Abstract:

Male infertility evaluation

INTRODUCTION

If a couple is unable to conceive a child after one year of unprotected intercourse, they are considered infertile. In North America, 15% of all couples are infertile. When broken down into statistics, an abnormality is found in only the man in 30% of the cases, while abnormalities detected in both partners occur in another 20%. Therefore, male factor infertility accounts for one half of couples with fertility problems.

ANATOMY & PHYSIOLOGY

In man, sperm are produced in the testicles. They then travel from the testicle to the epididymis, a small half moon shaped organ attached to each testicle. The epididymis is somewhat like a reservoir that allows sperm to mature while they move through it to the vas deferens. Sperm is mixed with fluid from the seminal vesicles and the prostate to produce semen. This semen travels out of body by way of the urethra and penis.

History and physical examination

Semen analysis (twice)

Improper timing

Semen analysis AN Counsel on habits / Stop medication

Semen vol < 1.5cc

Sperm concentration < 15 x 10^6/l

Sperm motility < 50%

Testicular pain

Varicocele correct

Post ejaculatory obstruction

Congenital absence of vas deferens

Etiology

Arbitrarily, we can classify male fertility causes as:

- Pretesticular (hypothalamus/pituitary) 1-2%
- Testicular 30-40%
- Posttesticular (obstruction) 10-20%
- Nonclassifiable 40-50%

In column is a list of the main factors involved in male fertility problem.
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Male infertility evaluation

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If a couple is unable to conceive a child after one year of unprotected intercourse, they are considered infertile. In North America, 15% of all couples are infertile. When broken down into statistics, an abnormality is found in only the man in 30% of the cases, while abnormalities detected in both partners occur in another 20%. Therefore, male factor infertility accounts for one half of couple with fertility problems.

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EVALUATION OF THE SUBFERTILE MAN

History and physical examination

Semen analysis (twice)

History and physical examination

Improper timing
Lubricant use / Gonadotoxins
Semen analysis AN Counsel on habits / Stop medication
Semen analysis AN Counsel on habits / Stop medication

Fertility factor

Semen analysis AN Counsel on habits / Stop medication
Semen analysis AN Counsel on habits / Stop medication

Varicoceles
Semen analysis AN Counsel on habits / Stop medication
Semen analysis AN Counsel on habits / Stop medication

History and physical examination

Semen analysis AN Counsel on habits / Stop medication
Semen analysis AN Counsel on habits / Stop medication

Post ejaculatory obstruction
Congenital absence of vas deferens
Varicocele
Varicocele

Etiology

Arbitrarily, we can classify male fertility causes as:

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- Nonclassifiable 40-50%

In column is a list of the main factors involved in male fertility problem.
Infertilité masculine :
Hypothalamic-portal disorders (GnRH and FSH deficiency)

**Clinical evaluation**
The basic evaluation includes a complete and surgical history (questionnaire), a physical examination, at least two properly performed semen analyses and a hormonal evaluation if the clinical evaluation or semen analysis warrants. A scrotal ultrasound is used to provide adequate assessment of testicular volume and intra-testicular pathology. The clinical evaluation is designed to uncover the possible etiology (cause) of the male infertility, including pathologies such as varicocele (dilated testicular veins), reproductive tract obstruction, hormonal abnormality, infection, immunologic problem, genetic abnormality or idiopathic (unknown) cause. Additional tests may be necessary and include genetic testing, trans-retal ultrasound and specialized sperm function tests (e.g. sperm DNA damage).

**HISTORY**
In the history taking we ask questions about the duration of infertility, whether is a female factor that may contribute to the infertility and whether previous treatments were used. As well, a sexual history including timing and mechanics of intercourse and use of lubricants is important.

Questions regarding childhood and development are important to uncover a possible history of undescended testicle (cryptorchidism) and delayed pubertal development, both associated with male infertility. Knowing the past medical history (systemic illness or genital infections such as urethritis or prostatitis) and a surgical history (particularly abdominal, pelvic or scrotal surgery) is important.

The influence of environmental toxins on sperm production has been recognised. A history of exposure to cigarette smoking, radiation or chemicals and significant alcohol consumption is important. In particular smoking has been associated with reduced sperm density and decreased sperm function. As well, certain medications can have direct or indirect effects on hormonal balance and sperm production and therefore cause infertility.

**PHYSICAL EXAMINATION**
The physical examination includes assessment of general body habitus (shape) and hair distribution. An abdominal and genitourinary exam is also performed. Examination of the scrotal contents reveals the size of the testicles, presence or absence of the normal ducts and presence or absence of varicocele (dilated testicular veins). Varicoceles are the most common identifiable causes of male subfertility. They are dilated internal spermatic veins. This condition is found in 40-50% of infertile men and 15% of the general population. Varicocele can lie corrected by surgical ligation of the dilated spermatic veins or by radiographic embolization of these veins. Between 50-75% of treated patients can expect an improvement semen quality after surgery. Thus the spontaneous pregnancy rate is improved and possibly some patients can use insemination intra uterine (courts ≤5 x10^³/!) instead of IVF/ICSI procedure.

**SEMEN ANALYSIS (W.H.O. 2000)**
The man provides a semen specimen by ejaculation. This could be provided by either masturbation (semen into a jar) or intercourse with a special condom (a semen collection device). The semen is examined rapidly (30-60min) for volume, presence of the normal ducts and presence or absence of varicocele (dilated testicular veins) - see figure 1). A scrotal ultrasound should be performed if the scrotal examination reveals a physical abnormality (e.g. testicular or epididymal mass, testicular atrophy). A trans-retal ultrasound (TRUS) is primarily used to assess prostate anatomy. In infertile men, a TRUS is used to evaluate the seminal vesicles and ejaculatory ducts in order to determine whether there is a genit al tract obstruction at this level. A trans-retal ultrasound should be performed if there is azoospermia (absence of sperm in semen) and a low semen volume.

**SPERMOGRAMME : PARAMÈTRES DE RÉFÉRENCES**

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<thead>
<tr>
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<tr>
<td>Volume</td>
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</tr>
<tr>
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<td>50% (A-B)</td>
</tr>
<tr>
<td>Morphology</td>
<td>14% (Tygerberg strict)</td>
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**Clinical disorders**
- Genetic GnRH deficiency (Kallmann syndrome)
- Hyperprolactinemia
- Drugs (e.g. estrogens, steroids, androgens, antihypertensives, corticosteroids, spasmolytics, hypnotics, excipients anticoagulants)
- Environmental toxins (e.g. alleno-metabolites, carbon dioxide, carbon monoxide, lead, mercury, environmental estrogens and phytoestrogens)
- Hypothyroidism
- Immunologic disorders, including polygalandular autoimmune disease
- Trauma

**Disorders of sperm transport**
- Epididymal dysfunction (e.g. infection)
- Abnormalities of the vas deferentia (compartmental absence, Thiersy’s syndrome, infection, masseteria)
- Epididymal dysfunction (e.g. in the vas deferentia, varicocele, epididymal mass)
- Spermatogenic dysfunction (e.g. varicocele, epididymal mass)

**Unexplained male factor infertility**

**Primary gonadal disorders**
- Klinefelter’s syndrome (XXY) and its variants (XXY/XY; XXXY)
- Cryptorchidism
- Myotonic dystrophy
- Varicocele
- Y chromosome deletions

**Acquired disorders**
- Viral orchitis (mumps, coxsackie, ovulation)
- Epididymitis-orchitis (enteroviruses, rickettsiae)
- Drugs (e.g. estrogens, steroids, androgens, antihypertensives, corticosteroids, spasmolytics, hypnotics, excipients anticoagulants)
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It must be remembered that there is a great variability day by day in man’s sperm quality, so we usually ask for at least 2 semen specimens at least 1 month apart and after abstaining from intercourse for 2 to 3 days prior to each sample). Standardisation of the techniques and report of the semen analysis is an important aspect of good practice. The parameters suggested in the box are the most recent W.H.O. guidelines. Also a systematic dosage of IgG IgA antisperm antibodies is done.

Also an abnormal sperm analysis can not be always equated with infertility but rather a diminished fertility potential. Finally a semen analysis does not assess sperm function. Specialized tests are under investigation to evaluate this factor (see DNA fragmentation).

**IMAGING STUDIES; ULTRASOUND**
Further assessment of reproductive tract anatomy is possible with the aid of ultrasonography. A scrotal/ testicular ultrasound is used for assessment of testicular volume and parenchyma, epididymal anatomy and presence or absence of varicoceles (dilated testicular veins - see figure 1). A scrotal ultrasound should be performed if the scrotal examination reveals a physical abnormality (e.g. testicular or epididymal mass, testicular atrophy). A trans-retal ultrasound (TRUS) is primarily used to assess prostate anatomy. In infertile men, a TRUS is used to evaluate the seminal vesicles and ejaculatory ducts in order to determine whether there is a genit al tract obstruction at this level. A trans-retal ultrasound should be performed if there is azoospermia (absence of sperm in semen) and a low semen volume.
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- Morphologie > 14% (Tygeberg strict)
A genetic disorder may alter spermatogenesis impair normal development of the genital tract and decrease sperm mobility and fertilisation capacity, any of which may lead to varying degrees of male subfertility or infertility.

It has been found that many cases of male infertility may be associated with a genetic defect (particularly, when the man has very low sperm count or absence of sperm in the semen – azoospermia). One concern we have is that the genetic defect responsible for the man’s infertility may be transmitted to his child through assisted reproductive technologies (e.g. in vitro fertilisation – IVF). In many cases this only causes the same problem in the next generation (infertility in a male child), but some genetic defects may cause other diseases, miscarriage, or even early (neonatal) death. Please know that at present there are no specific treatments (for example gene therapy) for the genetic defects themselves.

Genetic disorders may be characterized as karyotype abnormalities deletion of specific area of the Y chromosome, specific mutations within genes or DNA strand breaks. Karyotype abnormalities are more common in infertile men (8% than in a normal population (3%). Sex chromosome abnormalities are more common (4.2%) than autosomal anomalies (1.5). Klinefelter syndrome (KXY) is the most common sex chromosome disorder associated with the male infertility (95% of anomalies) it is present in 1/200 newborn males, 11% azoospermic and 79% of men with oligospermia. Located on the long arm of the Y chromosome the azoospermic factor region (AZF) is required for normal spermatogenesis. Microdeletions on this region is the second most frequent genetic cause of infertility after Klinefelter’s syndrome. These deletions are found in 4% of oligospermic males and 18% of non obstructive azoospermia

Sperm DNA integrity is increasingly recognized as being a valuable marker of male fertility potential. Sperm DNA damage beyond which no pregnancy is possible and the optimal assay (test) of sperm DNA damage.

Influence of the damage to the sperm’s DNA on the insemination (FR), quality embryos (EQ), pregnancy rate (PR) for IVF ± ICSI

<table>
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<th>Study</th>
<th>IVF</th>
<th>ICSI</th>
<th>FR</th>
<th>EQ</th>
<th>PR</th>
<th>Cutoff*</th>
<th>Assay used</th>
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<td></td>
<td>TUNEL</td>
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<td>0</td>
<td>0</td>
<td>4%</td>
<td>Comet</td>
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<tr>
<td>Tomlinson, 2001</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Host, 2000</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Comet</td>
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<tr>
<td>Lopes, 1998</td>
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<tr>
<td>Barkhord, 2003</td>
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<td>27%</td>
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Overall effect

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<th>FR</th>
<th>EQ</th>
<th>PR</th>
<th>Cutoff*</th>
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<tr>
<td>0</td>
<td>0</td>
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</table>

* indicates that the damage to the sperm’s DNA is associated with a reduced pregnancy potential. ** indicates that the sperm’s DNA damage is not associated with the pregnancy potential. * an admissible sperm DNA damage threshold for each application.** no change

The assessment of sperm DNA damage may be useful in the following circumstances: (1) prior to ARTs to help predict pregnancy outcome, (2) for couples with unexplained infertility, (3) for couples with repeated ART failures and (4) to assess response to male-directed therapy.

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Current recommendations for genetic testing for infertile men are as follows: (1) A karyotype (chromosome) analysis and a Y-chromosome microdeletion analysis are recommended for men with severe oligospermia (<5 million sperm/mL of semen) or non-obstructive azoospermia (absence of sperm caused by tubercular failure). (2) Cystic fibrosis mutation analysis is recommended for men with congenital absence of the vas deferens or those with idiopathic (unknown cause) obstructive azoospermia (absence of sperm caused by genital duct obstruction).

BIBLIOGRAPHY / BIBLIOGRAPHY

4. Brugh, VM and Lipshultz, LI, Male factor infertility evaluation and management. Rev. Urol., 2002;4;4-17
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Genetic testing and counselling

GENETIC ANOMALIES

The assessment of sperm DNA damage may be useful in the following circumstances, (1) prior to ARTs to help predict pregnancy outcome, (2) for couples with unexplained infertility, (3) for couples with repeated ART failures and (4) to assess reproductive outcome: implications for ART. To date, there is some evidence (uncorontrolled) demonstrating improved sperm DNA damage beyond which no pregnancy is possible and the optimal assay (test) of sperm DNA damage.

Specialized sperm parameters; ASSESSMENT OF SPERM DNA DAMAGE

Sperm DNA integrity is increasingly recognized as being a valuable marker of male fertility potential. Sperm DNA damage may predict the chances of a pregnancy both naturally (after intercourse) and with assisted reproduction (e.g. IVF or ICSI – intra-cytoplasmic sperm injection) (see Table 1). However, there is no consensus on the exact cut-off value of sperm DNA damage which no pregnancy is possible and the optimal assay (test) of sperm DNA damage.

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Influence of the damage to the sperm nucleus on fertilization (FR), quality embryos (EQ), pregnancy rates (PR) after IVF ± ICSI

Study | IVF | ICSI | FR | EQ | PR | Cutoff* | Assay used

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Overall effect | 0 | 0 | 0 | 0 | 0 | 0 | 0

* indicate that the damage to the sperm nucleus is associated to a lower pregnancy potential reproduced. ** indicate that the damage to the sperm nucleus is not associated to a lower pregnancy potential reproduc. The assessment of sperm DNA damage may be useful in the following circumstances: (1) prior to ARTs to help predict pregnancy outcome, (2) for couples with unexplained infertility, (3) for couples with repeated ART failures and (4) to assess reproductive outcome: implications for ART. To date, there is some evidence (uncorontrolled) demonstrating improved sperm DNA integrity with (1) varicocelectomy (varicocelect repair), (2) oral antioxidant therapy and (3) oral anti-inflammatory therapy.

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11. Henkel, 2003 208 54 9 0 0 TUNEL
12. Bergmann, 2004 109 61 0 0 0 Comet
13. Zini, 2005 50 54 9 0 0 Comet


table

Study | IVF | ICSI | FR | EQ | PR | Cutoff* | Assay used

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