Future use of clomiphene in ovarian stimulation

Will clomiphene persist in the 21st century?

Basil C. Tarlatzis1,2,3 and Grigoris Grimbizis1,2

1First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki and 2Infertility and IVF Center, ‘Geniki Kliniki’, Thessaloniki, Greece
3To whom correspondence should be addressed at: Infertility and IVF Center, Geniki Kliniki, 2 Gravias Street, Thessaloniki 546 45, Greece

Although the first in-vitro fertilization (IVF) pregnancy was established in a natural cycle by laparoscopic retrieval of the oocyte after accurate timing of the ovulation (Steptoe and Edwards, 1978), this natural-cycle IVF was soon replaced by IVF in stimulated cycles in order to bring multiple follicles to maturity and hence to increase the chances of conception. Clomiphene citrate was the first agent used for ovarian stimulation in 1981 (Trounson et al., 1981), but it was later replaced by gonadotrophins in order to increase further the number of fertilizable eggs (Lauf er et al., 1984). Furthermore, the implementation of gonadotrophin-releasing hormone (GnRH) agonists in various ovarian stimulation protocols was thought to be a significant improvement since it allowed an even more intense ovarian response and a better control over the stimulation process by avoiding interference from endogenous gonadotrophin secretion (Smitz et al., 1992; Tarlatzis and Grimbizis, 1997a).

However, the question is how many eggs are necessary to offer the best chances for conception in an IVF cycle, without increasing the risks for the patient. It is well known that the development of a high number of oocytes during the ovarian stimulation process and, subsequently, of many more embryos than required for a fresh embryo transfer does not really increase the success rate of the embryo transfer itself, but only makes embryos available for cryopreservation. However, only the good quality embryos can be stored; some of them are destroyed during the freezing–thawing process and the rest do not have the same implantation capacity as the fresh ones. It seems, therefore, that after a certain point, a significant part of the biological material obtained by ovarian stimulation is lost. Moreover, apart from the financial cost of cryopreservation, the medical and ethical problems raised are also important: how many years can these embryos be stored safely and what is the future of embryos abandoned by their owners? Is it ethically right to destroy them, as it was recently done in the UK? On the other hand, controlled ovarian hyperstimulation does not entail any risk-free process. It may lead to ovarian hyperstimulation syndrome (OHSS) which is a potentially life-threatening condition and its occurrence depends on the number of follicles developed; the higher the number of follicles the greater the possibility of OHSS.

From the early years of IVF, improvements in the culture conditions have increased the quality of embryos obtained and their implantation capacity. In centres with good laboratory conditions, the selective replacement of two good quality embryos in young patients offers the same chances of conception as the transfer of up to four embryos without increasing the multiple pregnancy rates (Staes en et al., 1992). Moreover, with recombinant DNA technology and highly defined cell-culture techniques, recombinant gonadotrophins are now available in the market. Although, their introduction appears to offer a significant improvement in the safety and efficacy of ovarian stimulation (Devroey and Grimbizis, 1997; Tarlatzis and Bili, 1997), their administration is also accompanied with an important increase in the cost of treatment.

In view of these developments and experience gained over the years, it is probably the right time to ask ourselves some crucial questions: What should be our ovarian stimulation strategy? What are the goals of an ‘ideal’ stimulated cycle? Is it time to think once again about our stimulation protocols? Can we simplify them?

Clomiphene citrate only?

Clomiphene citrate has been used in the treatment of anovulatory infertility since 1962. Clomiphene citrate is a racemic mixture of zucloclomiphen (cis-isomer with mild oestrogenic and anti-oestrogenic activity) and enclomiphene (trans-isomer with only anti-oestrogenic activity) and has both oestrogenic and anti-oestrogenic properties (Glasier, 1990; Dickey and Holtkamp, 1996). Acting as an anti-oestrogen on the central nervous system (CNS), it increases the pulse frequency and concentration of follicle stimulating hormone (FSH) and luteinizing hormone (LH), giving a moderate gonadotrophin stimulus to the ovary and, thus, overcoming ovulatory disturbances and increasing the cohort of follicles reaching ovulation (Dickey and Holtkamp, 1996; Kousta et al., 1997). Its administration in anovulatory patients is accompanied by a ~50% increase in endogenous FSH (Adashi, 1984), an ovulation rate of 60–85% and a pregnancy rate of 30–40% (Dickey and Holtkamp, 1996; Kousta et al., 1997).

However, ovarian stimulation for the various assisted reproduction technologies (ART) is applied in order to increase the cohort of follicles reaching maturation and not to restore ovulatory disturbances. The experience with clomiphene citrate in these cases seems to be limited (Adashi, 1996), although it was the first agent used (Trounson et al., 1981). Hence, it is not well-documented whether there is a dose-dependent increase in the number of follicles after clomiphene citrate administration in normo-ovulatory women. Shalev et al. (1989), in patients with regular cycles, reported an increase in the average number of developed follicles >15 mm in diameter, from 1.0
for 50 mg of clomiphene citrate to 2.4 for 200 mg of clomiphene citrate and a concomitant increase in the number of follicles 8–14 mm in diameter, from 0.4 for 50 mg of clomiphene citrate to 2.1 for 200 mg of CC. Other investigators also confirmed the increase in the number of pre-ovulatory follicles by giving clomiphene citrate to normo-ovulatory women (Marrs et al., 1984; Glasier et al., 1989). Therefore, the questions raised are: can we go further and what is the ideal dose? Furthermore, what is the quality of this smaller cohort of oocytes? Is their synchronization better, and what about their fertilization rates? Do we need as high a number of eggs as in conventional regimes?

On the other hand, it is not unusual for women with polycystic ovaries to be stimulated for IVF (Tarlatzis and Grimbizis, 1997b). It is well known that these patients have an inherent tendency for a multi-follicular response to the administration of ovulatory agents and this is why they are the most frequent candidates for the development of OHSS. Is the use of clomiphene citrate a better alternative to the conventional regimes in this group of patients, in order to avoid the consequences of an extreme ovarian response? And in this case, what is the dose required to obtain a satisfactory number of oocytes? Furthermore, age is one of the most well documented parameters affecting ovarian response to stimulation. If clomiphene citrate has any use in ovarian stimulation, one could not possibly ignore the role of age in selecting the proper patient population. It seems, therefore, that there may be some groups of patients where clomiphene citrate could be specifically indicated and the identification of these target groups would be very interesting.

Another well known problem is the anti-oestrogenic action of clomiphene citrate on the endometrium. Endometrial thickness seems to be impaired in clomiphene citrate cycles, with or without gonadotrophins (Yagel et al., 1984; Inoedemhe et al., 1987; Eden et al., 1989; Randall and Templeton, 1991; Rogers et al., 1991). This could interfere with endometrial receptivity and conception. Dickey and Holtkamp (1996) reported that in patients stimulated with clomiphene citrate for intrauterine insemination (IUI) no pregnancy was observed when the endometrial thickness was <6 mm on the day of human chorionic gonadotrophin (HCG) administration, while all preclinical abortions occurred when endometrial thickness was 6–8 mm. Are there any methods to overcome this problem?

Starting clomiphene citrate early on day 2 or 3 of the cycle (Dickey and Holtkamp, 1996), adding oestradiol in the follicular phase (Yagel et al., 1992), delaying administration of HCG (Dickey et al., 1993) or administering gonadotrophins for some days following clomiphene citrate have been proposed as alternatives. However, their relative effectiveness needs to be examined.

**Clomiphene citrate plus gonadotrophins: any alternative?**

If clomiphene citrate alone cannot offer a satisfactory solution, its concomitant or sequential use with gonadotrophins could be another option. The addition of gonadotrophins in clomiphene citrate cycles is accompanied by a more intense ovarian response than the use of clomiphene citrate alone, and a lower need for gonadotrophins compared with the GnRH agonist/gonadotrophin regimes as well as a better endometrial pattern and receptivity.

However, what happens to the endogenous LH secretion in clomiphene citrate cycles, with or without gonadotrophins? Although in cycles where clomiphene citrate is given alone attention should be paid to inject HCG at the appropriate time before the spontaneous LH surge, premature LH surges do not occur since the hypothalamic–pituitary–ovarian axis is not bypassed but simply augmented. On the other hand, during ovarian stimulation with clomiphene citrate and/or gonadotrophins the exaggerated oestradiol concentrations due to the multifollicular response provoke high LH concentrations during the follicular phase or untimely spontaneous LH surge. This may lead to cycle cancellation or impaired oocyte quality (Tarlatzis, 1992).

Although GnRH agonists offer an effective solution to avoid the interference of endogenous LH secretion, they cannot be combined with CC. Administration of GnRH agonists early in the cycle, as it is done in the various stimulation protocols, suppresses pituitary function which is a prerequisite for clomiphene citrate action. On the contrary, their administration in the late follicular phase could be compatible with clomiphene citrate use, but it can not effectively suppress LH secretion. So, could the use of GnRH antagonists be a solution?

The administration of GnRH antagonists is associated with an immediate suppression of LH endogenous secretion (Reissmann et al., 1995). Hence, if the main problem in clomiphene citrate/gonadotrophins stimulated cycles is the premature LH surges, the injection of GnRH antagonists could possibly prevent them. Nevertheless, the questions to be answered are whether there are any advantages in this practice and if this is more cost-effective?

**Clomiphene citrate: a safe option?**

The use of clomiphene citrate is the ‘chemical’, as opposed to the hormonal option in ovarian stimulation: a synthetic compound rather than a naturally occurring hormone is used to induce ovulation (Adashi, 1996). The side-effects that may accompany its use include hot flushes, central nervous symptoms (nervousness, mood swings, sleeplessness, headaches, dizziness, visual disturbances) and, rarely, psychiatric symptoms. However, the side-effects are dose-dependent and are completely reversible once the medication is stopped (Siedentopf et al., 1997).

Apart from its effectiveness and tolerance, the safety of its administration is an important issue. The impact of inadvertent clomiphene citrate administration during early pregnancy remains uncertain, but it can be avoided by testing to rule out gestation before clomiphene citrate use. However, the potential adverse effects of the usual preconceptional clomiphene citrate administration are important. It is known that the active isomeric form of clomiphene citrate racemic mixture is enclophene (trans-isomer), which has a short half-life. On the other hand, the inactive zuclomiphene (cis-isomer) has
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The introduction of clomiphene citrate, in the early 1960s, represented a major therapeutic breakthrough in the management of anovulatory infertility. On the other hand, its role in controlled ovarian hyperstimulation for various ART remains limited, since it has been replaced by gonadotrophins with or without GnRH agonists due to their comparative effectiveness to induce a more intense ovarian response. However, the developments and the accumulated experience over the last years may allow a re-evaluation of our stimulation strategy. Hence, it seems that there are some groups of patients where clomiphene citrate could be used alone to induce ovarian stimulation for ART. Furthermore, the introduction of GnRH antagonists could offer an alternative to the use of clomiphene citrate with gonadotrophins alone by preventing untimely LH rises. Although the current racemic mixture of clomiphene citrate seems to be safe, a monoisomeric preparation of clomiphene citrate containing only the active enclomiphene could be another option worth investigating.

Concluding remarks

The overall clinical experience until now indicates that the use of clomiphene citrate is associated with an incidence of birth defects similar to that observed in the general population (Adashi, 1996; Kousta et al., 1997). However, apart from the safety of the present racemic form, a monoisomeric preparation of clomiphene citrate containing only the active enclomiphene would be another alternative. Its use may be as effective as the racemic form and safer due to the shorter half-life (Adashi, 1996).

References


Clomiphene citrate or gonadotrophins for induction of ovulation?

Henk J.Out1 and Herjan J.T.Coeilngh Bennink

NV Organon, PO Box 20, 5340 BH Oss, The Netherlands

1To whom correspondence should be addressed

In the year 2000, nearly 40 years will have passed after the first description of a ‘chemically’ induced ovulation with clomiphene citrate (Greenblatt, 1961). This created great enthusiasm because it made it possible to induce follicular development without using pituitary extracts. Since then, its popularity has increased tremendously. In the US, the number of prescriptions for clomiphene citrate has increased from 390 000 in 1973 to 731 000 in 1991 or 14.6 cycles per thousand
women aged 15–44 years, which accounts for the largest proportion of the market of fertility drugs during this time period (Wysowski, 1993).

**Disadvantages of clomiphene citrate**

The cause for the popularity of this drug is obvious: it is easy to administer (orally), no close monitoring is needed, it is inexpensive. Its role and great value have been reviewed recently (Dickey and Holtkamp, 1996; Kousta et al., 1997). However, based on a recent review of the latest literature on clomiphene citrate (Out and Coelingh Bennink, 1998), we would like to challenge the role of this compound in the next decade.

We believe that clomiphene citrate has the following disadvantages. Firstly, the compound is a mixture of two ‘isomers’, Zu and En, with different pharmacokinetic and pharmacodynamic profiles. The active isomer is the En isomer, and the relatively inactive Zu isomer has a very long half-life. As a result, the half-life of clomiphene citrate is estimated to be 5–7 days and, therefore, accumulation of clomiphene citrate takes place every 28–40 days when a trial of clomiphene citrate is given (Clark and Markarevich, 1982).

Secondly, there are no published data on the multiple-dose pharmacokinetics of clomiphene citrate. In view of experiences with the structurally related compound diethylstilboestrol, this is amazing. The assessment of the impact of chemical agents circulating during early embryonic life is a major issue nowadays for pharmaceutical companies active in the field of reproductive medicines. This has never been investigated for clomiphene citrate. It is therefore highly unlikely that clomiphene citrate would be allowed to enter the market if registration were sought nowadays.

Thirdly, because many couples have been treated successfully during the last 30 years with clomiphene citrate and, hence, extensive experience has been gained, its use is considered to be safe. However, this conclusion is empirical, rather than the result of properly designed follow-up studies (Greenland and Ackerman, 1995). Negative side-effects therefore should not be excluded, especially in view of the extensive teratogenic and toxic effects that have been described in animals. In addition, because clomiphene citrate displays a tendency for prolonged nuclear receptor occupancy (Clark and Markarevich, 1982), in contrast to native oestrogens which are known to clear the cell within 24 h, a progressive nuclear accumulation upon repetitive administration may occur, possibly leading to lingering blastocystotoxic or teratogenic effects (Adashi, 1993).

Fourthly, the mechanism of action of clomiphene citrate is unclear and is a mixture of effects on the hypothalamus, pituitary and the ovaries. The following variables can be mentioned that will influence the final activity of clomiphene citrate: (i) the En/Zu-isomer ratio in the tablet; (ii) the En/Zu isomer ratio in the circulation; (iii) individual metabolism; (iv) route of administration; (v) dosage regimen; (vi) administration period relative to the cycle, if present; (vii) cause of anovulation; (viii) oestrogenic state of the patient; (ix) carry-over effects from previous clomiphene citrate cycle(s); and (x) effects of unknown metabolites; (see also Mikkelson et al., 1986; Szutu et al., 1989; Rossmanith et al., 1994).

Finally, there is a well-known discrepancy between the high ovulation rates after clomiphene citrate treatment, and a relatively low pregnancy rate. The following causes for this phenomenon have been described in (recent) literature: (i) anti-oestrogenic effects on the endometrium (Gonen and Casper, 1990; Yeko et al., 1992; Bonhoff et al., 1993; Massai et al., 1993; Wolman et al., 1994; Hosie and Murphy, 1995); (ii) anti-oestrogenic effects on the cervical mucus (Acharya et al., 1993; Asaad et al., 1993; Gelety and Buyalos, 1993; Massai et al., 1993); (iii) decrease of uterine blood flow (Hsu et al., 1995); (iv) impairment of placental protein 14 synthesis (Johnson et al., 1993); (v) subclinical pregnancy loss (Bateman et al., 1992; Saunders et al., 1992; Shoham et al., 1990); (vi) effect on tubal transport (Whitelaw et al., 1970); and (vii) detrimental effects on oocyte (Oelsner et al., 1987; Wramsby et al., 1987).

**Alternative strategies**

It is generally agreed upon that the therapeutic effect of clomiphene citrate in anovulatory patients is related to the increase of circulating gonadotrophins, especially follicle-stimulating hormone (FSH) (Glaisier, 1990). Usually, an initial rise in the early follicular phase is followed by a decrease in the midfollicular phase (Randall and Templeton, 1991; Kettel et al., 1993). However, the luteinizing hormone (LH) rise after clomiphene citrate treatment is not needed and might contribute to low quality eggs and increased abortion rates (Balen et al., 1993). The overall increase of FSH concentrations during clomiphene citrate treatment seems to be 50–60% from baseline (Polson et al., 1989; Butzow et al., 1995).

If the goal of clomiphene citrate administration is, temporarily, to increase FSH concentrations, it seems to us that from a pharmacological point of view that it makes much more sense to administer recombinant FSH, nearly 100% pure and indistinguishable from pituitary FSH, instead of using a racemic mixture with accumulating isomers and an unknown mechanism of action. The unpopularity of gonadotrophins in the treatment of World Health Organization (WHO) group II women as experienced in the 1960s, is not justified nowadays using the low-dose protocols. In three recently reported studies, ovulation rates were 72–95%, and pregnancy rates 40–48% (Homburg et al., 1995; Balasch et al., 1996; White et al., 1996). In these studies, a multiple pregnancy rate of 0–15% was observed in more than 1500 cycles, and only one case of severe ovarian hyperstimulation syndrome (OHSS). It should therefore be questioned whether clomiphene-resistance should always be a precondition for gonadotrophin treatment.

In addition, it might be speculated that a single shot of 200–300 IU of recombinant FSH on day 3, 4, or 5 after a spontaneous or progestagen withdrawal bleeding will do the same job as clomiphene citrate. With baseline FSH concentrations of 0.11–1.63 IU/l, the mean peak FSH concentrations after a single-dose of 300 IU of recombinant FSH in eight gonadotrophin-deficient volunteers was 4.3 IU (SD 1.7) with a \( T_{\text{max}} \) of 27 ± 5 h (Mannaerts et al., 1993). In most women,
the return to baseline values was seen after 11 days. The 50–60% increase from baseline of FSH concentrations as seen in patients with polycystic ovaries after the administration of 100–150 mg of clomiphene citrate (Polson et al., 1989; Butzow et al., 1995) can therefore easily be achieved and it can be postulated that a single administration of exogenous FSH might induce the development of one or more ovulatory follicles.

Conclusions

Current ideas on the future of ovarian stimulation emphasize the need for optimization rather than maximization. In other words, lower number of eggs but with a higher quality will reliably be achieved using exogenous (recombinant) FSH.

References


A role for clomiphene in the 21st century?

Richard P. Dickey¹,³, Steven N. Taylor¹, Phillip H. Rye¹ and Peter Y. Lu¹,²

¹The Fertility Institute of New Orleans, New Orleans, Louisiana, and ²Louisiana State University School of Medicine, Department of Obstetrics and Gynecology, Section of Reproductive Endocrinology, New Orleans, LA, USA

The serendipitous discovery of the ability of clomiphene citrate to induce ovulation in oligomenorrheic women, by Holtkamp et al. (1960), and its introduction into general clinical practice by Greenblatt et al. (1961) and others (Kistner, 1962; Tyler et al., 1962; Vorys et al., 1964) in the 1960s, revolutionized the treatment of infertility. Clomiphene citrate alone was responsible for the majority of pregnancies resulting from medical induction of ovulation, before the use of human menopausal gonadotrophin (HMG) for ovulation stimulation in in-vitro fertilization (IVF) cycles and intrauterine insemination (IUI) cycles, since only the small portion of oligomenorrheic or amenorrheic patients who had pituitary or hypothalamic causes of amenorrhoea required HMG.

Many IVF programmes used clomiphene citrate, in combination with HMG, for ovulation induction before gonadotrophin-releasing hormone agonist (GnRHa) for down-regulation came into clinical practice. Advantages of combined HMG/clomiphene citrate regimens were a lowered requirement for HMG and higher luteal phase progesterone concentrations, which often made luteal support unnecessary. At the Fertility Institute of New Orleans, GnRHa was used, beginning in mid-1987. Results of IVF cycles from 1983 to 1990 are shown in Table I. Clinical pregnancies and birth rates per retrieval were higher when HMG and clomiphene citrate combinations were used than when HMG was used alone, and were similar to results with GnRHa/HMG. The principle advantage of GnRHa/HMG was that fewer cycles were cancelled because of the luteinizing hormone (LH) surge. There were also more eggs and embryos with GnRHa and HMG combinations, and there were larger numbers of cryopreserved embryos.

Used alone, clomiphene citrate is the first line of treatment for anovulation in patients with polycystic ovaries, because of fewer multiple pregnancies, lower cost, ease of administration, and less risk of hyperstimulation, compared with HMG or follicle stimulating hormone (FSH). Pregnancy rates following clomiphene citrate for 5 days are half those following HMG for 7 or more days, but can be improved by adding HMG or FSH for 3 days following clomiphene citrate (Dickey et al., 1993). Twins occur in ~10% of clomiphene citrate cycles, compared with 20% of HMG cycles and clomiphene citrate + HMG sequential cycles. For patients aged >40 years, clomiphene citrate alone results in pregnancy rates equal to HMG following IUI (Dickey et al., 1997). This may be because only patients with the best ovarian reserve will respond to clomiphene citrate (Scott et al., 1995). When used alone for ovulation induction in oligomenorrhoea patients, clomiphene citrate allows natural selection of the dominant follicle or follicles. Although fewer preovulatory follicles develop than in HMG or FSH cycles, they may contain oocytes of better individual quality than occur following HMG or FSH.

The reasons often given for not using clomiphene citrate include increased risk of abortion and ectopic pregnancy. The impression that clomiphene citrate increased the incidence of spontaneous abortion was the result of lack of data concerning the incidence of abortion in untreated infertility patients of similar age. In the initial clinical study of clomiphene citrate, the incidence of abortion in 2196 pregnancies was 17.2% (MacGregor et al., 1968), which was not different from that subsequently reported for the general population (Zinaman et al., 1996). Adashi et al. (1979) found a spontaneous abortion rate of 26% in patients with polycystic ovaries treated with clomiphene citrate, compared with 22% in patients treated by wedge resection. A prospective multi-hospital comparative study found an abortion rate of 14.8% in 1034 pregnancies conceived following clomiphene citrate, compared with 19.4% in 186 pregnancies conceived following HMG, and 13.9% in 29,000 spontaneous conceptions (Kurachi et al., 1983). In a large, modern series, the incidence of spontaneous abortion following 1744 clomiphene citrate pregnancies was 23.7%, compared with 36.4% in 107 pregnancies following HMG + IUI, and 20.4% in 3484 spontaneous pregnancies in infertile couples (Dickey et al., 1996). The only modern prospective study which showed an increase in abortions when clomiphene citrate was used (Johnson and Pearce, 1990) was later retracted (Johnson and Pearce, 1995), when it was discovered that the data had been fabricated. Although several investigators have suggested that clomiphene citrate adversely affects the quality of oocytes or conceptus based on in-vitro studies in mice (Laufer et al., 1983) or chromosome studies in humans (Boe and Boue, 1973), Dlugi et al. (1985) found that clomiphene citrate did not impair oocyte quality or reduce the implantation rate in IVF cycles.

The possibility that clomiphene citrate might prevent abortion, due to luteal insufficiency, has been proposed by several authors (Garcia et al., 1977; Hammond and Taubert, 1982; Rodin et al., 1994). This was confirmed in our clinic, where the spontaneous abortion rate in patients with a preconception diagnosis of luteal insufficiency was 18.3% in patients treated with clomiphene citrate, compared with the 23.6% in spontaneous pregnancies (Dickey et al., 1996).

Similar to the lack of comparative data for abortion, were reports suggesting that clomiphene citrate was associated with increased incidence of ectopic pregnancy following coitus (Powell-Phillips, 1979; Chaukin, 1982; Marchbanks et al., 1986) or IVF (Cohen et al., 1986; Snyder and del Castillo, 1993).


Future use of clomiphene in ovarian stimulation
### References


### Clomiphene in the 21st century

**Ioannis E. Messinis**¹ and Spyros D. Milingos

Department of Obstetrics and Gynaecology, Medical School, University of Thessalia, 22 Papakiriazi street, 41224 Larissa, Greece

¹To whom correspondence should be addressed

The anti-oestrogenic compound clomiphene citrate has been used extensively during the last 30 years for the treatment of anovulatory infertility, particularly in women with polycystic ovary syndrome (PCOS) (Messinis and Milingos, 1997). In the majority of these patients clomiphene induces monovulation, while the incidence of multiple pregnancy is very low. When normally ovulating women are treated with clomiphene during the early follicular phase of the cycle, multiple follicular development can occur (Marrs et al., 1984; Quigley et al., 1984a). Such a treatment combined with intrauterine insemination has been used as an empirical method for the treatment of either unexplained infertility or infertility

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**Table 1. In-vitro fertilization (IVF) outcome with clomiphene citrate (CC) or gonadotrophin-releasing hormone analogue (GnRHa)**

<table>
<thead>
<tr>
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<th>HMG + CC</th>
<th>HMG</th>
<th>GnRHa + HMG</th>
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</thead>
<tbody>
<tr>
<td><strong>Cycles started</strong></td>
<td>1063</td>
<td>395</td>
<td>689</td>
</tr>
<tr>
<td><strong>Percentage of cancelled cycles</strong></td>
<td>23.5</td>
<td>35.2</td>
<td>10.9</td>
</tr>
<tr>
<td><strong>Number of eggs per retrieval</strong></td>
<td>6.4</td>
<td>7.4</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>Number of embryos per retrieval</strong></td>
<td>3.9</td>
<td>4.1</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>No. (%) of pregnancies per retrieval</strong></td>
<td>58 (21.8)</td>
<td>28 (16.4)</td>
<td>30 (22.5)</td>
</tr>
<tr>
<td><strong>No. (%) of births per retrieval</strong></td>
<td>44 (17.3)</td>
<td>23 (12.9)</td>
<td>21 (18.1)</td>
</tr>
</tbody>
</table>

HMG = human menopausal gonadotrophin.

1988). These early reports were not controlled for endometriosis or tubal disease. In a retrospective review in which these two factors were controlled for, no difference was found in the incidence of ectopic pregnancy following coitus, IUI, or IVF (Dickey et al., 1989).

If the goals of infertility treatment in the next century are to decrease the cost of medication and treatment and to reduce the number of multiple pregnancies, as emphasized by Edwards et al. (1997), both inside and outside the medical community, then clomiphene citrate and continuous GnRHa infusion are the only medications presently available to meet these goals. With questions about adverse effects of clomiphene citrate mostly resolved in favour of clomiphene citrate, the use of combinations of clomiphene citrate with recombinant FSH and GnRHa, as suggested by Tarlatzis and Grimbizis (1998), may resolve the problem of cancellation due to premature LH surge and deserves to be evaluated. Instead of discarding clomiphene citrate at the beginning of the 21st century, it may be time to re-examine the use of HMG and FSH in combination with clomiphene citrate, instead of GnRHa, for ovulation induction in IVF.

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**Clomiphene in the 21st century**
associated with various degrees of oligoasthenozoospermia (Dickey et al., 1992).

Clomiphene was one of the first drugs used in in-vitro fertilization (IVF) and embryo transfer programmes either alone or in combination with human urinary gonadotrophins (Lopata et al., 1978; Quigley et al., 1983, 1985). However, for the last 10 years, clomiphene has been abandoned and has been replaced by gonadotrophin-releasing hormone (GnRH) agonists in almost all IVF centres. Recently, new follicle stimulating hormone (FSH) preparations of high purity, containing no luteinizing hormone (LH), were produced by the recombinant DNA technology and were introduced in the market (Loumaye et al., 1995; Out et al., 1995). Furthermore, preliminary data on the use of GnRH antagonists in IVF programmes demonstrate their ability to substitute GnRH agonists in the prevention of premature luteinization (Olivennes et al., 1994).

It is clear that 20 years after the birth of the first IVF baby, there is not a clear thought about the best regimen that would provide the most optimal ovarian response and success of the treatment. A crucial factor that can potentially affect the routine use of IVF in the treatment of infertility is the high cost of the drugs, particularly of the new preparations. This, added to the high cost of new techniques, such as intracytoplasmic sperm injection (ICSI) that is applied to ~50% of all treatment cycles, may make the IVF treatment a difficult approach for many couples. A re-evaluation of the treatment regimens, in order to reduce the cost without affecting the success rate, is a possibility. Clomiphene is safe and cheap, but the extent to which this drug can be reintroduced in IVF programmes needs a thorough evaluation.

Monofollicular development

Anovulatory women with oligomenorrhea or amenorrhea responsive to progesterone are appropriate candidates for treatment with clomiphene. Most of these patients have PCOS. Clomiphene, by binding to the oestrogen receptors at the level of the hypothalamic–pituitary system, induces an intercycle-type of FSH increase, which usually results in the selection of a single dominant follicle (Shaw, 1976; Roseff et al., 1989). The recommended daily dose for the beginning of treatment is 50 mg for 5 days in the early follicular phase. An ovulation rate of 60–90% is achieved, but the pregnancy rate is much lower at 30–40%. This discrepancy is related to various factors and particularly to the anti-oestrogenic effects of the drug on different parts of the reproductive system. Nevertheless, when clomiphene is given to properly selected women with no other causes of infertility apart from anovulation, cumulative pregnancy rates of >60% after 6 months and >90% after 10–12 months have been reported (Hammond et al., 1983; Messinis and Milingos, 1997). Combinations of clomiphene with other drugs, such as naltrexone, in clomiphene resistant patients are also successful (Messinis and Milingos, 1997; Roozenburg et al., 1997). The low risk of the ovarian hyperstimulation syndrome (OHSS) and the low rate of multiple pregnancy during treatment with clomiphene makes it the safest way of treating anovulatory infertility in women belonging to WHO group II. A further advantage of treatment with clomiphene is that intense monitoring is not required. Obviously, the use of clomiphene for this purpose will continue without any reservation in the new century.

Multiple follicular development

Controlled ovarian hyperstimulation resulting in multiple folliculogenesis can be induced either for the treatment of unexplained infertility or for IVF. In unexplained infertility, treatment with clomiphene is only empirical. This drug is used either alone or in combination with gonadotrophins and although satisfactory results have been reported (Dickey and Holtkamp, 1996), its use is not entirely justified due to adverse effects exerted on the cervical mucus and the endometrial thickness, which may have an implication on the treatment outcome (Randall and Templeton, 1991; Fujii et al., 1997). If such an approach is going to be advocated before the application of IVF, gonadotrophins may be more appropriate than clomiphene.

Clomiphene alone or in various combinations with human gonadotrophins were the most popular regimens in IVF programmes in the early 1980s. With the use of clomiphene at doses of 50–150 mg per day, more than one follicle reached the preovulatory stage, however, on average only two or three oocytes were recovered from the majority of women (Marrs et al., 1984). In these cycles, corpus luteum function appeared to be normal and the endogenous LH surge was appropriately timed (Messinis and Templeton, 1986; Templeton et al., 1986; Messinis et al., 1987). Combinations of clomiphene with human gonadotrophins provided a better ovarian response with a greater number of oocytes than clomiphene alone (Quigley et al., 1984b). While during the use of gonadotrophins alone a premature LH surge occurred in several cycles (Vargyas et al., 1984), this was not a problem when clomiphene was combined with gonadotrophins in a sequential manner (Messinis et al., 1985; 1986a). In these cases, although an endogenous LH surge occurred invariably, it was appropriately timed in relation to the size of the preovulatory follicle, but markedly attenuated (Messinis et al., 1985; 1986a). This made the detection of the surge before the administration of human chorionic gonadotrophin (HCG) difficult, since intense monitoring with blood samples taken every 6 h for several days was required. The reason for an appropriately timed LH surge in clomiphene treated cycles seems to be related to the drug itself and particularly to its long half-life (Messinis and Templeton, 1988). It is possible that clomiphene, by remaining in the circulation for several days after its administration at the beginning of the cycle, occupies the oestrogen receptors at the hypothalamic–pituitary system for a long time (Terakawa et al., 1985). In that way, although serum oestradiol values exceed the threshold value for the positive feedback effect before the follicle has reached maturity, a premature LH surge does not occur. The time when clomiphene leaves the receptors coincides with the time when follicles reach the preovulatory stage.

Although during treatment with clomiphene the endogenous LH surge can be appropriately timed, this drug can have
several drawbacks. When clomiphene is given to women for 5 days during the early follicular phase of the cycle, it stimulates not only the secretion of FSH, but also of LH and this may result in relatively high LH concentrations during the late follicular phase (Messinis et al., 1986b), which may adversely affect the outcome of pregnancy (Stanger and Yovich, 1985). The combination of clomiphene with human gonadotrophins may suppress basal LH levels in late follicular phase more than clomiphene, but even then LH levels are still higher than with gonadotrophins alone, when serum LH values decline significantly within the first 24 h from the onset of treatment (Messinis et al., 1986b; Messinis and Templeton, 1987; Messinis et al., 1994). A theoretical approach to the use of clomiphene for ovulation induction would be to combine it with a GnRH antagonist in order to reduce LH values during the late follicular phase. Although this sounds interesting, because of the higher LH values in clomiphene cycles, higher doses of the antagonist may be required to suppress LH than in FSH treated cycles. In addition, follicles which have been recruited in the presence of high LH values, such as during treatment with clomiphene, may be dependent on the high LH for further growth which may be disturbed after the decrease of endogenous gonadotrophins by the antagonist. In that case, administration of exogenous FSH may be necessary to promote the growth of the follicles. Certainly, dose-related studies with the antagonists are required if one wants to take the benefit of the low cost of clomiphene treatment.

Furthermore, it is unclear whether clomiphene can adversely affect oocyte maturity and embryo development. Although fertilization of human oocytes in vitro is not influenced by the dose or the duration of clomiphene pretreatment (Messinis et al., 1986c), other studies have demonstrated an increased rate of chromosomal abnormalities of human oocytes (Wramsby et al., 1987) and a decreased potential of human embryos for in-vitro development (Oelsner et al., 1987). Occasionally, clomiphene can produce side-effects, such as hot flushes, headache, visual disturbances and psychiatric reactions (Siedentopf et al., 1997).

The ideal regimen

It is clear that the optimal regimen for induction of multiple follicular development in IVF programmes has not been found yet. Clomiphene is a cheap drug and when used alone is quite safe in terms of the risk of OHSS and multiple pregnancy. Also, the pregnancy rate is not much lower than that with the use of GnRH agonists (Messinis, 1989). In normally cycling women, clomiphene can stimulate more than one follicle, however, there is a limit to the extent this drug can induce multiple follicular development and in the majority of the cycles no more than three oocytes are recovered (Quigley et al., 1984a). Nevertheless, even if one considers that no more than three oocytes are required for a reasonable fertilization/ cleavage and pregnancy rate, this number may not be sufficient for the ICSI procedure, which is applied to ~50% of all cycles in the majority of IVF centres. This points out the necessity to combine clomiphene with gonadotrophins, which together with the needed intense monitoring to detect the endogenous LH surge may not substantially reduce the cost of the treatment.

So far, none of the regimens used in IVF programmes can induce synchronous recruitment of a cohort of follicles and maintain their growth to the preovulatory stage. Follicles recruited by the exogenous administration of FSH in the early follicular phase have their own FSH threshold value for further growth in mid- and late follicular phase (Lofts et al., 1995). If this value is exceeded, follicle recruitment will continue throughout the follicular phase. Therefore, an optimal regimen for ovulation induction would be to create a relatively narrow FSH window for synchronous follicular recruitment and then to induce a FSH threshold value adequate to support further growth of these follicles, but inadequate for the recruitment of new follicles.

There is no doubt that recombinant gonadotrophins are characterized by their purity compared with the urinary preparations and may have a greater biopotency (Out et al., 1995). However, recombinant gonadotrophins are expensive at the moment and when they are combined with GnRH agonists or antagonists, the cost increases further. An advantage of the use of these preparations is expected to be obtained from the production of various FSH isoforms. This may help in the development of more properly designed regimens for IVF, which may then make the treatment a cost-effective procedure. On the other hand, further experimentation with the GnRH antagonists may improve the protocols for the prevention of premature luteinization. Alternative treatments may include other drugs, such as for instance the anti-progestagenic compound mifepristone, which in a recent experimental protocol was able to postpone the implantation window during the luteal phase (Paulson et al., 1997), while in another study it blocked the endogenous LH surge in FSH treated cycles (Messinis et al., 1997). This drug is much cheaper than GnRH agonists or antagonists, but before its safety is ascertained, it cannot be used routinely.

Conclusions

IVF has been established as a routine method for the treatment of infertility. However, the cost for one attempt is very high, particularly with the use of recombinant FSH preparations. In an effort to decrease the cost, several thoughts have been proposed, such as the reintroduction of clomiphene in the ovulation induction regimens. Clomiphene, however, has a limiting ability to stimulate multiple follicular maturation in women and may induce high LH concentrations. This, together with possible adverse effects of this compound on various aspects of reproductive function, precludes it from use in the development of an optimal regimen in IVF programmes. Certainly, clomiphene is the recommended drug for the treatment of anovulatory infertility associated with PCOS, in which single follicle development is the goal. Within the context of an IVF programme, however, the majority of women will require gonadotrophins. Hope is expected from the production of recombinant FSH isoforms which may help in the design of more optimal ovulation induction regimens.
Future use of clomiphene in ovarian stimulation

References


