Chapter 3
Controlled Ovarian Stimulation for Follicular Recruitment and Oocyte Recovery in IVF

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Introduction

Results of in vitro fertilisation (IVF) treatment have much improved since its early days with live birth rates reaching around 33 % for women aged less than 35 years [1]. The introduction of controlled ovarian stimulation (COS) regimens has played a vital clinical milestone in improving IVF success and is mainly due to a paradigm shift from uni- or pauci-follicular natural IVF cycles to multi-follicular stimulated IVF cycles. Moreover COS allows control of the various events of follicular recruitment and oocyte maturation which are crucial for successful IVF. COS therefore remains an essential part and mainstay in IVF treatment. The aim of COS is to achieve efficacy and safety with assisted reproduction, to maximise live birth rates, to minimise side effects such as multiple pregnancy and ovarian hyperstimulation syndrome (OHSS), to maximise patient compliance and tolerability, and to minimise patient burden and costs.

Ovarian stimulation is considered an important aspect of IVF as the number of recruited follicles and oocytes retrieved is an important prognostic variable and a robust outcome for clinical success. There is a strong relationship between the number of oocytes retrieved and live birth following IVF in a fresh cycle. Analysis of over 400,000 IVF cycles has shown a steady increase in live birth rates up to 15 oocytes and a plateau between 15 and 20 oocytes followed by a decline in live birth rates beyond 20 oocytes in fresh IVF cycles [2]. This information is valuable in planning COS regimens in IVF and COS regimens should aim to optimise the number of oocytes retrieved. The ideal COS regimen obtains the best result at all stages of the in vitro fertilisation process: an optimal ovarian response (oocyte quantity and quality)

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E Scott Sills (ed.), *Screening the Single Euploid Embryo*,
DOI 10.1007/978-3-319-16892-0_3

leading to high fertilisation rates and development of good quality embryos. Availability of good quality embryos facilitates selection of the best single embryo for transfer with cryopreservation of the supernumerary embryos resulting in high success rates and at the same time reducing multiple pregnancies.

Individualisation of COS in IVF

The main objective of individualisation of treatment in IVF is to offer every single woman the best treatment tailored to her own unique characteristics, thus maximising the chances of pregnancy and eliminating the iatrogenic and avoidable risks resulting from ovarian stimulation. It is therefore important to categorise women based on their predicted response in order to individualise COS regimens. Women can be identified as having a poor response, normal response, or a hyper-response based on individual characteristics and ovarian reserve tests (ORTs). Among the various ORTs including basal follicle stimulation hormone (FSH), basal oestradiol, inhibin B, antral follicle count (AFC), and anti-Mullerian hormone (AMH), AFC and AMH have the highest accuracy for the prediction of either a poor or an excessive response following ovarian stimulation [3].

Recently published individual patient data (IPD) meta-analyses of patient characteristics and ORTs demonstrated age as being the most important among patient characteristics for the prediction of poor or excessive response and AFC or AMH as having the highest predictive accuracy among ORTs [4, 5]. The cutoff levels of AFC and AMH for prediction of poor response are an AFC of <5 to <7 and AMH of <0.5 ng/ml to <1.1 ng/ml [6]. The cutoff levels for AFC and AMH for the prediction of hyper-response are an AFC of >14 to >16 [7, 8] and AMH of 3.5–3.9 ng/ml [9, 10]. According to the European Society of Human Reproduction and Embryology (ESHRE) consensus, poor ovarian response is defined based on fulfilling two of the three criteria of (1) advanced female age ≥40 years, (2) previous poor response (≤3 oocytes) following conventional stimulation, and (3) abnormal ORT (AFC or AMH) [6]. In the absence of advanced female age or an abnormal ORT, two previous poor ovarian response cycles with maximal stimulation are sufficient to define poor ovarian response. The events involved in COS are pituitary suppression and ovarian stimulation with ovulation triggering as the penultimate step leading to oocyte maturation and retrieval. Individualisation of COS involves tailoring these events to suit each individual woman.

Pituitary Suppression Regimens in IVF

The introduction of GnRH agonists in assisted reproduction played an important role in the improvement of IVF treatment success by reducing the incidence of a premature LH surge which resulted in fewer cycle cancellations and higher

pregnancy rates [11] and allowed cycle programming. The GnRH agonists cause pituitary suppression by causing internalisation and downregulation of the pituitary receptors. GnRH antagonists, which prevent a premature LH surge by their more direct action, were subsequently introduced as an alternative to the GnRH agonists permitting a shorter duration of treatment. The GnRH antagonists competitively block the pituitary receptors and thereby cause immediate suppression of the LH [12]. The long GnRH agonist pituitary downregulation combined with exogenous gonadotrophins is the most frequently used in around 89.1 % of IVF cycles [13].

Commonly used pituitary suppression regimens in COS include the long GnRH agonist regimen, the short GnRH agonist regimen, and the GnRH antagonist regimen. With the long agonist regimen, pituitary desensitisation with the GnRH agonist is commenced in either the follicular phase or mid-luteal phase. The luteal phase regimen is more commonly used where the GnRH agonist is commenced on day 21 (in a 28-day menstrual cycle) of the previous cycle. After confirmation of ovarian quiescence approximately 2 weeks later, gonadotrophin for ovarian stimulation is commenced and continued with the GnRH agonist until ovulation triggering. In the short agonist regimen, the GnRH agonist is commenced in the early follicular phase of the cycle (day 1–3) followed by gonadotrophin (usually commenced a day later). Both the GnRH agonist and the gonadotrophin are continued until ovulation triggering. In the antagonist regimen, ovarian stimulation with gonadotrophin is commenced in the early follicular phase. The GnRH antagonist is commenced on day 6 of stimulation or when the leading follicle is ≥14 mm. Both the gonadotrophin and the GnRH antagonist are continued until the day of ovulation triggering.

GnRH agonists being small peptides are easily degradable by gastrointestinal enzymes and cannot be administered orally. They are administered parenterally, either via the intranasal route, as depot preparations, or intramuscular or subcutaneous injections. The GnRH antagonists are administered subcutaneously either as a single dose or as daily injections. Dose finding studies established that the GnRH antagonist could be administered either as 0.25 mg daily in a multiple dose protocol or as 3 mg in a single dose protocol to effectively suppress the LH surge and maintain IVF results [14] (Fig. 3.1).

Although early studies suggested the agonist regimen to be superior to antagonist regimen [15], later evidence suggested comparable pregnancy rates with the agonist and antagonist regimens [16]. The antagonist regimen is associated with a lower risk of ovarian OHSS and lower gonadotrophin consumption compared to the agonist regimen [16]. Between the long and the short GnRH agonist regimens, the long regimen has better outcomes in terms of the number of oocytes retrieved and pregnancy rates compared to the short regimen [17]. The GnRH antagonist and long GnRH agonist regimens are therefore suitable options for pituitary downregulation in unselected women.

A survey conducted in 2010 involving 196 centres from 45 countries showed a wide variation in the GnRH analogue regimens chosen for poor responders [18]. A recent randomised controlled trial comparing the long GnRH agonist regimen

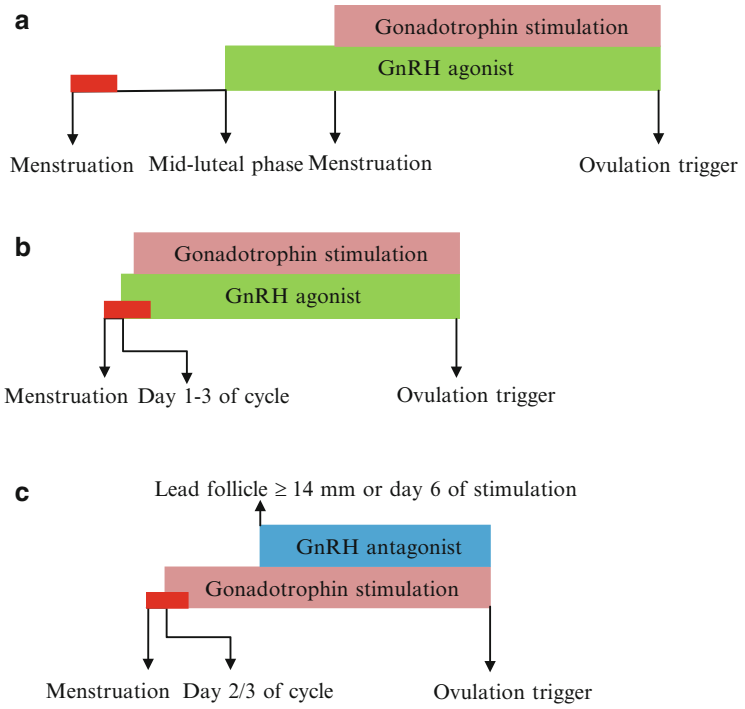

Fig. 3.1 Schematic representation of pituitary suppression regimens in IVF. (**a**) Long GnRH agonist regimen. (**b**) Short GnRH agonist regimen. (**c**) GnRH antagonist regimen

versus short GnRH agonist regimen versus GnRH antagonist regimen in women with a previous poor ovarian response demonstrated the long agonist and antagonist regimens to be suitable for these women with regard to the number of oocytes retrieved [19]. A worldwide survey in 2010 involving 179,300 IVF cycles from 262 centres in 68 countries showed the use of GnRH antagonist-based regimens in around 50 % of IVF cycles among women with polycystic ovarian syndrome (PCOS) [20]. A recent meta-analysis of studies comparing GnRH antagonist versus GnRH agonist protocols in women with PCOS involving nine RCTs from 2002 to 2013 showed comparable pregnancy rates between the two groups and a significantly lower incidence in severe OHSS in the GnRH antagonist group [21]. An added advantage with the use of GnRH antagonist-based protocols is the use of GnRH agonist trigger as a substitute for hCG in triggering of final oocyte maturation and potentially eliminating the risk of OHSS.

Ovarian Stimulation with Gonadotrophins

Gonadotrophin Dose

Exogenous gonadotrophin administration leads to supraphysiological circulating levels of FSH which facilitate recruitment of multiple follicles by exceeding the ovarian FSH sensitivity threshold [22, 23]. It is imperative to use the right gonadotrophin dose to optimise the number of oocytes retrieved and live birth rates following IVF and at the same time minimise risks such as OHSS and cycle cancellation. When exogenous gonadotrophin is administered, the number of mature follicles recruited largely depends upon the number of follicles attaining FSH sensitivity. Hence in women with a large antral follicle pool the administration of a high gonadotrophin dose may induce excessive ovarian response consequently leading to a high risk of OHSS. On the other hand, administration of an inappropriately low gonadotrophin dose may lead to the growth of a low number of follicles resulting in an 'iatrogenic' poor response.

An RCT comparing a gonadotrophin dose of 225 IU daily versus 150 IU daily in women aged 23–41 years undergoing IVF demonstrated the number of oocytes to be significantly higher with 225 IU daily compared to 150 IU daily [24]. This study excluded women with basal FSH > 10 IU/l, PCOS, previous poor response, and previous OHSS. Another RCT comparing gonadotrophin dose 225 IU daily versus 300 IU daily among women predicted as normal responders based on a total AFC of 8–21 showed no significant difference in the number of oocytes retrieved between the two doses [25]. This evidence would therefore suggest that the ideal gonadotrophin dose for women predicted as normal responders is 225 IU daily.

According to the worldwide survey on poor ovarian response, high gonadotrophin doses of >300 IU daily are used in around 50 % of IVF cycles for poor responders [18]. There is however no evidence to suggest that higher gonadotrophin doses result in a higher yield of oocytes and improve pregnancy outcome for poor responders. An RCT comparing gonadotrophin doses of 300 IU vs. 375 IU vs. 450 IU daily among women predicted as poor responders based on a total AFC of <12 showed no significant difference in the number of oocytes retrieved nor live birth rates between the three arms suggesting an unlikely benefit with gonadotrophin doses >300 IU daily [26]. The term hyper-response refers to the retrieval of >15 oocytes [27] or 20 oocytes [28] following conventional stimulation. It is vital to accurately predict women who are likely to have an excessive response and accordingly individualise the gonadotrophin stimulation dose to reduce the risk of OHSS. Women with PCOS and those predicted to have a hyper-response should be stimulated with a lower gonadotrophin dose of ≤150 IU daily as this will avoid excessive response. Excessive response (>20 oocytes) is also associated with a decrease in live birth rate in fresh IVF cycles [2] in addition to the higher incidence of OHSS with >18 oocytes [29–31].

Gonadotrophin Type

The successful therapeutic use of urinary gonadotrophins started with the first-generation product human menopausal gonadotrophin (hMG) or menotropin, which contained 75 IU of FSH and 75 IU of LH in each standard ampoule. This was followed in the early 1980s by the development of urofollitropin, the second-generation product from which the LH activity had been reduced to 0.1 IU/75 IU FSH [32]. Subsequently, the third-generation product, highly purified urofollitropin (Metrodin HP®) with practically no residual LH activity, was developed in the early 1990s. Due to its enhanced purity with very small amount of protein, Metrodin HP® could be administered subcutaneously which is an advantage over the previous generations which had to be administered intramuscularly. The more recent fourth-generation gonadotrophin is produced in vitro through recombinant deoxy ribo nucleic acid (DNA) technology, by genetically engineered Chinese hamster ovary cells. This is recombinant human FSH (r-FSH or follitropin) which is free of LH and contains less than 1 % of contaminant proteins [33]. There are two preparations of r-FSH that are commercially available for clinical use: follitropin-α and follitropin-β. There have been numerous RCTs comparing urinary gonadotrophins versus recombinant FSH for COS. Current evidence suggests that both the gonadotrophin preparations are comparable in IVF outcomes [34] (Fig. 3.2).

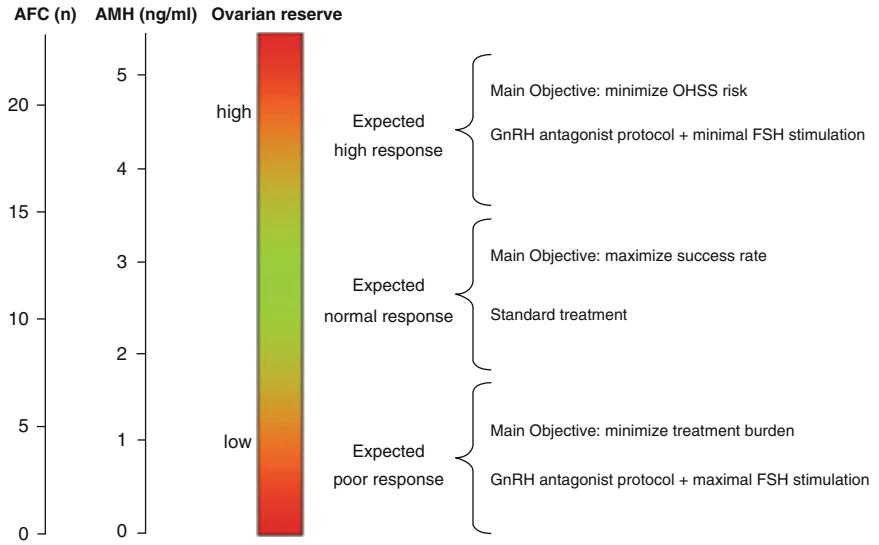

Fig. 3.2 Schematic representation of categorising women based on predicted response to individualise COS. Reproduced from La Marca & Sunkara [35]

Ovulation Trigger

Following recruitment and growth of follicles to the mature stage resulting from ovarian stimulation, the next step is maturation of oocytes facilitated by ovulation trigger in COS regimens. The LH surge that induces germinal vesicle breakdown and ovulation in a natural menstrual cycle is not reliable in stimulated multifollicular cycles necessitating artificial triggering of ovulation. hCG which is naturally produced by the human placenta and excreted in large quantities in the urine of pregnant women bears a close molecular resemblance to LH and has a similar effect on the LH receptor. hCG can be used because of its longer serum half-life (36 h) compared to the short serum half-life of LH (108–148 min) [36], thus avoiding the inconvenience of repeated administration. Administration of hCG results in luteinisation of the granulosa cells, progesterone biosynthesis, resumption of meiosis, oocyte maturation, and subsequent follicular rupture 36–40 h later. It is administered after the stimulated development of mature preovulatory follicles in order to induce maturation, but oocyte retrieval is undertaken before ovulation. The usual criteria for the administration of hCG is the presence of ≥3 follicles of ≥18 mm in diameter. The preparations of hCG that are available for clinical use are the urinary and recombinant forms and are comparable for IVF outcomes [37]. The usual dose of hCG for final ovulation triggering is between 5,000 IU and 10,000 IU as a single dose.

The GnRH agonist trigger has been proposed as an alternative to the hCG trigger by virtue of inducing an endogenous rise in LH and FSH due to its initial flare effect [38, 39]. The GnRH agonist trigger can only be used with COS regimens where prior pituitary suppression has not been achieved with a GnRH agonist, as the mechanism of action of the GnRH agonist for downregulation and desensitisation of the pituitary receptors precludes the use of the agonist trigger. Due to the specific mode of action of the antagonist by competitive blockade of the pituitary receptors and a shorter half-life, the pituitary remains responsive to the GnRH agonist, thus enabling its use for triggering ovulation. The Cochrane review comparing the GnRH agonist versus the hCG trigger in IVF demonstrated a significantly lower incidence of OHSS and a lower live birth rate with the GnRH agonist trigger [40]. It demonstrated significantly reduced live birth rates in fresh autologous cycles with the use of the GnRH agonist trigger, but there was no reduction in live birth rates in oocyte donor/recipient cycles. Following initial use of the GnRH agonist trigger, it was soon recognised of the need to modify the standard luteal support to obtain reliable reproductive outcomes [41]. Study groups have since endeavoured to fine-tune the luteal phase support in IVF cycles using the GnRH agonist trigger to optimise clinical outcomes [42, 43]. Recent suggestions and developments in overcoming the luteal insufficiency with the GnRH agonist trigger are use of (1) a “dual trigger” [44], (2) low-dose hCG supplementation [41, 43], (3) intensive luteal oestradiol and progesterone supplementation [42], (4) rec-LH supplementation [45], and (5) luteal GnRH agonist administration [46]. A recent RCT demonstrated that an individualised luteal support based on the number of follicles following the GnRH agonist trigger optimised the pregnancy rates [47]. This study proposed ovulation triggering with 0.5 mg buserelin subcutaneously followed by a bolus of 1,500 IU of hCG after

oocyte retrieval when the total number of follicles ≥11 mm was between 15 and 25 on the day of trigger and an additional 1,500 IU hCG bolus when the total number of follicles was ≤14 mm. All women received micro-ionised progesterone vaginally, 90 mg twice daily, and 4 mg of oestradiol orally commencing on the day of oocyte retrieval and continuing until 7 weeks of gestation.

Conclusion

The ultimate aim of IVF is to obtain a healthy singleton live birth with minimal adverse effects. Multiple pregnancies are recognised as a major avoidable complication of IVF. Planning of effective COS regimens is important as it leads to good quality embryos enabling selection of the best single embryo for transfer. After decades of IVF practice, it is now recognised that individualisation in IVF is the way forward. The long GnRH agonist and antagonist regimens are effective in normal responders and the ideal gonadotrophin dose is 225 IU daily. The GnRH antagonist regimen is ideal for women with PCOS and women categorised as hyper-responders. Whilst the pregnancy rates are comparable to the GnRH agonist regimen, the antagonist regimen significantly lowers the risk of OHSS in addition to enabling the use of the GnRH agonist trigger which potentially eliminates OHSS. A lower gonadotrophin dose ≤150 IU daily is recommended in these women. The long GnRH agonist and antagonist regimens are ideal for poor responders. Higher gonadotrophin doses >300 IU daily are unlikely to be beneficial in poor responders apart from higher costs and hence the maximal gonadotrophin dose should not exceed 300 IU daily.

Conflict of Interest The author declares no conflict of interest.

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