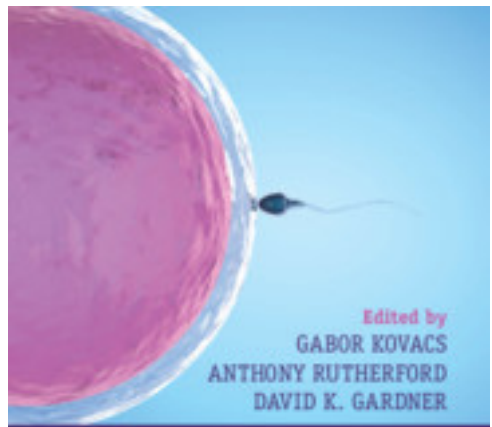

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HOW TO PREPARE THE EGG AND EMBRYO TO MAXIMIZE IVF SUCCESS

CAMBRIDGE Medicine

Chapter 8

Monitoring the Stimulated IVF Cycle

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8.1 Introduction

Historically, the first successful three births from in vitro Fertilization (IVF) cycles were conducted by tracking the natural cycle (Louise Brown in 1978, Alastair Macdonald in 1979 and Candice Reed in 1980). This followed that the two centres involved (in Oldham and Melbourne) had reached a point of frustration from nearly a decade of unsuccessful use of stimulated cycles. The first pioneers Steptoe and Edwards, working in Oldham, found that ovarian stimulation generated a disturbed luteal phase which they could not correct by progestogen supplements, mainly norethisterone. The Australian team working in Melbourne under Professor Carl Wood became divided into two programmes: one under gynaecologist Ian Johnston and scientist Alex Lopata pursuing natural cycles, and the other under gynaecologist John Leeton and veterinary scientist Alan Trounson pursuing Clomid (clomiphene citrate) stimulation with urine-derived human chorionic gonadotrophin (hCG) trigger. The former succeeded first, but the result was not readily reproduced; the latter began generating live births in 1981 and continued with a substantial ongoing pregnancy rate.

In those early years, tracking the natural cycle utilized the Higonavis multiwell test – sensitized sheep red cells would agglutinate in the presence of luteinizing hormone (LH) or hCG in a test urine sample which took around two hours to perform. It had to be performed 6–8 hourly and the subsequent arrangement for the laparoscopic follicle aspiration was an estimate, usually performed around 30–32 hours after the first positive Higonavis result. Louise Brown resulted from 4 pregnancies arising from 68 laparoscopies performed in Oldham, where 32 cases achieved an embryo transfer (ET) procedure (i.e. 5.9 percent of ovum pick-up (OPU) attempts or 12.5 percent of ETs). Of those four pregnancies, Louise was born on 25 July 1978; the next miscarried at 11 weeks and was shown to be a XXX triploidy; the third was a male delivered pre-term on 26 November (male, Courtney Cross died at birth and categorized as a post-amniocentesis loss at 21 weeks); and finally healthy boy Alistair Macdonald was delivered at term on 14 January 1979 [1].

The Monash programme applying stimulated cycles (Clomid/hCG) in Melbourne started delivering babies in 1981 from a series of 14 pregnancies arising from 115 initiated cycles (12.2 percent pregnancy rate), resulting in 9 births during 1981–1982 (7.8 percent live birth rate). Soon after, the group from Norfolk Virginia headed by Howard Jones delivered their first infant Elizabeth Carr in December 1981 following ovarian stimulation using urine-derived human menopausal gonadotrophins (uHMG; Pergonal), with hCG trigger

and Proluton injections providing progesterone for luteal support. In 1982, several other teams around the world delivered IVF infants, including my small team from Perth, Western Australia; Wilfred Feichtinger from Vienna, Austria; Seigfried Trotnow from Erlangen, Germany; Rene Frydman from Paris, France; and Paul Devroey from Brussels, Belgium – we all used some form of ovarian stimulation and hCG triggers. In fact my unit PIVET is so named as an acronym for 'Programmed' IVF & ET, representing the most efficient system from all perspectives – the patient, the clinic and the hospital services. HMG was also used by Subhas Mukherjee, who has been belatedly and posthumously acknowledged as generating the world's second IVF infant [2]: a girl born in Calcutta, India, on 3rd October 1978 (details published in 1997 by TC Anand Kumar [3], architect with Indira Hinduja of India's official first IVF infant, born in 1986).

All these early pregnancies were achieved with minimal monitoring, other than menstrual cycle timing and detection of the LH surge. There were two key advances in monitoring pre-ovulatory follicular development. The first was the development of ELISA – enzyme-linked immunosorbent assays on serum (to replace the tedious radio-immunoassay processes on 24-hour urine samples). These were developed in the 1970s and introduced into IVF monitoring by the early 1980s. The second was the progression to transvaginal ultrasound (U/S) for the accurate detection and measurement of follicles developing in the ovaries. It also was utilized in replacing laparoscopy by transvaginal ultrasound-guided needle aspiration for oocyte retrieval [4]. In fact, there were several European groups presenting the transvaginal ultrasound story at the 1984 meeting held at Finlandia Hall in Helsinki chaired by Marku Seppala [5] and which laid the foundations for ESHRE, the European Society of Human Reproduction and Embryology [6]. These included Susan Lenz, Matts Wickland, Lars Hamberger, Wilfried Feichtinger and Peter Kemeter.

The structure of gonadotrophin-releasing hormone (GnRH) was identified by Andrew Schally [7] and Roger Guillemin [8] independently in Baylor College Houston, for which they shared the Nobel Prize, 1977. This soon led to modifications of the decapeptide in the development of analogues, both agonist(GnRH-a) and antagonist (GnRH-ant). By the end of the 1980s, agonists were introduced to prevent premature LH elevations. By 2000, safer variants of the antagonists were introduced for immediate down-regulation, improving stimulation cycle control (using rFSH) and enabling agonist triggers, in such cycles, decreasing the chance of the life-threatening complication of ovarian hyperstimulation syndrome; OHSS.

8.2 Initial Screening Tests

Details of the screening tests for new patients, both male and female, are shown in Figure 8.1. All abnormal results require specific considerations, including referrals for specialist management – e.g. abnormal Pap smears, breast lump and testicular lump. Medical conditions must be stabilized prior to fertility treatment – e.g. abnormal liver, renal or thyroid function tests and evidence of genital tract infection. Specific management considerations will be highlighted for other detections – e.g. abnormal thrombophilia profile, varicocele detection and hyperprolactinaemia.

Some of these tests can ideally be incorporated in the recommended Assessment Cycle for logistic benefit. If more than one year advances since original screening, all tests require updating, including the recording of weight and height for body mass index (BMI) calculation, excepting those which do not change, e.g. blood group, karyotype and Rubella titre, when adequate.

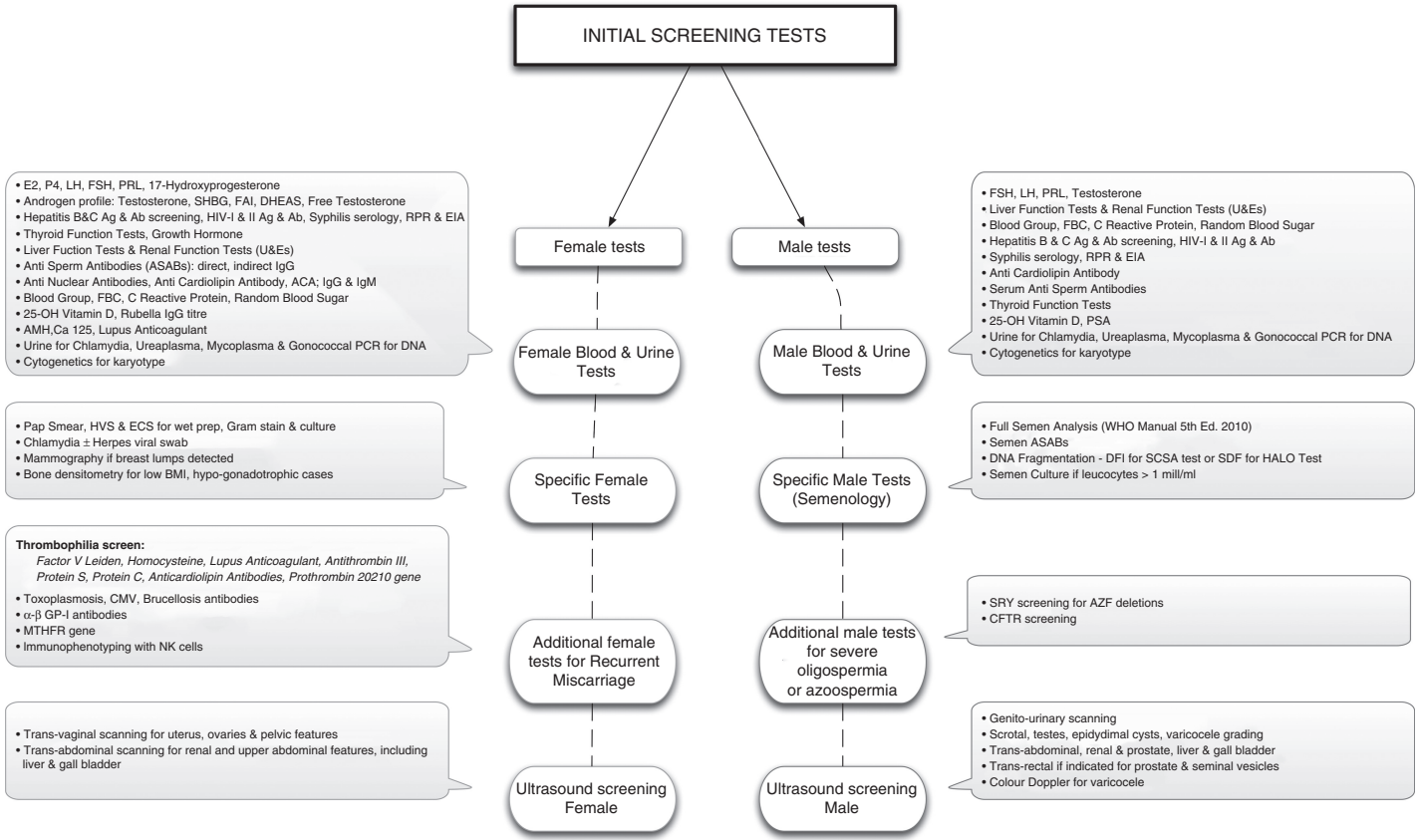

Figure 8.1 Initial screening tests for new couples attending for infertility and/or recurrent miscarriage

8.3 Assessment Cycle

Ideally, all new patients should conduct an Assessment Cycle which includes the described tests and a mid-luteal clinical review around day 21 to plan the specific Fertility Programme, including IVF cycle management. (Patients attending repeat cycles can attend day 21 without repeating the Assessment Cycle to arrange IVF or frozen embryo transfer (FET cycle.) The following describes a full fertility assessment, which can be modified for clear andrology cases or where restricting tests for 'bare essentials'. The Assessment Cycle is displayed in algorithmic form in Figure 8.2.

Day 2 Blood test to determine if hormones are baseline (see Box 8.1 for conversions):

Box 8.1 Conversion formulae from SI units to conventional units and weight vs IU

E2 oestradiol 17β, conversion pmol/L to pg/mL
250 pmol/L = 68 pg/mL
1,000 pmol/L = 272 pg/mL
12,000 pmol/L = 3269 pg/mL
P4 progesterone, conversion nmol/L to ng/mL
5.0 pmol/L = 1.6 ng/mL
60 pmol/L = 18.9 ng/mL
600 pmol/L = 189 ng/mL
PRL Prolactin, conversion mIU/L to ng/mL
750 mIU/L = 35.25 ng/mL
Testosterone, conversion nmol/L to ng/mL
2.0 nmol/L = 0.58 ng/mL
10 nmol/L = 2.9 ng/mL
20 nmol/L = 5.8 ng/mL
FSH & LH Gonadotrophins IU/L to mIU/ml
2 IU/L = 2 mIU/mL
12 IU/L = 12 mIU/mL
AMH Anti-Müllerian hormone
10 pmol/L = 1400 pg/mL
HCG Human Chorionic Gonadotrophin
25 IU = 25 mIU/mL
Ovidrel = rHCG Pregnyl = uHCG
Ovidrel 250 mcg ~ 6,500 IU uHCG
Ovidrel 250 mcg X2 ~ 13,000 IU uHCG
Ovidrel 250 mcg X3 ~ 19,500 IU uHCG
rHCG – recombinant Human Chorionic Gonadotrophin
uHCG – urinary Human Chorionic Gonadotrophin

Serum 17β Oestradiol	E2 <250 pmol/L
Serum progesterone	P4 <5.0 nmol/L
Serum Luteinizing hormone	LH< 12 IU/L
Serum Follicle Stimulating hormone	FSH < 12 IU/L
Serum prolactin	PRL < 750 mIU/L

Day 5 AFC (antral follicle count)

categorized A to E in PIVET algorithms

female androgen profile – Testosterone, Sex hormone binding globulin (SHBG), Free androgen index (FAI), androstenedione, Dehydroepiandrosterone sulphate (DHEAS)

Insulin growth factor IGF1, IGF binding protein (IGFBP3) for growth hormone

Days 7–10	HyCoSy (Hystero-Contrast-Sonography) evaluation of uterine cavity and patency of fallopian tubes along with check of pelvic features. Hysterosalpingogram (HSG) is a less preferred option.
Days 10–12	Blood test & Transvaginal Ultrasound; U/S ovarian Tracking Scan
Days 12–14	Post-coital test (PCT) 6–14 hrs post-coitus in the immediate pre-ovulatory phase. This includes Insler cervical scoring requiring score ≥6/12 and detection of motile spermatozoa within the mucus at HPF X400. Any sperm detected can be considered 'positive', but ≥5 motile spermatozoa constitutes a strongly positive test.
Day 21	Mid-luteal with blood (E2, P4 & resting cortisol) and Transvaginal U/S scan review to plan specific fertility programme.

After the review of the investigations, the ongoing management can include specific treatment of conditions (e.g. male referrals for varicocele and testicular lesions or female referral for auto-immune conditions or pituitary evaluation for hyper-prolactinaemia). Preliminary surgeries for the female include laparoscopic procedures for endometriosis, adenomyosis, fibroids, hydrosalpinges and ovarian cysts, as well as hysteroscopic procedures for endometrial polyps and septate uterus. Other configuration anomalies require strategic discussions [9]. At this stage consideration of gamete storage for sperm or oocytes should be considered. These may include considerations of malignancy or pre-chemotherapy or when there are logistic considerations, such as husbands working as FiFo (fly-in-fly-out) workers in remote locations. Otherwise cases will be considered for

1. a series (maximum × 3) of natural cycle tracking with timed intercourse ovulation induction ± timed intercourse (maximum × 3*)
2. intra-uterine insemination (IUI) (maximum × 3)
3. IVF-related protocols

Although each of these programmes would require up to ten treatments to fully explore their potential to generate a pregnancy, *we discourage more than three attempts, as those who fail experience physical, mental, emotional and financial

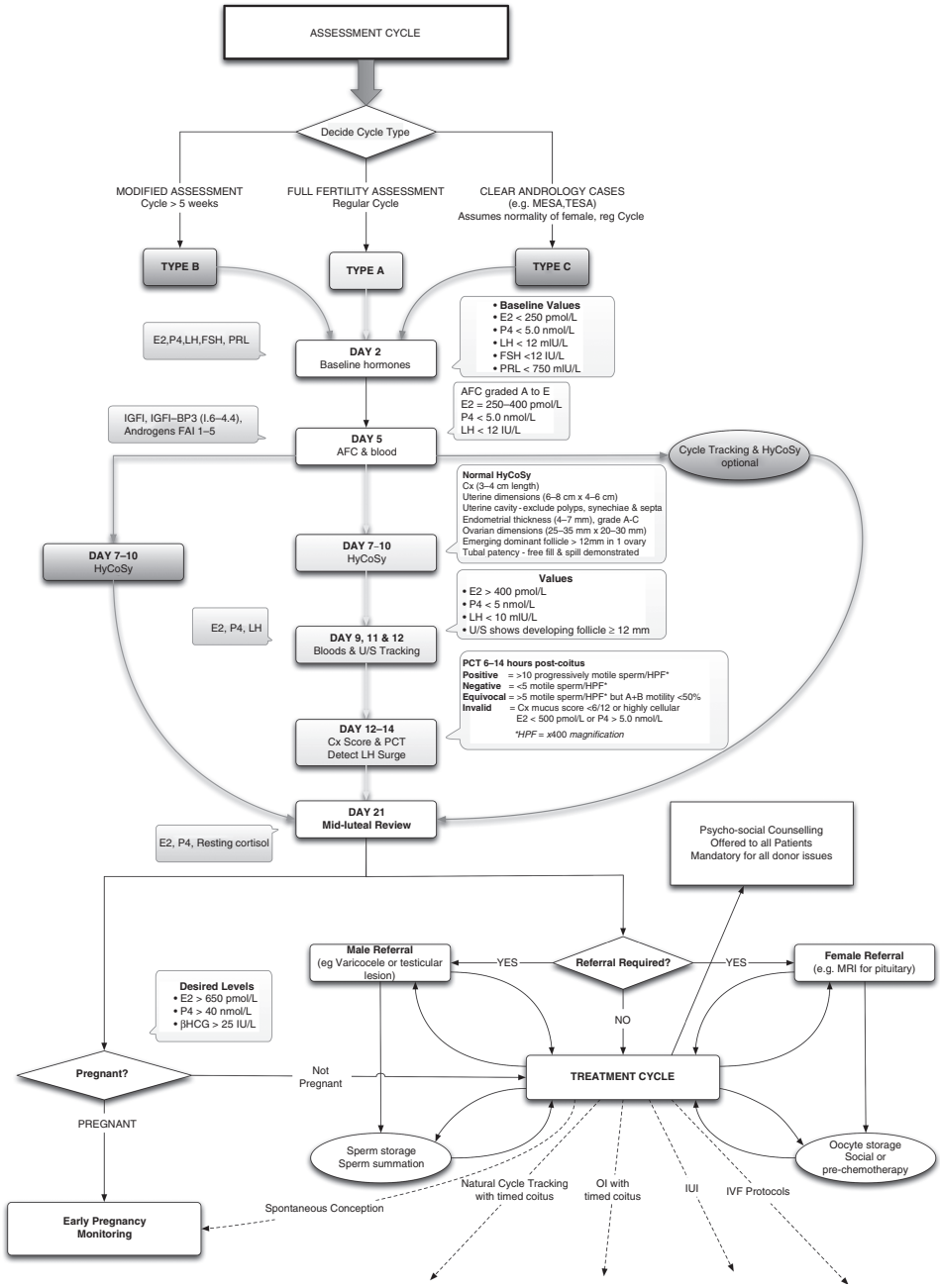

Figure 8.2 Algorithmic display of the Assessment Cycle which includes a mid-luteal clinical review at which the various clinical management programmes are considered along with specific medical and surgical management issues for each partner

exhaustion. This subsequently works against their opportunities within the more favourable IVF-related programmes. Furthermore, the time delay for females beyond age 35 years works unfavourably and causes them to avoid or restrict to one or two such 'low-prognosis' treatment cycles, in order to progress to the better-prognosis IVF-related opportunities.

The relevance of undertaking an 'Assessment Cycle' can be seen from many perspectives, including as a comparable therapeutic benefit. PIVET has recorded about a 5 percent persistent annual spontaneous pregnancy rate, resulting in over 36 years of conducting these cycles. Most of the pregnancies result from cycles with defined tubal patency and a strongly positive PCT, but a small number of pregnancies have also arisen following negative or equivocal findings at the PCT as well as the HyCoSy evaluation and sometimes both. We believe there are therapeutic benefits from the 'tubal flushing' process as well as 'arranging coitus' at the optimal time. HSG using lipiodol is also reported favourably in this regard.

8.4 Counselling

At this stage psycho-social counselling is offered to all patients but is mandatory where donor gametes or embryos are being considered, or where stress, depression or anxiety is a clinical feature. The number of such counselling sessions is predicated upon the circumstances of the couple, psychological needs identified by the counsellor and desires of individual patients, both males and females. Some patients benefit from psychiatric referral; others require special considerations, e.g. where histories include backgrounds of violence, criminal history or marital disharmony. It is unwise to proceed with IVF-related treatments unless both partners are comfortable with the processes, have provided fully informed consent and have resolved any outstanding domestic issues. Unresolved issues such as previous domestic conflict may require consideration by a clinical panel which includes the Counsellor, the Medical Director, a member of the Institutional Ethics Committee and a member of the Patient Support Group. The rights of patients, the need to avoid discrimination at any level, including age or disabilities, and the responsibilities of the clinic are all important considerations which are considered in relevant Codes of Practice along with State legislations [10].

It is against the above background that monitoring of the stimulated IVF cycle is described as practiced at PIVET.

8.5 Flare Agonist (GnRH-a) Protocol

Agonist Flare is preferred for women who do not have any significant risk for OHSS. This applies to older women ≥40 years old and those with lower AFC categories; C, D and E in the PIVET algorithms [11] and lower AMH ratings [12] (see Figures 8.3 and 8.4).

Day 21 Clinical Review

Transvaginal U/S and high vaginal swab (HVS); endo-cervical swab (ECS) (if not performed earlier within the Assessment Cycle).

Ensure appropriate control of medical conditions along with counselling and discussions about costs, prior to starting.

If an ovarian cyst is detected, this may be an obvious corpus luteum (tracked during an Assessment Cycle; otherwise of an uncertain nature). Ultrasound can be reviewed on day 2 or 3 of the treatment cycle, deferring stimulation if the cyst persists. In such a situation, combined oral contraceptive (COC) pill to suppress one or two cycles is administered and an ultrasound is performed on day 21 to recheck. (Routine use of COC prior to IVF is not favoured.)

Day 2 blood test to determine if baseline

E2 <250 pmol/L

P4 <5.0 nmol/L

LH <12 IU/L

FSH <12 IU/L

PRL <750 mIU/L

If elevated, review blood test in 2–3 days for baseline. If persistently elevated, cancel and consider Pill suppression prior to next cycle Day-2.

Commence GnRH-a

Decapeptyl® (triptorelin acetate) 100®mcg sc daily (mane); or

Lucrin® (leuprolide acetate) 500 mcg start, can reduce to 200 mcg sc daily (mane); or

Synarel® (nafarelin acetate) 1 puff (200 mcgm bd) each nostril – mane x1 & nocte x1

Day 3

Commence rFSH according to PIVET algorithm (Figure 8.3 for Gonal-f; Figure 8.4 for Puregon®). The rFSH dosage is selected depending on age and AFC category, choosing the box which accords with BMI. The dosage can then be adjusted downwards if AMH level is discordantly high, indicating that a lower rFSH dosage is needed. Other variables requiring adjustment include baseline (days 1 to 3) serum FSH level, smoking history and whether the programme is planned as a freeze-only of oocytes or embryos. As defined in the algorithm, these aspects translate to a higher rFSH dosage.

Some cases can be considered for the long-acting rFSH – corifollitropin (Elonva®) – as shown in the green sector (see following and Figures 8.3 and 8.4). As with Gonal-f® and Puregon®, Elonva® is given on day 3 and is followed by the calculated rFSH dosage from day 9 if not yet ready for the hCG trigger [13]. This applies to most cycles.

Day 9

Blood (E2, P4, LH)

Transvaginal U/S scan for ovarian follicles and endometrium (features and thickness). Endometrium should be advancing from hyperechoic to iso-echoic pattern at this stage with thickness > 6 mm.

Track follicles >10 mm

Note follicle number ≤10 mm

Gonal-F, Puregon & Elonva Desk Chart

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	
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		125.0	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	
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		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	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	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	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	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	

Age (years)

Increased FSH and Smokers

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

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

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

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

Oocyte Donors

Aiming for 10-12 oocytes,
move four columns to the right

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

12.5 IU increments suit Gonal-F Pen

25 IU increments also suit Puregon Pen

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

Version 12.1 3 April 2017

Figure 8.3 PIVET rFSH dosing algorithm designed for 12.5 IU increments which suits the Gonal-f pen. The green area covers dosages which can be replaced by Elonva (long-acting corifollitropin). Adapted from Dove Press article [11] and reported in Reprod Biomed Online [18].

Puregon, Gonal-F & Elonva Desk Chart

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
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	216.7	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	216.7	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	275.0	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	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	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	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	108.4	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	108.4	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	133.3	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 (years)

Increased FSH and Smokers

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

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

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

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

Oocyte Donors

Aiming for 10-12 oocytes,
move four columns to the right

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

8.3 IU increments suit Puregon Pen

25 IU increments also suit Gonal-F Pen

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

Version 12.1 3 April 2017

Figure 8.4 PIVET rFSH dosing algorithm designed for 8.3 IU increments which suits the Puregon pen. The green area covers dosages which can be replaced by Elonva (long-acting corifollitropin). Adapted from Dove Press article [11] and reported in Reprod Biomed Online [18].

E2 > 1000 pm/L (can increase rFSH if required)

P4 < 5.0 pm/L (consider early trigger if elevated; and cryopreserve best embryos).

If LH elevated (≥ 5 IU) or P4 elevated (≥5 nm/L) consider early trigger (if several pre-ovulatory follicles present) or switch to GnRH-ant 0.5 mg daily (this higher dose is required as the LH or P4 elevation indicates that down-regulation is inadequate).

If an excess of 15 or more follicles are developing, switch to GnRH-ant, enabling agonist trigger. This conversion requires at least two, preferably three, days to ensure that the agonist down-regulation effect has worn off enabling the agonist trigger to be effective, as a new flare effect.

GnRh-ant options

Cetrotide® (cetrorelix acetate)	Standard dose	0.25 mg
	High dose	0.5 mg
Ganirelix® (ganirelix acetate)	Standard dose	0.25 mg
	High dose	0.5 mg

Days 11–12

Blood (E2, P4, LH) and transvaginal U/S scan for endometrium (features and thickness) and ovarian follicles.

Endometrium should be advancing from iso-echoic to hypo-echoic pattern (compared with myometrium) and thickness >7.5 mm.

Trigger when 2 follicles ≥ 18 mm.

Otherwise continue stimulation and re-assess in two days.

If endometrial features or thickness is unfavourable, add Trental® (Pentoxifylline)/ Vitamin E regimen along with E2 or E2/Viagra® (sildenafil) pessary regimen daily until embryo transfer.

Trigger Options and Luteal Phase Management

Urinary hCG (uHCG; Pregnyl® 5000 IU, 10,000 IU & 20,000 IU) is nowadays replaced by recombinant rHCG (Ovidrel®). See Table 8.1 for conversion of units.

Ovidrel®	250 mcg x2 sc is standard
Ovidrel ®	250 mcg x1 sc if ≥15 follicles
(or agonist trigger if converted to antagonist)	
Ovidrel®	250 mcg x3 if ≤ 4 follicles despite high dosage rFSH ≥300 IU

OPU interval

Standard 36–37 hours

If leading follicle ≥22 mm, or previous history of premature egg release, add Nurofen® (ibuprofen) cover 200 mg tds after trigger.

Shorter interval may be considered if P4 and LH are elevated (indicating threatened premature surge); however, PIVET policy is to double GnRh-ant dosage to 0.5 mg in the morning and give standard trigger in the evening (Table 8.1). In such cases consider undertaking transvaginal U/S just prior to OPU, to determine if ovulated. If ovulation has taken place, pregnancies can occasionally be achieved following intercourse or IUI in such cases where fallopian tubes demonstrated patent on HyCoSy evaluation undertaken in the Assessment Cycle, but consider multiple pregnancy risk.

Table 8.1 Details of ovulation trigger strategies (dependent upon follicle numbers) and luteal management protocols (dependent upon number of oocytes retrieved) Trigger and Luteal Support Schedule for Standard IVF Cycles. All trigger cycles, the trigger day is 2. The presumed 'ovulation' day/TVOA is day 0. Ovidrel support when ordered is given on days 4, 7,10 & 13 post-TVOA 'ovulation' which is the same as days 6, 9, 12, & 15 post-trigger

	Follicle number (≥12 mm) & E2 at trigger	Trigger	Oocyte number at TVOA	Luteal support
1	≤4 follicles at high rFSH AACEP protocol Shanghai protocol All patients ≥40 yrs ≤2 MII oocytes previous E2 <4000 pm/L	Ovidrel x 3 pens	≤4 oocytes	Ovidrel 5 clicks, days 4,7,10,13 + P4 400 mg bd E2/P4 combo nocte *(commence day after TVOA)*
2	5–12 follicles **Or** E2 <12,000 pm/L	Ovidrel x 2 pens	5–12 oocytes	Ovidrel 5 clicks, days 4,7,10,13 + P4 400 mg bd *(commence day after TVOA)*
			13–15 oocytes	IMP Cabergoline regimen post-TVOA Reduce Ovidrel to 3 clicks, days 4,7,10,13 + P4 400 mg bd
			>15 oocytes	IMP Cabergoline regimen post-TVOA Replace Ovidrel with full HRT

Table 8.1 (cont.)

	Follicle number (≥12 mm) & E2 at trigger	Trigger	Oocyte number at TVOA	Luteal support
3	13–19 follicles **or** E2 >12,000 pm/L but <20,000 pm/L	Decapeptyl 100 mcg/mL x 2 **or** Synarel 0.2 mg x 2 *(1 puff each nostril)*	<20 oocytes	IMP Cabergoline regimen post-TVOA Commence full HRT day after trigger
4	≥20 follicles or E2 >20,000 pm/L ***Donors & cases with excess follicles 12–14 mm***	Decapeptyl 100 mcg/mL x 2 **or** Synarel 0.2 mg x 2 *(1 puff each nostril)*	≥20 oocytes	Cabergoline post-trigger ***Freeze All*** Provera 10 mg x 12 days starting from day after TVOA Arimidex 1 mg x 10 days from TVOA for cases ≥20 oocytes
5	***Replace Ovidrel with E2/P4 pessaries tds or full HRT- if blood test results during luteal phase: E2 >6000 pm/L P4 >600 nm/L***			

Note:
This new schedule removes the option of Ovidrel trigger for >12 follicles and assumes all high responses result from antagonist (or antagonist conversion) cycles.
If not an antagonist cycle, a high response cycle (≥13 oocytes or E2 >12,000 pm/L) should be cancelled for re-cycling to antagonist regimen.

Luteal phase day 9 post-trigger

(day 7 post-OPU)

Blood test for E2 and P4

Ideal E2 range 1000 pm/L to 6000 pm/L

Ideal P4 range 60 nmol/L to 600 nm/L

If levels below range, add appropriate pessary, e.g. P4 400 mg or E2/P4 (2mg/400mg) bd or tds.

If levels above range, indicates OHSS risk – hence cancel Ovidrel® injections; replace with P4 pessaries and monitor patient according to increased monitoring protocol (IMP) regimen (Box 8.2).

Box 8.2 Increased monitoring protocol for women at OHSS risk along with management strategy for cases developing severe OHSS

1 IMP

for women at risk for OHSS:

Do not use HCG in luteal phase; replace with HRT regimen
Introduce Cabergoline, ideally at time of trigger (see below)
Daily telephone or Skype contact with clinic
Report daily weight; notify if >1 kg increase per day
Maintain boosted fluid input 2–3 litres per day – sports drinks ideal
Report persistent dark urine (should be light lemon colour)
Report daily girth; notify if >4 cm increase
Return to clinic if any concern; e.g. abdominal distention, breathlessness
Check SG of urine:
SG ≥1015, for IV fluids; 2 litres over 2 hours
SG >1020, 3 litres iv fluids over 3 hours
SG >1030; 4 litres iv fluids over 4 hours saline/ Hartman's regimen
Anti-emetic and mild analgesics as required
Trans-abdominal ultrasound if distended or breathless
2. OHSS management:
Admit to hospital if major ascites or pleural effusion, or persistent nausea, pain or respiratory distress.
Closer attention to iv. fluid balance management ± urinary catheter
Consider paracentesis or pleural drain
Clexane cover (enoxaparin 40 mg daily) if high PCV, hypovolaemic or hypercoagulable state.
Cabergoline 1 mg daily (nocte) for 10 days, preferably beginning with trigger.
Aromatase inhibitor, e.g. Anastrozole 1 mg or letrozole 2.5 mg daily also useful to limit severity and duration of OHSS
Hyponatraemia and hypo-albuminaemia will self-correct slowly on above schedule (albumin infusion usually avoidable).

The final blood test for pregnancy detection is performed on day 17 post-OPU (day 19 post trigger) to measure E2, P4 and βhCG (see early pregnancy monitoring).

8.6 Antagonist (GnRH-ant) Protocol

Antagonist is the preferred protocol for all patients with higher AFC and AMH ratings [12], especially A groups and the first cycle with B groups (15–19 antral follicles according to PIVET algorithms). This protocol is mandatory for all donors and those undertaking oocyte banking where higher egg numbers are deliberately intended (with rFSH dosage adjusted upwards, i.e. four boxes to the right). GnRH agonist trigger should be used in such cases to counter any risk for OHSS.

Day 21 Clinical Review

Update any relevant tests if not part of the Assessment Cycle. Perform HVS and ECS to exclude pathogens, bearing in mind that transvaginal oocyte aspiration (TVOA) is

undertaken with minimized vulvo-vaginal preparation and no sterilizing fluids. Perform transvaginal U/S to exclude ovarian cysts.

Perform hormone test for FSH, LH, E2 and P4. In women with an irregular cycle or those who are amenorrhoeic, consider for start if baseline values are low (denote as day 2 as no cycle for dating).

Ensure appropriate control of medical conditions along with counselling and costing discussions prior to start.

Day 2 Blood test to determine if baseline

E2 <250 pmol/L

P4 <5.0 nmol/L

LH< 12 IU/L

FSH < 12 IU/L

PRL < 750 mIU/L

If elevated, review blood test in two to three days for baseline; otherwise cancel if FSH or LH levels show persisting elevation. Suppress levels with oral contraceptive for one to two months (oestrogenic pill, e.g. Microgynon® 50 preferred).

Day 2 (actual or adjusted). Commence antagonist, e.g. Decapeptyl® 100 mcg daily (mane preferred).

Day 3

Commence rFSH or uFSH according to PIVET Algorithm rFSH Gonal-f® or Puregon®

Pergoveris® (rFSH+rLH) can be used x1 amp if 150–250 IU; x2 amps if >250 IU to 450 IU

Long-acting corifollitropin (Elonva®) can be used if AFC gradings B to E (see green sector in Figure 8.5.)

Day 7

Blood test for response:

E2 >500 pm/L and <2000 pm/L

Adjust dosage rFSH accordingly by 1 increment (box to right if too low; rarely box to left if too high)

P4 <5.0 nm/L

LH <12 IU/L

Commence antagonist when E2>500 pm/L

250 ug daily; Cetrotide® or Orgalutran®

If P4 ≥5.0 nm/L or LH ≥12 IU/L, increase antagonist to 500 ug daily

If P4 ≥5.0 nm/L and LH <2.0 IU, commence Luveris® (rLH) 75 IU daily

Day 9 blood test + Transvaginal U/S scan for follicles and endometrium (features and thickness). Ideally iso-echoic and >6.5 mm at this stage.

E2: expect >100 percent rise from day 7

P4: expect <5.0 nm/L; otherwise ensure Luveris® 75 IU and increase antagonist to 500 mcg.

Gonal-F & Elonva Lite Desk Chart

AMH	>30 pm/L					25-29.9 pm/L					20-24.9 pm/L					15-19.9 pm/L					10-14.9 pm/L				
AFC*	A++ (≥ 40 follicles)					A+ (30-39 follicles)					A (20-29 follicles)					B (13-19 follicles)					C (9-12 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
Age (years) 20	25.0	25.0	37.5	37.5	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
21	25.0	25.0	37.5	37.5	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
22	25.0	25.0	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	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0
23	37.5	37.5	50.0	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	125.5
24	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	87.5	100.0	100.0	100.0	112.5	112.5	112.5	125.0	125.0	125.0	137.5
25	37.5	37.5	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	125.0	137.5	137.5
26	50.0	50.0	62.5	62.5	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
27	50.0	50.0	62.5	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
28	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	137.5	150.0	150.0
29	62.5	62.5	75.0	75.0	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
30	62.5	62.5	75.0	75.0	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
31	62.5	62.5	75.0	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
32	75.0	75.0	87.5	87.5	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
33	75.0	75.0	87.5	87.5	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
34	75.0	75.0	87.5	87.5	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
35	87.5	87.5	100.0	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	200.0	200.0
36	87.5	87.5	100.0	100.0	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	200.0	200.0
37	87.5	87.5	100.0	100.0	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	200.0	200.0	200.0	200.0
38	100.0	100.0	112.5	112.5	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	200.0	200.0	200.0	200.0
39	100.0	100.0	112.5	112.5	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	200.0	200.0	200.0	200.0	200.0
40	100.0	100.0	112.5	112.5	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	200.0	200.0	200.0	200.0	200.0	200.0
41	112.5	112.5	125.0	125.0	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	200.0	200.0	200.0	200.0	200.0	200.0
42	112.5	112.5	125.0	125.0	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	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
43	112.5	112.5	125.0	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	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
44	125.0	125.0	137.5	137.5	137.5	137.5	150.0	162.5	175.0	175.0	187.5	187.5	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
45	137.5	137.5	150.0	150.0	150.0	150.0	162.5	162.5	175.0	175.0	187.5	187.5	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0

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**

Algorithm dosages

Aiming for 4-8 oocytes
Antagonist cycle only

Use GnRH Agonist trigger
e.g., Tryptorellin 100 mcg x2

12.5 IU increments suit Gonal-F Pen

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

Version 1.1 6 December 2016

Figure 8.5 PIVET rFSH dosing algorithm designed for the LITE protocol. It aims to collect fewer eggs with minimized monitoring and out-of-pocket costs. It is modified from Figures 8.3 and 8.4 to select cases with a favourable prognosis for a single blastocyst embryo transfer

Transvaginal U/S scan – expect cohort of follicles 12–14 mm appearing (do not adjust rFSH dosage on basis of U/S; rely on E2 rise for guidance. Note that PIVET algorithm ensures stable dosage but elevation may be required for low dosages ≤100 IU).

If thin endometrium <6 mm add Vitamin E 1000 IU bd/Trental® 400 mg bd oral regimen. Ideally the endometrium should be iso-echoic or hypo-echoic (compared to the myometrium) at this stage.

Add oestradiol pessaries 10–20 mg nocte until embryo transfer, or if historical thin endometrium use E2/Viagra® pessaries 25 mg:25 mg up to twice daily (mane and nocte).

Days 11–12

Blood and Transvaginal U/S; expect

E2 6,000–12,000 pm/L

P4 <5.0 nm/L

LH <2.5 IU

If P4 or LH is elevated, increase antagonist dosage from 250 mcg to 500 mcg; may also consider early trigger if follicles are of sufficient pre-ovulatory size follicles.

Generally, trigger when 2 follicles ≥18 mm; otherwise continue stimulation and reconsider in two days.

The majority of triggers are given on day 11 or 12.

See Table 8.2 for triggers and Luteal phase management.

Trigger–OPU interval:

Standard 36–37 hours

If lead follicle ≥22 mm, or previous history of premature ovulation, 36 hours plus Nurofen® cover 200 mg tds after trigger.

May consider shorter interval if P4 and LH elevated (indicating threatened premature surge); however, PIVET policy is double antagonist in the morning and standard Ovidrel® or agonist trigger in the evening according to Table 8.1. In such cycles consider U/S just prior to OPU, to determine if ovulated. Pregnancies can occasionally be achieved following intercourse or IUI in such cases if fallopian tubes are patent, but consider multiple pregnancy risk.

Luteal phase day 9 post-trigger (= day 7 post-OPU)

Blood test for E2 and P4

Ideal E2 range 1000 pm/L to 6000 pm/L

Ideal P4 range 60 nmol/L to 600 nm/L

If levels below range, add appropriate pessary, e.g. P4 400 mg or E2/P4 (2 mg/400 mg bd or tds).

If levels above range, it indicates OHSS risk – hence cancel hCG injections; replace with P4 pessaries and monitor patient according to the IMP regimen.

Final blood test for pregnancy detection performed day 17 post-OPU (day 19 post-trigger) measuring E2, P4 and βhCG (see early pregnancy monitoring).

8.7 Long Down-Regulation (LDR) Protocol

The former gold standard, LDR is nowadays reserved for poor prognosis patients and specialized management cases.

Day 21 Clinical Review

Update any relevant tests, e.g. Pap smear or HPV screen.

Transvaginal U/S to exclude ovarian cysts.

Hormone test if irregular or amenorrhoeic cycle; may consider for start if certain of anovulatory or mid-luteal status.

Anovulatory amenorrhoeic

E2 <250 pm/L

P4 <5 nm/L

LH <12 IU/L

Mid-luteal

E2 250–650 pm/L

P4 20–60 nm/L

LH <12 IU/L

FSH <12 IU/L

PRL <750 mIU/L

Ensure appropriate control of medical conditions along with counselling and costing discussions prior to start.

Commence down-regulation, e.g. Lucrin® 500 mcg daily or Decapeptyl® 100 mcg daily.

Day 2 blood test to determine if baseline (down-regulated). Where amenorrhoeic, perform this test ten days after commencing down-regulation, classify as 'day 2'.

E2 <250 pmol/L

P4 <5.0 nmol/L

LH <12 IU/L

If not down-regulated, perform transvaginal U/S to check for ovarian cyst.

Repeat blood test and U/S in two to three days for baseline; otherwise cancel or adjust rFSH schedule if FSH or LH levels are elevated. May suppress cycle with COC; then resume schedule day 21 for day 2; otherwise revert to agonist regimen. Elevated E2 usually indicates persistent ovarian follicular cyst, elevated P4 indicates persistent luteal cyst. Such cycles best managed by cancellation and COC suppression.

Can reduce agonist dosage if clearly down-regulated;

E2 < 100 pm/L

P4 < 1.0 nm/L

LH < 2.0 IU

E.g. Lucrin® 200 mcg/day. No benefit to reduce Decapeptyl®

Commence rFSH on day 3 (actual or adjusted for amenorrhoeic cycles – 11 days after commencing down-regulation) as described for agonist cycle (above). Elonva® can be used as described (above and below).

Day 9

Blood (E2, P4, LH) & Transvaginal U/S scan

Track follicles >10 mm

Note follicle number ≤10 mm

E2 > 1000 pm/L (can increase rFSH if required)

P4 < 5.0 pm/L (consider early trigger if elevated; cryopreserve best embryos)

If LH elevated consider early trigger or switch to antagonist 0.5 mg daily (down-regulation inadequate).

If excess follicles, ≥15 emerging, switch to antagonist, as previously described, enabling agonist trigger.

Days 11–12

Blood (E2, P4, LH) & T/V scan

Trigger when 2 follicles ≥ 18 mm

Otherwise continue stimulation and re-assess in two days

Trigger and Luteal support according to Table 8.2

Luteal phase day 9 post-trigger (= day 7 post OPU)

Blood test for E2 and P4

Ideal E2 range 1000 pm/L to 6000 pm/L

Ideal P4 range 60 nmol/L to 600 nm/L

If levels below range; add appropriate pessary, e.g. P4 400 mg or E2/P4 (2 mg/400 mg bd or tds).

If levels above range, indicates OHSS risk hence cancel hCG injections; replace with P4 pessaries and monitor patient according to IMP regimen.

Final blood test for pregnancy detection performed day 17 post-OPU (=day 19 post-trigger) measuring E2, P4 and βhCG (see early pregnancy monitoring).

8.7.1 Long Down-regulation Variant: AACEP

This regimen was described by the Nevada group [13] when LDR was the 'gold standard'. It was intended for poor-prognosis cases (i.e. repetitive failures) and the acronym describes:

Agonist – antagonist conversion with oestrogen priming.

Day 21 commences as described above for LDR.

Day 2 blood test to confirm baseline levels. Day 2 is defined as day of menstrual cycle; alternatively for amenorrhoeic women, this is 10th day following commencement of agonist. If not adequately suppressed continue for three days and retest, until down-regulated; ideally:

E2 < 100 pm/L

P4 < 1.0 nm/L

LH < 2.0 IU

Can accept:

E2 <250 pm/L

P4 <5 nm/L

LH < 12 IU/L

At this stage, usually day 2, convert to antagonist 250 mcg on alternate days. (For amenorrhoeic cycles 'day 2' is ten days after commencing down-regulation – see above.) Also commence daily oestrogen. PIVET policy utilizes a vaginal pessary of micronized 17b-oestradiol, 5 mg applied daily.

Commence rFSH day 3, usually maximal dosage 450 IU.

Thereafter monitor as LDR with day 9 blood and U/S scan. However, the E2 level only reflects the effectiveness of the pessary; the follicle scanning becoming all important. P4 and LH are also monitored and managed as previously described for LDR.

The E2 effect is usually excellent for endometrial thickness and most cases develop 4±2 follicles. Our standard is to apply Ovidrel® x3 as the trigger, regarding the ovaries as 'under-vascularized'; however, these cases can certainly suit the idea of a Combined trigger (e.g. Ovidrel® + Decapeptyl®).

Depending upon the endometrial thickness, the E2 pessaries can be ceased at trigger, or continued to TVOA. Thereafter Luteal Support is according to the Table 8.2 schedule. This can include E2/P4 'combo' pessaries tds to maintain a thicker endometrium.

Mid-luteal and final 19 blood test is performed as standard.

8.8 Occasional Schedules

Several stimulation regimens are either entrenched historically or involve the introduction of new stimulatory agents. This chapter does not embrace the use of adjuvant therapies such as DHEA or Growth Hormone but includes those which most IVF units will apply for a small subset of patients, although occasionally as a preferred schedule. The use of biosimilar FSH preparations are embraced within the PIVET rFSH dosing schedules, having similar dosages.

8.8.1 Clomiphene or Tamoxifen

In Australia, these agents generated most of the first pregnancies and were continued through the 1980s until the introduction of GnRH analogues became more readily associated with the use of gonadotrophins [14]. The Clomiphene dosage was 50 mg–100 mg for five days; higher dosages were associated with scotomata and sometimes a permanent loss of parts of the visual fields. At the lower dosages there was a large safety factor as most cases generated only 1–4 follicles. In fact as ovulation induction, without any monitoring, the generation of twins was uncommon and triplets rather rare. In fact, the prevailing view was that eggs were failing to release, even with the use of hCG triggers [15]. Another view was that Clomiphene had adverse effects on the endometrium, inhibiting implantation. For this reason it was applied for only five days in the early follicular phase and the earlier schedule of days 5–9 was changed to 2–6 when applied for IVF. We still have a place for these oral agents, but the use of tamoxifen appears less detrimental to the endometrium and enables a schedule of days 2–10. OHSS was absolutely rare with these agents and caused some IVF facilities to revert to this 'Minimal Stimulation' schedule to avoid the problem [16].

Monitoring such cases could be done with minimal testing although our policy applied the same schedule as the flare agonist cycle. This lent itself well as increasingly programmes added (urinary) uFSH and later rFSH in order to maintain reasonable pregnancy rates [14]. This, of course, became associated with the problem of premature LH surges (which was uncommon with clomiphene or tamoxifen alone), hence the urgent uptake of GnRH analogues by the end of the 1980s, as soon as effectiveness was demonstrated.

8.8.2 Elonva® Schedule

The long-acting rFSH corifollitropin (Elonva®) is popular with those patients wishing to minimize injections. It has been advised for women classified as normo-responsive but avoided in over-responders [17]. Our experience with this preparation indicates:

It acts in a step-down fashion (boosting the first two to three days)

– this explains why many cases show rapid follicular growth

It carries its effect across six to seven days (fading over days 6–7)

It can be used with GnRH- agonist or GnRH-antagonist cycles

It can be used successfully across a broad range of rFSH dosage 200 IU – 375 IU in Categories B to E inclusive

It must not be used with AFC categories A, A+ or A+++ i.e. ≥20 antral follicles as the OHSS risk is inordinately high, hence Elonva is confined to the Green Sector in PIVET Algorithms.

On day 7 (cycle day 9) a decision is required to convert to standard rFSH daily dosage if not yet ready for trigger. Our published data [13] showed overall the median trigger day for Elonva across AFC categories B, C and D was cycle day 11 (ranging from day 9 to day 12), whereas for standard rFSH, the median trigger day was cycle day 13 (ranging day 10 to day 16).

Elonva dosage 100 mcg or 150 mcg is selected according to the woman's weight (≤60 kg or >60 kg respectively).

8.8.3 Shanghai Protocol

Designed for women with extremely poor prognosis whose main feature is POR (poor ovarian response). It involves immediate stimulation in the luteal phase after the first cycle OPU. Hence it is also known as the Dual Stimulation (Duo-Stim) protocol or Double Stimulation Protocol [19].

In Stage 1, it applies letrozole 2.5 mg days 2–5 along with clomiphene 50 mg for day 2 until trigger with Gonal-f ® 150 IU from day 6 until trigger.

Monitoring is not necessary until day 12, for consideration of trigger: E2, P4 and Transvaginal U/S only for ovarian follicle.

If follicle ≥16 mms trigger and collect – fertilize and cryopreserve at cleavage stage.

If follicle <16 mm, continue clomiphene and Gonal-f®; rescan and trigger when ≥16 mms, proceeding to TVOA.

If follicle fails to advance to ≥16 mm, give Decapeptyl® trigger but do not undertake OPU (ovum pick-up) procedure.

For advanced follicle ≥16 mm trigger with agonist, e.g.. Decapeptyl® 200 mcg and consider Nurofen® 200 mg tds if follicle ≥22 mm to avoid premature egg release. TVOA is undertaken at 36 hours.

Stage 2 commences day after TVOA or 3rd day after trigger without TVOA.

Letrozole 2.5 mg for five days from day after TVOA.

Gonal-f® 225 IU from 2nd day after TVOA until 2nd trigger

Provera® (medroxyprogesterone acetate) 10 mg b.d. from 3rd day after TVOA until 2nd trigger.

Monitoring unnecessary until 12th day after TVOA as no changes to the schedule will be undertaken.

Trigger: E2, P4 and Transvaginal U/S only for ovarian follicle.

if follicle ≥16 mms trigger and collect – fertilize and cryopreserve at cleavage stage.

If follicle <16 mm, continue clomiphene and Gonal-f®; trigger and TVOA if ≥16 mms

If failing to develop trigger but do not undertake OPU.

Trigger is agonist, e.g. Decapeptyl® 200 mcg and Nurofen® 200 mg tds are given to avoid premature egg release. TVOA is undertaken at 36 hours.

All resulting embryos are cryopreserved and no fresh embryo transfer procedures are undertaken. The woman is subsequently reviewed to plan for an FET cycle, ideally with an HRT schedule [20] as most women in this category have disordered menstrual cycles, not suited to natural cycle transfers.

Usually 1–2 oocytes are recovered at Stage 1 and 3–4 at Stage 2. However, occasionally nil are collected at either stage, indicating all options for autologous egg recovery are exhausted. Such cases have invariably progressed through various schedules including AACEP and minimal stimulation. Consideration for donor oocytes is recommended.

8.8.4 LITE Protocol

This schedule has been designed to reduce out-of-pocket costs to enable patients with a favourable prognosis to access IVF where financial considerations are an imperative. The term LITE, 'light', refers to an adjusted regimen designed to collect fewer (4–6) oocytes such that the likelihood will be the transfer of a single blastocyst and no embryos remaining for cryopreservation. Furthermore, the case selection and treatment schedule exclude the likelihood of OHSS, hence monitoring can be minimized.

Case selection requires BMI <32 Kg/m2, AMH >10 pm/L, AFC >8 antral follicles, baseline FSH <10 IU/L. Patients undertaking this regimen have standard consultations, examinations and Assessment Cycles. Complex treatment regimens are not suitable for LITE as full effort needs to be applied in such regimens. Similarly, those with underlying disorders, including medical, mental or gynaecological, e.g. endometriosis, are not eligible. Those seeking donor gametes or embryos, surrogacy or preimplantation diagnosis or screening, PGD/PGS, are also not eligible for this low-cost programme as the administrative costs are higher. The aim is to apply a minimized stimulation schedule without adjuncts, but includes IVF and ICSI with fresh or frozen sperm, aiming for blastocyst culture and a strict single embryo transfer (SET) policy. If more than one good quality blastocyst arises, patients have the option of cryopreservation at conventional costing. The cases are managed with minimized monitoring as follows: An antagonist regimen is applied using a modified

PIVET Algorithm with rFSH dosages reduced 4 boxes to the left from standard (Figure 8.5). This enables the Gonal-f® pen as well as Elonva® (in the green sector).

Day 21

Same as a standard antagonist cycle.

Day 2

Blood test to determine if baseline same as standard antagonist cycle.

Day 3

Commence rFSH (Gonal-f(R) or Elonva®) according to PIVET Algorithm. uHMG (Menopur®, Ferring) may be preferred as it contains LH activity; perhaps precluding need for LH add-back, although the latter appears more effective [21], especially in women with severely down-regulated or absent LH, such as those with hypothalamic hypogonadism.

Day 7

Blood test for response:

E2 >350 pm/L and <2000 pm/L

Adjust dosage rFSH accordingly by 1 increment (box to right if too low; rarely box to left if too high)

P4 <5.0 nm/L

LH <12 IU/L

Commence antagonist when E2>350 pm/L

250ug daily; Cetrotide® or Orgalutran®

If P4 ≥5.0 nm/L or LH ≥12 IU/L, increase antagonist to 500ug daily

If P4 <5.0 nm/L and LH <2.0 IU, commence Luveris® (rLH) 75 IU daily

Day 9 (not monitored in LITE)

Days 11–12

Blood and Transvaginal U/S; expect

E2 2,000–6,000 pm/L

P4 <5.0 nm/L

sLH <2.5 IU

If P4 or LH elevated, increase antagonist dosage from 250 mcg to 500 mcg immediately and consider early trigger.

Generally trigger when 2 follicles ≥18 mm; otherwise continue stimulation and reassess in two days.

The vast majority of triggers are given on day 11 or 12.

LITE cases for cancellation if follicles >12 or E2 ≥12,000 pm/l.

Patients may elect to convert to conventional programme with standard costings at this stage.

Trigger dosage is Ovidrel® 250 mcg x1.

Luteal Support is Crinone bd®

Mid-luteal bloods – not monitored

Final blood measure E2, P4 and βhCG for pregnancy detection performed day 17 post-OPU (day 19 post-trigger). Pregnancy is monitored to week 8 (see below) but without adjunctive hormonal supports, although such can be offered with attendant extra costs.

8.8.5 Pergoveris

The conversion from uHMG to rFSH around 1990 was driven by a safety concern to avoid any infective element derived from human tissues. Certainly, the revelation was that prions were behind the cases of Creutzfeldt–Jakob Disorder (CJD); this condition occurring in a small number of those given pituitary extracts such as HPG and HGH drove the recombinant technology. However, this led to concern from many long established IVF units that the ultra-refined rFSH product lacked some quality which may have been provided by the multiple isoforms of FSH or the LH/HCG activity present in the urinary products. The introduction of GnRH-ant regimens propelled this idea, hence Merck Serono has released Pergoveris®-150 IU rFSH +75 IU rLH in each ampoule. There is data suggesting that the rFSH/rLH combination may be superior to uHMG, especially in severely LH-suppressed women or those women with hypothalamic hypogonadism [21].

Nonetheless we propose to explore this gonadotrophin combination in an adapted PIVET Algorithm across the range of rFSH 150–350 IU using one ampoule (150 IU FSH/75 IU LH) in the range 150–225 IU rFSH or two ampoules (300 IU FSH/150 IU LH) for the range 250–300 IU rFSH. However, we have no useful data generated at this stage and we have some concern that those women requiring higher dosages of rFSH will concurrently be exposed to higher amounts of LH which may be seen as adverse in those women who have higher basal levels [21].

8.9 Early Pregnancy Monitoring

The blood test performed at the end of the IVF cycle on luteal phase day 19 post-trigger (day 17 post-OPU) is tested for βhCG, E2 and P4. Pregnancy is diagnosed with βhCG ≥25 IU/L applying the Siemens Centaur platform. Although the assay detects levels ≥2 IU with coefficient of variability <7 percent, it is our policy not to declare pregnancy at levels <25 IU as there may sometimes be a prolonged effect from the Ovidrel® injections when applied for luteal support despite the last being four days prior. Furthermore, pursuing pregnancy support treatments for levels <25 IU has proven fruitless in our experience but causes much anxiety from the patient's perspective. We have also found it relevant to undertake to also measure E2 (with ideal range 1000 pm/L to 6000 pm/L) and P4 (with ideal range 60 nmol/L to 600 nm/L).

PIVET policy undertakes hormonal monitoring each week thereafter to seven or eight weeks [22] until a clear diagnosis is determined by the finding of a viable fetus within an intra-uterine gestational sac. Again, although ultrasound may detect viable pregnancy as early as day 35 (five weeks), the failure to detect such can be flawed for many other causes, especially slower-developing or delayed-implantation pregnancies, where an accurate diagnosis cannot be certain until day 49 (seven weeks). It is therefore our policy to continue pregnancy supports in all cases where βhCG levels are rising until week 7.

Any support hormones given during the luteal phase of the IVF cycle is continued through to the seven-week diagnostic scan (other than Ovidrel® injections; except when indicated for recurrent miscarriage). If a viable intra-uterine pregnancy is detected, the

luteal supports are continued until nine weeks when a reducing schedule is introduced, ceasing all supports by week 12, excepting progestagens in high risk pregnancies.

For those with βhCG ≥25 IU at nominated 'week four', a blood sample is checked each week to week seven and hormonal supports are adjusted to maintain E2 >1000 pm/l and P4 above 60 nm/l. This means applying pessaries containing micronized progesterone 400 mg or P4/E2 500 mg/2 mg. This hormonal support regimen was developed following close tracking of many pregnancies from the earliest years of our programme [23]. However, despite this active support policy, not all pregnancies progress in a normal fashion and the following may also be identified: Biochemical pregnancy: these show a fading βHCG by week 7, sometimes falling below 25 IU. At these points, the support hormones are withdrawn and the patient usually has a typical 'delayed menses'. However, we have learnt to monitor these cases for at least one more week to ensure the βhCG level reduces below 10 IU when further monitoring is unnecessary. Ectopic pregnancy is diagnosed classically by a sub-optimally rising βHCG level, along with falling P4 levels and definitive ultrasound scan at day 49 showing an empty uterine cavity (or a pseudosac without fetal evidence). At this stage most cases are quite amenable to methotrexate (MTX) treatment. Such cases are monitored with blood and T/V scan over the next two weeks to determine an appropriate fall in βhCG levels. Sometimes a second MTX dose is required and occasionally a laparoscopy is required for definitive treatment of the ectopic pregnancy – usual tubal but ovarian and secondarily implanted cases have been found over our almost 40 years of experience.

We have also published on heterotopic pregnancies [24], sometimes with a surviving uterine pregnancy and associated ruptured tubal ectopic gestation. Suffice it to say that each of those cases has set its own challenge, but the best result has been achieved by applying hormonal supports to day 49, thereafter responding to the ultrasound evidence and proceeding to laparoscopy if the woman has pelvic pain and associated fluid (blood) in the Pouch of Douglas. Occasionally the diagnosis is actually ovarian torsion combined with a viable uterine pregnancy. Most cases have been amenable to laparoscopic unravelling of the ovarian ligament following which a plication suture is applied to prevent future episodes.

Pregnancy of unknown location (PUL) is increasingly diagnosed as we find the early application of methotrexate (MTX) resolves many uncertain cases. Sometimes this occurs at a combined hysteroscopic and laparoscopic search where ectopic gestation is suspected but no clear tubal or abdomino-pelvic pregnancy can be detected. The main possibility is of an early interstitial or cornual gestation, sometimes intramural in a former caesarean scar or occasionally as a cervical gestation. MTX 50 mg injected into each cornual site has resolved all cases we have experienced. A consensus statement on PULs covers nomenclature, definitions and outcomes [25].

The more common scenario of course is a failed intrauterine pregnancy described as a blighted ovum (no fetal detection) or a delayed miscarriage where viability of a detected fetus is not able to be confirmed. Our policy is to monitor to week 7 in such cases, maintaining the hormonal supports. A failed pregnancy will show a marked reduction in crown-rump length, often with associated sub-chorionic haematoma and continuing absence of fetal heart, whereas an occasional viable pregnancy will show enlargement and fetal heart detection; much to the surprise of the ultrasonographer. In our experience, approximately 50 percent of such cases have continued as normal pregnancies to term.

Progressing pregnancies are referred for obstetric management and includes first-trimester screening increasingly with non-invasive fetal DNA testing. This is beyond the

remit of this chapter, but suffice it to state that pregnancies arising from a subfertile background have a higher risk for fetal anomalies, pre-term births, intra-uterine growth restriction and complex obstetric outcomes. There are many advances in management of such issues in recent times; hence, the issue of careful monitoring is an essential continuum. The IVF clinic should hand over its pregnancies with clear management instruction such as the need for longer-term progesterone support in many higher-risk scenarios.

8.10 Conclusion

The earliest IVF cycles – both unstimulated and stimulated – were conducted with minimal monitoring. They were conducted on the principles of the natural menstrual cycle which indicated that the ovulatory LH surge occurred around day 12 and the egg was released sometime around 38 hours after its onset. Those early patients were young, certainly the women were <35 years, and to this day, that group has the best prognosis. However, the expectations arising from the assisted reproductive technologies around IVF have created a need to find solutions to treat the full array of infertility disorders, including male factor, across the entire reproductive age range. So too is ART expected to resolve associated challenges such as the problems of recurrent miscarriages and genetic disorders – both genetic mutations and chromosomal aneuploidies, particularly trisomies. These expectations have created a high demand for ART procedures, hence regulatory processes, both legislative and self-regulatory, have evolved. These increasingly expect absolute safety (e.g. avoiding OHSS) and demand sensitivity to community concerns (e.g. avoiding multiple pregnancies and adverse obstetric outcomes). To achieve these ideals explains the reasons for an increasingly sophisticated monitoring system behind each IVF treatment cycle and the ensuing pregnancy.

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