Ovulation induction: a mini review

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Ovulation induction is the method for treating anovulatory infertility. For patients with hypogonadotrophic hypogonadism, the treatment involves administration of both FSH and LH, while HCG is injected for follicle rupture. Pulsatile GnRH has the same effectiveness as gonadotrophins and the advantage of the low multiple pregnancy rate. In polycystic ovary syndrome (PCOS), the first treatment choice is clomiphene citrate. With this drug, in properly selected patients, the cumulative pregnancy rate approaches that of normal women. Low-dose protocols of FSH are the second line of treatment, effective in inducing monofollicular development. Laparoscopic ovarian drilling can be an alternative but not as a first choice treatment in clomiphene-resistant patients. Other treatments, such as pulsatile GnRH and GnRH agonists, are hardly used today in PCOS. However, in obese women with PCOS, weight loss and exercise should be recommended as the first line of therapy. Newer agents including aromatase inhibitors and insulin sensitizers, although promising, need further evaluation.

Key words: gonadotrophins/hypogonadotrophic hypogonadism/ovulation induction/polycystic ovary syndrome/pulsatile GnRH

Introduction

Ovulation induction is restricted to patients with anovulatory infertility. This Mini Review will provide a survey of the methods used for ovulation induction ranking them according to the frequency of their application in daily practice. Patients eligible for ovulation induction belong either to World Health Organization (WHO) group I, which includes women with hypogonadotrophic hypogonadism, or to WHO group II, in which the vast majority of the women have polycystic ovary syndrome (PCOS). Other patients who benefit from medical treatment include those with hyperprolactinaemia, but they are excluded from this article.

Hypogonadotrophic hypogonadism

Patients in this category have amenorrhoea and do not show withdrawal bleeding after treatment with progesterone. Because of the limited production of FSH and LH from the pituitary gland, administration of these two gonadotrophins would be regarded as substitution therapy, while the use of GnRH in a pulsatile way constitutes another alternative for ovulation induction.

Gonadotrophins

Gonadotrophins used for ovulation induction in women are either urinary or recombinant products. Urinary derivatives (HMG) contain 75 IU FSH and 75 IU LH per ampoule, a combination that is necessary for hypogonadotrophic-hypogonadic women, while the recombinant preparations contain either FSH or LH activity. Treatment of such women with recombinant FSH (rFSH) alone stimulates follicular growth, but results in inadequate estrogen production (Schoot et al., 1992). A dose-finding study has demonstrated that 75 IU of LH is the optimum amount that needs to be combined with 150 IU rFSH (European Recombinant Human LH Study Group, 1998), although activity of LH can be also obtained by the addition of HCG (50 IU/day) as has been shown in a woman with secondary amenorrhoea (Filicori et al., 1999). With the latter approach, however, a dose-finding study for HCG is required in order to eliminate the risk of ovarian hyperstimulation and multiple pregnancy.

Ovulation induction aims at the selection of a single follicle that will be able to reach the pre-ovulatory size and rupture. At the same time, estradiol (E2) levels and endometrial thickness should be appropriate. To avoid multiple follicular development, the ovarian sensitivity to FSH (FSH threshold) should be identified and the lowest effective dose should be used. Treatment is individualized and monitored by serum E2 measurements and ultrasound scans of the ovaries. The starting dose of HMG, although not fixed due to differences in body mass, is usually 150 IU/day given for ≥5 days and, unless a substantial increase in E2 concentrations occurs, the dose is increased by 33% every 5 days (Brown et al., 1969).

The criteria for the administration of HCG include serum E2 concentrations ≥2000 pmol/l (Messinis et al., 1988). Nevertheless, due to the high multiple pregnancy rate (Bergquist et al., 1983a), an ideal approach would be an E2 level ≥1000 pmol/l with only one follicle >16 mm in diameter by ultrasound. The ovulatory dose of HCG is 5000–10 000 IU i.m. for the urinary and 250–500 µg s.c. for the recombinant preparation. Extra HCG is administered during the luteal phase
(Townsend et al., 1966; Brown et al., 1969; Bergquist et al., 1983b), which decreases the incidence of luteal phase defects and increases the pregnancy rate significantly (Messinis et al., 1988).

Clinical results of HMG/HCG therapy in women with hypogonadotrophic hypogonadism have not been reported during the last few years. It is difficult to extrapolate results from the earlier studies since in several of them women had anovulation owing to various aetiologies, while there were differences in study intensity, data expression and methods of monitoring. Results from five studies with hypogonadotrophic women are summarized in Table I. The success rate (women who took home at least one living baby) was almost 56% (Oelsner et al., 1978; Messinis et al., 1988; Dale et al., 1989). A collection of published results in 14 studies from 1966 to 1984 showed considerable variation in the percentage of patients who conceived (16–78%) (Table I), but patients with PCOS and/or hyperprolactinaemia were also included (Hamilton-Fairley and Franks, 1990). However, cumulative pregnancy rates of 89% after six treatment cycles and 72% after seven ovulatory cycles have been reported in two small series of hypogonadotrophic women (Fluker et al., 1994; Tadokoro et al., 1997). The reported incidence of severe ovarian hyperstimulation syndrome (OHSS) is very low (∼1%) (Oelsner et al., 1978; Fluker et al., 1994), but the multiple pregnancy rate is high (up to 30%) even with the inclusion of the scans in the monitoring process (Martin et al., 1993; Tadokoro et al., 1997).

The use of recombinant gonadotrophins has given similar results. When a starting dose of 150 IU rFSH was combined with 75 IU rLH in a group of 38 hypogonadotrophic patients, a pregnancy rate of 18% per started cycle was obtained with the dose of 375 IU was able to sustain follicle maturation after selection by FSH (225 IU) plus LH (375 IU) (Balasch and Fabregues, 2003). On the other hand, in accordance with an ‘LH ceiling’ effect, increased doses of LH might be used to develop a schedule for optimizing treatment with FSH in ovulation induction programmes (Loumaye et al., 2003). This means that when excessive amounts of LH are given during the second half of the follicular phase, a spectrum of events from complete follicular growth arrest to impaired ability to luteinize can occur (Loumaye et al., 2003).

### Table 1. Summary of published results in anovulatory women treated with human gonadotrophins

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of women</th>
<th>No. of cycles</th>
<th>Pregnancy rate/cycle (%)</th>
<th>Patients who conceived (%)</th>
<th>Multiple pregnancy rate (%)</th>
<th>Miscarriage rate (%)</th>
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<tbody>
<tr>
<td>(A) Hypogonadotrophic–hypogonadic women</td>
<td></td>
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<tr>
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<td>156</td>
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<td>Gemzell (1975)</td>
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<td>78</td>
<td>26.9</td>
<td>87</td>
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<tr>
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<td>249</td>
<td>27</td>
<td>55.2</td>
<td>38</td>
<td>22.8</td>
</tr>
<tr>
<td>Schwartz et al. (1980)</td>
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<td>63.3</td>
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<td>167</td>
<td>23.3</td>
<td>66</td>
<td>31</td>
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<tr>
<td>(B) Patients with other pathology were not excluded</td>
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<td>–</td>
<td>–</td>
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<td>31.1</td>
<td>71.7</td>
<td>36</td>
<td>10.7</td>
</tr>
</tbody>
</table>

*Multiple birth rate.
cycles (Homburg et al., 1989; Martin et al., 1993). The miscarriage rate appears similar to that in the normal population (Filicori et al., 1991; Homburg and Insler, 2002), but higher rates have been shown in smaller series (Martin et al., 1993).

An advantage of GnRH treatment over the use of gonadotrophins is the low rate of multiple pregnancy (Shoham et al., 1990; Martin et al., 1993), although a rate as high as 17.4% (20 out of 116 pregnancies) has been reported (Braat et al., 1989). The rate is higher during the first treatment cycle (Homburg et al., 1989), especially if higher GnRH doses are used and HCG is injected to trigger ovulation (Braat et al., 1989). Nevertheless, there is no evidence that HCG is required, while lower doses of GnRH are recommended during the first treatment cycle. Disadvantages of this mode of treatment include the need for the pump to be connected to the body all day for a considerable number of days, the necessity to refill the pump at frequent intervals and the possible reactions of the skin at the site of injection, particularly during the s.c. administration. Finally, the formation of antibodies against the synthetic GnRH seems to be a rare possibility (Shoham et al., 1990).

**PCOS**

In patients with PCOS, ovulation is induced either with the use of pharmaceutical compounds, or the application of other methods, such as weight loss and exercise, or laparoscopic ovarian drilling. Antiestrogens and human gonadotrophins are common agents, while pulsatile GnRH and GnRH agonists are hardly used today. Recently, GnRH antagonists have been introduced, while insulin sensitizers and aromatase inhibitors are also currently employed.

**Antiestrogens**

The two main antiestrogens used for ovulation induction are clomiphene citrate and tamoxifen. Although tamoxifen is as effective as clomiphene in inducing ovulation, its use is very limited (Messinis and Nillius, 1982; Boostanfar et al., 2001). Clomiphene, by blocking the negative feedback effect of E₂, stimulates the secretion of gonadotrophins from the pituitary gland. This leads to follicle selection and estrogen production with the final occurrence of a midcycle LH surge (Shaw, 1976). Therefore, in patients treated with clomiphene there is no need to administer exogenous HCG for follicle rupture, unless ovulation does not occur despite the development of large follicles (Agarwal and Buyalos, 1995).

Clomiphene is given for 5 days following the onset of a spontaneous or a progestagen-induced period, starting any time from days 2, 3, 4 or 5, as there is no difference in the outcome between these time-points (Wu and Winkel, 1989). The recommended starting dose is 50 mg/day, as almost half of the pregnancies are achieved with this dose (Gysler et al., 1982). A simplified monitoring, when treatment starts on day 2, involves measurement of serum progesterone values on days 21 and 28 of the cycle (Messinis and Milingos, 1997). Unless normal ovulation occurs (progesterone ≥ 30 nmol/l), the dose is increased in each of the next cycles by 50 mg/day up to a maximum dose of 150 mg/day. As yet, no studies have investigated whether more intensive monitoring, such as by ultrasound, is needed during ovulation induction with clomiphene, unless intrauterine insemination (IUI) is also applied.

Clomiphene induces ovulation at a high rate (70–90%) and, although the pregnancy rate is lower (30–40%) (Messinis, 2002), in properly selected patients with no other causes of infertility it can be as high as 60% after six cycles (Messinis and Milingos, 1997) and 97% after 10 cycles (Hammond et al., 1983). The reasons for the relatively low pregnancy rate are not clear, but may be related to the high LH levels, the antiestrogenic effects of clomiphene and to adverse effects on the oocytes (Wramsby et al., 1987; Homburg et al., 1988). It should be also noted that the earlier studies did not use uniform criteria for patient classification. Although high in earlier studies, the miscarriage rate in the most recent studies is similar to that in the normal population (Hammond et al., 1983; Messinis and Milingos, 1997). Multiple pregnancy rate is 6–8%, mainly twins (Adashi, 1996), which is a rather low rate as compared to classical gonadotrophin regimens (Wang and Gemzell, 1980), but similar to that in the low-dose FSH protocols (Franks and White, 2002). OHSS is a rare event (Adashi, 1996).

About 10–30% of the patients will be ‘clomiphene resistant’ i.e. will remain anovulatory after 6 months of treatment (Hughes et al., 2000). Obese women with hyperandrogenaemia are less likely to respond to clomiphene (Imani et al., 1998). When pregnancy is not achieved despite ovulation, the term ‘clomiphene failure’ is used. Important parameters for prediction of conception include patient age and cycle history (Imani et al., 1999). In clomiphene resistance, some advocate a treatment period of >5 days with this drug (O’Herlihy et al., 1981; Fluker et al., 1996). Combinations with other drugs have been also used. Beneficial effects have been reported during co-administration of clomiphene with dexamethasone (Trott et al., 1996) or when clomiphene was preceded by the oral contraceptive pill (Branigan and Estes, 1999). Finally, in very few women with extremely sensitive ovaries, the starting dose of clomiphene may have to be as low as 25 mg/day.

**Human gonadotrophins**

Human gonadotrophins are used as a second line treatment for ovulation induction in PCOS, i.e. in cases of clomiphene resistance or failure. When a starting dose of 150 IU/day HMG was given to patients belonging to WHO group II, the success rate was significantly lower and the rate of the OHSS significantly higher than in patients belonging to WHO group I (Wang and Gemzell, 1980; Messinis et al., 1988). For these reasons, protocols involving chronic low doses of HMG were introduced in the early 1980s (Kamrava et al., 1982). An established method for patients with PCOS is the ‘low-dose step-up’ protocol, which involves a starting FSH dose of 75 IU/day given for 7–14 days (Polson et al., 1987). Treatment starts any time, provided low ovarian activity is present and is monitored by ultrasound scans. Unless a follicle ≥ 12 mm is seen in the ovaries, the dose is increased by 37.5 IU/day at weekly intervals up to a maximum dose of 225 IU/day. HCG is injected when the leading follicle is ≥ 18 mm in diameter with no other follicles > 14 mm, although in these patients the positive feedback mechanism is intact (Messinis and Milingos, 1997).
In a survey of 1391 cycles, 69% were uniovulatory with a very low incidence of OHSS (1.4%) and a multiple pregnancy rate of only 5.7% (Homburg and Howles, 1999). Similar results were obtained in a single centre including 1117 treatment cycles (Table II) (Franks and White, 2002). No differences in the outcome have been found between the use of HMG and either purified or rFSH (Sagle et al., 1991; Coelingh-Bennink et al., 1998). A starting FSH dose of 52.5 IU/day is as effective as 75 IU, with a lower miscarriage rate (20 versus 35%) (White et al., 1996). According to Franks and White, (2002), such a low starting dose (50 IU) can be the maximum daily amount of FSH required for the induction of single follicle ovulation in the majority of the cycles. However, in their series, obese patients had a poor result with an ongoing pregnancy rate of <10%, suggesting that the starting dose of FSH should be adjusted according to the body mass index (BMI) and the response in previous stimulated cycles (Franks and White, 2002).

Another approach to the treatment of PCOS patients with gonadotrophins is the ‘step-down’ protocol. The most recent modification of this protocol involves the administration of FSH at a starting dose of 150 IU/day until a follicle ≥10 mm is seen by ultrasound (Macklon and Fauser, 2002). The dose is then decreased by 37.5 IU/day and further to 75 IU/day 3 days later and is kept constant until the day of HCG administration. Monofollicular development has been found in 56% of the cycles with a pregnancy rate of 16% per treated cycle and a cumulative pregnancy rate of 47% (van Santbrink et al., 1995). These results have been considered comparable to those obtained with the step-up protocol, but with the step-down approach a shorter duration of treatment and a smaller total dose of FSH have been reported (van Santbrink et al., 1995). Such conclusions, however, are based on a comparison between data from different studies (Macklon and Fauser, 2002) and not between groups in the same study.

So far, the results from only small prospective comparative studies are conflicting (Table III). In one of them (Christin-Matrai and Hugues, 2003), a shorter duration of treatment was found in the step-down protocol, but monofollicular development was significantly lower (32 versus 68.2%) and multifollicular development (36 versus 4.7%), serum E₂ concentrations and the hyperstimulation rate (11 versus 2.25%) were significantly higher than in the step-up protocol. In a smaller study, the step-down was found to be superior to the step-up protocol regarding monofollicular development (Balasch et al., 2001), in agreement with a previous prospective randomized trial (van Santbrink and Fauser, 1997). However, in the study by Balasch et al. (2001), a modified step-down protocol was used, with a loading dose of 300 IU FSH followed by 3 days free of treatment and then by 75 IU FSH daily that was thereafter individually adjusted using a step-up protocol.

Recently, in an effort to optimize treatment with the step-down protocol, van Santbrink and Fauser (2003) have adopted a modified approach. In a first cycle, they applied a dose-finding low-dose step-up protocol in order to determine the FSH threshold for ovarian response (Imani et al., 2002a). Then, in the second cycle, the step-down protocol was used and the starting daily dose was the effective response dose of the first cycle increased by 37.5 IU. Comparing the first step-up and the second step-down cycle (Table III), no significant differences were found in terms of monofollicular development and pregnancy rates. There is no doubt that large prospective randomized studies are required to compare the two protocols.

When consecutive treatments with clomiphene as a first choice and gonadotrophins as a second choice were considered a continuous process, a cumulative pregnancy rate of 90% after 12 months in properly selected anovulatory PCOS patients (Messinis and Milingsos, 1997) and a singleton live birth rate of 50% after 12 months and 71% after 24 months of treatment in women belonging to WHO group II were obtained (Eijkemans et al., 2003). It is suggested that it might be worth attempting ovulation induction in PCOS for a period of >6 months. Parameters that can predict the outcome of treatment with clomiphene or human gonadotrophins are free androgen index, BMI, amenorrhoea, ovarian volume and age (Imani et al., 1998, 2002b; van Santbrink et al., 2002). Low responders have characteristics of more severe PCOS, such as obesity, hyperandrogenism and polycystic ovaries as compared with good responders (Mulders et al., 2003).

Finally, an approach to ovulation induction might be the development of protocols with the use of various FSH isoforms (Baird, 2001). Although this is theoretical at the moment, it may be feasible in the future based on the fact that some FSH isoforms, such as FSH-CTP and FSH-N2, have already been produced (Duijkers et al., 2002; Klein et al., 2003).

### Pulsatile GnRH

The outcome of treatment with pulsatile GnRH in patients with PCOS is rather poor, so that this treatment is hardly used today. In a large series of 292 women with anovulatory infertility, who were treated with pulsatile GnRH during 600 consecutive cycles, it was shown that the highest rates of ovulation (83%) and pregnancy (22%) were achieved in women with primary hypogonadotrophic hypogonadism and the lowest in the group of women with PCOS (65 and 13% respectively), while the miscarriage rate was higher in the PCOS group (45 versus 19%) (Filicori et al., 1994). However, when the pregnancy rate was corrected for the ovulatory cycles, the results were similar in the two groups (20 versus 23%). Also, an improvement in the outcome in terms of ovulation rate was seen in the PCOS group when the treatment with pulsatile GnRH was preceded by the administration of a GnRH agonist for 6–8 weeks (Filicori et al., 1994). It is suggested from these results that in women with PCOS the main problem during treatment with pulsatile

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**Table II.** Results of low-dose FSH treatment in a single centre using the step-up protocol in anovulatory women with polycystic ovary syndrome (Franks and White, 2002)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>269</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>1117</td>
</tr>
<tr>
<td>No. of ovulatory cycles</td>
<td>810 (73)</td>
</tr>
<tr>
<td>No. of uniovulatory cycles</td>
<td>585 (72)</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>129 (48)</td>
</tr>
<tr>
<td>No. of multiple pregnancies</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
GnRH is the difficulty of selecting a follicle for growth (Messinis and Milingos, 1997). Factors that may determine which patients will remain anovulatory during treatment with pulsatile GnRH include high BMI, hyperinsulinaemia, insulin resistance and increased androgen concentrations, while those who fail to become pregnant have higher free testosterone concentrations (Gill et al., 2001).

GnRH agonists

The idea behind the use of GnRH agonists in patients with PCOS was to suppress basal LH values when elevated and, therefore, to alleviate any adverse effects that high tonic LH might have on the outcome of treatment. Although earlier data regarding ovulation and pregnancy rates using the GnRH agonists in FSH-treated cycles were encouraging (Fleming et al., 1985; Dodson et al., 1987), subsequent studies demonstrated an increased risk of OHSS (Homburg et al., 1990; Scheele et al., 1993, van der Meer et al., 1996). This was evident even when a starting dose of FSH as low as 37.5 IU/day was used (Buckler et al., 1993). A retrospective analysis of data has shown that during treatment with FSH the use of a GnRH agonist leads to a significant reduction in the miscarriage rate (Homburg et al., 1993), but this has not been confirmed prospectively (Clifford et al., 1996). For these reasons and the fact that basal LH can also decline during treatment with FSH alone (Kamrava et al., 1982; Sagle et al., 1991; Messinis and Milingos, 1997), GnRH agonists are not recommended as a treatment of choice for ovulation induction in PCOS.

GnRH antagonists

The use of GnRH antagonists in combination with gonadotrophins for ovulation induction in PCOS has until now been very limited. There is only one report of two cases (Cardone, 2003) as well as one study, in which 18 patients were divided into two groups based on the degree of insulin resistance (Elkind-Hirsch et al., 2003). In that study, after pretreatment with the oral contraceptive pill, treatment started with the antagonist alone, while FSH was added when the LH concentrations had been suppressed. Patients with insulin resistance were obese and required a longer period of stimulation and a higher number of FSH vials. Nevertheless, there was no significant difference between the two groups in terms of pregnancy rate and ongoing pregnancy rate after IUI (Elkind-Hirsch et al., 2003). Large prospective studies are required to examine whether the GnRH antagonists in combination with FSH can have an advantage over the use of FSH alone.

Weight loss and exercise

It has been shown that loss of weight in obese patients with PCOS improves substantially hyperandrogenaemia and insulin sensitivity, decreases LH concentrations and restores normal fertility (Kiddy et al., 1992; Hoeger, 2001). Even a 5–10% reduction in body weight has been shown to be quite successful (Pasquali et al., 1989; Kiddy et al., 1992). In one study, in which 13 obese clomiphene-resistant women with PCOS lost 6 kg, ovulation was evident within a few weeks in 12 of them (Clark et al., 1995). Apart from diet, exercise is also important in improving insulin sensitivity. In a series of 67 obese anovulatory women, who after 6 months of lifestyle changes lost on average 10.2 kg/m², 60 (89.5%) resumed spontaneous ovulation.

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**Table III.** Prospective randomized trials comparing the step-up with the step-down protocol in anovulatory patients with polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Cycles</th>
<th>Mean days of treatment</th>
<th>Monofollicular development</th>
<th>Pregnancy rate/cycle (%)</th>
<th>Multiple pregnancy rate (%)</th>
<th>OHSS (%)</th>
<th>Miscarriage rate (%)</th>
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<tr>
<td>Step-up</td>
<td>19</td>
<td>19</td>
<td>18*</td>
<td>56*</td>
<td>13†</td>
<td>0</td>
<td>33.3</td>
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<tr>
<td>Step-down</td>
<td>18</td>
<td>18</td>
<td>9*</td>
<td>88*</td>
<td>31†</td>
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<td>Christin-Maitre et al. (2003)</td>
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<td>15.2</td>
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<td>15.8</td>
<td>25</td>
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<td>–</td>
<td>NR</td>
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<td>Step-down¶</td>
<td>61</td>
<td>–</td>
<td>NR</td>
<td>50d</td>
<td>16</td>
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<td>0</td>
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*Single follicle ≥16 mm.
*bSingle follicle >17 mm.
*cSingle follicle >16 mm.
*dSingle follicle >14 mm.
*Median value.
†Ongoing pregnancies.
‡A combination of step-down and step-up.
§Initial dose-finding step-up cycle.
¶Second step-down induction cycle (patients not becoming pregnant in the initial cycle).
OHSS = ovarian hyperstimulation syndrome; NR = not reported.
and 52 (77.6%) conceived (18 of them spontaneously) (Clark et al., 1998). Since weight loss and exercise are inexpensive, they should be recommended as the first choice for the management of obese women with PCOS. For those women who do not comply, clomiphene, as discussed above, should be the first line of treatment for ovulation induction.

**Insulin sensitizers**

Insulin-sensitizing agents that have already been tested in PCOS include metformin, an oral biguanide, the thiazolidinediones troglitazone, rosiglitazone and pioglitazone, and d-chiro-inositol, a mediator of insulin action (Cheang and Nestler, 2004). Individual studies have shown that metformin alone can restore regular menstrual cycles and reinstate ovulation in 25–95% of cases (Costello and Eden, 2003). The variability in the results among the different studies is probably related to differences in the design, the dosages used, the duration of treatment and the primary end-points.

A recent meta-analysis (Lord et al., 2003) of 13 randomized controlled trials has shown that metformin treatment increased the ovulation rate 3.88 times (95% confidence interval (CI): 2.25–6.69) compared to placebo or no treatment (seven trials) and 4.41 times (95% CI: 2.37–8.22) when it was administered in combination with clomiphene as compared to clomiphene alone (three trials). In clomiphene-resistant women (two trials), a significantly higher ovulation rate for metformin plus clomiphene treatment as compared to clomiphene plus placebo has been shown [odds ratio (OR): 9.34, 95% CI: 3.97–21.97]. In three trials, a significant increase in clinical pregnancy rate for metformin plus clomiphene as compared to clomiphene alone was also found (OR: 4.4, 95% CI: 1.96–9.85).

Similarly, a more recent meta-analysis (Kashyap et al., 2004) of eight randomized controlled trials has shown that metformin plus clomiphene may be superior to clomiphene alone or with placebo regarding ovulation (relative risk: 3.04, 95% CI: 1.77–5.24) and pregnancy rates (relative risk: 3.65, 95% CI: 1.11–11.99). A benefit of metformin versus placebo in pregnancy rate was not demonstrated, although all trials were underpowered to assess pregnancy as an outcome. However, in contrast to the concept of utilizing insulin sensitizers in PCOS, a recent randomized controlled trial (Baillargeon et al., 2004) in insulin-sensitive non-obese patients has shown that metformin, and to a lesser extent rosiglitazone, significantly improved ovulation as compared to placebo, while the combination of the two agents was not more potent (ovulations per subject in 6 months: metformin 3.3; rosiglitazone 2.4; combination 3.4; placebo 0.4). That study suggested either that clinical criteria for assessing insulin resistance are insensitive or that the ovaries of some women with PCOS over-respond to normal insulin levels.

Apart from metformin, other insulin sensitizers have been also used, but experience is limited. A small, observational, non-blinded study approaching the issue of PCOS women not optimally responsive to metformin has suggested that pioglitazone added to metformin could improve menstrual regularity as well as hormonal and metabolic milieu (Glueck et al., 2003). One of the thiazolidinediones, troglitazone, although effective in women with PCOS in increasing spontaneous ovulation as well as ovulation induced by clomiphene (Azziz et al., 2001), is no longer available due to severe hepatic side-effects. On the other hand, in a double-blind, placebo-controlled trial, rosiglitazone enhanced both spontaneous and clomiphene-induced ovulation in overweight and obese women with PCOS (Ghaezeri et al., 2003), while a recent randomized controlled trial has shown that pioglitazone increased ovulation rate as compared to placebo (Brettenthaler et al., 2004). Finally, d-chiro-inositol has also been found to improve ovulation rate as compared to placebo (Nestler et al., 1999).

Safety issues advocate metformin utilization since it appears to be safe during pregnancy. In addition, metformin reduces first trimester spontaneous miscarriage rate and the incidence of gestational diabetes (Glueck et al., 2001, 2002, 2004). However, rosiglitazone and pioglitazone should not be continued after conception.

With current knowledge, metformin can be administered to clomiphene-resistant PCOS women. Nevertheless, it is too early to know whether metformin should be used as a first line treatment in PCOS, replacing clomiphene, since there have been no randomized controlled trials to compare directly ovulation, pregnancy and live birth rates between metformin and clomiphene. The combination treatment of metformin and FSH in ovulation induction has not been thoroughly studied (Costello and Eden, 2003).

Despite the fact that metformin and the other insulin-sensitizing drugs are not licensed for ovulation induction, strategies for this implementation have already been published (Nestler et al., 2002; Cheang and Nestler, 2004). In the UK, the National Institute of Clinical Excellence (NICE) (2004) guidelines support the use of metformin in association with clomiphene in anovulatory infertility. An ongoing multicentre study in the USA [Pregnancy in Polycystic Ovary Syndrome Study (PPCOS)], aiming to determine the optimal pharmacological regimen for PCOS, will probably contribute towards the licensing of metformin for treatment of women with PCOS.

**Aromatase inhibitors**

Aromatase inhibitors are agents that suppress the biosynthesis of estrogen and, therefore, reduce the negative feedback effect on the hypothalamic–pituitary system. This results in increased secretion of FSH that can lead to follicle selection and maturation. The third generation compound, letrozole, has been recently used for ovulation induction in anovulatory PCOS women resistant to clomiphene or with inadequate endometrial thickness during clomiphene treatment. At a daily dose of 2.5 mg from days 3 to 7 of the menstrual cycle, ovulation was seen in nine of 12 cycles (75%) treated with letrozole and only in eight of 18 cycles (44.4%) treated with clomiphene, while endometrium on the day of HCG administration was thicker in the letrozole group (Mitwally and Casper, 2001). Pregnancy occurred in three patients treated with letrozole (25%). This compound was recently found to be more effective thanastrozole, another aromatase inhibitor, regarding ovulation rate (84.4 versus 60%) and pregnancy rate per cycle (18.8 versus 9.7%) in 22 anovulatory women with PCOS (Al-Omari et al., 2004).
2694). Before the onset of letrozole administration, early pregnancy should be ruled out, since information regarding possible teratogenic effects of this drug is limited (Casper, 2003). However, normal babies have been delivered so far. Large prospective randomized studies are required to investigate the effectiveness of aromatase inhibitors in ovulation induction.

**Laparoscopic ovarian drilling**

Surgical treatment of anovulation in PCOS patients by wedge resection of the ovaries has been abandoned due to serious adverse effects, such as adhesions and substantial tissue loss. Advances in laparoscopic techniques have rekindled interest in surgical induction of ovulation. Laparoscopic ovarian drilling (LOD) introduced by Gjönnaess (1984) restored ovulation in 92% of patients with a pregnancy rate of 69%. Ovarian drilling is performed by using a pointed monopolar or bipolar electrode or with laser energy, although considerable variation exists in the techniques used. Besides the usual laparoscopic access, the procedure has been also carried out by transvaginal hydro-laparoscopy (Fernandez et al., 2001). The mechanism of action of LOD is unclear, but it seems that destruction of the androgen-producing ovarian stroma plays a key role.

So far, many studies have suggested that LOD may provide an alternative treatment option for clomiphene-resistant PCOS patients. However, a percentage of patients as high as 43% may not ovulate spontaneously after LOD and this is related to the duration of infertility, BMI and free androgen index (Amer et al., 2004). A 9 year longitudinal follow-up study showed that about one-third of patients experienced regular menstrual cycles (Amer et al., 2002).

A meta-analysis (Farquhar et al., 2001) of six randomized controlled trials showed that the ongoing pregnancy rate 6–12 months after ovarian drilling compared to 3–6 cycles of ovulation induction with gonadotrophins was similar. Multiple pregnancy rate was reduced after LOD in four trials where there was a direct comparison with gonadotrophins (OR: 0.16, 95% CI: 0.03–0.98), but there was no difference in the miscarriage rate. Similarly, a recent randomized controlled trial (Bayram et al., 2004) including 168 clomiphene-resistant PCOS patients showed a 12 month cumulative ongoing pregnancy rate of 67% whether the women were treated with LOD combined with subsequent treatments of clomiphene and rFSH (in the case of persistent anovulation) or treated with rFSH alone. However, the major difference between the LOD strategy study arm (LOD alone, or LOD plus clomiphene, or LOD plus clomiphene plus rFSH) and the rFSH arm was the significantly higher multiple pregnancy rate found with FSH alone (one of 83 versus nine of 85 patients). A recent randomized controlled trial (Palomba et al., 2004) has shown that metformin treatment for 6 months in overweight anovulatory infertile clomiphene-resistant PCOS patients induced an ovulation rate comparable to LOD (54.8 versus 55.1%), but significantly higher pregnancy (18.6 versus 13.4%) and live birth (82.1 versus 64.5%) rates and a lower miscarriage rate (15.4 versus 29.0%).

The use of LOD, apart from the usual risks of laparoscopy and general anaesthesia, may be related to periadnexal adhesion formation in 19–43% of patients (Gurgan and Urman, 1994; Saravelos and Li, 1996) and theoretically to premature ovarian failure. Current evidence, although documenting the therapeutic efficacy of LOD, does not justify its use as a first line treatment for clomiphene-resistant PCOS patients. On the other hand, it is early to conclude whether insulin sensitizers can replace surgery in PCOS despite the fact that ovulation and pregnancy rates seem to be similar for both procedures (Pirwany and Tulandi, 2003).

**Conclusions**

Great progress in ovulation induction has been achieved during the last 20 years. Although conventional regimens are still in use, new modalities have been developed that may open up new methods in the treatment of anovulation. Infertility authorities have provided some strategies, but due to the limited experience with some methods there is no consensus regarding an algorithm for use in daily practice. Although some methods, such as weight loss, clomiphene citrate and gonadotrophins are widely recommended, others such as ovarian drilling, insulin sensitizers and aromatase inhibitors need to be further evaluated. It may be that until a consensus is reached, treatment should be individualized.

**References**


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