significant contributions by offering the literature review and revising the manuscript, providing substantial feedback that enriched its intellectual depth.

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