

## 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 (PCOS), ovarian failure). Only those causes of infertility which require a TUE will be addressed in this document.

<b>Ovulatory Dysfunction: Polycystic Ovarian Syndrome (PCOS)</b>	
<b>1. Diagnosis</b>	
<i>A. Medical history</i>	<ul style="list-style-type: none"> <li>- Absent or irregular menstrual cycles;</li> <li>- Clinical evidence of androgen excess (hirsutism, acne).</li> </ul>
<i>B. Diagnostic criteria</i>	<ul style="list-style-type: none"> <li>(1) Hyperandrogenism: Hirsutism and/or hyperandrogenemia and</li> <li>(2) Ovarian dysfunction: Oligo-anovulation and/or polycystic ovaries and</li> <li>(3) Exclusion of other androgen excess or related disorders.</li> </ul>
<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.

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<b>2. Medical best practice treatment</b>		
Prohibited substances:	<b>1. Clomiphene citrate</b> <b>2. Letrozole</b>	<b>3. Spironolactone</b>
<i>A. Name of prohibited substances</i>	First line therapy is <b>clomiphene citrate</b> , a weak anti estrogen, and <b>letrozole</b> , an aromatase inhibitor.	<b>Spironolactone</b> may be used in some geographic regions of the world as a secondary treatment in the management of hirsutism caused by PCOS.
<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

<p><b>3. Other non-prohibited alternative treatments?</b></p>	<p><b>1. Clomiphene citrate</b> <b>2. Letrozole</b></p>	<p><b>3. Spironolactone</b></p>
	<p>Subcutaneous exogenous <b>Follicle Stimulating Hormone (FSH)</b> can be used as an alternative.</p> <p><b>Metformin</b> has not proven to be as effective as clomiphene or letrozole as a first line treatment. However, in women who are non-responsive to clomiphene or letrozole, or who demonstrate insulin resistance, an insulin sensitizer such as metformin may be added.</p> <p><b>hCG</b> and <b>Progesterone</b> may be used as adjuncts to first line therapy.</p>	<p>Diane 35 (2 mg cyproterone acetate) and Yaz (3 mg drospirenone) 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 NuvaRing (11.7 mg etonogestrel) 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 [i.e. presence of hirsutism in the clinical picture of PCOS] and one or more of the following criteria:</p> <ul style="list-style-type: none"> <li>• A contraindication to a non-prohibited method;</li> <li>• An intolerance to a non-prohibited method;</li> <li>• A failed response to a non-prohibited method;</li> <li>• Inability to benefit from physical methods of hair removal due to prohibitive cost.</li> </ul>

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<b>4. Consequence to health if treatment is withheld</b>	<b>1. Clomiphene citrate</b> <b>2. Letrozole</b>	<b>3. Spironolactone</b>
	Significantly decreased quality of life if infertility is unresolved	Significant decreased quality of life for women with hirsutism resulting from PCOS.
<b>5. Treatment monitoring</b>	Blood estrogen, and Luteinizing Hormone (LH) and ultrasound scan of the ovaries for follicular growth monitoring.	Monitoring by gynaecologist, endocrinologist or dermatologist on a yearly basis is recommended.
<b>6. TUE validity and recommended review process</b>	2 years	10 years TUE with an annual review by a specialist can be granted for this substance as PCOS is a lifelong condition.
<b>7. Any appropriate cautionary matters</b>		

<b>Unexplained Infertility</b>	
<b>1. Diagnosis</b>	
<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
<b>2. Medical best practice treatment</b>	May be treated with clomiphene citrate (see PCOS), FSH/LH (TUE not required)

## References

1. 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>
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4. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sudgot-Borgen J, Warren MP, American College of Sports Medicine. The Female Athlete Triad. *Med. Sci. Sports. Exerc.* 2007; 39(10):1867-1881.
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6. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum. Reprod. Update* 2016;22(6):687-708.