Ovulation Stimulation and Cycle Management in IVF

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Introduction

The goal of ovarian stimulation is to induce ongoing development of multiple dominant follicles and to mature many oocytes to improve chances for conception. Ovarian stimulation enables the retrieval of many cumulus–oocyte complexes, and this allows for inefficiencies in subsequent oocyte maturation, fertilization in vitro, embryo culture, embryo selection for transfer, and implantation. However, in order to prevent premature luteinization and spontaneous ovulation, co-treatment with a GnRH agonist or antagonist is normally required.

Fresh embryo(s) can be transferred in the great majority of patients, and spare embryos may be cryopreserved to allow for subsequent chances of pregnancy without the need for repeated ovarian stimulation and oocyte retrieval. This paradigm has formed the basis of clinical practice since the early days of IVF. However, increased understanding of the intricacies of the follicular development and selection processes has been critical to many of the new developments in ovarian stimulation in clinical practice.

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Preparations Used for Ovarian Stimulation

Gonadotropins

In the 1960s, human urinary preparations of LH and FSH (Human Menopausal Gonadotrophin, hMG) were used for ovarian stimulation. The initial preparations were very impure but by the early 1980s, improved purification techniques enabled the production of purified urinary FSH (uFSH) by the use of monoclonal antibodies. With the advent of recombinant DNA technology in the 1990s, pharmaceutical companies were able to produce large commercial quantities of human recombinant FSH (rFSH) thereby bypassing dependence on the variable supply of human postmenopausal urine and also addressing concerns about batch-to-batch consistencies. Because of its purity, rFSH can now be administered by protein weight rather than bioactivity, and the so-called "filled-by-mass" preparations are now in clinical use. The use of gonadotrophins has therefore developed over a number of decades from preparations with hMG (containing both LH and FSH bioactivity), followed by purified uFSH and more recently rFSH,

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rLH, and rhCG. For a complete review of the development of gonadotropins in ovarian stimulation see Macklon et al. [1] and the American Society for Reproductive Medicine (ASRM) Educational Bulletin on this topic.

GnRH Analogs

Pituitary downregulation can be induced by the continued administration of GnRH which induces an initial stimulation of gonadotrophin release (the so-called flare effect) followed by a downregulation due to the clustering and internalization of the pituitary receptors. Without downregulation, a premature LH peak occurs in 20–25% of FSH or hMG stimulated cycles due to the positive feedback activity by high serum E_2 levels during the mid-follicular phase of the stimulation cycle [1]. In the 1980s, induced pituitary downregulation resulted in a significant reduction in the cancelation rate and improved the overall IVF outcome. Furthermore, the introduction of GnRH agonist (GnRHa) co-treatment facilitated scheduling of IVF and timing for oocyte retrieval.

Although GnRH antagonists (GnRHant) were developed soon after GnRHa, the low potency of the first two generations of drugs, and associated anaphylactic responses due to histamine release, delayed their clinical introduction until a third generation was shown to be safe and efficacious in IVF. Whilst the widely employed GnRHa long protocol requires a prolonged period of downregulation (usually 2 weeks) followed by high-dose FSH stimulation to induce multiple follicular growth, the immediate action of GnRHant means that it can be administered during the mid-to-late follicular phase to prevent premature luteinization. This avoids unpleasant "menopausal" side effects associated with pituitary downregulation, and allows the endogenous inter-cycle FSH rise to be utilized for follicle stimulation. The cyclic recruitment and the initial stages of dominant follicle selection can proceed within the natural cycle and the use of exogenous FSH for inducing multiple follicle growth can be restricted to the mid-to-late follicular phase, as in certain mild stimulation protocols [2]. Hence the overall length of stimulation is shorter than with conventional IVF. Other advantages of the GnRHant over agonist include the absence of the "flare effect" which may cause ovarian cyst formation and, in turn, lower oocyte quality, fertilization rate, number of oocytes retrieved and embryo quality [3].

Current Protocols in Ovarian Stimulation

GnRH Agonist Protocols

The long ovarian stimulation protocol combines the use of GnRHa with exogenous gonadotropin administration. This treatment regimen has remained popular since its introduction some 20 years ago. In the long protocol, the GnRHa is usually administered during the luteal phase in the preceding cycle and is continued until hCG administration (Fig. 3.1). In contrast, the so-called "short GnRH agonist protocol" or "flare" protocol delays administration of GnRHa until day 1–2 of the stimulation cycle, with the aim of utilizing the "flare" effect of the GnRHa as an additional initial stimulus for follicular recruitment. However, an early meta-analysis of studies comparing the long versus the short protocol for good prognosis patients revealed that although the long protocol required more gonadotrophins, it yielded more eggs and a higher pregnancy rate, and this perceived advantage served to restrict use of the antagonist [4]. Moreover, the long protocol was considered to be advantageous in that initiation of gonadotropin stimulation can be delayed, allowing scheduling of IVF cycles with no clear adverse effect on outcomes. However, the burden of treatment duration associated with this approach has been shown to be a significant cause of dropout from IVF treatment [5].

GnRH Antagonist Protocols

GnRHant protocols entered clinical practice after many years of refining of the GnRHa long protocol, with initial comparative studies indicating that a similar refinement of this new approach

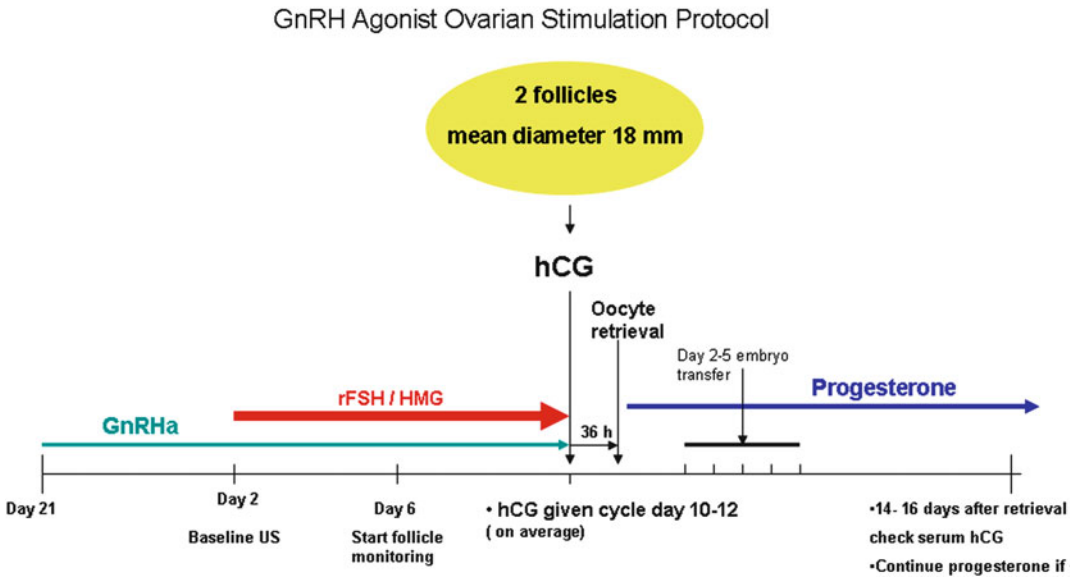

Fig. 3.1 Schematic diagram of the GnRH agonist (GnRHa), or "long" protocol

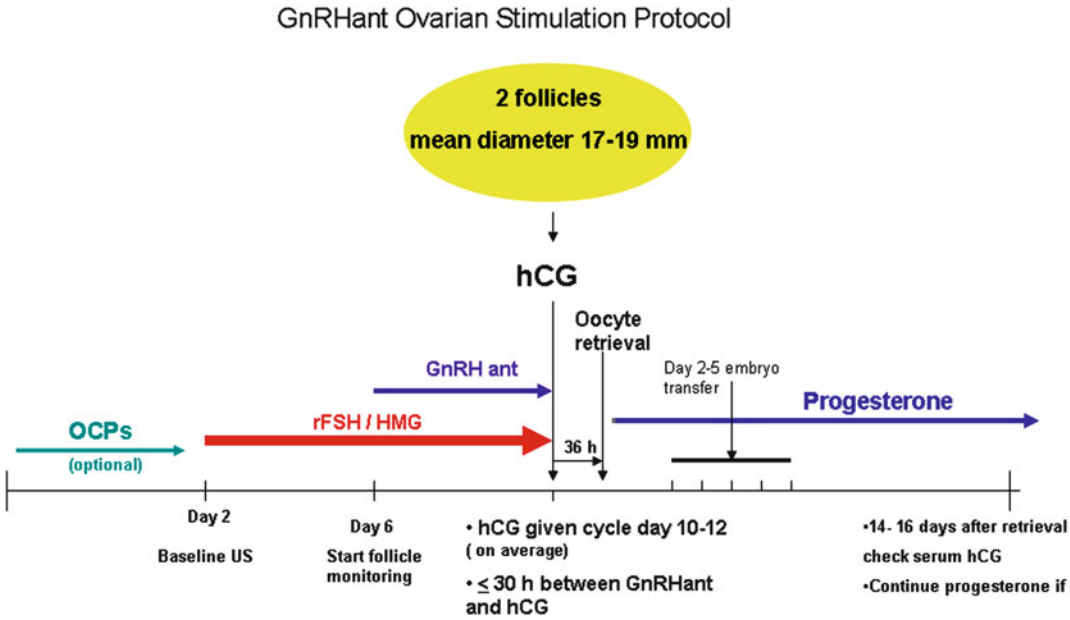

Fig. 3.2 Schematic diagram of the GnRH antagonist (GnRHant) protocol

was required. In the GnRHant protocol, ovarian stimulation with gonadotropins is begun on cycle day 2, and GnRHant administration is typically started on cycle day 6, when leading follicles are approximately 14 mm in diameter, and LH levels are increasing (Fig. 3.2). Oral contraceptive pills are often used as a lead-in prior to beginning the GnRHant cycle; indeed the early studies that lead to FDA approval of the GnRHant used OCPs. OCPs can be administered from 1 to 3 weeks, starting prior to menstrual cycle day 5 of the previous menstrual cycle, and can be helpful in

"programming" the likely day of hCG triggering to assist in scheduling. It must be made clear to the patient that if she uses only a week or two of OCPs the endometrium may be quite thin and she may not have a withdrawal bleed; in this case, the baseline scan is performed the fourth day after the last OCP (as discussed later in the chapter). Other potential benefits are suppression of potential stimulation of a persistent corpus luteum cyst.

There are few well done RCTs of hormonal pre-treatment prior to GnRHant cycles. However, a meta-analysis reported that the number of oocytes and embryos, fertilization and ongoing pregnancy rates are comparable but dose of gonadotropins are higher and treatment is effectively prolonged [6]. There is therefore no apparent medical indication for pretreatment of OCPs in GnRHant cycles.

GnRHa Versus GnRHant Protocols

The first meta-analysis that was published, comparing outcomes following co-treatment with antagonist versus agonist (involving five multicenter RCTs), concluded that the GnRHant was as efficient as GnRHa for preventing a premature LH surge. However, clinical pregnancy rates were shown to be lower in the GnRHa group. Although the reported 5% lower clinical pregnancy rate was thought to be of marginal clinical significance, these studies were not powered to show superiority of one product over the other; the data generated a significant amount of concern which resulted in a lower acceptance of GnRHant in ovarian stimulation in IVF [7]. Data from the German national IVF registry suggested that in reporting programs, this regimen was only used in patients with a poorer prognosis—those who were older and who had undergone more unsuccessful IVF cycles [8].

Recent systematic reviews which have included data from studies using more refined protocols have shown no differences in the live birth rate [9, 10]. The nonsignificant difference in the live birth rate should not be unexpected, because no clear difference between the two analogs has been demonstrated in terms of quality of either embryo [11, 12] or endometrium [13]. It has been proposed that early studies also revealed the presence of a "learning curve" associated with adoption of GnRH antagonist regimens, which could account for the relatively poor performance of the antagonist protocol in the early years. More recent randomized studies comparing the agonist and antagonist protocol have shown no significant differences in pregnancy outcomes in GnRHant despite fewer oocytes being obtained at retrieval than following a GnRHa protocol.

In addition to the markedly reduced burden of treatment, GnRHant protocols result in a lower risk of developing OHSS associated with hospital admission [10]. Moreover, the use of GnRHant in a stimulation cycle offers the possibility of replacing hCG used for triggering final oocyte maturation with a single bolus of GnRHa [14]. This approach, which has been shown to effectively eliminate the risk of developing severe OHSS, is discussed later in this chapter.

While more may still be learned regarding the optimal protocol for GnRHant, current evidence supports the use of this protocol [14] particularly for patients who are expected to be normal responders: i.e., patients with 5–9 antral follicles per ovary, age <35 years, no PCOS, normal menstrual cycle, no history of poor responses and no pelvic pathology.

Which Gonadotropin Preparation: Urinary or Recombinant?

Preparations of gonadotrophins available for ovarian stimulation were initially urinary hMG (containing both LH and FSH bioactivity, with a "75 IU" vial containing 75 IU of FSH and 75 IU of LH activity), followed by highly purified hMG (HP-hMG), purified urinary FSH (FSH-P), highly purified FSH (FSH-HP) and more recently, rFSH and rLH. Several randomized controlled trials (RCTs) comparing IVF outcomes in patients treated with hMG versus rFSH during the long GnRHa protocol have been summarized in the

most recent Cochrane systematic review and meta-analyses [15]. Of the 28 trials with live birth data, 11 trials compared rFSH versus hMG/HP-hMG, 5 trials compared rFSH with FSH-P and 13 trials compared rFSH with FSH-HP. There were significantly fewer live births after rFSH as compared to HMG (OR 0.84, 95% CI 0.72–0.99; 11 trials, $N=3197$), implying that for a live birth rate of 25%, use of rFSH instead would be expected to result in a live birth rate between 19 and 25%. There was no evidence of a statistically significant difference in live birth between rFSH and FSH-P (5 trials, $N=1430$; OR 1.26, 95% CI 0.96–1.64; I2 of 0%;) and between rFSH and FSH-HP (13 trials, $N=2712$; OR 1.03, 95% CI 0.86–1.22; I2 of 0%). The pooled data comparing rFSH versus all urinary products (HMG/HP-HMP/FSH-P/FSH-HP) showed no evidence of a statistically significant difference in the likelihood of live births or pregnancies ongoing beyond 20 weeks (28 trials, $N=7339$; OR 0.97, 95% CI 0.87–1.08). This latest review also showed no evidence of a difference in the OHSS rate (32 trials, 7740 couples, OR 1.18, 95% CI 0.86–1.61).

Only two RCTs have thus far evaluated IVF outcome stimulated with hMG versus rFSH in GnRHant cycles [16, 17]. In one study ($n=280$ women), the number of oocytes retrieved was significantly reduced in patients treated with hMG compared with those treated with rFSH (11.3 ± 6.0 versus 14.4 ± 8.1 oocytes; mean ± SD). However, live birth rates were not significantly different between patients randomized to receive hMG versus those randomized to receive rFSH (34.3% versus 31.4%, respectively, 95% CI: −8.1 to +13.7). In the more recent MEGASET (Menopur in GnRH antagonist cycle with single embryo transfer) study, again there was no difference in the ongoing pregnancy rate shown by intention to treat analysis (OR 2.2; 95% CI: −4.2 to 8.6).

Of continuing concern is the further consideration that urinary derived gonadotropins may pose the theoretical risk of transmission of prion proteins. Although the risk is now considered very low, and transmission has never been documented, it has influenced policy regarding the use of urinary versus recombinant gonadotropins in certain countries.

Exogenous LH During Ovarian Stimulation?

Studies treating women with hypogonadotropic hypogonadism with recombinant gonadotropins lacking LH activity demonstrated that LH is not required for follicular development to the pre-ovulatory stage [18]. However, the debate continues regarding the benefits of LH for oocyte maturation and quality. LH activity can be provided in the form of: (i) hMG (as urinary-derived LH activity), (ii) rLH, (iii) hCG, and (iv) rhCG. A recent meta-analysis assessed the benefits of the addition of rLH to rFSH during ovarian stimulation in IVF cycles [19]. No statistically significant differences in live birth rates were observed between patients who received rLH and those who did not. Based on these data, the addition of rLH during the follicular phase does not seem to increase the probability of pregnancy in patients treated with rFSH and GnRH analogs for the general population undergoing IVF. However, a Cochrane systematic review suggested that certain subgroups of patients with very low endogenous LH activity may benefit from the addition of LH [20].

It has been suggested that LH-induced androgen production prior to ovarian stimulation might lead to an increased follicular recruitment as intra-ovarian follicular androgens can promote the aromatase activity of antral follicles [21]. The potential role of LH activity in this context during early folliculogenesis was investigated in a recently published RCT [22]. In this randomized study, 146 women were treated in a long course high-dose GnRHa triptorelin acetate (Decapeptyl, Ferring Inc, Lausanne Switzerland, 4.2 mg s.c.) protocol and were randomized to receive rLH (Luveris, Serono Inc, Rockland MA; 300 IU/day) for a fixed 7 days, or no rLH treatment. This was followed by a standard rFSH stimulation regime (Gonal-F, 150 IU/day). The LH treatment was associated with increased number of small antral follicles prior to FSH stimulation ($P=0.007$), and an increased yield of normally fertilized (2 PN) embryos ($P=0.03$) but no difference in the ongoing pregnancy rate. Although more studies are required, at present rLH pretreatment of patients

undergoing ovarian stimulation with the use of GnRH agonists and rFSH does not seem to increase the probability of ongoing pregnancy.

Endogenous LH During Ovarian Stimulation

In recent years, several groups have focused on the potential significance of late follicular phase LH levels for clinical IVF outcome. Based on classical principles, both LH and FSH are required for adequate ovarian estrogen biosynthesis and follicle development. Theca-cell derived androgen production (under LH control) is mandatory as a substrate for the conversion to estrogens by FSH-induced aromatase activity in the granulosa cells. It has been shown that during the mid-to-late follicular phase, FSH induces LH/hCG receptor expression in granulosa cells of large follicles [23]. A number of studies have indicated that excessively suppressed late follicular phase LH may be detrimental to IVF outcome. In a meta-analysis of six studies which evaluated the association between endogenous LH levels during ovarian stimulation and the likelihood of ongoing pregnancy in normo-ovulatory patients treated for IVF with GnRH analogs, there was no evidence that low LH levels on day 8 of stimulation reduced ongoing pregnancy rates [24].

hCG Supplementation During Ovarian Stimulation

The demonstration of expression of LH receptors by follicles in the late follicular phase has led to a number of investigators advocating the substitution of FSH with the administration of hCG during the mid-to-late follicular phase of ovarian stimulation for IVF [25–28]. In one study, hCG (200–300 IU) was administered concurrently with a discontinued or reduced dosage of FSH (75 IU) when the leading follicle reached approximately 12–14 mm in diameter. Final oocyte maturation was then triggered when the follicles reached 18 mm. Although these studies did not show any differences in clinical pregnancy rate with and without hCG supplementation, the total dose of rFSH required for ovarian stimulation was significantly decreased in the low-dose hCG group. Evidence thus far suggests that hCG could partially or completely substitute the role of FSH during mid-to-late stages of the follicular phase in an ovarian stimulation cycle, without compromising pregnancy rates and leading to a significant reduction in the cost of IVF cycles.

Follicular Monitoring During Ovarian Stimulation

The Baseline Ultrasound

A baseline transvaginal ultrasound is typically performed in all ovarian stimulation cycles to ensure not only that there are no large cysts on baseline that could potentially undergo significant enlargement in response to gonadotropin stimulation, but also that small baseline simple cysts are not counted as developing follicles during stimulation. At Brigham and Women's Hospital (BWH) ovarian stimulation is not started if there is a simple cyst >5 cm or a complex cyst >3 cm, unless the patient has a known history of endometriosis. If a simple cyst >5 cm is present, it is aspirated and the fluid sent for cytologic evaluation prior to stimulation starting. Complex cysts ≥3 cm in maximal diameter, which are persistent, undergo cystectomy prior to start of ovarian stimulation, to ensure that there is no chance of ovarian malignancy. At the Complete Fertility Centre (CFC) evidence of a functional ovarian cyst such as thickened endometrium or a high estradiol level is a further indication to delay ovarian stimulation until the cyst has resolved.

Baseline Blood Testing

In GnRHa cycles, baseline estradiol and progesterone are often evaluated to ensure pituitary downregulation. The desired results depend on the assays used; at BWH the estradiol must be <50 pg/mL and the progesterone <1.0 ng/mL for downregulation to be confirmed. Alternatively, at

the CFC, a thin endometrium evident at baseline scan at least 2 weeks after commencing GnRHa treatment and following menstrual bleeding is taken to confirm pituitary downregulation.

Follicle Monitoring

In most ART programs, unless a patient has a history of rapid or exuberant response, ovarian stimulation is begun the day of the baseline ultrasound with blood testing, and continued for 4 days prior to the patient returning for testing. From that point on, at the BWH, estradiol measurements and ultrasound monitoring are performed, expecting follicular growth at 1–2 mm in mean diameter per day. Follicles are measured by placing calipers at right angles to each other in the longest follicular diameter first, and then at right angles to that. A mean of the two measurements is then taken. Generally testing to monitor the response is performed every 2 days, although less frequently in women with slow responses and daily in patients with high responses who require decreases in gonadotropin dosing. In cycles using only FSH as the follicle stimulation agent, particularly when GnRHa is used, estradiol levels will typically be lower than 100 pg/mature follicle. When LH is supplemented, the estradiol:follicle ratio is typically higher due to LH stimulation of ovarian theca cell androgen production. The added of value of routine estradiol monitoring in addition to ultrasound has been questioned in recent literature, and is not employed at the CFC unless the trajectory of follicle development is abnormal, or there is concern of developing hyperstimulation.

Adjusting Ovarian Stimulation Dosing Medications

There are no data to support increasing gonadotropin dosing during follicle monitoring, or after day 6 testing begins. It is tempting to increase dosing when faced with a few follicles, or a stimulation that appears to be moving excessively slowly. However, as oocyte recruitment is complete by cycle day 5; there is no evidence to support an improvement in outcomes [29]. In contrast, withholding or lowering gonadotropins during stimulation withdraws support to developing follicles and appears to reduce continued follicular recruitment and, in high responders, OHSS risk (see avoiding OHSS section)

Decision Making Regarding the Ovulatory Trigger

There is a great deal of inter-program variation, and even variation within programs, as to which ovulatory trigger to use, and at what point during ovarian stimulation to trigger. At the Complete Fertility Centre, hCG or GnRHa triggering is used when at least two follicles have a mean diameter of at least 17 mm. At BWH, two follicles with a mean diameter of 18 mm and an estradiol of >500 pg/mL are typically the goal (except when letrozole is used during stimulation as it maintains a low estradiol—see Chap. 13.) In a randomized trial, no difference in pregnancy rates were observed when hCG was administered a day later than the standard when at least three follicles with >16 mm mean diameter were present [30]. In a recent study, it was demonstrated that either delaying hCG or bringing it forward by 1 day had no impact on outcomes [31]. The flexibility this implies means that scheduling to avoid weekend retrievals is possible when co-treating with GnRH antagonist.

However, if a patient has a greater than expected response, hCG or GnRHa triggering may be done at smaller follicle diameters, in the hopes of reducing OHSS risk by triggering prior to recruitment of more follicles, albeit with an anticipated reduction in the average percentage of mature oocytes retrieved.

Contemporary Concepts in Ovarian Stimulation

The objectives of ovarian stimulation in ART are evolving, with more focus being placed on quality of the patient's experience. Whilst the end

point of traditional IVF was previously "pregnancy at any cost," there is a shift in modern ART towards achieving the optimal balance between treatment burden and effectiveness. The following section will highlight some of the new emerging approaches to ART, particularly regarding the trend towards milder stimulations used in Europe versus the more aggressive stimulations performed in the United States.

A European Approach: Milder Treatment Regimens

Increasing recognition of the detrimental effects of conventional profound stimulation regimens has led to a trend in Europe toward changes in the paradigm for ovarian stimulation in IVF. Milder regimens are being adopted as they reduce patient burden, risk of hyperstimulation and costs, and as the need for fewer embryos as single embryo transfer becomes more accepted in clinical practice. Moreover, possible additional benefits on embryo and endometrial quality are cited [32].

Key to the development of milder stimulation protocols has been the introduction of GnRHant, which allows for the initiation of the IVF treatment cycle in a normal menstrual cycle with an undisturbed recruitment of a cohort of follicles during the early follicular phase. This approach enables the endogenous inter-cycle FSH rise to be utilized rather than suppressed, resulting in a reduction of gonadotropins required. The treatment cycles are thus shorter and not associated with hypoestrogenic side effects related to GnRHa downregulation and reduced cancelation rates [33]. Cost analysis studies have also suggested these cycles to be overall cheaper and more cost effective [34].

Traditional IVF stimulation regimes are associated with aggressive use of gonadotrophins to stimulate the development of a large number of follicles. These regimens are often complex, expensive, extend over a prolonged period of time and require intensive monitoring. In recent years, it has become apparent that milder approaches aimed at generating the "optimum" rather than "maximum" number of oocytes are of benefit.

A retrospective analysis of 7,422 women who underwent oocyte retrieval after long protocol IVF (GnRHa) showed that overall the highest pregnancy rates per embryo transfer and per started cycle were observed when 13 oocytes were obtained (31 and 28% respectively) [35]. In a larger study of 400,135 IVF cycles performed in the United Kingdom from 1991 to 2008, the median number of oocytes obtained was 9, the overall live birth rate per cycle was 21.8%, and there was a strong association between the number of oocytes obtained and live birth rate. Live birth rate increased with oocyte yield up to 15, plateaued between 15 and 20, and declined after 40. Hence, using large doses of gonadotrophins to stimulate the development of more than 15 oocytes does not increase the pregnancy rate and may, in fact, increase patient discomfort, side effects and serious complications such as OHSS. Moreover, several randomized controlled trials have failed to demonstrate improvements in outcome when higher doses of FSH are used, even in poor response patients [36–39]. In a recent meta-analysis of studies comparing starting doses between 100 and 225 IU, 150 IU was found to provide the best balance of oocyte numbers versus risk of OHSS [40]. There is also evidence that ovarian stimulation and excessive response may be detrimental to oocyte and embryo quality. Furthermore, profound stimulation also has a detrimental effect on luteal phase endocrinology and in turn potentially impacts endometrial receptivity [41, 42].

Despite the increasingly recognized benefits of mild stimulation for some patients, one of the concerns for some IVF practitioners is that such a regimen has a lower oocyte yield and thus poorer pregnancy rates. A recent meta-analysis combining three studies with a total of 592 first treatment cycles, showed that the mild stimulation protocol resulted in a significant reduction of retrieved oocytes compared with conventional ovarian stimulation (median 6 versus 9, respectively; $P<0.001$) [43]. Optimal embryo implantation rates were observed with five oocytes retrieved following mild stimulation (31%) versus ten oocytes following conventional stimulation (29%) ($P=0.045$). It would appear that in this

study the modest number of oocytes obtained after mild ovarian stimulation was not a reflection of poor ovarian response and the authors claimed that "the fear of reducing the number of oocytes retrieved following mild ovarian stimulation appears to be unjustified." Milder stimulation regimens have been shown to produce proportionally more chromosomally normal embryos. The increased chromosomal abnormalities observed after conventional IVF are mainly due to an increased incidence of mitotic segregation errors resulting in chromosomal mosaicism [44].

It can be argued that the older patient with reduced ovarian reserve should be stimulated harder in order to achieve a higher egg yield to enable enhanced embryo selection which may potentially translate into a higher live birth rate. Several observational studies have suggested that "minimal stimulation of the older patient" has a high cancelation rate and a low pregnancy rate [45, 46]; one study including 250 cycles of "minimal stimulation" IVF found that 39.6% of cycles never underwent embryo transfer, compared to a cancelation rate of 13.7% for standard IVF. If embryo transfer was performed, ongoing pregnancy rates were 27.2% and 34.3%, respectively [45] and a further study of a series of 7,244 infertile women undergoing 20,244 cycles had a 22% rate of no retrieval, although the authors showed that if oocytes were obtained and fertilized, and transfers were performed, pregnancy rates were consistent with patient age [46]. However, it is crucial to note that these studies are observational and none are randomized or controlled. Decreased ovarian reserve, whether in the younger or older patient, despite the stimulation regimen, is associated with a lower delivery rate per initiated cycle.

"Minimal Stimulation" and Natural Cycle IVF

Key to an understanding of what constitutes "minimal stimulation" and "natural cycle," are clarifications of what constitutes a modified natural cycle versus "minimal" or "mild"stimulation. The recent definitions proposed by the International Society for Mild Approaches in Assisted Reproduction (ISMAAR) [47] are helpful in this regard: Natural and modified natural cycles aim to achieve monofollicular development, whereas the "minimal" stimulation protocols, exemplified by clomiphene citrate or letrozole use, target 2–3 follicles. The "mild" protocols involving either low-dose or late-start gonadotropin regimes are focused on producing 6–8 oocytes.

The use of natural cycle and "minimal" stimulation protocols has been re-gaining some support in recent US clinical practice. However, it is important to acknowledge that true natural cycle IVF does not employ any ovulation induction medications, is associated with a high spontaneous ovulation rate, a high rate of obtaining no oocytes, and low pregnancy and delivery rates [48]. Given the time and cost involved with monitoring a natural cycle, and the expected low delivery rate per cycle, it is not currently considered to be a cost effective therapy for the patient in most settings.

A US Approach to Ovarian Stimulation: BWH Experience

A concern related to universal adoption of mild stimulation stems from studies suggesting that, particularly in older patients, it is beneficial to have a larger number of embryos as this affords the opportunity for improved embryo selection. It can be argued that the older patient with reduced ovarian reserve should be stimulated with higher doses of gonadotropins in order to attempt to achieve a higher egg yield, better embryo selection which potentially translates into a higher live birth rate. Low dose stimulation in women with decreased ovarian reserve is unlikely to result in production of more than a few eggs and/ or embryos [45]. Thus, using a regimen with a high cancelation rate, and low pregnancy rate in older women who have a closing reproductive window would seem to be questionable.

For the young patient, transfer of one or two embryos can still result in reasonable pregnancy rates, though it is clear that decreased ovarian reserve is associated with lower delivery rates per initiated cycle even in young patients [49]. In

women of advanced maternal age, i.e. 40 or older, the increase in the proportion of oocytes with age-related chromosomal abnormality results in embryos with lower implantation, pregnancy and delivery rates. Experience at BWH has shown that patients in this age group who had five or more embryos transferred had significantly increased pregnancy and live birth rates, and significantly decreased miscarriage rates with no difference in the multiple birth rate compared with those patients with less than five embryos transferred [50]. Additionally, a SART data study showed that pregnancy, delivery, and multiple birth rates increased when up to three embryos were transferred in 38-year-olds and four in 39-year-olds but over this number only multiple birth rates increased. In women ≥40, both delivery rates and multiple rates increased with increasing numbers of transferred. Multivariate analysis confirmed the statistically significant effect of age, number of oocytes retrieved, and embryo cryopreservation on delivery and multiple rates [51].

Practice in Europe differs markedly; the number of embryos transferred is dictated by legislation in some European countries; for example, in the UK, transfer of three embryos is only permitted in women over 40 (see Chap. 15 for a more extensive discussion). The trend from the three to two embryo transfer practice was influenced by a study showing that transferring more than two embryos increased the multiple pregnancy rate without significantly impacting the pregnancy rate [52]. However, pregnancy rates were higher when 5–6 as compared to 3–4 eggs fertilized. This indicates the importance of using an ovarian stimulation protocol that will result in retrieval of enough eggs to allow for embryo selection.

Reducing the Burden of IVF Treatment

As covered in Chap. 16, the stress associated with IVF can be severe, and is often cited as the reason for couples electing not to proceed with treatment after initial failure [5]. The introduction of a long-acting FSH preparation that reduces the number of injections required during an IVF treatment cycle reduces the burden of ovarian stimulation. Corifollitropin α is a recombinant fusion protein composed of FSH and the carboxy terminal peptide (CTP) of the hCG β-subunit which has a two-fold longer elimination half-life and an almost fourfold extended time interval to peak serum concentration than rFSH preparations. This allows a single injection of corifollitropin α to initiate and sustain multiple follicular growth for up to 7 days. Furthermore, after its injection, peak FSH activity is reached in 2 days compared to that of rFSH in 4–5 days. A recent multicentre "double-blind double dummy" randomized controlled study comparing corifollitropin α and rFSHin a GnRH antagonist protocol reported no difference in the pregnancy rate of the corifollitropin α treatment group compared to the rFSH treatment group [53]. This preparation will become available for the treatment of women with an antral follicle count (AFC) of less than 20, who are co-treated with GnRHant, as data from GnRHa co-treatment studies remains sparse. A recent uncontrolled phase III study found that the cumulative ongoing pregnancy rate after three cycles of corifollitropin α, including frozen-thawed embryo transfer cycles and spontaneous pregnancies, was 61% (95% CI: 56–65%)[54], consistent with expected outcomes in the literature using other preparations (see Chap. 1, Fig. 9).

Clomiphene citrate starting day 2–3 of the menstrual cycle for 5 days and followed by gonadotropins, or concurrently with low-dose gonadotropins has also been shown to reduce the cost of ovarian stimulation in IVF in good prognosis patients, albeit with pregnancy rates that appear somewhat lower than with standard regimens [55, 56].

Luteal Phase Support

For many years progesterone has been administered for luteal phase support during IVF cycles. The mechanisms underlying the abnormal luteal phase after ovarian stimulation have long been debated. It has been proposed that luteal support is necessary in GnRHa cycles because endogenous progesterone is decreased due to GnRH

downregulation and to disruption of mural granulosa cells at oocyte retrieval [1–4]. However, recent studies have demonstrated that the key mechanism causing suppression of gonadotropin and thus progesterone in the luteal phase is the high level of negative feedback to the pituitary caused by supraphysiological sex steroid levels at the end of the follicular phase [1]. Concerns remain however that the oocyte retrieval itself, which results in removal of mural granulosa cells as well as the oocyte and coronal complex, could theoretically result in suboptimal ovarian progesterone secretion, and thereby cause a detrimental effect on development of a secretory endometrium that is in phase with the developing embryo.

A Cochrane review restricted to randomized trials concluded that pregnancy rates in IVF are indeed higher after progesterone supplementation compared to no supplementation or placebo. HCG administered for luteal support also led to a higher pregnancy rate than no treatment or placebo, but also, and not surprisingly, it resulted in a high rate of OHSS due to the long half-life of hCG and its stimulatory effect on follicular VEG-F production.

There is no consensus about whether intramuscular progesterone results in higher pregnancy rates than does intravaginal progesterone. However, there is good evidence that oral progesterone undergoes extensive hepatic metabolism and therefore has poor bioavailability [57].

Randomized trials required by the FDA to bring new products to market are powered to show equivalence, and not superiority between a new product and an established one. Older data support vaginal progesterone suppositories 200 mg pv tid being comparable to intramuscular progesterone 50 mg IM qd for luteal support [58]. A retrospective, multivariate analysis compared IM progesterone 50 mg per day starting the day after oocyte retrieval to crinone gel 8% (Serono Inc, Rockland MA) and found a lower live birth rate after crinone: 24.5% versus 39.4%, OR 2.00, 95% CI 1.10–3.70 [59]. The authors theorized that as the nonpregnant patients using crinone bled several days earlier than the patients on IM progesterone, this might be due to high drug delivery between the vaginal mucosa and the endometrium, advancing the endometruim too rapidly. To test this possibility, a prospective randomized trial was then performed using crinone 8% starting 2 days (rather than 1 day) following the oocyte retrieval and compared this to IM progesterone (50 mg) starting the day following oocyte retrieval. This study found equivalent pregnancy rates between patients randomized to crinone and those randomized to IMP: 45.2% for Crinone versus 42.2% for IMP, OR 1.1, 95% CI 0.8–1.7 [59]. *Indeed* early evidence suggests that the timing of progesterone administration may be of importance; a prospective randomized trial assigned 282 IVF patients to 12.5 mg IM progesterone starting the day prior to oocyte retrieval, or 25 mg starting the day of oocyte retrieval. The clinical pregnancy rate was 12.9% in the first group and 24.6% in the second [60]. Administration of progesterone before oocyte retrieval negatively impacts the implantation rate. No formulation was clearly better than any other [61]. Patients prefer vaginal progesterone formulations for ease of use, and reduction of systemic absorption [62].

In summary, there is considerable heterogeneity concerning progesterone utilization between IVF programs, with no clear benefit from any specific regimen. At Brigham & Women's Hospital, patients start Crinone 8% once per day starting 2 days after oocyte retrieval, or IM progesterone 50 mg starting the day after oocyte retrieval. Both are continued until the tenth week of gestation when the luteal placental shift should be complete. Many centers continue luteal support for a similar period. However, two randomized controlled trials comparing treatment for 2 weeks with prolonged treatment have shown no significant impact on pregnancy rates [30, 63]. It is important to counsel patients using vaginal progesterone that it is messy and that vaginal discharge will persist until after the progesterone is discontinued. Patients using IM progesterone must be carefully taught IM injection technique to ensure that they do not hit a major nerve, such as the sciatic, and to watch for signs of allergy or infection at the injection sites.

Ovarian Hyperstimulation Syndrome

The most important and sometimes life-threatening complication of IVF treatment remains the risk of developing severe ovarian hyperstimulation syndrome (OHSS). Mild hyperstimulation may be difficult to differentiate from ovaries still enlarged status post oocyte retrieval, but in the literature has been defined as ovarian enlargement up to 5 cm without ascites. Moderate ovarian hyperstimulation has been defined as ovarian enlargement with ovaries >5 to <10 cm in diameter, and severe hyperstimulation defined as ovarian enlargement (ovaries >10 cm) with ascites or pleural effusions, significant hemoconcentration (hematocrit >50), and/ or elevated liver transaminases [64, 65].

OHSS is moderated by vascular endothelial growth factor secreted from the ovaries in response to hCG. The syndrome typically appears 7–10 days following oocyte retrieval, but can occur earlier. Patients with severe OHSS typically present with abdominal distension, weight gain due to intraperitoneal fluid accumulation, and if ascites is tense, shortness of breath and pain when walking.

Treatment of Ovarian Hyperstimulation Syndrome

Patients with mild and moderate OHSS should be monitored, and remain in contact with the clinic to ensure that their condition is not worsening. Pelvic rest is sometimes recommended to avoid potential trauma to enlarged ovaries with distended capsules during intercourse. Treatment of severe OHSS is largely supportive but should be prompt for patients with weight gain of >2 lbs in a day or decreased urine output or shortness of breath; hemoconcentration can lead to intravascular coagulation and pulmonary embolism in rare cases. Care must be taken to avoid intravascular fluid depletion, so patients must be encouraged to drink solute-rich fluids such as Gatorade; if hemoconcentration becomes severe, hospitalization for intravenous fluids and thromboprophylaxis is prudent, and plasma expansion with albumin may be helpful. Though not commonly employed, diuretics may be used after intravenous fluids are replaced, but serum chemistries must be followed to avoid hyponatremia and hyperkalemia, and worsening intravascular depletion avoided. If patients are uncomfortable, but hemodynamically stable, outpatient paracentesis is easy to perform with ultrasound guidance in the outpatient setting, either transvaginally or transabdominally [66]. Transvaginally, an oocyte retrieval needle may be used; abdominally, at BWH we generally use a thoracentesis kit; a large bore angiocatheter may also be used. It is safe to remove as much fluid as will drain; using intravenous line tubing connecting the paracentesis needle to negative pressure bottles facilitates removal of fluid. Ascites is exudative, so it is common to see a low serum albumin in patients with significant ascites. In the absence of pregnancy, symptoms generally abate within a week. In pregnant patients, however, the production of hCG 7–10 days post oocyte retrieval often increases symptoms and in severe cases ascites may persist for several weeks before spontaneously resolving.

Avoiding OHSS; GnRHa Trigger in GnRHant Cycles

It is clearly best to avoid OHSS risk altogether. Less aggressive stimulation protocols provide the opportunity to reduce the rate of this complication [67]. However, occasionally it can arise even when milder regimens are used. The introduction of GnRHant has enabled the use of GnRHa for triggering oocyte maturation by inducing an endogenous LH surge. This more physiological approach promises to reduce the risk of OHSS known to be associated with the administration of hCG to trigger final oocyte maturation. The GnRH agonist displaces the GnRH antagonist from the receptor and initiates a “flare up effect” seen typically in the use of GnRH long protocol. Moreover, the luteal phase steroid concentrations may approximate more closely to the physiological range with possible benefits for improving endometrial receptivity [68]. Initial studies

showed the resultant LH peak to be short lived [69] raising concerns that the early luteal phase may be inadequately supported by this regimen. A recent systematic review compared the effectiveness of a GnRHa with HCG for triggering final oocyte maturation in IVF and ICSI patients undergoing controlled ovarian hyperstimulation in a GnRHant protocol followed by embryo transfer; 11 RCTs ($n=1055$) were identified. Eight studies assessed fresh IVF cycles and three studies assessed donor-recipient cycles. In the fresh cycles, GnRHa was less effective than hCG in terms of the live birth rate per randomized woman (OR 0.44, 95% CI 0.29–0.68; 4 RCTs). Moderate to severe OHSS incidence per randomized woman was significantly lower in the GnRH agonist group compared to the hCG group (OR 0.10, 95% CI 0.01–0.82; 5 RCTs). In donor recipient cycles, there was no evidence of a statistical difference in the live birth rate per randomized woman (OR 0.92, 95% CI 0.53–1.61; 1 RCT) [70]. The decreased clinical pregnancy rate observed was likely due to a luteal phase defect and poorer endometrial function despite luteal phase support with progesterone and estradiol due to the shorter half-life (24–36 h) and lower amplitude of the GnRH a induced endogenous LH surge compared to that of a natural cycle (48 h) [71]. This was supported by good birth rates in the frozen–thawed embryo replacement cycles in the cycles where GnRHa has been used as a trigger for oocyte maturation [72]. More recent studies have addressed how best to support the luteal phase when GnRHa is used as a trigger. Several studies have examined the role of using hCG concurrently with GnRHa as the ovulation trigger compared to hCG (10,000 IU) alone. A small dose of hCG (1,500 IU) has been used as a supplementary dose after GnRHa administration as a trigger for final oocyte maturation [73]. Whilst both groups showed similar miscarriage, ongoing pregnancy and delivery rates when compared to 10,000 hCG in ovulation induction cycles, no OHSS cases were seen in the GnRHa group. Several dosing schedules may be used for GnRHa triggering of final oocyte maturation. Using a single dose of 20–40 units of leuprolide acetate (1–2 mg) 36 h prior to oocyte retrieval appears reliable.

Luteal Phase Support with Use of the GnRHa Trigger

Current evidence seems to support the fact that the luteal phase in IVF cycles, with final oocyte maturation triggered by GnRHa, can be rescued by the use of LH activity, resulting in reproductive outcome comparable to that of hCG triggered final oocyte maturation. Given the risks of exacerbating the effects of ovarian hyperstimulation in the event of a successful implantation, the alternative strategy will be to "freeze all" the embryos and perform a frozen embryo transfer in the subsequent cycle, although this may have cost implications for the patients, depending on local health care context.

Other Approaches to Avoiding OHSS

Other approaches, which may help reduce the risk of developing severe OHSS, include the use of adjuvant therapies such as the dopamine agonist cabergoline. This treatment (0.5 mg daily) normally given daily for 8 days from the day of hCG administration is thought to act by reducing VEGF production [74]. Initial clinical studies indicated that cabergoline can reduce the rate of OHSS compared with placebo [75]. In a meta-analysis of four studies, the incidence but not the severity of OHSS was found to be reduced by the drug, without reducing pregnancy rates [76].

Towards Individualized Protocols

In assisted conception, unsuccessful treatment cycles are often due to a suboptimal individual response to treatment. Hence there has been great interest in identifying factors which enable the optimal individual dose to be determined for each patient.

Fine-tuning of the FSH dosage can be achieved by adding specific patient markers such as smoking status, ovarian ultrasound features, and age into a scoring system. This system was shown to improve pregnancy outcome compared with fixed dosing [77]. With regard to whether and how the

dose should be increased for poor responders and decreased with overresponders is still unclear.

Managing the High Responder

Although PCOS is considered to be a major risk for OHSS, a meta-analysis of women with PCOS undergoing IVF suggested only a trend towards higher OHSS rate [78]. This is likely due to the fact that young women with excellent ovarian reserve may also be at high risk of exuberant responses to stimulation accompanied by OHSS. Similarly, increasing the dosages for women who are deemed poor responders (obese, older women and previous failed response) is not well supported by research evidence. In a randomized, placebo-controlled trial of 120 PCO patients at high risk of OHSS, the use of 500 mg metformin three times a day during ovarian stimulation resulted in a reduced number of small <10 mm follicles and OHSS risk (0.28 CI: 0.11–0.67) [79].

The CONSORT study utilizes a dosing algorithm that individualizes rFSH doses (starting from 37.5 IU rFSH) according to patient characteristics (basal FSH, body mass index, age and antral follicle count) [80]. Overall, a median of 9.0 oocytes were retrieved (8.5, 8.0, 10.0, 12.0, and 8.0 in the 75, 112.5, 150, 187.5, and 225 IU groups, respectively). Clinical pregnancy rates/cycle started were 31.3, 31.1, 35.3, 50.0 and 20.0%, respectively (overall, 34.2%). Two patients had severe OHSS. The authors concluded that individualized dosing in increments of 37.5 IU of rFSH to achieve a good rate of oocyte retrieval and pregnancy is possible through the use of the CONSORT dosing algorithm.

Ovarian Reserve Testing and Gonadotropin Dosing

Recently, there has been increased interest in the use of anti-Mullerian hormone (AMH) to help predict dosing regimens. Seifer et al. [81] first reported that a higher AMH level on day 3 was associated with a greater number of oocytes retrieved. Since then, a number of retrospective and prospective studies have demonstrated similar findings [82–84]. A recent meta-analysis [85] of 13 studies reporting on AMH and 17 on antral follicle counts (AFC) showed that in terms of predicting poor response and nonpregnancy, there was no significant difference in terms of the predictive value of AMH over ACF. The advantage of AMH over any menstrual cycle dependent predictor marker is its low inter- and intra-cycle variability. La Marca et al. [86] first demonstrated that AMH measured during any time of the menstrual cycle predicted a reasonable response for ovarian stimulation cycles. More recent work by the same author showed that in a cohort of 389 women, AMH and age permitted the identification of live birth with a sensitivity of 79% and specificity of 44% [87]. Hence, whilst serum AMH measurements may be effective in predicting response, they have not been shown to effectively predict the likelihood of achieving pregnancy after ART. Moreover, it is important to note that with extremely low-serum AMH levels, moderate, but reasonable pregnancy and live birth rates are still possible. A recent study examined 128 women with mean (±SD) age of 40.8 ± 4.1 years who underwent a total of 254 IVF cycles where the mean (±SD) AMH of 0.2 ± 0.1 ng/ml. Twenty clinical pregnancies were recorded (7.9% per cycle start [95% confidence interval (CI): 4.9–11.9%]; 15.6% cumulative [CI: 9.8–23.1%]) [88]. Hence, extremely low levels of AMH should not be used as a sole deciding factor to withhold treatment.

Given that the use of AMH can predict response, albeit not outcome, one line of treatment strategy has emerged whereby AMH alone (excluding age or BMI of patient) is utilized to provide individualized treatment. Nelson et al. [84] demonstrated that aggressive dosing of patients who have AMH <5pmol/l (i.e., <0.7 pg/mL) is safe whilst that of the normally suggested 150 IU FSH dosage for women with an AMH >15 pmol/l (2.1 pg/mL) led to a high incidence of OHSS. This dosing regimen was associated with reduced treatment burden, cycle cancelation and a trend towards more cycle efficacy. However, these data derive from a nonrandomized study, and future well-designed studies will be required to confirm the cost/benefit and clinical efficacy of

such a regimen. There may also be substantial benefit combining AMH testing with protocols in mild stimulation treatment strategies as described by Popovic-Todorovic et al. [77], so that ovarian stimulation regimes can be tailor made for patients according to their needs.

A US Approach to the "Poor Responder"

The approach to treating women who are expected to produce only a few follicles during IVF stimulation depends, to a certain extent, on physician preferences and on how many embryos are felt to be ideal to optimize pregnancy rates. As previously mentioned, most US practitioners prefer to produce supernumerary embryos, in the hope that during the culture process "survival of the fittest" will be demonstrated, with a cohort of the embryos growing optimally and allowing for embryo selection and cryopreservation.

There is no clear consensus as to what criteria constitute a "poor responder." A patient who develops fewer than six follicles on a standard long GnRHa protocol using 300–450 IU FSH per day, or 300–375 IU per day on a GnRHant protocol is likely to have decreased ovarian reserve based on criteria used in many IVF programs, and is perhaps reasonably labeled as such. ESHRE has defined the poor responder as a patient with decreased ovarian reserve testing or poor responses to maximal ovulation induction dosing [89].

The literature is replete with a multitude of protocols designed to maximize follicular recruitment, and minimize ovarian suppression, in an effort to enable such patients to successfully undergo oocyte retrieval and embryo transfer. A review of 19 studies of poor responders demonstrated that (1) pregnancy rates are lower in this patient group; (2) prognosis is far better in young versus old poor responders, with pregnancy rates of 13–25% compared to 1.5–12.7% respectively; and (3) that pregnancy rates were reduced when 1 versus 4 oocytes were obtained (0–7% versus 11.5–18.6% [90].

It is clear from a Cochrane review that in poor responders, the long GnRHa protocol is more likely to result in both cycle cancelation and fewer eggs despite utilization of more gonadotropins, than GnRHant protocols or protocols in which the GnRHa is stopped at the time ovulation induction begins [91]. There was no evidence that increasing FSH dose beyond 450 IU improves outcomes.

When poor response is previously encountered during a long GnRHa protocol, the likelihood of obtaining oocytes may be better with either the GnRHant protocol and its variations, such as the estrogen "priming protocol" or a microdose GnRHa protocol. In the "microdose lupron protocol," oral contraceptives are generally used for a short course of 7–14 days followed by aggressive stimulation with at least 450 IU per day FSH, and twice daily dosing of diluted GnRHa throughout stimulation (see Table 3.1, Fig. 3.3). In the luteal estradiol/ GnRHant protocol, or "estrogen priming protocol," an estradiol transdermal patch (0.1 mg) or oral estradiol, is administered starting approximately 10 days following the prior cycle LH surge, as well as a few days of GnRHant; this is done to theoretically synchronize the follicular cohort and prevent recruitment of a corpus luteum cyst, and suppress circulating FSH, increasing induction of FSH receptors in follicles to be recruited (Fig. 3.4). In one study of 186 young poor responders less than 35 years old, ongoing pregnancy rates per initiated cycle were 37% versus 25% respectively [92]. This has been confirmed in a small randomized trial in 54 poor responders [93]. Letrozole and gonadotropins have also been used, with letrozole 2.5–5.0 mg employed generally starting cycle day 2 for 5 days, with gonadotropins used from the start of letrozole, or after letrozole is discontinued [94, 95].

At present there is little evidence to support one "poor responder" protocol over another. Ovarian stimulation protocols used at the Complete Fertility Centre Southampton, UK (Table 3.2) and Brigham and Women's Hospital (Table 3.1), demonstrate inter-practice variations. Patients must be treated as individuals, so that if the preferred ovarian stimulation method is unsuccessful, discussion of alternative protocols with the patient, including the lack of definitive evidence that one is superior to the other, should be undertaken.

Table 3.1 Brigham and Women's Hospital ovarian stimulation guidelines for IVF/ICSI cycles

Estimated ovarian response	Age	GnRH Antagonist	GnRH Agonist	Gonadotropin starting dose
		Start antagonist when lead follicle 14 mm or stimulation day 6	*Long protocol*: start agonist approximately 1 week after LH surge or after documentation of ovulatory progesterone until menses or minimum of 10 days	Dose as below or based on prior response [unclear if doses >450 IU per day increase oocyte yield] Doses over 300 IU per day or protocols using hMG given in divided doses (twice per day)
Normal responder	≤39	OCPb starting cycle days 1–4 for 2–3 weeks if indicated	*Long protocol* with full strength leuprolide acetate 0.5–0.25 mg with stimulation start	187–225 IU/day
	≥40	OCPs × 7–14 days	*Long protocol* with diluted leuprolide acetate 0.05–0.025 mg with stimulation start	300–450 IU/day
Poor responder	Any	No OCPs *Estrogen priming protocol*: start antagonist and 0.1 mg transdermal estradiol patch 10 days after LH surge. Change patch every other day. Menstrual cycle day 2 stop patch and antagonist and start stimulation; restart antagonist as standard	*Long protocol* with diluted leuprolide acetate 0.05–0.025 mg with stimulation start or "*Microdose*" *leuprolide acetate*: Menstrual cycle day 1 start 7–10 days OCPs. Day 2 of menstrual bleed following pills or by day 4 after OCP ends, start 0.05 mg leuprolide acetate bid until hCG. Gonadotropin stimulation starts day 2 of leuprolide acetate	450–600 IU/day hMG/FSH mixed protocol
High responder	Any	OCP × 3 weeks	Long protocol with full strength leuprolide acetate 0.5–0.25 mg with stimulation start or 1.0–0.5 mg with stimulation start Overlap lupron with last week of OCP	75–150 IU/day

AMH: Low <0.9, Normal: ≥1.0–3.0, High: >3.0 pg/mL
AFC: Low <6, Normal 6–11, High ≥12
FSH: Low >10, Normal <10 mIU/mL. Note: Elevated FSH reflects decreased ovarian reserve and low response; due to suppression of FSH by estradiol, a very low FSH (e.g. <4) is not predictive of high response
[a]Ovarian reserve test results by expected response: Dosing is by AMH if AMH is discrepant with FSH or AFC results
[b]OCP used is always a low dose combination oral contraceptive

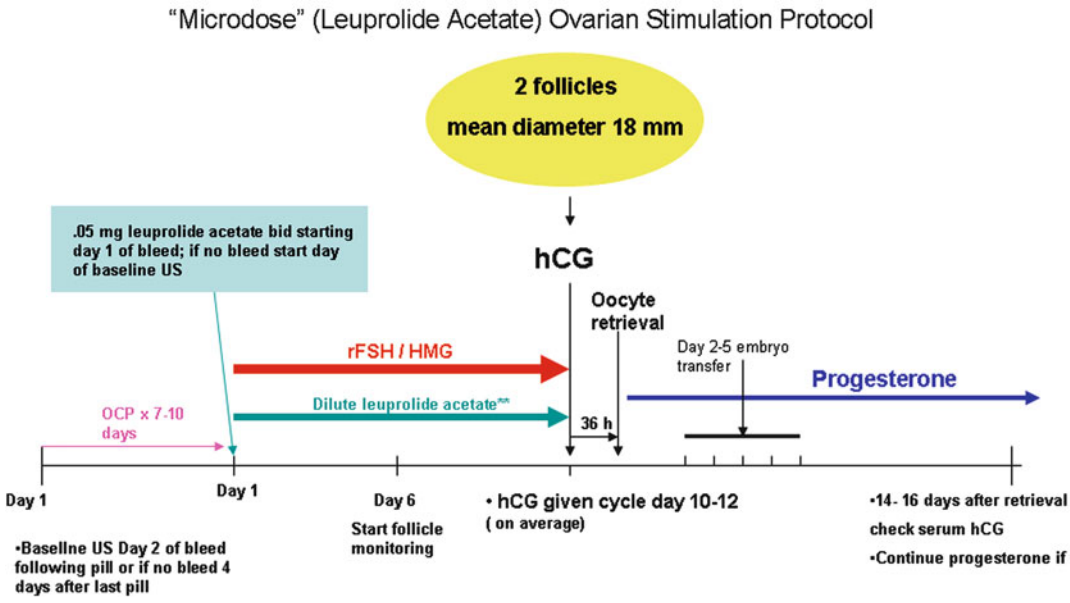

Fig. 3.3 Schematic diagram of the "microdose" or "microflare" protocol

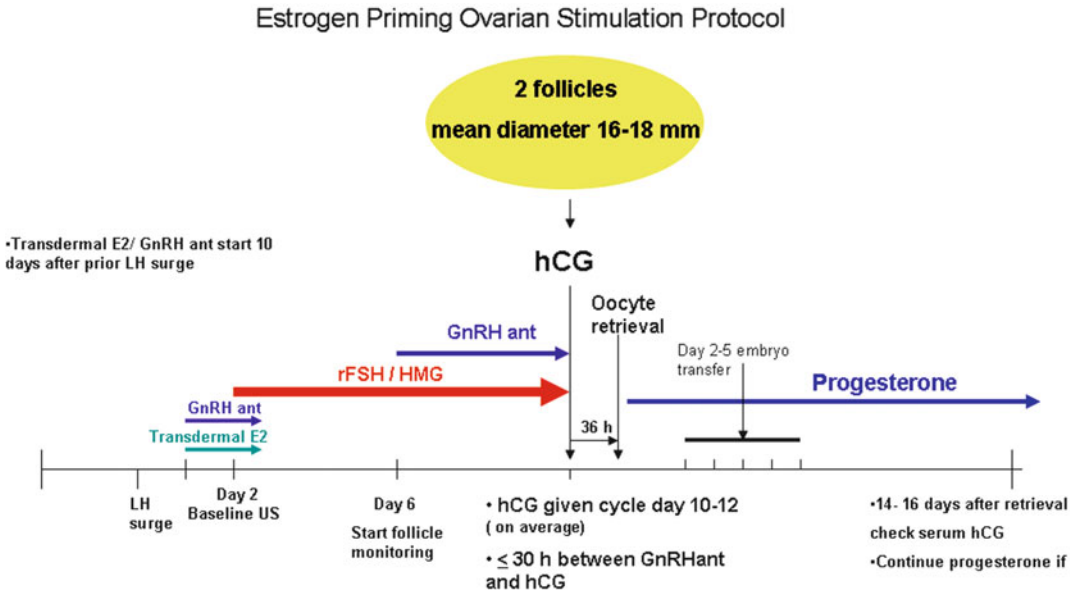

Fig. 3.4 Schematic diagram of the estrogen priming protocol

Table 3.2 Complete Fertility Centre, Southampton UK, IVF ovarian stimulation protocol

	Age	GnRH ant	GnRH a	rFSH Starting Dose/day[a]
		Start antagonist cycle day 6		Start rFSH cycle day 2
AMH ≥ 15 pmol/L (>2.1 ng/mL) AFC ≥ 15	Any	Yes	No	112.5–150 IU
AMH 7–15 pmol/L (1.0–2.1 ng/mL)	<37	Yes	No	150 IU
	38–39	Yes	No	225 IU
	40–42	Yes	No	300 IU
AFC 6–15	Any	Yes	No	150 IU
AFC ≤ 6 AMH < 7 pmol/L (<1.0 ng/mL)	Any	Yes		300 IU (first cycle) 450 IU (second cycle)
Endometriosis patients and patients with dyssychronous prior ovulation induction (1–2 follicles at 18 mm mean diameter, with rest of follicles 13–14 mm)	Any	No	yes	Consider GnRH agonist cycle and dose as with GnRH antagonist cycles, according to age, AMH/AFC

No OCP lead-in employed
[a]Urinary products e.g. HMG considered after first cycle if poor response
[b]If AMH level is not available dosing is based on AFC performed at baseline ultrasound

Table 3.3 Cumulative live birth rates per woman from linkage between SART cycles within Massachusetts ($n = 14{,}265$ women)

Cycle No.	Total cycles at each level (n)	Live births (n)	Live birth/ cycle (%)	95% CI	Cumulative live births (n)	Cumulative live birth rate/woman (%)	95% CI
1	14,265	4,331	30.4	29.6–31.1	4,331	30.4	29.7–31.1
2	7,125	1,848	25.8	24.8–26.9	6,179	43.3	42.5–44.1
3	3,550	825	23.2	21.9–24.6	7,004	49.1	48.3–49.9
4	1,685	396	23.5	21.5–25.5	7,400	51.9	51.1–52.7
5	752	169	22.5	19.5–25.5	7,569	53.1	52.3–53.9
6	316	68	21.5	17.0–26.1	7,637	53.5	52.6–54.4
7	118	25	21.2	13.8–28.6	7,662	53.7	52.9–54.5
8	47	10	21.3	9.6–33.0	7,672	53.8	53.0–54.6
9–11	21	3	14.3	0.0–29.3	7,675	53.8	53.0–54.6

Adapted from Stern Fertil Steril 2010

Counseling About Oocyte Donation

One of the most difficult discussions to have with a patient is one in which moving on to donor oocyte is recommended. There are no strict criteria to guide a physician as to when to advise a patient to move on to donor egg, versus to continuing to attempt conception with one or two follicles. Clearly as maternal age advances, the chances of a single oocyte resulting in delivery become lower. Pregnancy rates in IVF decrease slowly with successive attempts. In patients <35, 35–37, 38–40 and 41–42 the likelihood of live-birth on the fourth IVF attempt in the Massachusetts' population is still 30, 21.2, 14.2, 9.4, and 5.0% respectively (Table 3.3). After four cycles, cumulative live birth rates per age were over 60% in women <35 but less than 9% in women >43 (Fig. 3.5) [96]. In a life table analysis performed by a large single US center, the delivery rate in the sixth IVF attempt in patients proceeding with six autologous cycles without a prior delivery was 13% [97]. It is difficult to determine which patients should be encouraged in continued attempts to conceive with their own oocytes and which should not. ASRM guidelines suggest that if program statistics show that the likelihood of delivery is less than 5% (very poor),

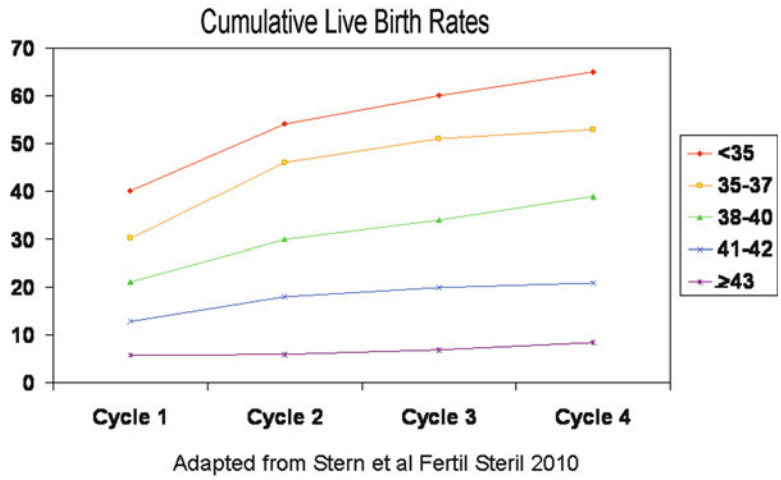

Fig. 3.5 Cumulative live birth rates after four IVF/ICSI cycles using autologous oocytes, from the Massachusetts SART data linkage study

that continued treatment should be discouraged and if less than 1% should be considered futile and not undertaken [98]. Each program must determine from their own experience and thorough patient counseling when "enough is enough" and the patient should be encouraged to move to alternative methods of having or completing her family. At BWH criteria include patient age and the ability to produce embryos deemed of sufficient number and morphology.

Conclusions

Advancement in modern medicine now provides an opportunity for patient treatments to be more individualized. In women with normal ovarian reserve, a mild stimulation regimen with GnRH antagonist regimen has an equivalent live birth rate to a conventional IVF stimulation regimen, and has advantages of tolerability and safety. Though not uniformly accepted, protocols for women with decreased ovarian reserve may increase the likelihood of undergoing successful oocyte retrieval and embryo transfer. Attention to all aspects of ovarian stimulation including ovulatory triggering and luteal support is important. In addition, patient education regarding ovarian stimulation treatment decisions is necessary in order for her to having the best possible experience. Despite impressive development in ovarian stimulation preparations and regimens, the principal determinant of outcome from ovarian stimulation remains the patient and her age and ovarian reserve.

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