Reproductive BioMedicine Online (2012) **24**, 281–292

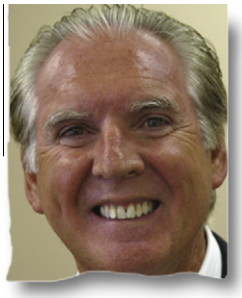
www.sciencedirect.com
www.rbmonline.com

ARTICLE

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

John Yovich *, James Stanger, Peter Hinchliffe

PIVET Medical Centre, Perth, Western Australia, Australia
* Corresponding author. *E-mail address:* jlyovich@pivet.com.au (J Yovich).



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

1472-6483/$ - see front matter
doi:10.1016/j.rbmo.2011.11.014

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;

Table 1 Patient demographics and outcomes prior to and during targeted stimulation.

	Pre-algorithm	*Algorithm*
Duration of study (months)	21	15
Age (years, *n* (%))		
<35 years	341 (41%)	187 (32%)
35–39 years	300 (36%)	214 (37%)
≥40 years	189 (23%)	176 (31%)
Cycles	862	598
Cancelled	32 (3.7)	21 (3.5)
Total oocyte retrievals (*n* (IMP *n*, %))[a]	830 (164, 20%)	577 (32, 6%)
Stimulation (*n* (IMP *n*, %))		
Long down-regulation	47 (20, 43%)	15 (2, 13%)
Flare method	320 (71, 22%)	154 (4, 3%)
Antagonist	399 (71, 18%)	343 (24, 7%)
AACEP	64 (2, 3%)	65 (2, 3%)
Transfers (*n*, % per retrieval)	741 (89%)	540 (94%)
Freeze all for OHSS (*n*, % per retrieval)	40 (5%)	9 (2%)
Single-embryo transfers (*n*, % per transfer)	480 (65%)	349 (65%)

AACEP = agonist/antagonist conversion with oestrogen priming; IMP = increased monitoring programme; OHSS = ovarian hyperstimulation syndrome.
[a]Retrievals are counted regardless of whether oocytes were recovered.

grade D, 5–10 follicles; grade C, 10–15 follicles; grade B, 15–20 follicles; grade A, >20 follicles; grade A+, >30 follicles; grade A++, >40 follicles. In this study, women with an AFC of A or greater were deemed to be at risk and analysed separately. From 2009, women were assessed annually for serum AMH (Clinipath, Australia; Beckman Coulter, Australia) and concentrations were shown to correlate well with the AFC rating.

Pivet algorithm

Prior to the introduction of the algorithm, the standard rFSH dosage was 150 IU daily for women aged <35 years, rising to 225 or 300 IU with age or repeat attempts. Dose concentrations of between 300 and 600 IU were applied for older women or very poor responders (Yovich and Stanger, 2010).

The introduction of AFC estimations in 2008/2009 focused attention on the identification of women at high risk for OHSS prior to starting treatment. During this period, preliminary attempts to modulate doses based upon the AFC were explored. However, sufficient variability in AFC measurements, a clinical desire to increase dose regimens where response was minimal and persistent OHSS led to a need for a more structured approach and the subsequent development of the PIVET algorithm (**Table 2**).

The algorithm was an extension of current gonadotrophin dosage policies at PIVET, incorporating the parameters day-2 FSH, AMH, AFC, BMI, age and smoking (Waylen et al., 2009), and exploited the potential subtle changes in doses available following the introduction of the pen injection devices for Puregon (Merck Sharpe Dome, Sydney, Australia) and Gonal-F (Merck-Serono, Sydney, Australia). The philosophy was to create a template that PIVET clinicians could use to fix the dose of rFSH according to the specific patient parameters at the start of the treatment cycle. The algorithm involved smoothing doses between key factors where any variation in any parameter caused the dose to increment one click of the rFSH pen (**Figure 1**). The smoothing was developed in accordance with the doses available with the incremental steps provided by the rFSH pens. Since the Puregon pen had smaller increments (8.3 IU per 'click'), this was preferred at the lower doses while the Merck-Serono pen (increments of 37.5 IU per 'click') was an equally used alternative with higher doses. Therefore in this study, Puregon rFSH was used for all at-risk cases. While the higher doses for poor responders were largely unchanged, the real aim was to restrict the rFSH dose for women at a perceived risk of OHSS. The target number of oocytes was considered to be 10 since few women with a lower number of retrieved oocytes ever experience OHSS. The algorithm was applied on a case-by-case basis and where discordance between the AFC and AMH values occurred, the patients were reclassified to the AFC rating associated with the lower FSH dosage. Serum FSH was also analysed at various points during the follicular phase of the cycles but the concentrations were not used in clinical decisions.

Subtle variations in rFSH dose attempted to reflect the potential impact of the response. For instance, low starting FSH or elevated FSH prompted two clicks on the pen (2×8.3 IU rFSH), starting serum FSH of between 8 and 12 IU a response of one click; and smoking, one additional click. On average, it was observed that a 100 IU dose of rFSH approximates to ~10 IU serum FSH: therefore, one click roughly may translate to 1 IU serum FSH. This dosage was maintained for 7 days prior to monitoring. The response to the dosage concentration was reviewed after 7 days and if the rise in oestradiol was considered inadequate (<500 pmol/l), the dose was increased by 1–2 notches of the Puregon pen and thereafter reviewed every second day. If the serum oestradiol exceeded 500 pmol/l, this indicated that some recruitment had occurred even though it may not have been visible on ultrasound and clinicians were encouraged to maintain the dose defined by the algorithm. Effectively, >80% of treatment cycles maintained the starting

dosage throughout. Where LH concentrations were shown to be persistently <1.2 IU during monitoring, including two cases of hypothalamic hypogonadotrophic amenorrhoea and also often noted following introduction of antagonist, 150 IU HCG supplementation on alternate days was added. There were no cases where coasting or step-down dosage changes to management were employed.

Ovulation induction and luteal support

Ovulation induction was initiated after the leading 2 follicles exceeded 18 mm in diameter subject to their availability usually with a single dose of 10,000 IU HCG. In cases with <4 follicles or a previous poor recovery, 20,000 IU has historically been used as the trigger and was used only for poor responders and therefore those at low risk for OHSS. In the few antagonist cycles with excessive follicle recruitment (>20 follicles) and a decision made not to transfer the embryos, including all ovum donor cycles, gonadotrophin-releasing hormone agonist (Lucrin) trigger of one 50 IU injection was used. Egg recovery was at 35–36 h post trigger.

Luteal support was based upon oocyte recovery. Routinely, 500–1000 IU HCG was given every 3 days from day 4 until day 13 when oocyte numbers were between 5 and 15. When >15 oocytes are recovered, progesterone pessaries (500 mg t.i.d.) for 5 days, thereafter 2 mg oestradiol/500 mg progesterone combination pessaries t.i.d., were prescribed along with cabergoline (see below). The pessaries were made by a local pharmacy to PIVET specifications using pure powder in a standard fatty acid base (LetCo Medical, USA).

All cases selected for IVF were included in this study without any exclusion criteria. The algorithm also managed poor responders since it was intended for both high-risk and low-risk patients. None of the regimen strategies employed for managing poor responders have any bearing on the incidence of OHSS. In addition to high-dose rFSH, poor responders or women with an AFC <5 or AMH <5 pmol/l may also have been offered growth hormone (Yovich and Stanger, 2010) with or without dehydroepiandrosterone (Barad and Gleicher, 2005, 2006) or included in the AACEP protocol (Fisch et al., 2008).

Referral to the increased monitoring programme (IMP)

In 2007, a policy was developed to manage all women at risk of OHSS. The aim of the policy was both to identify and document any patient with a potential for OHSS. While the vast majority did not develop clinical OHSS, the policy allowed the auditing and clinical review of all women at any possible risk and has become part of the study centre's quality management programme. The policy called for the clinician performing the oocyte retrieval to review the patient and refer them to the IMP if any of the following were true; oocyte number ≥12, oestradiol >10,000 pmol/l, the patient was unwell and any other adverse reaction to treatment. The women reported any level of discomfort, any abdominal distension, any respiratory difficulty, reduced urine output and dark urinary colouration. If untoward features were reported, the woman attended the clinic for closer clinical observations that include temperature, blood pressure, pulse, PaO_2, respiration rate, weight and measurement of abdominal circumference along with urine analysis including specific gravity. The women were phoned daily and any action such as further blood tests, ultrasound scans, clinical appointments and hospitalization are organized if there was a significant change in circumstance. On completion, the file was logged and referred to the senior medical staff for review. Placement on the list was precautionary and implied there was at least a minimal risk of OHSS albeit not the actual clinical condition.

Cabergoline administration

Cabergoline (Dostinex, Pfizer Australia) was prescribed after informed consent for 8 days from the day of oocyte retrieval at a dose of 0.5 mg b.i.d. when the number of oocytes was between 12 and 22. Transfers were cancelled (freeze-all policy) and all the suitable embryos were cryopreserved at the pronuclear, day-3 or blastocyst stage in women with >22 oocytes, where fewer oocytes recovered but clear symptoms of OHSS were apparent or where otherwise clinically indicated.

In the context of this paper, OHSS is defined as referral to the IMP on the basis that such a referral constituted a potential risk to the patient and to the clinic: potential OHSS. In reality, very few women in the study period required admission to hospital and only one required paracentesis but this criterion is considered as an extreme measure. Since OHSS may variably develop in women with only average follicle numbers, using a 12-oocyte cut-off seemed prudent. According to policy, 12 or more oocytes prompted cabergoline consideration and daily contact. The degree of OHSS therefore was evident as management continued. Three levels of OHSS were defined: mild (monitoring only without cabergoline or clinical intervention), moderate (modification of management, cabergoline administration, cancellation of embryo transfer) and severe (clinical OHSS, paracentesis, cautionary hospital admission). While all were considered potential OHSS, patients classified as mild OHSS experienced minimal to moderate discomfort, remained in contact with the clinic and were otherwise free to resume normal activities.

Measures

This paper used one measure, AFC performed initially during the preliminary assessment cycle and reinforced on subsequent cycles to estimate a subpopulation considered to be 'at risk' of OHSS. AMH was included as a subsequent confirmation of the AFC when this test became available. When discordance was observed, clinicians were advised to select the parameter (AFC or AMH) which dictated the lower dosage of rFSH. Regardless of the at-risk status, all couples were exposed to the dosage as outlined in the algorithm where the at-risk women received lower dosage regimens and for the remainder doses were largely unchanged. Rather than use egg or embryo numbers or hospital admissions, the algorithm was applied with the aim of removing any clinical consequence of OHSS that necessitated continued supervision rather than the acute symptoms of OHSS.

Therefore, the outcomes measured and analysed in this study were: referral for increased monitoring, the degree

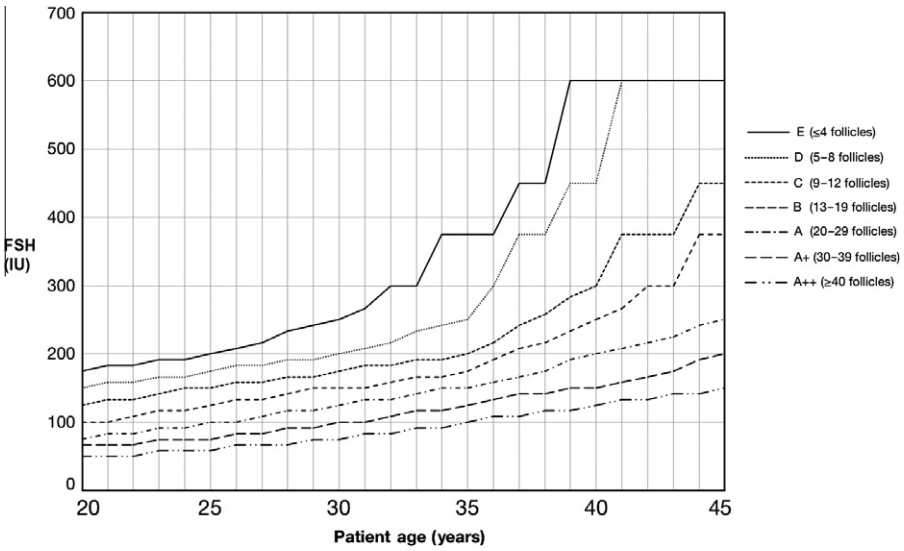


Figure 1 Model of FSH dose according to the PIVET algorithm for patients aged 20—45 years with body mass index 20—29 kg/m^2.

of OHSS (mild, moderate or severe), the incidence of freeze-all cycles, the prescription of cabergoline, the clinical pregnancy rate per fresh transfer and basic embryology data including oocyte recovery, fertilization and utilization rates (number of embryos transferred or cryostored/number of pronuclear embryos). Rates were expressed as either per oocyte retrieval (transvaginal ovum aspiration) or per embryo transfer. Referral to the IMP was based upon their potential risk (i.e. >10 oocytes) as well as actual at-risk status (>20 oocytes and/or clinical symptoms). The incidence of the actual symptoms were compared with an equivalent time period preceding the introduction of the algorithm and the incidence of the actual risks in the women with a potential risk was used to test the efficacy of the algorithm.

Ethical consideration and audit

Specific ethical approval was not considered necessary since the algorithm did not include any new drugs for consideration. PIVET is accredited with both the Australian Reproductive Technology Committee (RTAC) and the Reproductive Technology Council (RTC) of Western Australia that functions under statutory regulation. These agencies are aware of the aforementioned protocols and demand real-time data provision for annual audits as well as ensuring all new procedures and drugs have been approved by the Institutional Ethics Committee.

Statistical analysis

Student's t-test was used to compare means while percentages were analysed by chi-squared analysis.

Results

The incidence of an excessive number of oocytes collected has fallen at PIVET since 2002 in keeping with the worldwide trend for milder stimulation protocols. The proportion of cycles of women aged <40 years with elevated egg recovery is shown in **Figure 2**. The data shows a steady decline in the proportion of women undergoing freeze-all cycles, i.e. where >20 oocytes were recovered. While the proportion of cases with >10 oocytes fell slightly in 2009—2010, the critical change occurred in the proportion of cases with high egg recovery rates. For instance, the proportion of cases with >20 eggs was 15% in 2002 falling to <8% prior to 2008 and, following the introduction of the algorithm, to 2% in 2010 ($P < 0.001$).

The algorithm was applied from late 2009 to the end of 2010. The impact was compared with the preceding period of similar duration from 2008 to 2009 (**Table 1**). The cancellation rate in the pre-algorithm and the study period was equally low (3.7% versus 3.5%). The proportion of women using long down-regulation was low and both flare and antagonist cycles were in similar numbers. Referral to the IMP following introduction of the algorithm fell by similar amounts for each stimulation modality. The proportion proceeding to transfer and the incidence of single-embryo transfers was also the same.

In the 47 cases where the starting dose was <100 IU, this was not altered in 22 cycles. For these 22 cycles the mean oocyte number was 8.5 ± 4.5, all oocyte retrievals had a transfer, which resulted in seven pregnancies (31.8%). In the 25 cycles where the dose was increased, the mean oocyte number was 9.3 ± 6.3, in three cases freeze-all was undertaken and three of the 22 who had single-embryo transfers were pregnant (36.4%). The one violation of the algorithm, where the dose was increased unnecessarily and excessively from 83.3 IU to 150 IU, resulted in 29 oocytes and this became the one case of severe OHSS resulting in hospitalization and paracentesis. This outcome was truly avoidable as the decision to increase the dosage was made on the apparent lack of follicle recruitment by ultrasound following 7 days of 83.3 IU. The rise of oestradiol to 700 pmol/l was not factored into the decision and should have been according to the rules of the algorithm, which indicated that the dose of 83.3 IU did not require change.

Table 2 PIVET algorithm.

PIVET FSH Dosage Algorithm

AMH		>30 pm/L					25-29.9 pm/L					20-24.9 pm/L					15-19.9 pm/L					10-14.9 pm/L					5-9.9 pm/L					< 5.0 pm/L				
AFC*		A++ (≥ 40 follicles)					A+ (30-39 follicles)					A (20-29 follicles)					B (13-19 follicles)					C (9-12 follicles)					D (5-8 follicles)					E (≤4 follicles)				
BMI		16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	30-35
Age (yrs)	20	41.7	41.7	41.7	50.0	58.3	58.3	58.3	58.3	66.7	66.7	66.7	66.7	66.7	75.0	83.3	91.7	91.7	91.7	100.0	108.3	116.7	116.7	116.7	125.0	133.3	141.7	141.7	141.7	150.0	150.0	166.7	166.7	166.7	175.0	175.0
	21	41.7	41.7	41.7	50.0	58.3	58.3	58.3	58.3	66.7	75.0	75.0	75.0	75.0	83.3	91.7	91.7	91.7	91.7	100.0	108.3	125.0	125.0	125.0	133.3	141.7	150.0	150.0	150.0	158.3	158.3	175.0	175.0	175.0	183.3	183.3
	22	41.7	41.7	41.7	50.0	58.3	58.3	58.3	58.3	66.7	75.0	75.0	75.0	75.0	83.3	91.7	100.0	100.0	100.0	108.3	116.7	125.0	125.0	125.0	133.3	141.7	150.0	150.0	150.0	158.3	158.3	175.0	175.0	175.0	183.3	183.3
	23	50.0	50.0	50.0	58.3	66.7	66.7	66.7	66.7	75.0	83.3	83.3	83.3	83.3	91.7	100.0	108.3	108.3	108.3	116.7	125.0	133.3	133.3	133.3	141.7	150.0	158.3	158.3	158.3	166.7	166.7	183.3	183.3	183.3	191.7	191.7
	24	50.0	50.0	50.0	58.3	66.7	66.7	66.7	66.7	75.0	83.3	83.3	83.3	83.3	91.7	100.0	108.3	108.3	108.3	116.7	125.0	141.7	141.7	141.7	150.0	158.3	158.3	158.3	158.3	166.7	166.7	183.3	183.3	183.3	191.7	191.7
	25	50.0	50.0	50.0	58.3	66.7	66.7	66.7	66.7	75.0	83.3	91.7	91.7	91.7	100.0	108.3	116.7	116.7	116.7	125.0	133.3	141.7	141.7	141.7	150.0	158.3	166.7	166.7	166.7	175.0	175.0	191.7	191.7	191.7	200.0	200.0
	26	58.3	58.3	58.3	66.7	75.0	75.0	75.0	75.0	83.3	91.7	91.7	91.7	91.7	100.0	108.3	125.0	125.0	125.0	133.3	141.7	150.0	150.0	150.0	158.3	166.7	175.0	175.0	175.0	183.3	183.3	200.0	200.0	200.0	208.3	208.3
	27	58.3	58.3	58.3	66.7	75.0	75.0	75.0	75.0	83.3	91.7	100.0	100.0	100.0	108.3	116.7	125.0	125.0	125.0	133.3	141.7	150.0	150.0	150.0	158.3	166.7	175.0	175.0	175.0	183.3	183.3	208.3	208.3	208.3	216.7	216.7
	28	58.3	58.3	58.3	66.7	75.0	83.4	83.4	83.4	91.7	100.0	108.3	108.3	108.3	116.7	125.0	133.3	133.3	133.3	141.7	150.0	158.3	158.3	158.3	166.7	175.0	183.3	183.3	183.3	191.7	191.7	225.0	225.0	225.0	233.3	233.3
	29	66.7	66.7	66.7	75.0	83.3	83.4	83.4	83.4	91.7	100.0	108.3	108.3	108.3	116.7	125.0	141.7	141.7	141.7	150.0	158.3	158.3	158.3	158.3	166.7	175.0	183.3	183.3	183.3	191.7	191.7	233.3	233.3	233.3	241.7	241.7
	30	66.7	66.7	66.7	75.0	83.3	91.7	91.7	91.7	100.0	108.3	116.7	116.7	116.7	125.0	133.3	141.7	141.7	141.7	150.0	158.3	166.7	166.7	166.7	175.0	183.3	191.7	191.7	191.7	200.0	200.0	241.7	241.7	241.7	250.0	250.0
	31	75.0	75.0	75.0	83.3	91.7	91.7	91.7	91.7	100.0	108.3	125.0	125.0	125.0	133.3	141.7	141.7	141.7	141.7	150.0	158.3	175.0	175.0	175.0	183.3	191.7	200.0	200.0	200.0	208.3	208.3	258.3	258.3	258.3	266.7	266.7
	32	75.0	75.0	75.0	83.3	91.7	100.0	100.0	100.0	108.3	116.7	125.0	125.0	125.0	133.3	141.7	150.0	150.0	150.0	158.3	166.7	175.0	175.0	175.0	183.3	191.7	208.3	208.3	208.3	216.7	216.7	258.3	258.3	258.3	300.0	300.0
	33	83.3	83.3	83.3	91.7	100.0	108.3	108.3	108.3	116.7	125.0	133.3	133.3	133.3	141.7	150.0	158.3	158.3	158.3	166.7	175.0	183.3	183.3	183.3	191.7	200.0	225.0	225.0	225.0	233.3	233.3	300.0	300.0	300.0	300.0	300.0
	34	83.3	83.3	83.3	91.7	100.0	108.3	108.3	108.3	116.7	125.0	141.7	141.7	141.7	150.0	158.3	158.3	158.3	158.3	166.7	175.0	183.3	183.3	183.3	191.7	200.0	233.3	233.3	233.3	241.7	241.7	300.0	300.0	300.0	375.0	375.0
	35	91.7	91.7	100.0	100.0	108.3	116.7	116.7	125.0	125.0	133.3	141.7	141.7	141.7	150.0	158.3	166.7	166.7	166.7	175.0	183.3	191.7	191.7	191.7	200.0	208.3	241.7	241.7	241.7	250.0	250.0	300.0	300.0	300.0	375.0	375.0
	36	100.0	100.0	100.0	108.3	108.3	125.0	125.0	125.0	133.3	133.3	150.0	150.0	150.0	158.8	167.1	183.3	183.3	183.3	191.7	200.0	208.3	208.3	208.3	216.7	225.0	300.0	300.0	300.0	300.0	300.0	375.0	375.0	375.0	375.0	450.0
	37	100.0	100.0	100.0	108.3	108.3	133.3	133.3	133.3	141.7	141.7	158.3	158.3	158.3	166.7	175.0	200.0	200.0	200.0	208.3	216.7	233.3	233.3	233.3	241.7	250.0	300.0	300.0	300.0	375.0	375.0	450.0	450.0	450.0	450.0	450.0
	38	108.4	108.4	108.4	116.7	116.7	133.3	133.3	133.3	141.7	141.7	166.7	166.7	166.7	175.0	183.3	208.3	208.3	208.3	216.7	225.0	250.0	250.0	250.0	258.3	266.7	375.0	375.0	375.0	375.0	450.0	450.0	450.0	450.0	450.0	600.0
	39	108.4	108.4	108.4	116.7	116.7	141.7	141.7	141.7	150.0	150.0	183.3	183.3	183.3	191.7	200.0	225.0	225.0	225.0	233.3	241.7	275.0	275.0	275.0	283.3	300.0	375.0	375.0	375.0	450.0	450.0	600.0	600.0	600.0	600.0	600.0
	40	116.7	116.7	116.7	125.0	125.0	141.7	141.7	141.7	150.0	150.0	191.7	191.7	191.7	200.0	208.3	241.7	241.7	241.7	250.0	258.3	300.0	300.0	300.0	300.0	300.0	450.0	450.0	450.0	450.0	450.0	600.0	600.0	600.0	600.0	600.0
	41	125.0	125.0	125.0	133.3	133.3	150.0	150.0	150.0	158.8	166.7	200.0	200.0	200.0	208.3	216.7	258.3	258.3	258.3	266.7	275.0	300.0	300.0	300.0	375.0	375.0	450.0	450.0	450.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0
	42	125.0	125.0	125.0	133.3	133.3	158.3	158.3	158.3	166.7	175.0	208.3	208.3	208.3	216.7	225.0	258.3	258.3	258.3	300.0	300.0	375.0	375.0	375.0	375.0	450.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0
	43	133.3	133.3	133.3	141.7	141.7	166.7	166.7	166.7	175.0	183.3	216.7	216.7	216.7	225.0	233.3	300.0	300.0	300.0	300.0	375.0	375.0	375.0	375.0	375.0	450.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0
	44	133.3	133.3	133.3	141.7	141.7	183.3	183.3	183.3	191.7	200.0	233.3	233.3	233.3	241.7	250.0	300.0	300.0	300.0	375.0	375.0	375.0	375.0	375.0	450.0	450.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0
	45	141.7	141.7	141.7	150.0	150.0	191.7	191.7	191.7	200.0	208.3	241.7	241.7	241.7	250.0	258.3	300.0	300.0	300.0	375.0	375.0	450.0	450.0	450.0	450.0	450.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0

Increased FSH and Smokers

Where FSH is less than 8 IU/L, with no history of smoking, use values as shown
— Smokers move two columns to the right

Where FSH is between 8 & 12 IU/L, with no history of smoking, move one column to the right
— Smokers move two columns to the right

Where FSH is greater than 12 IU/L, move two columns to the right
— Smokers and non-smokers read same column

***Antral Follicle Count based on number of antral follicles < 1.0 cm**

Oocyte Donors

Aiming for 10-12 oocytes,
move four columns to the right
Consider Lucrin trigger if > 10 follicles

PIVET MEDICAL CENTRE
The Miracle Of Life

Version 3.0 2 July 2010

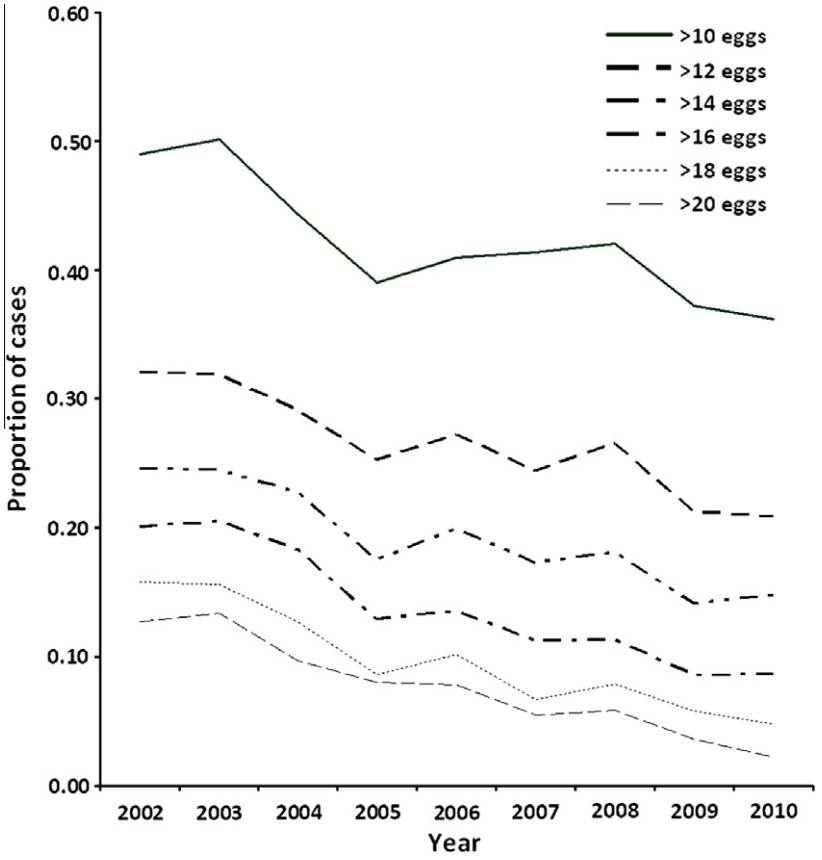


Figure 2 The proportion of oocyte retrievals per year in women aged <40 years, stratified according to the number of oocytes retrieved. Each line represents the proportion of cases with oocyte recovery above the criterion (e.g. >10 eggs) compared with the oocyte retrievals with oocyte recovery below the criterion.

Table 3 Patients referred to the increased monitoring programme prior to and during targeted stimulation.

	<35 years	*35–39 years*	*≥40 years*	*Total*
Mild OHSS risk				
Pre-algorithm	80/295 (27.1)	38/277 (13.7)	15/169 (8.9)	133/741 (17.9)
Algorithm	14/177 (7.9)[a]	9/194 (4.6)[b]	2/169 (1.2)	25/540 (4.6)[a]
Moderate OHSS risk				
Pre-algorithm	20/295 (6.8)	8/277 (2.9)	0/169 (0)	28/741 (3.8)
Algorithm	6/177 (3.4)	0/194 (0)	0/169 (0)	6/540 (1.1)[c]
Severe OHSS				
Pre-algorithm	2/295 (0.7)	1/277 (0.4)	0/169 (0)	3/741 (0.4)
Algorithm	1/177 (0.6)	0/194 (0.0)	0/169 (0.0)	1/540 (0.2)
Total				
Pre-algorithm	102/295 (34.6)	47/277 (17.0)	15/169 (8.9)	164/741 (22.1)
Algorithm	21/177 (11.9)[a]	9/194 (4.6)[a]	2/169 (1.2)[b]	32/540 (5.9)[a]

Values are *n*/total embryo transfers (%).
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

Table 4 At-risk patients (antral follicle count >20) referred to the increased monitoring programme prior to and during targeted stimulation.

	<35 years	*35–39 years*	*≥40 years*	*Total*
Mild OHSS risk				
Pre-algorithm	23/66 (34.8)	8/46 (17.4)	2/3 (66.7)	33/115 (28.7)
Algorithm	9/98 (9.2)[a]	4/48 (8.3)	2/5 (40.0)	15/151 (9.9)[a]
Moderate OHSS risk				
Pre-algorithm	6/66 (9.1)	2/46 (4.3)	0/3 (0)	8/115 (7.0)
Algorithm	2/98 (2.0)	0/48 (0)	0/5 (0)	2/151 (1.3)
Severe OHSS				
Pre-algorithm	0/66 (0.0)	0/46 (0)	0/3 (0)	0/115 (0)
Algorithm	1/98 (1.0)	0/48 (0)	0/5 (0)	1/151 (0.7)
Total				
Pre-algorithm	29/66 (43.9)	10/46 (21.7)	2/3 (66.7)	41/115 (35.7)
Algorithm	12/98 (12.2)[a]	4/48 (8.3)	2/5 (40.0)	18/151 (11.9)[a]

Values are *n*/total increased monitoring programme (%).
[a]$P < 0.001$.

Table 5 Incidence of freeze-all cycles prior to and during targeted stimulation.

	<35 years	*35–39 years*	*≥40 years*	*Total*
All cycles				
Pre-algorithm	32/341 (9.4)	7/300 (2.3)	1/189 (0.5)	40/830 (4.8)
Algorithm	4/187 (2.1)	4/214 (1.9)	1/176 (0.6)	9/577 (1.6)
Total	36/528 (6.8)[a]	11/514 (2.1)	2/365 (0.5)	49/1407 (3.5)[a]
At-risk cycles				
Pre-algorithm	14/82 (17.1)	1/52 (1.9)	0/3 (0)	15/137 (10.9)
Algorithm	3/102 (2.9)	3/53 (5.7)	1/8 (12.5)	7/163 (4.3)
Total	17/184 (9.2)[a]	4/105 (3.8)	1/11(9.1)	22/300 (7.3)[b]

Values are *n*/total retrievals (%).
[a]$P < 0.001$.
[b]$P < 0.05$.

Table 6 Incidence of cabergoline prescription prior to and during targeted stimulation.

	<35 years	*35–39 years*	*≥40 years*	*Total*
Pre-algorithm	95/341 (27.9)	65/300 (21.7)	10/189 (5.3)	170/830 (20.5)
Algorithm	26/187 (13.9)	24/214 (11.2)	7/176 (4.0)	57/577 (9.9)
Total	121/528 (22.9)[a]	89/514 (17.3)[a]	17/365 (4.7)	227/1407 (16.1)[a]

Values are *n*/total retrievals (%).
[a]$P < 0.001$.

This case led to firmer discipline and adherence to the rules of the algorithm.

This paper compared the incidence of potential OHSS between two closely related time frames that were very similar in cycle management, staffing and policies and procedures (except the algorithm). The study periods also coincided with the development of the IMP for OHSS. Comparing the two study periods, the introduction of the algorithm significantly reduced referral to the IMP from 19.8% to 5.5% of oocyte retrievals ($P < 0.001$; **Table 1**). This was significant in all age groups and most pronounced in women aged <35 years, falling from 27.1% to 7.9% of transfers ($P < 0.001$; **Table 3**). Most of the decrease was for mild and moderate OHSS. The number of severe OHSS (i.e. requiring hospitalization and/or paracentesis) remained the same (0.4% versus 0.2% of all patients) but these rates are markedly lower than in previous years (range 1.3–1.7%). At-risk women (>20 small follicles) had a similar response to

Table 7 Oocytes recovered prior to and during targeted stimulation.

	<35 years	35–39 years	≥40 years	Total
All cycles				
Pre-algorithm	10.5 ± 4.4 (341)[a]	9.0 ± 5.0 (300)	6.4 ± 4.0 (189)	9.0 ± 5.6 (830)[a]
Algorithm	9.6 ± 5.1 (187)	9.1 ± 5.3 (214)	6.0 ± 4.2 (176)	8.3 ± 5.2 (577)
At-risk cycles				
Pre-algorithm	11.9 ± 5.4 (82)[a]	11.6 ± 5.4 (52)	11.0 ± 4.4 (3)	11.8 ± 6.6 (137)
Algorithm	10.2 ± 5.6 (101)	13.0 ± 5.1 (53)	13.4 ± 4.6 (8)	11.3 ± 5.5 (162)

Values are mean ± SD (total retrievals).
[a]$P < 0.05$.

Table 8 Pronuclear embryos prior to and during targeted stimulation.

	<35 years	35–39 years	≥40 years	Total
All cycles				
Pre-algorithm	6.2 ± 4.6 (341)	5.6 ± 3.8 (300)	3.4 ± 2.5 (189)	5.5 ± 4.0 (830)[a]
Algorithm	6.0 ± 3.6 (187)	5.4 ± 3.8 (214)	3.3 ± 3.0 (176)	5.0 ± 3.6 (577)
At-risk cycles				
Pre-algorithm	7.0 ± 5.5 (82)	7.2 ± 3.8 (52)	6.3 ± 1.5 (3)	7.1 ± 4.8 (137)
Algorithm	6.3 ± 3.8 (101)	7.6 ± 4.0 (53)	8.6 ± 5.4 (8)	6.9 ± 4.0 (162)

Values are mean ± SD (total retrievals).
[a]$P < 0.05$.

Table 9 Clinical pregnancy rates prior to and during targeted stimulation.

	<35 years	35–39 years	≥40 years	Total
All cycles				
Pre-algorithm	137/295 (46.4)	94/277 (33.9)	26/169 (15.4)[a]	257/741 (34.7)[a]
Algorithm	77/177 (43.5)	60/194 (30.9)	13/169 (7.7)	150/540 (27.7)
Total	214/472 (45.3)	154/471 (32.7)	39/338 (11.5)	407/1281 (31.8)
At-risk cycles				
Pre-algorithm	29/66 (43.9)	15/46 (32.6)	0/3 (0)	44/115 (38.3)
Algorithm	43/98 (43.9)	17/48 (35.4)	0/5 (0)	60/151 (39.7)
Total	72/164 (43.9)	32/94 (34.0)	0/8 (0)	104/266 (39.1)

Values are *n*/total transfers (%).
[a]$P < 0.005$.

the introduction of the algorithm, although the statistical difference was lower (**Table 4**). The effect was noted mainly in women aged <35 years and referred to the IMP.

Perhaps a better index of the impact of the algorithm was in the reduced incidence of freeze-all cycles (**Table 5**), from 5% to 2% over the whole population ($P < 0.001$), from 9% to 2% in all women aged <35 years ($P < 0.001$) and from 17% to 3% in at-risk women aged <35 years ($P < 0.001$). Women aged 35–39 years in the at-risk group showed a modest increase in freeze-all cycles (from 2% to 6%) indicating that excessive follicle recruitment is not the prerogative of the young although it was indeed uncommon in women aged ≥40 years (0.5%).

Cabergoline treatment also decreased following the introduction of the algorithm, falling from 28% to 14% in women aged <35 years ($P < 0.001$), from 22% to 11% for women aged 35–39 years ($P < 0.001$) and overall from 20% to 10% ($P < 0.001$). There was no change in women aged ≥40 years (**Table 6**).

The mean number of oocytes retrieved also fell overall from 9.0 to 8.3 ($P < 0.05$, **Table 7**). This decrease was in younger women (<35 years; from 10.5 to 9.6 in the total population and 11.9 to 10.2 in the at-risk subgroup; $P < 0.05$; **Table 7**). There was little change in oocyte numbers in women aged ≥35 years. In the at-risk older population, oocyte numbers showed a non-significant trend towards higher values with the algorithm, supporting an observation above that the algorithm needs to enable higher dosages in older women (**Table 7**). This decrease was not reflected in the number of pronuclear embryos in each age group but overall, the number of pronuclear embryos did fall slightly after the algorithm was introduced

(**Table 8**) and usable embryos (i.e. those deemed suitable for transfer or cryopreservation) were not reduced (3.4 vs 3.4 for both periods; data not shown). Since in younger women, the number of oocytes fell and the number of embryos did not under the influence of the algorithm, this implied that the lower doses used in the algorithm did not affect the number of viable follicles, only the immature ones. Finally for women aged <40 years, there was no change in the clinical pregnancy rate per transfer between the periods before and after the algorithm was introduced in both the overall population and in the at-risk subgroup (**Table 9**) (46% to 44% for women aged <35 years). In this study, the clinical pregnancy rate was lower only in women aged ≥40 years. This caused the total clinical pregnancy rate to decrease from 34.7% to 27.7%. The reasons for this reduction, which was observed only in this subgroup with lower risk for OHSS, remain unclear but may relate to the increasing application of single embryo transfers.

Discussion

OHSS is the single remaining disadvantage of the ovarian stimulation model. As late as 2010, the ANZARD report for 2008 tabled an incidence of 196 cases that required hospitalization, 171 of which were linked to egg recovery rates of 10 eggs or more (Sullivan et al., 2010, Table 33). This represents 15 cases of OHSS in Australia per month. The OHSS rate for cases with >20 oocytes was 3.5% of oocyte retrievals. The introduction of dopamine agonists (Álvarez et al., 2007) has significantly reduced the number of women needing hospitalization such that future estimates of OHSS are likely to continue to fall in forthcoming years. Unfortunately, the risk of OHSS will remain even with the use of dopamine agonists since many women may appear well and continue to proceed to embryo transfers but remain at risk from pregnancy-associated OHSS. In the ANZARD report for 2008, >40% of IVF cycles recovered 10 oocytes or more. This essentially means that 40% of women undertaking IVF in Australia were potentially at risk from some degree of OHSS, of which 1.2% actually developed the condition.

The results from PIVET between 2002 and 2010 further illustrate that the proportion of women with excessive oocyte recovery has continued to fall over time (**Figure 2**) particularly those with >16 oocytes falling from 25% to 9% over 8 years. There has been a lesser decline for cases where >10–14 oocytes were recovered but even at this level, there is a 0.6% risk of hospitalization. What is clear is that if oocyte recovery rates were restricted to <12 eggs, OHSS would virtually cease to exist as a risk factor of IVF. The PIVET algorithm was specifically developed with this as the goal for the desired number of oocytes.

This study has shown that, following the introduction of the PIVET algorithm, key indicators of potential OHSS fell compared with the preceding period of similar duration without diminishing the clinical pregnancy rate. This occurred both in the overall patient population and also in those identified by AFC to be at risk. Not only was referral to the IMP significantly lower but also other more tangible markers such as the number of freeze-all cycles and cabergoline prescriptions also fell. The number of oocytes fell significantly in all women aged <35 years to 9.6/oocyte retrieval and to 10.2/oocyte retrieval in those age <35 years considered at risk (**Table 7**). Referral to the IMP decreased by the same order with each type of ovarian stimulation. Although there was a steady decline in oocyte numbers (**Figure 2**) and therefore OHSS over 9 years due to many factors (e.g. introduction of antagonist cycles), the two study periods were very similar and the further reduction in oocyte numbers and OHSS is essentially driven by the algorithm.

The essence of the algorithm was to attempt to subtly influence serum FSH concentrations at the level where follicles are recruited. Under normal ovarian stimulation, sufficient rFSH is administered to raise the serum FSH sufficiently above the basal concentration to allow recruitment of any competent follicle. Follicle numbers are rarely in excess of this critical number in non-polycystic ovary (PCO) women. In targeted stimulation, the aim is to marginally elevate the basal FSH such that only the most responsive follicles are recruited. The basal FSH therefore is an important predictor since a low serum FSH may require a higher rFSH dosage to reach recruitment concentrations. Stimulation methods may also influence the initial rise in serum FSH, although in this study both flare and antagonist have a similar IMP referral. The nature of the control over follicle selection remains unclear with perifollicular blood flow (Robinson et al., 2009), ovarian blood flow (Popovic-Todorovic et al., 2003), FSH sensitivity (Andersen et al., 2008; de Koning et al., 2004; Genro et al., 2011) and a range of intra-ovarian regulators (Oktem and Uramn, 2010) have all been implicated. While de Koning et al. (2004) reported increased FSH threshold in women with an elevated basal FSH, more relevantly Genro et al. (2011) has suggested that raised AMH in at-risk women appeared to suppress follicle recruitment. Furthermore, there are suggestions that granulosa cells from PCO women responded differently to FSH than from normal women. The doses employed for the at-risk women in the current study were significantly less than routinely used in IVF, being as low as 41.7 IU for young women with low BMI, marked PCO and high AMH.

There have been other reports describing targeted FSH dose, the largest being the CONSORT study (Olivennes et al., 2009). In young, non-PCO patients stimulated by long down-regulation, the CONSORT study found that the dose of rFSH using a model based on basal serum FSH, BMI, age and AFC all significantly influenced oocyte recovery. The authors reported that the optimal dose of 185.5 IU produced 12.7 oocytes per recovery. Interestingly, using a programmed dose of 112.5 IU/day generated 9.6 oocytes in normal, young women, which is the same recovery rate produced by the PIVET algorithm over the whole patient cohort (women aged <35 years). The CONSORT study also reported similar pregnancy rates over the doses produced by their model, a result also found with the PIVET algorithm and others (Sterrenburg et al., 2011). While the model did show that a calculated dose based upon basic predictors influenced the oocyte number, the study did not address that the outcome with at-risk patients excluded PCO women, whereas the current study included all women and had no exclusions. La Cour Freiesleben et al. (2011) extended this concept by developing risk models for high (>20 eggs) or

poor (<5 eggs) using prognostic indicators including age, FSH, BMI, ovarian volume, AFC and cycle length. While the models have not been applied clinically, they illustrate how these indicators may be applied in a clinical environment to anticipate high-risk patients and modify the dose accordingly. AMH and AFC are the main prognostic indicators used in the algorithm to anticipate risk of either a hyper- and a hypo-response (Al-Azemi et al., 2011). Both have recently been reviewed by Broer et al. (2011) who concluded after a meta-analysis that both were equally effective in predicting excessive response but both have an error associated with their estimation. Recognizing this occasional discordance between AFC and AMH, the PIVET algorithm requires adjusting the AFC/AMH category which projects the lower dose of rFSH.

As far as is known, this report is one of the first to approach the concept of risk aversion to OHSS by applying known predictors into a practical model for clinical application. While excessive recruitment was still occasionally observed, from a clinical perspective the positive outcomes were fewer freeze-all cycles, fewer prescriptions of OHSS-minimizing dopamine agonists and fewer referrals to an institutionalized monitoring programme after the algorithm was introduced and enforced. The outcomes were achieved with no decrease in the pregnancy rates for at-risk and normal patients, indicating that excessive egg numbers play no beneficial role in current IVF practice. While some studies have not found effects of high oestradiol concentrations on oocyte and embryo quality (Ng et al., 2000; Papageorgiou et al., 2002; Peña et al., 2002; Ziebe et al., 2004), other studies have linked OHSS to increased miscarriage rates (Raziel et al., 2002) and high rFSH doses to decreased oocyte quality (Nelson et al., 2007, 2009; Rubio et al., 2010). These reinforce the view that a high follicle number is associated with other consequences in addition to OHSS.

The algorithm explored the opportunities presented by the introduction of the rFSH pens. The Puregon pen was utilized more frequently at the lower concentrations to apply a mechanism able to fine-tune the dose to each individual's history only because the incremental steps were smaller and allowed a one-click adjustment to a wide variety of patient factors. At present, subtle variations for non-PCO women or poor responders is most likely of little consequence; nevertheless, it allowed the algorithm to be viewed in a total perspective ensuring that all women (including the PCO and high AMH groups) were included in its use. From a clinical perspective, this made patient management by a number of clinicians more streamlined.

However, subtle incremental doses for at-risk patients lie at the heart of the algorithm. In the 47 cases where the starting dose was <100 IU, the dose was not changed in 22 and adequate egg numbers were obtained. In the remaining 25 cases where the day-7 oestradiol was <500 pmol/l, a one- or two-click (8.3–16.7 IU) adjustment barely altered the measurable serum FSH, but recruitment was apparent. In some of these cases, the starting day-2 FSH was very low and may have some bearing on why the dose needed to be increased, i.e. they may represent a subclinical hypothalamic, hypopituitary subgroup. This observation was raised to explain that, in flare and antagonist cycles, the total serum FSH is derived from endogenous secretions and exogenous administrations, the sum representing the true stimulation dose. None the less, the cancellation rate in both the study period (3.5%) and the pre-algorithm period (3.7%) was equally low, indicating adequate responsiveness in virtually all cases. The only case of severe OHSS requiring hospitalization occurred when the rules of the algorithm were breached and the dosage (83.3 IU) was increased to the standard pre-algorithm concentration (150 IU). It is believed that this case of severe OHSS was totally avoidable without reducing the chance of pregnancy.

Healthy women attending for IVF should remain healthy and the algorithm is an approach to achieve this. This is different from minimal stimulation where the approach is to recover only limited number of oocytes (Collins, 2009; Verberg et al., 2009a,b; Zhang et al., 2010). These and other studies have reinforced the view that the fresh clinical pregnancy rate is largely unaffected by oocyte numbers as long as fertilization and transfer is achieved. The downside is that many cycles do not proceed to transfer and few cycles have surplus embryos for cryopreservation. The study centre's view differs slightly since, in its experience, cryopreservation cycles (frozen–thawed or vitrified–warmed embryo transfers) are equally productive as fresh transfers. Therefore, the study centre aims to achieve a fresh transfer with at least one cryopreserved embryo and no OHSS. This maximizes the cumulative pregnancy rate. Targeting the at-risk women with a specific view to minimize or remove their chance of OHSS while maintaining stimulation regimens for non-PCO women seems a more productive approach when linked to single-embryo transfers. The results from this single-centre, retrospective study will need to be validated in larger, prospective, randomized controlled trials.

References

Al-Azemi, M., Killick, S.R., Duffy, S., Pye, C., Refaat, B., Hill, N., Ledger, W., 2011. Multi-marker assessment of ovarian reserve predicts oocyte yield after ovulation induction. Hum. Reprod. 26, 414–422.

Álvarez, C., Alonso-Muriel, I., García, G., Crespo, J., Bellver, J., Simon, C., Pellicer, A., 2007. Implantation is apparently unaffected by the dopamine agonist cabergoline when administered to prevent ovarian hyperstimulation syndrome in women undergoing assisted reproduction treatment. Hum. Reprod. 22, 3210–3214.

Andersen, A., Balen, A., Platteau, P., Devroey, P., Helmgaard, L., Arce, J.C., 2008. Predicting the FSH threshold dose in women with WHO Group II anovulatory infertility failing to ovulate or conceive on clomiphene citrate. Hum. Reprod. 23, 1424–1430.

Barad, D., Gleicher, N., 2005. Increased oocyte production after treatment with dehydroepiandrosterone. Fertil. Steril. 84, 756–758.

Barad, D., Gleicher, N., 2006. Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum. Reprod. 21, 2845–2849.

Broer, S.L., Dollemann, M., Opmeer, B.C., Fauser, B.C., Mol, B.W., Broekmans, F.J.M., 2011. AMH and AFC as predictors of excessive response in a controlled ovarian hyperstimulation: a meta-analysis. Hum. Reprod. Update 17, 46–54.

Collins, J., 2009. Mild stimulation for in vitro fertilization: making progress downward. Hum. Reprod. Update 15, 1–3.

De Koning, C., Schoemaker, J., Lambalk, C., 2004. Estimation of the follicle-stimulating hormone (FSH) threshold for initiating the final stages of follicular development in women with

elevated FSH levels in the early follicular phase. Fertil. Steril. 82, 650—653.

Fisch, J., Keskinteppe, L., Sher, G., 2008. Gonadotrophin-releasing hormone agonist/antagonist conversion with estrogen priming in low responders with prior in vitro fertilization failure. Fertil. Steril. 89, 342—347.

Genro, V., Grynberg, M., Scheffer, J., Roux, I., Frydman, R., Fanchin, R., 2011. Serum anti-Müllerian hormone levels are negatively related to Follicular Output RaTe (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Hum. Reprod. 26, 671—677.

La Cour Freiesleben, N., Gerds, T., Forman, J., Silver, J.D., Nyboe-Andersen, A., Popovic-Todorovic, B., 2011. Risk charts to identify low and excessive responders among first-cycle IVF/ICSI standard patients. Reprod. Biomed. Online 22, 50—58.

Nelson, S., Yates, R., Fleming, R., 2007. Serum anti-Müllerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles—implications for individualization of therapy. Hum. Reprod. 22, 2414—2421.

Nelson, S.M., Yates, R.W., Lyall, H., Jamieson, M., Traynor, I., Gaudoin, M., Mitchell, P., Ambrose, P., Fleming, R., 2009. Anti-Müllerian hormone-based approach to controlled ovarian stimulation for assisted conception. Hum. Reprod. 24, 867—875.

Ng, E.U., Yeung, W., Lau, E.Y.L., Ng, E.H.Y., Yeung, W.S.B., Lau, E.Y.L., So, W.W.K., Ho, P.C., 2000. High serum oestradiol concentrations in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent frozen—thawed embryo transfer cycles. Hum. Reprod. 15, 250—255.

Oliviennes, F., Howles, C.M., Borini, A., Germond, M., Trew, G., Wikland, M., Zegers-Hochschild, F., Saunders, H., Alam, V., 2009. Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study. Reprod. Biomed. Online 18, 195—204.

Oktem, O., Uramn, B., 2010. Understanding follicle growth *in vivo*. Hum. Reprod. 25, 2944—2954.

Papageorgiou, T., Guibert, J., Goffinet, F., Patrat, C., Fulla, Y., Janssens, Y., Zorn, J.R., 2002. Percentile curves of serum estradiol levels during controlled ovarian stimulation in 905 cycles stimulated with recombinant FSH show that high estradiol is not detrimental to IVF outcome. Hum. Reprod. 17, 2846—2850.

Pelinck, M.J., Knol, H.M., Vogel, N.E.A., Arts, E.G.J.M., Simons, A.H.M., Heineman, M.J., Hoek, A., 2008. Cumulative pregnancy rates after sequential treatment with modified natural cycle IVF followed by IVF with controlled ovarian stimulation. Hum. Reprod. 23, 1808—1814.

Pena, J.E., Chang, P.L., Chan, L.K., Zeitoun, K., Thornton II, M.H., Sauer, M.V., 2002. Supraphysiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. Hum. Reprod. 17, 83—87.

Popovic-Todorovic, B., Loft, A., Lindhard, A., Bangsboll, S., Andersson, A.M., Nyboe Andersen, A., 2003. A prospective study of predictive factors of ovarian response in standard IVF/ICSI patients treated with recombinant FSH. A suggestion for a recombinant FSH dosage normogram. Hum. Reprod. 18, 781—787.

Raziel, A., Friedler, S., Schachter, M., Strassburger, D., Mordechai, E., Ron-El, R., 2002. Increased early pregnancy loss in IVF patients with severe ovarian hyperstimulation syndrome. Hum. Reprod. 17, 107—110.

Robinson, R.S., Woad, K.J., Hammond, A.J., Laird, M., Hunter, M.G., Mann, G.E., 2009. Angiogenesis and vascular function in the ovary. Reproduction 38, 869—881.

Rubio, C., Mercader, A., Alamá, P., Lizan, C., Rodrigo, L., Labarta, E., Melo, M., Pellicer, A., Remohi, J., 2010. Prospective cohort study in high responder oocyte donors using two hormonal stimulation protocols: impact on embryo aneuploidy and development. Hum. Reprod. 25, 2290—2297.

Sterrenburg, M.D., Veltman-Verhulst, S.M., Eijkemans, M.J.C., Hughes, E.G., Maklon, N.S., Broekmans, F.J., Fauser, B.C.J.M., 2011. Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis. Hum. Reprod. Updates 17, 184—196.

Sullivan, E.A., Wang, Y.A., Chambers, G., 2010. Assisted reproductive technology in Australia and New Zealand 2008. Cat. No. PER 49. AIHW, Canberra.

Matsuura, T., Takehara, Y., Kaijima, H., Teramoto, S., kato, O., 2008. Natural IVF cycles may be desirable for women with repeated failures by stimulated IVF cycles. J. Assist. Reprod. Genet. 25, 163—167.

Verberg, M.F.G., Eijkemans, M.J.C., Macklon, N.S., Heijnen, E.M.E.W., Baart, E.B., Hohmann, F.P., Fauser, B.C.J.M., Broekmans, F.J., 2009a. The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis. Hum. Reprod. Update 15, 5—12.

Verberg, M.F.G., Macklon, N.S., Nargund, G., Frydman, R., Devroey, P., Broekmans, F.J., Fauser, B.C.J.M., 2009b. Mild ovarian stimulation for IVF. Hum. Reprod. Update 15, 13—29.

Waylen, A.L., Metwally, M., Jones, G.L., Wilkinson, A.J., Ledger, W.L., 2009. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. Hum. Reprod. Update 15, 31—44.

Yovich, J., Stanger, J., 2010. Growth hormone supplementation improves implantation and pregnancy productivity rates for poor-prognosis patients undertaking IVF. Reprod. Biomed. Online 21, 37—49.

Zhang, J., Chang, L., Sone, Y., Silber, S., 2010. Minimal ovarian stimulation (mini-IVF) for IVF utilizing vitrification and cryopreserved embryo transfer. Reprod. Biomed. Online 21, 485—495.

Ziebe, S., Bangsbøll, S., Schmidt, K.L.T., Loft, A., Lindhard, A., Nyboe Andersen, A., 2004. Embryo quality in natural versus stimulated IVF cycles. Hum. Reprod. 19, 1457—1460.

Declaration: The authors report no financial or commercial conflicts of interest. Neither MSD nor Merck Serono provided any support for this study except for partial reimbursement for travel costs associated with the presentation of an early draft of this study at the International Meeting on Minimal Stimulation (ISMAAR) in Yokohama, Japan 2010.

Received 7 April 2011; refereed 7 November 2011; accepted 16 November 2011.