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# Diagnosis of Male Infertility: Diagnostic Work-up of the Infertile Man

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**Abstract**

The diagnostic workflow to evaluate male infertility follows a systematic approach to elucidate previous factors influencing fertility and the present status. The medical history should be taken, preferably in the presence of the female partner, and a clinical examination focusing on testicular morphology and function is done, followed by laboratory tests of gonadotropins and androgens as well as semen analysis according to the World Health Organization criteria. Depending on the results, more elaborate investigations may be necessary, such as the genetic background of male infertility or analysis of testicular spermatogenesis. To better characterize the functional capability of spermatozoa, modern analytical instruments such as DNA fragmentation and methylation analysis or Raman spectroscopy of spermatozoa are used for scientific evaluation. Finally, the differential diagnosis of hypothalamic–pituitary or testicular malfunction will determine the treatment options. Endocrine, surgical, or empirical treatment options such as assisted reproductive techniques can be applied after interdisciplinary diagnosis of both partners, male and female, by the andrologist and a specialized gynecologist to obtain optimal treatment options for the couple.


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## 1. Introduction

The diagnostic work-up of the infertile man aims at identifying disorders of male infertility for a better understanding of the reasons for a couple's childlessness, to offer adequate counseling, and to offer the best treatment options either to improve fertility for spontaneous conception or to apply assisted reproductive techniques (ART). A diagnostic work-up should be started after 1 yr of regular sexual intercourse without spontaneous induction of pregnancy. Overall, 10–15% of couples are affected, and in about half of those, male factors contribute to childlessness (Table 1).

Disorders of male infertility can arise from dysfunction of the hypothalamic–pituitary region, from the testes themselves, or from post-testicular problems. In general, male infertility is a poor prognostic indicator of a couple's chances of achieving natural conception.

The approach to the diagnostic work-up should be systematic and structured (Table 2) and should start with noninvasive investigations.

## 2. Medical history

The purpose of taking the medical history is to get information about a variety of factors such as the duration

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**Table 1 – Frequency of diagnosis in infertile patients at a tertiary center**

| Diagnosis | Unselected patients ($n$ = 12 945), % |
|---|---|
| Idiopathic infertility | 30.0 |
| Varicocele | 14.8 |
| Infections | 9.3 |
| Maldescended testis | 8.4 |
| Oncologic diseases (cryopreservation of semen) | 7.8 |
| Immunologic infertility | 3.9 |
| Klinefelter's syndrome | 2.6 |
| Disorders of erection or ejaculation | 2.4 |
| Primary hypogonadism | 2.3 |
| Late-onset hypogonadism | 2.2 |
| General systemic diseases | 2.2 |
| Obstructive azoospermia | 2.2 |
| Secondary hypogonadotropic hypogonadism | 1.6 |
| Testicular tumor | 1.2 |
| Y-chromosomal deletions | 0.3 |
| Other chromosomal aberrations | 0.2 |
| XX men | 0.1 |
| | |
| Others | 8.6 |

Adapted from Tüttelmann and Nieschlag [24] with permission from Springer.

of infertility, the age and gynecological cofactors of the female partner, previous or present medication used that may affect the hypothalamic–pituitary–gonadal axis, a history of cryptorchidism, sexual and ejaculatory disorders including frequency of sexual intercourse, exposure to toxic agents such as smoking and alcohol, previous pelvic or genital surgery, pubertal development or disorders, and clinical symptoms of androgen deficiency.

Short duration of infertility, young age of the female partner, and previous induction of a pregnancy, preferentially in the same partnership, can be considered indicators of good prognosis.

Medication can affect the hypothalamic–pituitary–gonadal axis. In particular, prior treatment of oncologic diseases with chemo- or radiotherapy lead to impairment of male fertility in >60%, resulting in either oligozoospermia (30.7%) or severe infertility with cryptozoospermia and azoospermia (6.4% and 25.8%, respectively) without any chance of spontaneous conception [1,2]. If patients have been offered semen cryopreservation for fertility protection before starting oncologic treatment, ART with cryopreserved spermatozoa can be offered [3–5]. However, only 38% of oncologists regularly offer fertility preservation to eligible patients [6].

Apart from gonadotoxic medication, testosterone is one of the medications used in infertility patients, although it is contraindicated. Because testosterone, through negative feedback, affects the hypothalamic–pituitary axis, it has been proven to have contraceptive efficacy in men [7]. In infertile men, testosterone medication will, albeit reversibly, further suppress spermatogenesis to oligozoospermia or azoospermia, and recovery of spermatogenesis to normal levels will take at least 3–6 mo. Today, the abuse of testosterone for its anabolic effects (eg, in body building) is common and should be evaluated during history taking. Recovery of spermatogenesis in men with long-term anabolic abuse is not certain [8].

Antihistamines, H2-receptor blockers, and antidepressants may affect the pituitary axis, for example, by increasing prolactin levels, and thus can interfere with normal gonadotropin secretion.

A history of cryptorchidism, especially if bilateral, may severely affect spermatogenesis, even after correction early in life. Unilateral cryptorchidism may also lead to impairment of sperm production if correction is done late (ie, around puberty). Rarely, adult patients present with existing cryptorchidism and then with only minimal chances of persisting sperm production.

Smoking reduces sperm fertilization capacity by about 50% in couples using ART. The odds ratios for failure of intracytoplasmic sperm injection (ICSI) treatment and in vitro fertilization (IVF) are 2.95 and 2.65, respectively [9], and spontaneous conception rates may also be reduced. Couples may be shocked when confronted with these figures and make an effort to reduce or stop smoking.

**Table 2 – Systematic diagnostic work-up of infertile patients**

| | Impaired hypothalamic-pituitary function | Impaired testicular function | Post-testicular dysfunction | Idiopathic infertility |
|---|---|---|---|---|
| Testis volume | <6 ml | <12 ml | ≥12 ml | ≥12 ml |
| FSH | <1 IU/l | >7 IU/l | ≤7 IU/l | Normal or elevated |
| T | <8 nmol/l | <12 nmol/l or ≥12 nmol/l | ≥12 nmol/l | ≥12 nmol/l |
| Sperm count | Azoospermia | <39 million per ejeculation | Azoospermia or <39 million per ejaculation | Variable |
| α-glucosidase (mU/ejaculate) | <20 | ≥20 | <20 | ≥20 |
| | | | | |
| Genetic testing | | | | |
| Karyotype | Yes | If sperm concentration <10 million/ml | No | If sperm concentration <10 millon/ml |
| AZF deletions | no | If sperm concentration < 5 million/ml | no | If sperm concentration <5 million/ml |
| Genes for hypo hypo | Yes | No | No | No |
| CFTR mutations | No | No | Yes, if CBAVD suspected | No |

AZF = azoospermia factor; CBAVD = congenital bilateral absence of the vas deferens; FSH = follicle-stimulating hormone; hypo hypo = hypogonadotropic hypogonadism; T = testosterone.