Does previous response to clomifene citrate influence the selection of gonadotropin dosage given in subsequent superovulation treatment cycles?

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Abstract *Purpose:* To determine whether ovarian response to previous clomifene treatment could influence the selection of the starting dose of gonadotropins in subsequent *in vitro* fertilization (IVF) or intra uterine insemination (IUI). *Methods:* Forty three anovular women who had received clomifene for ovulation induction followed by gonadotropins for IUI or IVF superovulation were reviewed retrospectively. Data on gonadotropin dose were compared between clomifene-resistant patients and clomifene responders. *Results:* IVF patients who had had prior superovulation/IUI treatment received similar doses of gonadotropins regardless of response to clomifene (1610 IU versus 1560 IU, $p = 0.74$). In IVF patients not receiving prior IUI treatment, the clomifene-resistant women were given higher doses of gonadotropins than those responding to clomifene (2500 IU versus 1440 IU, $p = 0.042$). *Conclusions:* We found that, in our Unit, clinicians appeared to use prior non-response to clomifene as a reason for prescribing a higher starting dose of gonadotropins in IVF treatment, a practice that is not evidence-based.

Keywords Clomifene · Gonadotropin · *In vitro* fertilization · Intra-uterine insemination. Ovulation induction · Superovulation

Introduction

The treatment of anovulatory infertility is usually initiated with clomifene citrate. Patients who do not conceive using clomifene are then offered gonadotropin ‘superovulation’ treatment in combination with intra uterine insemination (IUI) or *in vitro* fertilization (IVF).

Models have been proposed to individualize the response to gonadotropins based on initial screening parameters [1]. However, the extent to which ovarian response to previous clomifene treatment might be related to gonadotropin dosage given in IUI or IVF has not been studied. The aim of the present work was to determine whether previous response to clomifene influences the selection of gonadotropin dosage given in subsequent IUI/IVF treatment.

Materials and methods

Subjects

All patients studied had undergone standard clomifene therapy. In this, clomifene is given at a dose of 50 mg for five days from the second day of the cycle. If ovulation occurs, this dosage regimen is maintained for 6–12 months or until the patient becomes pregnant. If ovulation has not been induced, the dose is increased by 50 mg each cycle to a maximum of 150 mg per day. All the patients, who did not become pregnant with clomifene, then received superovulation treatment with gonadotropins for IUI or IVF.

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Inclusion criteria were: (i) ages between 20 and 39 years at initial clomifene treatment; (ii) a maximum period between previous clomifene cycles and subsequent gonadotropin cycles of 48 months. Exclusion criteria were: (i) unexplained infertility; (ii) uterine abnormalities; (iii) non-PCOS patients who had endocrine or metabolic abnormalities including hepatic disease, adrenal disease, hyperprolactinemia, hypothyroidism or hyperthyroidism.

Ovarian stimulation regimen

For IVF, pituitary desensitization was achieved with either a GnRH agonist (1 mg daily, Suprecur®) or a GnRH antagonist (Orgalutran®, Organon). If the former was used, the treatment was begun on day 21 of the cycle preceding gonadotropin treatment. Patients were considered to be pituitary-desensitized if serum estradiol concentrations were below 50 pg/ml, had no follicles of more than 10 mm in diameter, and had an endometrial thickness of less than 7 mm measured by transvaginal ultrasound. Gonadotropin treatment (Puregon®, Organon) was then initiated, at a dose ranging from 50 to 300 IU daily, and continued until the day of human chorionic gonadotropin (hCG) administration. In patients receiving the GnRH antagonist, it was given (0.25 mg daily) from day 6 of the cycle. Gonadotropin administration was begun on day 2 of the cycle and continued until the day of hCG administration.

The patients were considered to be eligible to receive hCG when at least three dominant follicles had diameters of 17 mm or more. hCG (Profasi®; Serono Pharmaceuticals) was administered subcutaneously or intramuscularly at a dose of 10,000 IU, and oocyte retrieval was carried out 34–38 h later. Embryo transfer was performed 2 or 3 days after oocytes were retrieved.

For IUI, gonadotropin stimulation was initiated on day two of the cycle, at a dose ranging from 50 to 150 IU daily, and maintained until the day of hCG injection. 5000 IU of hCG was administered when at least one follicle of 16 or more mm in diameter was observed on a transvaginal ultrasound scan. One insemination was performed 36–38 h later with prepared sperm.

Serum progesterone, FSH and LH concentrations were measured by well-established assays [2]. Ovulation was assumed to have occurred if the progesterone concentration at mid-cycle was 30 ng/ml or higher. Ultrasound scans were performed using a 6 mHz vaginal transducer (Sonolayer SSA-250A, Toshiba, U.K.).

Data analysis

Data are presented as mean $\pm$ SEM. Statistical significance was assumed at a *p* value of 0.05 or less. The data, as assessed by the Shapiro-Wilks *W* test and by distribution plots,

were found not to be normally distributed and were logarithmically transformed. Data were analysed using the Statistics Package for Social Sciences (SPSS) software (version 12). The study was approved by the South Sheffield Research Ethics Committee. Since this was an anonymised retrospective study, the Ethics Committee deemed it unnecessary to obtain consent from the participants.

Results

One hundred and fifty anovulatory patients treated with clomifene were identified retrospectively from case notes, 43 of whom subsequently received gonadotropin superovulation treatment followed by IUI/IVF. Details of the treatment given to the patients and its outcome are given in Fig. 1. Twenty one patients were resistant to, and 22 were responsive to clomifene. In the clomifene resistant group, 48, 33 and 19% of patients received 50, 100 and 150 mg of the drug, respectively. In responders, 77, 14 and 9% received these doses of clomifene, respectively. The demographic and infertility characteristics of the two groups of patient were comparable (Table 1).

Factors contributing to anovulation in the clomifene resistant and responsive women were mild endometriosis (15.8% versus 19.2%), mild male infertility (21.6% versus 24.4%) or unilateral tubal factor (19.8% versus 15.5%).

Both starting and total gonadotropin doses in IUI patients were found to be significantly higher in the clomifene-resistant group than in the group that ovulated (125 IU versus 77 IU, 95% confidence interval (CI) on the difference: 3 to 94 and 1345 versus 791 IU; 95% CI: 51 to 1059, respectively) (Fig. 2a). However, in the IVF patients, a significant difference was not observed (188 IU versus 157 IU, 95% CI: –23 to 86 and 1772 IU versus 1635 IU, 95% CI: –344 to 617, respectively) (Fig. 2b).

IVF patients were further divided into two subgroups: one undergoing IUI before IVF superovulation and the other undergoing direct IVF without prior IUI. In the former subgroup, no significant difference in total gonadotropin dose was observed between clomifene responders (*n* = 5) and non-responders (*n* = 5) (1610 IU versus 1560 IU respectively, 95% CI: –293 to 393) (Fig. 3). There were no significant differences in the duration of ovarian stimulation (9.2 days versus 8.6 days, 95% CI: –2.4 to 1.2), peak estradiol concentration (6085 pmol/l versus 5511 pmol/l, 95% CI: –4089 to 5216), the number of follicles $\geq$ 14 mm at the day of hCG administration (11.8 versus 11.6, 95% CI: –3.48 to 3.88), the number of oocytes retrieved (7.6 versus 7.4, 95% CI: –2.25 to 2.65), and the pregnancy rate (20% versus 20%, respectively, *p* > 0.5).

In contrast, in IVF patients with no prior IUI, the total dose of gonadotropins used in clomifene-resistant patients

Fig. 1 Flowchart of patients who had clomifene citrate (CC) treatment

($n = 5$) was significantly higher than in those that ovulated ($n = 6$) (2500 IU versus 1440 IU respectively, 95% CI: 221 to 1898) (Fig. 3). On the other hand, there were no significant differences in the duration of ovarian stimulation (9.6 versus 9.8 days, 95% CI: -1.65 to 1.18), peak estradiol concentration (8539 pmol/l versus 7549 pmol/l, 95% CI: -3170 to 5152), the number of follicles ≥ 14 mm at the day of hCG administration (12.4 versus 14, 95% CI: -4.45 to 1.25), the number of oocytes retrieved (7.4 versus 8.6, 95% CI: -3.8 to 1.45), and the pregnancy rate (20% versus 33.3%, $p = 0.18$).

Discussion

There is no consensus about the starting dose of gonadotropins in superovulation for IVF, and dose selection seems to be empirical. Several factors are frequently cited as being of significance when deciding on the starting dose for patients who have not previously received gonadotropin treatment. In this context, age, BMI, and the results of ovarian reserve tests are useful indicators [3]. However, the influence of the extent of previous ovarian response to clomifene on gonadotropin dosing for superovulation treatment in subse-

quent IUI/IVF cycles has, to our knowledge, not been considered.

Our data suggest that prescribing doctors use information from previous clomifene treatment when selecting the starting dose of gonadotropins for the patients who have moved to IVF treatment. However, clomifene resistance did not appear to be a determinant of gonadotropin resistance in subsequent IVF superovulation treatment. Thus, if information from gonadotropin treatment in IUI was available, a low dose of gonadotropins was chosen for IVF, whether or not patients had ovulated after clomifene. The similar outcome between clomifene-sensitive and clomifene-resistant women indicates that using the high-dose regimen to treat “poorly responsive” patients is not justified.

Differences in the metabolism and clearance of exogenous gonadotropins are thought to be responsible for the large variation in individual response. As a result, increasing gonadotropin dosage has been suggested as a means of overcoming such variability [4]. However, this hypothesis has not been confirmed in clinical studies. In one prospective, randomized trial, van Hooft et al. [5] evaluated the efficacy of doubling the human menopausal gonadotropin (hMG) dose from 225 to 450 IU in patients undergoing IVF treatment. However, no differences in the duration of

Table 1 Demographic and infertility characteristics of the population studied

Patients (n)	CC-Resistant	CC-Responders	Difference	95 % CI	p -value
	21	22			
Age (y)	32 $\pm$ 6.3	31 $\pm$ 5.6	1.0	-2.2 to 4.1	0.3 ^a
Duration of infertility (y)	2.65 $\pm$ 2.1	2.77 $\pm$ 1.7	-0.12	-1.05 to 1.42	0.8 ^a
Type of infertility					
Primary infertility	44%	42%	?	?	0.36 ^b
Secondary infertility	56%	58%	?	?	0.42 ^b
BMI (kg/m ²)	27.8 $\pm$ 2.4	26.5 $\pm$ 3.2	1.3	-0.16 to 2.16	0.09 ^a
Basal FSH (IU/l)	6.2 $\pm$ 2.28	5.87 $\pm$ 2.02	0.33	-0.23 to 2.78	0.09 ^a
Basal LH (IU/l)	3.9 $\pm$ 1.63	4.07 $\pm$ 2.1	-0.17	-2.43 to 0.59	0.22 ^a

Note. Value were mean $\pm$ SEM; CI: Confidence interval.

^aStudent t test.

^b χ^2 -test.

Fig. 2 Starting dose and total dose of gonadotropins in the two subgroups: (a) 11 CC-Resistant Patients and 11 CC-Responders who underwent IUI. (* $p = 0.037$, ** $p = 0.033$) and (b) 10 CC-Resistant Patients and 11 CC-Responders who underwent IVF. ($p = \text{NS}$). CC, clomifene citrate

stimulation, peak oestradiol concentration, the number of follicles ≥ 14 mm on the day of hCG administration, fertilization rate and pregnancy rate were found. Similarly, Out et al. [6] in a randomised, double-blind study compared two starting doses of recombinant gonadotropins (Puregon®) in assisted reproduction programmes. Patients were randomised to receive 100 or 200 IU of gonadotropins daily. Although

Fig. 3 Total gonadotropin dose in CC-Resistant Patients and CC-Responders with or without prior IUI treatment who were undergoing IVF. (* $p = 0.042$). CC, clomifene citrate

the number of oocytes retrieved was significantly higher in the 200 IU group compared to the 100 IU group, the pregnancy rate was similar between the two groups in both per started cycle and per embryo transfer. In agreement with the above observations, neither Wikland et al. [7] nor Yong et al. [8] in prospective, randomised trials, found significant differences in the number of oocytes retrieved or pregnancy rates when either 150 or 225 IU of recombinant gonadotropins was used as the starting dose in IVF. The use of low doses of gonadotropins has been supported by one clinical trial [9]. In this, fifty-one young unselected patients were treated with 100 IU of recombinant gonadotropins in IVF/ICSI cycles. The outcomes were remarkably good, with an average of 16.3 oocytes retrieved. Although this study was not randomized and comprised a relatively young population, the findings suggest that a low-dose FSH regimen might be sufficient to induce multiple follicle development in young anovular patients.

In conclusion, it appeared that clinicians in our Unit used prior non-response to clomifene as a basis for prescribing a higher starting dose of gonadotropins for IVF. However, in IUI, in which the aim is to stimulate only one or two oocytes to the pre-ovulatory stage in order to reduce the risk of multiple pregnancy, a more conservative policy was adopted. The latter was then maintained if IVF treatment was subsequently begun, since information on ovarian response to gonadotropins was available from the IUI cycles. However, because of the limited number of patients in the present study, the results should be treated with caution.

The use of a higher dose of gonadotropins for IVF in clomifene-resistant women is not evidence-based, but appears to be driven by the preconception of the prescribing clinicians. A low dose strategy might reduce costs and the risk of complications such as ovarian hyperstimulation syndromes. Prospective, randomised studies are needed to explore further the possible relationship between ovarian responsiveness to clomifene and gonadotropins.

References

1. Macklon N. Gonadotropins in ovulation induction. *Reprod Biomed Online* 2005;10:25–31.
2. Li TC, Spuijbroek MD, Tuckerman E, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. *BJOG* 2000;107:1471–9.
3. Macnamee MC. Superovulation strategies in assisted conception. In: Brinsden P, editor. *A textbook of in vitro fertilization and assisted reproduction*. Carnforth: The Parthenon Publishing Group, 1999. p. 91–107.
4. Ben-Rafael Z, Strauss JF, 3rd, Mastroianni L, Jr, Flickinger GL. Differences in ovarian stimulation in human menopausal gonadotropin treated woman may be related to follicle-stimulating hormone accumulation. *Fertil Steril* 1986;46:586–92.
5. van Hooff MH, Alberda AT, Huisman GJ, Zeilmaker GH, Leerentveld RA. Doubling the human menopausal gonadotrophin

- dose in the course of an in-vitro fertilization treatment cycle in low responders: a randomized study. *Hum Reprod* 1993;8:369–73.
6. Out HJ, Lindenberg S, Mikkelsen AL, Eldar-Geva T, Healy DL, Leader A, Rodriguez-Escudero FJ, Garcia-Velasco JA, Pellicer A. A prospective, randomized, double-blind clinical trial to study the efficacy and efficiency of a fixed dose of recombinant follicle stimulating hormone (Puregon) in women undergoing ovarian stimulation. *Hum Reprod* 1999;14:622–7.
 7. Wikland M, Bergh C, Borg K, Hillensjo T, Howles CM, Knutsson A, Nilsson L, Wood M. A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI. *Hum Reprod* 2001;16:1676–81.
 8. Yong PY, Brett S, Baird DT, Thong KJ. A prospective randomized clinical trial comparing 150 and 225 IU of recombinant follicle-stimulating hormone (Gonal-F*) in a fixed-dose regimen for controlled ovarian stimulation in *in vitro* fertilization treatment. *Fertil Steril* 2003;79:308–15.
 9. Devroey P, Tournaye H, Van Steirteghem A, Hendrix P, Out HJ: The use of a 100 IU starting dose of recombinant follicle stimulating hormone (Puregon) in *in-vitro* fertilization. *Hum Reprod* 1998;13:565–6.