Improving the patient’s experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment

Paul Devroey, Mohamed Aboulghar, Juan Garcia-Velasco, Georg Griesinger, Peter Humaidan, Efstratios Kolibianakis, William Ledger, Candido Tomás, and Bart C.J.M. Fauser

1Center for Reproductive Medicine, Dutch-Speaking Brussels Free University, Laarbeeklaan 101, Brussels 1090, Belgium 2The Egyptian IVF-ET Centre, Cairo University, 3 St 161, Hadaek El Maadi, Maadi, Cairo 1143, Egypt 3Instituto Valenciano de Infertilidad Madrid, Madrid, Spain 4Department of Obstetrics and Gynecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany 5The Fertility Clinic, Viborg Hospital (Skive), Skive DK 7800, Denmark 6Unit for Human Reproduction, 1st Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Nea Efarmpia Peripheral Road, Thessaloniki 54603, Greece 7The Jessop Wing, Centre for Reproductive Medicine and Fertility, Sheffield Teaching Hospitals Trust, University of Sheffield, Sheffield S10 2SF, UK 8AVA Clinic, Fertility Center, Tampere, Finland 9Department of Reproductive Medicine and Gynecology, University Medical Center, Heidelberglaan 100 3584, CX, Utrecht, The Netherlands

10Correspondence address. E-mail: paul.devroey@uzbrussel.be

Patients undergoing IVF/ICSI frequently experience substantial treatment burden, risk and psychological distress. These three related elements contribute to a negative patient experience that can lead to treatment discontinuation if pregnancy is not achieved. One approach to minimize these factors is the use of protocols designed to achieve high term, singleton birth rates per IVF treatment started, while improving the patient’s welfare. Gonadotrophin-releasing hormone (GnRH) antagonists may be suitable for inclusion in such a protocol. In clinical trial data and meta-analyses, treatment with these agents is associated with similar live birth rates but reduced treatment burden (duration and side effects) and less risk of ovarian stimulation syndrome, compared with GnRH agonist long protocols. GnRH antagonists may also be associated with reduced psychological distress compared with agonists, but so far, the evidence for this is inconclusive. To facilitate the implementation of treatments that optimize the patient’s experience, a simple GnRH antagonist protocol for use in predicted normal responders is proposed.

Key words: GnRH antagonist / IVF / ICSI / patient’s experience / live birth rate

Introduction

Infertility is a source of profound psychological distress for patients (Al-Inany et al., 2006; Cousineau and Domar, 2007). Those who choose to undergo IVF, however, often suffer additional anxiety and concern. Unsuccessful cycles and the threat of failure cause significant psychological distress (Verhaak et al., 2005, 2007). The use of subcutaneously administered agents may worsen patients’ perception of treatment, and another factor that may lead to a negative perception is the side effects caused by ovarian down-regulation (de Klerk et al., 2006, 2007). The costs of treatment and medical aspects of the procedures (e.g. surgery, anaesthesia and pain) can cause concern and dropout from treatment (Klonoff-Cohen and Natarajan, 2004; Dawson et al., 2005; Polinder et al., 2008).

Several authors have raised the need to improve the welfare and safety of patients undergoing IVF/ICSI, while maintaining satisfactory pregnancy rates (Fauser et al., 1999; Fauser and Devroey, 2005; Ledger, 2007; Nargund et al., 2007; Pennings and Ombelet, 2007; Ubaldi et al., 2007). Pennings and Ombelet (2007) have expressed support for patient-friendly assisted reproduction technology, meaning a policy that is cost-effective, available to the widest possible range of people and minimizes risks and burden for the patient.

One way by which the patient’s experience may be improved is through the use of gonadotrophin-releasing hormone (GnRH)
antagonists rather than agonists (Tarlatzis et al., 2006). Although
gnRH antagonists have been used successfully in normal responders in
clinics worldwide, most clinics currently use them mainly in patients
with unfavourable prognoses (e.g. older patients) or those in whom
previous cycles have been unsuccessful (Griesinger et al., 2005). A
wide variety of GnRH antagonist protocols have been proposed,
reflecting the fact that the protocol is still undergoing refinement.
The ‘ideal’ protocol is yet to be determined (Macklon et al., 2006;
Huirne et al., 2007). The present article attempts to address some
of these issues and concerns, and proposes a simple GnRH antagonist
protocol designed to improve the patient experience.

**Benefits of GnRH antagonists**

**Treatment burden**

Two factors constitute the bulk of treatment burden in IVF: length of
treatment and side effects.

For over 20 years, GnRH agonists have been used to prevent the
midcycle luteinizing hormone (LH) surge that results from multiple
follicular development. In the long protocol, GnRH agonist treatment
is initiated in the midluteal phase or on Day 1 of the cycle.
Administration causes an initial flare of gonadotrophins, followed by
down-regulation of GnRH receptors and a consequent reduction in
the release of gonadotrophins, which in turn leads to inhibition of
androgen and estrogen production. Pituitary desensitization is usually
achieved after ~2 weeks of treatment, after which ovarian stimulation
with exogenous gonadotrophins can begin (reviewed in Macklon
et al., 2006).

GnRH antagonists suppress premature LH surges during ovarian
stimulation (Lambalk et al., 2006) and, unlike GnRH agonists, cause
immediate and rapid suppression of gonadotrophin production.
They are therefore administered only when there is a risk of a prema-
ture rise in LH—usually between Days 5 and 7 of stimulation. This
avoids the initial gonadotrophin flare and subsequent pituitary down-
regulation associated with GnRH agonists (Borm and Mannaerts,
2000; European and Middle East Orgultran Study Group, 2001;
Fluker et al., 2001).

Patients receiving GnRH antagonists thus have high intercycle
dependent follicle-stimulating hormone (FSH) concentrations, which
induce secondary follicle recruitment. In contrast, in the GnRH long
agonist protocol, stimulation with exogenous gonadotrophins is
started following pituitary down-regulation and subsequent ovary sup-
pression (reviewed by Fauser and van Heusden, 1997). Because of
these differences, the treatment cycle is significantly shorter with
GnRH antagonist than with GnRH agonist co-treatment (Al-Inay
et al., 2007). This difference may be important in clinical practice.
Medical aspects of the IFV process are a significant concern for patients
(Klonoff-Cohen and Natarajan, 2004), who are likely to prefer shorter
cycles with reduced drug exposure. The long GnRH agonist protocol
typically involves ~3 weeks of GnRH analogue treatment per cycle,
whereas each GnRH antagonist cycle usually requires only a few days
of analogue administration (Fluker et al., 2001).

GnRH antagonist treatment does not produce an initial flare of
gonadotrophins, which may cause ovarian cysts (Qublan et al.,
Cyst formation lowers oocyte quality, fertilization rate, number of
oocytes retrieved and embryo quality; increases the probability of
cycle cancellation and is associated with decreases in implantation
and pregnancy rate (Qublan et al., 2006).

Moreover, GnRH antagonist treatment is not associated with the
Profoundly suppressed estrogens may be associated with side effects
that include weight gain, headache, hot flushes, night sweats, mood
swings, breast tenderness, abdominal pain, diarrhoea and nausea
(Fauser et al., 1999). Compared with IVF patients receiving GnRH
antagonist co-treatment, patients treated with the long GnRH
agonist protocol report significantly more physical discomfort during
the week before ovarian stimulation (de Klerk et al., 2006).

**Burden of risk**

The most serious complication of ovarian stimulation is severe ovarian
stimulation syndrome (OHSS), a potentially life-threatening condition
characterized by ovarian enlargement, pleural effusion, ascites, oliguria,
haemoconcentration and thromboembolism. Death due to OHSS is
rare, with a mortality rate estimated at 1:400 000—1:500 000 stimu-
lated cycles (Brinsden et al., 1995). Nevertheless, OHSS remains a
source of significant and distressing morbidity. Thromboembolism
represents the greatest cause of morbidity and potential mortality in
patients with OHSS, caused, in part, by increased blood coagulation
and reduced venous return from the lower limbs, which may lead to
dep deep venous thrombosis. Overall, OHSS results in hospitalization
in ~1.8% of patients (Mocanu et al., 2007).

Apart from cycle cancellation, there is currently no means of elimi-
nating the risk of OHSS completely, and any measures that lowers risk
are to be welcomed. The risk can be reduced substantially by screen-
ing for risk factors such as polycystic ovary syndrome (PCOS), high
estradiol levels and a decreased ratio of mature to very small follicles
(reviewed in Aboulghar and Mansour, 2003). In a recent report, basal
serum anti-Müllerian hormone predicted the occurrence of OHSS
(Lee et al., 2008). Coasting and cryopreservation are the two
methods currently used to prevent OHSS (Aboulghar and Mansour,
2003). However, as our understanding of the molecular mechanisms
driving OHSS improves, more targeted prophylactic treatment
becomes a possibility. One such treatment, cabergoline, inhibits signal-
ling through the vascular endothelial growth factor receptor and has
been tested in patients at risk of developing OHSS. Administration
of low doses of cabergoline, for 8 days from the day of human chor-
ionic gonadotrophin (hCG) administration, significantly reduced the
risk of moderate OHSS compared with placebo (Alvarez et al.,
2007; Soares et al., 2008).

Apart from the obvious safety benefits, development of protocols
that lowers risk might also encourage patient groups to re-evaluate
the safety of assisted conception, as well as reassuring individual
patients (Pennings and Ombelet, 2007). In a Cochrane review,
GnRH antagonist therapy was associated with a 39% relative risk
reduction for severe OHSS, compared with agonist therapy [risk
ratio 0.61, 95% confidence interval (CI) 0.42–0.89; P = 0.01] (Al-Inay
et al., 2007). In another meta-analysis, the relative odds of
hospital admission for OHSS was reduced by 54% with antagonists
compared with agonists (odds ratio 0.46, 95% CI 0.26–0.82; P =
0.01) (Kolibianakis et al., 2006).
Distress and discontinuation

Distress is commonly reported by patients undergoing IVF/ICSI treatment (Cousineau and Domar, 2007), particularly during ovarian stimulation (de Klerk et al., 2006). Reduction of the treatment burden may go some way to alleviate such distress: in a study involving 391 patients, those undergoing conventional IVF with the GnRH agonist long protocol reported statistically, significantly more symptoms of depression during the week before stimulation than control patients who were due to undergo IVF but did not experience down-regulation (de Klerk et al., 2006).

The patients’ experience may influence success in assisted conception, but this needs to be confirmed (Cousineau and Domar, 2007). In a multicentre study, anxiety did not influence pregnancy rates, whether experienced before or during treatment (Lintsen et al., 2006). However, in a study that enrolled 151 patients, levels of stress at baseline were significantly associated with pregnancy rate, live birth rate and birthweight, and stress experienced ‘during’ treatment was significantly associated with the number of oocytes retrieved and fertilized (Klonoff-Cohen et al., 2001; Klonoff-Cohen and Natarajan, 2004). To further complicate the picture, in another study of 391 patients, those who expressed more negative emotion (negative affect) before treatment had an increased probability of live birth from the first IVF cycle than those who expressed less negative emotion (de Klerk et al., 2008).

Most studies investigating discontinuation in IVF do not specify the type of GnRH analogue used, but the rate is generally high: nearly 50% of couples who initiate IVF treatment drop out, often citing stress, fear or ambivalence about the IVF process (Cousineau and Domar, 2007; Verberg et al., 2008). In a Dutch study of 202 patients for whom multiple cycles were provided by the national health insurance system, the dropout rate after three cycles was 62%, only 14% being on the advice of the treating clinician (Land et al., 1997). Similarly, in a study in Sweden, 54% of couples who did not achieve a live birth after the first attempt chose not to proceed with the full treatment programme of three cycles, offered free of charge (Olivius et al., 2004). The main reason cited for discontinuing was the psychological burden of treatment. Primarily, psychological reasons for discontinuation have also been reported in other European studies (Schroder et al., 2004; Rajkhova et al., 2006). Treatment strategies with reduced treatment burden and reduced risk would be expected to reduce psychological distress and therefore discontinuation rates. One study investigating this issue compared conventional IVF and transfer of two embryos with ‘mild treatment’ (delayed gonadotrophin administration, e.g. cycle Day 5) and GnRH antagonist co-treatment and single embryo transfer (SET) (de Klerk et al., 2006, 2007; Heijnen et al., 2007; Verberg et al., 2008), making it difficult to distinguish any putative effects on psychological variables or discontinuation rates of replacing GnRH agonist with GnRH antagonist treatment from those of other components of the strategy used in the study. ‘Mild treatment’ will be discussed in the ‘Future Prospects’ section below.

Maintaining success

A protocol intended to improve the patient experience should not only provide advantages in terms of treatment burden, risk and distress, but also maintain IVF/ICSI success. The meaning of ‘success’ in the context of IVF has been much debated in recent years. Different authors have defined success in different ways, to encompass the risks associated with multiple births and premature births, as well as the welfare of mother and child (e.g. Griesinger et al., 2004; Heijnen et al., 2004; Min et al., 2004; Pinborg et al., 2004). Pregnancy rate and live birth rate are important influences on the treatment choices of patients (Marcus et al., 2005; Twisk et al., 2007). There appears to be no clinically significant difference in terms of live birth rate between GnRH antagonists and agonists: two meta-analyses comparing the two classes of GnRH analogue calculated almost identical odds ratios (0.82–0.86) for the probability of live birth, although the difference was statistically significant in one analysis (Al-Inany et al., 2006) and not in the other (Kolibianakis et al., 2007a). First (a Cochrane review), the number needed to treat 1 patient to benefit from clinical pregnancy was 21, meaning that for every 21 patients treated with GnRH agonists rather than antagonists, there would be one additional clinical pregnancy.

The long GnRH agonist protocol is associated with a higher number of oocytes retrieved than GnRH antagonists (Albano et al., 2000; Borm and Mannaerts, 2000; Olivennes et al., 2000; Flikker et al., 2001; Roulier et al., 2003; Al-Inany et al., 2006; Kolibianakis et al., 2006). GnRH agonists suppress endogenous FSH and stimulate synchronized follicular development, producing a cohort of oocytes similar in size. The GnRH antagonist protocols, on the other hand, allow endogenous FSH to initiate the growth of a few leading follicles before exogenous FSH is added. As a result, the cohort of follicles achieved with GnRH antagonist protocols is more heterogeneous in terms of size compared with the long GnRH agonist protocol (Huirne et al., 2007). Few studies have compared cumulative pregnancy rates per started cycle between GnRH agonists and antagonists, and it cannot be excluded that GnRH antagonist protocols are associated with lower cumulative pregnancy rates compared with the standard long GnRH agonist protocol. This issue remains to be clarified in future research.

As mentioned previously, many IVF centres currently use GnRH antagonists as a second choice treatment option in patients who have failed previous IVF cycles or in older patients (Griesinger et al., 2005). However, when patients with equal demographic and clinical characteristics are compared, the two classes of GnRH analogue are equivalent in terms of pregnancy rate (Engel et al., 2006).

More recent trials of GnRH antagonists have reported better pregnancy rates than earlier trials, which used antagonist protocols that would now be recognized as suboptimal. The available evidence suggests that the live birth rate attained following IVF/ICSI is influenced primarily by factors such as patient age, health and lifestyle, and by laboratory practices and facilities, rather than the type of GnRH analogue (or gonadotrophin) used (Al-Inany et al., 2006; Kolibianakis et al., 2006).

The evidence presented in this paper (summarized in Table I) suggests that GnRH antagonist protocols have a number of advantages over GnRH agonists in terms of improving the patient experience, and therefore deserve at least trial use in all IVF centres.

A suggested protocol to optimize the patient experience

At least 20 different GnRH antagonist protocols have been reported (summarized in Kolibianakis et al., 2006; Tarlatzis et al., 2006),
## Table I Summary of key points

| Compared with GnRH agonists, GnRH antagonists are associated with reduced treatment duration and reduced risk of ovarian hyperstimulation syndrome (Kolibianakis et al., 2006; Heijnen et al., 2007). Use of GnRH antagonists avoids pituitary down-regulation, which is associated with hypo-estrogenic adverse events (Tarlatzis et al., 2006). Meta-analyses comparing GnRH agonists and antagonists have calculated almost identical odds ratios (0.82–0.86) for the probability of live birth, although the difference was statistically significant in one analysis (Al-Inany et al., 2006) and not in another (Kolibianakis et al., 2007a). The difference is unlikely to be of clinical significance.
| A GnRH antagonist protocol for predicted normal responders is suggested. Further data are required on the following elements of GnRH antagonist protocol:
| Patient suitability
| Much published data on the use of GnRH antagonists relate to patients at high risk of OHSS, such as those with PCOS. In such patients, the use of GnRH antagonists (with a GnRH agonist used for triggering of ovulation) is associated with a reduced incidence of mild and moderate OHSS, compared with the long agonist protocol (Engmann et al., 2008). Similarly, in a meta-analysis of the limited data available for PCOS patients, GnRH antagonist co-treatment was associated with a shorter duration of stimulation, compared with cycles using the long agonist protocol (standardized difference −0.86, 95% CI −1.14 to −0.59; P < 0.01) (Griesinger et al., 2006b). However, GnRH antagonists were developed for regular patients undergoing regular IVF, and the protocol presented in Fig. 1 is intended as a starting point for clinics considering using GnRH antagonists in such patients (i.e. those aged <35 years, with 5–9 antral follicles, no diagnosis of PCOS, no history of poor responses and no endometriosis).
| Investigations
| In the suggested protocol, preliminary investigations are carried out on cycle Day 2. The value of particular ultrasound investigations (e.g. antral follicle count and ovarian volume) remains to be determined, although antral follicle count and ovarian volume may both predict

### Gonadotrophin stimulation

Stimulation with patient-administered FSH is usually started on cycle Day 2 or 3. In patients aged <35 years, an initial dose of FSH 150 IU/day is suggested. There appear to be few clinically significant differences when comparing different (low) doses of FSH in predicted normal responders (Wikland et al., 2001; Out et al., 2004). One study investigated the influence of initial FSH dose in 120 regular patients undergoing ovarian stimulation with GnRH antagonist co-treatment (Wikland et al., 2001). More oocytes were retrieved from patients receiving 225 IU/day than from those receiving 150 IU/day, but there was no difference in pregnancy rate. In another study of 257 patients treated with GnRH antagonists, FSH 200 IU/day and FSH 150 IU/day were associated with comparable oocyte numbers and pregnancy rates (Out et al., 2004).

For better fine-tuning of the initial FSH dose in patients receiving GnRH agonist co-treatment, a ‘bedside’ scoring system has been proposed, based on ovarian sonography variables, age and smoking status (Popovic-Todorovic et al., 2003b). The total score indicates the dose of FSH expected to yield 5–14 retrieved oocytes. Among ‘standard’ patients (normal basal serum FSH, presence of both ovaries, regular menstrual cycle, age <39 years and no endocrine disorders) undergoing ovarian stimulation with GnRH agonist co-treatment, use of this system for FSH dosing was associated with an increased rate of appropriate responses (5–14 oocytes) and of ongoing pregnancy, compared with fixed dosing of 150 IU/day (Popovic-Todorovic

### Figure 1 Suggested GnRH antagonist treatment protocol for normal responders. US, ultrasound.

This suggested protocol represents a ‘best estimate’ given current data and clinical experience. Further data are required before more concrete recommendations can be made.

<table>
<thead>
<tr>
<th>For regular IVF patients: 5–9 antral follicles per ovary</th>
<th>Age &lt;35 years</th>
<th>No PCOS</th>
<th>No history of poor responders</th>
<th>No endometriosis</th>
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<td>Cycle day 2 Transvaginal US + (if desired) hormonal profile</td>
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<td>Cycle day 2+3 Start FSH 150–200 IU. Continue</td>
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<td>Stimulation days 5–6 Start GnRH antagonist administered daily. Continue</td>
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<td>Monitoring according to clinic practice</td>
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<td>+ US (= blood leak if required)</td>
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<td>+ FSH dose adjustments may be considered</td>
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<td>Duration of treatment based on clinical judgement in consultation with patient (usually 2 USs)</td>
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<td>3 follicles 15–19 mm</td>
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<td>Day of triggering</td>
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<td>+ Ensure interval between antagonist and hCG does not exceed 30 h</td>
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<td>+ hCG 5000–10000 IU</td>
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<td>36 h</td>
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<td>Oocyte retrieval</td>
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et al., 2003a). This approach has been discussed recently (Fauser et al., 2008).

Whether the starting dose of gonadotrophin should be decreased for potentially high responders is uncertain. Some PCOS patients have a tendency to over-respons and are at increased risk of cycle cancellation compared with non-PCOS patients (Heijnen et al., 2006). Whereas PCOS is often considered a major risk factor for OHSS (Aboulghar and Mansour, 2003), a meta-analysis of outcomes of women with PCOS undergoing IVF treatment showed only a trend towards increased risk of OHSS in this population (Heijnen et al., 2006). It is recommended that all PCOS patients be monitored closely for signs of OHSS (Aboulghar and Mansour, 2003), whereas it seems logical to decrease the starting gonadotrophin dose in such patients (e.g. 100 IU/day); further data are required to determine the optimal protocol.

Similarly, whether or not the starting dose of gonadotrophin should be increased for potentially poor responders is an issue yet to be resolved. These patients include overweight/obese patients, older patients and patients who have previously failed to respond.

Maternal obesity has short- and long-term deleterious health implications for the patient and offspring (Catalano and Ehrenberg, 2006), and in some circumstances, fertility treatment should be deferred in obese patients, according to national guidelines. The prevalence of overweight/obesity (BMI ≥ 25 kg/m²) in patients undergoing IVF/ICSI in European countries is reportedly 22–28% (Wittemer et al., 2000; Fedorcsak et al., 2004). The common practice of increasing the gonadotrophin dose in such patients (up to 250 IU/day) (Borini and Dal, 2005) is not supported by much evidence, although the pharmacokinetic profile of recombinant FSH may be altered in obese versus non-obese women (Steinkampf et al., 2003). Compared with normal BMI, obesity has been associated with a decreased probability of live birth following IVF/ICSI (Fedorcsak et al., 2004), and in some retrospective studies, with reduced numbers of oocytes retrieved, transferred embryos and embryo transfers performed following IVF/ICSI (Lewis et al., 1990; Wittemer et al., 2000; Fedorcsak et al., 2004). However, one study of 368 patients found no effect of BMI on fertilization rate (Lewis et al., 1990) and a later study of 333 patients failed to find a significant influence of BMI on number of follicles aspirated, number of oocytes retrieved, number of embryos and clinical pregnancy rate (Lashen et al., 1999). Some national guidelines recommend deferring fertility treatment in obese patients, under normal circumstances. Compared with younger patients, older patients undergoing IVF/ICSI have increased serum FSH levels (Tufan et al., 2004), decreased numbers of oocytes retrieved and decreased pregnancy rates (Sharif et al., 1998). It would seem logical to increase the starting gonadotrophin dose in older patients (e.g. to 250 IU), but this is again an issue for further research (Borini and Dal, 2005). Increasing the gonadotrophin dose in GnRH agonist cycles from 150 to 225 IU in women over 33 years was associated with a reduced cancellation rate due to insufficient ovarian response (Yong et al., 2003). On the other hand, in the same study, 225 IU was not associated with benefits in terms of fertilization rate, number of embryos formed or pregnancy rate, compared with 150 IU (Yong et al., 2003). In another study of patients aged 37–39 years receiving GnRH antagonist co-treatment, FSH 250 IU was not associated with a significant difference in number of oocytes retrieved compared with FSH 150 IU (Out et al., 2004).

There is little evidence to support an increase in the starting gonadotrophin dose in patients who have previously failed to respond, and there are no data relating to GnRH antagonist cycles (Ubaldi et al., 2005). Despite an early report suggesting benefit (Hofmann et al., 1989), several studies in the early 1990s reported no clinical benefit from increasing the starting dose up to 450 IU in previous non-responders (Karande et al., 1990; van Hooff et al., 1993; Land et al., 1996). It seems likely that in these patients, poor ovarian reserve leads to a poor outcome that is not influenced by gonadotrophin dose (Ubaldi et al., 2005). Furthermore, pregnancy rates in this patient population seem to be inversely correlated with the amount of gonadotrophins used (Ubaldi et al., 2005).

In conclusion, the administration of gonadotrophins is very similar in GnRH antagonist and agonist protocols, involving the same considerations and decision-making processes.

### GnRH antagonist administration

Initiation at Day 6 of FSH administration has been associated with significantly higher incidences of LH rises and surges than long GnRH agonist protocols (Kolibianakis et al., 2006). On the other hand, data from large, randomized controlled trials of GnRH antagonists versus agonists indicate that early LH rises prior to GnRH antagonist treatment do not reduce either suitability for embryo transfer or pregnancy rate (Borm and Mannsmaers, 2000; European and Middle East Orgalutran Study Group, 2001). Although fewer oocyte complexes are generally retrieved using GnRH antagonists than with agonists, the difference is small: the weighted mean difference found was −1.07 (95% CI −1.52 to −0.61) (Al-Inany et al., 2006) in the Cochrane review and −1.19 (95% CI −1.82 to −0.56) in the other meta-analysis (Kolibianakis et al., 2006). As discussed above (‘Maintaining success’), this does not translate into a clinically relevant difference in live birth rate.

Until more concrete conclusions can be drawn, it is recommended that a GnRH antagonist be started on Days 5 to 6 of FSH administration. The time between each GnRH antagonist injection should not exceed 30 h.

### Monitoring

After administration of the GnRH antagonist, the patient should be monitored according to routine clinic practice. This may include transvaginal ultrasound scanning of the ovaries and endometrium and monitoring of hormone levels. In theory, adjustment of the FSH dose according to follicle size (e.g. in increments of 75–100 IU) would allow greater flexibility in the timing of particular stages of the protocol, but this issue requires further research. There appears to be no clinical benefit from increasing the FSH dose by 75 IU on the day of GnRH antagonist administration (Aboulghar et al., 2004; Propst et al., 2006).

### Triggering of final oocyte maturation

In the suggested protocol, the triggering of final oocyte maturation is timed by follicle size and number. This criterion (at least three follicles at 15–19 mm) represents a ‘best estimate’ based on clinical experience, and encompasses the criterion of ‘three follicles ≥17 mm’, used in many clinical trials (Borm and Mannaeers, 2000; European and Middle East Orgalutran Study Group, 2001; Fluker et al., 2001).
Further research is required on the optimal criterion: as discussed below, the timing of this stage in GnRH antagonist cycles appears to be important and have consequences for endometrial histology and pregnancy rate (Kolibianakis et al., 2004a, 2005a). If the GnRH antagonist is usually administered by the patient in the morning, the GnRH antagonist should still be administered on the day of triggering. If the GnRH antagonist is administered in the evening, however, the time between the last GnRH antagonist injection and hCG administration should not exceed 30 h.

In the proposed protocol, hCG 5000–10 000 IU is administered to trigger final oocyte maturation. Large-scale, multicentre trials of GnRH antagonists have used hCG 10 000 IU (Albano et al., 2000; Borm and Mannsart, 2000; European and Middle East Orgaletan Study Group, 2001; Fluker et al., 2001), but administration of 5000 IU appears to be equally effective in GnRH agonist cycles (Wikland et al., 1995) and in patients with PCOS receiving a GnRH antagonist (Kolibianakis et al., 2007b). GnRH antagonist protocols allow the use of a single bolus of GnRH agonist to trigger oocyte maturation, as discussed below.

Subsequent procedures

Oocyte retrieval should take place 36 h after triggering. The criteria for oocyte retrieval and subsequent procedures are the same as in standard protocols.

Luteal support is essential following ovarian stimulation with GnRH antagonist co-treatment, just as with GnRH agonist co-treatment (Beckers et al., 2003). However, much of the data regarding the details of luteal support come from trials that used GnRH agonists, and the potential problems of extrapolating these data to patients who have received GnRH antagonists should be borne in mind.

The timing of the start of luteal support varies a great deal among clinics. Pregnancy rates are comparable when luteal support is started on the day of triggering with hCG, oocyte retrieval or embryo transfer (Baruffi et al., 2003; Mochtar et al., 2006). However, starting luteal phase support ‘before’ oocyte retrieval after ovarian stimulation with GnRH agonist treatment appears to be associated with lower pregnancy rates, compared with starting it after oocyte retrieval (Sohn et al., 1999). In addition, after GnRH agonist cycles, delaying luteal phase support to 6 days after oocyte retrieval is associated with decreased pregnancy rates, compared with starting it 3 days after oocyte retrieval (Williams et al., 2001). On the basis of the available evidence, it is suggested that luteal support [e.g. vaginal (600 mg/day) or intramuscular (50 or 100 mg/day) progesterone] be started on the day of oocyte retrieval. Despite reports suggesting that luteal support in early pregnancy is unnecessary (Schmidt et al., 2001; Nyboe Andersen et al., 2002; Proctor et al., 2006), the evidence is currently inconclusive, and it is suggested that luteal support be continued for a minimum of 2 weeks. Data from a randomized study show no benefit in terms of pregnancy rate of extending luteal support beyond the day of the first ultrasound (6–7 weeks) (Abouhajar et al., 2008).

Progesterone is recommended for luteal support. No other agent has been shown conclusively to provide benefit in terms of pregnancy rate, and hCG is associated with an increased risk of OHSS (Daya and Gunby, 2004). A Cochrane review found some evidence of benefit from intramuscular progesterone compared with vaginal preparations (Daya and Gunby, 2004). The optimal dose of progesterone has not been evaluated, but 600 mg/day is frequently used when progesterone is administered vaginally. IVF or ICSI and embryo transfer should be performed according to the clinic’s routine practice.

Scheduling

Protocols using GnRH antagonists can present unfamiliar challenges concerning patient scheduling and IVF cycle management. Many IVF centres have become accustomed to the tight control of cycle scheduling offered by the long GnRH agonist protocol, in which initiation of FSH can be timed early in the week to allow subsequent oocyte collection and embryo transfer on week days (Ledger, 2002). GnRH antagonist cycles, on the other hand, may require greater flexibility from the clinic, including changes to working patterns (including weekend working) and altered monitoring schedules (Fleming, 2002; Ledger, 2002).

In practice, many clinicians use computerized scheduling of procedures and allow some flexibility in the protocol (e.g. by varying the day of stimulation start or day of hCG administration). This is an area that requires much research, but some data suggest that the delay of hCG administration in GnRH antagonist cycles leads to reduced pregnancy rates compared with no delay: in a prospective study of 413 patients undergoing ovarian stimulation with GnRH antagonist co-treatment, prolongation of the follicular phase (delaying the administration of hCG for 2 days after the point at which at least three follicles are ≥ 17 mm) resulted in a lower probability of ongoing pregnancy per oocyte retrieval and per embryo transfer, compared with no delay (Kolibianakis et al., 2004a). This difference was probably due to secretory changes in the endometrium (Kolibianakis et al., 2005a). Bringing the day of hCG administration ‘forward’ is a common practice, although the clinical implications require investigation.

Pretreatment with oral contraceptive agents allows programming of cycles, whereby stimulation can be started during a 2–5 day interval following withdrawal of the oral contraceptive (Meldrum et al., 2002; Barmat et al., 2005; Huime et al., 2007). In a meta-analysis of four randomized controlled trials, oral contraceptive pretreatment was associated with increased total gonadotrophin dose and duration of stimulation (Griesinger et al., 2007), with a trend towards a reduction in ongoing pregnancy rate. A subsequent open-label, non-comparative single-arm trial also found poor clinical response among patients pretreated in this way (Meldrum et al., 2008). In addition to these clinical disadvantages, oral contraceptive pretreatment increases the length of the perceived treatment considerably and it could be argued that this mitigates one of the central advantages of GnRH antagonists over agonists, namely a reduction in treatment burden.

Future prospects

Mild treatment

One approach designed to improve the patient experience is so-called ‘soft’ or ‘mild’ treatment (Nargund et al., 2007), with delayed administration of gonadotrophin (e.g. in the mid-to-late follicular phase) and GnRH antagonist co-treatment. In a randomized trial of 404 patients in The Netherlands, mild IVF treatment involving a combination of mild ovarian stimulation (including GnRH antagonist co-treatment) and SET (Group 1) was compared with the long GnRH agonist protocol and...
the transfer of two embryos (Group 2) (Heijnen et al., 2007). Patients in Group 1 were offered reimbursement for one extra cycle in addition to the three cycles ordinarily reimbursed in The Netherlands. Overall, over 1 year, the cumulative rate of pregnancy leading to a live term birth was similar in both groups: 43.4% in Group 1 and 44.7% in Group 2 (difference +1.3% in favour of standard treatment, lower limit of one-sided 95% CI – 9.8%). Compared with Group 2, Group 1 had significantly lower rates of multiple pregnancies and of mild, moderate and severe OHSS. The mean total costs were also significantly lower in Group 1 (difference £2412, 95% CI 703–4131).

There is currently little evidence of reduced psychological impact from mild versus standard strategies. In the study described above, there were no significant differences between the two treatment strategies in terms of anxiety, depression or sleep quality (Heijnen et al., 2007). There was, however, a lower dropout rate among patients in Group 1 versus Group 2 (Verberg et al., 2008). In one study, mild treatment and SET was not associated with more or fewer psychological complaints during treatment than conventional treatment and transfer of two embryos (de Klerk et al., 2006), despite the fact that on average more mild IVF cycles than conventional cycles were performed in the time period studied. However, patients undergoing mild treatment and SET experienced less psychological distress after cycle cancellation (de Klerk et al., 2006) and, if treatment was unsuccessful, had significantly fewer symptoms of depression 1 week after treatment end (de Klerk et al., 2007). Whether GnRH antagonists have ‘independent’ benefits in terms of reduced psychological burden or reduced discontinuation rates remains to be determined.

Despite data demonstrating the benefits and reduced costs of mild approaches, there are a number of barriers to their widespread adoption, such as the reduced number of oocytes retrieved and insufficient responses to stimulation (Ubaldi et al., 2007).

**GnRH agonist for triggering oocyte maturation**

One potential advantage of GnRH antagonist protocols is the possibility of triggering final oocyte maturation with a bolus of GnRH agonist rather than hCG, which may reduce the risk of OHSS, particularly in patients with PCOS or polycystic ovary morphology and other high responders. Randomized trials have reported reduced pregnancy rates with this approach (Fauser et al., 2002; Humaidan et al., 2005; Kolibianakis et al., 2005b), and in a recent meta-analysis it was associated with comparable numbers of oocytes retrieved but lower ongoing pregnancy rates, compared with hCG (Griesinger et al., 2006a). These outcomes may be due to luteal phase insufficiency, with hCG acting as a luteotrophic agent to support the corpora lutea after the bolus dose (Beckers et al., 2003).

However, a recent study suggested that the initial problems associated with luteal phase insufficiency can be resolved with hCG supplementation after induction of ovulation (Humaidan et al., 2006). This study used hCG 1500 IU either 12 or 35 h after triggering of ovulation with a GnRH agonist, and reported comparable pregnancy rates using either hCG or a GnRH agonist to trigger oocyte maturation. Two small studies also recently explored the use of a GnRH agonist to trigger oocyte maturation in patients at high risk for OHSS. After the triggering bolus of GnRH agonist and aspiration, patients either had a total freeze and subsequent frozen embryo transfer (Griesinger et al., 2007) or embryo transfer (Engmann et al., 2008). In both studies, patients received progesterone and estradiol during the luteal phase. No cases of moderate or severe OHSS were observed when a GnRH agonist was used to trigger final oocyte maturation. These promising data require confirmation in future trials.

**Discussion and conclusions (Table I)**

The protocol proposed here is for predicted normal responders. There may be patients (e.g. those with a previous poor response or endometriosis) in whom more monitoring and protocol adjustments are warranted, and clinics will need to modify the proposed protocol to suit working practices and the patient’s situation. Further refinement of GnRH antagonist protocols may lead to further improvements in pregnancy rates.

Although there is emerging evidence for improved psychological outcomes with ‘mild treatment’, including GnRH antagonists in association with delayed gonadotrophin administration, it remains uncertain whether GnRH antagonists have independent psychological benefits. Future clinical trials of GnRH antagonists should include rigorous assessments of the effects of treatment on quality of life, in both successful and unsuccessful cycles. This will be crucial in further research comparing the health economic aspects of different protocols. Such research should balance quality of life outcomes against the financial costs of treatment, as well as the costs of healthcare resources: during IVF/ICSI treatment, during pregnancy, at parturition and immediately after pregancy. Reasons for dropout should be studied more closely, and the ability of patient-centred treatments to reduce dropout and increase cumulative pregnancy rates should be investigated prospectively.

A universally accepted measure of IVF success is essential for such comparisons, but remains controversial. In the research setting, a single measure of IVF success would be useful, but in the clinical setting, patients may define success differently from clinicians. In addition, patients’ perceptions of treatment may differ widely: a patient with a poor prognosis, for example, may find greater risk and treatment burden more acceptable, compared with a patient with a relatively good prognosis.

In conclusion, the patient’s experience of IVF/ICSI can often be marred by treatment burden, exposure to risk and psychological distress. Ovarian stimulation with GnRH antagonist co-treatment can provide live birth rates (per embryo transfer) comparable to those achieved with the standard long GnRH agonist protocol, and has advantages in terms of tolerability and safety. GnRH antagonist protocols, such as that outlined in this article, may be implemented with the aim of improving the patient experience in normal responders, while maintaining high cumulative pregnancy rates.

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