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Advancement in Field of in vitro Fertilization (IVF)

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ABSTRACT

One of the most revolutionary advances in science and technology has been the advancement in in vitro fertilization to treat infertility. Increased demand for in vitro fertilization as a result of socio-demographic trends, with new technologies facilitating supply. Technology is used in conjunction with IVF to improve the outcome by facilitating each step of the process. IVF advancements are likely the most exciting scientific developments in infertility treatment. In the past years, the field of in vitro fertilization has undergone technological advancements that were unimaginable including endometrial receptivity array (ERA), in vitro gametogenesis, mitoscore, microfluidic technology, cryopreservation of surplus embryos and ovarian tissues, intracytoplasmic sperm injection (ICSI), testicular sperm extraction (TESE), chromosomal screening through preimplantation genetic diagnosis (PGD), mitochondrial manipulation methods (MMT), autologous germline mitochondrial transfer (AUGMENT), uterine transplantation, laser assisted hatching, embryoscope, endometrial coculture, intrauterine insemination (IUI), gamete intrafallopian transfer (GIFT), fallopian tube sperm perfusion (FSP), surrogacy motherhood, bovine somatic cell nuclear transfer (SCNT), frozen-thawed embryo (FET), organ culture systems, embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), spermatogonial stem cells, micromanipulation and many different methods to improve the quality of infertility treatments. Current breakthroughs in IVF technology, such as controlled ovarian hyperstimulation, luteal phase support and improved culture media were completed quickly. Reproductive medicine, particularly IVF is fast changing how people reproduce, and as a result, it will always be crucial to science and society. The goal of this article is to provide an overview of emerging technologies that have the potential to significantly increase IVF utilization.

KEYWORDS: ARTs, IUI, In vitro fertilization, PGD, PGS, FET.

1. INTRODUCTION

Infertility is defined as the inability to conceive within 12 months of regular and unprotected sexual contact (Arora *et al.*, 2022). To overcome the problem of infertility, in vitro fertilization (IVF) in conjunction with various technologies are employed (Thapa and Heo, 2019). IVF-related procedures that are used in New Zealand and Australia include: Intracytoplasmic sperm injection (ICSI) and Gamete intrafallopian transfer (GIFT) (Fitzgerald et al., 2018). The goal of IVF was to solve the problem of infertility, but a challenge arose when couples with poor sperm quality and quantity were unable to undergo development in which a single spermatozoan is injected directly through the oocytes' zona pellucida. The procedure is known as intracytoplasmic sperm injection (Thapa and Heo, 2019). Gamete intrafallopian transfer, in which mature oocytes and sperm are placed directly into a woman's fallopian tubes for in vivo fertilization (Fitzgerald *et al.*, 2018). Due to the fact that fewer sperm are implanted in the oviduct, GIFT may be employed for sub-fertile stallions with poor sperm output (Carnevale, 2004). The procedure is now a recognized method of treating infertility brought on by endometriosis and cervical causes (Hewitt, 1991).

The different methods of artificial insemination are; Fallopian tube sperm perfusion (FSP) is with 4 mL inseminate. The cervix was clamped to prevent inseminate leakage, and the pressure buildup in the uterine cavity caused uterotubal flushing. Intra tuboperitoneal insemination (IUTPI), using 10 mL of inseminate. The uterine cavity might be filled with 10 mL of inseminate, which would then be able to travel through the interstitial region of the tubes and the ampulla before arriving at the peritoneal cavity and the Douglas pouch, where it would mix with the peritoneal and follicular fluids. Intra-uterine insemination (IUI), using 0.5 mL of inseminated fluid (Mamas, 2006). It is a method of treating infertility that entails injecting the ready sperm into the uterine cavity at a time close to ovulation. This can be carried out either during a natural cycle or in conjunction with ovarian stimulation. For couples with particular indications, IUI is a less expensive and time-consuming therapeutic option for conceiving a child (Kandavel and Cheong, 2018).

In Surrogacy motherhood agreements, a woman the "gestational carrier" agrees to bear a child for an individual or couple, the intended parent (Fitzgerald *et al.*, 2018). In South America, embryo industry is remarkably active due to use of in vitro fertilization methods like micromanipulation, intracytoplasmic sperm injection (ICSI), somatic cell nuclear transfer (SCNT) and ovarian stimulation in mostly bovine species for better production in South American embryo industry (Viana *et al*., 2018). Bovine somatic cell nuclear transfer (SCNT) embryos can develop to the blastocyst stage at a rate comparable to that of in-vitro fertilized embryos. However, due to the high embryonic and fetal losses after embryo transfer, the full-term developmental rate of SCNT embryos is very low (Akagi, Geshi and Nagai, 2013). Micromanipulation in ART has proved very beneficial in treating infertile individuals and in helping to comprehend the fundamental ideas of fertilization and embryo development. From the pronuclear until the blastocyst stage, embryo micromanipulation is possible. The method was initially simple but ended up becoming more intricate. Embryo micromanipulation at the cleavage stage involves a variety of methods, such as splitting the embryo or opening the zona pellucida to increase the likelihood of implantation (Halvaei *et al.*, 2018).

Cryopreservation is the process of storing biological materials such as cells, tissues, and other components at extremely low temperatures typically in liquid nitrogen for later use (Thapa and Heo, 2019). IVM (in vitro maturation) oocyte cryopreservation entails retrieving immature oocytes from ovaries after minimal or no gonadotropin priming and then either cryopreservation at the immature or mature stage after IVM. It has many benefits, including simplified treatment, lower costs, and the avoidance of potential side effects such as ovarian hyperstimulation syndrome (Son *et al*., 2019). In vitro maturation (IVM) is the method of harvesting immature human oocytes and completing the prophase I to metaphase II transition, including the ejection of the first polar body, in vitro. Substantial innovations have been made to IVM protocols over the past ten years, including priming with hCG, follicle stimulating hormone (FSH), and/or luteinizing hormone (LH), as well as particular adjustments to the media used for IMV oocyte culture (Brezina *et al.*, 2012). FET is indeed an IVF technique, and while advances in cryopreservation technologies are currently being made, the quality and chances of a frozen-thawed embryo implanting are comparable to those of fresh embryos (Roque *et al*., 2018). When compared to fresh embryo transfer, benefits of FET consist of lower incidence of low birth weight, small for gestational age, preterm delivery, placenta previa, placental abruption, and perinatal death (Singh *et al.*, 2020). In Sweden, techniques like TESE and open biopsies, conventional testicular sperm extraction, and percutaneous biopsies are used (Westlander, 2020). Some men with non-obstructive azoospermia may be eligible for testicular sperm extraction (TESE), which can yield spermatozoa for ICSI. For men with nonobstructive azoospermia, microdissection TESE can increase sperm retrieval over what was attained with previously published biopsy procedures (Schlegel, 1999).

The technologies used for evaluating embryos are; MitoScore is a relatively new method of evaluating embryos. MitoScore is a number that indicates the standardized amount of mitochondrial DNA (mtDNA) in embryos. MitoScore is a relatively new approach to embryo evaluation (Arora *et al.*, 2022). Secretomics and metabolomics provide another method for determining which embryos are best for uterine transfer. The study of specific protein profiles found in the media culture fluid surrounding the developing embryo is known as secretomics. Metabolomics is the study of metabolic byproducts found in embryo culture media. The use of time lapse imaging and videography is another recent advancement in noninvasive evaluation of developing embryos. Recent advancements in incubators that include established time lapse and video equipment now allow for real-time evaluation of the dynamic modifications that take place during early embryo development (Brezina *et al*., 2012). In August 2015, the first Iranian live birth utilizing a time lapse method to identify the finest embryos for transfer was reported (Faramarzi and colleagues; 2017). With the use of time-lapse incubators, embryo culture has already been entirely automated, allowing for continuous observation of embryo growth. Machine learning may be used to analyze data provided by time-lapse incubators to help in the selection of embryos with the highest pregnancy potential, as embryo culture increases chances of conception, so act as a major protocol in IVF (Armstrong *et al.*, 2015). In Saudia Arabia and France, pre-implantation genetic diagnosis (PGD) and pre-implantation genetic testing was recently introduced in the field of IVF. PDG testing is the process of acquiring a cellular biopsy sample from a developing human oocyte or embryo obtained through an IVF cycle, assessing the genetic composition of this sample; and using this information to decide which embryos will be ideal for subsequent uterine transfer (Abotalib, 2013). Preimplantation genetic testing for aneuploidies is now done using high-throughput next-generation sequencing (NGS) methods.

This method is crucial for achieving pregnancy and a successful embryo transfer, which cuts down on the time and expense of further cycles (Alyafee *et al.*, 2021). Various techniques for multiple ovulation and embryo transfer have been done in Nepal and Srilanka on certain species of cattle and goats to upgrade variations in genetic traits by superovulation, embryo evaluation and artificial insemination (Bajagai, 2013). The pri-implantation embryo needs to hatch in order to leave its zona pellucida and become implantable, called hatcting. Different varieties of assisted hatching have been developed to aid embryos in escaping from their zonae during blastocyst growth. While zona slitting is done in the same way as partial zona dissection, zona drilling entails making an incision in the zona with acidified media. When the zona is thinned, no holes or slits are produced; the zona is simply made thinner over the targeted area. Laser-assisted hatching has more recently been developed in IVF, and it considerably increases the capacity of in vitro-grown blastocysts to hatch by creating an artificial gap in the zona pellucida (De Vos and Van Steirteghem, 2000). To limit the risk of poor outcomes associated with multiple gestations, single embryo transfer (SET) is currently regarded as the best practice in IVF cycles (Faramarzi *et al.*, 2017). Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) both entail taking one or more cells from the developing embryo and studying their genetic make-up to look for a particular genetic flaw known to exist in the parents or to check for the presence of embryo aneuploidy (Brezina *et al;* 2012). It includes the investigation of single cells (blastomeres) biopsied from incipient organisms 3 days after fertilization, or polar bodies expelled from oocytes during meiosis. The reason for such tests is to figure out which undeveloped organisms, out of a partner produced utilizing ART, are unaffected by chromosomal unevenness (Kahraman *et al.*, 2015).

Controlled ovarian hyper stimulation (COH) is used to improve the number of available oocytes for IVF. COH entails numerous gonadotropin injections and multiple trips to the fertility clinic for transvaginal ultrasound examinations and circulating hormone levels. As a result, COH is sophisticated, time-sensitive, and intense. Several options for minimizing the frequency of injections by using long-acting gonadotropins or oral medicines are currently available and gaining popularity in the field for the treatment of specific patient populations (Kushnir, Smith and Adashi, 2022). Some many trials have shown that using such protocols, which use small concentrations of injectable gonadotropins, results in roughly similar pregnancy rates as there are fewer medical complications and costs because once particularly in comparison to more standard COH protocols (Brezina *et al.*, 2012). Minimal ovarian stimulation procedures have been established to encourage the formation of numerous follicles in normo-ovulatory women, to facilitate retrieval of multiple oocyte in single IVF cycle (Fauser *et al.*, 1999).

Freeze-all cycles are new ART treatments in which all oocytes or embryos are frozen for future use. This increasingly common practice is used for an assortment of reasons, such as lowering the likelihood of ovarian hyperstimulation syndrome (OHSS), improving endometrial - embryo synchronicity, as part of a PGT cycle are used in Australia and New Zealand (Fitzgerald *et al.*, 2018). Canadian and United Arab Emirates groups asserted that autologous type of MMT called autologous germline mitochondrial transfer showed marked improvements in pregnancy rates. An autologous type of mitochondrial manipulation methods is autologous germline mitochondrial transfer (AUGMENT). It involves extracting mitochondria from an infertile patient's 'egg precursor cells' and injecting them into the patient's oocyte (Ishii and Hibino, 2018). Endometrial receptivity array (ERA) help to upgrade new techniques in IVF, it is a technique to determine timing to transfer of an embryo by observing the endometrium's genomic expression (Nafees *et al.*, 2021). Microfluidic technology has been one of the most effective technologies. The study of the behaviour, precise control, and manipulation of fluid in microenvironments is referred to as microfluidic technology. The use of microfluidics in the IVF process is expanding. Maturation, insemination, and oocyte manipulation, as well as other microfluidic-based processes, are now fairly common in IVF (Thapa and Heo, 2019). Embryo co-culture has been found to be an interesting technique, for producing a large number of blastocysts for transfer. With the use of co-culture methods, a good number of embryos reach the blastocyst stage, which appear to boost human embryonic development by assisting embryos in recovering from poor culture conditions (Olivennes *et al.*, 2018). For gamete intra fallopian transfer therapy-produced extra oocytes, the intra-vaginal culture approach has been used (Hewitt, 1991). The fluorescent in situ hybridization (FISH) technology, it can be used to identify balanced or normal embryos from polar bodies or blastomeres of cleaving embryos. There may not be enough oocytes recruited as a result of the process, especially in women with advanced maternal age, which reduces the number of embryos that may be examined (Abotalib, 2013).

2. MATERIAL AND METHODS

The current data is a secondary analysis of advancement in field of IVF, several techniques and procedures were followed to ensure recent advances in IVF. Comprehensive and progressive articles and journals from 2000 to 2022 are used for data and information used in this review article.

3. CONCLUSION

According to current research, infertility affects 8-12% of the global population. As a result of these issues, assisted reproductive technologies have had a significant impact on the therapeutic management of infertility. In many parts of the world, it is likely that IVF will be used to conceive up to 10% of all children in the near future. Given the rapid scientific and technological evolution of IVG and reproductive genetics, it is critical that both the public and regulatory bodies work together to develop a framework for the ethical assessment of emerging technologies. Through the use of IVF about eight million plus new born babies came into this world by the new technology IVF in 2018. IVF availability and use vary greatly throughout the world, with the equivalent statistics now standing at 4.1% in Australia and New Zealand, 1.9% in the United States, and 1.7% in China, and is increasing worldwide. The increase use of IVF will change the way a large part of human population reproduces, it is likely that in near future, as many as 10% all children will be conceived through IVF worldwide. It is quickly revolutionizing human reproduction and will thus remain vital to both science and society. According to the latest preliminary report from International Committee Monitoring ART in 2016, Japan was second largest national user globally, techniques like frozen embryo transfer and fresh cycles increase live births in Japan up to 97%, moreover gamete intrafallopian transfer (GIFT) and controlled ovarian stimulation (COS) were also used. In United States, embryo cryopreservation with subsequent FET has increased from 7.9% of cycles in 2004 to 40.7% in 2013.

The development of ART in Russia reported by the Russian Association for Human Reproduction (RAHR), since 1995 and due to the use of various new techniques no of children has been growing rapidly, almost 35,000 per year in 2017. In Europe and Denmark, Intrauterine insemination (IUI) technique is used. In South America, embryo industry is remarkably active due to use of in vitro fertilization methods. The most recent techniques used in Latin America are; single embryo transfer, pre-implantation genetic diagnosis, intrauterine insemination, and laser assisted hatching, and laser assisted hatching, which are gradually increasing the production rate of children in America. In Sweden, techniques like TESE and open biopsies, conventional testicular sperm extraction, and percutaneous biopsies are commonly used to bring back sperm for intra cytoplasmic sperm injections to cure non-obstructive azoospermia. In Saudia Arabia and France, pre-implantation genetic diagnosis (PGD) and pre-implantation genetic testing was recently introduced in the field of IVF. Microfluidic technology has been one of the most effective technologies developed for the advancement of this field. Freeze-all cycles are new ART treatments used for fertility preservation, or as a clearly intentional therapeutic option used by some clinicians in Australia and New Zealand. Mitochondrial manipulation methods (MMT) have been created and employed in reproductive clinics. The world's first successful mitochondrial manipulation methods case was reported from the United States in 1997. Controlled ovarian hyperstimulation (COH) is used to improve the number of available oocytes for IVF. The first COH protocol used 150 IU of human menopausal gonadotropin (hMG), resulting in an average of 3.7 oocytes retrieved per IVF cycle. As a result, COH is sophisticated, time-sensitive, and intense. Canadian and United Arab Emirates groups developed autologous type of MMT known as autologous germline mitochondrial transfer, was reported in 2015.

Furthermore, the incorporation of novel technologies into clinical practice must be scientifically sound and supported by well-designed clinical trials. Premature commercialization of costly and unproven "add-ons" to IVF has been a persistent issue in the field, spanning procedures, medicines, and laboratory techniques. The routine use and marketing of unproven IVF add-ons may erode public trust in the reproductive medicine field as a whole. As a result, the field must prioritize requiring confirmation of the effectiveness and safety of technologies before allowing them to be provided routinely to IVF patients. Reproductive medicine, primarily IVF, is rapidly transforming human reproduction and will thus continue to be of utmost important to both science and society.

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