GEORGIA UROLOGY

11459 Johns Creek Pkwy. Suite 170
Johns Creek, GA 30096
Phone: (678) 417-0400
Fax: (678) 417-0483
www.gaurology.com

EVALUATION AND TREATMENT

Infertility, as defined by the failure to conceive after one year of unprotected intercourse, affects 15-20% of couples with a male-related problem wither directly responsible or contributory in up to 50% of all cases. Infertility is a couple phenomenon and evaluation and treatment for both male and female factors should be carried out at the presentation to maximize the couple's reproductive potential. Age related decline in female fertility has been well documented and as the general population continue to postpone childbearing, previously compensated male factor cases are likely to become more apparent as the female partners get older.

Recent advances in assisted reproductive technology, namely in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI), has offered hope for couples with severe male factor infertility previously considered not manageable; this initial success has led some to suggest that evaluation and treatment for male factor infertility is no longer pertinent provided that minute quantity of sperm are available for IVF/ICSI. This "IVF for all" approach was based on premature enthusiasm using "best case scenario" pregnancy rate and failed to consider the following facts:

1. Significant medical conditions, including life threatening ones such as testis cancers, may present as male infertility. Diagnosis and cause-specific treatment of these conditions is possible only after a thorough male factor evaluation.

2. The progressive and potentially irreversible nature of varicocele-induced testicular injury: varicocele may lead to the progressive deterioration of semen quality as shown by Cheval and others. Despite the fact that varicocele repair in the subfertile, males is unequivocally beneficial as demonstrated by Madgar's cross-over study, not all men showed improvement following varicocele repairs. In a large retrospective review of 15 papers encompassing 2466 men, Pryor and Howards reported an overall rate of improvement in semen quality of 66% with an overall pregnancy rate of 43%. As such, varicocele-related subfertility should be promptly treated to prevent progressive testicular injury and to maximize the chance of recovery.

3. The significant cost advantage of cause-specific treatment for male infertility when compared with IVF/ICSI: the cost per live birth following varicocelectomy ($26,268) and vasectomy reversal ($25,475) was significantly lower when compared to IVF/ICSI ($72,521 to $89,091).

4. The potential for both short and long term female side effects following ovarian hyper stimulation for IVF. It is then logical that a potential male factor should be considered as an integral part of a couple's infertility evaluation and if present, be investigated and specifically treated if possible.

Despite our increasing understanding of male infertility, many men with abnormal seminal analyses for whom no definitive explanation exist; evaluation in these men nevertheless serves to exclude the presence of any treatable conditions and allows for the selected use of empiric medical treatment, ART or other reproductive options such as donor insemination and adoption. It also serves to avoid unnecessary expenditure in time and valuable resources on measures, which are unlikely to be productive.

The evaluation for male infertility is straightforward and can be promptly accomplished in most men. The standard approach has not changed significantly and is familiar to all urologists. Recent advances with IVF/ICSI and our increasing understanding in the genetics of male reproduction have allowed us to modify the traditional approach to reflect these advances. As with the investigation of other medical conditions, a cost effective approach requires the working knowledge of the male reproductive biology, detailed history and physical examination (H&P) and the selective use of available tests in order to formulate a streamlined diagnostic and treatment strategy; especially if one considers the fact that many couples are self-paying due to the constraints imposed by managed care.

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Several recent developments in male infertility warrant brief discussion:

1. *Cystic Fibrosis (CF) and vasal agenesis:* CF mutations may result in congenital bilateral or unilateral absence of vas deferens (CBAVD/CUAVD) and congenital vaso-epididymal or intratesticular obstruction. Most men with vasal agenesis will be carriers of CF mutations and do not require renal imaging studies unless otherwise indicated. This is in contrast to those with non-CF related vasal agenesis in whom co-existing renal anomalies are frequent due to a common development defect of the mesonephric duct. We proceed initially with CFTR blood test (CF Transmembrane conductance Regulator) and if the CFTR is negative, we then obtain either renal ultrasound or IVP. Careful physical examination is all that is necessary to confirm the diagnosis of vasal agenesis without the need for surgical exploration.

2. *Y-chromosome microdeletion and male infertility:* Numerical and structural chromosomal abnormality, such as Klinefelter's, has long been associated with male infertility. Recent advances in molecular biology have found portions of the Y-chromosome critical in the normal spermatogenesis. Deletions of sequences within this region (AZF) in men with normal karyotype are responsible for up to 13% of men with non-obstructive azoospermia (NOA, or testicular failure) and to a lesser extent, men with severe oligospermia. AZF testing is based on polymerase chain reaction (PCR) using DNA obtained from peripheral lymphocytes and is available at several research institutions. Y-microdeleted men may present with various testis size, FSH levels and testis histology; some of the azoospermic men may be managed with testicular sperm extraction (TESE) in conjunction with IVF/ICSI.

3. *Testis Biopsy in men suspected of NOA:* The dictum that significant testicular pathology exists in azoospermic men with elevated serum FSH levels and small testes continues to be valid and testis biopsy is not indicated unless the couple is interested in pursuing TESE with IVF/ICSI. We obtain karyotype and AZF testing in men suspected of NOA prior to testis biopsy since the finding of a genetic factor may influence the couple's decision to proceed. In addition to the standard testis biopsy for histology, one to two additional samples are also submitted to the andrology lab for attempted TESE in order to further identify those with whom IVF/ICSI will be feasible (Table 1); previously successful TESE has a 80% predictive value for subsequent sperm retrieval provided that a 6 moths waiting period is allowed for testicular recovery. Testis tissue is cryopreserved for future IVF/ICSI use if sperm are found.

4. *Partial Ejaculatory Duct (EJD) Obstruction:* Incomplete obstruction of the EJD is being increasingly recognized in the infertile men. Complete EJD obstruction presents with the classic findings of low volume azoospermia with normal testes and FSH levels. Semen analysis in partial EJD obstruction is more variable and should be suspected in men with low or normal volume ejaculates with either severe oligospermia and/or low motility. TRUS is the initial test and the presence of distended SV (>1.5cm AP diameter) and/or dilated EJDs with or without a centrally located EJD cyst or calcification is the most common findings. Some cases may not exhibit significant TRUS abnormalities and other studies such as SV aspiration, seminal track washout and empiric TUR-EJD may be needed. Vasogram alone in partial EJD obstruction is less helpful since the sperm sampling for motility and count comparison to the ejaculates; significant disparity between the two supports the presence of partial EJD obstruction.

Clinical evaluation of male infertility:

1. *Pre-visit preparation:* Most sub-fertile men are referred to the urologists with semen analysis already performed, typically via the wife's gynecologist. As a university center, we also see men from afar with evaluations already initiated. Every effort is made to review all the pertinent information, including the actual testis biopsy, prior to or at the time of the initial visit. Such preparation also

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allows for provisions to be made for additional diagnostic studies such as TRUS at the initial visit. Wives are always encouraged to be present to provide pertinent female history.

2. *History:* The reproductive history of both partners should be considered. Decision to repair a varicocele in a man with borderline semen analysis or to surgically reconstruct previously failed vasectomy reversals may be dependent on coexisting female factors, including her age. A male infertility questionnaire is time saving and ensures completeness. Secondary male factor may be seen with varicocele due to progressive testicular injury; obstructions at the epididymal or EJD levels should also be considered in these men.

3. *Physical Examination:* The male reproductive track lends itself well to physical examinations, which is much more than simply determining the presence of varicocele. Reduction in testicular size and consistency with collapsed epididymis is an azoospermic or severely oligospermic man is like due to testicular failure whereas azoospermia with normal feeling testes and epididymal distention, ductal obstruction is more likely. Similarly, agenesis of the scrotal vas should be readily apparent on physical exam. We diagnosis varicoceles by palpation and reserve color Doppler ultrasound (CDU) for those whose physical exam is indeterminate. We do not use CDU to screen for subclinical varicoceles since repair of these “varicoceles” have not been shown to be beneficial and are not being sought as a diagnostic entity in our practice