

Review Article

Indian J Med Res 148 (Supplement), December 2018, pp 10-14
DOI: 10.4103/ijmr.IJMR_636_18



Infertility & assisted reproduction: A historical & modern scientific perspective

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Received March 30, 2018

Infertility has always been considered as a social stigma and has often been treated as socially, mentally and physically damaging experience for the childless women rather than man. Fatherhood was more a social rather than biological concept, thereby making childlessness a legitimate ground for divorce and a matter of disgrace for women. Every country has its own set of customs and traditional beliefs for the relief of childlessness. While introducing a second wife was one way to overcome the predicament of childlessness, divorce was also an available choice. There were several myths that contemplated the human concerns and their needs during ancient times. It is evident that types of the infertility and their treatment in the modern era have some historical background and different representations in the ancient civilizations. The present review discusses the historical and modern perspectives of infertility and assisted reproduction and their importance in different cultures.

Key words Assisted reproductive technology - childlessness - cryopreservation - culture - fecundity - fertilization - history - *in vitro* fertilization - infertility - surrogacy

Introduction

Affirmations from the present day modern science managing cells, molecules, genes, DNA and on assessing ancient Indian Vedic literature, it appears that parenthood is an instinct-driven physiological experience¹⁻³. It is also evident that there is inherent and deep-seated desire in all adult females to have a child. Instinct of parenthood is the most powerful desire that exists in all the living beings that include all the creatures and people¹⁻³.

Reproduction is unique in many ways, and it performs a very important role in the process of immortality. Inability to have children, in general, is considered as a personal failure and tragedy around the world. The infertility does not end the life of a person but it incurs wrecking impact on the life of that person for not full filling the biological role of parenthood. The historical perspective and modern scientific knowledge described the intricacy of infertility, and in this review, efforts have been made to highlight these intricacies.

Historical perspective

The ancient era (3500 BC-500 AD)^{4,5}

This era marks the beginning of the advancement of civilizations from Indus Valley to Vedic Civilizations. During this period, the tradition of Niyoga pratha or Levirate⁶ was prevalent to produce the child. It was also evident from the Vedic literature that the general population during that time was familiar with the idea of artificial insemination (AI) which involved the manual injection of semen into the reproductive tract of the women⁷. Enchantment mixtures ('Magic potions') created by the sages for the queen of childless kings to make them pregnant was a typical practice during this era⁷. Thus, the people during that time were aware about the ideas of assisted conception and gamete manipulation⁸.

The common era (c.300 CE-c.400C)^{4,5}

During this time, bareness was typically presented as a problem for women. It was considered as a tragedy for a woman in the ancient east since the barren wife was likely to be despised by her husband, family and society⁹. The value of the women during Common Era was determined by her purity and after marriage by her reproducibility¹⁰. Although the introduction of a second wife was a way of avoiding childlessness, divorce was also an option. In the Common Era, the marriage agreement was thought to be completed not at consummation but with child birth¹¹. One of the major causes of divorce during that time was women's infertility; as mentioned in majority of the Egyptian marriage contracts, polygamy was very common and the reason for a man opting for more than one wife¹².

The medieval period to the middle ages (ca. 500-1500)^{4,5}

The suffering of women for not bearing the child continued from the medieval period to middle ages. Wide range of religious views on infertility, existed from the late medieval period to the middle ages where the concepts of gender equality came into existence; the necessity of procreation was understood as important carrier of lineage ahead for the continuity and extension of the family¹³. Although religious discourse about infertility in those times focused mainly on women, men also were considered as culprits for not producing the child. Polygamous marriage was an ancient and long-standing solution to infertility in the Middle East. Sometimes, the spouse was sought to make a temporary alliance only for the purpose of obtaining a child from them^{14,15}.

Modern scientific perspective

The extension of the Middle Ages to modern history was the Renaissance period, during which the scientific progress was made in the field of modern medicine including the infertility treatment. The practice of modern medicine originated in Greece about 7th century B.C. Ancient Greeks believed in the conventional methods of treatment that were based on the religion, magic and superstitions; eventually after the beginning of medical science, the physicians and surgeons disregarded the time-honoured elements of superstition and magic and were more in favour of the factual medicine¹⁶. Later on, the famous physician Hippocrates evolved a system of scientific reasoning based totally on rational thinking¹⁷. Infertility was recognized as a medical problem requiring diagnosis and treatment. Hippocrates during that time had formulated various treatment options for the infertile couples. While treatment in modern medicine focuses more on pharmacological and surgical procedures, Hippocratic therapies were primarily based on lifestyle changes.

The development of techniques for the treatment of infertility can be traced back to the period when physicians began to think scientifically about the reasons of infertility. In 1677, Antonie Philips van Leeuwenhoek¹⁸ first discovered spermatozoa through microscope. He named them as animalcules and claimed their importance in the formation of embryos. After the discovery of spermatozoa, advancements were made in modern medicine to understand the reproductive physiology, process of gamete interaction and to treat and resolve infertility problems¹⁹.

Evolution of infertility treatment

Artificial insemination

In 1779, the essentiality of spermatozoa for fertilization was demonstrated by an Italian priest and physiologist named Lazzaro Spallanzani who proved that a spermatozoon contained a nucleus and cytoplasm through a laboratory experiment¹⁶. It was established for the first time that the embryo develops as a result of physical contact between the egg and the sperm²⁰. With this new discovery, Spallanzani successfully inseminated dogs²¹. He also performed an experiment to show that the spermatozoa could be inactivated by cooling and reactivated later²². Another important discovery was that of Carl Ernst Von Baer who in 1827 discovered the mammalian ovum and made significant contribution to embryology¹⁶.

Pioneering efforts by Ivanow (1922)²³ to establish AI as a practical procedure had begun in Russia. This development by Ivanow led to further advancement in the techniques and stimulated research outside Russia to other western countries²³. But while the AI of animals quickly became an industry, it took several years to use this technology to humans. Eleven years after Spallanzani's experiment, the first successful attempt of AI was made in a woman. First documented report of application of AI was by a Scottish surgeon Dr John Hunter in late 1770s²⁴. The real beginning of assisted reproductive technology (ART) started almost a century later when the first report on human AI was published by Guttmacher (1943)²⁵. Since then, AIs have been reported for many years only in cases of physiological and psychological dysfunction. Around 1909²⁶, donor insemination - another aspect of AI gained popularity. While the procedure of AI was gaining popularity throughout the world, in India Sampat Kumaran reported the first AI in Halliker cows at Palace Dairy Farm Mysore in 1939²⁷.

Concept of cryopreservation

The continued development in the field of AI provided impetus for improved methods of collection of semen and its preservation. The development in the cryopreservation protocols for future use culminating into the modern techniques of sperm preservation was a natural outcome of the progression of AI. Until mid 1800s, the efforts to actually freeze sperm did not start. Later in 1866²⁸, Mantegazza became the first to visualize the need of banks for frozen human sperm. Around 150 years later, when the servicemen who were capable and without a doubt opted to freeze and store specimens of their sperm before leaving for battle during the Gulf war crises in 1992²⁹, the vision of Mantegazza's turned into reality. The substantial groundwork of Polge with glycerol laid the foundation for the cryopreservation of human sperm³⁰. In 1953, Sherman froze human sperms using glycerol with slow cooling of sperm and dry ice as refrigerant. He further established that on thawing of frozen sperm samples, the thawed sperm retained their fertilizing potential and induced normal development of the egg²⁴ which led to the first successful human pregnancy with frozen sperm. As a result of these improvements, the concept of sperm banking came into existence.

In vitro fertilization (IVF) revolution

The upsurge from AI to IVF was a massive one, both experimentally and publically. Semen preparation

techniques were developed and intrauterine insemination became popular, being more safe and painless. During 1920-1930s, the role of hormones in reproduction and conception was substantially examined; this led to the use of synthetic hormone substitutes in the 1940s which today form an essential part of all infertility treatments. The history of early attempts of IVF dates back to 1890 when Prof. Walter Heape reported the first case of embryo transplantation in rabbits in Cambridge university³¹. By the end of the 18th century, the concepts of reproduction became clear and fertilization was described as the fusion of nuclei of male sperm and the female egg³², and embryo thus created *in vitro* laid a significant milestone due to its potential ability to progress to blastocyst stage, getting implanted and be carried out to full-term gestation. Around 80 years, later Robert G. Edwards and Patrick Steptoe performed the successful IVF in human leading to birth of Louise Joy Brown, the first test tube baby on July 25, 1978³³.

In vitro fertilization - The Indian scenario

The history of IVF in India for infertility treatments has come a long way. Just 69 days after the birth of Louise Brown, Dr. Subhas Mukherjee - an Indian scientist from Kolkata announced the birth of Kanupriya alias Durga following an IVF procedure using cryopreserved embryo on October 3, 1978, world's second and India's first test tube baby. Unfortunately, his work could not be published in the absence of scientific evidence. The detailed work of Subhash Mukherjee was later submitted in the form of a report to the Government of West Bengal, India, his significant work in IVF was also presented at the Indian Science Congress in 1978 and was also published in 1978³⁴. Dr Mukherjee developed novel and relatively unknown techniques at that time such as use of gonadotropins for ovarian stimulation, cryopreservation techniques, freezing, storing and thawing the embryos^{35,36}.

In 1982, the Indian Council of Medical Research (ICMR) a pioneering Indian organization in the field of Biomedical Sciences took initiative realizing the importance of treatment of infertility and initiated a project (led by T.C. Anand Kumar and Indira Hinduja) at its Institute for Research in Reproduction (now ICMR-National Institute for Research in Reproductive Health) at Mumbai. As a result, India's first fully scientifically documented test tube baby, 'Harsha', was born on August 6, 1986³⁷. Due to ever increasing

demand for management of infertility in country led to the mushrooming of the IVF clinics in the country. ART in India is facing major safety concerns and risks that need to be evaluated at a large scale since in the absence of any regulations, the services offered by the ART clinics are questionable. To regulate these clinics the ICMR developed the National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India in 2005³⁸ which were later translated into Assisted Reproductive Technology (Regulation) Bill, 2017³⁹ and Surrogacy (Regulation) Bill, 2016⁴⁰.

Conclusion

The rapid evolution of ART for the treatment of infertile couple was among one of the extraordinary restorative accomplishments all through the world. Infertility has remained a social taboo since ages; with changing times and rapid developments taking place in the field of modern science, our philosophies have evolved eventually but the desire of the child, a family successor continues to be a major concern. The researchers continued to make dynamic advances in the journey that probably began centuries ago, and led to improvements in the modern medicine giving a ray of hope to the millions of infertile couples towards finding suitable treatment options for them. Thus extensive refinement of techniques in the field of assisted reproductive technology open up opportunities finding solutions to fertility problems for wider population, which in the ancient times were considered impossible to overcome.

Financial support & sponsorship: None.

Conflicts of Interest: None.

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