

Chapter 33

Why evaluate the infertile male in the era of ART?

Medical and surgical therapies for male infertility

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With in-vitro fertilization (IVF) employing intracytoplasmic sperm injection (ICSI), live births can be achieved with only a handful of sperm. So why bother evaluating the male?

- 1) There is a 3 to 10 times higher incidence of testicular cancer in men with severe male factor infertility compared to age-matched controls.
- 2) There is a 30 to 100 times higher incidence of genetic abnormalities in infertile men. A majority of these abnormalities being Klinefelter syndrome (with 47 XXY karyotype)
- 3) Varicocele, a dilation of the pampiniform plexus of veins, affects both spermatogenesis and Leydig cell function. At every age, men with varicocele have lower testosterone levels than men without varicoceles.
- 4) Most couples prefer to conceive as naturally as possible. Treatment of the male often allows upgrading of fertility status: from adoption or the use of donor sperm, to testicular or epididymal sperm retrieval for IVF/ICSI. Treatment can induce appearance of sperm in the ejaculate, allowing IVF/ICSI without the need of surgery for sperm retrieval. Men with only enough sperm for IVF/ICSI can be upgraded to intrauterine insemination (IUI).
- 5) Finally, treatment of the male may allow natural conception.

Obstructive azoospermia

All azoospermia is either obstructive, wherein the male has normal production of sperm, or non-obstructive, where the problem is lack of sperm production. In men with obstructive azoospermia, presence of circulating antibodies against sperm confirms the presence of spermatogenesis and obviates the need for testis biopsy. The most common causes of obstructive azoospermia are: prior vasectomy,

iatrogenic injury due to prior hernia repair (vasal obstruction), hydrocelectomy (epididymal obstruction), orchiopexy for torsion (obstruction from a stitch going through the epididymis), or any other scrotal or inguinal procedure. Vasovasostomy is a highly successful microsurgical procedure for reversing obstruction. Microsurgical vasovasostomy (Fig. 1) results in the appearance of sperm in the ejaculate in over 90% of men and pregnancy rates, that are dependent on female partner age, vary from 50 – 80%, depending on when the obstruction occurred. Epididymal obstruction requires vaso-epididymostomy, with current techniques yielding patency rates of over 80% and pregnancy rates of 40%. Men with congenital absence of the vas deferens (usually associated with CFTR mutations) or with unreconstructable obstructions, are successfully treated with microsurgical sperm aspiration from the vas, epididymis and testis, performing assays of sperm DNA integrity, e.g., a TUNEL assay. This allows the urologist to tell the andrologist which sperm source has the best DNA integrity, allowing a significant improvement in live birth rates compared to just using sperm morphology and motility to select the best sperm for ICSI.

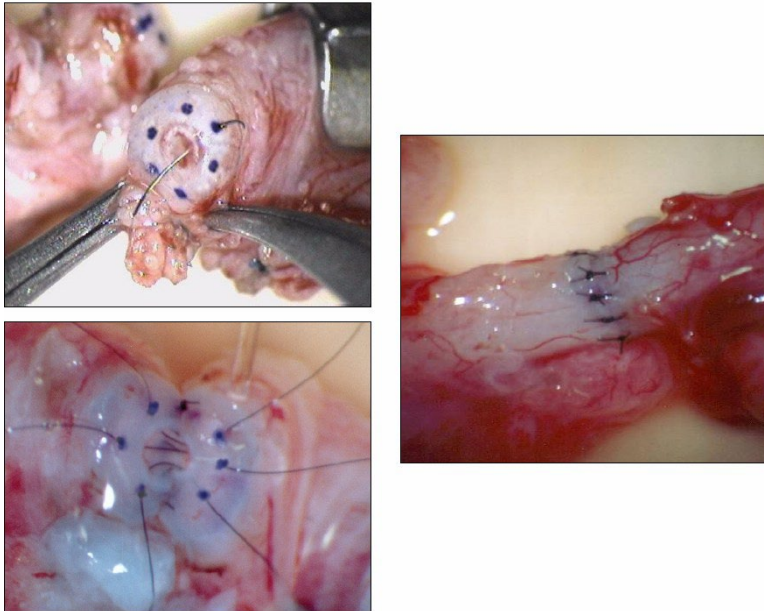


Figure 1. Surgical procedures involved in microsurgical vasovasostomy.

Retrograde ejaculation (often the first presenting sign of diabetes mellitus) can be treated with sympathomimetic drugs or retrieval of sperm from the urine for use with either IUI or IVF/ICSI, again using an assay of sperm DNA integrity to determine the best sperm source. The use of microfluidics to select sperm with dramatically better DNA integrity is also a promising new approach for some couples. Treatment of anejaculation, due to either spinal cord injury, diabetes mellitus, retro-peritoneal lymph node dissection for testicular cancer, or psychogenic anejaculation, should be tried first with penile vibratory stimulation. If that is not successful, electroejaculation should be used; it is highly successful in obtaining sperm.

Non-obstructive azoospermia

Endocrinopathies such as hypogonadotropic hypogonadism (H-H), called Kallmann's Syndrome if anosmia is present, usually present as failure to go through puberty due to lack of testosterone and is caused by a lack of hypothalamic GnRH (LHRH). Therefore, the pituitary gonadotropes are not stimulated to produce LH and FSH. Treatment entails replacement of pituitary hormones with LH, and, once normal testosterone levels are achieved, FSH is added. After six to twenty four months of treatment, the majority of such men goes through normal puberty and begins to have the appearance of sperm in the ejaculate, with good naturally conceived pregnancy rates.

Klinefelter's Syndrome (47XXY) may present in a similar fashion, with the failure to go through puberty, and feminized habitus (Chapter 37). Unlike H-H patients, who have undetectable levels of testosterone, LH and FSH, Klinefelter's men have low testosterone levels, but elevated LH and FSH (i.e. hypergonadotropic hypogonadism). Testosterone replacement will get them through puberty, but this will not induce spermatogenesis. These men are treatable with testicular sperm extraction, which is successful in obtaining sperm in 60% of cases, with a live birth rate of 30% in these men in whom sperm were found.

Men with micro deletions of the Y chromosome in the regions AZFa, AZFb and AZFc usually present with non-obstructive azoospermia. Men with an AZFc deletion are most likely to have either rare sperm in the ejaculate or 60% of the time on testicular microdissection, adequate sperm can be found for use with IVF/ICSI. Men with complete deletions of the AZFa or b segment have never had sperm found.

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Idiopathic non-obstructive azoospermia is challenging to treat. If men have palpable varicoceles, microsurgical repair will induce the appearance of viable sperm in the ejaculate in about 40% of men. Empiric treatment of men with low serum testosterone levels, using either clomiphene citrate or the aromatase inhibitors anastrozole or testolactone, has resulted in sperm in the ejaculate in some of these men. When all treatments have failed, these men are candidates for testicular microdissection for sperm retrieval for ICSI with a success rate of 60% and live delivery rates of 40% when sperm are successfully retrieved.

Oligoasthenoteratozoospermia

Isolated defects of sperm count, motility or morphology are rare. The majority of infertile men present with low counts, impaired motility and abnormal morphology. The most common etiology for this is varicocele, found in 30% - 40% of infertile men, 70-80% of men with secondary infertility, but only 15% of the general population. Of all men who have varicoceles, approximately 20% are grade III or large varicoceles. These are visible through the scrotal skin, and are the ones most likely to respond to treatment. This means that approximately 3% of all men in the general population have grade III varicoceles. Prophylactic varicocelectomy in young men or boys with grade III varicoceles can prevent future infertility and androgen deficiency. Microsurgical techniques for the repair of varicocele make it extremely safe and effective. There is a significant increase in sperm count and quality in 70% of men undergoing the procedure with naturally conceived pregnancy rates of over 40%. In addition, microsurgical varicocelectomy significantly increases testosterone levels and is already accepted as a treatment for androgen deficiency.

When there is no identifiable etiology, empiric treatments with clomiphene citrate and/or anastrozole, which combines with estrogen receptors and therefore blocks the negative feedback to the hypothalamus and pituitary and increases LH and FSH levels, can improve sperm production in some men.

Prevention

The testis manufactures approximately 1,000 sperm every heartbeat and is regarded as the “canary” of the human body. It is exquisitely sensitive to the adverse effects of environmental

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disrupters and gonadotoxins (Chapters 41-43). Lifestyle recommendations include avoiding gonadotoxins such as alcohol, marijuana and cocaine. Be aware of the adverse effect of prescribed medications, such as the sulfa drugs used for treating inflammatory bowel disease, calcium channel blockers used for treating hypertension, as well as chemotherapeutic agents and radiation therapy used for treating cancer. All post-pubertal boys and men in whom chemotherapy or radiation therapy is planned should be counseled on the importance of sperm cryopreservation prior to treatment (Chapters 24, 47). Experimentally, prepubertal boys with cancer who will undergo chemotherapy or radiation therapy may have testis tissue removed and cryopreserved for possible future maturation in vitro. Testosterone, an effective contraceptive for men, is to be avoided when future fertility is an issue. In androgen deficient men, unresponsive to other treatments, there is some evidence that treatment with testosterone plus clomiphene citrate and/or hCG can prevent the negative effect of exogenous testosterone on spermatogenesis.

Summary

In summary, there are many compelling reasons for treating male infertility. Evaluation and treatment by a specialist trained in male infertility and microsurgery results in optimal outcomes. Collaboration with specialists in assisted reproductive technology optimizes outcomes for infertile couples allowing the majority of men to have their own children.

Suggested reading

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