

Female infertility

Prohibited substances: clomiphene, letrozole

1. Introduction

Infertility is a disease state defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. It is estimated that about 10-15 percent of couples have infertility problems.

There are various causes of infertility. In general, about one third of infertility could be related to a female factor, another third to a male factor and the rest may be caused by a mixture of male and female problems or by unknown causes. Infertility is usually a couple problem. Female infertility due to male factor problems may require a female to go through treatments even if she is healthy and has no diagnosed problems.

Female infertility may be caused by ovulatory dysfunction, blocked fallopian tubes, endometriosis, abnormalities of the uterus or cervix and unexplained infertility. In turn, ovulatory dysfunction can be caused by hypothalamic dysfunction, polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, or premature ovarian insufficiency (POI).

Only those causes of female infertility which require a TUE will be addressed in this document. Furthermore, there is a separate PCOS guideline for the treatment of PCOS related infertility.

2. Diagnosis

a. Medical history

The female medical history generally includes details of menstrual cycle regularity, cycle length, previous pregnancy or miscarriage, sexually transmitted disease, gynaecological medical conditions or surgery. Furthermore, past history or symptoms of endocrine disturbance such as hirsutism, acne, galactorrhea, hot flushes and sweating, or fatigue should be considered.

Lifestyle factors are also important including being overweight or underweight, weight loss or weight gain, diet, type of exercise/sport and amount of training, coffee drinking, smoking and alcohol use.

Many chronic diseases and/or their medications can affect fertility such as asthma, diabetes, epilepsy, and mental illness.

b. Diagnostic criteria

The criterion for diagnosis of infertility is the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. The initial investigation aims at diagnosing the underlying causes. These causes can be multifactorial and can establish prognosis for successful pregnancy with and without treatment. Investigation usually includes both members of a couple. It is recognized that not all testing or imaging may be available to all athletes.

c. Physical examination

A general physical examination including a gynaecological examination, may be useful in excluding identifiable causes of infertility. The body mass index and signs of, for example, hirsutism or acne should be recorded.

d. Imaging and other investigations

Imaging and other investigations should be tailored to the individual and may include:

- Gynaecological examination including vaginal ultrasound is performed for assessment of uterus and ovaries in relation to menstrual cycle phase and age. Antral follicle count (AFC) is measured and the development of the preovulatory follicle and its transformation to corpus luteum could be followed by ultrasound. Furthermore, the specific changes of the endometrium could be determined.
- Hystero-salpingo contrast sonography (HyCoSy) or hysterosalpingography (HSG) are used to evaluate the uterine cavity and for diagnosing tubal occlusion. Importantly, use of an iodine contrast medium such as Lipiodol may also be therapeutic as well as diagnostic in checking tubal patency. However, there is a potential risk of infection by these methods.
- Laparoscopy is the best method for diagnosing tubo-peritoneal pathology related to, for instance, previous infection or endometriosis. However, there is a risk of complications such as damage to vessels, the intestine, and the urinary tract, which is why laparoscopy is rarely done when non-invasive tests can suffice.
- Hysteroscopy can be used as a diagnostic tool and as a therapy, as it can be used therapeutically to remove intrauterine abnormalities such as uterine polyps or fibroids.

Laboratory testing

The ovarian reserve testing is considered a part of standard practise. The ovarian reserve is estimated by serum analysis of anti-müllerian hormone (AMH) and follicle-stimulating hormone (FSH) on cycle day 3 to 5 together with AFC by ultrasound. Ovulation is confirmed by an increase in serum progesterone at mid-luteal phase about one week before the start of next menstruation.

Depending on the underlying cause of female infertility, further laboratory tests may be required. For example, luteinizing hormone (LH), estradiol, thyroid hormone status (TSH and free T4), prolactin, testosterone, and sex hormone-binding globulin (SHBG).

e. Summary

In accordance with the International Standard for TUEs and consistent with current best medical practice, the medical file required to support an application for a TUE in the case of an athlete with *female infertility* should include the following details:

- medical history and a general physical examination
- results of laboratory tests, imaging or other investigations that may help confirm the diagnosis
- a list of past and/or current therapies

3. Treatment

The treatment of female infertility in athletes should follow the same international guidelines as for any individual, whether or not they are an athlete. Nevertheless, the treatment is chosen individually, and there may be geographical differences in the availability of the treatments.

- 1) Expectant management with ovulation monitoring
- 2) Ovulation stimulation with oral or injectable agents including clomiphene citrate, letrozole, inositol, metformin, or gonadotrophins such as FSH or human menopausal gonadotrophins (HMG).
- 3) In vitro fertilisation (IVF), by different possible protocols, depending on the predicted response. The standard steps in an IVF-cycle include:
 - i) Suppression of spontaneous ovulation by gonadotropin releasing hormone (GnRH) agonist or antagonist
 - ii) Ovarian hyperstimulation by daily subcutaneous injections of FSH or combination FSH/LH
 - iii) Oocyte maturation induction by a single injection of human chorionic gonadotropin (HCG) or buserelin
 - iv) Transvaginal egg-retrieval
 - v) Sperm retrieval
 - vi) Fertilization by co-incubation of the egg and the sperm
 - vii) Embryo transfer into the woman's uterus
 - viii) Luteal support by vaginal progesterone

One cycle of IVF can take about two to three weeks, and several cycles may be required.

a. Name of prohibited substances

Letrozole (aromatase inhibitor) 2.5 mg - 10 mg per day orally for five days (cycle day 3 to 7) is used for ovulation stimulation.

Clomiphene 50 – 150 mg orally per day for five days (cycle day 5 to 9) is an alternative for ovulation stimulation.

There is no scientific evidence to support adjuvant androgenic supplements such as testosterone or DHEA in IVF treatment.

Note that it is not necessary to try and fail alternatives before using the Prohibited Substance or Prohibited Method. The physician must explain why the treatment chosen was the most appropriate e.g., based on experience, side-effect profiles or other medical justifications, including, where applicable, geographically specific medical practice, and the ability to access the medication.

4. Non-prohibited alternative treatments

Gonadotrophins (FSH or FSH/LH) alone or in conjunction with IVF.

Human Chorionic Gonadotropin (hCG) is prohibited at all times in males, but it is not prohibited in females. hCG is given as a single dose for ovulation induction, and also in luteal phase as 1-2 injections.

Metformin

Inositol and related products.

5. Consequences to health if treatment is withheld

Significantly decreased quality of life if infertility is unresolved. If treatment is delayed, age-related infertility can exacerbate underlying causes of infertility.

6. Treatment monitoring

Fertility treatment is monitored individually by blood tests for hormone analyses and by frequent ultrasound examinations.

7. TUE duration

The recommended duration of a TUE for female infertility is 1 year. Documentation of effects of the treatment(s) should be provided when applying for a TUE after the initial treatment period.

8. Appropriate precautionary matters

In vitro fertilization requires injectable gonadotrophins and hormone analogues including GnRH agonists and antagonists. Some treatments require prolonged pre-treatment with GnRH agonists.

References

1. Fertility problems: assessment and treatment Clinical Guideline (CG156). Published date: February 2013. Last updated September 2017. National Institute for Health Care Systems. www.nice.org.uk.
2. ESHRE Guideline on Ovarian Stimulation for IVF/ICSI 2019.