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DEBATE

Is there a future for ovulation induction in the current era of assisted reproduction?

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The clinical use of medical induction of ovulation in normogonadotrophic anovulatory women (WHO II), including polycystic ovary syndrome, is increasingly questioned. However, we believe that this treatment modality still represents a highly effective means of fertility treatment in women with low pregnancy chances without intervention. A conventional treatment algorithm involving clomiphene citrate (CC) followed by FSH induction of ovulation may result in a 71% cumulative singleton live birth rate. In attempts to improve treatment outcome further and reduce complication rates, new compounds such as insulin-sensitizing agents or aromatase inhibitors are currently used increasingly. Approaches such as patient selection for different treatment modalities on the basis of initial screening characteristics and alternative protocols for FSH ovulation induction may also be proposed to render treatment algorithms more patient tailored and therefore improve overall outcomes. More research is needed in this area, rather than referring these patients to assisted reproduction prematurely. This may lead to a more individually tailored approach for ovulation induction in a given patient, resulting in a further improvement of the balance between chances for success versus complications.

Key words: anovulation/FSH/ovulation induction/prediction model/step-down

Classic induction of ovulation strategies [clomiphene citrate (CC) followed by FSH injections] in patients with normogonadotrophic anovulation (World Health Organization, 1993; ESHRE Capri Workshop Group, 2003) can be experienced as a time-consuming and ineffective treatment modality with high complication rates. To deal with this, patients are increasingly offered 'controlled' ovarian stimulation combined with intrauterine insemination or IVF as first-line treatment, regardless of the type of infertility (Homburg and Insler, 2002). This alteration in treatment strategy is not based on sound scientific evidence and is likely to result in substantially higher multiple pregnancy rates and a major increase in overall treatment costs. The objective of this debate is, in response to treatment strategy alterations as mentioned above, to discuss the efficacy and efficiency of current ovulation induction strategies and point out possibilities for improvement.

In a prospective follow-up study, starting in 1993, of 240 WHO II patients in our fertility clinic, effectiveness of the approach of classical ovulation induction (CC as first-line, exogenous FSH as second-line treatment) was evaluated (Imani *et al*., 2002a; Eijkemans *et al*., 2003). Initial treatment with CC (highest daily dose of 150 mg for a maximum of six cycles) resulted in ovulation in 77% of all patients. A pregnancy occurred in 47% of all patients and in 61% of ovulatory patients (cumulative singleton live birth rate 41% and multiple live birth rate 2%). Both chances for ovulation (Imani *et al*., 1998, 2000) and pregnancy (Imani *et al*., 1999) may be predicted on the basis of initial screening characteristics such as age, body mass index (BMI = weight/height^2), free androgen index [(FAI = testosterone $\times$ 100/sex hormone-binding globulin (SHBG)], cycle history and polycystic ovaries.

Subsequently, second-line FSH induction of ovulation in our study population failing to ovulate or conceive after CC resulted after a mean of 3.5 stimulation cycles in an ovulation rate of 82%, a cumulative pregnancy rate of 56%, a singleton live birth rate of 43% and a multiple live birth rate of 5% (Mulders *et al*., 2003a). Overall, treatment outcome in our study population resulted in a cumulative singleton live birth rate of 71% after 'classical' ovulation induction using CC followed by exogenous FSH (Eijkemans *et al*., 2003). The remaining group was exposed to IVF, resulting in a live birth rate of 40% after a maximum of three cycles (Mulders *et al*., 2003b).

Efforts to enhance efficiency and safety of FSH ovulation induction treatment include the use of new gonadotrophin preparations, alternative treatment dose regimens and prediction models (ESHRE Capri Workshop Group, 2003). Initial patient characteristics may be able to predict chances of treatment response and outcome of both CC and FSH ovulation induction. In this way, it may also be possible to identify women who would benefit from alternative treatment algorithms, including first-line treatment with insulin-sensitizing drugs (Lord *et al*., 2003), aromatase inhibitors (Mitwally and Casper, 2003) or ovarian drilling (Farquhar *et al*., 2001; Pirwany and Tulandi, 2003). For these new treatment modalities, it can be concluded that, although initial studies are promising, their role in everyday clinical practice remains uncertain until data from prospective follow-up studies become available regarding large series of well defined patient groups.

A major difficulty associated with FSH ovulation induction is the individual variability in ovarian response to a given dose. Treatment regimens which involve a stepwise increase in low dosages of gonadotrophin during follicular development ('step-up' regimens) are now in common clinical use. The conventional step-up regimen employed relatively high initial doses of gonadotrophins. While ovulation rates of 70% were achieved, multiple pregnancy rates were observed to occur in 36% of pregnancies, and the potentially life-threatening ovarian hyperstimulation syndrome (OHSS) in 14% (Dor *et al*., 1980). The subsequently introduced 'low-dose, step-up' regimen is associated with considerably lower complication rates (White *et al*., 1996), and this regimen is now employed in most European centres. Studies of the endocrine physiology of normal follicular development have highlighted the essential unphysiological nature of step-up regimens (van Santbrink *et al*., 1995a). In an attempt to mimic physiology more closely in anovulatory women, a stimulation regimen has been developed which involves reducing (instead of increasing) the dose of gonadotrophins administered during the period of follicular development (van Santbrink and Fauser, 1997). This 'low-dose, step-down' regimen has proven itself as a reliable clinical tool for the induction of ovulation in our tertiary referral centre, although monitoring of a step-down cylcle may need more experiece and skills compared with a low-dose, step-up regimen (van Santbrink *et al*., 1995b). In a small prospective randomized trial, the low-dose, step-down and the low-dose, step-up regimen gave comparable clinical outcomes. However, in the step-down group, a substantially reduced stimulation period was required with a more physiological late-follicular FSH serum profile. This resulted in more mono-follicular stimulation cycles, coinciding with more cycles in which estradiol (E_2) serum levels were within the physiological range (van Santbrink and Fauser, 1997). As we know, multi-follicular growth and high late follicular phase E_2 serum levels are associated with increased multiple gestation rates and higher chances for ovarian hyperstimulation (Haning *et al*., 1983; Blankstein *et al*., 1987)

In a recently published randomized multi-centre study reported in this journal, comparing a low-dose, step-up versus a step-down gonadotrophin protocol in polycystic ovary syndrome (PCOS) (Christin-Maitre *et al*., 2003), 83 patients were included over an extended period of time in 11 centres. This, again emphasizes how difficult it currently is to execute these kind of studies with sufficient patient numbers. It strongly suggests that many PCOS patients are indeed treated differently. Patients included in the study presented with oligo-amenorrhea, normal BMI (23.5 ± 4.4 kg/m^2), no signs of hyperandrogenism (testosterone < 1 ng/ml) and sonographic mild polycystic ovary (PCO) criteria. Hence, this seems like a group with potentially favourable ovulation induction outcome, since overweight and hyperandrogenaemia are clearly associated with poor ovulation induction results, as discussed earlier. Treatment results showed a relatively high cancellation rate (38% versus 15%) in the step-down compared with the step-up group, but a similar overall ovulation rate (62% versus 70%). Pregnancy rates were comparable, but there was a clear tendency for hyperstimulation in the step-down group (multi-follicular growth and high serum E_2 concentrations). These findings are not surprising considering that a step-down protocol with a starting dose of 100 IU was applied to an unselected, mild (or non) PCOS population. Most of these patients can be expected to be good responders to FSH stimulation, i.e. low FSH response dose (Imani *et al*., 2002b). Chances for multiple follicle development during FSH induction of ovulation may be predicted by a model in which initial serum androstenedione (AD), ovarian response during preceding CC treatment and number of antral follicles upon initial screening are represented (van der Meer *et al*., 1998; van Santbrink *et al*., 2002; Jonard *et al*., 2003; Mulders *et al*., 2003c). As multiple follicle growth is associated with chances for OHSS and multiple pregnancy (Blankstein *et al*., 1987), patients at risk may be identified using this prediction model. Study data (Christin-Maitre *et al*., 2003) confirm this contention since at least 55–73% of the patients randomized for the step-up protocol did not need a dose increase to develop a pre-ovulatory follicle.

Accordingly, in our selected (tertiairy referral) study population, 31% of the patients developed a pre-ovulatory follicle without a dose increase in the low-dose, step-up protocol (E.J.P.van Santbrink, unpublished) (see also Table I). These patients were shown to be good responders to the initial starting dose of gonadotrophins. Evaluation of late follicular phase characteristics of similar patients demonstrated a decremental FSH serum profile close to physiology, probably due to the negative feedback of the growing follicle on pituitary FSH release (Schoot *et al*., 1992; van Santbrink and Fauser, 1997). It may be proposed, as reported earlier, that these women would hyper-respond in cases where a step-down regimen was offered with a relatively high starting dose, resulting in increased chances for treatment complications. In an attempt to avoid this, new patients for induction of ovulation with gonadotrophins are currently offered first a 'dose-finding' low-dose, step-up induction cycle in our centre, in which the FSH response dose is determined (Imani *et al*., 2002b). After that, step-down induction cycles are applied with a starting dose 37.5 IU above the effective response dose in the initial low-dose, step-up cycle. A fixed dose is applied in the following cycle if the patient responded with sufficient follicle growth in response to the starting dose during the dose-finding first low-dose, step-up induction cycle. Treatment results of the dose-finding low-dose step-up cycle and following step-down induction cycle are shown (Table I). Comparing the results of ovulation induction of the multi-centre trial (Christin-Maitre *et al*., 2003) with the results in our sequential low-dose step-up followed by step-

Table I. Treatment results of 83 normogonadotrophic anovulatory patients in three consecutive FSH ovulation induction cycles randomized for a low-dose step-up or step-down protocol (Christin-Maitre *et al*., 2003) and 91 normogonadotropic anovulatory patients during FSH ovulation induction treated according to a first dose-finding low-dose step-up cycle followed by a step-down cycle in women in which the FSH starting dose was determined by the response-dose in the first treatment (E.J.P.van Santbrink, unpublished)

	Low-dose step-up	Step-down	Initial dose-finding step-up cycle	Second step-down induction cycle[a]
	Christin-Maitre *et al*. (2003)		E.J.P.van Santbrink (unpublished)	
Patients (*n*)	44	39	91	61
Cycles (*n*)	85	72	–	–
Monofollicular growth (%)	68[b]	32[b]	70[c]	50[c]
Ovulation (%)	70	62	85	66
No dose increase (%)	55–73	NR	31	NR
Pregnancy rate (%)	23[d]	18[d]	15	16
Multiple pregnancy[e] (%)	10	43	0	0
OHSS[f] (%)	2	11	1	1
Miscarriage rate (%)	13	17	0	0

[a]Patients responding to the starting dose of the first dose-finding low-dose, step-up induction cycle were not converted to a subsequent step-down regimen and therefore not analysed.
[b]Monofollicular growth = 1 follicle >16 mm in diameter.
[c]Monofollicular growth = 1 follicle >14 mm in diameter.
[d]After one ovulation induction cycle.
[e]Percentage of total pregnancies.
[f]Only mild OHSS occurred, no hospitalization needed.

down treatment group (E.J.P.van Santbrink, unpublished observations), it can be concluded that the low-dose step-up results show comparable monofollicular development rates, ovulation rates and (ongoing) pregnancy rates (see Table I). In addition, the step-down results are also comparable except for the monofollicular development rates (32% versus 50%). It should be noticed that patient characteristics in both step-down populations are very different. Substantially more severe PCOS characteristics (obesity, hyperandrogenism and more frequent PCO ovaries) are found in the low responder group (Mulders *et al*., 2003a) compared with good responders. A recent systemic review regarding patient characteristics predicting ovulation induction outcome could confirm these findings (Mulders *et al*., 2003a).

A new approach to prevent hyperstimulation in gonadotrophin ovulation induction due to a starting dose far above the FSH threshold may be to determine the individual effective FSH starting dose using a prediction model. Time-consuming low-dose increments may be overcome by starting with a higher dose in women with an augmented FSH threshold. It may also reduce chances for hyper-response in women with a low FSH threshold. Initial patient and treatment characteristics (BMI, ovarian response during preceding CC therapy, insulin-like growth factor 1 and basal FSH) may be able to predict the individual response to FSH (Imani *et al*., 2002b). Obviously, more widespread clinical use of these predictors awaits external validation of the developed model.

In conclusion, it can be proposed that: (i) it is more difficult to induce ovulation in patients with more severe PCOS criteria (overweight, hyperandrogenaemia and with polycystic ovaries); (ii) an FSH starting dose >50–75 IU may result in ovarian hyperstimulation in at least 30% of an unselected PCOS population; (iii) it remains questionable if IVF with or without in-vitro maturation of oocytes provides improved efficacy and safety compared with ovulation induction strategies; and (iv) classical induction of ovulation is a highly effective treatment modality and there is still room for improvement applying new compounds and prediction models, resulting in a more individually tailored approach

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