



INFERTILITY/POLYCYSTIC OVARIAN SYNDROME

Introduction

Infertility is defined as the absence of pregnancy following 12 months of unprotected intercourse. Infertility may be caused by Ovulatory Dysfunction, Blocked Fallopian Tubes, Male Factor Infertility or Unexplained Causes. Ovulatory Dysfunction can be caused by hypothalamic causes, endocrinopathies (hyperprolactinemia, thyroid dysfunction) or ovarian causes (Polycystic Ovarian Syndrome, ovarian failure). Only those causes of infertility which require a TUE will be addressed in this document.

Ovulatory Dysfunction: Polycystic ovarian syndrome (PCOS)

1. Diagnosis	
<i>A. Medical history</i>	<ul style="list-style-type: none"> - Absent or irregular menstrual cycles; - Clinical evidence of androgen excess (hirsutism, acne).
<i>B. Diagnostic criteria</i>	<p>History as above as well as one of:</p> <ul style="list-style-type: none"> - Ultrasound evidence of ovarian volume 10cm³, >12 follicles between 2-9 mm per ovary; - Altered hormonal profile is not necessary for diagnosis as serum as androgen levels (testosterone, androstenedione, DHEAS) may be in the normal or high range.
<i>C. Relevant medical information</i>	Some women with PCOS will have associated insulin resistance which may manifest as impaired glucose tolerance or overt diabetes.
2. Medical best practice treatment	

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Prohibited substances:	Clomiphene citrate	Spirolactone
<i>A. Name of prohibited substances</i>	<p>First line therapy is clomiphene citrate, a weak anti estrogen.</p> <p>Alternates to clomiphene: Metformin has not proven to be as effective as clomiphene as a first line treatment.¹ Exogenous gonadotrophins are much more expensive and are only available in an injectable form. In women who are non responsive to clomiphene, or who demonstrate insulin resistance, an insulin sensitizer such as metformin may be added. If this is not successful, FSH s/c may be given.</p>	<p>Spirolactone may be used in some geographic regions of the world as a secondary treatment in the management of hirsutism caused by PCOS.</p>
<i>B. Route</i>	Oral	Oral
<i>C. Frequency</i>	5 days per month	Daily
<i>D. Recommended duration of treatment</i>	9 – 12 months	Long-term use is necessary
3. Other non-	Clomiphene citrate	Spirolactone

¹ *N Engl J Med.* 2007;365:551-566, 622-624

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<p>prohibited alternative treatments?</p>	<p>hCG, Progesterone may be required in addition to clomiphene</p>	<p>Diane 35 (3 mg cyproterone acetate) and Yaz are two oral contraceptives with anti-androgenic effects that are used as first line therapy for the treatment of hirsutism caused by PCOS. Any oral contraceptive or the Nuva-ring will increase sex hormone binding globulin as a result of the increased estrogen. This will decrease free unbound, circulating androgens resulting in decreased hirsutism. For more severe or long standing cases, larger doses of cyproterone acetate (25-50mg) may be necessary. In some areas of the world, oral flutamide (non-steroidal anti-androgen) is used to treat hirsutism. Hormonal therapy can be combined with physical hair removal techniques such as laser or electrolysis. A TUE may be granted for spironolactone should the athlete have proved:</p> <p>The necessity [ie presence of hirsutism in the clinical picture of PCOS] and one or more of the following criteria:</p> <ul style="list-style-type: none"> • A contraindication to a non-prohibited method; • An intolerance to a non-prohibited method; • A failed response to a non-prohibited method; • Inability to benefit from physical methods of hair removal due to prohibitive cost.
<p>4. Consequence to health if treatment is withheld</p>	<p style="text-align: center;">Clomiphene citrate</p> <p>Significantly decreased quality of life if infertility is unresolved.</p>	<p style="text-align: center;">Spironolactone</p> <p>Significant decreased quality of life for women with hirsutism resulting from PCOS.</p>

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5. Treatment monitoring	Blood estrogen, and LH and ultrasound of the ovaries for follicular growth monitoring.	Monitoring by gynaecologist, endocrinologist or dermatologist on a yearly basis is recommended.
6. TUE validity and recommended review process	2 years	8 years TUE with an annual review by a specialist can be granted for this substance as PCOS is a lifelong condition.
7. Any appropriate cautionary matters	Nil	Nil

Bilateral Blockage of Fallopian Tubes

1. Diagnosis	
<i>A. Medical history</i>	Cannot be diagnosed by history.
<i>B. Diagnostic criteria</i>	Evidence of proximal or distal blockage of tubes by hysterosalpingogram, sonohysterogram or surgery.
<i>C. Relevant medical information</i>	Nil
2. Medical best practice treatment	In vitro fertilization: This requires controlled ovarian hyperstimulation with FSH, or FSH/LH combination. Prior to stimulation the patient may receive oral contraceptives or GnRH agonists, or may receive GnRH antagonists during stimulation. Pain management during the procedure may include: morphine, meperidine (pethidine), ketorolac, fentanyl or midazolam, as well as local lidocaine or bupivacaine.
<i>A. Name of prohibited substances</i>	GnRH agonists (nafarelin or buserelin), and GnRH antagonists (ganirelix or cetrorelix). Narcotics may be required during the procedure – which are prohibited during competition only.
<i>B. Route</i>	Sc
<i>C. Frequency</i>	Daily 10-14 days
<i>D. Recommended duration of treatment</i>	3 – 6 cycles

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3. Other non-prohibited alternative treatments?	hCG, Progesterone may be required in addition.
4. Consequences to health if treatment is withheld	Significantly decreased quality of life if infertility is unresolved.
5. Treatment monitoring	Blood hormonal profiles and ultrasound to assess ovarian response over two-week period.
6. TUE validity and recommended review process	<p>A TUE is required for the use of the GnRH agonists and antagonists. The procedure is usually repeated at three month interval for an average of three times.</p> <p>The recommended duration of a TUE for Infertility/Polycystic Ovarian Syndrome is 2 years. If narcotics are used during the procedures, a TUE would be required but narcotics are only prohibited during the in-competition period.</p> <p>A TUE will be required for the procedure if narcotics are used should the procedure occur during the in-competition period only.</p>
7. Any appropriate cautionary matters	IVF is not recommended during the competitive period.

Male Factor Infertility necessitating advanced reproductive technologies

1. Diagnosis	
<i>A. Medical history</i>	Cannot be diagnosed by history.
<i>B. Diagnostic criteria</i>	Abnormal semen analysis showing hypomobility, a high incidence of abnormal forms or decreased overall sperm count.
<i>C. Relevant medical information</i>	Nil
2. Medical best practice treatment	IVF see Bilateral blockage of fallopian tubes (above) May also be treatable with injectable medications and intrauterine insemination for which a TUE is not required.

Unexplained Infertility	
1. Diagnosis	
<i>A. Medical history</i>	No pregnancy despite regular ovulatory cycles, open tubes, regular timed intercourse and normal semen analysis.
<i>B. Diagnostic criteria</i>	As above
<i>C. Relevant medical information</i>	Nil
2. Medical best practice treatment	May be treated with clomiphene citrate (see PCOS), FSH/LH (TUE not required) or IVF (see Bilateral blockage of fallopian tubes).

Other References

CFAS (Canadian Fertility & Andrology Society) Consensus Document for the Investigation of Infertility By First Line Physicians 2003
<http://cfas.cfwebtools.com/index.cfm?objectid=62E48386-9027-F64A-799957D994FC5F65>

Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008; 89(3): 505-522

Handelsman DJ, The Rationale For Banning Human Chorionic Gonadotrophin and Estrogen Blockers in Sport JCEM 19:16461653, 2006

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