Evaluation and assessment of male infertility in Primary care; A review

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Abstract

Infertility is a common condition seen in primary care practices. The World Health Organization estimates that 9% of couples worldwide struggle with fertility issues and that the male factor contributes to 20-30% of all infertility cases. The diagnosis of infertility in men is primarily based on semen analysis. The main parameters of semen include concentration, appearance, and motility of sperm. Recently, the demand for infertility services has increased, and infertile couples are seen frequently by primary care physicians. A flexible, patient-centred approach is indicated. This article outlines the Family Physician`s evaluation of male infertility and indications for referral to a male infertility specialist.

Key words: Male infertility, primary care, spermatogenesis, azoospermia.

Definitions and Epidemiology

Couple infertility has been recently defined per NICE as the “inability to achieve conception despite one year or more of frequent, unprotected intercourse” (NICE, 2013). Infertility affects about 15% of couples worldwide, totaling 48.5 million couples. Males are determined to be solely responsible for 20-30% of infertility cases (Jarow, 2007), and they contribute to 50% of all instances (Winters and Walsh, 2014). ‘Normal’ male fertility hinges on the production and transport of sperm, a highly complex process that involves the endocrine, immune and neural systems. Evaluating the fertility potential of the male partner represents an important part of the assessment of a couple who has failed to achieve pregnancy. The most important test for men is a semen analysis. Male infertility is often defined as abnormal semen parameters however may be seen with normal semen analysis (WHO 2010).
The diagnostic workup of men presenting with suspected infertility includes performing an in-depth history and focused physical examination. The male fertility history is one of the most comprehensive histories performed in the field of urology, focusing on the many identified risk factors (Kumar, 2015). This article reviews the Primary care evaluation of male infertility and indications for referral to a male infertility specialist.

Clinical Case Scenario

A 35-year-old male presented with inability to conceive for 18 months. His partner is 29 years old. She has regular cycles, and no previous obstetric history. All previous investigations were normal. The male partner had no significant past medical or surgical history apart from mumps as a child. Initial sperm analysis has shown oligospermia of 5 million per milliliter (normal 20 million per milliliter). His physical examination was unremarkable. However, mild skin pigmentation on the flanks was noted. The repeat semen analysis demonstrated oligoasthenoteratospermia at 5.5 million per milliliter, motility at 15% (normal, 40%), and morphology of 1% (normal, 4%). Scrotal ultrasound revealed homogenous parenchyma bilaterally, a mild bilateral hydrocele, a 9-mm left epididymal cyst and subclinical left varicocele. Initial blood test carried out by the GP was normal. The patient was subsequently referred to the infertility services. Assessment revealed markedly elevated ACTH. An endocrinology referral was done for further workup of adrenal insufficiency. The patient was diagnosed with Addison's disease and hyperthyroidism. A few months later he was seen in the infertility clinic, his sperm count improved, and the couple were offered In vitro fertilization (IVF) treatment.

Aetiology

The causes of infertility include abnormalities of any portion of the male or female reproductive system. The causes of male infertility can be stratified per mechanism into three main categories:

1. Pre-testicular causes: This results from decreased production of FSH and LH secondary to hypothalamic or pituitary dysfunction, which leads to failure of spermatogenesis and testosterone secretion by the testes. Such as:

- **Hypogonadotropic hypogonadism (Kallmann Syndrome)** - is rare and accounts for <1% of male factor fertility problems (Jarow, 1989). It is characterized by reduced hypothalamic or pituitary activity resulting in abnormally low serum FSH and LH levels. Any hypothalamic or pituitary disease can cause gonadotropin-releasing hormone (GnRH) or gonadotropin deficiency (hypogonadotropic hypogonadism) and, therefore, infertility (Jarow etal., 1989). Although uncommon, these conditions should be diagnosed, as thei treatment is straightforward and can restore fertility in most of the cases.
- **Pituitary related conditions:** such as Pituitary insufficiency (tumours, radiation, surgery, Hyperprolactinaemia or Exogenous hormones (anabolic steroids, glucocorticoid excess, hyper- or hypothyroidism).
- **Medications:** Infertility may result from the use of various drugs. This phenomenon may be the result of an effect on the hypothalamic-pituitary- gonadal axis or a direct toxic effect on the gonads. Some of the drugs are antineoplastic agents (cyclophosphamide, chlorambucil, busulphan, and methotrexate), glucocorticosteroids, hormonal steroids (diethylstilbestrol, medroxyprogesterone acetate, estrogen, and the constituents of oral contraceptives), antibiotics (sulfasalazine and cotrimoxazole), thyroid supplements, spironolactone, cimetidine, colchicine, marijuana, opiates, and neuroleptic agents.

2.Testicular causes: This is the most common cause of infertility in men. Primary testicular failure is major cause of non-obstructive azoospermia and oligospermia. It is classified as genetic or acquired.

- Genetic causes are Kleinfelter syndrome 47, XXY, Noonan syndrome, or Y chromosome microdeletions.
- Acquired:
  - o Varicocele: this is the dilatation of the scrotal veins. The impact of varicocele on male fertility remains controversial. It has a detrimental effect on semen quality and sperm function (Jensen et al., 2017).
  - o Injury (orchitis, torsion, trauma)
  - o Cryptorchidism especially if left uncorrected until puberty.
  - o Infections such as Mumps orchitis and severe epididymo-orchitis Can contribute to spermatogenesis failure.
  - o Systemic disease (renal failure, liver failure)
  - o Exposure to chemotherapy or radiotherapy
  - o Testicular tumours
  - o Idiopathic: This is defined as infertile man with a normal semen analysis and no apparent cause for infertility. It can be seen in 10-20% of cases (Balen, 2008).

3. Post-testicular causes (obstruction):

- Congenital:
  - o cystic fibrosis, congenital absence of the vas deferens (CAVD)
  - o Young's syndrome
- Acquired
  - o Vasectomy
  - o Iatrogenic vasal injury
  - o Infection (chlamydia, gonorrhoea)
  - o Disorders of sperm function or motility (Immotile cilia syndrome)
  - o Immunological infertility
  - o Sexual dysfunction (reduced libido, timing and frequency of intercourse)
  - o Erectile/ ejaculatory dysfunction. (Wilcox et al., 1995) also may be contributing factors to male infertility.
  - o Environmental factors: The rise in environmental pollution causes a significant increase in disease burden and costs in treating infertility disorders. Exposure to heat, chemicals and ionizing irradiation can damage sperm production (Grandjean and Bellanger, 2017).

Diagnostic strategy

Initial evaluation of the infertile couple should focus on the nature of the problem and identification of possible risk factors for infertility. Both partners should be involved in the management of infertility (RCOG, 1998 and Jenkins et al 2003). The main goals of evaluating the subfertile men are to identify correctable causes of infertility and to help to conceive by the most natural, least invasive means possible. In addition, the evaluation may uncover significant underlying medical or genetic pathology.

1. History:
A careful history can offer clues to the underlying cause of infertility and provide an assessment of the man's fertility potential. The evaluation of an infertile man should begin with a detailed history that focuses on potential causes of infertility. The clinician needs to take a full medical, sexual and reproductive development history. Enquire about number of children (from the same partner or different partner), length of time to conceive or any difficulty of sexual intercourse.

The clinician should also review for history suggestive of previous testicular problems such as trauma, testicular cancer, history of infections like mumps, sexual transmitted infections or previous corrected congenital abnormalities; also, looking for any systemic illness such as thyroid disorders, uncontrolled diabetes, cardiac failure, chronic renal failure, and neoplasia.

Check for any ejaculatory or erectile dysfunction. Postcoital micturition that is cloudy might indicate retrograde ejaculation. Risk factors for ejaculatory problems include diabetes, multiple sclerosis and some medications like antidepressants. Obtain a detailed drug and occupational history. Evidence shows that rise in testicular temperature may decrease sperm quality (Wang C et al.1997).

It is vital to assess the sensitivity of this issue and psychological impact on couples with fertility problem (NICE 2013). It is important to assess the anxiety-related sexual dysfunction and other marital conflict that might contribute to the main issue. A list of information relevant to the infertility history is summarised in Table 3.

2. Physical examination:
The physical examination is useful for increasing or decreasing the probability of certain causes of male infertility. The aim of the physical examination is to look for evidence of systemic disease, genetic abnormalities, or androgen dysfunction. Height, weight, body mass index, and waist-hip ratio will diagnose obesity that might contribute to subfertility. Systemic examination to check for any goiter, secondary sexual characteristics, lumps or skin changes.

External genitalia examination: Scrotal examination looking for lumps, varicocele or hernia. A small soft testis may indicate hypogonadism or undescended testis. The penis should be examined for any structural abnormalities.

3. Semen analysis:
Semen analysis is the key laboratory assessment of the male partner of an infertile couple. Due to the marked inherent variability of sperm concentrations in semen samples, minimum 2 samples are needed and one week apart between each sample (Gnoth et al., 2005). Recently, WHO has published lower reference limits for semen analyses (Jenkins, 2003) . (See Table 1)

Semen sample should be obtained following abstinence for 2-3 days. Condom or lubricant jelly should not be used. Collection to be collected in a wide-mouthed sterile bottle, labeled carefully and delivered to the laboratory as soon as possible. The sample should be protected from extremes of temperature. Ideally, if the results were "abnormal"; the sample should be repeated in 3 months. However, in case of azoospermia (absence of sperm) or severe oligozoospermia (very few sperm number or more abnormal forms or more of reduced motility) the repeat test should be undertaken as soon as possible (NICE, 2004).

4. Endocrine evaluation:
More specialized testing may be required based on the outcome of this initial evaluation. Some of these tests would require a referral to secondary care. Whenever suspecting hypogonadism (clinically or in the presence of azoospermia or severe oligospermia on semen analysis) evaluation of the HPG axis can provide valuable information regarding sperm production. FSH, LH, testosterone and prolactin should be measured (Sigman, 1997). Raised prolactin can be seen in prolactinoma or with some medications (e.g. antipyschotics) (Haddad and Wieck, 2004).

5. Other tests:
Checking for chlamydia and other STI can be arranged for full workup. A first-catch urine specimen is as accurate as a urethral swab for males. Postcoital testing and antisperm antibody testing are no longer considered useful (Kamel, 2010) and (NICE, 2004).

Furthermore, other testing may be needed based on circumstances, including testicular biopsy, genetic testing, and imaging.

Scrotal ultrasound can be performed if an abnormality detected on physical examination such as a testicular tumour. Ultrasound can also be useful in the clinical diagnosis of varicocele.

Management

1. Initial review:
Involving both partners in all aspect of investigation and counselling is needed. Discussion and offer information regarding all aspects is essential. Male fertility can be affected by several lifestyle and environmental factors. General advice about modifiable factors that may affect fertility should be considered and discussed at the initial consultation. (see Table 2)

Men should be advised to wear loose underwear, avoid hot baths, and hot occupational environment to avoid increased scrotal temperature (NICE, 2004). Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. They should be warned against recreational drugs usage to maintain good sperm quality. Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health (Jenkins, 2003). Men with infertility should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality (NICE, 2004).

Family Physicians should be able to provide information and explain to couples about every stage of infertility management. Couples should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognized as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media (NICE, 2004).

2. Psychosocial review:
During this management process a few issues might emerge. Stress can be seen in many couples. Hence, GPs should inform the couples that stress in male and female partners can affect the relationship and lead to reduced libido and frequency of sexual intercourse (Bagshawe and Taylor, 2003). This can be avoided through good communication and adequate provision of information and services access. GPs can play a crucial role in supporting couples and direct them towards several infertility support groups and agencies. NICE guidelines advise to provide counselling for couples through referral to specialist counselling service in secondary care.

3. Management and referral to secondary care:
Underlying etiology determines the management, although male infertility is unexplained in 40% to 50% of cases (Jungwirth et al., 2012). When the semen analysis is abnormal, referral to a male fertility specialist or reproductive endocrinologist is necessary. When anatomic variance or obstruction is suspected, referral for surgical evaluation and treatment is appropriate. Men who are known to have obstructive azoospermia may benefit from treatment of epididymal blockage. If an endocrinopathy, such as hyperprolactinemia, is diagnosed, the underlying cause should be treated. Dopamine agonists such as Cabergoline can be used to manage hyperprolactinaemia. In patients with varicocele, there is insufficient evidence to suggest corrective surgery will increase live birth rates, despite improvement in semen analysis results (Chehval, 1992).

Two commonly used assisted reproductive techniques (ART) are invitro fertilization (IVF) and intrauterine insemination (IUI). IUI involves passing sperms through a plastic catheter into the women's uterus. This is recommended in some mild forms of oligozoospemia. NICE guidelines suggest that IUI should not be routinely offered unless where it is very difficult to have vaginal intercourse due to physical disability or psychosexual problem or those who are using partner or donor sperm and in people of same sex relationships. The second technique is IVF. This involves the retrieval of multiple oocytes, which are subsequently combined with sperm in vitro and incubated. Then the blastocyst is transferred into the uterus. It is recommended in couples with unexplained infertility, mild endometriosis or mild male factor infertility.

Table 1: Normal values of semen variables (WHO 2010)

Volume	>2ml
PH	7-8
Sperm concentration	>15 million spermatozoa/mL (95% CI 12-16)
Total sperm number	>39 million spermatozoa per ejaculate
Motility	40% total and >32% progressive motility
Morphology	4% of normal forms
Vitality	58 % or more live spermatozoa
WBC (leucocytes)	<1 million / ml
Mixed antiglobulin reaction	< 50% spermatozoa with adherent articles

Table 2: Summary of general advice given to patients in primary care

Summary of general advice given to patients in primary care	
Alcohol	Both couples to limit their alcohol intake. Consumption of 3-4 U per day is unlikely to affect sperm quality.
Smoking	All couples should be counseled to abstain from tobacco use
BMI	High BMI > 30 is known to reduce fertility
Medication	Certain medication (including OTC and recreational medication) can interfere with fertility
Occupation	Counselling for occupational risk of exposure to certain factors such as heat, toxins, ionizing radiation and vibration that might affect fertility
Frequency of intercourse	Discussion regarding implantation window and frequency
Temperature	Advise men to wear loose fitting underwear and trousers and avoid conditions that could elevate scrotal temperature.

Table 3

Components of infertility history in the male	
Medical history	Recent illness History of systemic illness such as diabetes or Multiple sclerosis Genetic disorders – cystic fibrosis, Klinefelter syndrome Psychological evaluation
Surgical history	Undescended testes correction surgery Hernia repair Previous testicular tumour or trauma Pelvic, bladder or retroperitoneal surgery
Fertility history	Previous pregnancies – with current and previous partners Duration of infertility Previous infertility treatment
Sexual history	Erection or ejaculation problems Frequency of intercourse
Medication	Nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers, methotrexate, colchicine, amiodarone, antidepressants, phenothiazines, chemotherapy
Social history	Alcohol, smoking, anabolic steroids, recreational drugs Exposure to ionising radiation Chronic heat exposure Aniline dyes Pesticides Lead exposure