

Infertility: an update for the family practitioner

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Abstract

The incidence of infertility is approximately 15–20% (one in every five to six couples). The investigation of the infertile couple begins with a careful history, followed by a physical examination. If any abnormality is observed in the history, the couple must be referred. The principle of evaluation of the infertile couple is to establish if the female is ovulatory or anovulatory. If ovulatory, the couple must be referred for more detailed examinations. If anovulatory and her prolactin and TSH as well as his semen analysis are normal, ovulation induction with a low dose of clomiphene citrate can be offered. On the other hand, if her prolactin and TSH as well as his semen analysis are abnormal, it is best to refer the patient.

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Introduction

The incidence of infertility is approximately 15–20% (one in every five to six couples).¹ It is estimated that in 40–50% of infertile couples, the male is subfertile/infertile, which, in the general population, equals about 5–10% of all married men.² However, infertility should be viewed not as solely male-related or female-related but as a question of varying degrees of fertility potential in both partners. Marginal male fertility can often be offset by excellent female fertility and vice versa. Therefore, it is strongly advised that both partners simultaneously undergo a fertility evaluation.

Definitions

- **Primary female infertility** implies that a woman has never conceived.
- **Secondary infertility** indicates that at least one previous conception has taken place, irrespective of the outcome of the conception.
- Generally, **infertility** is regarded as the inability to achieve pregnancy after one year of regular, unprotected sexual exposure.
- **Reproductive failure** is regarded as the repeated failure to carry a pregnancy to viability.
- The term '**sterility**' is used when an individual has a condition, a so-called absolute factor, that prevents conception. This implies that the condition is irreversible.

Evaluation

During the evaluation of a couple, it is helpful to categorise the various factors involved in order to cover all areas of importance (see Table I). The investigation of the infertile couple begins with a careful history, followed by a physical examination. The interview is probably the most important part of the entire infertility investigation.

History

It is important to approach both husband and wife with empathy and to win their confidence. It is also important to understand that some infertility conditions can be solved without advanced technology. The information that must be obtained is outlined below.

Infertility-related history

- Age of each partner
- Primary or secondary infertility: previous marital and reproductive history, including live births, abortions, ectopic pregnancies and puerperal infections
- Menstrual history: age at menarche, regularity and length of cycle and dysmenorrhoea. A woman with a normal, regular menstrual cycle is most probably ovulatory.
- Previous contraception and complications, if any
- Previous pelvic infections
- Breasts: thelarche, development, galactorrhoea and premenstrual tenderness
- Skin abnormalities: acne and abnormal hair growth
- Mass: sudden increase or decrease

Table I: Basic infertility evaluation

Anatomical factors

- Vagina: Anatomical defects, infections, lubricants and psychosomatic manifestations
- Cervix: Anatomical defects, infections, absent or excessive mucus production and surgery
- Uterus: Anatomical defects, infections and surgery
- Fallopian tubes: Anatomical defects, infections and surgery
- Pelvic peritoneum: Adhesions, endometriosis and infection
- Ovaries: Functional disorders, infection, surgery and endometriosis

Systemic factors

- Pathological conditions of the hypothalamus, pituitary gland, thyroid gland, adrenal glands, cardiovascular system, liver and kidney

Immunological factors

- Male or female immunological factors

Pharmacological factors

- Opioids, antiprostaglandins, chemotherapy and antidepressants

Environmental factors

- Smoking and excessive alcohol consumption
- Drugs: antidepressants and drugs causing hyperprolactinaemia
- Previous surgery: intra-abdominal or pelvic
- Sexual history: This must be done tactfully once confidence between doctor and patients has been established. Dyspareunia and frigidity must be excluded. Duration of sexual exposure: Has intercourse occurred at regular intervals over the last year? Are both partners aware of the fertile period? The opportunity is used to inform the couple about the most fertile period, that is, 12–14 days before the next menstruation.
- Various vaginal lubricants, such as KY jelly as well as saliva, used to improve coital satisfaction, may interfere with sperm transport or may be spermicidal. The use of these agents should be identified.
- Details of any previous infertility evaluation are important, including review of basal body temperature charts, previous laboratory studies and hysterosalpingograms (HSG).

General history

A general history should be taken, covering all general aspects and previous diseases.

Social history

The social history of the infertile couple may be obtained through enquiry about socio-economic factors, which can be of practical importance.

Family history

The family history may be of importance.

Physical examination

A complete physical examination should include the following:

- Assessment of stature, body length and mass
- Assessment of secondary sexual characteristics and hair distribution
- Assessment of breast development and exclusion of galactorrhoea
- An abdominal examination: Surgical scars should be noted, and tenderness as well as intra-abdominal masses should be excluded

- A complete gynaecological examination
- A rectovaginal examination to exclude possible endometriosis

Causes of male infertility

Male infertility can be categorised into five aetiological groups (see Table II):

- Pretesticular or pregerminal causes
- Testicular causes
- Posttesticular causes
- Genitourinary infections
- Immunological causes

Table II: Causes of male infertility

Pretesticular or pregerminal causes

- Central gonadotropin deficiency
 - Hypothalamic: congenital GnRH deficiency; tumour, infection and head trauma
 - Pituitary: congenital FSH/LH deficiency; tumour, infarction, infection and trauma
 - Other: sarcoidosis and haemochromatosis
- Endocrine excess syndromes
 - Oestrogen: functional tumour of adrenal gland; cirrhosis
 - Androgen: congenital adrenal hyperplasia; androgen-producing tumour
 - Glucocorticoid: Cushing's syndrome; steroid treatment (ulcerative colitis and asthma)
- Other
 - Hypothyroidism
 - Diabetes mellitus

Testicular causes

- Chromosomal abnormalities
 - Klinefelter's syndrome (47, XXY)
- Cryptorchidism, unilateral or bilateral
- Radiation and chemotherapy
- Mumps and viral orchitis
- Trauma
- Sertoli-cell-only syndrome
- Idiopathic maturation arrest
- Androgen receptor abnormality
 - Androgen insensitivity syndrome

Posttesticular causes

- Congenital ductal obstruction
 - Vas deferens and epididymis
- Acquired ductal block
 - Infection: gonorrhoea and tuberculosis
 - Vas ligation
- Impaired motility
 - Kartagener's syndrome
 - Immotile cilia syndrome
 - Enzyme deficiencies
 - Protein carboxymethylase

Genitourinary infections**Immunological causes****Evaluation of the male**

The family practitioner can request a semen analysis (SA) from a recognised andrology laboratory at this stage. If a subfertile SA is obtained, the patient can be referred to a

clinic or colleague specialising in human reproduction. It is important to follow the following guidelines:

- Interpret an SA with care.
- Do not rely on one abnormal SA.
- Choose wording carefully and inform the patient that the presence of abnormal semen requires further investigation. This does not necessarily mean that there is a male factor, but an expert opinion at this stage is necessary. In the past it was found that incorrect information was given to patients on the basis of only one SA.
- A second SA is thus necessary when there is any abnormality in the first analysis. The quality and characteristics of the ejaculate may be improved by the following measures:
 - Restricting smoking and excessive alcohol intake.
 - Following a proper diet, getting adequate rest, finding relief for emotional tension and getting treatment for any chronic illness or metabolic disease.
 - Avoiding underwear that keeps the testicles in contact with the body and heat exposure during excessively prolonged hot tubs or steam baths because heat is deleterious to testicular function.
 - Getting specific hormone therapy. However, it is estimated that this will benefit only 10% of men with idiopathic oligospermia or hypogonadotropic hypogonadism.
 - Taking the correct vitamin supplementation, for example Spermiprove® (available at local pharmacies or fertility clinics).

Special investigations

Basic SA

The basic SA is still the cornerstone of tests used to evaluate male fertility. The semen specimen is usually obtained by masturbation and must be collected after two to three days of abstinence to standardise the SA in all patients. The family practitioner should make use of a laboratory that has the necessary expertise. The clinical technologist involved in the SA should have been trained at a teaching hospital and should hold a qualification equivalent to a certificate from the Health Professions Council in Reproductive Biology. For normal values see Table III.

Mixed agglutination reaction test (MAR test)

This test is part of the basic semen analysis. This is a simple screening method for sperm antibodies that may impair male reproductive ability. The test detects IgG antibodies in the semen sample. After several modifications, the MAR test has become one of the two mixed agglutination assays routinely used to demonstrate membrane-bound antibodies on sperm.

Table III: Classification of male fertility potential used at Tygerberg Hospital

Semen parameter	Infertile*	Subfertile	Fertile
Concentration (x 10 ⁶ /ml)	< 2.0	2.0–9.9	> 10
Motility (% motile)	< 10	10–29	> 30
Forward progression (0–4)	< 1.0	1.0–1.9	> 2
Motility index	< 20.0	20.0–49.9	> 50
Morphology (% normal)	< 5***	< 5	> 5 (5–14% & > 14%)**
Volume (ml)	< 1.0	> 6.0	1.0–6.0

* Infertile is not sterile. Spontaneous pregnancies can even occur in this group.

** 5–14% = G pattern or good prognosis pattern. > 14% = N pattern or normal prognosis pattern. Both patterns are considered to be fertile.

*** <5% = P pattern or poor prognosis pattern

Immunobead test

If the MAR test is positive, the immunobead test is performed next. This assay employs immunoglobulin-coated latex particles as an indicator source. It also uses antiglobulin to produce a mixed agglutination between antibody-bound sperm and the indicator. The assay not only demonstrates the presence of antibodies but also indicates the region of binding on the sperm surface and determines the class and/or subclass of immunoglobulin involved. The types of antisperm antibody detected with the immunobead test in the semen sample are IgG, IgA and IgM.

Treatments for different male factor conditions

The first principle of treatment of male infertility is to make sure that the female is fertile. By correcting her fertility, a pregnancy will often follow. In severe cases of male infertility, intracytoplasmic sperm injection (ICSI) is indicated.

Micromanipulation – ICSI

Micromanipulation is a new development in the field of male infertility used for injecting selected spermatozoa into the oocyte. Indications for this treatment are the following: if the patient has a very low sperm count (oligozoospermia), severe asthenozoospermia, severe teratozoospermia or azoospermia. In the case of azoospermia, spermatozoa can be obtained and injected after testicular biopsy. A biopsy specimen can also be frozen in small quantities and used when required with excellent results. In these cases micromanipulation can be applied in conjunction with *in vitro* fertilisation (IVF) to try to achieve a pregnancy.

The current pregnancy rate at our institution is 40% per cycle in the most severe cases, if embryo quality is good. The cumulative pregnancy rate is ± 60–70% in three treatment cycles in patients for whom no pregnancy chance or treatment could be offered a few years ago.

Guidelines to management

An attempt should be made by the family practitioner to classify female patients into one of two categories, namely ovulatory or anovulatory (see Table IV). This will help with the management of these patients.

Table IV: Symptoms and signs of ovulation/anovulation

Ovulatory cycles

- Regular cycle (individual variation from 26 to 32 days)
- Mid-cycle pain
- Biphasic basal body temperature chart
- Adequate mid-cycle mucus secretion

Anovulation

- Abnormal menstruation
- Amenorrhoea
- Oligomenorrhoea (cycles longer than 35 days)
- Irregular cycles

Laboratory investigations

- Progesterone on day 21 (> 30 nmol/l = ovulation)
- E2 (oestradiol on day 12–14, normal = 700–1 200 pmol/l)
- Endometrial biopsy (day 24–26: secretory pattern on histology)
- LH and FSH (> 30 IU on two occasions indicates ovarian insufficiency)

The ovulatory patient

The properties of mid-cycle cervical mucus should be evaluated. During the periovulatory period, the patient should be examined on a daily basis for cervical mucus secretion. Adequate mucus should have the following characteristics:

- There should be a sufficient amount.
- The ability of the mucus to stretch (*spinnbarkeit*) should be 8–10 cm or more.
- The macroscopic appearance should be watery, thin, clear and transparent.
- When dried on a slide, it should form a distinct microscopic pattern called ferning.

Poor mucus at mid-cycle is a physical barrier that decreases sperm penetration and may require a procedure to achieve fertilisation (for example artificial insemination).

If the patient is ovulatory, the problem is usually of a more complex nature, thus requiring more sophisticated laboratory facilities for diagnosis and treatment. Tubal factors as well as male factors are the most common causes of infertility in this category.

A colleague with the necessary expertise should evaluate the reproductive organs and, in particular, the Fallopian tubes. The decision whether a patient should have reconstructive surgery or IVF is made laparoscopically, usually in conjunction with hysteroscopy or a hysterosalpingogram and chromopertubation.

If the patient has irregular cycles, do a TSH, FSH and Prolactin on the third day of the cycle (see Figure 1). If the results are normal, one can proceed with ovulation induction using clomiphene citrate 25 mg/day for five days from day 4–8 of the cycle. Fertile days are day 12–19 of the cycle. Confirm ovulation by doing a progesterone test on day 24. If the woman is not pregnant in three months, the couple must be referred to an infertility specialist.

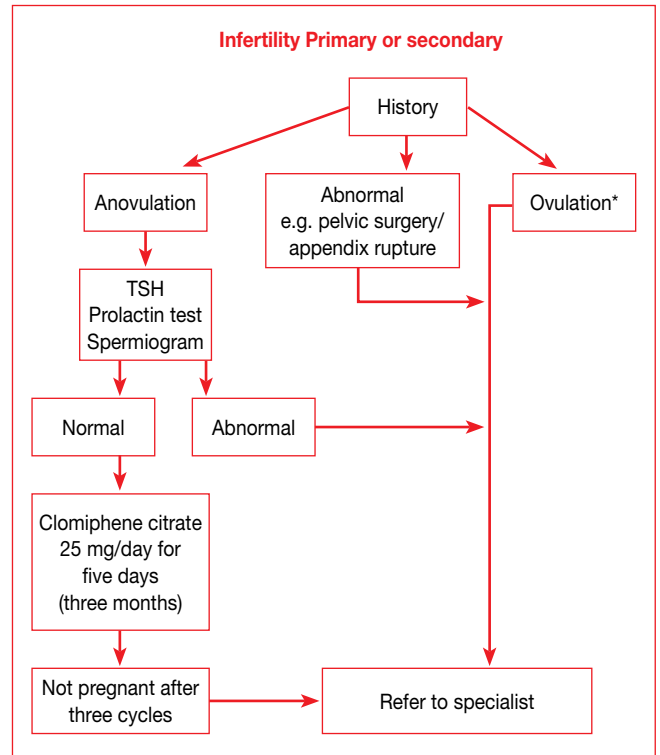


Figure 1: Management of the infertile couple

* If patient has been ovulatory for > one year, other causes must be ruled out; for that reason, refer to specialist

Conclusion

The family practitioner should strive to help the couple to see their infertility problem from as wide a perspective as possible. Pregnancy, although the ultimate goal, is not always possible. Thus, success should also be measured by other parameters, that is, improvement of the marital relationship and acceptance of unsuccessful treatment.

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