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ARTICLE

Targeted gonadotrophin stimulation using the PIVET algorithm markedly reduces the risk of OHSS

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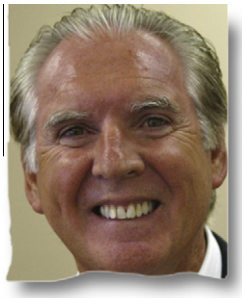

Dr John L Yovich, MBBS, MD, FRANZCOG, FRCOG, CREI, has published extensively in many areas of fertility management over more than 30 years and has a major interest in minimally invasive surgery of the female as well as both clinical and surgical management of the male. He strongly believes that assisted reproductive technology can be improved further, mainly by automated developments at egg retrieval and within the laboratory.

Abstract PIVET Medical Centre has developed an empirical algorithm for the dose of FSH administration based upon day-2 FSH, antral follicle count, anti-Müllerian hormone, body mass index, age and smoking parameters in an attempt to reduce the incidence of ovarian hyperstimulation syndrome particularly in at-risk women with elevated antral follicle count and anti-Müllerian hormone. The algorithm utilized the incremental dosage capabilities of the recombinant FSH pens to fine-tune the daily concentration of FSH. Application of the algorithm aimed to minimize any form of excessive follicle recruitment that necessitated increased clinical awareness. The measure used to assess the impact of the algorithm was the number of women who, after oocyte retrieval, were considered to be potentially at risk of any degree of OHSS and were allocated to increased monitoring. Compared with the previous 20-month period, introduction of the algorithm significantly reduced both the incidence of referral for increased monitoring, treatment for OHSS and the incidence of freeze-all cycles (all $P < 0.05$). This was particularly focused on those considered to be at risk without reducing the fresh cycle pregnancy rate.

KEYWORDS: IVF, rFSH dose, ovarian hyperstimulation syndrome (OHSS), antral follicle count (AFC), anti-Müllerian hormone (AMH), BMI

Introduction

Historically, ovarian stimulation was viewed as a major advance in IVF, leading to multiple-embryo transfer procedures and increased cumulative pregnancy rates. A significant advantage of ovarian stimulation cycles is that surplus embryos may be cryostored allowing for future attempts at pregnancy without the exposure to gonadotrophins or need for a further oocyte retrieval procedure. When introduced in the early days of IVF, the purity of the hormone preparation was highly variable and resulted in increased and unpredictable numbers of women who experienced ovarian hyperstimulation syndrome (OHSS). The introduction of recombinant FSH (rFSH) reduced the variation between batches of FSH and provided a more rational basis for manipulating FSH doses but has not significantly reduced the incidence of OHSS. While relatively uncommon, such iatrogenic cases posed unacceptable risks to otherwise

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healthy women. In the early days for IVF, ovarian stimulation resulted in high rates of both multiple pregnancy (>30%) and OHSS (>10%). The primary management of OHSS was to freeze all the embryos to ensure there was no subsequent pregnancy-related OHSS and then medically treat the OHSS. This often included hospitalization and paracentesis. Ironically, women who required freeze-all management had a high probability of pregnancy following the transfer of frozen embryos in cycles where there was no risk of pregnancy-associated OHSS. In recent years, the trend towards single-embryo transfers has largely removed the frequency of multiple pregnancies; however, OHSS has remained a risk factor for women undertaking IVF.

Recently minimal stimulation regimens have been proposed to redress OHSS (Collins, 2009; Pelinck et al., 2008). While OHSS should not occur, the disadvantage of minimal stimulation is the number of cycles that do not proceed to transfer and low number of frozen embryo transfers. (Matsuura et al., 2008). In reality, only a small proportion of women undertaking IVF are at risk of OHSS, yet the minimal stimulation protocol is universally applied, meaning a reduction in cumulative pregnancy opportunity.

An alternative approach is to use recent tools such as antral follicle count (AFC) or serum anti-Müllerian hormone (AMH) to predict the likelihood of a hyper-response, and, on an individual basis, apply minimal stimulation targeted to the relevant at-risk group. While minimal stimulation by-and-large seeks to collect a minimal number of oocytes, targeted stimulation seeks to maximize the number of oocytes but in a rational manner to avoid OHSS. In other words, the aim of targeted stimulation is to recruit sufficient follicles to allow an optimal number of embryos for selection and transfer (and cryostorage) without any risk of OHSS both after trigger and after the establishment of pregnancy. This retains the benefit of cumulative pregnancy for a single oocyte recovery procedure.

Over the years, a policy developed by PIVET as a tool to manage potential risks was the establishment of a set of guidelines whereby patients with an elevated number of oocytes or discomfort at oocyte retrieval were then proactively monitored for symptoms of OHSS and, recently, cabergoline prescribed where clinically indicated. This set of guidelines is referred to as increased monitoring protocol (IMP) and reflects patients at possible or potential risk of OHSS. In the study centre, none of the patients not referred to the IMP developed any symptom of OHSS requiring medical intervention. The application of dopamine agonists such as cabergoline has significantly reduced but not eliminated the severity of OHSS such that clinically relevant cases requiring hospitalization have become quite rare (at least in Australia; Sullivan et al., 2010). However, the problem remains that excessive follicle recruitment is a risk factor in itself and using dopamine agonists to reduce the severity is largely masking the problem. The aim of targeted stimulation, therefore, is not to manage but to remove the need to monitor women and avoid the use of dopamine agonists such that there is every likelihood of a normal pregnancy without any requirement for additional clinical supervision. Therefore the number of patients referred to the IMP was viewed as a measure of the rate of 'potential' OHSS and the aim of any management strategy to limit OHSS could use the rate of referral as a measure of the success of that strategy.

The study centre has approached this goal by utilizing the incremental dosing capabilities of the new range of rFSH pens to fine-tune the dose of FSH at the start of stimulation, utilizing the ideas developed by the group from Copenhagen and presented at the Amsterdam meeting (2009) of the European Society of Human Reproduction and Embryology discussing risk charts to identify the low and excessive responders in IVF (La Cour Freiesleben et al., 2011; Popovic-Todorovic et al., 2003). A dosage schedule was then developed, in an empirical manner but based upon 30 years of clinical experience, to utilize key parameters such as basal serum FSH, age, body mass index (BMI) and history of smoking along with new prognostic indicators such as AFC and AMH to determine the original starting dose of gonadotrophins. The schedule, called the PIVET algorithm, has as its aim to maintain the pregnancy rate per fresh transfer, recover <10 oocytes and restrict the referral of patients to the IMP. The combination of subtle variations in the starting dose and the algorithm provides an almost infinite range of doses to initiate recruitment. At its heart is an appreciation that in women at risk of OHSS, the serum FSH delivered to the follicles has a narrow threshold between limited and excessive recruitment. The concentration is both a combination of endogenous and administered FSH. Therefore, while many see OHSS as a manageable condition, the study centre's view was that no cases should require increased monitoring. This article reports on the impact the PIVET algorithm has on the key parameters for OHSS: freeze-all cycles, cancellation of human chorionic gonadotrophin (HCG) in the luteal phase, use of cabergoline and referral for increased monitoring.

Materials and methods

The study period reviewing the impact of the algorithm included all cases treated between October 2009 and December 2010. This 15-month period was compared with the immediately preceding 21-month period, between January 2008 and September 2009. The stimulation regimens used by PIVET clinicians included long down-regulation flare cycle agonist/antagonist conversion with oestrogen priming (AACEP; Fisch et al., 2008) and antagonist protocol that have largely been described elsewhere (Yovich and Stanger, 2010). While the selection of the stimulation protocol was at the discretion of the clinician and may have been modified between cycles, during 2008–2010, the preference was increasingly the antagonist regimen (**Table 1**).

The treatment cycle was formalized at a consultation with a PIVET fertility specialist during the preceding assessment cycle where day-2 FSH and AFC measured on day 5 ± 1 along with cycle tracking, hysterosalpingo-contrast-sonography test, post-coital evaluation and mid-luteal serum progesterone were available. The assessment cycle was performed primarily to collect information on the relevant reproductive factors prior to commencing IVF treatment as both the stimulation regimen and algorithm-driven FSH starting dose were defined from this information. Follicles with diameters ≤10 mm were included in the AFC tally (i.e. 2–10 mm). The criteria for AFC were: grade E, <5 follicles;