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FROM HOPE TO REALITY: THE JOURNEY AND FUTURE OF IN-VITRO FERTILIZATION – A REVIEW

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Abstract

In-vitro fertilization (IVF) offers new hope for couples facing infertility challenges. Since its invention in 1978, over 2 million babies have been born through IVF, with approximately 12 million babies born each year using IVF and other assisted reproductive technologies. The history of IVF dates back to 1903 but culminated in the successful live birth of Louise Brown in 1978. IVF involves several complex steps, but it does not require surgery. The procedure takes into account the female's natural cycle to retrieve eggs. Sperm is collected and allowed to fertilize an egg in a laboratory setting. Finally, a healthy embryo is implanted in the woman's uterus. Despite the advancements in IVF, Pakistan still faces significant infertility issues, with a reported rate of 21%. Contributing factors include a lack of awareness about IVF and its unaffordability. Additionally, various complications and health risk factors are associated with the process. Nevertheless, IVF has a significant impact on reducing infertility rates globally. It has been declared legal by the Inter-American Court of Human Rights and is endorsed by religious scholars for use exclusively by married couples.

INTRODUCTION

Assisted Reproductive Technology (ART) encompasses techniques that assist individuals in conceiving by working with eggs and embryos in a laboratory environment. It is important to clarify that ART does not include procedures that involve only sperm, such as intrauterine insemination (IUI), nor

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does it cover the use of medication to stimulate egg production without retrieving the eggs. ART specifically involves manipulating eggs or embryos outside of the body. ART is a treatment for infertility in which an egg is fertilized in vitro with sperm, and the resulting embryo is then implanted back into the female's uterus. While ART primarily focuses on the management of eggs, sperm, and embryos in vitro, it does not only pertain to sperm-related procedures or conditions affecting the female partner [1]. The term "in vitro" means "outside of the body." It indicates that in IVF, eggs are fertilized outside of the female body in a laboratory. In 1978, Robert Edwards and Patrick Steptoe achieved the first successful live birth. For this achievement, they were both awarded the Nobel Prize in Medicine in 2010. Louise Brown was the first test tube baby conceived through IVF in 1978 [2]. Louise Brown was the first test tube baby conceived through IVF in 1978. Over the decades, research in reproductive medicine has led to numerous advancements. Assisted reproductive technologies (ART) have enabled millions of couples to conceive. Worldwide, over 2 million babies are born through ART. In the United States alone, 48,000 babies were born through ART in 2003, and over 100,000 ART cycles were performed that year. ART has made significant progress, providing hope to many couples experiencing infertility [3]. Many couples around the world, approximately 48.5 million, experience difficulties in conceiving. This issue affects roughly 186 million people in total [13]. Each year, about 12 million babies are born worldwide through in vitro fertilization (IVF) and other assisted reproductive technologies (ART). In the UK, 55,000 women underwent 76,000 IVF cycles in 2021, marking an increase of 2,000 cycles since 2019. Australia also reported a 6.2% increase in IVF cycles from 2018 to 2019. Notably, Japan recorded 498,140 IVF cycles in 2021, the highest number on record. Overall, IVF cycles are increasing globally, with year-on-year growth observed in several countries [4]. Since its introduction in 1978, IVF (In Vitro Fertilization) has revolutionized the way people conceive. Initially intended for infertile couples, IVF is now utilized for various medical and genetic conditions, as well as for fertility preservation. As accessibility improves, IVF is expected to become even more popular in the future [5]. More than 8 million babies have been born worldwide through in vitro fertilization (IVF) since the first IVF baby was born 40 years ago. By the year 2100, it is estimated that 400 million people—approximately 3% of the global population—will be alive thanks to IVF and other fertility treatments [6].

2. Historical Background of Assisted Reproductive Technology (ART) and In Vitro Fertilization (IVF)

In 1930, Deansley, Fee, and Parkes discovered that mating in rabbits triggers the release of hormones from the pituitary gland, which is essential for ovulation. In 1929, Friedman demonstrated that injecting hormones (pituitary extracts or prolan) could induce ovulation in rabbits. Bellerby, in the same year, found that ovulation occurs approximately 10 hours after hormone injection in rabbits. In 1903, Heape observed that polar bodies are formed in rabbit eggs after mating; however, this statement was later partially corrected by research indicating that only one polar body is formed [7]. In 1934, an article was published proving that eggs manipulated in a laboratory (in vitro) could develop into healthy offspring. To confirm this finding, researchers transferred these eggs into a female rabbit, successfully producing offspring. They also generated offspring from eggs cultured in a lab before transfer, providing the first strong evidence that mammalian eggs could be manipulated in vitro to yield viable offspring [8]. Between 1940 and 1950, Menken and Rock attempted to make in vitro fertilization (IVF) work for humans. They observed human eggs beginning to divide in the lab and published their findings in a medical journal, marking them as early pioneers in the effort to make human IVF successful [9]. Eventually, Menken left the project, and upon her return, she discovered that Rock had shifted his focus to developing the birth control pill. About a decade later, in 1962, Bedford and Chang successfully fertilized a rabbit egg in a laboratory setting, leading to the birth of a baby rabbit [10]. When Chang achieved IVF success with rabbits, he was not interested in applying this technique to help humans conceive. Meanwhile, Robert Edwards, an expert in animal reproduction, proposed a new approach: using hormones to stimulate the ovaries to release more eggs. This concept laid the groundwork for modern ovarian stimulation and IVF for humans [11]. Before the birth of Louise Brown in 1978, Robert Edwards' team

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attempted to transfer embryos created through IVF over 100 times, but none of those pregnancies were successful. The likely cause was the hormonal treatments, which created an unfavorable environment in the womb. Edwards' team revised their strategy by discontinuing hormone use and instead monitoring the woman's natural cycle by checking her urine for luteinizing hormone. This new method proved effective, resulting in the birth of Louise Brown, the first baby conceived through IVF without hormone stimulation [12].

Dates	Scientists Names	Achievement
1903	Heape	Polar bodies were observed forming in rabbit eggs after mating. Subsequent research demonstrated that only one polar body is produced.
1929	Friedman	The administration of hormonal injections from the pituitary gland or a specific plant extract could stimulate ovulation.
1929	Bellerby	I found that ovulation occurs 10 hours after the injection.
1930	Deansley, Fee, and Parkes	The release of a pituitary hormone was discovered after mating in rabbits.
1934	Gregory, Pincus and E.V.Enzmann	It was demonstrated that eggs fertilized in vitro can successfully develop into embryos after being transferred.
1940-1950	John Rock and Miriam Menken	The first successful human in vitro fertilization (IVF) took place when scientists observed a human egg dividing in its early stages in a laboratory.
1950	Miriam Menken	The research discovered that the rock had shifted, leading to the development of the birth control pill.
1962	Bedford and M.C.Chang	Successfully fertilized the rabbit egg in vitro, leading to the birth of rabbit offspring.
1970	Robert Edwards and team	Conducted 100 IVF transfers to human females, but all died due to hormonal uterine issues.
1978	Robert Edwards and team	The first successful human conceived through IVF was produced using a natural cycle.

The above table explains the historical background of IVF.

3. Types of invitro fertilization

Conventional In Vitro Fertilization (cIVF), the egg is fertilized by sperm outside the female body, typically in a petri dish [13]. Among the numerous sperm present, only one is allowed to fertilize the egg naturally. The sperm surround the egg, and only the fittest sperm can enter and fertilize it. To promote the growth and maturation of eggs in the ovaries, hyperstimulation drugs are used [14].

Intracytoplasmic Sperm Injection (ICSI) is a specialized form of IVF in which a single sperm is directly injected into the cytoplasm of the egg. This technique is more advanced than cIVF and involves selecting a high-quality sperm from the individual for fertilization. Professionals use a microscope to identify the best sperm, especially in cases of poor sperm quality. ICSI has become a widely used technique in IVF over the past two decades [13, 15].

Donor Egg and Embryo IVF, Egg sharing is a type of egg donation in which two individuals who do not know each other collaborate; one person donates eggs to help the other achieve pregnancy [16].Donor eggs and embryos can assist individuals or couples facing infertility when the woman's eggs are not viable or available, and methods like IVF and embryo transfer are not possible with their own eggs. In a donor egg

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program, donor eggs are fertilized with the sperm of the recipient's partner, while a donor embryo program involves using donor sperm. Embryos can be transferred as either fresh embryos or frozen-thawed embryos. This option provides hope for individuals or couples who previously had no chance of achieving pregnancy [17].

Sperm Donor IVF, Eggs are fertilized by donor sperm in the laboratory after the collection of eggs from the female. The healthy embryo is transferred into the female uterus [18]. The baby's biological father is a sperm donor but has no legal rights to claim the fatherhood of the child. Artificial insemination (AID) is achieved in this way by using donated sperm to have a baby [19]. This technique is used for intrauterine insemination (IUI) and IVF [20].

Surrogacy with IVF, In this type of IVF, surrogate mothers carry embryos. The embryo of the couple is transferred to the surrogate mother. The surrogate mother does not have any genetic relationship with the embryo. This method is intended for women who wish to have a baby but cannot carry a pregnancy due to various medical and career challenges [21]. In return, the surrogate receives compensation for carrying the pregnancy [22].

Preimplantation IVF, In this IVF technique, a single cell is taken from an embryo to test for chromosomal abnormalities. Only embryos with normal chromosomes are selected for transfer [23]. Women of advanced maternal age (over 35) often experience lower pregnancy rates with IVF, primarily due to two factors: aneuploidy, which refers to an abnormal number of chromosomes in eggs or embryos, and non-disjunction, an error that occurs during chromosome separation in cell division. To improve pregnancy rates, Preimplantation Genetic Testing (PGT) or Preimplantation Genetic Diagnosis (PGD) is utilized [24].

Natural Cycle IVF operates by leveraging a woman's natural hormones and ovulation cycle, without the use of ovarian hyperstimulation drugs. Modified Natural Cycle IVF (MNC-IVF) incorporates some medications to better control ovulation. This approach is cost-effective, saves money, and carries a lower risk due to the minimal medication used. It is particularly suitable for younger women and those with a low ovarian reserve. However, the time to achieve pregnancy may be slightly longer compared to conventional IVF [25].

4. Mechanism of IVF

In vitro fertilization (IVF) is not simply about collecting and mixing eggs and sperm. Although theoretically, you could collect eggs and sperm after natural ovulation, combine them, and return them to the uterus, this approach is usually ineffective on its own, with very low chances of achieving pregnancy. To improve these odds, standard IVF involves several additional steps including Ovarian Hyperstimulation, Egg Retrieval, Fertilization, Embryo Selection, and Embryo Transfer. While the core concept of IVF is straightforward, modern techniques include these extra steps to significantly enhance the likelihood of a successful pregnancy.

Ovarian hyperstimulation is a medical treatment designed to stimulate the ovaries to produce multiple eggs. This process suppresses natural ovulation while allowing the growth of eggs in the ovaries. The medications used for ovarian hyperstimulation include gonadotropins, which are injected to promote egg growth, and GnRH agonists or antagonists, which help suppress natural ovulation. The primary goal of ovarian hyperstimulation is to increase the chances of pregnancy through IVF by producing multiple eggs [26]. Second step is Egg retrieval, also known as oocyte collection, is performed 34-36 hours after the hCG injection using an ultrasound-guided transvaginal aspiration technique. The ovaries are visualized with vaginal ultrasound, and a needle guide directs the needle into each follicle. The oocytes (eggs) and surrounding fluid are then aspirated (removed). The female patient is either sedated or relaxed with intravenous sedation for comfort during the procedure [27]. Fertilization which is third step of IVF, in which sperm and eggs are combined in a special culture medium at a ratio of 75,000 sperm per 1 egg. The mixed sperm and eggs are left together for a specific incubation period. Research indicates that allowing them to interact for 1-4 hours can lead to higher pregnancy rates compared to a longer interaction time of 16-24 hours. This means that the chances of successful fertilization and pregnancy are

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increased when sperm and eggs are incubated for a shorter period [28]. Before fertilization, the eggs are removed from surrounding cells and prepared. Only those eggs that are mature and ready for fertilization, known as metaphase II eggs, are selected for the process [29].There are two methods of fertilization first is Insemination, involve mixing sperm with an egg in a laboratory dish. ICSI (Intracytoplasmic Sperm Injection) is second method of fertilization, a single sperm is injected directly into the egg. In both cases, the sperm is separated from other components of the semen, cleaned, and treated to enhance its fertility. ICSI is specifically used to address male infertility issues. In summary, there are two ways to fertilize an egg: by mixing it with sperm or by injecting a single sperm into the egg. ICSI is often employed when there are concerns regarding sperm quality or quantity [27]. Embryo selection and transfer is the fourth step in the IVF process. During this stage, laboratories use a grading system to evaluate the quality of embryos. Among the various methods used, assessing the appearance of embryos has been shown to be the most effective way to identify those that are likely to result in a successful pregnancy. [30]. Scientists are currently developing Artificial Intelligence (AI) and Deep Learning technologies, such as a program called ERICA, to enhance the embryo selection process. ERICA employs a non-invasive approach to analyze embryos and provides a ranking system based on their predicted genetic health. This advanced software aims to replace traditional manual classifications, making the embryo selection process more accurate and efficient [31]. Embryos can be transferred either three days after fertilization (during the cleavage stage) or five days after fertilization (at the blastocyst stage). Transferring embryos at the blastocyst stage increases the chances of live births, requires fewer embryos to be transferred, and reduces the risk of multiple pregnancies [27]. The embryo is transferred using a thin plastic catheter that passes through the vagina and cervix, which enhances the likelihood of successful implantation and pregnancy [32]. The luteal phase support is the final step in the IVF process. It involves administering medication to help a fertilized egg implant and to support early pregnancy in females. Common medications used for this purpose include progesterone and hCG (human chorionic gonadotropin). These treatments can enhance the chances of a successful pregnancy and live birth [33].

5. IVF in Pakistan

According to a report published in 2024, the infertility rate in Pakistan is approximately 21%. This high rate often leads to infertility being viewed as a shameful issue, particularly for women, causing many couples to hesitate in seeking help, such as in vitro fertilization (IVF). Several factors contribute to this situation, including poverty. A significant portion of the population, over 39%, is unable to afford IVF treatment and a lack of awareness on IVF [34]. About 78% of people lacking knowledge about IVF, which results in many misunderstandings about the procedure. Common fears surrounding IVF include concerns about multiple births, potential C-sections, and the risk of birth defects [34, 35]. Although these fears exist, the actual risks are very low, increasing by only about 1%. Overall, social stigma, poverty, and a lack of knowledge discourage many individuals and couples in Pakistan from pursuing IVF treatment [34].

6. Complications and Risk Factors in IVF

Ovarian Hyperstimulation Syndrome (OHSS) is a serious complication that can occur when the ovaries are stimulated to produce eggs. Minor symptoms include bloating, nausea, and vomiting. Severe symptoms may involve intense pain, fluid buildup, breathing difficulties, and kidney problems. Risk factors associated with OHSS include the potential for blood clots, kidney failure, and bleeding issues. It is important to note that OHSS is quite rare, occurring in about 0.2% to 1% of fertility treatment cycles [36]. The number of twin births has increased between 1980 and 2015, and in vitro fertilization (IVF) is a contributing factor. Approximately 1 in 5 twins and 1 in 4 triplets are born as a result of IVF. Carrying twins or triplets raises the risk of conditions such as high blood pressure during pregnancy and premature birth. However, it's noteworthy that pregnancies involving twins conceived through IVF do not have a higher risk of high blood pressure compared to naturally conceived twins. While multiple pregnancies do carry certain risks, IVF twins are not more likely to experience blood pressure issues than their naturally conceived counterparts [37, 38].

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7. Significance of IVF

In Vitro Fertilization (IVF) is a medical procedure designed to assist individuals and couples struggling with infertility. It is particularly beneficial for women with blocked or damaged fallopian tubes, men with low-quality sperm or low sperm count, and cases of unexplained infertility, where no specific cause can be identified [39]. Globally, the application of IVF varies significantly. In some European countries, more than 5% of babies are born through IVF. Other countries, such as Australia, New Zealand, the USA, and China, are also experiencing a rise in the use of this reproductive technology. Overall, the popularity of IVF is increasing worldwide, making it a more common option for people seeking to have children [5]. Success in IVF can be defined as either a confirmed pregnancy or a live birth. The success rates for IVF, specifically live birth rates, improved from 76% in 2005 to 80% in 2010. One significant change contributing to this improvement is that doctors are now transferring fewer embryos, which has resulted in a decrease in the number of multiple births, such as twins, from 25% to 8% [40]. Approximately 10% of couples experience infertility, which drives the demand for IVF treatments. Many women are delaying childbearing due to education, career pursuits, and effective contraception. In several countries, fertility rates have fallen below replacement levels (the average number of children a woman needs to have over her lifetime). As women are having children later in life, this has led to increased infertility and a higher demand for IVF. The COVID-19 pandemic further complicated family formation, resulting in a significant decline in birth rates, particularly in Chinese cities during this period. These trends indicate that the utilization of IVF is likely to continue growing in the coming decades [5].

8. Legal Status

In 2000, Costa Rica's Supreme Court banned in vitro fertilization (IVF), arguing that the procedure destroys embryos and thus violates the "right to life." However, many people contended that this ban infringed upon their human rights as outlined in the American Convention on Human Rights, to which Costa Rica had agreed to adhere. The Inter-American Court of Human Rights ultimately ruled that Costa Rica's ban was unlawful, declaring that it violated the rights of individuals seeking to utilize IVF. This case highlights the tension between the right to life of embryos and the reproductive rights of individuals [41]. Many Muslim scholars have extensively examined bioethics, focusing on important topics such as in vitro fertilization (IVF), abortion, and organ donation. Their goal is to provide Islamic viewpoints on these critical issues.

Key Points

1. A majority of Muslim scholars permit IVF when it is performed between a husband and wife during their marriage.
2. Some scholars emphasize the significance of Islamic principles and jurisprudence in guiding bioethical decisions.
3. Others investigate the relationship between Islamic ethics, morality, and religious revelation in addressing contemporary bioethical challenges [42].

Conclusion

In vitro fertilization (IVF) has provided hope for couples struggling with fertility issues. Many couples who previously faced generational challenges now have the opportunity to create their own families. It is a complex process with serious health complications like ovarian hyperstimulation. It has made it easier for females who do not carry a pregnancy due to their careers and health issues. IVF is legally supported. The future of IVF is bright by reducing the infertility rate.

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