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Title

Finding a place for Corifollitropin within the PIVET FSH Dosing Algorithms

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Abstract

PIVET rFSH dosing Algorithms have been designed for rFSH injection pens, and they provide optimal pregnancy and livebirth productivity rates, whilst minimising risk and occurrence of ovarian hyperstimulation syndrome. Recently, the long acting recombinant gonadotrophin corifollitropin (Elonva) was approved for use in assisted reproduction, and welcomed by patients as the single injection allowed ovarian stimulation over 7 days without the need for multiple injections. Consequently, we devised another rFSH dosing Algorithm to incorporate Elonva, and compared these cycles to standard rFSH agents, Gonal f and Puregon. Initiated Elonva cycles (n=165) were compared to 972 cycles initiated with standard rFSH. Elonva replaced standard rFSH dosages across the 200-400 IU range, but provided equivalent oocyte retrieval numbers and livebirth outcomes. Elonva is considered risky for women whose antral follicle count is ≥20 follicles, and was inadvertently administered contra-protocol in 19 cycles with ≥20 follicles. However, while oocyte retrieval numbers were higher, raising the risk for OHSS, no actual cases ensued. Taken together, our data indicated that Elonva was equivalent to standard rFSH stimulation, and consequently has been added to our rFSH Algorithms for medium to lower antral follicle counts. It is represented by a green color-coding in the existing PIVET Algorithmic charts.

Keywords: PIVET Algorithm; antral follicle count AFC; recombinant follicle stimulating hormone rFSH dose; Corifollitropin; Elonva.

Introduction

The PIVET recombinant follicle stimulating hormone (rFSH) dosing Algorithms were devised as one approach to avoid the problem of severe ovarian hyperstimulation syndrome (OHSS), a condition which is indeed life-threatening (Braat et al., 2010). Advancing on the published concepts of risk charts to identify the full ranges of low ovarian responses through to excessive responses (Popovic-Todorovic et al., 2003; La Cour Freiesleben et al., 2011), we developed our first rFSH Algorithm adjusting for patient parameters such as age, antral follicle count (AFC), BMI, anti-Mullerian hormone (AMH) level, day-2 FSH and history of smoking. (Yovich et al., 2012). Implementation of this targeted gonadotrophin stimulation schedule markedly reduced the incidence of OHSS hospital admissions from an already reduced rate of 1.7% to 0.2% (1 case only from 577 oocyte retrievals) (Yovich et al., 2012). The Algorithm was developed following the availability of the Puregon follitropin-β injection pen introduced in 2007 (MSD, Australia), which allowed controlled incremental rFSH dosage increases by approximately 8.3 IU. Application of the Puregon Algorithm proved successful in that pregnancy rates were maintained, >80% of women responded adequately to the calculated dosage, the others responding to an increase of only one or two clicks (8.3 IU to 16.7 IU) (Yovich et al., 2012). This meant most women generated 8-12 oocytes on retrieval, where 25% of patients required <150 IU and 10% responded adequately to <100 IU rFSH. The proportion of women generating >20 oocytes fell from 15% to 2%, whilst cancellation rates were not increased (Yovich et al., 2012). The number of women producing >12 oocytes and consequently entering our increased monitoring protocol (IMP), or those who may be considered for freeze-all due to excessive response, was reduced markedly.

In 2011 a new Gonal f follitropin-α rFSH injection pen (Merck Serono) was introduced, and was guaranteed to deliver 12.5 IU increments, which replaced the older Gonal f pen with 37.5 IU incremental dosages. We generated a new Gonal f Algorithm to accommodate the new injection pen and adjusted the dosage range such that 450 IU became the maximum scheduled as per Australian regulations (Yovich et al., 2016a). The Algorithm allowed individualized controlled ovarian stimulation with similar pregnancy productivity rates and avoidance of OHSS (Yovich et al., 2016a) in comparison to the Puregon Algorithm. Specifically, applying the two Algorithms together in routine clinical operations for 2822 ovum pick-up procedures (OPU), resulted in a controlled oocyte yield of 10±2 oocytes, with only 11.4% of OPUs leading to >15 oocytes and a minimal 3.9% of cycles producing >20 oocytes. The starting rFSH dose was unchanged for 80% of patients stimulated according to the Algorithms, and 24% responded well with dosages <150 IU. Many women responded well to dosages ≤75 IU, with 30% of this group not requiring any further rFSH adjustment. OHSS remained very low at 0.3%, and as adherence to the Algorithm protocols is tightening, current annualised OHSS rates (2015-2016) are at 0.1%, which demonstrates the effectiveness of these Algorithmic approaches.

Since Puregon and Gonal f require multiple injections, Elonva was developed by Schering Plough, now acquired by Merck Sharpe Dohme (MSD), as an alternative with a single rFSH injection strategy. Elonva is a glycoprotein with the same 92-amino acid α-subunit as human FSH, but the β–subunit has been extended from 110 to 138 amino acids with a 28 amino acid carboxy-terminal peptide identical to the βhCG β–subunit terminal sequence (Fauser et al., 2009). This configuration extends rFSH half-life from ~30 hours for Puregon to 69±10 hours for Elonva enabling a duration of FSH activity above the therapeutic threshold for ~7 days. However, it differs from both Puregon and Gonal f in that the injection is followed by

significantly higher FSH activity over the first 4 days than those daily, sequential rFSH injections (Fauser et al., 2010). The concept of 1 injection replacing 7 is popular among women undertaking assisted reproduction (Requena et al., 2013), hence we decided to trial Elonva and integrate it into the existing PIVET dosing Algorithms. The aim was to apply Elonva based on the conditions advised by MSD (Corifollitropin Alfa Dose-finding Study Group, 2008) – namely to avoid using it in women with AFC >20 follicles, and administer based on patient weight. We integrated Elonva as an alternative agent in cases where the standard rFSH Algorithm initially indicated a 200 – 400 IU dose of Puregon or Gonal f. The primary outcomes for comparison included mean number of oocytes retrieved, cases of OHSS or requiring IMP (>12 oocytes retrieved), proportion of cases with >15 oocytes retrieved, embryo utilisation and fertilisation rates, and finally pregnancy and live birth outcomes.

Materials and Methods

Study Design

The study was established as an observational cohort study, retrospectively analysed to compare cycles from those selecting Elonva to those selecting Puregon or Gonal f (as a combined group). The decision to use Elonva, Puregon or Gonal f was based on discussions between the patient and the consulting clinician, independent of the researchers. Over the period June 2013 to December 2015 inclusive, 165 autologous (non-donor) IVF treatment cycles were initiated using Elonva with 155 cases reaching OPU and having complete data including AFC rating. To ensure the same clinical and embryological procedures, 972 initiated autologous IVF cycles using Gonal f or Puregon rFSH from the same period were analysed for comparison, with 950 having AFC gradings and 872 of these reaching OPU. The

cut-off date of end December 2015 enabled the tracking of all IVF cycles and ensuing pregnancies through to delivery by October 2016.

Elonva Dosage Selection and Administration

The 2016 PIVET Algorithms for Puregon and Gonal f with increments of 8.3 or 12.5 IU rFSH respectively (Yovich et al., 2016a), were both adjusted to enable a choice for Elonva in the 200 – 400 IU range, and highlighted in green in the Puregon and Gonal f specific Algorithms (Fig. 1 & 2, respectively). MSD protocols advised to refrain from using Elonva if the patient AFC was ≥20 small antral follicles (AFC A category). In addition, Elonva stimulation may not be sufficient for women with ≤4 small antral follicles who require higher initial dosages, exceeding 400 IU (AFC E category). Consequently, if patients required an initial standard rFSH dose between 200 – 400 IU according to the Algorithm (green band, Fig. 1 & 2), the decision to use single injection Elonva became a matter of discussion between the patient and the consulting clinician. However, once Elonva was selected, the actual dosage applied was strictly chosen according to the manufacturer guidelines where women weighing ≤60 kg required a single dose of 100 μg, whilst women >60 kg received a single dose of 150 μg. It was administered subcutaneously in the lower abdominal wall between a pinched fold in 0.5 ml volume. Importantly, in a small group of patients and contra-protocol, Elonva was administered in 19 initiated cycles with AFC A patients (≥20 follicles), and in 15 initiated cycles with AFC E patients (≤4 follicles). These cycles were included in the analysis for comparative purposes with standard rFSH.

Stimulation and Clinical Managment

For both Elonva and standard rFSH (Puregon or Gonal f), the starter injections were given on Day-3 following the demonstration of basal hormonal levels on Day-2 (E2 <200 pmol/L, P4

<5 nmol/L, LH <12 IU/L and FSH measured for Algorithmic adjustment; rFSH dosage increased if FSH >8 IU/L and again if FSH >12 IU/L). The majority of cycles were conducted using an Antagonist protocol and a small proportion had Flare protocols, when rFSH dosages proscribed ≥400 IU. Both groups had a blood test performed on day-7 (Day-6 avoiding Sunday) to determine the commencement of the Antagonist (Orgalutron; MSD), 0.25 mg daily. This was given when E2 ≥500 pm/L indicating an adequate response. On Day-9 a blood test was again performed measuring E2 expecting ≥1000 pm/L and P4 expecting <5 nm/L. Transvaginal ultrasound (TVUS) was also performed on Day-9 to check for follicular development. On this day (Elonva +6), decisions were made regarding cancellation of cycle due to inadequate response, or to increase dosage. In the Elonva cycles this meant prescribing the proscribed standard rFSH dosage to commence the next day (menstrual cycle Day-10, Elonva day-7). The stimulation protocols for both groups continued for 2 or 3 days (eg Monday to Wednesday; or Friday to Monday) with blood test (for E2 and P4) and TVUS scan for follicle dimensions. The majority of IVF cycles in both groups had the rhCG Trigger (2 x Ovidrel 250 micrograms; Merck Serono) on menstrual cycle Day-12 or Day-13 if the number of follicles were ≤12 and E2 ≤12,000 pm/L. Where exceeded, the Trigger following an Antagonist stimulation regimen, was by the GnRH agonist leuprolide acetate (Lucrin: Abbott Australasia Pharmaceuticals, Australia) 50 IU. Luteal phase management consisted of rhCG injections where deemed safe and a variable hormonal support schedule depending upon the number of oocytes retrieved, mid-luteal E2 or P4 levels, or other parameters from increased monitoring when oocyte retrieval exceeded 12. These have all recently been described in detail (Yovich et al., 2016a).

Statistics

This study was designed to find a place for a new drug within an existing rFSH treatment Algorithm. The success of the endeavour would be represented by non-inferiority, where no statistical differences would be found in comparison to Puregon/Gonal f in terms of number of oocytes retrieved per OPU, number of OHSS or IMP cases, and pregnancy and live birth outcomes. Continuous data (e.g. mean oocytes collected) were compared using ANOVA with Holm Sidak's post-hoc test, while the number of cases or proportions were compared using Fisher chi square tests. For figure 3A and B, best fit lines were applied to the responses according to AFC grading or FSH dosage using Graph Pad Prism, and slopes of the lines compared statistically. All data was analysed using either SPSS vs 24 or Graph Pad Prism, and considered significant if p-values were <0.05.

Ethical considerations

Specific ethical approval to use Elonva was not required as it is approved by the Australian Therapeutic Goods Administration. PIVET Medical Centre is accredited under a national scheme (RTAC; Reproductive Technology Accreditation Committee) as well as a state body – the Reproductive Technology Council - acting under Western Australian statutory regulation. The focus for both authorities is to minimise the number of OHSS cases as well as multiple pregnancies. The Human Research Ethics Committee (HREC) of Curtin University has provided approval for retrospective data analysis and publication under item RD-25-10 (2015).

Results

The embryological outcomes of 165 and 950 IVF cycles with AFC measurements, initiated with Elonva and standard rFSH, respectively, is shown in Table 1 and demonstrates the

number of cases proceeding to OPU. The outcomes are categorised according to the AFC groupings and show the age range within each group. The main outcomes recorded were total number of oocytes retrieved, the fertilisation rate and embryo distribution (fresh embryo transfer or cryopreservation with subsequent frozen embryo transfer). The embryo utilisation rate along with pregnancy and livebirth productivity rates, terms introduced by PIVET and previously reported (Yovich et al., 2016b), were also calculated (Table 2). For Elonva, an average of 10.0 oocytes were recovered per OPU procedure and contra-protocol, this ranged from a low of 3.1 oocytes for AFC group E sequentially rising up to 15.2 oocytes for AFC group A (Table 1 & Fig. 3A). However, AFC groups A and E included small case numbers (19 and 15 respectively), with the majority of Elonva treatments undertaken in AFC groups B, C and D and comprising 79.4% of Elonva cycles (Table 1). For the comparative group using standard rFSH (Puregon or Gonal f), overall oocytes retrieved averaged 9.3 and also showed the sequential rise from a low of 3.7 for AFC group E to 13.3 oocytes for AFC group A, the latter of which being 2 oocytes less than Elonva (Table 1 & Fig. 3A). To assess the concordance between the treatments and oocyte yield, a regression line was calculated and demonstrated an $R^2 = 0.980$ with a 1/slope of -0.342 for Elonva, which was slightly steeper than the rFSH series ($R^2 = 0.999$ and a 1/slope of -0.418) (Fig. 3A), but the oocyte retrieval response was not statistically different between treatments (p=0.074). This was further evident when data from the extreme AFC groups were excluded (i.e. groups A & E) (p=0.828) (data not shown). In addition, when the mean oocyte retrievals for each AFC grading were directly compared by ANOVA according to treatment (Elonva v rFSH), there was no significant difference (Fig. 3A).

The fertilisation rates and embryo utilisation rate, which is the percentage of usable embryos cryopreserved or transferred were similar overall for Elonva versus rFSH (Table 1). There

were some significant differences based on AFC group for fertilisation rate, and embryo utilisation rate per two pronuclei zygote generated being higher for AFC group A in the rFSH group. Embryo utilisation appeared higher in AFC group E for both treatments, but this is an aberration reflecting the desperate nature of this poor-prognosis group and did not translate into more births when live birth productivity rate per OPU was considered. There was no significant difference between Elonva (3/15; 20.0%) and rFSH (8/127; 6.3%) cycles in terms of live birth productivity rate per initiated cycle. Overall, pregnancy and live birth rates were not statistically different beween rFSH and Elonva. However, there were some significant differences observed within AFC categories between the treatment groups (Table 2), particularly for AFC group C, where rates were higher in Elonva-treated patients. When grouped according to dosage (Table 4), the rates were largely the same between treatment groups. There was a slight difference in frozen embryo pregnancy rates, although live birth rates were the same.

Treatment cancellation for poor Elonva response occurred in 10 cases (6.1%); mostly from the low AFC groups D and E and largely embracing the poor ovarian response group according to the Bologna Criteria (Ferraretti et al., 2011). This was not statistically different from standard rFSH cycles, with an overall cancellation rate of 8.2%, and also mostly in AFC group E (p=0.43). For Elonva, over-response was a greater issue with 22 cases retrieving more than 15 oocytes (13.3%), but not statistically difference from rFSH at 13.0 % (p=0.90). The majority of these Elonva cases were from AFC group A (9), but a few from group B (8) and even from group C (5). In two cases, 24 oocytes were recovered from an AFC grade A and an AFC grade B patient who were both stimulated on the Flare protocol. For standard rFSH group, over-response (>15 oocytes recovered) occurred in 126 cases (13.0%) mostly in Groups A (70 cases) and B (33 cases). Although no Elonva case required hospitalisation for

OHSS, these cases were still classified as OHSS-risk and required IMP, avoidance of HCG in the luteal phase and Cabergoline administration. There was a total of 42 Elonva cases yielding >12 oocytes (25.5%), and consequently these also entered the IMP, but again this was not statistically different from rFSH at 23.9% (p=0.69). For Elonva, the majority of cases were from AFC group A, but a small fraction were derived from AFC groups B and C. Hospital admissions for OHSS in the entire standard rFSH group was required for 3 women; each having a major breach from the PIVET protocols identified. Specifically, the use of a Flare regimen in women with AFC Groups A (contra-protocol); using an HCG Trigger with follicle numbers exceeding 12 (GnRH agonist advised but requires Antagonist rFSH regimen); and prescribing HCG in the luteal phase for women having >12 oocytes recovered (contra-protocol). These 3 cases of OHSS arose from a total 1137 stimulated rFSH cycles, providing an overall risk of 0.26%, and was statistically higher compared to Elonva (0 cases from 165 initiated cycles, p=0.03).

Across the AFC categories B, C and D, the median number of days of additional rFSH dosages for the 126 Elonva cases reaching OPU was 2 days (ranging from a median 1 to 3 days). For those 19 cases given Elonva in category A, the median number of days of additional rFSH was 1 day (ranging 0 to 2 days) and for the 15 cases in category E, the median number was 3 days (ranging from 2 up to 5 days for one case). A further point of interest illustrated in Fig. 3A, is that the standard deviation of oocytes recovered was greatest for AFC group A being 5.9 for Elonva and 6.7 for rFSH demonstrating the variable response in this AFC group.

Oocyte retrieval numbers and clinical outcomes were also compared on the basis of the initial rFSH starting dose derived from the Algorithm for each cycle, and categorised as <200, 200-

299, 300-400 and ≥400 IU (Tables 3 & 4). The patterns were similar with higher rFSH dosages associated with lower oocyte yields. For Elonva, oocyte retrieval numbers ranged from a mean 5.2 to 11.7 with standard deviations ranging up to 5.5 for the <200 IU dosages (Fig. 3B and Table 3). For the rFSH series oocyte numbers ranged from a mean 5.4 to 12.2 with standard deviations ranging up to 6.8 for the <200 IU dosages (Fig. 3B and Table 3). The regression lines were again comparable for Elonva (R^2= 0.951; 1/slope -0.463; Fig. 3B) and rFSH dosing (R^2= 0.940; 1/slope -0.476; Fig. 4B) with no significant difference between slopes (p=0.912) or between the means as determined by ANOVA. There was a trend for a higher oocyte yield using Elonva for designated rFSH doses <200 IU and lower oocyte numbers for those women using Elonva for designated rFSH dosage ≥400 IU.

Discussion

A number of clinical trials, namely Engage, Ensure and Pursue have investigated the use of long acting corifollitropin (Elonva) in ovarian stimulation in GnRH antagonist cycles (Devroey et al., 2010; Cochrane database; Pouwer et al., 2015). More recent studies and meta-analyses confirmed the earlier reports of non-inferiority when important parameters such as number of oocytes retrieved, pregnancy and live birth rates were compared to rFSH stimulation (Boostenfar at al., 2015; Greisinger et al., 2016). However, the optimal Elonva dosage still requires investigation and validation (Pouwer et al., 2015). Our study reports on the validity of incorporating Elonva into the PIVET dosing Algorithms, which selects rFSH dosages according to a number of physiological parameters, but predominantly age and AFC category. In particular, the critical requirements of controlled oocyte retrieval yields and avoidance of OHSS were observed applying this methodology, whilst optimum pregnancy and livebirth outcomes were also maintained.

This study confirmed that Elonva generated similar oocyte yields as rFSH cycles, and this was across the various AFC categories within the PIVET Algorithms. Furthermore, the oocytes recovered for both treatment strategies largely showed comparable utilisation rates, pregnancy and live birth rates, in addition to productivity rates, with some slight, but specific differences depending on AFC grading. These rates were similar for initiated cycles, OPU and embryo transfers, which indicated non-inferiority for the respective ovarian stimulation methods. However, contra-protocol, Elonva was used in women with an AFC rating ≥20 follicles, and although there was no statistically significant difference, there was a concerning trend showing a mean of 2 more oocytes were recovered in those cases. This raised the mean number above 15 oocytes, which was undesirable. Furthermore, the Trigger day was reached faster in these cases, often requiring no additional rFSH adjustment. This group was intended to be excluded from the original study protocol as previous reports indicated they carried an increased OHSS risk. Interestingly, OHSS did not actually develop in any Elonva case, but the group was comprised of a small number of cases. Understandably, they had a high rate of inclusion for increased clinical monitoring (IMP), which included OHSS avoidance strategies, hence indicating a high potential risk. Although the regression slope for mean oocytes recovered across the AFC range for Elonva and rFSH was not significantly different, the recovery trend may imply that if more AFC A cases were included, the OHSS risk would likely increase further. Thus, these data support excluding all AFC category A cases from Elonva treatment within the Algorithm.

Similarly, at the opposite end of the AFC spectrum with Elonva, there was a mean 1 oocyte fewer in AFC category E and the number of days of added rFSH doses to reach the Trigger were greater (median 3 days but ranging up to 5 days). Again it was not intended to explore this part of the Algorithm and only a small number were inadvertently included. Nonetheless,

the observation is very similar to a reported RCT in poor responders (Kolibianakis et al., 2015). While the difference in oocyte yield between rFSH and Elonva in AFC E patients was not statistically significant, it affirms our view that Elonva may further compromise the chances of this group who are already classified as poor ovarian responders within the Bologna criteria. From the earlier reported experience of outcomes from the PIVET Algorithms it appears reasonable to suggest that a lower oocyte recovery number, hence poorer chance of pregnancy, would arise from all cases with Algorithmic dosages >400 IU, covering through parts of AFC categories C, D and E. Consequently, patients falling into these categories should be carefully assessed for Elonva treatment.

Taken together, the designated replacement schedule of standard rFSH dosages between 200 to 400 IU with Elonva in the Algorithm is justified, and shown to be validated according to the similar responses with respect to oocyte retrievals in Fig. 3. Elonva has now become routinely applied according to the coloured Algorithm depicting the options of Elonva (green values) in the Puregon and Gonal f Algorithms (Fig. 1 and 2, respectively). Although the data is not shown, our experience indicates that similar results occur with either of the standard rFSH pens as the Algorithms were designed for matching dosages.

Elonva was given on day 3 of the treatment cycle, matching the start day for rFSH and it was seen that the majority of cases in both groups had the Trigger injection on Day 12 apart from the exceptions described for AFC category A and B, reaching Trigger earlier and later, respectively. It was reported that rFSH dosages could be significantly reduced by giving Elonva on day 4 rather than day 2 (Blockeel et al., 2014). Our commencement day 3 does not demonstrate any such benefit except for AFC category E where the Trigger usually occurs a day or more earlier on day 12 for rFSH cases, mostly receiving 450 iu from day 3.

We therefore offer these PIVET Algorithms, adjusted for Elonva, for general use in ART programmes to enable targeted dosing schedules. The Algorithms have been demonstated to minimise OHSS risk to 0.26%, and have the potential to eliminate hospitalisation for severe OHSS completely when there is strict adherence to the advised protocols. This can be achieved whilst maintaining optimum pregnancy and livebirth productivity rates from initiated ovarian stimulation cycles. Furthermore, the Algorithms can be easily adjusted e.g. 4 steps to the left for milder stimulation schedules to reduce oocyte numbers; or 4 steps to the right for higher oocyte numbers appropriate for ovum donors or autologous ovum banking where GnRH Trigger will be applied following an Antagonist regimen for freeze-all.

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Legends

Fig. 1

PIVET rFSH dosing Algorithm designed for ~8.3 IU increments up to 300 IU suited to the Puregon pen; coloured red. For dosages ≥300 IU, increments of 25 IU suit both Puregon and

Gonal-f pens; coloured orange. Dosages of 200 to 400 IU rFSH daily can be replaced by Elonva (100 µg or 150 µg according to the woman's weight; covers for 7 days); coloured green.

Fig. 2

PIVET rFSH dosing Algorithm designed for 12.5 IU increments up to 300 IU suited to the Gonal f pen; coloured red. For dosages ≥300 IU, increments of 25 IU suit both Puregon and

Gonal-f pens; coloured orange. Dosages of 200 to 400 IU rFSH daily can be replaced by Elonva (100 µg or 150 µg according to the woman's weight; covers for 7 days); coloured green.

Fig. 3

Mean number of oocytes recovered at OPU categorised according to AFC grouping (A) and rFSH dosage (B). Ovarian stimulation was conducted with Elonva (closed grey circles; n=155 cycles) or with standard rFSH (open black squares; 872 (A) and 894 (B) cycles). The response of oocyte retrieval was analysed using a best fit regression line, and the slopes compared statistically. In addition, the mean oocyte yield for each AFC group was compared between treatments using ANOVA. No statistical difference was observed between treatments for regression slopes or mean comparisons.

Table 1

Embryological data from IVF cycles categorised according to AFC grouping within the PIVET rFSH dosing Algorithm. Ovarian stimulation was conducted with Elonva (165 initiated cycles), or standard rFSH including Puregon or Gonal f (950 initiated cycles). No significant difference was observed between Elonva and rFSH for any parameter when the

total cases were analysed. However, there were some significant differences for specific AFC ratings. Data was compared using chi square analysis with Fisher's exact test or ANOVA as appropriate. *indicates that the value for standard rFSH is significantly different from the corresponding AFC Elonva group.

Table 2

Clinical outcome data from IVF cycles categorised according to AFC grouping within the PIVET rFSH dosing Algorithm. Ovarian stimulation was conducted with Elonva (165 initiated cycles), or standard rFSH including Puregon or Gonal f (950 initiated cycles). There were no significant difference in pregnancy or birth rates when total rates were compared between rFSH and Elonva. However, there were some significant differences for specific AFC groups, mostly in group C. Data was compared using chi square analysis with Fisher's exact test. *indicates that the value for standard rFSH is significantly different from the corresponding AFC Elonva group.

Table 3

Embryological data from IVF cycles categorised according to four rFSH groupings within the PIVET rFSH dosing Algorithm. Ovarian stimulation was conducted with Elonva (165 initiated cycles), or standard rFSH including Puregon or Gonal f (972 cycles initiated). No significant difference was observed between Elonva and rFSH for any parameter when the total cases were analysed. The only significant difference observed between treatments was for AFC group A and in the fertilisation rate as a proportion of MII injected oocytes. Data was compared using chi square analysis with Fisher's exact test or ANOVA as appropriate. *indicates that the value for standard rFSH is significantly different from the corresponding AFC Elonva group.

Table 4

Clinical outcome data from IVF cycles categorised according to four rFSH groupings within the PIVET rFSH dosing Algorithm. Ovarian stimulation was conducted with Elonva (165 initiated cycles), or standard rFSH including Puregon or Gonal f (972 cycles initiated). There were no significant difference in pregnancy or birth rates when total rates were compared between rFSH and Elonva. However, there was a small but significant difference for frozen pregnancy rates in the higher dosage group. Data was compared using chi square analysis with Fisher's exact test. *indicates that the value for standard rFSH is significantly different from the corresponding AFC Elonva group.

Table

Table 1

	Standard rFSH (Puregon & Gonal f)						Elonva					
AFC grouping (follicle #)	A (≥ 20)	B (13 - 19)	C (9 - 12)	D (5 - 8)	E (≤ 4)	Total	A (≥ 20)	B (13 - 19)	C (9 - 12)	D (5 - 8)	E (≤ 4)	Total
Total Initiated Cycles, N	247	192	184	200	127	950	19	49	43	39	15	165
Total Cancelled Cycles, N (% per initiated cycle)	15 (6.1%)	11 (5.7%)	11 (6.0%)	13 (6.5%)	28 (22.0%)	78 (8.2%)	0 (0.0%)	2 (4.1%)	0 (0.0%)	3 (7.7%)	5 (33.3%)	10 (6.1%)
Age Range, Years	22 - 45	22 - 47	24 - 47	24 - 48	30 - 51	22 - 51	29 - 43	27 - 43	25 - 44	27 - 44	27 - 47	25 - 47
Total Cycles Reaching OPU, N	232	181	173	187	99	872	19	47	43	36	10	155
Total Oocytes Retrieved, N (Mean per OPU)	3087 (13.3)	1983 (11.0)	1529 (8.8)	1172 (6.3)	368 (3.7)	8139 (9.3)	288 (15.2)	546 (11.6)	449 (10.4)	237 (6.6)	31 (3.1)	1551 (10.0)
[1]Total MII Oocytes, N (Mean per OPU)	1805 (7.8)	1277 (7.1)	985 (5.7)	742 (4.0)	299 (3.0)	5108 (5.9)	206 (10.8)	369 (7.9)	337 (7.8)	169 (4.7)	24 (2.4)	1105 (7.1)
Total 2PN Generated, N (Mean per OPU)	1747 (7.5)	1078 (6.0)	835 (4.8)	630 (3.4)	208 (2.1)	4498 (5.2)	203 (10.7)	311 (6.6)	251 (5.8)	133 (3.7)	22 (2.2)	920 (5.9)
Fertilisation Rate, % (2PN per total oocytes retrieved)	56.6%*	54.4%	54.6%	53.8%	56.5%	55.3%	70.5%	57.0%	55.9%	56.1%	71.0%	59.3%
Fertilisation Rate, % (2PN per total MII injected)	96.8%	84.4%	84.8%*	84.9%	69.5%*	88.0%	98.5%	84.3%	74.5%	78.7%	91.7%	83.3%
Total # of Embryos Cryopreserved, N	566	309	186	165	69	1295	48	106	71	29	7	261
Embryos Cryopreserved (% per 2PN generated)	32.4%	28.7%	22.3%	26.2%	33.2%	28.8%	23.6%	34.1%	28.3%	21.8%	31.8%	28.4%
Total # of Embryos Transferred Fresh, N	209	175	164	173	67	788	18	45	47	39	8	157
Embryos Transferred Fresh (% per 2PN generated)	12.0%	16.2%	19.6%	27.5%	32.2%	17.5%	8.9%	14.5%	18.7%	29.3%	36.4%	17.1%
Total # of Embryos Cryopreserved or Transferred, N	775	484	350	338	136	2083	66	151	118	68	15	418
[2]Embryo Utilisation Rate, % (per 2PN generated)	44.4%*	44.9%	41.9%	53.7%	65.4%	46.3%	32.5%	48.6%	47.0%	51.1%	68.2%	45.4%
[2]Embryo Utilisation Rate, % (per oocytes retrieved)	25.1%	24.4%	22.9%	28.8%	37.0%	25.6%	22.9%	27.7%	26.3%	28.7%	48.4%	27.0%

[1] *Identified from Oocyte Cumulus Complexes prepared for ICSI*

[2] *Embryo Utilisation Rate; total number of embryos transferred or cryopreserved*

**Indicates significant difference compared to corresponding (+)Elonva value*

Table 2

	Standard rFSH (Puregon & Gonal f)						Elonva					
AFC grouping (follicle #)	A (≥ 20)	B (13 - 19)	C (9 - 12)	D (5 - 8)	E (≤ 4)	Total	A (≥ 20)	B (13 - 19)	C (9 - 12)	D (5 - 8)	E (≤ 4)	Total
Age Range, Years	22 - 45	22 - 47	24 - 47	24 - 48	30 - 51	22 - 51	29 - 43	27 - 43	25 - 44	27 - 44	27 - 47	25 - 47
Total Initiated Cycles, N	247	192	184	200	127	950	19	49	43	39	15	165
Total Cancelled Cycles, N (% per initiated cycle)	15 (6.1%)	11 (5.7%)	11 (6.0%)	13 (6.5%)	28 (22.0%)	78 (8.2%)	0 (0.0%)	2 (4.1%)	0 (0.0%)	3 (7.7%)	5 (33.3%)	10 (6.1%)
Total Cycles Reaching OPU, N	232	181	173	187	99	872	19	47	43	36	10	155
Total Cycles with Embryo Transfer, N	346	246	208	215	81	1096	32	74	57	46	8	217
Fresh Embryo Transfer Cycles, N	188	149	135	138	52	662	17	41	37	33	5	133
Frozen Embryo Transfer Cycles, N	158	97	73	77	29	434	15	33	20	13	3	84
Total # Embryos Transferred Fresh & Frozen, N	375	278	239	253	101	1246	34	80	68	53	12	247
# Fresh Embryos Transferred, N	209	175	164	173	67	788	18	45	47	39	8	157
# Frozen Embryos Transferred, N	166	103	75	80	34	458	16	35	21	14	4	90
Mean Embryos Transferred per Cycle, N	1.08	1.13	1.15	1.18	1.25	1.14	1.06	1.08	1.19	1.15	1.50	1.14
Mean Fresh Embryos Transferred per Fresh Cycle, N	1.11	1.17	1.21	1.25	1.29	1.19	1.06	1.10	1.27	1.18	1.60	1.18
Mean Frozen Embryos Transferred per Frozen Cycle, N	1.05	1.06	1.03	1.04	1.17	1.06	1.07	1.06	1.05	1.08	1.33	1.07
Pregnancy Rates:												
Fresh Pregnancy Rate, N (% per initiated cycle)	79/247 (32.0%)	41/192 (21.4%)	29/184 (15.8%)	31/200 (15.5%)	3/127 (2.4%)	183/950 (19.3%)	2/19 (10.5%)	9/49 (18.4%)	11/43 (25.6%)	7/39 (17.9%)	1/15 (6.7%)	30/165 (18.2%)
Fresh Pregnancy Rate, N (% per OPU)	79/232 (34.1%)*	41/181 (22.7%)	29/173 (16.8%)	31/187 (16.6%)	3/99 (3.0%)	183/872 (21.0%)	2/19 (10.5%)	9/47 (19.1%)	11/43 (25.6%)	7/36 (19.4%)	1/10 (10.0%)	30/155 (19.4%)
Frozen Pregnancy Rate, N (% per initiated cycle)	73/247 (29.6%)	41/192 (21.4%)	25/184 (13.6%)	25/200 (12.5%)	14/127 (11.0%)	178/950 (18.7%)	6/19 (31.6%)	12/49 (24.5%)	10/43 (23.3%)	2/39 (5.1%)	2/15 (13.3%)	32/165 (19.4%)
Frozen Pregnancy Rate, N (% per OPU)	73/232 (31.5%)	41/181 (22.7%)	25/173 (14.5%)	25/187 (13.4%)	14/99 (14.1%)	178/872 (20.4)	6/19 (31.6%)	12/47 (25.5%)	10/43 (23.3%)	2/36 (5.6%)	2/10 (20.0%)	32/155 (20.6%)
[1] *Pregnancy Productivity Rate, N (% per initiated cycle)*	152/247 (61.5%)	82/192 (42.7%)	54/184 (29.3%)*	56/200 (28.0%)	17/127 (13.4%)	361/950 (38.0%)	8/19 (42.1%)	21/49 (42.9%)	21/43 (48.8%)	9/39 (23.1%)	3/15 (20.0%)	62/165 (37.6%)
Pregnancy Productivity Rate, N (% per OPU)	152/232 (65.5%)*	82/181 (45.3%)	54/173 (31.2%)*	59/187 (29.9%)	17/99 (17.2%)	361/872 (41.4%)	8/19 (42.1%)	21/47 (44.7%)	21/43 (48.8%)	9/36 (25.0%)	3/10 (30.0%)	62/155 (40.0%)
Live Birth Rates:												
Fresh Live Birth Rate, N (% per initiated cycle)	63/247 (25.5%)	36/192 (18.8%)	25/184 (13.6%)	20/200 (10.0%)	1/127 (0.8%)	145/950 (15.3%)	1/19 (5.3%)	7/49 (14.3%)	8/43 (18.6%)	6/39 (15.4%)	0/15 (0.0%)	22/165 (13.3%)
Fresh Live Birth Rate, N (% per OPU)	63/232 (27.2%)	36/181 (19.9%)	25/173 (14.5%)	20/187 (10.7%)	1/99 (1.0%)	145/872 (16.6%)	1/19 (5.3%)	7/47 (14.9%)	8/43 (18.6%)	6/36 (16.7%)	0/10 (0.0%)	22/155 (14.2%)
Frozen Live Birth Rate, N (% per initiated cycle)	53/247 (21.5%)	27/192 (14.1%)	15/184 (8.2%)*	12/200 (6.0%)	7/127 (5.5%)	114/950 (12.0%)	5/19 (26.3%)	7/49 (14.3%)	9/43 (20.9%)	1/39 (2.6%)	3/15 (20.0%)	25/165 (15.2%)
Frozen Live Birth Rate, N (% per OPU)	53/232 (22.8%)	27/181 (14.9%)	15/173 (8.7%)*	12/187 (6.4%)	7/99 (7.1%)*	114/872 (13.1%)	5/19 (26.3%)	7/47 (14.9%)	9/43 (20.9%)	1/36 (2.8%)	3/10 (30.0%)	25/155 (16.1%)
[2] *Live Birth Productivity Rate, N (% per initiated cycle)*	116/247 (47.0%)	63/192 (32.8%)	40/184 (21.7%)*	32/200 (16.0%)	8/127 (6.3%)	259/950 (27.3%)	6/19 (31.6%)	14/49 (28.6%)	17/43 (39.5%)	7/39 (17.9%)	3/15 (20.0%)	47/165 (28.5%)
Live Birth Productivity Rate, N (% per OPU)	116/232 (50.0%)	63/181 (34.8%)	40/173 (23.1%)*	32/187 (17.1%)	8/99 (8.1%)	259/872 (29.7%)	6/19 (31.6%)	14/47 (29.8%)	17/43 (39.5%)	7/36 (19.4%)	3/10 (30.0%)	47/155 (30.3%)

[1] *Pregnancy Productivity Rate; sum of pregnancies from fresh and corresponding frozen cycles*

[2] *Live Birth Productivity Rate; sum of live births from fresh and corresponding frozen cycles*

**Indicates significant difference compared to corresponding (+)Elonva value*

Table 3

	Standard rFSH (Puregon & Gonal f)					Elonva				
rFSH Starting dose (IU)	< 200	200 - 299	300 - 399	≥ 400	Total	< 200	200 - 299	300 - 399	≥ 400	Total
Total Initiated Cycles, N	429	131	99	313	972	61	49	33	22	165
Total Cancelled Cycles, N (% per initiated cycle)	32 (7.5%)	2 (1.5%)	10 (10.1%)	34 (10.9%)	78 (8.0%)	3 (4.9%)	0 (0.0%)	2 (6.1%)	5 (22.7%)	10 (6.1%)
Age Range, Years	25 - 47	30 - 43	31 - 44	34 - 45	25 - 47	25 - 47	30 - 43	31 - 44	34 - 45	25 - 47
Total Cycles Reaching OPU, N	397	129	89	279	894	58	49	31	17	155
Total Oocytes Retrieved, N (Mean per OPU)	4842 (12.2)	1222 (9.5)	792 (8.9)	1509 (5.4)	8365 (9.4)	681 (11.7)	519 (10.6)	262 (8.5)	89 (5.2)	1551 (10.0)
[1]Total MII Oocytes, N (Mean per OPU)	2868 (7.2)	811 (6.3)	535 (6.0)	998 (3.6)	5212 (5.8)	465 (8.0)	400 (8.2)	173 (5.6)	65 (3.8)	1103 (7.1)
Total 2PN Generated, N (Mean per OPU)	2763 (7.0)	691 (5.4)	433 (4.9)	728 (2.6)	4615 (5.2)	402 (6.9)	315 (6.4)	151 (4.9)	52 (3.1)	920 (5.9)
Fertilisation Rate, % (2PN per total oocytes retrieved)	57.1%	56.5%	54.7%	48.2%	55.2%	59.0%	60.7%	57.6%	58.4%	59.3%
Fertilisation Rate, % (2PN per total MII injected)	96.3%*	85.2%	80.9%	72.9%	88.5%	86.5%	78.8%	87.3%	80.0%	83.4%
Total # of Embryos Cryopreserved, N	954	195	87	106	1342	146	81	26	8	261
Embryos Cryopreserved (% per 2PN generated)	34.5%	28.2%	20.1%	14.6%	29.1%	36.3%	25.7%	17.2%	15.4%	28.4%
Total # of Embryos Transferred Fresh, N	317	111	88	287	803	52	46	39	20	157
Embryos Transferred Fresh (% per 2PN generated)	11.5%	16.1%	20.3%	39.4%	17.4%	12.9%	14.6%	25.8%	38.5%	17.1%
Total # of Embryos Cryopreserved or Transferred, N	1271	306	175	393	2145	198	127	65	28	418
[2]Embryo Utilisation Rate, % (per 2PN generated)	46.0%	44.3%	40.4%	54.0%	46.5%	49.3%	40.3%	43.0%	53.8%	45.4%
[2]Embryo Utilisation Rate, % (per oocytes retrieved)	26.2%	25.0%	22.1%	26.0%	25.6%	29.1%	24.5%	24.8%	31.5%	27.0%

[1] *Identified from Oocyte Cumulus Complexes prepared for ICSI*

[2] *Embryo Utilisation Rate, total number of embryos transferred or cryopreserved*

**Indicates significant difference compared to corresponding (+)Elonva value*

Table 4

	Standard rFSH (Puregon & Gonal f)					Elonva				
rFSH Starting dose (IU)	< 200	200 - 299	300 - 399	≥ 400	Total	< 200	200 - 299	300 - 399	≥ 400	Total
Age Range, Years	25 - 47	30 - 43	31 - 44	34 - 45	25 - 47	25 - 47	30 - 43	31 - 44	34 - 45	25 - 47
Total Initiated Cycles, N	429	131	99	313	972	61	49	33	22	165
Total Cancelled Cycles, N (% per initiated cycle)	32 (7.5%)	2 (1.5%)	10 (10.1%)	34 (10.9%)	78 (8.0%)	3 (4.9%)	0 (0.0%)	2 (6.1%)	5 (22.7%)	10 (6.1%)
Total Cycles Reaching OPU, N	397	129	89	279	894	58	49	31	17	155
Total Cycles with Embryo Transfer, N	582	175	106	261	1124	87	73	36	20	216
Fresh Embryo Transfer Cycles, N	304	98	72	203	677	49	43	27	14	133
Frozen Embryo Transfer Cycles, N	278	77	34	58	447	38	30	9	6	83
Total # Embryos Transferred Fresh & Frozen, N	606	195	124	348	1333	91	78	50	28	247
# Fresh Embryos Transferred, N	317	111	88	287	803	52	46	39	20	157
# Frozen Embryos Transferred, N	289	84	36	61	530	39	32	11	8	90
Mean Embryos Transferred per Cycle, N	1.04	1.11	1.17	1.33	1.19	1.05	1.07	1.39	1.40	1.14
Mean Fresh Embryos Transferred per Fresh Cycle, N	1.04	1.13	1.22	1.41	1.19	1.06	1.07	1.44	1.43	1.18
Mean Frozen Embryos Transferred per Frozen Cycle, N	1.04	1.09	1.06	1.05	1.19	1.03	1.07	1.22	1.33	1.08
Pregnancy Rates:										
Fresh Pregnancy Rate, N (% per initiated cycle)	109/429 (25.4%)	36/131 (27.5%)	14/99 (14.1%)	28/313 (8.9%)	187/972 (19.2%)	14/61 (23.0%)	12/49 (24.5%)	3/33 (9.1%)	1/22 (4.5%)	30/165 (18.2%)
Fresh Pregnancy Rate, N (% per OPU)	109/397 (27.5%)	36/129 (27.9%)	14/89 (15.7%)	28/279 (10.0%)	187/894 (20.9%)	14/58 (24.1%)	12/49 (24.5%)	3/31 (9.7%)	1/17 (5.9%)	30/155 (19.4%)
Frozen Pregnancy Rate, N (% per initiated cycle)	128/429 (29.8%)	28/131 (21.4%)	13/99 (13.1%)	16/313 (5.1%)*	185/972 (19.0%)	15/61 (24.6%)	9/49 (18.4%)	4/33 (12.1%)	4/22 (18.2%)	32/165 (19.4%)
Frozen Pregnancy Rate, N (% per OPU)	128/397 (32.2%)	28/129 (21.7%)	13/89 (14.6%)	16/279 (5.7%)*	185/894 (20.7%)	15/58 (25.9%)	9/49 (18.4%)	4/31 (12.9%)	4/17 (23.5%)	32/155 (20.6%)
[1] *Pregnancy Productivity Rate, N (% per initiated cycle)*	237/429 (55.2%)	64/131 (48.9%)	27/99 (27.3%)	44/313 (14.1%)	372/972 (38.3%)	29/61 (47.5%)	21/49 (42.9%)	7/33 (21.2%)	5/22 (22.7%)	62/165 (37.6%)
Pregnancy Productivity Rate, N (% per OPU)	237/397 (59.7%)	64/129 (49.6%)	27/89 (30.3%)	44/279 (15.8%)	372/894 (41.6%)	29/58 (50.0%)	21/49 (42.9%)	7/31 (22.6%)	5/17 (29.4%)	62/155 (40.0%)
Live Birth Rates:										
Fresh Live Birth Rate, N (% per initiated cycle)	96/429 (22.4%)	22/131 (16.8%)	9/99 (9.1%)	22/313 (7.0%)	149/972 (15.3%)	11/61 (18.0%)	9/49 (18.4%)	2/33 (6.1%)	0/22 (0.0%)	22/165 (13.3%)
Fresh Live Birth Rate, N (% per OPU)	96/397 (24.2%)	22/129 (17.1%)	9/89 (10.1%)	22/279 (7.9%)	149/894 (16.7%)	11/58 (19.0%)	9/49 (18.4%)	2./31 (6.5%)	0/17 (0.0%)	22/155 (14.2%)
Frozen Live Birth Rate, N (% per initiated cycle)	86/429 (20.0%)	18/131 (13.7%)	8/99 (8.1%)	8/313 (2.6%)	120/972 (12.3%)	11/61 (18.0%)	6/49 (12.2%)	3/33 (9.1%)	2/22 (9.1%)	22/165 (13.3%)
Frozen Live Birth Rate, N (% per OPU)	86/397 (21.7%)	18/129 (14.0%)	8/89 (9.0%)	8/279 (2.9%)	120/984 (13.4%)	11/58 (19.0%)	6/49 (12.2%)	3/31 (9.7%)	2/17 (11.8%)	22/155 (14.2%)
[2] *Live Birth Productivity Rate, N (% per initiated cycle)*	182/429 (42.4%)	40/131 (30.5%)	17/99 (17.2%)	30/313 (9.6%)	269/972 (27.7%)	22/61 (36.1%)	15/49 (30.6%)	5/33 (15.2%)	2/22 (9.1%)	44/165 (26.7%)
Live Birth Productivity Rate, N (% per OPU)	182/397 (45.8%)	40/129 (31.0%)	17/89 (19.1%)	30/279 (10.8%)	269/894 (30.1%)	22/58 (37.9%)	15/49 (30.6%)	5/31 (16.1%)	2/17 (11.8%)	44/155 (28.4%)

[1] *Pregnancy Productivity Rate; sum of pregnancies from fresh and corresponding frozen cycles*

[2] *Live Birth Productivity Rate; sum of live births from fresh and corresponding frozen cycles*

**Indicates significant difference compared to corresponding (+)Elonva value*

Puregon,Gonal-F & Elonva Desk Chart

AMH	>3D pm/L					211-211.1 pm/L					20-24.1pm/L					111-1U pm/L					10-14.I pm/L					11-l.lpm/L					cli.Dpm/L				
MC•	A++ (40 follicles)					A+ (30-39 follicles)					A 12()-29 follicles)					B (13-19 follicles)					C (9-12 follicles)					D (5-8 follicles)					E (s4 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	3().35	16-17	18-19	20-21	22-29	30-35	16-17	18-19	20-21	22-29	3().35	16·17	18·19	20-21	22·29	30-35
20	41.7	41.7	41 .7	50.0	58.3	58.3	58.3	58.3	66.7	66.7	66.7	75.0	75.0	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	58.4	58.3	58.3	66.7	75.0	75.0	75.0	83.3	83.3	91.6	91.7	100.0	100.0	108.3	116.6	125.0	125.0	125.0	133.3	141.6	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	58.4	58.3	58.3	66.7	75.0	75.0	75.0	83.3	83.3	91.6	100.0	100.0	100.0	108.3	116.6	125.0	125.0	125.0	133.3	141.6	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	66.6	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	200.0
24	50.0	50.0	50.0	58.3	66.6	66.7	66.7	66.7	75.0	83.3	83.3	83.3	91.7	91.7	100.0	108.3	108.3	116.7	116.7	125.0	133.3	141.7	141.7	150.0	150.0	158.3	158.3	158.3	166.7	166.7	183.3	183.3	191.7	200.0	200.0
25	50.0	50.0	50.0	58.3	66.6	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	200.0	20-21	200.0
26	58.3	58.3	58.3	66.7	75.0	75.0	75.0	75.0	83.3	91.6	91.7	91.7	100.0	108.3	108.3	125.0	125.0	125.0	133.3	141.6	150.0	150.0	150.0	158.3	166.6	175.0	175.0	175.0	183.3	183.3	191.7	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	91.6	100.0	100.0	100.0	108.3	116.6	125.0	125.0	125.0	133.3	141.6	150.0	150.0	150.0	158.3	166.6	175.0	175.0	175.0	183.3	183.3	200.0	208.3	208.3	216.7	216.7
28	58.3	58.3	58.3	66.7	75.0	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	2 16.7	225.0	225.0	233.3	233.3
29	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	175.0	183.3	183.3	183.3	200.0	208.3	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	200.0	208.3	208.3	216.7	241.7	241.7	241.7	250.0	275.0
31	75.0	75.0	75.0	83.3	91.6	91.7	91.7	91.7	100.0	108.3	125.0	125.0	125.0	133.3	141.6	141.7	141.7	141.7	150.0	158.3	175.0	175.0	175.0	183.3	191.6	200.0	200.0	200.0	208.3	216.7	225.0	250.0	250.0	275.0	300.0
32	75.0	75.0	75.0	83.3	91.6	100.0	100.0	100.0	108.3	116.6	125.0	125.0	125.0	133.3	141.6	150.0	150.0	150.0	158.3	166.6	175.0	175.0	175.0	183.3	200.0	208.3	208.3	208.3	2 16.7	225.0	250.0	275.0	300.0	325.0	350.0
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	200.0	208.3	225.0	225.0	225.0	233.3	250.0	275.0	300.0	325.0	350.0	375.0
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	200.0	208.3	216.7	233.3	233.3	233.3	250.0	215.0	300.0	350.0	400.0	425.0	450.0
35	83.3	83.3	83.3	91.7	100.0	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	200.0	208.3	216.7	225.0	241.7	241.7	250.0	275.0	300.0	350.0	400.0	425.0	450.0	450.0	
36	100.0	100.0	100.0	108.3	116.6	100.0	100.0	108.3	116.6	150.0	150.0	150.0	158.3	166.6	183.3	183.3	191.7	200.0	208.3	216.7	216.7	225.0	225.0	250.0	275.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	
37	100.0	100.0	100.0	108.3	116.6	100.0	100.0	108.3	116.6	158.3	158.3	158.3	166.7	175.0	183.3	191.7	200.0	208.3	216.6	225.0	225.0	233.3	250.0	275.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	
38	108.3	108.3	108.L	116.7	125.0	108.3	108.3	108.3	116.7	125.0	166.7	166.7	166.7	175.0	183.3	191.7	208.3	208.3	216.7	225.0	250.0	250.0	250.0	275.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0
39	108.3	108.3	108.L	116.7	125.0	108.3	108.3	108.3	116.7	125.0	183.3	183.3	183.3	191.7	200.0	208.3	216.7	225.0	233.3	241.6	266.7	275.0	275.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0
40	116.7	116.7	116.7	125.0	133.3	116.7	116.7	116.7	125.0	133.3	191.7	191.7	191.7	200.0	208.3	225.0	241.7	241.7	250.0	258.3	275.0	275.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
41	125.0	125.0	125.0	133.3	141.6	125.0	125.0	125.0	133.3	141.6	200.0	200.0	200.0	208.3	216.6	258.3	258.3	258.3	266.7	275.0	300.0	300.0	325.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
42	125.0	125.0	125.0	133.3	141.6	125.0	125.0	125.0	133.3	141.6	208.3	208.3	208.3	216.7	225.0	283.3	283.3	283.3	300.0	300.0	325.0	350.0	350.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
43	133.3	133.3	133.3	141.7	150.0	133.3	133.3	133.3	141.7	150.0	216.7	216.7	216.7	225.0	233.3	300.0	300.0	300.0	300.0	325.0	350.0	375.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
44	133.3	133.3	133.3	141.7	150.0	133.3	133.3	133.3	141.7	150.0	233.3	233.3	233.3	241 .7	250.0	300.0	300.0	300.0	325.0	350.0	375.0	375.0	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
45	133.3	133.3	133.;;	141.7	150.0	141.7	141.7	141.7	150.0	158.3	241.7	241.7	241.7	250.0	258.3	300.0	300.0	300.0	350.0	375.0	400.0	425.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0

Age (yrs)

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
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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 GnRH Agonist trigger if >10 follicles
e.g., Tryptorellin 100 mcg x2

D 8.3 IU increments suit Puregon Pen

D 25 IU increments also suits Gonal-F Pen

— Elonva — 1 x 100µg for wt s60kg
1 x 150µg for wt >60kg

Version 12 3 Apr 2011

Gonal-F, Puregon & Elonva Desk Chart

AMH	>311 pmol/L					25-21.Dpm/L					21).24.1 pm/L					111-11.D pm/L					10-14.I pm/L					II-I.I pm/L					c&.D pm/L				
MC*	A++ (>40 follicles)					A+ (30-39 follicles)					A (20,29follicles)					B (13-19 follicles)					C (9-12follicles)					D (5-8 follicles)					E (≤4follicles)				
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
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	2 12.5	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	2 12.5	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	2 12.5	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	2 12.5	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	2 12.5	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	2 12.5	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	2 12.5	225.0	237.5	250.0	262.5	275.0	287.5	300.0	325.0	350.0	375.0	400.0	425.0
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	400.0	425.0	450.0
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	450.0
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	2 12.5	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	450.0	450.0
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	2 12.5	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	450.0	450.0	450.0	450.0
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	450.0	450.0	450.0	450.0	450.0
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	450.0	450.0	450.0	450.0	450.0	450.0
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	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
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	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
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	400.0	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
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	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
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	425.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0

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*Antral Follicle Count based on number of antral follicles ≤10 mm

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Aiming for 10-12 oocytes,
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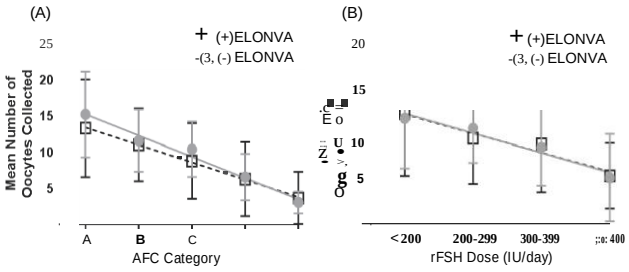
Consider GnRH Agonist trigger if >10 follicles
e.g., Tryptorelin 100 µg x2

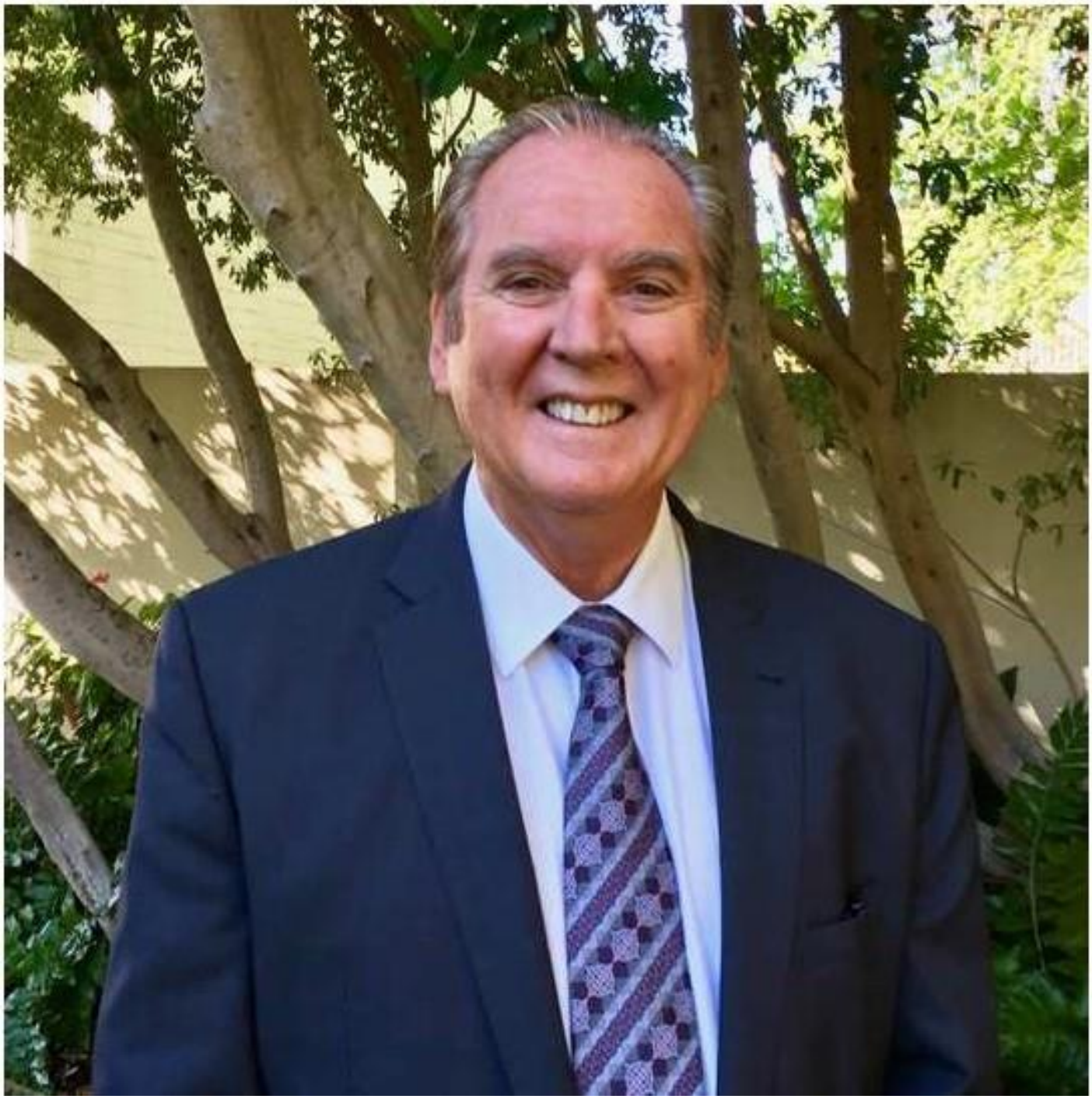
- 12.5 IU increments suit Gonal-F Pen
- 25 IU increments also suits Puregon Pen
- Elonva — 1 x 100µg for wt ≤60kg
  1 x 150µg for wt >60kg

Version 12.1 3 April 2017

Figure


(A)
(+)ELONVA
-(3, (-) ELONVA
Mean Number of Oocytes Collected
25
20
15
10
5
A
B
C
AFC Category
(B)
(+)ELONVA
-(3, (-) ELONVA
20
15
10
5
<200
200-299
300-399
rFSH Dose (IU/day)

•Author photo



***Author Biography (50 words max.)**

Professor John Yovich graduated in Medicine at the University of Western Australia in 1970, progressing into specialist O&G practice in 1976. Thereafter he completed his MD thesis "*Human pregnancies achieved by In-Vitro Fertilisation*" following laboratory research and clinical work undertaken with Professor Ian Craft at the RFH in London; 1976-1980.

***Key Message (50 words max.)**

Elonva can be utilized across the rFSH range 200-400 IU quite safely and effectively; but carries higher OHSS risk for women with AFC >20 follicles. On the other end, Elonva may be inadequate as a replacement for AFC <5 follicles where individualised rFSH dosages >400 IU were more effective.

***Ethical Approval Documentation**

Specific ethical approval to use Elonva was not required as it is approved by the Australian TGA (Therapeutic Goods Administration). PIVET Medical Centre is accredited under a national scheme (RTAC; Reproductive Technology Accreditation Committee) as well as a state body – the Reproductive Technology Council - acting under Western Australian statutory regulation. The focus for both authorities is to minimise the number of OHSS cases as well as multiple pregnancies. The Human Research Ethics Committee (HREC) of Curtin university has provided approval for retrospective data analysis and its publication under item RD-25-10 (2015).