



## CFAS Position Statement on the Use of Letrozole for the Management of Infertility

Clomiphene citrate (Clomid™ and Serophene™) is a trusted medication for the management of ovulatory disorders such as polycystic ovarian syndrome (PCOS). Clomiphene citrate is presently the only oral fertility medication approved by Health Canada, and is the main medical fertility treatment prescribed by family physicians and obstetricians/gynaecologists. Recently, the only manufacturer of clomiphene citrate discontinued its production and unless other suppliers emerge the world-wide supply will be exhausted later this year.

Letrozole (Femara™) is an effective oral ovulation induction agent and appears to be more effective than clomiphene citrate for achieving live birth in patients with ovulatory disorders<sup>1</sup>. For many fertility specialists, letrozole is the first-line treatment for the management of ovulatory infertility. For the management of unexplained infertility both clomiphene citrate and letrozole appear to be equally effective, but less effective than gonadotropin-based treatments<sup>2,3</sup>. However, as a low risk, low cost, oral medication, we expect that the demand for letrozole will increase dramatically as the supply of clomiphene citrate depletes.

Letrozole has been used as an ovulation induction agent since 2000 with a growing body of evidence for its use. However many physicians are reluctant to prescribe it due to a statement issued by the manufacturer Novartis on November 17<sup>th</sup>, 2005, warning against its use in premenopausal women due to the potential for fetal toxicity and malformation (Femara\_DHCP\_E\_2005\_Nov.pdf). This formal statement was prompted by a single abstract presented at the CFAS-ASRM annual meeting in 2005<sup>4</sup>. One hundred fifty babies resulting from the use of letrozole born from couples with unexplained infertility or PCOS were compared to a database of over 36,000 normal deliveries. The abstract reported no difference in the overall rate of all malformations, but reported an increase in locomotor and cardiac malformations in the babies born after letrozole treatment. Beyond the small size of the study group, this comparison is limited because infertility itself is a significant risk factor for fetal malformations and the controls were babies born to normally fertile couples. This study was never published, and larger published cohort studies have since demonstrated no increased risk of malformations after letrozole use<sup>5,6</sup>.



Over a decade of clinical use and scientific observations demonstrate the safety and efficacy of letrozole in the management of infertility. Therefore, the CFAS supports the use of letrozole for the treatment of ovulatory dysfunction and unexplained infertility, after an appropriate infertility work-up and under the care of a physician educated in its use.

#### References

1. Legro et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014;371:119-29.
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3. Liu et al. Letrozole versus clomiphene citrate for unexplained infertility: a systematic review and meta-analysis. *J Obstet Gynaecol Res* 2014;40:1205-16.
4. Biljan et al. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. *Fertil Steril* 2005;84(Supp 1):S95.
5. Sharma et al. Congenital malformations among babies born following letrozole or clomiphene for infertility treatment. *PLoS One* 2014;9(10):e108219.
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