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An overview of advancements in *in vitro* fertilization

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Abstract
The techniques used in *in vitro* fertilisation (IVF) have made significant progress since the birth of the first IVF baby in 1978. Initially producing success rates in the single digits, *in vitro* fertilisation (IVF) now achieves success in about 50% of cases involving women under the age of 35. In this article, we discuss the enhancements in laboratory techniques and advancements in our capacity to influence reproductive physiology that have contributed to this progress. In addition, we outline the measures taken to uphold safety standards in this highly competitive industry.

Keywords: *In vitro* fertilisation (IVF), reproductive physiology, controlled ovarian stimulation

Introduction
The field of human reproduction research has consistently faced scientific and ethical obstacles, which initially impeded the progress of infertility treatments. During the 1960s and 1970s, our comprehension of the processes involved in human oocyte fertilisation advanced to the extent that it became feasible to perform *in vitro* fertilisation (IVF) of human oocytes. The acquisition of this knowledge ultimately resulted in the highly praised first successful birth of a "test tube baby," Louise Brown, in England in 1978. In this groundbreaking IVF birth, the mother underwent a natural menstrual cycle, during which physicians used laparoscopy to retrieve a single oocyte from her ovary before it was released. The oocyte was then fertilised outside the body and the resulting eight-cell embryo was transferred into her uterus.

After a span of three years, the inaugural IVF infant in the United States, and the fifteenth globally, came into existence. In this instance, instead of depending on the one oocyte that would occur naturally, the mother received injections of human menopausal gonadotropin over a span of several days. This was done to stimulate the production of several follicles in the ovary, resulting in the production of multiple oocytes. Following the procedure known as controlled ovarian stimulation (COS), doctors surgically extracted the eggs before they were released, fertilised them outside the body, and subsequently implanted the resulting embryos into the mother's uterus on either the third or fifth day. The inaugural IVF baby in Missouri was born in 1985 to a couple who had IVF treatment at Washington University and gave birth at what is presently known as Barnes-Jewish Hospital. Since then, the practice of *in vitro* fertilisation (IVF) has continued to advance rapidly.

Currently, *in vitro* fertilisation (IVF) is responsible for a significant number of births globally, representing 1-3% of all annual births in the United States and Europe. This growing demand for fertility therapy is pushing the advancement of technology aimed at improving the effectiveness and outcomes of IVF procedures. Infertile couples typically receive therapy in the vast majority of *in vitro* fertilisation (IVF) instances to achieve conception of a child who is genetically linked to them. Nevertheless, couples are also opting for *in vitro* fertilisation (IVF) to subject their embryos to genetic testing, aiming to reduce the transmission of single-gene mutations linked to health issues. Moreover, the utilisation of donor sperm and oocytes is progressively more prevalent, allowing women who are unable to carry a pregnancy to resort to gestational carriers. Here, we outline some significant achievements that have greatly enhanced the effectiveness of IVF as a strategy for treating these individuals.

Regulated Ovarian Stimulation

Initial studies on *in vitro* fertilisation (IVF) in women with natural menstrual cycles showed an average of 0.7 oocytes retrieved per cycle and a pregnancy rate of 6% per cycle. In the 1980s, researchers at the Jones Institute in Norfolk, Virginia, started administering gonadotropins to women to stimulate the production of multiple ovarian follicles and increase the number of oocytes. The oocytes were subsequently fertilised outside the body, and the most robust-looking embryos were then placed into the woman's uterus. The introduction of controlled ovarian stimulation (COS) led to an increase in the average number of eggs produced per cycle, ranging from 2.1 to 2.6. Additionally, the average pregnancy rates improved to 23.5% in 1982 and 30% in 1983. Initially, human chorionic gonadotropin (hCG) was used to stimulate ovulation because it is similar to luteinizing hormone, which naturally triggers ovulation. In the initial stages of *in vitro* fertilisation (IVF), a significant issue was the occurrence of premature ovulation. This would render the retrieval of oocytes unfeasible, despite the meticulous and labor-intensive controlled ovarian stimulation (COS) process. Nevertheless, the introduction of two advancements in IVF techniques, namely the utilisation of gonadotropin releasing hormone (GnRH) agonists in the 1980s and GnRH antagonists in 2001, has enabled the prevention of premature ovulation and the consistent management of oocyte retrieval. There are several pharmaceutical regimens available, but they all work on the same principle: injectable medications increase the production of natural hormones to stimulate the growth of multiple ovarian follicles, resulting in the extraction of multiple eggs.

Ovarian Hyperstimulation Syndrome (OHSS)

Two issues arose due to the administration of excessive dosages of gonadotropins. Initially, in order to enhance the likelihood of a woman achieving pregnancy with a single foetus that would successfully develop until birth, doctors started the practice of fertilising numerous eggs and then implanting multiple embryos. This procedure occasionally leads to women conceiving twins and even larger numbers of foetuses, which increases the danger of the foetuses being born with low birth weight and prematurely. Furthermore, ovarian hyperstimulation syndrome (OHSS) is the prevailing and most serious iatrogenic consequence associated with ovarian stimulation. Ovarian hyperstimulation syndrome (OHSS) arises when the ovaries are excessively stimulated and subsequently triggered by either administered hCG to induce ovulation or by the natural increase in hCG that takes place when a woman becomes pregnant. OHSS is characterized by hemoconcentration from leaky vessels and third spacing of fluid that leads to ascites and electrolyte problems. The symptoms of this condition can vary from little swelling in the abdomen to kidney failure and even death due to blood clot-related events or damage to vital organs. Although there has been much research, the precise cause of this condition is still uncertain. However, it is observed that the syndrome becomes more common as the number of growing follicles and levels of estradiol, which is produced by the ovarian follicles, increase. To address this worry, in 1979, clinicians began monitoring COS by serially testing the serum estradiol levels and transvaginally evaluating ovarian follicles to better monitor for risk factors. By identifying patients who are at risk, clinicians can take proactive actions such as modifying medications as needed and closely monitoring symptoms on a more frequent basis.

The present drawback to COS is that it requires time and labor-intensive monitoring. Additionally, gonadotropin is rapidly degraded in the body, therefore women have to have daily injections for 10 days. However, scientists such as Washington University professor Irving Boime are creating long-acting versions of gonadotropins that may one day minimise the number of necessary injections and the quantity of monitoring.

Embryo Culture

Since the inception of *in vitro* embryo culture, there have been continuous efforts to enhance the culture system in order to maximise embryo development and augment the quantity of high-quality embryos for transfer. Originally, embryo culture media was created using media designed for the culture of somatic cells and enhanced with serum. Researchers have since improved the media for embryo metabolism and development by adding different macromolecules, adjusting the composition of energy substrates and amino acids, and including growth factors. In the past, laboratories used to create their own culture media. However, nowadays it is commercially manufactured, leading to better consistency and quality control across different laboratories and practices. There is a strong focus on improving culture media to enhance embryo development and clinical outcomes.

Advancements in embryo culture techniques have enabled us to prolong the growth of embryos in a laboratory setting until they reach the blastocyst stage. This allows for a more thorough examination of their physical characteristics and improves the process of selecting the most suitable embryos for transfer. This has proved crucial in our capacity to optimise pregnancy rates in *in vitro* fertilisation (IVF) while minimising the number of embryos transplanted and, consequently, reducing the danger of multiple pregnancies. Extended culture has facilitated the ability to do preimplantation genetic testing of embryos. This method is most effective when the embryos have reached a sufficient level of development in culture, allowing for the extraction of several cells for genetic testing.

Enhanced embryo cultivation, along with enhanced controlled ovarian stimulation (COS), enables us to produce a greater number of embryos than those first transferred. Currently, almost 50% of *in vitro* fertilisation (IVF) cycles conducted by controlled ovarian stimulation (COS) at our facility yield surplus embryos of high quality, which can be cryopreserved for the patient's future needs. Therefore, the lady can frequently prevent the need for additional COS injections and invasive oocyte retrieval. Currently, this procedure has reached a level of efficiency where women who are receiving gonadotoxic therapies, such as chemotherapy, can retain their fertility for the future by undergoing controlled ovarian stimulation (COS) and having their eggs extracted and frozen.

Preimplantation Genetic Testing

Prior to 1990, the available methods to avoid the transmission of genetic disorders were restricted to intrusive procedures like chorionic villus sampling and amniocentesis. If the foetus was found to be afflicted, termination of the pregnancy might be considered as an

option. In the 1990s, advancements were made in utilising surplus embryos to identify chromosomal imbalances or specific gene disorders before transferring them to the uterus. This was done by examining embryos between days three and five after fertilisation. Initially, fluorescence in situ hybridization was used to screen cleavage-stage embryos, but it was later discovered that this method reduced birth rates and caused more harm than good. Currently, cells are biopsied from the trophectoderm of blastocyst-stage embryos (see Figure 1), and one of two types of preimplantation genetic testing is performed. Preimplantation genetic diagnosis (PGD) is used when one or both genetic parents have a mutation, such as those associated with Huntington's disease or cystic fibrosis. This testing is done to confirm that the embryo has not inherited the single-gene trait. Polymerase chain reaction (PCR) is the preferred method for performing preimplantation genetic diagnosis (PGD) because to its superior accuracy compared to fluorescence in situ hybridization (FISH). PCR also enables us to extract an adequate amount of genetic material for evaluation from a small number of cells, hence reducing potential injury. While the process of vitrifying the embryo is necessary for analysis, recent studies indicate that using frozen and fresh embryos have similar success rates. This makes it a viable option for couples. It is worth noting that preimplantation genetic diagnosis (PGD) does not seem to raise the risk of obstetric complications, such as foetal malformation caused by the biopsy procedure.

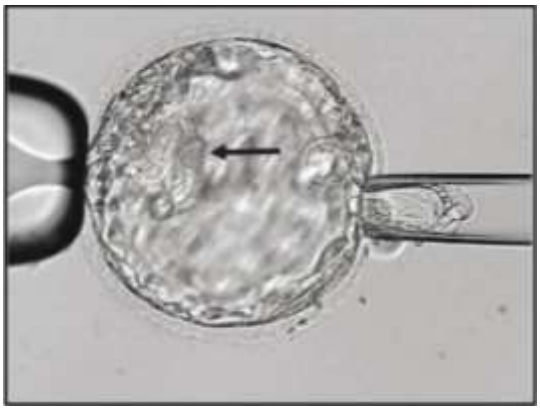

Fig 1: A pipette is being used to retain a blastocyst near the inner cell mass, indicated by an arrow, while a needle is used to biopsy trophectoderm cells.

Another form of testing is preimplantation genetic screening (PGS), which is utilised to detect embryonic aneuploidy. While PGS is not commonly advised as a normal practice in IVF due to the lack of evidence showing improved outcomes in low-risk individuals, it can be advantageous for specific groups of patients. PGS has predictive significance for patients classified as high-risk for embryo aneuploidy, such as individuals of advanced maternal age (≥35 years old) and those with a history of recurrent pregnancy loss. Prior to choosing preimplantation genetic screening (PGS) or preimplantation genetic diagnosis (PGD), it is imperative for patients to undergo genetic counselling in order to assure their comprehensive comprehension of the potential hazards and constraints associated with these methodologies. The field of reproductive health will undoubtedly be significantly influenced by genetics in the future. Despite several advancements, there is still a need to determine the optimal use of preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) in *in vitro* fertilisation (IVF).

Minimising the likelihood of multiple pregnancies linked to *in vitro* fertilisation (IVF)

In the initial stages of *in vitro* fertilisation (IVF), numerous embryos were inserted into the uterus with the expectation that at least one would successfully develop, frequently resulting in the delivery of multiple offspring. In 2004, 36.6% of women below the age of 35 who had IVF treatment successfully gave birth to a live baby after having an average of 2.5 embryos implanted every cycle. Consequently, 32.7% of the women gave birth to twins and 4.9% gave birth to triplets. Advancements in embryo culture and cryopreservation methods, along with recommendations on the optimal number of embryos for transfer (refer to Table 1), have resulted in a decrease in the quantity of embryos transferred while enhancing their quality. Consequently, this has led to a reduction in the likelihood of multiple pregnancies. In 2014, 48.7% of women under the age of 35 who had IVF successfully gave birth to a live baby. Out of these births, 11.8% were twins and 0.4% were triplets. The decrease in multiples is primarily due to the reduction of the number of embryos transferred to a single one.

Table 1: Prescribed guidelines for the maximum number of embryos to be transferred

Age (years)	< 35	35–37	38–40	41–42
Prognosis				
Cleavage Stage Embryos				
- Favorable	1	1	≤ 3	≤ 4
- All others	≤ 2	≤ 3	≤ 4	≤ 5
Blastocysts				
- Euploid	1	1	1	1
- Favorable	1	1	≤ 2	≤ 3
- All others	≤ 2	≤ 2	≤ 3	≤ 3

Derived from the ASRM Committee Opinion: Restrictions on the quantity of embryos for transfer. The publication is titled "Fertil Steril 2017."

Reporting of *In vitro* Fertilisation (IVF) outcomes

The endeavour to monitor *in vitro* fertilisation (IVF) activities and results commenced in 1985 and was first optional. Since the passing of the Fertility Clinic Success Rate and Certification Act in 1992, fertility clinics are required to report data on the success rates of *in vitro* fertilisation (IVF) to the Centres for Disease Control (CDC). This is done to ensure transparency and protect patients from false claims about IVF success. The public reporting of outcomes has been seen as a promising strategy to improve healthcare outcomes. IVF success rates for reputable clinics can now be found on the websites of both the CDC and the Society for Assisted Reproductive Technology (SART), which is affiliated with the American Society for Reproductive Medicine. SART is a valuable resource for patients and physicians, providing detailed information on various ART protocols and procedures, as well as success rates of different technologies used in practices across the country. Their initial yearly release occurred in 1988 and has since been progressively employed to facilitate the ongoing enhancement and assessment of ART programmes. The SART reporting system differs from that of the CDC in

that it provides information on the start of each treatment cycle, while the CDC only provides statistics on completed cycles. More than 90% of clinics in the U.S. are members of SART, and the SART registry publishes data on over 95% of assisted reproductive technology (ART) treatment cycles in the country. The presence of two reporting systems provides an extensive amount of information, enabling in-depth study of data to provide transparency and ongoing chances for enhancing patient outcomes. SART also facilitates patients' comprehension of the IVF lab's quality, which is a significant determinant of their likelihood of having a successful live birth via IVF.

Conclusion

The science of reproductive endocrinology and infertility has made remarkable advancements in the last thirty years, with the introduction of novel techniques, drugs, diagnostics, and strategies to address infertility in couples. Currently, some couples who were previously unable to have children are now capable of conceiving, maintaining pregnancy, and giving birth to their own healthy offspring. Although much progress has been made as outlined in this article, there is still a significant focus on evaluating the future consequences for children born through *in vitro* fertilisation (IVF). It is worth noting that the oldest individual conceived by IVF is currently just 38 years old. The primary objective of infertility treatment remains consistent over time, which is to facilitate the creation of robust and thriving families.

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