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PIVET rFSH dosing algorithms for individualized COS enables optimised pregnancy productivity rates and avoidance of OHSS

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PIVET rFSH dosing algorithms for individualized COS enables optimised pregnancy productivity rates and avoidance of OHSS

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Abstract

Purpose

To design gonadotrophin dosing algorithms with either ~8.3 or 12.5 IU increments for establishing optimum rFSH starting dose, and the overall aim of collecting 8-12 oocytes in most patients in order to minimise the risk of OHSS for all patients.

Method

Retrospective study of 2822 IVF stimulations covering a 73-month period from 1st April 2008 into 30th April 2014 in a private IVF clinic during which two separate PIVET dosing algorithms were used. Both PIVET algorithms are based on age, antral follicle count with adjustments for anti-Müllerian hormone, body mass index, day-2 FSH along with smoking history, and covers all patient groups from hyper-responders through to poor-responders.

Results

Less than one third of women received conventional dosages of rFSH (150 – 300 IU) during the study period, and the overall percentage of patients continuing at their starting dosage was 79.1 %. In the low rFSH group (≤75 IU), 30.1 % responded without any change in starting dose. Only 0.3 % patients were diagnosed with severe OHSS, and all of these cases were associated with deviations from the described protocols.

Conclusion

This observational study shows the data of IVF stimulation after using PIVET algorithms adjusted for ~8.3 IU or 12.5 IU increments over a 73-month period. The aim was to collect 8-12 oocytes for optimal benefit to effectively remove the risk of OHSS. The data from this report shows that applying the PIVET algorithms makes this eminently feasible.

Introduction

In assisted reproductive technologies (ART), the starting dose of gonadotrophin is important for achieving optimal numbers of oocytes in order to produce viable embryos and diminish the risk of ovarian hyper-stimulation syndrome (OHSS), a potentially lethal condition. However, most clinicians still rely on a standard dose of gonadotrophin, typically 150-225 IU, with adjustments based on each clinician´s experience and the patient´s previous response. There have been former attempts to create Algorithms on various biological and anthropometric parameters. A group from Copenhagen constructed their risk algorithm based on antral follicle count (AFC), ovarian volume, Doppler score, age and smoking habits [1, 2]. However, some of these parameters are not commonly used or are unobtainable in most clinics. Howles et al. evaluated several potential variables and identified four important parameters; FSH level at screening, body mass index (BMI), age and number of follicles <11 mm and found them to be the most predictive factors. A formula was calculated; the CONSORT algorithm [3] based on these four variables. This algorithm was tested in a multicentre study on 172 normo-ovulatory women age 18 – 34 years and a mean of 10.3 oocytes was retrieved, however the cancellation rate was as much as 17 %, which was rather high in this potentially good-responder group [4].

Recently PIVET Medical Centre published an algorithm [5], designed to calculate the appropriate dosage of recombinant follicle stimulating hormone (rFSH) to provide 8 – 12 oocytes from all women within the IVF program and to reduce the risk of severe OHSS. The algorithm covered all patients from very poor-responders to hyper-responders. The rationale behind that algorithm was to target those women at higher risk for OHSS with smaller dosages of rFSH than was standard practice. This was enabled by the introduction of the Puregon Pen by MSD (Merck Sharp Dome) into Australia in 2007 and which enabled a dial-up dosage of 25 IU increments, but with 3 subdivisional “clicks”. PIVET´s algorithm then enabled much lower dosages to be provided to women with high AFC ratings, those with anti-Müllerian hormone (AMH) levels in the higher ranges, and adjusted the dose downwards for younger women and those with low BMI ratings. Furthermore the algorithm was designed to ensure poorer responders would safely have larger doses to maximise their opportunity for pregnancy.

The PIVET algorithm enabled rFSH dosages which were much lower than the usually administered 150-225 IU and still enabled an adequate response but with minimal risk of over-response and the associated concomitant risk of severe OHSS. In addition, incremental adjustments could be as little as ~8.3 IU. According to the algorithm such dosage could range as low as 41.7 IU daily for very young women with BMI as low as 16 Kg/m^2, often with typically enlarged polycystic ovaries and AMH levels >30 pm/l. Such women had "targeted mild stimulation" but still had the benefits of sufficient oocytes to enable blastocyst culture and single embryo transfers, as well as the benefit of some embryos for cryopreservation enabling a higher productivity rate [6] from a single trans-vaginal oocyte aspiration (TVOA). From PIVET's perspective, this strategy is superior to the idea of minimal stimulation protocols using clomiphene citrate, where few eggs are recovered, many cases are cancelled, and minimal cases have the benefit of additional cryopreserved embryos for future use [7].

At the time PIVET commenced the algorithm study (October 2009) only the Puregon pen enabled small dosage increments (assumed to be ~8.3 IU) whilst the competitive Gonal-F pen (Merck Serono) only allowed 37.5 IU increments, which in our pilot studies proved to be unsatisfactory in achieving our aims. Merck Serono subsequently introduced a new pen early in 2011, which enabled 3 "clicks" between the previous dosages i.e. increments of 12.5 IU/click and filled-by-mass with dosages assured. PIVET elected to design a second algorithm in March 2011 adjusted to 12.5 increments as a supplementary to the previous algorithm, thus providing clinicians with the option to use either of the rFSH products with a view to targeted low-dose stimulation of those women at increased risk of OHSS.

The current observational study shows the data of IVF stimulation after using PIVET algorithms adjusted for ~8.3 IU or 12.5 IU increments over a continuous 6-year period. The aim was to collect 8-12 oocytes for optimal benefit and 4-8 oocytes in the very high-risk group, while maintaining a minimum risk of overstimulation. These data show that applying the PIVET algorithms makes these aims eminently feasible.

Materials and Methods

Study design

This retrospective study covers a continuous 6-year period at PIVET (from 1st April 2008 through to 30th April 2014) during which period the PIVET algorithms were used to determine the rFSH starting dose. The data was drawn from the entire PIVET database containing all cases treated in this 73-month period (Flow chart, Figure 1). The data period enabled all pregnancies to be tracked through to deliveries. Few patients with BMI >36 kg/m^2 were treated during the entire period, and they were treated according to the algorithms as if the BMI was 35 kg/m^2. The protocol was the same as applied previously during the first period [5] and the new algorithm was introduced at PIVET in April 2011 with the launch of the new Gonal-f pen, which enabled the possibility of 12.5 IU increments. Dosages were adjusted to be close to the original Puregon dosages and both rFSH products were used based on clinicians' choice. All clinical and laboratory management of IVF/ICSI procedures were not altered during the entire 6-year study period, apart from trends in embryo transfers; namely more cases committed to blastocyst culture, more single embryo transfers and more cases with selective cryopreservation of the better quality embryos.

Patient Management

All IVF patients had previously undergone an Assessment Cycle following their primary consultation and within 1-2 months immediately prior to the IVF treatment cycle. However, if a further fresh cycle was planned, the essential measurement parameters, serum day-2 FSH, AMH, BMI and AFC were repeated in the month prior to cycle and the rFSH dosage calculated at the day-21 pre-IVF check. Clinicians were instructed to avoid adjusting dosages on the basis of previous responses (e.g. oocytes collected), but to simply calculate using the updated parameters. New couples presenting with infertility undergo an Assessment Cycle after the primary consultation. This included examining collected information for use in the PIVET algorithm namely, serum day-2 FSH and AMH, AFC measured day 5±1 along with cycle tracking, a hysterosalpingo-contrast-sonography (HyCoSy) test day 7 to 9, peri-ovulatory post-coital evaluation and mid-luteal serum progesterone. At this latter, mid-luteal point, the couple are reviewed for consideration of treatment

proposals. For those proceeding to IVF, the clinician decides the stimulation protocol and the starting gonadotrophin dosage is calculated from the appropriate algorithm.

PIVET Algorithms

The PIVET algorithms evolved out of the PIVET database, which by 2002 was shown to be well consolidated and validated on several testing modalities. PIVET's electronic record-keeping system integrates the demographic data and billing system (Jam software; Med4i Accounts & Billing, Australia)) with the Filemaker-Pro 12 (Apple, USA) database. This integrated system has proven to be sufficiently robust in providing accurate data to the National Perinatal Statistics Unit (as required for the national accreditation process in Australia and New Zealand) as well as the Reproductive Technology Council, as required by Western Australian state legislation.

Examination of more than 5000 IVF cycles along with tracking the destiny of more than 50,000 recovered oocytes, created a profile of those protocols leading to the development of 8-12 follicles and oocytes according to the background AFC ratings. These data were then compared with the risk charts (chance of pregnancy vs risk of OHSS) published from the Copenhagen Group [1, 2]. As the algorithms evolved we applied data modelling and graphic smoothing techniques to create a continuously rising dosage schedule, without irregularity. As previously stated, we commenced by applying the Puregon Pen which is filled by bio-assay and provides MSD-guaranteed dosages of 25 IU rFSH. We made an assumption that each "click" of the pen provides one third dosage, i.e. 8.3 IU/click, although this has never been endorsed by MSD, hence ~8.3 IU increments [5]. Following release of the new Gonal-f pen in early 2011, we applied the closest dosage schedule to match the Puregon pen algorithm, with further data modelling and graphic smoothing techniques applied to create the model shown in Table 1. Merck-Serono indicates that its pen is filled by mass hence all dosage increments of 12.5 IU are fully endorsed.

For starting dosages <300 IU rFSH, increments of 12.5 IU means percentage increases of ~17% for the dose increase from starting dose 75 IU to 87.5 IU and ~5% for dosages between 250-300 IU. For dosages greater

than ≥325 IU the algorithm provides for increments of 25 IU, which applies suitability for both the Puregon and Gonal-f pens. Such increments means dosage increases from 8.3% at 300IU to 5.6% at 450 IU, consistent with the lower starting dosages.

Selecting rFSH dosage from the PIVET Algorithm

The main parameters relevant to the algorithm are female age and current AFC rating, where all detectable follicles 2-10 mm are included. Definition of ratings are, grade E, ≤4 follicles; grade D, 5-8 follicles; grade C, 9-12 follicles; grade B, 13-19 follicles; and grade A, 20-29 follicles. Patients in the latter grade belong to the high-risk polycystic ovary group, and are further sub-classified as grade A+, 30-39 follicles and grade A++, ≥40 follicles.

In selecting the AFC grading, the AMH level was also factored in as a modulator, adjusting the AFC grading category upwards if AMH implied a higher AFC rating (e.g. if the AFC categorised to B, but AMH categorised to A, the patients would be categorised as an A grading). Internal correlation studies at PIVET show high correlation between AMH and AFC, but there can be discordance in ~15% of cases (Keane et al; unpublished data, in preparation). By moving the AFC rating upwards ensured a lower dosage of rFSH would be selected, ensuring safety and reduced risk of overstimulation and OHSS. The current AMH levels were determined using Gen II (Beckman Coulter, Australia) and commenced in June 2010, but may read ~40% higher than the previous Gen1 assay [8].

Adjustments within the algorithm include BMI, smoking history and day-2 serum FSH, the latter adjusting 1 or 2 readings to the right (i.e. higher rFSH dosage; Table 1). Patients classified as egg donors or those having egg storage, have their rFSH dosage adjusted 4 readings to the right (i.e. higher rFSH dosage), as they will have an Antagonist stimulation cycle with agonist (e.g. Lucrin; leuprolide acetate, Abbott Australasia) trigger [9] and no luteal support drugs.

Ovarian stimulation Regimens

Women with high AFC ratings (all A categories and some B if AFC >15 antral follicles) were treated by an Antagonist regimen preferentially. Those with low categories (D and E) were treated by a Flare regimen with some very poor responders treated by an AACEP (Agonist Antagonist Conversion with Estrogen Priming) regimen [10]. Women with AFC category B <15 antral follicles and category C could be treated by either regimen or even a long down regulation (LDR) protocol at clinician's discretion. The LDR protocol was also preferred for cases of underlying adenomyosis and endometriosis. This approach accords with the Nelson algorithm [11].

Adjusting rFSH dosage

IVF cycle management commences with day 2 parameters of E2 <200 pm/l, P4 <5.0 nm/l and LH <10 IU/l. FSH levels are measured and may lead to adjustment of the Algorithm dosage if different from previous e.g. FSH 20 IU may cause rFSH dosage selection 2 squares to the right. Most cycles utilise the Antagonist regimen, with rFSH commencing on day 3, but Agonist Flare cycles means that patients commence Lucrin 4 IU on day 2, followed by rFSH day 3. Serum E2 levels are determined at day 7, and if >500 pm/l, the dosage of rFSH remains unchanged. Conversely, lower levels will require 12.5 IU incremental rises in dosage. The antagonist (Orgalutran: MSD or Cetritide; Merck Serono) 0.25 mg is introduced with E2 levels >500 pm/l. Thereafter, E2, P4 and LH levels are measured every 2 - 3 days along with follicle tracking by transvaginal ultrasound from day 9. Most cases present with 2 or more leading follicles, >18 mm on day 12 of the cycle, the most common day for giving the ovulatory trigger, and TVOA is scheduled for 37 hours post-trigger.

Trigger and Luteal Support

Recombinant human chorionic hormone (rhCG: Ovidrel; Merck Serono) was used as ovulation Trigger in doses 6500 – 1300 IU (1 ampoule or 2 ampoules). However, in cases considered at high risk of developing OHSS (≥12 follicles or ≥12,000 pm/L E2) and treated with an antagonist regimen, GnRHa (Lucrin 50 IU)

was used as the ovulatory trigger. Luteal support is given as earlier described [5], and includes rhCG 500-1000 IU days 4,7,10 & 13 after TVOA for those cases with <12 follicles and < 12 oocytes according to long-standing practice at PIVET [12, 13] all other cases receiving Progesterone 400mg thrice daily. Cases with >12 oocytes were given Cabergoline 1 mg nocte for 10 days and cases >20 oocytes had freeze-all except if the Trigger was Lucrin.

Intensive Monitoring Protocol (IMP)

Women were classified as OHSS risk at 2 occasions – firstly at Trigger if E2 was ≥12,000 pm/L or ultrasound revealed ≥12 follicles ≥12mm; and secondly at TVOA if ≥12 oocytes were recovered. Such patients were instructed to record abdominal girth at the umbilicus each day and reported her measurement and wellness (especially noting breathing difficulty, urine flow and colour, as well as any nausea and/or vomiting) daily to the clinic nurse. A blood test was performed every third day and concern was considered for E2 >6000 pm/L or P4 >600 nm/L; such cases having luteal phase support adjusted to exclude rhCG if previously prescribed. Women exceeding safe parameters were arranged for abdominal ultrasound to check for OHSS (and need for paracentesis), along with urine sample to detect specific gravity (SG); and need for iv hydration if SG >1015.

Embryo transfer trends

In the late algorithm period, there were some changing trends in embryo transfer policies. Overall there was a strong Australian drive to minimise multiple pregnancies, hence elective single embryo transfers were encouraged. There was also a concern that those cycles characterised by rising progesterone levels prior to trigger would result in disturbances affecting embryo-endometrial synchrony, therefore PIVET policy changes encouraged cryopreservation by vitrification of the best-quality embryos, and fresh transfer of those embryos graded in the lower tier. The trend also included an increased blastocyst culture policy, consequently, fewer embryos became available for transfer or cryopreservation.

Oocyte Retrieval and Pregnancy Outcomes

Two utilisation measures were calculated to summate the proportion of 'usable' embryos transferred or vitrified arising from the total number of two pronucleate embryos generated from a single oocyte retrieval procedure **(embryo utilisation rate)**, or the proportion of 'usable' oocytes transferred and vitrified arising from the total number of oocytes retrieved from a single oocyte retrieval procedure **(oocyte utilisation rate)**. The outcomes of treatment cycles is categorised for cycles initiated, fresh cycles per TVOA or per embryo transfer (ET). They are categorised as clinical pregnancy rate (detectable FH at 7 weeks) or livebirth rate (at least one live, surviving infant after 28 weeks). The pregnancy and livebirth productivity rates include the subsequent FET outcomes arising from the single TVOA procedure from an individual IVF treatment cycle. PIVET introduced this terminology to avoid confusion with the term "cumulative pregnancy rate", which mostly relates to outcomes from more than one IVF treatment cycle [5, 6]. By using productivity rates, the outcomes of IVF treatments, where top-quality embryos are frozen for various reasons; e.g. elevated late follicular progesterone levels or risk of OHSS, can still be favourably reflected.

Ethical consideration and audit

General Approval for Retrospective data analysis was provided from Curtin University (HREC) number RD-25-10 (2015) and PIVET Medical Centre is accredited with both the Australian Reproductive Technology Committee (RTAC) and the Reproductive Technology Council (RTC) of Western Australia that functions under statutory regulation. Both authorities conduct annual accreditation reviews for licencing of ART clinics, with a focus on multiple pregnancies and OHSS rates being of concern if elevated beyond currently adjusted standards.

Statistical analysis

Data was analysed using Prism 6 (Graphpad software, Inc.) Student´s t-test was used to compare the means of two groups. Ratios were compared using Chi Square contingency tables and applying Yates correction for large data-sets. P values <0.05 were considered statistically significant.

Results

Patient´s demographics are shown in Table 2. The mean age for the total women treated during the 73-month study period is 36.2 years, which reflects a private fertility clinic where ages ranged from 20 to 51 years. The most commonly applied stimulation protocols were the antagonist regimen (57.4% of cases) followed by the flare protocol (30.1% of cases). Only a small group of patients (12.5 %) were treated by variant protocols including the AACEP regimen and the long agonist down regulation protocol.

The cancellation rate before trans-vaginal oocyte retrieval (TVOA) was 6.2 % and included all cancellations after starting rFSH stimulation (i.e. initiated cycle). However, only 15 of 173 (8.7 %) patients were cancelled in the low FSH group (≤75 IU), which is suitably favourable when compared with the CONSORT algorithm, that showed a cancellation rate in a good-responder group of 17%. Most cancellations occurred in the group of older patients.

As part of the Australia-wide drive to decrease the twin rate there was an increasing rise in the transfer of single embryos during the study period, being 78.4% of all transfers with some variation among the age groups. Younger patients (<30 years) had a mean of 1.1 embryo transferred and the mean increased in the elder age groups to a maximum of 1.5 embryos in the group of 40 – 44 years.

The mean number of oocytes collected through the study period was 8.7 for all women and 9.8 for those women <40years. With respect to age groupings, the mean number of oocytes retrieved are shown in Table 3. Women aged under 30 years had 11.0 oocytes recovered, whilst women between 40 and 44 years had lower but satisfactory oocytes collected (mean of 6.2), and even those with the poorest prognosis of age >45 years had a mean of 4.1 oocytes recovered. When the oocyte distribution was examined in relationship to the AFC categories (Table 5), the highest AFC ratings showed a mean number of 12 oocytes, despite the very low rFSH starting doses. With respect to BMI groupings shown in Figure 1, the mean number of oocytes recovered were equivalent among different BMI groups, ranging from 7.4 ±5.9 in the lowest BMI group

(<18 kg/m2) to 8.6 ±5.4 in a higher BMI group (18 – 19 kg/m2), but these minimal differences across the BMI groups were not significant.

Table 4 shows the pregnancy outcomes categorised according to different age groups. The data shows an expected decreasing pregnancy and live birth rate per embryo transfer with increasing age groups, from 43.4 % and 36.4 % in the young group respectively, decreasing to 11.7 % and 7.5 % in the group of 40 – 44 years, respectively. Some women treated in the later study period will not yet have had spare embryos returned in an FET cycle, however the live birth productivity rate in the young group (<30 years) was as high as 57.1 % per initiated cycle and 60.1% per TVOA (data not shown).

The incidence of women needing admission to hospital for various diagnoses is shown in Table 2. In order to track all patients developing OHSS, 483 risk patients had the intensive monitoring protocol (IMP) applied during the period. Furthermore, 308 patients with >12 oocytes were treated with Cabergoline to diminish or prevent OHSS symptoms. Nine cases were categorised as severe OHSS requiring paracentesis or drainage of pleural effusion (1 case), and were 0.3% of all cases receiving rFSH stimulation. Only one case of severe OHSS occurred during the reporting period of the first algorithm publication [5] and that related to a marked violation of protocol. In this full study period, each of the 9 cases had identifiable non-compliance issues in 4 areas. These areas of "protocol violation" were 1. Excessive starting dosage (due to adjusting the AFC rating the wrong way once the AMH level was factored); 2. Incorrect elevation of dosage (due to increasing more than 12.5 IU when hormonal or ultrasound monitoring indicated a need for elevation); 3. Inappropriate trigger when E2 >10,000 pmol/l or follicle number ≥12 (usually because a Flare-cycle had prevented use of a GnRHa trigger); and 4. Wrongful use of hCG during the luteal phase (sometimes a patient from a remote location self-administering Ovidrel prior to receiving approval from the clinic during IMP). Each time the OHSS was exacerbated by superimposed pregnancy (so-called late onset OHSS in all 9 cases).

From Figure 1 it can be seen that 513 women (18.2 %) had starting doses <125 IU and half of these patients did not require any increase in dosage (Figure 2) even for those starting at ≤75 IU, one third had no change in

dosage. The overall percentage of patients continuing at their starting dosage was 79.1 % during the entire study period. Examining the data for dosages outside the usual range of 150 IU to 300 IU rFSH, 667 (23.7 %) received <150 IU; whilst 1343 (47.6 %) received >300 IU. This means that fewer than one third of women (29.7%), received conventional dosages of rFSH during the study period using the PIVET algorithms.

The distribution of oocyte numbers recovered is shown in Figure 3, where it can be seen that half of the patients had from 6 to 15 oocytes retrieved. The greatest distribution being in the 1 - 5 and 6 - 10 oocyte collection groups. The main contribution to the first group (low oocyte numbers), came from elderly patients. Very few women had 15 - 20 oocytes recovered (7.6 %) and an absolute minimum of cases had >20 oocytes recovered (4.0 %), most cases attributed to non-compliance of protocols.

Discussion

PIVET is developing unique algorithms to assist clinicians to select appropriate rFSH dosages with a view to accommodating modern trends of milder stimulation, whilst maintaining high pregnancy rates but minimising or even completely removing, the risk of OHSS. Since the first PIVET algorithm was published [5], the ART world has continued to evolve with several new trends. These include the idea of removing the risk of OHSS completely by advising an antagonist stimulation schedule with GnRH agonist trigger and freeze-all embryos for subsequent FET procedures. There has also been a strong push, led by Australia and New Zealand [14], to commit to an elective single embryo transfer policy. Along with that concept, the idea of blastocyst culture with a better embryo selection policy, has developed and goes hand-in-glove with the emergent idea of advanced genetic screening of embryos [15, 16]. Consequently, the pregnancy and live birth productivity rates show persisting high levels, in keeping with the oocyte retrieval numbers [6]. Although it has been shown that 15 oocytes collected per TVOA may be the optimal number for the highest pregnancy and live birth rates from fresh embryo transfers [17, 18], as well as for pregnancy and livebirth productivity rates [6], the risks for severe OHSS rises drastically after collection of 12 oocytes. Furthermore, trying to schedule for 12-15 oocytes retrieval, means that many cases will unintentionally result in >16 oocytes, or even >20 oocytes collected,

while the OHSS risk rises exponentially. Under the PIVET algorithms these rates were low at 4% for >20 oocytes.

During the entire study period, OHSS prevention has been the main focus and other preventive initiatives were also undertaken, including the management of more cycles by an antagonist regimen, which provided the clinician with an opportunity to trigger with a GnRH-agonist and decrease the risk of OHSS [19]. Furthermore, patients were offered increased monitoring to ensure all patients with OHSS symptoms were detected at the earliest possible stage, and that relevant expedient steps could be implemented, such as intravenous fluids to counteract hypovolaemia, which were often enough to prevent the complete disorder from developing. The high number of patients on increased monitoring did not necessarily reflect many patients at risk of developing OHSS, but only as a relevant service to detect all cases and expedite early management. In addition, the freeze-all strategy to prevent OHSS in high-risk scenarios [20] was used throughout the entire study period. However, despite the various preventive strategies, OHSS cases were encountered at the same rate during the period (0.3%), but each and every case was shown retrospectively to be non-compliant with the PIVET protocols and regimens as defined in the methodology section. All the cases of severe OHSS were late onset, associated with pregnancy, but also had one of 4 identifiable non-compliance issues with the advised protocols as defined above. We are aware of the controversy over use of HCG as luteal support, but have data supporting its use to improve the chance of pregnancy [21] and believe it can be used safely as defined in the PIVET protocols. Its use is clearly safe in women with lower AFC and AMH levels, e.g. categories C, D and E of the algorithms; perhaps further restrictions need to be considered for the A groups, as well as some group B cases. We have now adjusted the protocols to avoid luteal phase HCG in all cases with either AFC rating ≥15 antral follicles or AMH levels ≥15pm/L, in addition to the existing restriction of recovery of ≥12 oocytes at TVOA.

High cancellations rates prior to oocyte retrieval can be explained by insufficient follicle development as a result of an inappropriately low rFSH starting dose. However, only 15 of 173 (8.7 %) patients were cancelled in the low FSH group (≤75 IU). Young patients with high AFC/AMH often expressed disappointment as they

were part of the distribution grouping of 1-5 oocytes. However, their pregnancy rates were actually high, in-keeping with our earlier published data that <5 oocytes from younger high-responders generate embryos which have a higher implantation rate than those from higher order oocyte collections [6]. Furthermore, we noted higher embryo utilisation rates over oocyte utilisation rates in all cases, but both of these rates were increased in older patients. The higher embryo utilisation rate reflects the higher number of usable, mature and fertilisable M II eggs, and is a useful index signifying the proportion of eggs which are actually mature. The higher rates in older women may reflect the request by older women to undertake a transfer of lower graded embryos.

In conclusion, both dosing algorithms, adjusted for ~8.3 or 12.5 IU increments, have proven effective in meeting the aims of collecting 8-12 oocytes from the majority of women undergoing ovarian stimulation for IVF procedures. Furthermore the number of cases with >15 oocytes was kept at a low of 11.4 % and very few exceeding 20 oocytes. This is comparable with modern trends of milder stimulation with a view of absolute minimisation of the risk of OHSS. It is our view that such risk can be reduced under 0.01% but this will require a more determined clinical approach, with stronger adherence to the protocols described here, along with appropriately restricted use of HCG for triggering in tandem with its careful use in the luteal phase.

Although PIVET has published data showing excellent high rates of pregnancy from FET cycles, particularly where these are undertaken under HRT control [22], we are not supportive of the view that fresh embryo transfers should be avoided [20]. We believe the application of the PIVET algorithms provides a rational approach enabling fresh and frozen embryo transfers with optimal pregnancy productivity rates, along with potentially, the complete avoidance of severe OHSS cases.

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Figure Legends:

Figure 1.

Flow Chart showing the derivation of 2822 cases of IVF initiated over a 6-year period at PIVET Medical Centre applying PIVET algorithms.

Figure 2.

Figure showing the proportion of patients in each rFSH starting dose category, who responded adequately to the starting dose of FSH and required no adjustment (elevation) to achieve at least 4 follicles (for the high AFC groups) and 8-12 follicles for the remainder. Where adjustments were made, this was mostly one, or occasionally two dose increments.

Figure 3.

Figure showing the distribution of oocytes recovered, indicating that only 11.4% of all women had more than 15 oocytes recovered including less than 5% having more than 20 recovered; most resulting from breaches of the described protocols.

Table 1.

PIVET algorithm designed to suit rFSH dosages of 12.5 IU increments up to 300 IU and 25 IU for dosages ≥325 IU. Red values depict 12.5 IU increments, while purple values represent 25 IU increments.

Table 2.

Patient demographics and treatment flow for women initiating rFSH stimulation under PIVET algorithms.

Table 3.

Oocytes recovered and embryo/oocyte utilisation rates for all women having a TVOA procedure categorised by age groupings.

Table 4.

Clinical pregnancy and live birth outcomes for all women having a TVOA procedure categorised by age groupings.

Table 5.

Oocytes recovered for all women having a TVOA procedure categorised by AFC groupings.

Figure 1.
Click here to view linked References

Figure 1: Flow Chart

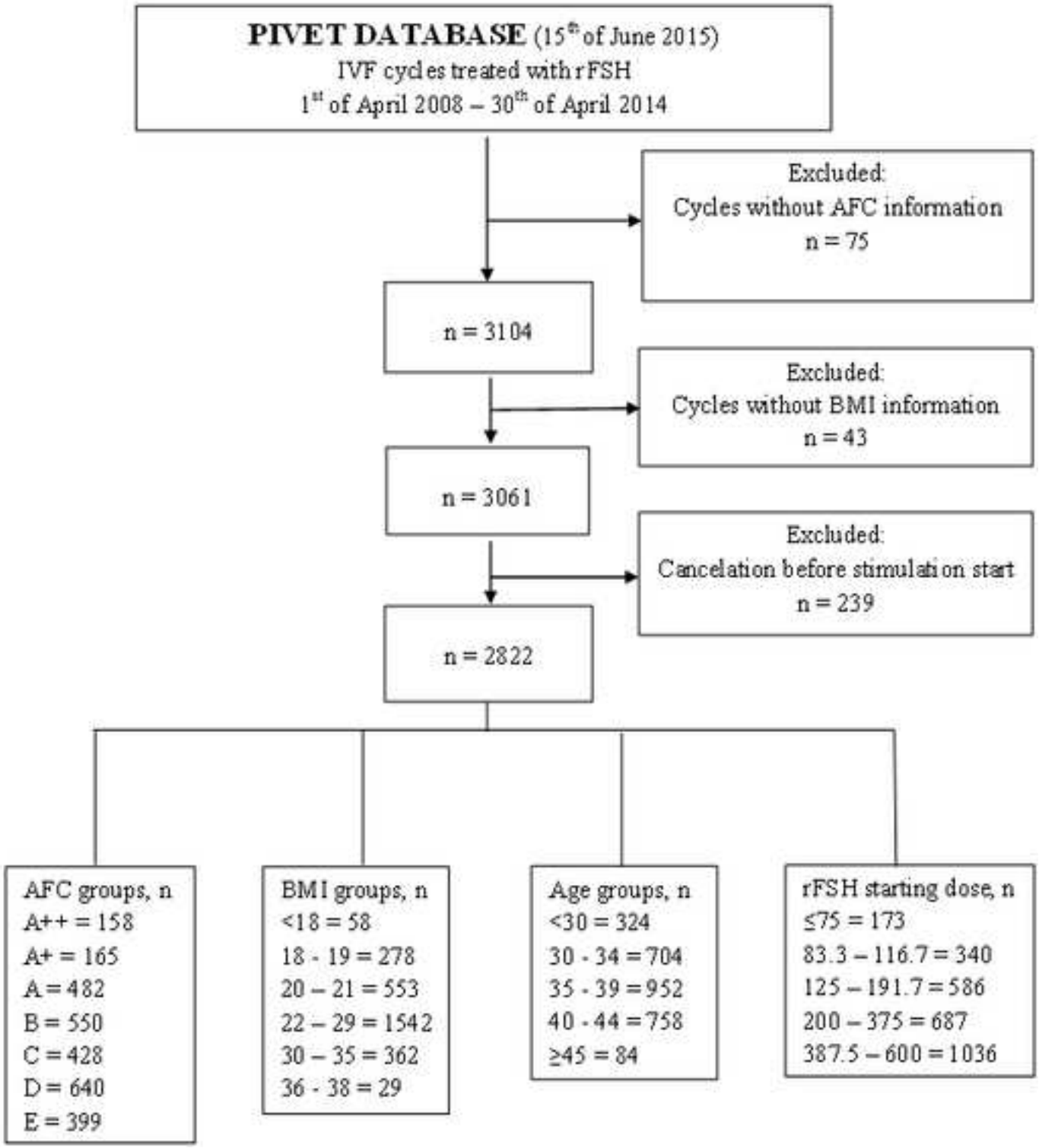

Figure 2.
Click here to view linked References

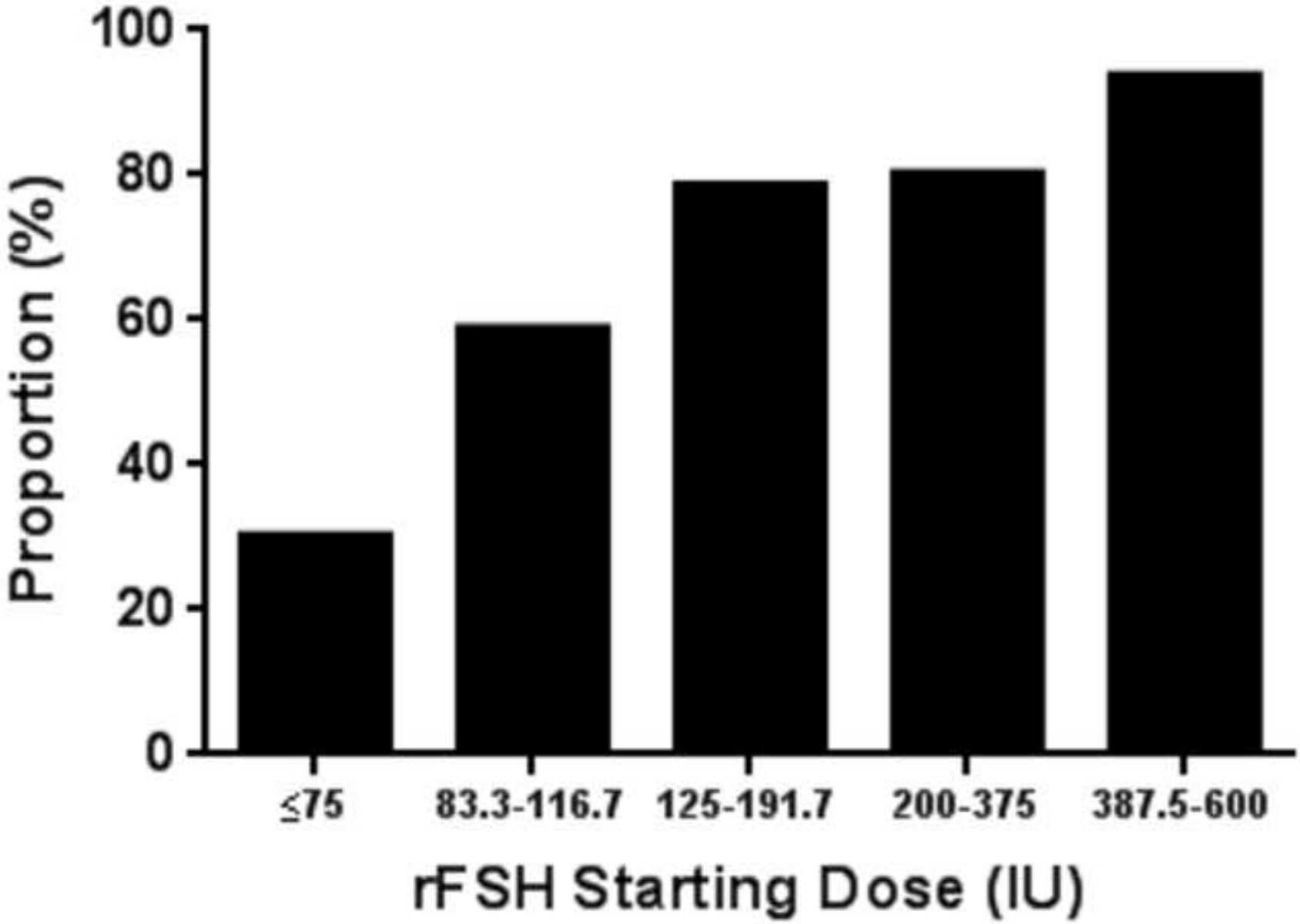

Figure 3.
Click here to view linked References

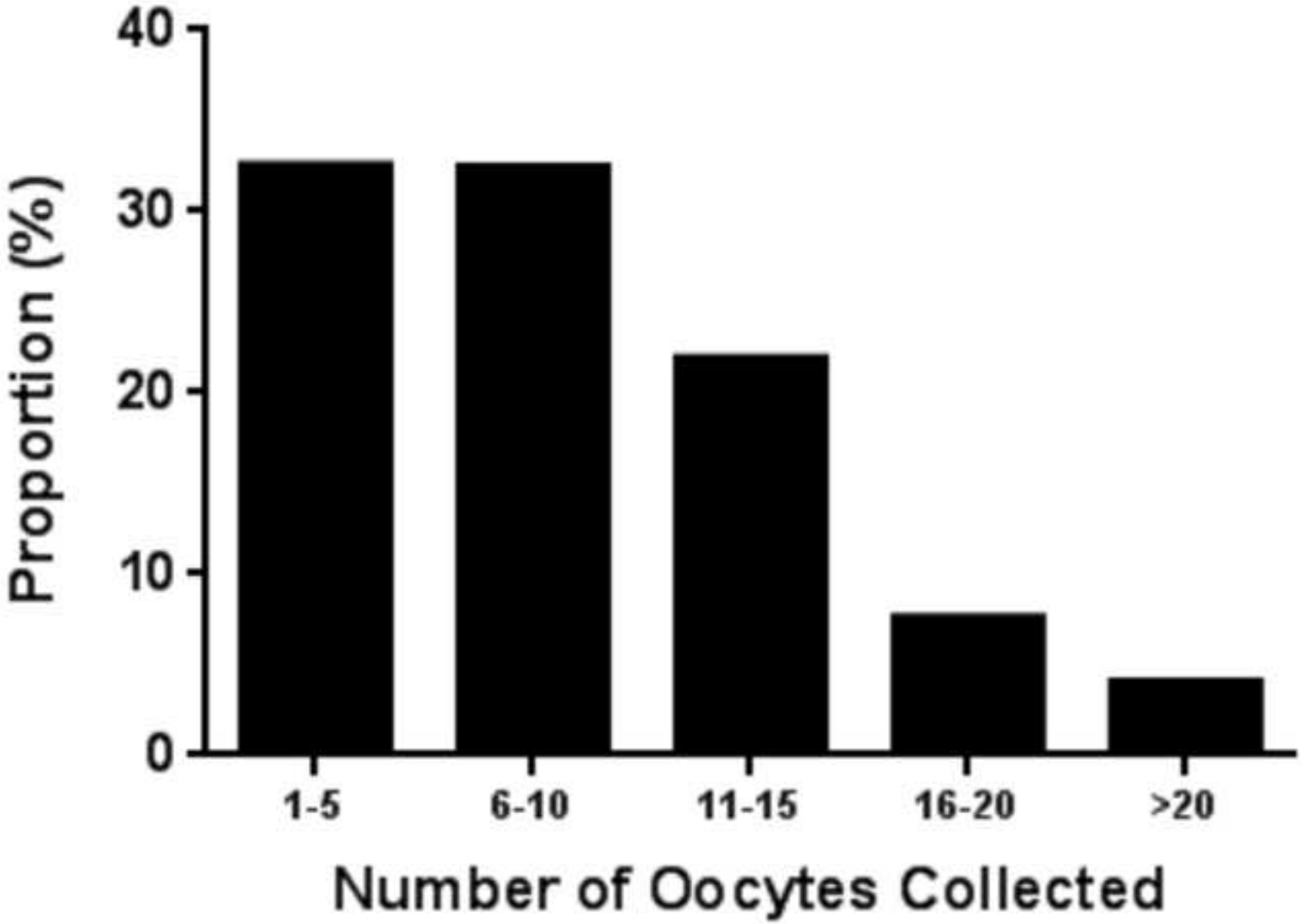

Table 1

PIVET FSH Dosage Algorithm (suits 12.5 IU & 25 IU increments)

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	37.5	37.5	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.7	137.7	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0
	21	37.5	37.5	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.7	137.7	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0
	22	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0
	23	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0	212.5
	24	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0	212.5	212.5
	25	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	200.0	212.5	212.5
	26	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0
	27	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0
	28	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5
	29	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5	250.0
	30	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5	250.0	262.5
	31	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5
	32	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0
	33	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	187.5	200.0	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0	337.5
	34	87.5	87.5	100.0	100.0	112.5	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0	337.5	350.0	362.5
	35	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	175.0	187.5	200.0	200.0	212.5	225.0	237.5	250.0	275.0	287.5	300.0	325.0	350.0	362.5	375.0	387.5	400.0	400.0
	36	100.0	100.0	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	200.0	200.0	225.0	225.0	237.5	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0
	37	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	362.5	375.0	400.0	425.0	450.0	475.0	500.0
	38	112.5	112.5	125.0	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0
	39	112.5	112.5	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	275.0	287.5	300.0	312.5	325.0	350.0	375.0	400.0	425.0	450.0	500.0	525.0	550.0	575.0	600.0
	40	112.5	112.5	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	187.5	187.5	200.0	225.0	237.5	250.0	262.5	275.0	300.0	312.5	325.0	337.5	350.0	375.0	400.0	425.0	450.0	475.0	500.0	550.0	600.0	600.0	600.0
	41	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	162.5	175.0	187.5	187.5	200.0	200.0	225.0	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0	575.0	600.0	600.0	600.0
	42	125.0	125.0	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0	575.0	600.0	600.0	600.0	600.0
	43	125.0	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	212.5	237.5	250.0	262.5	275.0	287.5	300.0	312.5	350.0	375.0	387.5	400.0	437.5	450.0	475.0	500.0	550.0	575.0	600.0	600.0	600.0	600.0	600.0
	44	137.5	137.5	150.0	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	225.0	237.5	250.0	275.0	275.0	312.5	325.0	350.0	375.0	400.0	412.5	425.0	450.0	475.0	500.0	525.0	550.0	600.0	600.0	600.0	600.0	600.0	600.0
	45	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	225.0	250.0	250.0	287.5	300.0	325.0	350.0	362.5	400.0	412.5	425.0	450.0	475.0	500.0	525.0	550.0	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 or elective Freeze-all

Aiming for 12-15 oocytes,
move four columns to the right
Antagonist/Lucrin trigger

Cycle Information (01/04/2008 - 30/04/2014)		**Age groups**		**Stimulation Protocols**	
Cycles initiated, n	2822	<30 years, n (%)	324 (11.5)	Antagonist, n (%)	1619 (57.4)
TVOA, n	2646	30 - 34 years, n (%)	704 (24.9)	Flare Agonist, n (%)	850 (30.1)
Cancellation before oocyte retrieval, n (%)	176 (6.2)	35 - 39 years, n (%)	952 (33.7)	AACEP, n (%)	204 (7.2)
No. of Embryo Transfer, n (% of retrievals)	2211 (83.6)	40 - 44 years, n (%)	758 (26.9)	Long Agonist, n (%)	107 (3.8)
Single embryo transfer, n (% of embryo transfers)	1588 (71.8)	≥45 years, n (%)	84 (3.0)	Variants, n (%)	42 (1.5)
Increased monitoring program, n (% of retrievals)	483 (18.3)	Mean age (±SD), years	36.16 (±5.27)		
Cases admitted to Hospital, n (% of started cycle)	31 (1.1)				
Paracentesis, n (% severe OHSS)	9 (0.3)				
Freeze all for OHSS (% of retrievals)	55 (2.1)				

Table 2. Patient demographics and treatment flow for women initiating rFSH stimulation under PIVET algorithms

	Age Group				
	<30 years	**30 – 34 years**	**35 – 39 years**	**40 – 44 years**	**≥45 years**
Mean oocytes retrieved (±SD)	11.02 (±6.21)	10.20 (±5.93)	9.10 (±5.48)	6.18 (±4.38)	4.07 (±4.11)
Oocyte Utilisation Rate, %	27.8	29.5	28.3	31.2	35.0
Embryo Utilisation Rate, %	50.3	50.4	49.8	60.5	64.7

Table 3. Oocytes recovered and embryo/oocyte utilisation rates for all women having a TVOA procedure categorised by age groupings.

	Age Group				
	<30 years	**30 – 34 years**	**35 – 39 years**	**40 – 44 years**	**≥45 years**
Clinical pregnancy rate per embryo transfer, %	43.4	39.9	28.6	11.7	0.0
Live birth rate per embryo transfer, %	36.4	33.5	22.4	7.5	0.0
Live birth rate per initiated cycle, %	29	27.7	18	5.5	0.0
Freezing rate per initiated cycle, %	64.2	64.6	51.3	28.4	9.5
Live birth productivity rate, per initiated cycle, %	57.1	51.7	33.2	8.4	0.0

Table 4. Clinical pregnancy and live birth outcomes for all women having a TVOA procedure categorised by age groupings.

AFC Group	Mean oocytes retrieved (±SD)
A++	12.35 (±6.85)
A+	11.82 (±5.85)
A	12.26 (±6.16)
B	9.98 (±4.62)
C	8.33 (±4.41)
D	5.32 (±3.70)
E	4.90 (±4.53)

Table 5. Oocytes recovered for all women having a TVOA procedure categorised by AFC groupings.

Tables 1 Greyscale

PIVET FSH Dosage Algorithm (suits 12.5 IU & 25 IU increments)

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	37.5	37.5	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.7	137.7	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0
21	37.5	37.5	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.7	137.7	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0
22	37.5	50.0	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0
23	50.0	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	187.5	200.0	212.5
24	50.0	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0	212.5	212.5
25	50.0	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	200.0	212.5	212.5
26	62.5	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0
27	62.5	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0
28	62.5	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5
29	75.0	75.0	75.0	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5	250.0
30	75.0	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	225.0	237.5	250.0	262.5
31	75.0	75.0	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5
32	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0
33	87.5	87.5	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	175.0	187.5	200.0	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0	337.5
34	87.5	87.5	100.0	100.0	112.5	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	312.5	325.0	337.5	350.0	362.5
35	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	175.0	187.5	200.0	200.0	212.5	225.0	237.5	250.0	275.0	287.5	300.0	325.0	350.0	362.5	375.0	387.5	400.0	400.0
36	100.0	100.0	112.5	112.5	125.0	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	200.0	200.0	225.0	225.0	237.5	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0
37	100.0	100.0	112.5	112.5	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	362.5	375.0	400.0	425.0	450.0	475.0	500.0
38	112.5	112.5	125.0	125.0	125.0	125.0	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0
39	112.5	112.5	125.0	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	225.0	237.5	250.0	275.0	287.5	300.0	312.5	325.0	350.0	375.0	400.0	425.0	450.0	500.0	525.0	550.0	575.0	600.0
40	112.5	112.5	125.0	137.5	137.5	137.5	150.0	150.0	162.5	162.5	175.0	187.5	187.5	200.0	200.0	225.0	237.5	250.0	262.5	275.0	300.0	312.5	325.0	337.5	350.0	375.0	400.0	425.0	450.0	475.0	500.0	550.0	600.0	600.0	600.0
41	125.0	125.0	137.5	137.5	150.0	150.0	150.0	162.5	162.5	162.5	175.0	187.5	187.5	200.0	200.0	225.0	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0	575.0	600.0	600.0	600.0
42	125.0	125.0	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0	450.0	475.0	500.0	525.0	550.0	575.0	600.0	600.0	600.0	600.0
43	125.0	137.5	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	212.5	212.5	237.5	250.0	262.5	275.0	287.5	300.0	312.5	350.0	375.0	387.5	400.0	437.5	450.0	475.0	500.0	550.0	575.0	600.0	600.0	600.0	600.0	600.0
44	137.5	137.5	150.0	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	225.0	237.5	250.0	275.0	275.0	312.5	325.0	350.0	375.0	400.0	412.5	425.0	450.0	475.0	500.0	525.0	550.0	600.0	600.0	600.0	600.0	600.0	600.0
45	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	212.5	225.0	225.0	250.0	250.0	287.5	300.0	325.0	350.0	362.5	400.0	412.5	425.0	450.0	475.0	500.0	525.0	550.0	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 or elective Freeze-all

Aiming for 12-15 oocytes,
move four columns to the right
Antagonist/Lucrin trigger