A Review on Role of Assisted Reproductive Technology (IVF) in Modern Society: Hope, Opportunity, and Ethics

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Abstract

Assisted reproductive technologies are a boon to humankind as they are changing lives of couples which are struggling to have offspring's. Over the last few decades, they are widely spread around the globe. During this review will discuss about the success, advantages, and drawbacks of several assisted reproductive technologies such as In-Vitro Fertilization (IVF), gamete transfer and Intracytoplasmic Sperm Injection (ICSI). This review also covers the factors which lead to the infertility in both male and females such as routine life and environmental factors. In conclusion, reproductive technology has changed the field of reproductive medicine and brought hope and opportunities to people and couples who are having trouble conceiving or having children due to genetic diseases or any socio-environmental factors. There are some ethical issues also connected with bad practices of ART's. In order to navigate the ethical dilemmas and ensure that reproductive technologies are used in a manner that promotes the well-being and rights of all individuals involved. It is the moral duty of policymakers, health professionals, health advisors and above all, the whole community to develop and practice a better policy.

Keywords: *Assisted reproductive technologies, In-Vitro Fertilization, gamete transfer, Intracytoplasmic Sperm Injection, Infertility, Genetic diseases.*

1. INTRODUCTION

Reproduction is the important part for survival of all the living being. It is the process in which new offspring's produced. The sex chromosomes are majorly responsible for the functioning of male and female reproductive systems1. Infertility refers to the sexual abnormalities present in either male or female. It is defined when there is no pregnancy caused in one year even after the regular and unprotected sexual intercourse2. Nowadays infertility became a major concern because of life style changes and mental stress in couple3.

Infertility is very common in today's generation and is caused due to stress, anxiety, depression, alcohol, drugs, smoking, poor nutrition, and obesity and high body mass index4. Male infertility is caused when the quality of semen is depleted or the count of sperms is very low. Also, it is caused due to endocrine problems, drugs, radiations, infections, hormonal imbalance or the blockage of man duct's system5. Pesticides or chemical dust present in the environment can also play a major role in causing male infertility6.Pesticides such as DDT (1,1,1-trichloro-2,22-bis(p-chlorophenyl) ethane), pollutants like dioxin and anti-cancer drugs and PCBs (Polychlorinated biphenyls) directly or indirectly causes the male infertility7.

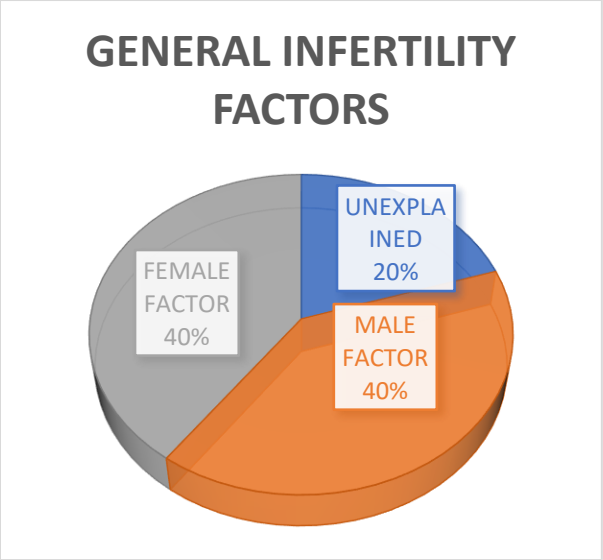
Female infertility is defined when the woman is not able to conceive. It is caused when the hormones are imbalanced or eggs are not produced at certain levels8. It is caused due to many hereditary disorders like polycystic ovaries syndrome [PCOS] and several other medical conditions responsible for causing infertility9.Age is also a major factor in female infertility. In many infertility cases the fallopian tube gets blocked or the ovulation does not occur in the body by which eggs are not able to release in the ovaries10.

1.1 INFERTILITY FACTORS

There are no specific cures to treat female infertility. No dietary sources or organic sources can help to avoid infertility. It naturally occurs in the body after some specific age. The assisted reproductive technologies show a connection with epigenetics in the human genetics11. The term epigenetics refers to the branch of science which deals with the gene interaction and the product phenotype, and was discovered by an embryologist and developmental biologist: Conrad Waddington in 1940s. The branch mainly focuses on the gene expression and the gene control12.The phenotype refers to the traits which can be observed whereas the genotype refers to the gene collection of an individual13.

Assisted reproductive technologies are widely used all over the world to treat infertility among couples. Assisted reproductive technologies include In Vitro Fertilization [IVF], Embryo Transfer [ET], Intra Cellular Sperm Injection [ICSI], Embryo Biopsy, Pre implantation genetic testing, cryopreservation of either embryos or gametes14.

Figure 1: Gender wise distribution of infertility



When assisted reproductive technologies were first known or came into cause, the people were not much aware of so as a result the children born has a lower ratio to identify the outcome differences15. In Vitro Fertilizationled to the first successful birth in assisted reproductive technologies. Babies born through IVF are referred to as test tube babies.On July 25,1978 Louis Brown was born through IVF16. He was the first child born throughout the world by this technique. After this it led to the global spread of Assisted Reproductive Technologies. In vitro fertilization also shows the interconnection between the two terms i.e., 'in glass' and 'in vitro'. In glass is defined as the processes carried outside the body in the glass materials like test tube and petri dishes and in vivo is defined as the processes carried out inside the body17.

Around 45 years ago, the "fertility industry" was not much known and people were not aware of these technologies but gradually with time, today it is the most known and growing industry in India. The IVF technology has never been a flowing hand in India18. The first child born in India through IVF is 'Harsha' born on 16 august 1986. The procedure was carried out by the Indian council of medical research (ICMR) under T.C. Annand Kumar19.

Table 1: Timeline of things achieved in assisted reproductive technologies 20.

1978	First baby was born through IVF Natural Cycle.
1983	Using oocyte donation technique of IVF first pregnancy occurred. With the help of cryopreserved embryos first baby was born through IVF.
1984	Gamete Intra Fallopian Transfer [GIFT] was introduced.
1987	Oocyte retrieval guided by transvaginal US
1990	Preimplantation Genetic Diagnosis [PGD] was introduced for sex-linked diseases.
1991	ICSI was introduced and with the help of it first baby was born through IVF.
1993	Using testicular sperm extraction first baby was born through IVF.
1997	First baby was born using cryopreserved embryos.
2001	PGD was first used for HLA-haplotype matching.
2004	First baby was born from orthotopic transplantation of cryopreserved ovarian tissue.

As in vitro fertilization is also known as test tube babies the embryos are generated outside the body at the optimum temperatures so there's a chance that the microorganisms present in the environment may contaminate the embryos. Bacterial and fungal contaminants affect the developing embryos, sperms and oocytes21. IVF carries various processes like the embryo transfer. When the embryos are transferred into the body there is a chance that they can carry microorganisms to the body which further alters the implantation and also pregnancy22.

The source through which microorganisms can enter in the laboratories are the endogenous sources. The reagents, devices, equipment's, even the air present carries the main risk of contamination23.

Infertility can be caused due to many factors which plays a major role in shaping the health of both males and females. The major factors which can cause infertility in human beings are the environmental factors which in contrast impact the lifestyle and the physiology24. The common factors which cause infertility in both males and females are diabetes, excessive use of alcohol, toxins present in the environment, radiation therapies given to the cancer patients, sexually transmitted diseases (STDs), smoking, stress and weight problems. Age is one of the major factor25.

AGE: Age plays an important role in the fertility of human beings. Fertility decreases with age and so infertility increases. There are less or no chances of infertility below the age of 35 for women and 40 for men26. After a certain age group, the risk of infertility increases gradually as the sperm motility and the sperm concentration decreases thus decreasing the sperm count in males. When the semen analysis is done the sperm defects are shown abnormality in sperm morphology, motility and the number of sperms27. Female fertility is highest in between the age of 18 years and 30 years. After this the fertility starts to decrease and infertility occurs28.

OBESITY: One of the major causes of infertility is the weight problems which includes obesity. It is caused due to unhealthy eating habits. The increased ratio of obesity in females has increased the risk of reproductive problems, psychological issues and the decreased rate of metabolism which leads to various health diseases like cardiovascular diseases and diabetes. If a female develops early obesity in adolescence it may lead to irregular menstrual cycles, polycystic ovary syndrome (PCOS) and infertility29. An obese woman has increased body mass index as compared to non-obese woman. Obese woman has more risks of developing infertility than non-obese woman approximately three times more chances30. With body mass index greater than 27kg/m2, the ovarian dysfunction can occur31. The major hormone estrogen which plays various roles in the body like in females, it develops and maintains the reproductive organs which are secreted by the primary sex organs and the fat cells of the body32. Obesity increases the production of estrogen which depletes the rate of pregnancy by interrupting as a birth control.Also, lower weight or less amount of body fat leads to insufficient estrogen and thus causes irregular menstrual cycles.Proper diet and nutrition factors are connected to the later years of fertility. Changes in the reproductive period in females vary because of obesity33. In obese women menopause occurs in smaller age than in non-obese women. Obese women develop higher risk of maternal death, miscarriages, urinary tract infections, hypertension and various other pre and post pregnancy complications34.

STRESS: Stress is a very common and challenging psychological situation for the human body. Individuals' behaviour and physiology is affected by physical and psychological stress35. A working woman faces both types of stress in their day-to-day life. Psychological stress includes the stress of balancing professional and physical life increases the level of stress in women. Societal pressure also increases the stress levels. Working women decreases the chance of conception and affect 30% of women.Stress hormonal changes triggers mood swings and unhealthy dietary changes causing malnutrition or obesity.. Chronic stress causes menstrual dysregulation, reduction in gonadotrophin releasing hormone (GnRH), luteinizing hormone (LH), and follicular stimulating hormone (FSH) 36.

Stress provokes the level of corticotrophin releasing hormone (CRH). It creates the contractions in the myometrium via cytokine induced labour pain37. If CRH levels in a pregnant woman increases during the second trimester and giving birth to immature baby marks the effect of stress on the reproductive organs.Excessive stress can also cause depression in severe cases. It causes behavioural changes in the later stages of life. Body responses to stress signals affect the neuroendocrine part which causes or result in infertility38.

ALCOHOL: Alcohol nowadays is consumed by everyone in today's generation on regular basis. Both males and females consume alcohol but excessive consumption of alcohol may cause a chance of infertility or sub fertility.Excessive alcohol is also associated with the abnormal menstrual cycles, abortion, low birth weight, defects in birth, stunted growth. Developing foetus can also develop disabilities39. It also decreases the chance of conceiving by about 50%. It also increases the risk of heart failure or depression in the mother. In severe cases, that is consumption of alcohol at the maximum level can cause preterm delivery and Chances of immature baby with disabilities increases40.

Alcohol consumption at higher levels can elevate the level of estragon and this elevation in estrogen reduces the secretions of follicular stimulating hormone (FSH). Alcohol is normally consumed in peer pressure, exaggeration, depression, environmental changes. It is also a basic lifestyle choice41.

SMOKING: Smoking is very common in this generation. Every third person smokes on regular basis even after knowing its harmful effects on health and how injurious it is to our body. Smoking cigarettes, vapes, hookah or drugs is very dangerous as it directly attacks to the brain. It also affects the fertility rate in both males and females42.

Tobacco smoking or smoking cigarettes, hookah, vapes and drugs contains various harmful chemical ingredients like nicotine which acts as a barrier in the estrogen synthesis. It also interferes with the transfer of embryos during In Vitro Fertilisation (IVF), uterine blood flow and uterine myometrium43.

Smoking can attack our body by both means, that is, either directly or indirectly in young females like ovulatory disorders. It can also affect the development of a baby or the genetical changes can occur inside the mother's stomach and may also lead to the death of the child.Smoking decreases the level of oxygen in our body, so the sufficient oxygen required to both baby and the mother for a living is not provided leading to the death of either mother or child or in some cases both.Pregnancy rates or rate of conceiving is less or nearly negligible

in the young women who smokes on regular basis44.

CAFFEINE: Caffeine is widely consumed through every individual in one form or other. Caffeine is found in tea, coffee, cocoa, soft drinks and medications.It might be good for the body to remove various toxins but in limited amounts. Excessive consumption of caffeine can increase the risk of toxicity, infertility, cancer and heart diseases.It can also increase the rate of abortion or delay in conceiving as caffeine crosses the placenta affecting the growth of foetus45.

ENVIRONMENTAL FACTORS: Environmental factors also affect the fertility of humans. Environment contains many radiations, pesticides, toxins, pollutants and many more particles or chemicals which can affect our body's health in various means. Intake of these pollutants can also cause difficulty in breathing or other breathing problems. Harmful chemicals like chlorinated hydrocarbons and fumicides are highly associated with the spontaneous miscarriages in women46.

Also, exposure to these chemicals can reduce the fertility rates, stillbirth, low birth weight, premature delivery, ovarian disorders and abortions. It is also found to alter the time-to-pregnancy (TPPs). Women who are highly exposed to the high level of pesticide exposure are associated with prolonged TPPs. Direct contact with chemicals or environmental toxins leads to the infertility either primary or secondary47.

Air pollutants are a major cause for pollution. Some common air pollutants change/modify DNA by altering/changing the gene expression/epigenetic marks. Heavy metals like Pb, Zn, Cu; endocrine disruptors like polycyclic aromatic hydrocarbons (PAHs) they generate oxygen species (ROS) (NO_2, O_3). Exposure to radiation rays can be both ionising and non-ionising radiation. Ionising radiations include x-rays, gamma rays and non-ionising radiations include radio waves, ultrasound, and electromagnetic waves48. They generate heat and alter the biochemical structures of DNA, proteins. Radiation exposure can harm the germ cells as gonads are highly sensitive to radiation exposure. These radiations have long-term/lifelong effects on pregnancy. Medical tests like sonography, x-rays are done but at a particular temperature. High number of radiations can either lead to the abnormal child with disabilities or the death of the child.

2. ASSISTED REPRODUCTIVE TECHNOLOGIES [ART]

Assisted Reproductive Technology is used to treat infertility in human and helps in conceiving a child. As nowadays, infertility is a very common issue so to come up with this, various methods/procedures of assisted reproductive technologies were introduced. ART basically refers to the formation of gametes or fertilisation of gametes outside the body in some specific conditions. It helps in the fertility of humans49.

The various procedures are known in the assisted reproductive technologies, such as In Vitro Fertilisation (IVF), Embryo Transfer (ET), Intracytoplasmic Sperm Injection (ICSI), Gamete intrafallopian transfer (GIFT), Zygote intra-fallopian transfer (ZIFT), Intra Uterine Injection (IUI). Among all the widely and the most common procedures used around the globe are In Vitro Fertilisation, Intracytoplasmic Sperm Injection and Embryo Transfer50.

2.1 IN VITRO FERTILISATION (IVF)

In Vitro Fertilisation is the most common procedure used to treat infertility and also helps in conceiving a baby. This procedure is used worldwide. The first successful birth through IVF took place on July 25, 1978 of Louis Brown. He was the first child born throughout the world by this technique.After this it led to the global spread of Assisted Reproductive Technologies. IVF refers to the In Vitro Fertilization where 'in vitro' means 'in glass'. That is fertilization take place outside the body in glass dishes or petri dishes under some specific conditions in the artificial environment51. The mature eggs are collected from the ovaries of female and sperms are retrieved from the male by the procedure called as sperm retrieval and the eggs are fertilized in a sperm in a petri dish. The procedure is followed in the IVF laboratories under the temperature required for the fertilization of gametes, temperature is as same as the temperature of the mother's womb. The proper warmth is provided in the laboratory. Then the embryos which are fertilized in the lab is transferred to the uterus with the help of the process named as embryo transfer52. The one IVF cycle takes around 3 weeks to complete the procedure. Sometimes the process can take longer. A couple can use their own eggs and sperms to carry out the procedure. In some cases, a donor can also provide with the sperm if the quality of the sperm is poor to fertilize with the egg.It is comparatively an expensive treatment. The chance of giving birth to a healthy baby depends on various factors includes Maternal age, Embryo status, Lifestyle factors and Reproductive history53.

IVF technology can be useful for the patients with history of blockage of sperms, tubal damage or the poor quality of sperms in male patients. Other patients suffering uterine fibroids which are fibroids present in the uterus as the benign tumors can interrupt in the implantation of the fertilized egg in the uterus also benefited by IVF technology54. IVF technology also helps patients of tubectomy (refers to the surgery of fallopian tube in which the tube is cut and tied; this lowers the chance of getting pregnant naturally), Genetic disorder which causes miscarriages or abnormal births, Poor mobility of sperms (the mobility of sperms is poor the sperm is not able to fertilize the egg to form an embryo), Ovulation disorders (few eggs are left to be fertilized, this happens only if ovulation is absent or is infrequent) and Endometriosis55.

IVF's success rate depends on the various things like age, reason of infertility, sperm mobility, eggs or any other medical issues. A patient is asked to fill all the details before the procedure is being started. Various screenings of test are done at the clinic if a couple has to use their own eggs and sperms for the procedure:

Ovarian Reserve Testing: This test is done in females whose eggs are to be used to check the quality and quantity of eggs produced by the ovaries. The concentration of follicle stimulating hormone [FSH], estrogen and anti-Mullerian hormone is checked in the blood in the first few days of the menstrual cycle. The test results determine how the ovaries will respond to the particular medication56.

Semen Analysis: This test is done in males to check the quality and quantity of sperms. This test can either be done initially or just before the treatment57.

Infectious Disease Screening: To check the diseases this can be transmitted to the child from the couple58.

Mock Embryo Transfer: This test is just done to check the depth of the uterine cavity so that embryos can be placed successfully through a catheter59.

Before starting the IVF procedure all the necessary detail and consent of the patient recorded. IVF cycle involved 4 main steps followed sequentially first one is egg retrieval then sperm retrieval after that fertilization and then embryo transfer60.

2.1.1 EGG RETRIEVAL

Eggs are retrieved from the female body which is undergoing the treatment.Egg retrieval is done 34-36 hours before the ovulation and after the final injection.In this process, patient is given sedative drugs to make her sleep and some medications are given to relieve the pain.Eggs are retrieved by transvaginal ultrasound aspiration method. A thin needle is inserted to guide the ultrasound through the vagina and follicles to retrieve the eggs.If transvaginal ultrasound aspiration method fails to guide the follicles, an abdominal ultrasound is used to guide the needle61.The needle is connected to the suction device and then the eggs are removed from the follicles.In about 20 minutes, many eggs can be removed/retrieved.Once the eggs are retrieved or egg retrieval process is done one might feel pressure or cramps.The mature retrieved eggs are then placed in the culture media [nutritive liquid] and then incubated.All the eggs incubated are not matured so eggs which are matured and appear to be healthy are then mixed with sperm for fertilization to occur and further creates embryos62.

Egg Collection: The eggs are collected from the ovaries of females with the help of transvaginal ultrasound method. The follicular fluid collected from the female reproductive tract contains eggs. The eggs are then separated from the fluid in the lab under the microscope. The separated eggs are kept in a separate dish. The eggs are separated from the fluid using the micropipettes. After the egg collection is done, the separated eggs are denudated or cleaned and the pure eggs are again washed and separated in a FERT dish. This process of cleaning the eggs is referred to as egg denudation. The grading of eggs is done. The dish is now kept in an incubator to prevent it from contamination63.

2.1.2 SPERM RETRIEVAL

Sperms are retrieved from the male body which is undergoing the treatment.Sperms are retrieved by giving the semen sample at the clinic on the morning of egg retrieval.Semen sample is usually collected through masturbation (ejaculation) but sometimes the sperms are directly extracted from the testicle using a needle and the process is named as testicular aspiration64. Sperms are then separated from the seminal fluid in the lab using the centrifugation method. In this method, the semen sample is taken in a test tube using a dropper and is kept in a centrifugation machine for 8 minutes. When the machine stops the test tube is taken out and all the liquid is discarded and only the sperm palette is kept for the ICSI.The sperms separated are then mixed with eggs for fertilization to occur and further creates embryos66.

2.1.3 FERTILISATION

Fertilization occurs when the matured eggs and sperms are mixed together in a glass dish in a very special fluid or oil which provides all the nutrients required for fertilization. The dish is kept in the CO2 incubator overnight. Intracytoplasmic sperm injection [ICSI] is a form of in vitro fertilization [IVF].In this, the sperm is directly injected into the egg in the lab and leads to the formation of a mature

egg.Intracytoplasmic sperm injection is usually done when the semen quality or sperm number is low or have many failed IVF cycles in the past.After incubation, the fresh embryos are picked upby the embryologist using a microscope and then transferred to the female reproductive tract by the process called as embryo transfer67.

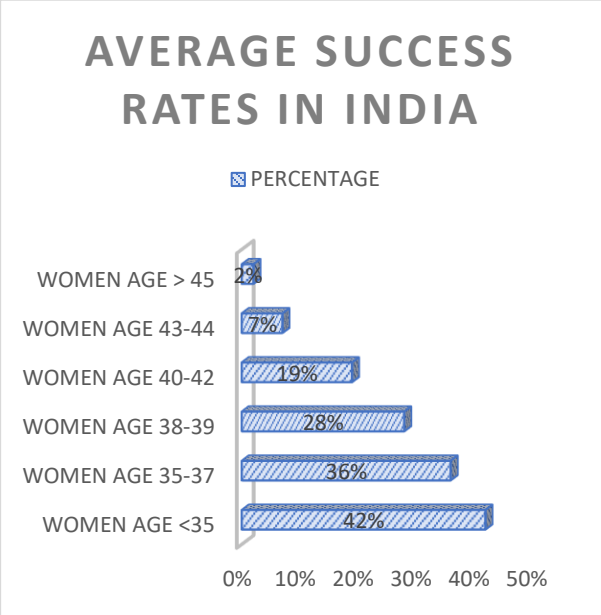
2.1.4 EMBRYO TRANSFER

Embryo transfer is done after 2-5 days of egg retrieval. It is a process in which 2-3 embryos are picked and loaded in a very fine, long tube known as a catheter.The catheter is then slowly inserted into the vagina through the cervix into the cavity of uterus.Embryos are generally transferred at 2-4 cell stage or at any stage between pronucleate to blastocyst stage.It is a real quick and a painless process. The patient can go home after 2-3 hours of embryo transfer. If the embryo transfer is successful, an embryo will implant a lining of the uterus. It can be confirmed by taking a pregnancy test after 10 days of egg retrieval68.

3. RISKS OF IN VITRO FERTILISATION

IVF technology is quite efficient and continuously improving day by day but as everything has some flaws, IVF is also associated with several risks. These risks include miscarriages (sudden loss of pregnancy before 2nd trimester), ectopic pregnancy (Implantation of embryo in fallopian tube in place of womb), low birth weight, Pre mature delivery (Child birth before completion of 3rd trimester), stress, cancer and other ovarian disorders. Chances of successful IVF are also dependent on age, social life and environmental factor of patients69. In India average rate of IVF is almost highest in female patient which are below 35 ages and after age of 45 chances is successful IVF is very low depict in figure.

Figure 2: Success rate of IVF technologies as compared with age



4. MICROBIAL CONTAMINATION

Microbial contamination in embryos can be bacterial or fungal. If embryos are kept in exposure to the environment or any radiations it can undergo the formation of bacterial and fungal growth which further destroys the embryos and failure of embryo transfer. If the follicular fluid is kept outside for a long period of time it may also lead to contamination and destroys the eggs. The contamination which occurs is endogenous in nature. Embryos, eggs and sperms are also affected by bacterial and fungal contaminants70.

It's crucial to keep aseptic environment all the time during procedure. Effect of microbes on ARTs can depends on the severity of the infection, the stage of ART being conducted, and the particular procedures. Safety measures adopted by the fertility clinic or ART provider play a key role during the ARTs. Optimizing the effectiveness and safety of ARTs depends on proper microbial infection screening, diagnosis, and management. Several bacterial,

fungal and viral infections can be spread during ART procedure (Table 2).

Table 2: Infection of ARTs and their related microbes

Type of Infection	Microbes Associated	Effects on ARTs	References
Bacterial infection	*Chlamydia trachomatis*	Can cause tubal damage and pelvic inflammatory disease (PID), leading to infertility and ectopic pregnancies. In ARTs, may require treatment with antibiotics and can affect success rates of in vitro fertilization (IVF).	**21, 43**
Bacterial infection	*Neisseria gonorrhoeae*	Can cause PID and tubal damage, leading to infertility and ectopic pregnancies. In ARTs, may require treatment with antibiotics and can affect success rates of IVF.	**12, 45**
Bacterial infection	*Ureaplasma spp.*	Can cause inflammation of the reproductive tract and adverse effects on sperm quality. In ARTs, may require treatment with antibiotics and can affect sperm quality, embryo development, and pregnancy outcomes.	**11, 43**
Bacterial infection	*Mycoplasma hominis*	Can cause inflammation of the reproductive tract and adverse effects on sperm quality. In ARTs, may require treatment with antibiotics and can affect sperm quality, embryo development, and pregnancy outcomes.	**34, 43**
Bacterial infection	*Listeria monocytogenes*	Can cause severe foodborne illness and infections during pregnancy, leading to fetal harm, premature birth, and miscarriage. In ARTs, may require screening of embryos and appropriate food safety measures to prevent infections.	**43**
Fungal infection	*Candida spp.*	Can cause vaginal yeast infections, which can affect sperm quality and embryo implantation. In ARTs, may require treatment with antifungal medications and	**33**

		can affect success rates of IVF.	
Viral infection	*Human papillomavirus (HPV)*	Can cause genital warts and persistent infections, which may require treatment and can affect sperm quality, embryo implantation, and pregnancy outcomes in ARTs.	**17, 49**
Viral infection	*Herpes simplex virus (HSV)*	Can cause genital herpes outbreaks and persistent infections, which may require treatment and can affect embryo implantation and pregnancy outcomes in ARTs.	**49**
Viral infection	*Cytomegalovirus (CMV)*	Can cause congenital infections during pregnancy, leading to birth defects and developmental delays in infants. In ARTs, may require screening of donors and appropriate precautions to prevent infections.	**49**
Parasitic infection	*Toxoplasma gondii*	Can cause toxoplasmosis during pregnancy, leading to birth defects and developmental delays in infants. In ARTs, may require screening of donors and appropriate precautions to prevent infections.	**46**

5. CONCLUSION

All living things depend on reproduction to survive, yet infertility is a serious issue in today's generation due to a number of causes like stress, lifestyle changes, and environmental contaminants. Poor semen quality, hormone abnormalities, and exposure to toxins and pesticides can all contribute to male infertility. Hormonal imbalances, genetic problems, and obstructed fallopian tubes can all contribute to female infertility. Female infertility cannot be specifically treated, although assisted reproductive technologies, like in vitro fertilization (IVF) and embryo transfer (ET), are frequently employed to address the problem. In upcoming times fertility will definitely became a huge issue as like environmental pollution. Proper monitoring of ART treatment and non-ART treatment has to be accounted. Further research is also required for root cause analysis of infertility and consequences during miscarriage.

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