The use of aromatase inhibitors for ovulation induction

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Purpose of review
Approximately 15% of the infertile population faces an ovulatory disorder; most of them classified as WHO class two anovulation [polycystic ovarian syndrome (PCOS) prototype]. Worldwide, this translates into millions of patients and emphasizes the need of a simple, effective and well tolerated method of ovulation induction. In this review, we will revisit letrozole use in the subset of WHO class two ovulatory problems and evaluate the contribution of the last year's literature to its practice.

Recent findings
In a multicentre, randomized controlled trial comparing letrozole with clomiphene in 750 PCOS patients having regular intercourse, live birth rates were significantly higher for the letrozole group [rate ratio 1.44, 95% confidence interval (95% CI) 1.10–1.87]. In a meta-analysis summarizing clinical trials testing aromatase inhibitors used alone or with other medical therapies for ovulation induction in PCOS patients, live birth rates were again significantly higher when letrozole was compared with clomiphene citrate [odds ratio (OR) 1.64, 95% CI 1.32–2.04]. A retrospective analysis of children born to infertile women assessed the congenital malformation rate after exposure to letrozole in comparison to clomiphene citrate and to natural conceptions. No significant differences in malformation rates were detected between the groups (2.9, 2.5 and 3.9%, respectively).

Summary
High-level evidence supports letrozole as the first drug of choice for ovulation induction in the PCOS population. The increasing use of letrozole with pregnancy follow-up provides additional reassurance for foetal safety.

Keywords
congenital abnormalities, evidence-based medicine, letrozole, polycystic ovary syndrome

INTRODUCTION

It has been more than a decade since aromatase inhibitors were introduced as an alternative treatment for ovulation induction in women with polycystic ovarian syndrome (PCOS) [1]. The initial patient population, studied for proof of concept, comprised women with WHO class two ovulation disorder who either failed to respond to clomiphene citrate or who demonstrated a thin endometrial lining as a result of oestrogen receptor depletion after clomiphene citrate treatment [1]. The results of this preliminary study were positive, thereby promising an alternative to the existing ovulation induction agents. Since then, multiple clinical studies have consistently reinforced the efficiency of aromatase inhibitors for WHO type II anovulation and infertility [2–5]. Letrozole, a third-generation aromatase inhibitor, is the most commonly used for ovulation induction protocols [6,7] and has been integrated into clinical practice to varying degrees. Letrozole's only current registered indication is postmenopausal oestrogen receptor positive breast cancer, but it is prescribed off-label worldwide for inducing ovulation. In the past year, publications have appeared containing high-level evidence supporting the use of letrozole as a first-line ovulation induction agent [8▪▪,9▪▪]. In addition, there is a growing acceptance and understanding of the uses of aromatase inhibitor agents in broader aspects of reproductive medicine including ovarian hyperstimulation syndrome (OHSS) risk reduction [10], endometrial preparation in frozen embryo

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KEY POINTS

- Letrozole is superior to clomiphene citrate in terms of live birth rate following ovulation induction in PCOS patients.
- Letrozole is superior to clomiphene citrate for successful ovulation induction in PCOS patients.
- Letrozole results in fewer multiple pregnancies than clomiphene citrate when used for ovulation induction in PCOS patients.
- There is no increase in birth defects with letrozole or clomiphene citrate when compared with spontaneous conception in an appropriate infertile control group.

transfer (FET) cycles [11], as an adjuvant in ovarian stimulation protocols for fertility preservation in oncology patients [12] and more [13].

BIOLOGIC RATIONALE

Clomiphene citrate has been used for decades for the purpose of ovulation induction and has led to successful ovulations, pregnancies and live births. Despite this long history of use in reproductive medicine, clomiphene citrate is associated with a substantial number of side effects and limitations that led to the search for an alternative therapy [1]. Some of the problems arise from clomiphene citrate's mechanism of action [a selective oestrogen receptor modulator (SERM) with predominantly antagonistic effects on the oestrogen receptor] and include hypoestrogenic side effects (hot flushes, headaches and mood changes) as well as hypoestrogenic effects on the cervical gland production of mucus and endometrial growth, which probably reduce the chances for conception even in a successful ovulatory cycle. Other limitations involving clomiphene citrate are its limited efficiency (25% resistance rate for ovulation) and a rather high incidence of multiple pregnancy (5–8%) [14]. Metformin is another oral agent studied for its potential to improve the clomiphene citrate profile, but recent data suggest that metformin does not increase the pregnancy rate, either by itself or in combination with clomiphene (PPCOS I study) [14]. Other ovulation induction options include injectable gonadotropins with substantial costs and the need for intensive monitoring, or surgical procedures such as laparoscopic ovarian drilling with high costs, complexity, possible intraoperative complications and pelvic adhesions.

As a result of the above-mentioned problems with the current oral or injectable ovulation induction agents, in 2001, aromatase inhibitors were suggested as an alternative [1]. The rationale was that inhibition of aromatase, the rate-limiting enzyme in oestrogen biosynthesis, would release the hypothalamic-pituitary-gonadotropin axis from exposure to oestrogenic negative feedback, thus leading to an increase in gonadotropin secretion and the stimulation of ovarian follicle development. The relatively short half-life of aromatase inhibitor compared with clomiphene citrate enabled rapid elimination from the body and was therefore associated with short-term hypoestrogenic effects. In addition, in contrast to clomiphene citrate, oestrogen receptor depletion did not occur with aromatase inhibitor and no adverse effects on oestrogen target tissues were expected.

TRENDS IN THE USE OF LETROZOLE

Despite these advantages and despite the supportive evidence of multiple clinical trials, by 2013, letrozole had not gained a first-line role in the field of ovulation induction. In December 2013, physicians' attitudes towards prescribing letrozole were addressed and published. The study involved a large survey encompassing Society for Assisted Reproductive Technologies clinics across the USA [15]: Only 14.9% of the clinics reported letrozole as their drug of choice for WHO II ovulatory disorders and approximately 20% of clinics reported having never used the medication. When the reasons for their attitude towards aromatase inhibitor were addressed, the majority of physicians expressed they were either happy with the other treatment options or expressed a concern about the Novartis warning letter. The Novartis warning was published in 2005 following an abstract presentation at ASRM suggesting an increased cardiac (and other) anomaly rate in letrozole-induced pregnancies as compared with spontaneous conceptions. The study methodology was flawed, and therefore it was never published, but was enough to alert the medication's manufacturer and subsequently the U.S. Food and Drug Administration (FDA) to warn against the use of letrozole in the premenopausal population due to concern of foetal malformations. Subsequently, a multicentre Canadian study including 911 babies born after clomiphene citrate or letrozole demonstrated an overall congenital malformation and chromosomal abnormality rate of 14 of 514 babies in the letrozole group (2.4%) and 19 of 397 babies in the clomiphene citrate group (4.8%) [16]. The major malformation rate in the letrozole group was 1.2% (six of 514) and in the clomiphene citrate group was 3.0% (12 of 397). These differences in rates were not statistically significant. However, seven newborns in the clomiphene citrate group (1.8%) as opposed to one in the letrozole group (0.2%) had congenital

cardiac anomalies ($P = 0.02$). This study was published only 1 year after the Novartis letter but has not resulted in any change in policy or a withdrawal of the previous expressed concerns.

THE NICHD REPRODUCTIVE MEDICINE NETWORK STUDY COMPARING LETROZOLE AND CLOMIPHENE

A multicentre study by the Nichd Reproductive Medicine Network (RMN) published in the *New England Journal of Medicine* in July 2014 [9▪▪] enrolled 750 PCOS patients who were randomized to either clomiphene citrate or letrozole for up to 5 months in a double-blind design. The primary endpoint was live birth rate during the study period. The importance of this publication results from its meticulous methodology and adequate power to detect live birth rate differences. All patients had documentation of at least one patent tube and a normal uterine cavity and their partners had a sperm concentration of at least 14 million/ml and documented motility in at least one ejaculate during the year prior to recruitment. The initial dose was 2.5 mg for letrozole and 50 mg for clomiphene citrate, both prescribed for 5 consecutive days from cycle day 3 following spontaneous or induced menstruation. Both groups were stepped up in dosage if no response (lack of ovulation). All couples had regular intercourse during the study period. As the researchers hypothesized, the live birth rate in the letrozole arm was significantly higher than the clomiphene citrate arm: rate ratio 1.44 [95% confidence interval (95% CI) 1.10–1.87] with no difference in pregnancy loss rates after conception. The ovulation rate was also significantly higher with letrozole than with clomiphene citrate and when conception rates were tested only among those who successfully ovulated, there was still a significantly higher live birth rate in the letrozole group. Importantly, there was a significantly higher chance for a singleton live birth with letrozole than with clomiphene citrate ($P = 0.03$), though the study was underpowered to detect differences in multiple pregnancy rates. No significant differences were reported for treatment-related adverse effects or for pregnancy-associated complications. The authors concluded that letrozole is superior to clomiphene citrate for ovulation induction in the PCOS population and further studies are encouraged to address the issues of drug safety through enlarging the number of neonates followed.

THE COCHRANE META-ANALYSIS

The objective of this Cochrane review was to determine whether clomiphene citrate or letrozole is the more efficient drug for ovulation induction in the PCOS population [8▪▪]. The Cochrane group performed a meta-analysis of all randomized controlled trials (RCTs) testing aromatase inhibitors used alone or with other medical therapies for ovulation induction in PCOS patients. The primary outcomes were live birth and OHSS and the analysis was published this year. Live birth rates were based on data from nine studies ($n = 1783$) and showed a significantly higher birth rate when letrozole was compared with clomiphene citrate for ovulation induction followed by timed intercourse: odds ratio (OR) 1.64 (95% CI 1.32–2.04). OHSS was an absent or rare event altogether and there was no evidence for a difference when letrozole was compared with clomiphene citrate (seven studies, $n = 1808$). Secondary outcomes reported were miscarriage and multiple pregnancy rates: No differences were recorded for miscarriage rate OR 0.91 (95% CI 0.61–1.36), but a significantly lower multiple birth rate was calculated for the letrozole group: OR 0.38 (95% CI 0.17–0.84) than clomiphene citrate. Of note is the fact that the quality of the evidence was rated as low for live birth and pregnancy outcomes, probably reflecting the poor reporting of study methods and possible publication bias of the studies involved. Specifically, results may be somewhat less favourable to letrozole in the studies that reported live birth. With this caution, the authors concluded that letrozole is superior to clomiphene citrate for ovulation induction in PCOS patients who have had no previous infertility treatment or who are resistant to clomiphene citrate.

RECENTLY PUBLISHED DATA REGARDING CONGENITAL MALFORMATIONS FOLLOWING LETROZOLE

In October 2014, a retrospective analysis [17▪] of 623 children born to infertile women was performed in order to reassess the congenital malformation rate after exposure to letrozole or clomiphene citrate for ovulation induction or for ovulation augmentation in unexplained infertility. The importance of the study arises not only from its reassurance regarding safety but also from its design. The researchers compared children born between January 2007 and December 2011 with infertile couples who conceived naturally or following clomiphene citrate or letrozole treatment. This specific design allows comparison of the drug-exposed groups with a highly appropriate control group, that is infertile couples who conceived naturally during the initial steps of their infertility evaluation or while they were waiting for a treatment cycle to begin. This provides an important background figure of congenital anomaly rates that strengthen the validity of this publication. The study groups included 171 babies in the natural

conception arm, 201 babies in the letrozole arm and 251 babies in the clomiphene citrate arm. The overall malformation rates (including both structural and congenital anomalies) were 2.9, 2.5 and 3.9%, respectively, and there was no significant difference between the groups. When further subdivided into structural versus chromosomal anomalies, no significant difference was detected between the groups as well.

CONCLUSION

This past year has provided two major publications, both classified at the highest level of evidence-based medicine, which are likely to change the current practice for ovulation induction for PCOS patients. A year ago, physicians were wary of prescribing letrozole for ovulation induction let alone considering letrozole as their drug of choice for the PCOS population. It will be interesting to see whether this attitude will change after exposure to the publications described above. We believe that letrozole use will likely spread and be adopted by clinicians worldwide.

We have also described birth defect results suggesting safety of both letrozole and clomiphene citrate in a well designed retrospective study that was recently published. The increasing use of letrozole will provide more future data regarding neonatal outcomes and presumably further reassurance concerning foetal safety. Meanwhile, we suggest that the current literature favours letrozole as first-line treatment for ovulation induction in WHO class 2 patients.

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Conflicts of interest

R.F.C. reports consulting and SAB fees from AbbVie, Actavis, Bayer, Boehringer-Ingleheim, EMD Serono, Ferring, Merck, OvaScience, Pfizer and royalties from Up-to-Date and Teva. A.H.C. has no conflicts to report.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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This study examines data from nine RCTs ($n = 1783$) and showed a significantly higher birth rate when letrozole was compared with clomiphene citrate for ovulation induction followed by timed intercourse. Although the quality of the data was rated as low, the authors concluded that letrozole is superior to clomiphene citrate for ovulation induction in PCOS patients who have had no previous infertility treatment or who are resistant to clomiphene citrate.

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This study compared the rate of birth defects following clomiphene citrate or letrozole compared with infertile women who conceived spontaneously. The spontaneous conception group provides an important background rate of congenital anomalies that strengthens the validity of this publication.