Hum. Reprod. Advance Access published September 21, 2010
Human Reproduction, Vol.00, No.0 pp. 1–7, 2010
doi:10.1093/humrep/deq247

human reproduction DEBATE

Mild ovarian stimulation for IVF: 10 years later

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Ovarian stimulation to achieve multiple follicle development has been an integral part of IVF treatment. In the context of improved laboratory performance, the need for a large number of oocytes as an integral part of a successful IVF programme may be questioned. The aim of the current debate is to summarize the studies performed during the last decade to develop the concept of mild stimulation aiming to obtain fewer than eight oocytes. Here we examine the balance between IVF success and patient discomfort, and complications and cost, and how these might improve by simpler ovarian stimulation protocols aimed at retrieving fewer oocytes. We intend to analyse why progress has been rather slow and why there is much resistance to mild stimulation. Finally, presumed useful directions for future research will be discussed.

Key words: mild ovarian stimulation / IVF / GnRH antagonist / infertility / FSH

Definition of mild ovarian stimulation for IVF

The administration of low doses (fewer days) of exogenous gonadotrophins in GnRH antagonist co-treated cycles, and/or oral compounds (like anti-estrogens, or aromatase inhibitors) for ovarian stimulation for IVF, aiming to limit the number of oocytes obtained to less than eight.

Introduction

Ovarian stimulation to achieve multiple follicle development has been an integral part of IVF treatment for the past 30 years. Multiple oocytes subsequently retrieved, compensate for inherent biological limits along with imperfect laboratory performance in relation to *in vitro* oocyte fertilization, embryo development in culture, embryo selection for fresh transfer and the cryopreservation of surplus embryos (Fauser *et al.*, 2005). In the context of improved laboratory performance, the need for a large number of oocytes as an integral part of a successful IVF programme may be questioned. In contrast to current approaches, mild ovarian simulation for IVF intends to limit the number of oocytes obtained to fewer than eight (Nargund *et al.*, 2007a; Zegers-Hochschild *et al.*, 2009).

IVF is increasingly applied worldwide, with a delivery rate per started cycle of around 22% and close to 250 000 children born according to the most recent global registry involving the year 2002 (ICMART, 2009). Twenty-six percent of pregnancies were twins and 2.5% triplets. Much effort is geared towards maximizing pregnancy rates per cycle, representing the 'success' parameter usually applied by national and international registries (Nyboe Andersen *et al.*, 2009). In recent years, increasing attention is being paid to the significance of the birth of a singleton healthy baby and the avoidance of long-term inter-generational effects of ovarian stimulation as well as IVF itself.

Protocols currently applied in most clinics—with a target of generating between 8 and 15 oocytes—are complex, time consuming and expensive and may give rise to considerable patient discomfort and chances for complications, especially the ovarian hyperstimulation syndrome (OHSS) (Macklon *et al.*, 2006). Although studies published to date concerning long-term health implications of (repeated) ovarian stimulation seem reassuring, more adequately powered prospective reports with a sufficient duration of follow up should be awaited before definitive conclusions can be drawn.

Medication frequently applied for ovarian stimulation includes combined steroid contraceptive pretreatment, GnRH agonist initiated in the pre-stimulation cycle (to induce pituitary quiescence

2–3 weeks later), daily gonadotrophin injections for almost 2 weeks (using different doses and preparations) and a bolus dose of hCG to induce final oocyte maturation at the end of the stimulation phase. Such stimulation regimens may easily involve 2 months of medication, requiring close monitoring of ovarian response and frequent visits to the clinic. In many countries, medication and monitoring expenses outweigh the cost of the IVF procedure itself. These medication regimens may allow flexibility in terms of programming oocyte retrieval and subsequent IVF procedures and may therefore serve the logistics of the clinic. However, it is increasingly questioned whether the interest of the patient is served by such an approach.

Despite the notion that use of GnRH antagonists allows for less complex and shorter stimulation procedures, its clinical acceptance has been rather slow (Tarlatzis *et al.*, 2006; Devroey *et al.*, 2009). Moreover, the availability of GnRH antagonists has allowed for the development of simpler, milder and cheaper stimulation protocols (Fauser *et al.*, 1999; Verberg *et al.*, 2009a). Mild ovarian stimulation has not yet been tested in the context of ovarian aging.

The current state of affairs

Eleven years ago an editorial appeared in this journal aiming to evaluate the pros and cons of mild ovarian stimulation protocols for IVF (Fauser *et al.*, 1999). Since then, progress in their use has been rather slow and the concept of mild stimulation (Nargund *et al.*, 2007a) has been accepted by only a few clinicians (Pennings and Ombellet, 2007; Ubaldi, 2008; Verberg *et al.*, 2009a; Aanesen *et al.*, 2010).

The aim of the current debate is to summarize the studies performed during this decade (2000–2010) to develop the concept of mild stimulation and analyse why progress has been rather slow. Finally, presumed useful directions for future research will be discussed. We have chosen to use a format often applied in a business environment, the so-called SWOT (Strength Weakness Opportunity Threat) analysis which is occasionally applied in biomedicine (Ferrer *et al.*, 2009).

Strength

GnRH antagonist

Although the use of GnRH antagonist co-treatment may not be an absolute requirement for mild ovarian stimulation (Fernandez-Shaw *et al.*, 2009), it certainly facilitated the development of this concept since no medication is required for the stimulation of follicle development during the early follicular phase of the menstrual cycle (for review, see Fauser and Van Heusden, 1997) (Fig. 1).

There may be room for a short (so-called 'flare') GnRH agonist protocol in the development of mild ovarian stimulation, although no data are currently available in this context. A single retrospective study proposed the possibility of mild IVF using a GnRH agonist long protocol and 100 IU/day recombinant FSH (Fernandez-Shaw *et al.*, 2009).

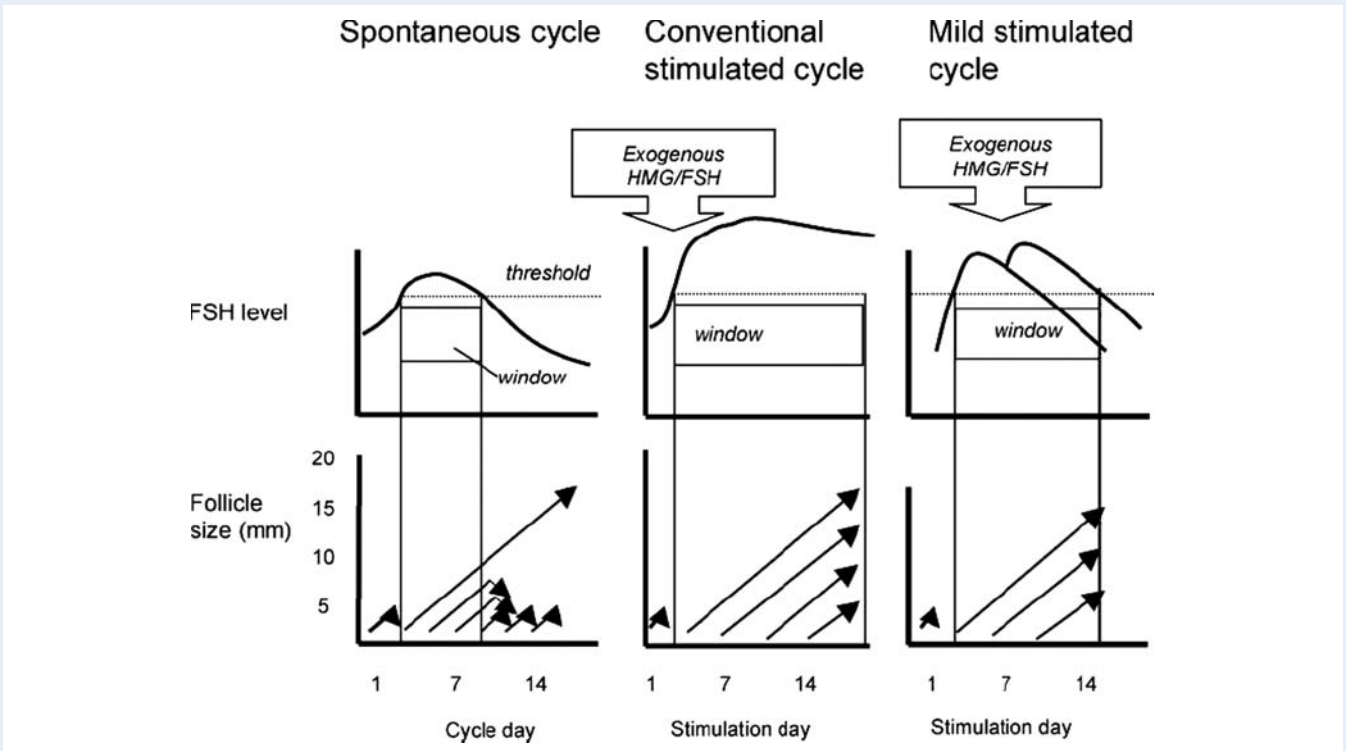

Figure 1 Schematic representation of the FSH threshold/window concept in relation to single dominant follicle selection during the follicular phase of the normal menstrual cycle, multiple follicle development and high FSH levels in conventional ovarian hyperstimulation when compared with more subtle interference with decreasing FSH concentrations. From Macklon *et al.* Endocrine Reviews 2006 (with permission).

Similar live birth rates per started treatment

Mild stimulation regimens applying a daily dose of 150 IU recombinant FSH starting on cycle Day 5, along with GnRH antagonist flexible start, reported a 35% reduction in the number of oocytes retrieved, with a median of six compared with nine following standard stimulation (Verberg *et al.*, 2009b). A randomized controlled comparative trial testing the strategy of mild stimulation combined with single embryo transfer reported term live birth over a 1-year treatment period to be similar compared with conventional IVF (Heijnen *et al.*, 2007).

Reduced complexity, patient discomfort and risk

Mild stimulation is meant to apply lower doses and fewer days of gonadotrophins (which may be combined with oral off-patent drugs), and be less complex, improving compliance. This may diminish patient distress (de Klerk *et al.*, 2007) and complications such as OHSS (Heijnen *et al.*, 2007), and may reduce the need for frequent visits to the clinic resulting from intense monitoring of ovarian response. Mild stimulation protocols have been shown to decrease drop-out rates and to allow a higher acceptance of repetitive IVF cycles (Højgaard *et al.*, 2001; De Klerk *et al.*, 2007; Pelinck *et al.*, 2007; Verberg *et al.*, 2008).

Reduced cost

Improved overall health economics of mild IVF treatment has been reported. Medication costs per cycle were significantly less, but this should be viewed in the context of reduced pregnancy rates per cycle. Over 1 year of treatment, medication costs were similar comparing mild versus standard stimulation (involving on average 2.2 and 1.8 cycles, respectively). When mild stimulation is combined with a single embryo transfer policy, costs associated with pregnancy complications were dramatically decreased (Polinder *et al.*, 2008).

Beneficial effect on oocyte/embryo quality

The essential aim of mild stimulation is to remain as close as possible to normal ovarian physiology (Fauser and van Heusden, 1997), allowing for only few follicles to continue their development by restricting ovarian stimulation to the mid- to late-follicular phase (Macklon *et al.*, 2006). Preliminary studies suggest that this approach may be beneficial for both oocyte/embryo quality (Baart *et al.*, 2007) and endometrial receptivity (Devroey *et al.*, 2004).

Weakness

Lower pregnancy rates per cycle

In the large RCT of conventional versus mild IVF the ongoing pregnancy rate per started cycle was reduced from 29 to 18%, respectively (Heijnen *et al.*, 2007), especially because of a high cancellation rate. However, cancellation criteria following mild stimulation may need to be revised. The optimal number of oocytes seems to be significantly lower with mild IVF (Verberg *et al.*, 2009b).

Lower 'success' rates

Even though the mild stimulation approach with single embryo transfer reduced the observed pregnancy rates per cycle, the overall delivery rate at term during a 12-month treatment period was the same as conventional IVF (Heijnen *et al.*, 2007). However, national as well as regional registers (Nyboe Andersen *et al.*, 2009) only publish delivery rates per individual cycle, where a mild approach will invariably fall short in comparison. In the British Human Fertilization and Embryology Authority reporting (www.hfea.gov.uk), delivery rates per cycle from individual clinics are disclosed to the patients: this could cause concerns for any clinic, if data of this type of 'league table' exclusively focus on efficacy.

Excessive responses

Even mild ovarian stimulation may give rise to an excessive oocyte number in a proportion of women (Verberg *et al.*, 2009b). This may be related to the inherent modest prediction capacity of known response prediction parameters (Popovic-Todorovic *et al.*, 2003; Fauser *et al.*, 2008). The use of antral follicle counts and serum anti-Mullerian hormone levels may assist in the design of future studies as well as clinical decision-making.

Cost of medication still high

Current mild stimulation protocols are still too expensive for developing countries. Even though gonadotrophin consumption is less in GnRH antagonist co-treatment cycles, the current price of 3–5 doses of GnRH antagonist equals the cost of an agonist. Moreover, the cost of luteal phase supplementation will be the same.

Less margin for suboptimal laboratory performance

When starting with a limited number of oocytes, excellent laboratory performance is an absolute requirement for mild stimulation to generate acceptable pregnancy rates. Hence, oocyte fertilization rates, development rates of good-quality embryos and implantation rates of embryos transferred should be optimal.

Fewer embryos for cryopreservation

Fewer cryopreserved embryos per oocyte harvest may give rise to fewer added deliveries following thawing and thus reduce the overall efficacy of a single stimulated cycle. For example, in Finland, the delivery rate per stimulated cycle has been estimated to increase from 21.3% after fresh transfer to 31.6% when thawed embryos are also included (Nyboe Andersen *et al.*, 2009).

Difficult programming of the cycle

Programming of IVF cycles is performed using oral contraceptive (OC) pretreatment. Some of the advantages of a short medication period disappear when OC or other drugs are used. In addition, a recent meta-analysis suggests that OC pretreatment lowers the pregnancy rates (Griesinger *et al.*, 2010).

The use of alternative medication in the luteal phase for timing of the withdrawal bleeding and programming of the IVF cycle (Fanchin, 2005; Guivard-Leveque *et al.*, 2010) needs to be studied further before being implemented. Implications of the advancement or delay of hCG to avoid weekend oocyte retrievals also requires further investigation (Kolibianakis *et al.*, 2005; Tremellen and Lane, 2010).

Individualized FSH-dosing algorithms not yet available

Presently, algorithms for individualized FSH dosing based on initial patient characteristics (Popovic-Todorovic *et al.*, 2003; Fauser *et al.*, 2008; Olivennes *et al.*, 2009) are not yet available for mild stimulation. There is a clear need to further develop models and test interventions in relation to individualizing FSH doses in mild ovarian stimulation strategies (Verberg *et al.*, 2007).

Lack of 'robustness'

With mild IVF using either a late start of stimulation (Kolibianakis *et al.*, 2004) or low FSH doses, follicle growth dynamics may be different compared with the GnRH agonist long protocol. When the antagonist protocols were introduced, it was indeed suggested that clinicians had to go through a 'learning curve' when switching from use of agonists to antagonists. The window of scheduling hCG using GnRH antagonist co-treatment seems narrower compared with agonist cycles (Kolibianakis *et al.*, 2005).

Opportunities

Further development of low cost stimulation regimens

Although the use of clomiphene citrate in ovarian hyperstimulation went out of fashion in the 1990s, more recent reports describe clomiphene citrate in combination with GnRH antagonist as a viable alternative to exogenous FSH in good-prognosis patients (Lin *et al.*, 2006). A larger number of oocytes may not equate to a larger number of euploid embryos (Baart *et al.*, 2007). Accepting that fewer oocytes are needed opens the possibility of using unconventional stimulation regimes, including those with clomiphene citrate or aromatase inhibitors. Modifications of the revived clomiphene citrate protocols (Lu *et al.*, 1996; Branigan *et al.*, 2000; Williams *et al.*, 2002) have given pregnancy rates per started cycle of 21–29%. If drug cost has to be reduced substantially allowing its use in low-resource settings, oral compounds like clomiphene citrate alone with no luteal phase support may be preferred (Ingerslev *et al.*, 2001).

Mild ovarian stimulation has not yet been studied in women of more advanced reproductive age. Although IVF success rates will be low following mild stimulation (just like any other approach in such patients), mild regimens may still be preferred for health economics and patient discomfort reasons. In the future, the low-dose hCG may replace FSH in the late-follicular phase in GnRH antagonist cycles (Blockeel *et al.*, 2009). Finally, effects of mild versus conventional ovarian stimulation in relation to oocyte/embryo chromosomal competence, as well as endometrial receptivity, should be studied in greater detail.

Many European countries are struggling with economic recession and patients will demand full value for money from their IVF clinic. This again presents an opportunity for mild IVF. Mild IVF requires fewer clinic visits for monitoring, with less interruption to the woman's working life (Dixon *et al.*, 2008; Polinder *et al.*, 2008).

Improved safety

Meta-analysis clearly shows a reduction in the incidence of OHSS in GnRH antagonist cycles when compared with the GnRH agonist long protocol (Kolikianakis *et al.*, 2006). While mild stimulation alone may not eradicate OHSS, the number of patients with the severe form of the disorder is reduced to approximately half (Heijnen *et al.*, 2007). This will potentially reduce health risks for women and government costs involved in hospitalization and management of OHSS. Reducing the trigger dose of hCG could also lower the incidence of OHSS (Nargund *et al.*, 2007b). The use of a GnRH agonist bolus dose to trigger final oocyte maturation instead of hCG seems also useful in preventing OHSS in GnRH antagonist cycles (Kol and Dor, 2009).

Increased access to treatment

Mild IVF will allow more patients to be treated, at lower cost, with less delay and with greater patient safety and acceptability in both the developing and the developed world. Although cost of medication per cycle is reduced using mild stimulation, this approach is still way too expensive to really improve access to IVF treatment in developing countries.

Improved performance of embryo cryopreservation programmes

The high pregnancy rates seen with vitrified frozen embryos provide further opportunities in mild IVF cycles. It may be that in the future, clinicians will choose to avoid embryo transfer in the stimulated cycle altogether. It is clear that endometrial biology is significantly altered after a cycle of FSH stimulation when compared with the natural cycle (Devroey *et al.*, 2004), which is hardly surprising given the unphysiological concentrations of sex steroids, inhibins and growth factors which result (Simon *et al.*, 1995).

Increasing focus on patient-centred approaches

Mild ovarian stimulation with GnRH antagonists and low-dose FSH stimulation is preferred by women over the traditional long protocol (Verberg *et al.*, 2008). Acceptability may be further enhanced by a reduction in the number of injections when using the long-acting gonadotrophin preparations (Fauser *et al.*, 2009), or—in the future- oral gonadotrophin-like compounds.

As shown in GnRH antagonist and very-low-dose FSH protocols for intrauterine insemination, the use of dosing models based on simple parameters, such as body weight and antral follicle count, increases the number of cycles with appropriate ovarian response (Freiesleben *et al.*, 2008). There seems much room for further adjusting mild stimulation regimens based on individual patient characteristics (Verberg *et al.*, 2007). Altered FSH doses and starting days should be studied in the context of various patient characteristics, such as age, ovarian reserve parameters (Broekmans *et al.*, 2009) and body weight. Individualized mild stimulation approaches may reduce chances for both hypo- and hyperresponse.

In addition, women may feel it more natural to conceive in a normal, drug-free monthly cycle rather than in the stimulated cycle, with an acceptance of replacement of one embryo at a time over several months in a practically stress free environment. The use of GnRH antagonist could help to reduce cancellations and improve live birth rates in modified natural cycle IVF (Pelinck *et al.*, 2005; Nargund *et al.*, 2007a).

Developing IVF for non-infertility indications

The future will see an expansion in the number of women using IVF for unconventional reasons. IVF required to allow PGD or for oocyte cryopreservation in young women with cancer, demands the safest and least unpleasant strategies for ovarian stimulation to be used. This group will be particularly attracted to a mild approach, which also allows more rapid completion of the stimulation cycle compared with GnRH agonist long protocol. However, with 25–50% chances for genetic abnormalities, more embryos may be required for successful PGD treatment. Great care is also required in the stimulation of oocyte donors—often young women at high risk of OHSS. In addition, oocyte donors may benefit from triggering oocyte maturation with GnRH agonist, which will reduce post-retrieval side effects.

Threats

The external threats to the wider use of mild stimulation IVF can be grouped as those coming from clinicians, those associated with patient characteristics and a third group of cost considerations.

Clinical resistance

IVF has established protocols that are yielding increasingly good results (Nyboe Andersen *et al*., 2009). Clinicians are comfortable with long GnRH agonist protocols and their IVF clinic routines would need adjustment in order to adopt mild stimulation protocols (which call for the use of GnRH antagonist). Having to revise scheduling makes mild stimulation less attractive. Changing clinical routines may cause more trouble with less programming of oocyte retrievals on weekends.

Also, mild stimulation protocols are associated with lower pregnancy rates per cycle although term birth rates after 1 year were similar (Heijnen *et al*., 2007). Clearly there are clinical barriers to protocols that require more cycles to achieve similar results, even if there are fewer multiple births. There is pressure on clinicians to achieve the highest results in each stimulation cycle without regard to the rewards for the patient and offspring from single fresh and cryopreserved embryo transfer cycles. IVF is often offered in a successful commercial environment that would inhibit the adoption of new approaches that may impose financial risks.

A final issue is resistance to change, which may be fuelled by competition among service centres, and by the difficulty of adapting IVF registries to record healthy singleton live births per started IVF treatment rather than per cycle.

Patient characteristics

One patient characteristic that threatens wider uptake of mild stimulation IVF is the ever-increasing age of women with infertility who seek IVF. Because dose-finding trials for gonadotrophin stimulation generally do not involve older women, mild ovarian stimulation has not yet been tested in women who are more than 38 years of age.

Cost considerations

Paying for IVF by the stimulated cycle is another threat to wider use of mild stimulation IVF. The economics of IVF differs among countries and among regions within countries, but in most cases the focus is on public or private payment per stimulated cycle. The benefit of mild stimulation IVF is a reduced frequency of OHSS and, with single embryo transfer, a reduced likelihood of multiple births. Since it takes more IVF cycles to achieve an equivalent live birth rate, the downside of this benefit can be avoided only through the provision of additional mild stimulation cycles. Paying a fixed price for a given IVF cycle is a barrier to optimal utilization of the embryos from that cycle because cryopreserved cycles are an additional cost burden.

Another threat to mild stimulation IVF is coverage of a fixed number of cycles by public or private health insurance plans, which does not allow for the additional cycles needed to achieve equivalence in outcomes compared with conventional stimulation IVF. The savings of mild IVF may not be so evident to the policy analysts advising on IVF coverage, however, if newborn costs are paid from a different budget from IVF costs (Polinder *et al*., 2008).

Proposed directions for further research in the development of mild ovarian stimulation for IVF

- A shift in emphasis from mild stimulation towards mild ovarian response. Such an approach may reduce both cancellation and over-response rates by developing more individualized treatment regimens based on initial patient characteristics, such as age, body weight and ovarian reserve characteristics.
- Further improvement of the quality of embryo development, embryo selection for transfer and cryostorage of surplus embryos increasing the overall (cumulative) pregnancy chance per stimulation cycle applying a strict single (fresh and cryopreserved) embryo transfer policy.
- Developing cheaper stimulation regimens (using oral off-patent drugs) meeting the immense challenge of improving overall global access to IVF treatment.
- Establish improved patient acceptance (also involving reduced drop-out rates from successive IVF cycles), reduced complication rates and improved children outcomes applying mild IVF in everyday clinical practice.
- Test the effectiveness of mild ovarian stimulation in women of more advanced reproductive age.
- Rethink the definition of ‘successful’ IVF (and modify national and global IVF registries accordingly) better representing the interests of the woman, the child and society.

Authors’ roles

All authors declare that they have been involved in designing the outline of this paper, and in the actual writing of sections of the paper. They have all read and approved the final version of the manuscript and take full responsibility for its content.

Funding

B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order); Andromed, Ardana, Ferring, Genovum, Glycotope, Merck Serono, Organon, Pantharei Bioscience, Philips, PregLem, Schering, Schering Plough, Serono and Wyeth. G.N. has nothing to declare. R.N. has received fees and grant support from

Schering Plough, Merck Serono and IBSA. B.B.T. received unrestricted research and travel grants from Merck Seronoand Organon Schering Plough and travel grants from IBSA and Ferring. A.N.A. has participated in international multicentre trials and served in *ad hoc* advisory boards involving, Merck Serono, Schering-Plough/Organon and Ferring. J.B. has received research funding from Merck Seronoand honorariums from Schering Plough. W.L. has participated in consultancy activities for Schering Plough and SPD, and obtained research support from Ipsen, Ferring and Merck Serono.

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