Symposium: Endocrinology in ovarian stimulation

Factors influencing response to ovarian stimulation

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Abstract

Ovarian stimulation is an integral part of assisted reproduction treatments. Ovarian response to gonadotrophin treatment, besides other factors, determines the outcome of treatment, as the number and quality of oocytes retrieved are related to the chance of achieving a pregnancy. A number of factors have been identified that might predict ovarian response, such as age of the patient and antral follicle count. In addition, it has been shown that genetic factors such as the patient's FSH-receptor genotype also determine individual response to FSH treatment. Besides patient-related factors, the choice of drugs for ovarian stimulation plays a significant role. Until recently, biopotency of gonadotrophin preparations was tested by an in-vivo bioassay with an intrinsic variability up to 20%. Due to a superior manufacturing technique, follitropin alpha can now be filled by mass. This allows assessment of FSH with a precise SE-HPLC assay and variability of the FSH content between production lots has now been estimated at 1.6%. Results of recent studies indicate that treatment with follitropin alpha filled by mass results in consistent ovarian response, fewer treatment days and fewer cancelled cycles. This is an important step towards further minimizing drug-related variability of ovarian response to FSH treatment.

Keywords: *consistency, filled-by-mass, follitropin alpha, gonadotrophin preparations, ovarian stimulation, recombinant FSH*

Introduction

Ovarian stimulation is an integral part of assisted reproductive techniques. The number and quality of oocytes retrieved are determinants of success: even if a high number of oocytes as such does not predict a good outcome (Inge *et al.*, 2005), it has been shown that the number of fertilized oocytes achieved is directly related to the chance of achieving a pregnancy (Templeton, 2000).

Several predictive factors such as age, antral follicle count, day 3 FSH concentrations, inhibin B and anti-Müllerian hormone have been shown to be related to the individual outcome of a treatment cycle. Furthermore, genetic factors such as FSH-receptor genotype (Greb *et al.*, 2005) or oestrogen receptor polymorphism (Georgiou *et al.*, 1997; Sundarrajan *et al.*, 1999) help to classify patients as low responders, normal responders or high responders and hence adapt the dose for gonadotrophin treatment accordingly. Genetic variations in the metabolism of clomiphene have been described to explain the different response rates to this drug (Rostami-Hodjegan *et al.*, 2004). Obviously, these patient-related factors cannot be changed in order to influence ovarian response. However, in addition to patient-related factors, the choice of a specific drug for ovarian stimulation might influence ovarian response. Therefore, this paper will also address the question as to whether or not different gonadotrophin preparations influence ovarian response.

In summary, this article addresses the phenomenon of intra-individual cycle-to-cycle variation in the ovarian response to ovarian stimulation regimens. The physiological basis for this phenomenon as well as strategies to minimize the impact of this variation will be discussed.

Ovarian folliculogenesis

In women with adequate ovarian reserve, response to stimulation treatment only varies within a certain range (Wheeler *et al.*, 1989). In these women, it has been shown that antral follicle count may be used as a predictor of ovarian response, as this determines the number of follicles that will grow in response to gonadotrophin stimulation in that particular cycle (Hendriks *et al.*, 2005).

However, in patients with diminished ovarian reserve, there

seems to be much more variability in response to gonadotrophin stimulation due to higher variability of antral follicles available.

This varying number of antral follicles available is reflected by the change in FSH concentrations from cycle to cycle in these patients (Landgren *et al.*, 2004; Miro *et al.*, 2004). This also explains why measuring FSH in two consecutive spontaneous cycles may predict the remaining ovarian reserve better than with a single measurement (Bancsi *et al.*, 2004). However, even with two measurements, a substantial number of patients are still misdiagnosed with regard to their ovarian responsiveness (Bancsi *et al.*, 2004; Kwee *et al.*, 2004).

Repetitive stimulation procedures and cycle-to-cycle variability

Patients undergoing repetitive cycles of ovarian stimulation did not demonstrate a decrease in the number of oocytes produced (Ron-El *et al.*, 1990). This was confirmed by the limited variation in consecutive cycles for intrauterine insemination treatment of regularly menstruating ovulating patients (Ahmed Ebbiary *et al.*, 1995). The OMEGA project group, which is an ongoing prospective cohort study in the Netherlands, could not demonstrate a decrease in the number of oocytes retrieved in those patients, who underwent at least seven consecutive IVF cycles, from cycle number 1 to cycle number 6 after adjusting for patients' age (de Boer *et al.*, 2004). Similar observations have been published by other workers (Kolibianakis *et al.*, 2002; Schroder *et al.*, 2004).

Caligara *et al.* studied oocyte donors and could not see an impairment of oocyte number or quality in consecutive cycles. However, one has to be aware that oocyte donors would not have pre-existing impairment of ovarian function compared with infertile patients (Caligara *et al.*, 2001). Therefore, if ovarian function is already impaired before stimulation therapy, a decrease in the number of oocytes retrieved may occur, as was shown in patients with ovarian endometriomas (Al Azemi *et al.*, 2000).

In conclusion, in patients with intact ovarian reserve, repetitive high-dose ovarian stimulation does not increase the risk of higher cycle-to-cycle variability. However, in patients with impaired ovarian function, it might decrease the number of oocytes retrieved after consecutive stimulation cycles. The number of oocytes retrieved is usually chosen as the primary end-point to look at cycle-to-cycle variability, as the majority of studies published so far lack the statistical power to look at clinical pregnancy rate or even live birth rate. Nonetheless, these would be the most relevant end-points to look at in order to find out whether cycle-to-cycle variability is just a phenomenon that might be observed during ovarian stimulation without any clinical relevance, or whether this really impacts on the overall outcome of assisted reproduction treatment.

Cycle-to-cycle variability in different stimulation regimens

Clomiphene citrate

There are no data available on the cycle-to-cycle variability in the response to clomiphene citrate. However, the differences in metabolism (Rostami-Hodjegan *et al.*, 2004) and the individual receptor distribution, i.e. the genetic disposition of the patient, may play a role in the different response of the endometrium as well as the pituitary release of FSH to stimulate the ovary endogenously.

Since the body mass index (BMI), the severity of oligo/amenorrhoea and the grade of hyperandrogenaemia are predictors of the ovarian response to clomiphene citrate (Imani *et al.*, 1998, 1999) in polycystic ovary syndrome (PCOS) patients, the biological variations of these parameters, especially hyperandrogenaemia, may influence the response to the drug.

The variation of ovarian response to different doses of clomiphene or from cycle-to-cycle may be small, since overall the number of stimulated follicles does not vary widely when 50 mg clomiphene citrate are compared with 100 mg or 150 mg for 5 days. This is reflected in the relatively low risk of multiple pregnancies with clomiphene citrate treatment, about 10–15% (Kousta *et al.*, 1997), even if high order multiple gestations are possible (Rosa *et al.*, 1995). This leads some authors to suggest monitoring only the first cycle with a certain dose, since cycle-to-cycle variation seems to be small (Nasseri and Ledger, 2001).

Ovulation induction with low-dose gonadotrophins

Low-dose ovarian stimulation, especially in patients classified in WHO group II (patients with hypothalamic–pituitary dysfunction and oligo/amenorrhoea) suffering from PCOS, has been evaluated extensively (Imani *et al.*, 2002; van Santbrink *et al.*, 2002; Eijkemans *et al.*, 2003a; Mulders *et al.*, 2003). These authors mainly concentrated on the predictability of the ovarian stimulation overall, and did not look for variation in the cycle-to-cycle response.

It is recommended, however, that in a step-up protocol the last dose used should be chosen as the initial dose in a new treatment cycle with the step-down protocol after cancellation of the stimulation cycle for no response of follicular growth (Imani *et al.*, 2002; Eijkemans *et al.*, 2003b; Mulders *et al.*, 2003). This reflects the experience of an apparently relatively constant dose–response from cycle to cycle.

Van Santbrink *et al.* (2002) described a group of 56 patients, who had been treated for ovulation induction with a step-down protocol. In 25% of the patients, the dose was changed initially from the standard of 150 IU daily to either a higher or a lower starting dose for the subsequent cycle, based on experiences with previous stimulation cycles (van Santbrink *et al.*, 2002). The authors observed three groups of patients during the actual treatment cycle: those who had an early step down of the urinary human menopausal gonadotrophin (uHMG) dose (group a), those with the standard procedure (group b) and those with a dose increase or no change of the initial dose (group c). Interestingly, those in group a had a mean of 28.5 IU above the predicted effective starting dose, those in group b of 13 IU above the predicted dose, and those in group c of 43 IU under the predicted starting dose in the subsequent cycle. This prediction was made using a previously established model

(Imani *et al.*, 2002). The authors argue that cycle-to-cycle variation occurs only in a small range (van Santbrink *et al.*, 2002). However, they also agree, that this hypothesis has to be proven in future studies.

Ovarian stimulation for assisted reproduction cycles

In cases of an assisted reproduction cycle for IVF or intracytoplasmic sperm injection (ICSI), usually higher doses of gonadotrophins are chosen to achieve polyfollicular growth. The required maximum dose of gonadotrophins is limited by the physiological response possibilities of the ovary to these drugs (Dorn, 2005).

A cycle-to-cycle variation of gonadotrophin response is a well-established clinical fact, which sometimes cannot be sufficiently explained by clinical data. Even if sometimes dramatic changes in ovarian response from cycle to cycle are observed, the overall intraindividual variability seems to be small (Wheeler *et al.*, 1989). Especially in long gonadotrophin-releasing hormone (GnRH) agonist protocols, severe suppression of endogenous gonadotrophins may result in a higher dose of gonadotrophins required for follicular stimulation. This grade of suppression can be measured by the FSH to LH ratio (Yamashita *et al.*, 1996). In GnRH antagonist cycles, the suppression of endogenous gonadotrophins is far less pronounced and only apparent over a short period of the stimulation cycle. Therefore overall gonadotrophin consumption in GnRH antagonist cycles is lower compared with the long agonist protocol (Al-Inany *et al.*, 2002).

Controlling the variables

Despite the use of different drugs for ovarian stimulation and the different treatment protocols the question remains as to whether or not different manufacturing processes of gonadotrophins may have an influence on treatment outcome. Does the consistency of the FSH content, the level of purity or contamination, or indeed the structural integrity of the FSH molecule affect the ovarian response?

Manufacturing processes – international standards

The production of parenteral drugs for human use requires the manufacturer to meet certain international standards. These standards are determined by ratified bodies, Regulatory Agencies, and are encompassed under the general term cGMP (current Good Manufacturing Practice). The objective of these standards is to ensure that all drugs meet the documented safety, efficacy and quality as submitted in the original dossier. The role of the manufacturer is to ensure that the drug meets all the quality aspects required of the product (e.g. US Code of Federal Regulations Title 21, parts 210–226). The quality aspects are also regulated through product monographs as published in International Pharmacopoieas (e.g. United States Pharmacopeia, European Pharmacopoiea) The monographs determine the minimum quality required for a drug product. If no monograph exists then the quality of the drug product is determined by the specific criteria proposed by the manufacturer and approved by the Regulatory Agencies.

Monographs for FSH

At present there is only one monograph for FSH. This monograph is published in the European Pharmacopoiea and is only applicable to urinary-derived FHS preparations (uFSH) (EP, 5th edition, Monograph, 01/2005:0958, Urofollitrophin).

Another monograph exists for uHMG and is published in both the British Pharmacopoeia and the United States Pharmacopeia (BP 1998 vol. 1: 855–857, *Monograph for Menotrophin*; USP vol. 29, 2nd supplement to USP 27, Monograph for Menotropins for Injection).

There are no official monographs, to date, for highly purified urine-derived gonadotrophins or recombinant FSH. However there is a draft monograph for highly purified urine-derived gonadotrophins (USP vol. 27, *Pharmacopeial Forum, In-Process Revision*, pp. 2207, 2001, urofollitropin, highly purified).

The monographs mentioned above represent the minimum quality that is required to release the drug product for human use (see **Table 1**).The FSH potency is assessed with the in-vivo bioassay (Steelman and Pohley, 1953). There are no specific criteria in the approved monographs for assessing the purity, the presence of contaminants, the level of degradation of the FSH molecule, or the distribution of the glycoforms. In fact, the only relevant assessment is the biological potency as measured by ovarian growth in immature rats against a background of LH/human chorionic gonadotrophin (HCG). The FSH bioassay is also specified in International Pharmacopoeias, and requires that the test is calibrated against the relevant WHO International Standard. Even with this apparent harmonisation of the FSH bioassay, the Pharmacopoeia Monographs allow a variability of actual potency (80–125% of the stated potency) within and between preparations.

Assessment of FSH potency

FSH demonstrates extensive heterogeneity, primarily due to the heterogeneous nature of the carbohydrate side-chains and in particular the sialic acid residues (Baenziger and Green, 1988). The carbohydrate side-chains have a specific role in receptor binding and activation, the biological activity and the systemic half-life (Lambert *et al.*, 1998). The in-vivo bioassay response to the different FSH glycoforms has been previously reported, with low sialic acid content glycoforms (more basic) having a relatively lower biopotency (Burgon *et al.*, 1993).

The glycoform pattern of uFSH preparations and recombinant FSH preparations are different (Robertson, 1977). The uFSH products are more acidic, due to the acidic nature of FSH produced in menopausal women, and are similar in pattern to the follicular or early mid-cycle in women. However, the recombinant FSH products are more basic and appear to be more similar to the pattern seen in late follicular or mid-cycle in women (Lambert *et al.*, 1995; Harris *et al.*, 1996; Anobile *et al.*, 1998).

The in-vivo bioassay assessment of any gonadotrophin preparation can give a potency of 75 IU, irrespective of the glycoform distribution (Mulders *et al.*, 1997). It is also apparent that the FSH glycoform, or isoform pattern, of the urine-derived

Table 1. Comparison of pharmacopoeial standards for release of gonadotrophins.

Release test	*Menotropin*	*Urofollitropin*	*Urofolllitropin, highly purified*
Biological assay	FSH : not less than 80% and not more than 125% of the potency stated on the label in terms of USP FSH LH: not less than 80% and not more than 125% of the potency stated on the label in terms of USP LH	FSH: not less than 80% and not more than 125% of the potency stated on the label in terms of USP FSH Not less than 90 IU/mg of protein	FSH: not less than 80% and not more than 125% of the potency stated on the label in terms of USP FSH Not less than 10,000 IU/mg of protein
Bioidentity test	n.a.	n.a.	Not less than 10,000 IU/mg of protein
Dimers and aggregates	n.a.	n.a.	Not more than 3% of the urofollitropin
Residual LH	n.a.	Not more than 1.7% of the urofollitropin	Not more than 0.01% of the urofollitropin
Isoforms	n.a.	n.a.	No isoforms outside pI 3.5–5.2, and isoforms between pI 4.0–5.0 represent not less than 70%
Purity	n.a.	n.a.	Not less than 97%
Constituted solution	As per USP	As per EP	As per USP
Sterility	As per USP	As per EP	As per USP
HIV and hepatitis virus	n.a.	Not detected	n.a.
Bacterial endotoxin	Not more than 2.5 USP endotoxin units per USP FSH unit	n.a.	Not more than 0.8 USP endotoxin units per USP FSH unit

n.a. = not applicable; USP = United States Pharmacopeia; EP = European Pharmacopoiea.

FSH products (or HMG) may not be routinely assessed during the manufacture and is not required to release the product for human use.

Physicochemical characterization of FSH

The current pharmacopoeial monographs do not require any assessment of the purity and quality of the FSH in urine-derived preparations. However the manufacturers of recombinant human FSH (rhFSH) routinely assess the purity, the presence of potential contaminants, the integrity of the FSH molecule, the glycoform pattern and the biopotency (De Boer and Mannaerts, 1990; Siebold, 1996; Driebergen and Baer, 2003; Gervais *et al.*, 2003; Bassett and Driebergen, 2005).

Analytical assessment of many urine-derived FSH preparations has demonstrated that the FSH purity is low, with identified protein contaminants and high concentrations of degraded FSH (Giudice *et al.*, 1994, 2001; van der Weijer *et al.*, 2003; Bassett *et al.*, 2005). As these elements are not routinely measured or required for release for human use, they must be regarded as uncontrolled parameters. The very high purity of rhFSH allows the characterization of the molecule in every production lot (de Leeuw *et al.*, 1996; Siebold, 1996; Horsmann *et al.*, 2000; Bagatti *et al.*, 2001).

The in-vivo bioassay assessment of these urine-derived preparations can give a potency of 75 IU irrespective of the FSH purity, level of contaminants and integrity of the FSH.

Consistency of FSH preparations

There has been renewed interest in the consistency of commercially available FSH preparations. Previously it was stated that the FSH and LH bioactivity content of urine-derived preparations varied considerably (Rodgers *et al.*, 1993, 1995), and thus the glycoform composition was also inconsistent (Lambert *et al.*, 1998). Further studies on a highly purified urofollitropin demonstrated that the degree of sialylation of the oligosaccharides, biological and immunological content were consistent (Wolfenson *et al.*, 2005). However, the data was limited and no isoform or quantitative purity assessment was performed.

In contrast, rhFSH preparations have been more extensively studied, and the anticipated improvement in quality (Lambert *et al.*, 1998; Rose *et al.*, 2000) has been demonstrated (Driebergen and Baer, 2003; Bassett and Driebergen, 2005; Mulders *et al.*, 2005).

Evidently the urine-derived and recombinant preparations deliver the same potency (75 IU or the relevant target

potency) but with limited confidence of 80–125%. This level of confidence can be improved to 90–110% by repeating the bioassay multiple times (Mulders *et al.*, 1997).

However, the FSH present in urine-derived preparations can vary in terms of purity, level of contaminants, concentration of degraded FSH and the isoform pattern (Giudice *et al.*, 1994, 2001; van der Weijer *et al.*, 2003).

Alternatives to biopotency

Recently, another approach to assessing the FSH content of rhFSH was proposed (Driebergen and Baer, 2003). The manufacturer has demonstrated that the rhFSH (follitropin alpha) produced has a consistent glycoform pattern and hence a strong relationship of FSH protein content to biopotency. This approach allows the FSH to be assessed with a precise size exclusion high performance liquid chromatography (SE-HPLC) assay. The variability of the FSH content between production lots has now been estimated at 1.6%, in combination with high purity, no contaminants, an intact FSH molecule with low levels of degradation, and a consistent glycoform pattern (Bassett and Driebergen, 2005).

Now a preparation of 75 IU has a consistent FSH content, and the clinical response will not be affected by variations between product lots.

The ability to produce a hormone preparation that can be characterized and confirmed as consistent and pure means that this product can now be quantified in terms of its mass, in micrograms of protein. The quantity of follitropin alpha in any given sample can be measured by using an optimized physicochemical method, SE-HPLC. The specific activity of the rhFSH is expressed in IU/mg protein, and specific activity data have been analysed for 100 follitropin alpha drug substance batches manufactured over a 3-year period, from nine different bioreactor runs. This analysis showed that the specific activity of follitropin alpha batches was normally distributed, stable, and that there was no effect of different bioreactor runs. The average specific activity of the product is 13,645 IU/mg, and therefore a mass of 5.5 µg is equivalent to 75 IU (Driebergen and Baer, 2003). These values were subsequently confirmed on a total of 309 batches of follitropin alpha drug substance (Bassett and Driebergen, 2005).

There is a general trend for European regulatory agencies (European Directive 86/609) as well as a commitment of the European Pharmacopoeia Commission (Technical Guide for elaboration of Monographs for Biologicals, 2003) to recommend replacing the International Unit as a standard of measurement (ICH guideline Q6B), by using reliable and precise physicochemical analytical methods instead of in-vivo bioassays. As a result of the tightly controlled manufacturing process and sophisticated characterization methodology that ensures the integrity and consistency of each batch of the final product, follitropin alpha can now be filled according to mass (micrograms of protein) (follitropin alpha filled by mass: FbM), instead of relying on bioactivity as measured by an imprecise in-vivo bioassay (follitropin alpha filled by bioassay: FbB). A recent analysis assessed the manufacturing consistency of the rhFSH follitropin alpha, and compared the analytical data for follitropin beta (Bassett and Driebergen, 2005). The data showed high purity and batch-to-batch consistency for follitropin alpha in terms of specific activity, protein content, glycan mapping, isoform pattern and purity. The batch-to-batch variability of FSH in protein content and isoform distribution was lower for follitropin alpha FbM batches analysed (1.6%, n = 30) than for follitropin beta batches analysed (12%, n = 10). The thorough characterization and improvements in quality and consistency of recombinant human follitropin alpha now allows it to be reliably quantified by mass, so that one of the major goals in controlling the variables – the quest for consistency – has been fulfilled.

Role of isoforms

It has been demonstrated that follitropin alpha (FbM) not only has a consistent FSH content, but also has a consistent isoform profile from batch to batch. It is also clear that the isoform profile of u-FSH and rhFSH preparations are different, with uFSH composed of more acid complex glycoforms, and rhFSH composed of more basic simple glycoforms. Only recently, the potential clinical significance of the FSH isoform profile (Yding Andersen *et al.*, 2004) was discussed and the meta-analysis suggested that rhFSH preparations perform better than u-hFSH, especially with regard to parameters related directly to the effect of FSH on the follicle. In addition, it can also be assumed that an rhFSH preparation with a consistent FSH isoform profile will perform more consistently.

So, from a pharmaceutical perspective, the physiological response of the FSH receptor can be affected by the absolute quantity of exogenous FSH present and by the FSH isoform distribution. It has been demonstrated that rhFSH preparations that are based on FSH protein content are more consistent between production lots when compared with preparations based on bioassay (Bassett and Driebergen, 2005). This increased consistency improves the confidence that the FSH content injected is within a very narrow range. Furthermore, the FSH isoform profile has a profound effect on FSH receptor affinity and elimination by the liver (Lambert *et al.*, 1998). An rhFSH preparation with a consistent isoform profile could provide a more consistent FSH-receptor response.

Clinical benefits of follitropin alpha FbM

The physicochemical characteristics, consistency and isoform profile for follitropin alpha FbM have been discussed. However, the question remains as to whether or not the higher consistency of this product compared with other gonadotrophin preparations has a clinical impact. The efficacy of follitropin alpha FbM has been investigated in a number of studies on both ovulation induction and IVF/ICSI.

Ovulation induction

Yeko *et al.* (2004) compared follitropin alpha FbM versus follitropin-alpha FbB in patients with WHO II ovarian insufficiency. These patients (PCOS) are at high risk of developing ovarian hyperstimulation syndrome (OHSS) under ovarian stimulation therapy. Yeko *et al.* showed that

follitropin-alpha FbM allows more precise dosing compared with follitropin alpha FbB, leading to improved control of follicular development. This was reflected by a decrease in the percentage of cancelled cycles. Furthermore the number of treatment days and mean dosage required was less for patients treated with follitropin alpha FbM compared with those treated with follitropin-alpha FbB. Looking at pregnancy rates for both groups, Yeko *et al*. (2004) showed that patients treated with follitropin-alpha FbM achieved higher pregnancy rates in the first and second treatment cycle as well as higher cumulative pregnancy rates compared with patients treated with follitropin-alpha FbB; however, differences between the groups were not significant.

IVF/ICSI

Hugues *et al*. (2003) presented a multicentre, prospective randomized study comparing follitropin alpha FbM versus follitropin-alpha FbB in a double-blind design. Three centres participated in the study. They used four lots of rhFSH filled by bioassay (IU) versus four batches rhFSH filled by mass (FbM). Hugues *et al*. showed that patients treated with follitropin alpha FbM had a more consistent ovarian response compared with patients treated with follitropin-alpha FbB. There were fewer cycles with hypo- or hyper-response respectively in the FbM group. Furthermore pregnancy rates achieved were more consistent between the centres in the follitropin-alpha FbM group.

Balasch *et al*. (2004) compared follitropin-alpha FbM versus follitropin-alpha FbB in 250 patients. A total of 125 patients were randomized per group undergoing their first IVF/ICSI cycle. Balasch showed that treatment with rhFSH FbM was more effective, in particular with respect to a significantly shorter duration of ovarian stimulation and a trend for higher clinical pregnancy rates. In their discussion, the authors suggested that the shorter treatment duration was due to higher batch-to-batch consistency of FbM and that the higher implantation and pregnancy rates were due to more synchronized follicle recruitment (Balasch *et al*., 2004).

In addition to the above-mentioned studies, a number of multicentre trials have been published looking at efficacy and safety of follitropin-alpha FbM (Abuzeid *et al*. 2001; Lass and McVeigh, 2004; Ludwig and Bilger, 2004). Although these are not randomized controlled comparative trials, they show how the new rhFSH preparation (FbM) is used in daily practice. The study reported by Ludwig and Bilger (2004) is a post-marketing surveillance analysis. In this analysis data from 10,469 patients undergoing 12,375 treatment cycles were investigated. The authors reported a remarkably low incidence of OHSS (grade III), as low as 0.42%. This was confirmed by Lass and Mc Veigh (2004), who reported on the use of follitropin-alpha FbM in 21 IVF centres. A total of 1427 patients were included in the study and only five cases of severe OHSS were reported. The results of these observational trials indicate that not only under properly controlled randomized controlled trial conditions but also under routine clinical conditions, follitropin-alpha FbM allows an accurate and precise dosing, resulting in consistent ovarian response and thereby widely avoiding excessive response leading to OHSS.

Conclusion

This article addresses the question of predictability of ovarian response. Patient related factors as well as drug related factors are discussed.

Cycle-to-cycle variability for gonadotrophin treatment in patients with intact ovarian reserve is rather limited. However, in patients with impaired ovarian function repetitive treatment cycles usually lead to a decrease in the number of oocytes retrieved.

There seem to be individual differences in clomiphene citrate metabolism as well as in individual receptor distribution that contribute to differences in patients' responses to clomiphene. However, solid data on cycle-to-cycle variability under clomiphene citrate treatment are not available.

Besides patient-related factors, variability in ovarian response may be influenced by different drugs used for ovarian stimulation. At present available hFSH preparations widely differ in purity, consistency, degree of contamination and isoform profile. Biopotency of gonadotrophins was traditionally measured by the Steelman–Pohley assay, a bioassay with an intrinsic variability up to 20%.

Recombinant follitropin alpha has been shown to have a consistent FSH isoform profile, strongly related to FSH biopotency. Therefore follitropin alpha can now be filled by mass. It has been shown that 5.5 µg follitropin alpha is equivalent to 75 IU. Results of recent studies indicate that treatment with follitropin-alpha FbM results in consistent ovarian response, fewer treatment days and fewer cancelled cycles. This is an important step towards further minimizing drug-related variability of ovarian response.

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