Clomiphene citrate—end of an era? a mini-review

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The purpose of this review is to examine whether the time has come to replace clomiphene citrate (CC) as the first line therapy for WHO group II (eu-oestrogenic) infertility, the majority of which is associated with polycystic ovary syndrome. CC has been the first line therapy for these cases for the last 40 years. It is a simple, cheap treatment, almost devoid of side effects which yields a single live birth rate of ~25% of starters. Non-response to CC and the gap between ovulation and pregnancy rates have variously been attributed to its anti-estrogen effects, and high LH and androgen concentrations. Three possible contenders for the replacement of CC as first-line treatment are scrutinized: metformin, aromatase inhibitors and low-dose FSH. Each has their advantages and disadvantages, but none of them, while showing much potential promise, has been proven, as yet, to be a feasible replacement for CC in this role. For CC, it may not yet be the end of an era but it may be the beginning of the end.

Key words: aromatase inhibitors/clomiphene citrate/low-dose FSH/metformin/PCOS

Introduction

It is now >40 years ago that Greenblatt first reported a new compound, the anti-estrogen MRL-41, capable of inducing ovulation for anovulatory women (Greenblatt et al., 1961). Later to become known as clomiphene citrate (CC) this compound has had a remarkably sustained career as the first-line treatment for women with absent or irregular ovulation due to hypothalamic–pituitary dysfunction associated with normal basal levels of endogenous estradiol (WHO group II). The vast majority of these patients probably some 80% are now known to be oligo- or anovulatory due to polycystic ovary syndrome (PCOS). Until the introduction of CC the only plausible treatment for these patients who wished to conceive was bilateral wedge resection of the ovaries. Although this abdominal surgical procedure had some considerable success in restoring ovulation and even inducing pregnancy it later fell from grace due to the generation of pelvic adhesions following the operation in a large number of patients and the emergence of medical means to induce ovulation. CC was the first medication capable of inducing ovulation and as such created a welcome revolution in the treatment of infertility associated with anovulation.

Many years later, a further suggested indication was its empirical use for ovarian stimulation in idiopathic (‘unexplained’) infertility. Here its success was more limited but, with the introduction of assisted reproductive technology, it became widely used as a ‘booster’ to ovulatory capacity in conjunction with intrauterine insemination (IUI) and, with the rising costs of gonadotrophin preparations, as an adjuvant to gonadotrophin stimulation of the ovaries in preparation for IVF.

Despite the use of CC in controlled ovarian stimulation, its original indication of ovulation induction for WHO group II classification of oligo- or anovulation, particularly when associated with PCOS, remains its most frequent and most successfully treated indication. The fact that CC is an orally administered, relatively cheap preparation, has proved an enormous advantage over its injected and expensive competitors. However, the field is becoming replete with alternatives for the same indication and the time is ripe to re-evaluate the place of CC in our armamentarium of ovulation-inducing agents.

Mode of action

Clomiphene contains an unequal mixture of two isomers as their citrate salts, enclomiphene and zuclomiphene. Zuclomiphene is much the more potent of the two for induction of ovulation, accounts for 38% of the total drug content of one tablet and has a much longer half-life than enclomiphene, being detectable in plasma 1 month following its administration. Rostami-Hodjegan et al. (2004) have suggested that wide variability in the metabolism of the zuclomiphene component contributes to variability in response to the drug.

CC is capable of inducing a discharge of FSH from the anterior pituitary and this is often enough to reset the cycle of events leading to ovulation into motion. The release of even small amounts of FSH into the system will often induce ovulation and pregnancy in a proportion of eu-oestrogenic anovulatory women. This is achieved indirectly, through the action of CC, a non-steroidal compound closely resembling an estrogen, in blocking hypothalamic estrogen receptors, signalling...
a lack of circulating estrogen to the hypothalamus and inducing a change in the pattern of pulsatile release of GnRH.

**Dose**

CC is given orally in a dose of 50–250 mg per day for 5 days from day 2, 3, 4 or 5 of spontaneous or induced bleeding, starting with the lowest dose and increasing the dose in increments of 50 mg/day per cycle until an ovulatory cycle is achieved. The starting day of treatment, whether on day 2 or through day 5 of the cycle, does not influence the results (Wu and Winkel, 1989). Although 50 mg/day is the recommended dose in the first cycle, a meta-analysis of 13 published reports (Rostami-Hodjegan et al., 2004) suggests that only 46% will respond to this dose with ovulation, a further 21% will respond to 100 mg and another 8% will ovulate with 150 mg/day. There is no apparent advantage of using a daily dose of >150 mg which seems to significantly increase neither the ovulation rate nor follicular recruitment (Dickey et al., 1997). Some practitioners often use a starting dose of 100 mg/day from day 4 or 5, only resorting to 50 mg/day in the case of exquisite sensitivity or persistent cyst formation. The advantage of starting with a 100 mg daily dose rather than 50 mg is that it will cut down the number of ‘superfluous’ cycles of treatment until ovulation is achieved and until those resistant to CC are identified. It is difficult to state what effect, if any, this course of action has on the multiple pregnancy rate.

**Results**

A compilation of published results regarding ovulation and pregnancy rates following treatment with CC is shown in Table I. It reveals an ovulation rate of 73% and a pregnancy rate of 36% in data from 5268 patients. To the data on pregnancy, abortion and live birth rates in Table I, I have added similar data from four further studies dealing with the pregnancies and their outcome. From a grand total of 4054 pregnancies, ~20% terminated in a spontaneous abortion and almost all the rest in a live birth (Table II). From this collection of results, it was very difficult to estimate the multiple pregnancy rate which was rarely addressed. However, from the available numbers and from other review publications (Scialli et al., 1986), this is estimated to be 8–13%, the vast majority being twin pregnancies. Obviously a collection of results of this nature comprises very heterogeneous series but nevertheless gives a very good idea of the efficiency of CC for the induction of ovulation, and is generally consistent from series to series.

From these data, a theoretical projection of the results of CC induction of ovulation in 100 women starting treatment has been made (Table III, column 2), concluding that 25 of these 100 will succeed in delivering a singleton, healthy baby. Although CC will restore ovulation in ~73% of patients, it will result in pregnancy in only ~36%. The 27% of anovulatory women with normal FSH concentrations who do not respond at all are considered to be ‘CC resistant’.

**Failure to ovulate**

Inability of CC to induce ovulation is more likely in patients who are obese, insulin resistant and hyperandrogenic compared with those who do respond (Imani et al., 1998). This careful prospective study pinpointed a high free androgen index as the best predictor of non-response to CC. Although it is virtually impossible to predict who will respond to which dose of CC, if at all (Imani et al., 2002), body weight has been found to be an impeding factor. Overweight women respond less well (Polson et al., 1989) and the dose of CC needed to induce ovulation correlates with body weight (Lobo et al., 1982).

**Failure to conceive**

It is frustrating that the restoration of ovulation by CC does not produce a much higher pregnancy rate. This discrepancy between ovulation and pregnancy rates (only 50% of those who ovulate will conceive) may be partly explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH. While the depression of the cervical mucus, occurring in ~15% of patients, may be overcome by performing IUI

<p>| Table I. Results of treatment with clomiphene citrate: a collection of published data |
|----------------------------------|-----------|----------|----------|----------|-----------|</p>
<table>
<thead>
<tr>
<th>No of patients</th>
<th>Ovulation</th>
<th>Pregnancy</th>
<th>Abortion</th>
<th>Live birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGregor et al. (1968)</td>
<td>4098</td>
<td>2869</td>
<td>1393</td>
<td>279</td>
</tr>
<tr>
<td>Garcia et al. (1977)</td>
<td>159</td>
<td>130</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>Gysler et al. (1982)</td>
<td>428</td>
<td>364</td>
<td>184</td>
<td>24</td>
</tr>
<tr>
<td>Hammond (1984)</td>
<td>159</td>
<td>137</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Kousta et al. (1997)</td>
<td>128</td>
<td>113</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>Messinis and Milingos (1998)</td>
<td>55</td>
<td>51</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Imani et al. (2002)</td>
<td>259</td>
<td>194</td>
<td>111</td>
<td>11</td>
</tr>
<tr>
<td>Total (% of patients)</td>
<td>5268 (100)</td>
<td>3858 (73)</td>
<td>1909 (36)</td>
<td>357</td>
</tr>
</tbody>
</table>

| Table II. Outcome of pregnancy following treatment with clomiphene citrate |
|----------------------------------|-----------|----------|-----------|
| Total data from Table I | 1909 | 357 | 1550 |
| Ahlgren et al. (1976) | 159 | 18 | 141 |
| Adashi et al. (1979) | 86 | 23 | 62 |
| Correy et al. (1982) | 156 | 16 | 140 |
| Dickey et al. (1996) | 1744 | 413 | 1331 |
| Total (% of pregnancies) | 4054 (100) | 827 (20.4) | 3224 (79.5) |

Results from four further publications dealing with the outcome of pregnancy are added to data from Table I.
suppression of endometrial proliferation, unrelated to dose or duration of treatment but apparently idiosyncratic, indicates a poor prognosis for conception if the endometrial thickness on ultrasound scanning does not reach 8 mm at ovulation. In our experience, the prevalence of endometrial suppression is one in every 6–7 patients and, if noted in the first cycle of treatment with CC, it will almost certainly be seen in repeated cycles in the same woman. There is little point in persisting after even one cycle, and a step-up to other forms of ovulation induction is recommended.

The main action of CC, indirectly stimulating GnRH secretion, not only increases the desired FSH release but also produces an undesirable increase in LH concentrations. This increase in LH, whose basal level is often already high in women with PCOS, may compromise pregnancy rates in those receiving CC (Homburg et al., 1988a; Shoham et al., 1990). We have demonstrated that pre-treatment with micronized progesterone is capable of modulating LH pulsatility, reducing LH concentrations and inducing a more favourable environment for ovulation induction with CC (Homburg et al., 1988b). This treatment initiated a response to CC and yielded consequent pregnancies in previous non-responders to CC.

A course of six ovulatory cycles is usually sufficient to know whether pregnancy will be achieved using CC before moving on to more complex treatment as it has been reported that 71–87.5% of the pregnancies achieved with CC occur within the first three cycles of treatment (Gysler et al., 1982; Kousta et al., 1997; Imani et al., 1998). From our own very large (unpublished) database, we noted that no further pregnancies at all were obtained with CC following seven ovulatory cycles, although others have found that a further 5–6% do conceive between treatment cycle number 6 and 12 (Kousta et al., 1997). In properly selected patients with no other causes of infertility, the cumulative conception rate may reach as high as 60% after six cycles (Messinis and Milingos, 1998).

### Outcome of pregnancies

CC blocks the negative feedback mechanism which the eventually rising estradiol levels would normally invoke to reduce discharge of FSH. The continued flow of FSH encourages multiple follicle development which is relatively common. The risk of multiple gestation is therefore increased and is estimated at ~8–13% (Schenker et al., 1981; Scialli et al., 1986; Kousta et al., 1997; Eijkmans et al., 2003). The vast majority of these are twin pregnancies, but the risk may be reduced considerably by ultrasound monitoring and withholding HCG, IUI or intercourse if more than two follicles >15 mm diameter are seen (Homburg and Insler, 2002).

Although there are conflicting reports, the prevalence of spontaneous abortion of a clinical pregnancy following CC therapy has a reported mean of ~20% (McGregor et al., 1968; Dickey et al., 1996; Kousta et al., 1997), slightly higher than the 12–15% of clinically recognized spontaneous miscarriages in the normal population (Warburton and Fraser, 1964; Wentz and Cartwright, 1988). Although a very controversial issue due to a lack of evidence for a direct causal relationship, several investigators have found in retrospective studies that an increased prevalence of miscarriage is associated with high serum LH concentrations in the mid-follicular phase (Homburg et al., 1988b; Regan et al., 1990). The increased prevalence of miscarriage following CC therapy may, in part, be due to the high LH values induced immediately after this treatment. Kousta et al. (1997) found significantly higher LH levels post-CC in those who miscarried compared with those who delivered, and just 37% of the ongoing pregnancy group had LH >10 IU/l compared with 75% of those who aborted. We postulated that this is due to a premature maturation of the oocyte caused by high LH concentrations and resulting in an ‘aged’ oocyte which is difficult to fertilize and, if fertilized, is more likely to abort (Homburg et al., 1988a).

The prevalence of congenital abnormalities following CC treatment is no different from those seen in spontaneously conceived pregnancies (Correy et al., 1982).

### Side effects

Unpleasant side effects of CC are few and far between, although some women will complain of hot flushes and some of nausea. CC is, however, usually very well tolerated. While mild ovarian enlargement is relatively common, in almost 40 years of practice, I have never seen a full blown ovarian hyperstimulation syndrome (OHSS) as a result of CC treatment. Occasional cyst formation can be treated conservatively.

### Monitoring

CC is often given without any observation of the events of the cycle. However, monitoring of the CC-treated cycle by ultrasound evaluation of follicular growth and endometrial thickness on days 12–14 of the cycle is justified by the identification of those who are not responding or have depressed endometrial thickness, and is helpful in the timing
of natural intercourse or IUI. Confirmation, or otherwise, of ovulation can be obtained with estimation of the progesterone concentration in the assumed mid-luteal phase which is preferable to a basal body temperature chart. The added expense of careful monitoring is neutralized by the prevention of protracted periods of possibly ineffective therapy and delay in the inception of more efficient treatment.

**Adjuvants**

In order to improve the outcome of treatment with CC, several adjuvants to CC treatment have been suggested. A correctly timed ovulation-triggering dose of HCG (5000–10000 IU) is only theoretically warranted when the reason for a non-ovulatory response is that the LH surge is delayed or absent despite the presence of a well developed follicle. Although the routine addition of HCG at mid-cycle seems to add little to the improvement of conception rates (Agarwal and Buyalos, 1995), we have found it very useful, if given when an ultrasonically demonstrated leading follicle attains a diameter of 19–24 mm, for the timing of intercourse or IUI. The addition of dexamethazone as an adjunct to CC therapy in a dose of 0.5 mg at bedtime is said to suppress adrenal androgen secretion and induce responsiveness to CC in previous non-responders, mostly hyperandrogenic women with PCOS and elevated concentrations of dehydroepiandrosterone sulphate (DHEAS) (Daly et al., 1984). However, glucocorticoid steroid therapy often induces side effects including increased appetite and weight gain, and should probably be reserved for women who have congenital adrenal hyperplasia as a cause for their anovulation.

**Indications other than ovulation induction**

CC has also been employed for ovarian stimulation in ovulating women, mainly for idiopathic (unexplained) infertility and often combined with IUI. The rationale is presumably that CC overcomes a subtle defect in ovulatory function or increases the number of mature follicles so increasing the likelihood of pregnancy (Guzick et al., 1998). Here the success rate has been, understandably, notably less than in anovulatory women. In a collection of data on the efficacy of treatment for unexplained infertility, the use of CC alone produced a pregnancy rate of 5.6% per cycle and CC combined with IUI 8.3% per cycle (Guzick et al., 1998). While this is significantly superior to timed intercourse alone, it should be remembered that the baseline level from merely expectant treatment in these cases ranges from 1.3 to 4.1%.

In IVF, co-treatment with CC and gonadotrophins has enjoyed brief periods of popularity as an attempt to decrease costs of medications. However, this co-treatment never seemed to achieve the same results as the more favoured protocols of today, and this combination is rarely used now.

**Possible alternatives to clomiphene**

Three possible contenders have emerged as the replacement of CC as primary, first-line treatment for oligo- or anovulation and WHO group II infertility: (i) metformin; (ii) aromatase inhibitors; and (iii) recombinant FSH.

**Metformin**

PCOS is associated with ~75% of all cases of anovulatory infertility. Insulin is of prime importance in the pathophysiology of PCOS. The rate of insulin resistance in women with PCOS is 50–80%, which means that a very large proportion of cases of anovulation and infertility is associated with hyperinsulinaemia and that the lowering of insulin concentrations provides a new therapeutic pathway. Weight loss in the obese is a very effective way of achieving this, but weight loss and lifestyle change often seem to be insurmountable objects for the obese patient with PCOS and are not applicable for lean patients. The alternative possibility of using insulin-lowering drugs (particularly metformin) is presently undergoing a thorough examination.

Metformin is an oral biguanide, well established for the treatment of hyperglycaemia, that does not cause hypoglycaemia in normoglycaemic patients. It is an insulin sensitizer which reduces insulin secretion and, consequently, lowers circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism. Importantly, it also seems to have a direct action on ovarian theca cells to decrease androgen production (Attia et al., 2001; Mansfield et al., 2003).

Metformin is taken orally in a dose of 1500–2500 mg. About 15–20% of patients may suffer from gastrointestinal side effects. The indications for giving metformin to women with anovulatory PCOS have become progressively wider as it seems to be difficult to predict which individuals will respond well with this medication (Fleming et al., 2002). The difficulties of accurately measuring insulin sensitivity in all PCOS patients and the suggestion that metformin may also be effective in non-hyperinsulinaemic subjects (Baillargeon et al., 2004) has encouraged ‘blanket’ treatment with metformin of all PCOS patients in many centres. The wisdom of this strategy awaits ratification or, as noted by Harborne et al. (2003) in a critical review of the literature, clinical practice is ahead of the evidence.

Here I will consider the best available evidence for the treatment of anovulatory infertility with metformin, both as a single agent and in combination with CC.

**Metformin alone.** There are now a large number of studies published on the effect of metformin in a dose of 1500–2550 mg/day in women with PCOS. The majority of these studies have demonstrated a significant improvement in insulin concentrations, insulin sensitivity and serum androgen concentrations, accompanied by decreased LH and increased sex hormone-binding globulin (SHBG) concentrations (Nestler et al., 2002). The restoration of regular menstrual cycles by metformin has been reported in a large majority of published series, and the reinstatement of ovulation occurred in 78–96% of patients (Velazquez et al., 1997; Nestler et al., 1998, Nestler et al., 2002; Moghetti et al., 2000; Ibanez et al., 2001; Fleming et al., 2002; Harborne et al., 2003; Baillargeon et al., 2004; Kashyap et al., 2004). Fleming et al. (2002), in the largest randomized placebo-controlled trial,
demonstrated a significantly increased frequency of ovulation with metformin (850 mg, twice a day) compared with placebo in a group of 92 oligomenorrheic women with PCOS. Although significant, the increased frequency of ovulation was modest [relative risk (RR) 1.29, 95% confidence interval (CI) 1.00–1.66]. In a systematic review (Kashyap et al., 2004), metformin was found to be 50% better than placebo for ovulation induction in infertile PCOS patients (RR 1.5, CI 1.13–1.99). In a meta-analysis (Lord et al., 2003), the superiority of metformin over placebo in inducing ovulation was emphatic [odds ratio (OR) 3.88, CI 2.25–6.69].

Interpretation of studies evaluating the effect of metformin as a sole agent for the induction of ovulation is made difficult by their heterogeneity as regards selection of patients whether hyperinsulinaemic, hyperandrogenaemic, diagnosis of PCOS, obese or slim, duration of metformin administration and dose, etc. Although it now seems obvious that metformin is superior to placebo in inducing ovulation, none of the studies was powered to assess pregnancy as an outcome.

Comparisons of CC with metformin as single agents for the induction of ovulation and attainment of pregnancy must therefore await the results of a sufficiently powered randomized controlled trial (RCT), directly comparing the two. **Metformin + CC.** The combination of CC and metformin, at the present state of knowledge, seems to be more effective than either CC or metformin given alone regarding both ovulation induction and pregnancy. This would seem to be the case reflected by two meta-analyses (Lord et al., 2003; Kashyap et al., 2004). In the first, metformin + CC was found to be more effective than CC alone in achieving ovulation (OR 4.41, CI 2.37–8.22) and also demonstrated a significant effect for the combination on pregnancy rates (OR 4.4, CI 1.96–9.85). In the second, metformin + CC was 3–4 times superior to CC alone for both ovulation induction and achievement of pregnancy. However, caution is advised as numbers are small in both these analyses, and some recently conducted large RCTs comparing metformin + CC versus CC alone are not demonstrating any significant differences. As these results have not yet been officially published, judgment should be reserved, but initial enthusiasm will probably be dampened.

It is, however, interesting to examine the individual published studies. In an RCT performed on CC-resistant infertile patients with PCOS, compared with CC and placebo, metformin markedly improved ovulation and pregnancy rates when combined with CC (Vandermolen et al., 2001). In a large study, 46 anovulatory obese women with PCOS who did not ovulate on metformin or placebo for 35 days were given 50 mg of CC daily for 5 days while continuing metformin or placebo. Of those on metformin, 19 of 21 ovulated compared with two of 25 on placebo (Nestler et al., 1998). In an interesting RCT, CC-resistant women with PCOS received either metformin for 6 months and then CC, or HMG alone for ovulation induction (George et al., 2003). In this small study, as metformin + CC was equally as effective as HMG, less expensive and more convenient, it was suggested as an intermediary step for CC-resistant patients, worth trying before resorting to HMG.

**Safety.** The evidence is so far encouraging concerning the efficiency and safety of metformin as a single agent or in combination with CC for induction of ovulation in women with hyperinsulinaemic PCOS (Homburg, 2002). In addition, metformin seems to be safe when continued throughout pregnancy, having no increase in congenital abnormalities, teratogenicity or adverse effect on infant development (Glueck et al., 2002). Preliminary data even suggest that this strategy can significantly decrease the high miscarriage rate usually associated with PCOS and reduce the incidence of gestational diabetes, pre-eclampsia and fetal macrosomia (Glueck et al., 2002; Jacobowicz et al., 2002). The apparent lack of teratogenicity of metformin has earned it a B classification and, hopefully, these apparently beneficial effects of metformin given throughout pregnancy will be confirmed by future studies.

The glitazones, notably rosiglitazone and pioglitazone, which also have the property of lowering insulin concentrations, are also under investigation for similar indications. It is too premature to judge their effect on ovulation induction for WHO group II anovulation. A positive effect for rosiglitazone when used alone and more so when combined with CC was demonstrated for ovulation induction in women with PCOS (Ghaezeri et al., 2003). In women with PCOS but normal insulin sensitivity, metformin proved more efficient than rosiglitazone in restoring ovulation (Baillargeon et al., 2004).

**Aromatase inhibitors**

A compound capable of inducing ovulation but devoid of the adverse anti-estrogen effects of CC could be a serious challenger for the role of first-line treatment for WHO group II oligo/anovulation.

Aromatase inhibitors are non-steroidal compounds that suppress estrogen biosynthesis by blocking the action of the enzyme aromatase which converts androstenedione and testosterone to estrogens. Letrozole, the most widely used aromatase inhibitor, has mainly been employed for the treatment of post-menopausal women with advanced breast cancer. It is given orally in a dose of 2.5–5 mg/day and is almost free of side effects.

It has been hypothesized, in particular by Mitwally and Casper (2001), that the efficient estrogen-lowering properties of the aromatase inhibitors could be utilized to temporarily release the hypothalamus from the negative feedback effect of estrogen so inducing an increased discharge of FSH. Although the final pathway, the sought-after discharge of FSH, is common to both aromatase inhibitors and CC, their mechanism of action is obviously very different and this would seem to confer several advantages to aromatase inhibitors for the induction of ovulation.

Unlike CC, which blockades and depletes estrogen receptors, aromatase inhibitors have no effect on estrogen receptors. Aromatase inhibitors should, therefore, not have any deleterious effect on cervical mucus or endometrium, quite frequently a side effect of CC which interferes with the attainment of a pregnancy during ovulation induction therapy and is probably the main reason for the gap between
ovulation and pregnancy rates. This can theoretically be avoided when aromatase inhibitors are used for the same purpose.

With aromatase inhibitors, estrogen production is eventually advanced by the induced FSH discharge but, in contrast to the use of CC, the hypothalamus is able to respond to the estrogen feedback with a negative feedback mechanism. This will modulate an overzealous discharge of FSH which in turn is more likely to result in a monofollicular ovulation with moderate estrogen concentrations. This is all the more poignant as aromatase inhibitors have a much shorter half-life (~2 days) than CC. This confers an additional theoretical advantage to aromatase inhibitors as the prevalence of multiple pregnancies could therefore be expected to be less than that witnessed with the use of CC for ovulation induction.

The solid, evidence-based data that are needed to convert these hypothetical advantages into demonstrable practical expression are, at the time of writing, still thin on the ground. However, much groundwork to examine the use of the aromatase inhibitor letrozole in reproductive medicine has come from the team of Casper and Mitwally.

In a preliminary trial, 12 anovulatory PCOS patients and 10 ovulatory patients were given letrozole 2.5 mg/day on days 3–7 of the cycle. Endometrial thickness, which had been severely depressed in previous CC-treated cycles, was markedly improved by letrozole which was as efficient as CC for ovulation induction. A direct comparison of letrozole with 50 mg/day of CC in ovulatory women in an RCT showed similar effects on stimulation of folliculogenesis, whilst endometrial thickness was maintained by letrozole despite much lower estradiol concentrations than with CC at mid-cycle (Fisher et al., 2002).

A comparison of a very large number of cycles for timed intercourse or IUI included natural (423), CC- (994) and letrozole- (167) treated cycles (Mitwally and Casper, 2003). The pregnancy rate with letrozole was more than twice that in natural or CC-stimulated cycles, while both multiple pregnancy and abortion rates were significantly lower in letrozole compared with CC cycles. A small pilot study comparing CC (100 mg/day) with letrozole in IUI cycles demonstrated significantly less estradiol and fewer follicles developing in the letrozole cycles (Fatemi et al., 2003).

The conclusion for the moment is that, although some groundwork has been done, before aromatase inhibitors can be regarded as possible replacements for CC for the first-line treatment of anovulatory infertility, some solid, evidence-based medicine is badly needed.

The use of aromatase inhibitors should theoretically result in an accumulation of androgens whose conversion to estrogens is being blocked. This would, theoretically, be an unwanted by-product, especially for women with PCOS who already have an excessive production of androgens. However, paradoxically, this may be a further advantage as androgens may have a stimulatory role in early follicular growth by augmenting follicular FSH receptor expression and therefore amplifying FSH effects (Weil et al., 1999). This may explain the relative success of combined letrozole and FSH for ovarian stimulation in improving the response to FSH, reported in two studies. The first (Mitwally and Casper, 2002) is a report in which a group of poor responders to FSH for IUI were given co-treatment with letrozole, 2.5 mg/day from day 3 to day 7 of the cycle. A lower FSH dose and a significantly higher number of mature follicles were achieved with the combined treatment. These preliminary findings were confirmed in a large series, albeit retrospective and non-randomized, comparing stimulation with FSH alone (145 cycles) or the combined therapy (60 cycles) (Healey et al., 2003). The addition of letrozole to gonadotrophin treatment again decreased the dose of gonadotrophins and increased the number of pre-ovulatory follicles. Prospective, randomized trials are needed to verify these interesting findings.

A subgroup of infertile women have been found to express high levels of aromatase P450 in the endometrium, and this was associated with poor IVF outcomes (Brosens et al., 2004). This raises the interesting question of whether letrozole or anastrozole could alleviate this situation and improve results.

Many other questions regarding the use of aromatase inhibitors in the treatment of infertility still remain (de Ziegler, 2003). Trials with aromatase inhibitors have, reasonably, mimicked treatment with CC, being administered on days 3–7 of the cycle. Would treatment beyond day 7 interfere with the estradiol rise induced by rising FSH concentrations and have a deleterious effect on the endometrium and oocyte quality? In his commentary, de Ziegler (2003) also questions the timing of aromatase inhibitor administration when the intention is to enhance the sensitivity to FSH receptors by increasing follicular androgen content. Would it not be more logical to prime with aromatase inhibitors before exposure to FSH? Further, although the dose of 2.5 mg of letrozole is standard for the treatment of breast cancer, should the same dose be used for the treatment of infertility? Biljan et al. (2002), for example, found that a daily dose of 5 mg/day produced more mature follicles apparently by further extending the FSH window.

It is a little too early to enthuse optimistically about the chances of letrozole and anastrozole conquering the fertility market, but now the initial pilot studies have been completed, I believe that there is enough there to encourage serious trials for this potentially valuable, simple and inoffensive treatment.

**Low-dose FSH**

The third possible alternative to CC as first-line treatment for WHO group II infertility is low-dose FSH. In contrast to the conventional gonadotrophin regimen for treating this group of patients, in particular those with PCOS, the low-dose protocol is designed to attain and maintain follicular development, ideally one dominant follicle, without exceeding the FSH threshold requirement of the ovary (Polson et al., 1987). Now in common use, the common complications of conventional gonadotrophin therapy have been severely reduced. With low-dose FSH, multiple pregnancy rates should not exceed 6% and OHSS is almost completely eliminated, while acceptable pregnancy rates are achieved (Table IV). A consistent rate of 70% of monofollicular...
Until criteria for HCG administration are reached. Follicular development is initiated, that dose is maintained necessary after 14 days and then at weekly intervals. Once incremental dose rises (25–37.5 IU) on the starting dose if a low starting dose (usually 50–75 IU of FSH) with small ovulation in achieved in these cycles (Homburg and Howles, 1999).

Updated from Homburg and Howles (1999).

- OHSS 0.14%
- No. of cycles 1556
- FSH, step-up FSH

Results of treatment of clomiphene-resistant patients with low-dose FSH are a feasible proposition.

| Table IV. Results of treatment of clomiphene-resistant patients with low dose, step-up FSH |
| No. of patients | 841 |
| No. of cycles | 1556 |
| Pregnancies (% patients) | 320 (38%) |
| Fecundity/cycle | 20% |
| Uni-ovulation | 70% |
| OHSS | 0.14% |
| Multiple pregnancies | 5.7% |

These are almost identical figures to those that had been pre-conceived on CC and 40% of those who would be CC resistant would also conceive on low-dose FSH, 45 of 100 starters could expect a singleton live birth and three a multiple pregnancy (Table III, column 4). If this supposition is confirmed, then the treatment–conception interval would be considerably reduced and efficiency greatly increased by eliminating the time and the need for monitoring and treatment costs of 3–12 cycles of CC therapy. Although costs of medication and patient comfort obviously differ, these may well be negated by a much more efficient first-line treatment.

One, single centre, randomized trial has tested this hypothesis (Lopez et al., 2004) but, unfortunately, the size of the groups (38 patients in each arm) did not allow firm conclusions. Nevertheless, the RR and 95% confidence intervals were 1.78 (0.92–3.54) for pregnancy rate per woman and 1.83 (0.79–4.40) for live births per woman in favour of FSH. These are almost identical figures to those that had been predicted, prior to this study, in Table IV, based on assumptions and previous results (1.72 for pregnancy rates and 1.80 for live birth rates in favour of FSH).

A sufficiently powered, multicentre, multinational trial is now well under way to compare CC with low-dose FSH as first-line treatment for women with anovulatory infertility associated with PCOS. Combined with a cost-efficiency assessment, it will tell us whether replacing CC with low-dose FSH is a feasible proposition.

**Other possible first-line therapies**

The use of pulsatile GnRH for the treatment of anovulatory (WHO group II) infertility has largely been abandoned. Although a normal pattern of pulsatile release of GnRH can be superimposed on the abnormal pattern found in these women, results regarding pregnancy rates have been impeded by obesity, hyperandrogenaemia and a high miscarriage rate, although multiple pregnancies could be largely avoided (Homburg et al., 1989).

Laparoscopic ovarian drilling, although a very viable second- or third-line therapy for anovulation associated with PCOS, especially in normal weight patients with a high LH concentration, has not seriously been considered as an alternative to CC as first-line treatment.

**Conclusions**

The possibility of replacing CC as first-line treatment for anovulatory eu-estrogenic infertility with either metformin, aromatase inhibitors or low-dose FSH still needs to be substantiated. RCTs are underway to examine all these possibilities, all of which are theoretically well based. At least until the publication of the results of these trials, CC will remain the first-line treatment for eu-estrogenic anovulatory infertility although, in my humble opinion, aromatase inhibitors and/or low-dose FSH therapy may well take its place in the next few years.

**References**


Warburton D and Fraser FC (1964) On the probability that a woman who has had a spontaneous abortion will abort in subsequent pregnancies. J Obstet Gynaecol Br Commonw 68,784–789.


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