Chapter 35
What are the assisted reproductive technologies for male infertility?

Indications for IVF/ICSI/IUI, surgical sperm retrieval techniques

Peter N. Schlegel

Male fertility problems can occur when sperm are limited in number or function. In some cases, sperm washing is used to concentrate spermatozoa and deliver them through the uterus at the time of ovulation. In order for this treatment (referred to as intrauterine insemination [IUI]) to be successful, it was previously thought that 5 million motile sperm must be present in the ejaculate. More recent data from a large study showed that IUI success rates increased from about 7% pregnancy rate per treatment cycle when 1-2 million motile sperm were available after processing, up to about 15% when 5-7 million motile sperm or more were available for insemination. This limited procedure (requiring only sperm washing and insemination of the washed sample into the uterus) had reasonable cumulative pregnancy rates, but often required several treatment cycles to be successful.

A more advanced technique for enhancing the interaction of sperm and egg is in vitro fertilization (IVF). IVF is an involved process that includes treatment of the woman using a series of hormone injections to stimulate the ovaries to produce multiple eggs, egg retrieval, and fertilization of those eggs outside of the body. A limited number of the fertilized eggs (embryos) are then transferred back to the woman's uterus after incubating in the laboratory for 3-5 days. This process may also allow for embryo biopsy (sampling of 3-5 cells for their genetic content), typically performed before embryos are frozen at the 5-day stage or later.

It was initially recognized that impaired sperm would not fertilize eggs very efficiently, even when sperm are put directly next to the eggs in the laboratory. Indeed, it was recognized early on in IVF that if sperm had abnormal morphology, then IVF was not very successful; only normally shaped sperm will naturally bind to the cumulus complex around the oocyte and fertilize. Conditions where

very impaired sperm are present include men who have very few sperm in the ejaculate, when motility of sperm is severely impaired, or the shape of the sperm was abnormal. All of these conditions may be present for men with severely impaired sperm production. When there is severe deficiency of sperm number and/or limited ability of the sperm to fertilize during IVF, then the adjunctive treatment of intracytoplasmic sperm injection (ICSI) may be required to provide any reasonable chance of oocyte fertilization and pregnancy to occur for these patients.

The solution of ICSI to enhance the ability of impaired sperm to fertilize an egg was identified in 1991 by Drs. Gianpiero Palermo and Andre Van Steirteghem in Belgium. During an attempt to place a sperm close to an egg, Dr. Palermo accidentally injected a spermatozoon directly into an egg. The injected egg fertilized, developed into an embryo, was transferred back to the woman's uterus and resulted in a pregnancy with delivery of a normal, healthy child. With this "accident," a revolution in fertility treatment (especially the treatment of men with severe fertility problems) was started. Subsequently, ICSI has been used to expand the spectrum of male-factor infertility cases that can be treated for infertility. Whereas sperm from the testis or epididymis were thought to be incapable of fertilization, ICSI has changed our view of the fertilizing ability of sperm from semen samples with impaired motility, morphology or of limited number as well as "immature" sperm that are surgically retrieved from the male reproductive tract.

Men with azoospermia (a lack of sperm in the ejaculate) can commonly be treated with sperm retrieval and assisted reproduction with ICSI. Azoospermia can be due to a blockage/lack of development of the structures of the male reproductive tract (obstructive azoospermia) or from spermatogenic failure, where sperm production is so low that no sperm reach the ejaculate.

In obstructive azoospermia, sperm are produced and reabsorbed within the male reproductive tract, so the most viable sperm are often present closer to the testis than the point of obstruction (typically in the epididymis or vas deferens). These men have plentiful sperm production, so sperm retrieval from the testis or epididymis can be done with needle aspiration or biopsy. A larger number of sperm can be retrieved with a minor surgical procedure in the epididymis (microsurgical epididymal sperm aspiration), where more abundant sperm with better motility (and ability to be frozen for subsequent use in multiple aliquots) is possible than with testicular sperm retrieval.

In distinction, most men with non-obstructive azoospermia have either low levels of sperm production throughout multiple areas of tissue or focal areas of sperm production in isolated sections of the testis. For these men, sperm retrieval is most effectively accomplished with the microsurgical procedure referred to as microTESE (microsurgical testicular sperm extraction), where the surgeon uses an operating microscope to identify the focal areas with larger seminiferous tubules. The larger tubules contain more germ cells and therefore are more likely to contain sperm than the smaller tubules. Even men with conditions that severely limit sperm production such as Klinefelter syndrome (Chapter 37) can have sperm retrieved in 40-70% of cases. Since microTESE follows the natural anatomy of the testis and its blood supply, it is also safer than simple random biopsies of the testis.

So, applications of ICSI extend to patients with limited sperm number (oligozoospermia), severely impaired motility (asthenozoospermia), and sperm that are not normally shaped (teratozoospermia) possible to use for ICSI, as well as sperm surgically taken from the epididymis or testis that have not passed through the male reproductive system can also be used for ICSI. Most fertility centers now use ICSI for any IVF cycle when even marginal sperm abnormalities are present. The development of ICSI also encouraged us to consider treating men with azoospermia, not only for men who have reproductive tract obstruction, but also for men with sperm production so poor that no sperm are present in the ejaculate (non-obstructive azoospermia).

ICSI is only performed as an adjunctive procedure during IVF. Individual spermatozoa are selected based on their appearance and the presence of motility which confirms the viability of the spermatozoon to be used for injection. The sperm is manipulated to limit that motility (avoiding physical disruption of the oocyte after injection by a motile sperm). The oocyte is punctured by an injection pipette, and a single spermatozoon is injected per oocyte. This process allows fertilization and pregnancy with a very limited number of spermatozoa.

The fertilized oocytes (now embryos) are then maintained in culture for 3-5 days before transfer back to the woman. The chance of an individual embryo implanting and developing into a fetus is limited to 20-50%, depending on how well the embryo developed prior to transfer. Overall, the chance of pregnancy for each IVF attempt varies based on the age of the female partner. The chance of delivering a child for an individual IVF attempt from initial

stimulation of egg production averages about 30-40%, but the chance of pregnancy when a woman is over 40 years of age drops to a level as low as 10% per initiated IVF cycle.

Since the sperm that are selected for IVF and ICSI would not have naturally fertilized eggs in the past, concern existed about the risk of potential birth defects after application of IVF/ICSI (Chapter 38). To-date, the risk of birth defects does not appear to be any higher with sperm selection during ICSI, although a small but statistically significant increase in chromosomal abnormalities occurs after ICSI. The increase of chromosomal abnormalities in children increases from 0.2 to 0.8% with ICSI; this may occur because of abnormalities in the sperm provided by the man or the ICSI procedure itself.

The development of the advanced reproductive techniques of IVF and ICSI have revolutionized the treatment of severe male infertility. Many men are now routinely able to be treated using IVF/ICSI who could not have naturally fathered children before. Male infertility can be managed with specific treatment of men, correcting hormone abnormalities, obstructive conditions in the male or repair of varicoceles, allowing for natural fertility. However, ICSI has allowed new groups of men to be treated, including men who require sperm retrieval because of a lack of sperm in the ejaculate.

Suggested reading

Alukal JP, Lamb DJ. Intracytoplasmic sperm injection (ICSI)--what are the risks? Urol Clin North Am. 2008;35(2):277-88, ix-x.

Del Giudice F, Belladelli F, Chen T, Glover F, Mulloy EA, Kasman AM, Sciarra A, Salciccia S, Canale V, Maggi M, Ferro M, Busetto GM, De Berardinis E, Salonia A, Eisenberg ML. The association of impaired semen quality and pregnancy rates in assisted reproduction technology cycles: Systematic review and meta-analysis. Andrologia. 2022;54(6):e14409.

Muthigi A, Jahandideh S, Bishop LA, Naeemi FK, Shipley SK, O'Brien JE, Shin PR, Devine K, Tanrikut C. Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates. Fertil Steril. 2021;115(6):1454-60.

Neri QV, Takeuchi T, Palermo GD. An update of assisted reproductive technologies results in the United States. Ann N Y Acad Sci. 2008;1127:41-8.

Nyboe Andersen A, Carlsen E, Loft A. Trends in the use of intracytoplasmatic sperm injection marked variability between countries. Hum Reprod Update. 2008;14(6):593-604.

Sarkar NN. Intracytoplasmic sperm injection: an assisted reproductive technique and its outcome to overcome infertility. J Obstet Gynaecol. 2007;27(4):347-53.

Schlegel PN. Nonobstructive azoospermia: a revolutionary surgical approach and results. Semin Reprod Med. 2009;27(2):165-70.