Controlled ovarian stimulation for in-vitro fertilization

ABSTRACT

Controlled ovarian stimulation with gonadotrophins is an essential part of in-vitro fertilization treatment. The aim is to produce an optimum number of oocytes to maximize success in the safest possible way. Pituitary downregulation with a gonadotrophin-releasing hormone agonist and stimulation with recombinant follicle-stimulating hormone is used widely. However, there are many different protocols in use with little evidence to determine the optimum regimen. Markers of ovarian reserve and patient characteristics are used in an attempt to individualize treatment. However, these do not necessarily reflect the quality of the oocytes and resultant embryos. Inadequate doses of gonadotrophins can lead to a poor response resulting in treatment failure. However, higher doses can lead to a hyper response, resulting in ovarian hyperstimulation syndrome which is potentially life-threatening. Both poor and hyper response are associated with reduced pregnancy rates. Various strategies, such as electively freezing all the embryos, are being introduced to optimize outcomes while ensuring patient safety.

Infertility affects 1 in 7 couples in the UK, with many requiring in-vitro fertilization (National Institute for Health and Care Excellence, 2017). The first baby born from in-vitro fertilization was in England in 1978 following a natural cycle without ovarian stimulation. Since then huge advances have been made, improving safety and success rates. An integral part of modern in-vitro fertilization is controlled ovarian stimulation. This aims to stimulate multiple follicles, ensuring an adequate number of oocytes is available to create high quality embryos (Gallos et al, 2017). The controlled ovarian stimulation regimen is key to both the quality and number of oocytes obtained. However, there is uncertainty over the optimal protocol and this article reviews the current evidence. *Table 1* outlines a standard in-vitro fertilization cycle.

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Predictors of ovarian response

The ovarian response to stimulation is associated with the live birth rate and the incidence of ovarian hyperstimulation syndrome. A target yield of 8–14 oocytes has been suggested as optimum. More than 15 oocytes significantly increases the risk of ovarian hyperstimulation syndrome without an increased live birth rate (Nyboe Andersen et al, 2017). Several different parameters can be used to predict a women's response to stimulation with increasing evidence that these can be used to tailor individual treatment (Mascarenhas and Balen, 2017; van Tilborg et al, 2017). The commonly used markers of ovarian reserve are described in *Table 2*.

National Institute for Health and Care Excellence guidance recommends the use of anti-Mullerian hormone levels, follicle-stimulating hormone levels or antral follicle count to predict ovarian response to gonadotrophin stimulation (National Institute for Health and Care Excellence, 2017). However, markers of ovarian reserve do not necessarily reflect the quality of the eggs and resultant embryos.

A recent randomized non-inferiority trial compared individualized dosing of recombinant follicle-stimulating hormone (follitropin delta) with conventional doses of

Table 1. Steps of the in-vitro fertilization cycle

Component	Indication	Options
Downregulation	To prevent premature surge of luteinizing hormone	Gonadotrophin-releasing hormone antagonist Gonadotrophin-releasing hormone agonist
Stimulation	Multi-follicular development	Follicle-stimulating hormone Follicle-stimulating hormone and luteinizing hormone
Trigger	Final oocyte maturation before oocyte retrieval	Human chorionic gonadotrophin Gonadotrophin-releasing hormone agonist
Oocyte retrieval and embryo transfer	To collect oocytes before in-vitro fertilization	Ultrasound-guided collection. Ideally transfer of a day 5 blastocyst
Luteal support	To support implantation and ongoing pregnancy	Progesterone Human chorionic gonadotrophin

an alternative recombinant follicle-stimulating hormone (follitropin alfa). The dosage of follitropin delta was individualized according to the patient's body weight and levels of anti-Mullerian hormone. Individualized dosing of follitropin delta increased the number of women with target oocyte yield and reduced the number requiring preventative measures to reduce ovarian hyperstimulation syndrome. Anti-Mullerian hormone stratification reduced both poor and hyper response to stimulation (Nyboe Andersen et al, 2017). A further multicentre study suggested that dose individualization increased costs with no improvement in live birth rate. However, it showed reduced rates of hyper response and ovarian hyperstimulation syndrome, suggesting that dose individualization may be appropriate in selected patient groups (van Tilborg et al, 2017). An awaited Cochrane review will consider the safety and efficacy of tailoring gonadotrophins in women stratified by their expected response based on tests of ovarian reserve.

Downregulation

The in-vitro fertilization cycle begins with pituitary downregulation using gonadotrophin-releasing hormone analogues. These inhibit pituitary function, preventing a premature endogenous luteinizing hormone surge, and improve in-vitro fertilization success rates. Without downregulation premature ovulation occurs in 35% of cycles. Downregulation is confirmed by a thin endometrium and quiescent ovaries on ultrasound. There are different ways to achieve downregulation.

Gonadotrophin-releasing hormone agonist

Traditionally gonadotrophin-releasing hormone agonists have been used in a long protocol and this remains the most common regimen used worldwide. After an initial stimulatory effect, they suppress gonadotrophin-releasing hormone receptors and inhibit post receptor events (Siristatidis et al, 2015). Continued stimulation desensitizes the pituitary gland, reducing the release of gonadotrophins. The three main agonist protocols are described in *Table 3*.

Commencing agonists in the mid-follicular phase on a long cycle has been associated with formation of ovarian cysts. Whether these impact negatively on in-vitro fertilization remains unclear as does their optimal management (Farquhar et al, 2017).

Women with endometriosis experience increased infertility. They have lower pregnancy rates with in-vitro fertilization than women with other causes of infertility. A 2006 Cochrane review (Sallam et al, 2006) found that the use of gonadotrophin-releasing hormone agonists for 3–6 months before in-vitro fertilization increased the pregnancy rate more than four-fold. It is unclear whether this is a result of improved oocyte quality or endometrial receptivity.

Table 2. Markers of ovarian reserve

Marker	Discussion
Anti-Mullerian hormone	Produced by antral and pre-antral follicles
	Declines with advancing age
	Does not vary throughout cycle
	Shown to be superior to other markers for predicting ovarian response
	Increased oocytes retrieved in high anti-Mullerian hormone groups
Follicle-stimulating hormone	Must be measured on day 2–5 of menstrual cycle
	Follicle-stimulating hormone less predictive with increasing age of the patient
	Lower predictive value than anti-Mullerian hormone and antral follicle count
Antral follicle count	Number of antral follicles (2–10 mm) counted
	Cycle dependent and therefore best performed early follicular phase
	Assessed by transvaginal ultrasound
	Increased resources and observer error
	Less than or equal to four predicts poor ovarian response to gonadotrophins
	Predictive value greater with increasing age
Age	There is an exponential decline in fertility with advancing age as a result of reduced quantity and quality of oocytes
	Ovarian reserve tests superior to age alone

From Broer et al (2013), Arce et al (2014), Lensen et al (2017), National Institute for Health and Care Excellence (2017), Nyboe Andersen et al (2017), van Tilborg et al (2017)

> The starting gonadotrophin dose is usually based on age, previous in-vitro fertilization outcomes and ovarian reserve.

Siristatidis et al (2015) reviewed different agonist protocols and found no difference in live birth rate or pregnancy rate when comparing long and short protocols. There was no difference in outcomes when the agonist was started in the luteal or follicular phase. The number of oocytes retrieved did not vary between protocols except in two studies of low responders suggesting increased oocytes with a long protocol *vs* short. It concluded further high-quality studies were required before recommending a specific agonist protocol. The National Institute for Health and Care Excellence advises offering gonadotrophin-releasing hormone agonists only to women at low risk of ovarian hyperstimulation syndrome and using a long protocol (National Institute for Health and Care Excellence, 2017).

Gonadotrophin-releasing hormone antagonists

Gonadotrophin-releasing hormone antagonists directly block receptors resulting in immediate inhibition of function. This rapid action means they can be started any time in the follicular phase to prevent premature luteinizing hormone surge (Nardo et al, 2013). Owing to the reduced time of pituitary suppression patients avoid the hypo-oestrogenic side effects associated with long agonist protocols. Antagonists can be given at a low dose from day 6 of stimulation or as a one off late in the stimulation phase (Al-Inany et al, 2016). This rapid onset is useful for patients requiring urgent treatment before gonadotoxic therapy such as chemotherapy. A review (Al-Inany et al, 2016) comparing an antagonist with a long agonist protocol found no difference in live birth rate or pregnancy rate but a significantly reduced risk of ovarian hyperstimulation syndrome when using an antagonist.

Gonadotrophin stimulation

Following downregulation gonadotrophins are commenced to recruit multifollicular development. Initially urinary human menopausal gonadotrophins were used, but these contained contaminants and variable concentrations of luteinizing hormone and follicle-stimulating hormone. Subsequently recombinant follicle-stimulating hormone and luteinizing hormone were developed providing consistent dosing and widely available drugs (Nardo et al, 2013). A 2011 Cochrane review (van Wely et al, 2011) compared recombinant follicle-stimulating hormone with urinary gonadotrophins and found no clinically significant difference in live birth rate or ovarian hyperstimulation syndrome rates. It recommended that gonadotrophin choice should depend on local availability and costs.

The starting gonadotrophin dose is usually based on age, previous in-vitro fertilization outcomes and ovarian reserve. The number of oocytes retrieved is associated with the dose of gonadotrophins but this can vary between individual women (Lensen et al, 2017). A starting dose of 150 international units (IU) daily is commonly used, suggested as the optimum dose for women with an expected normal response (Broer et al, 2013). the National Institute for Health and Care Excellence (2017) recommends doses should not exceed 450 IU per day, but Jayaprakasan et al (2010) showed no benefit to daily doses greater than 225 IU.

Altering doses during stimulation in response to a poor or hyper response has a delayed effect and is unlikely to be beneficial. Dose alterations take several days to be effective because of a delay in follicle-stimulating hormone levels falling below the threshold stimulating the follicles. Commencing an optimum fixed dose will have the best outcome, which relies on accurate prediction of ovarian response (Jayaprakasan et al, 2010).

Coasting is the continuation of pituitary suppression while withholding gonadotrophins and measuring daily oestradiol levels. When oestradiol levels fall a trigger injection is given and oocytes are collected. Withdrawal of follicle-stimulating hormone causes smaller follicles to undergo atresia while the larger follicles continue to mature as they are less dependent on follicle-stimulating hormone (Mathur and Tan, 2014). Coasting reduces rates of moderate and severe ovarian hyperstimulation syndrome (D'Angelo et al, 2017), but it may be associated with poorer cycle outcomes such as reduced pregnancy rate (Mathur and Tan, 2014).

Gonadotrophin-releasing hormone analogues suppress release of follicle-stimulating hormone and luteinizing hormone. Subsequent luteinizing hormone deficiency may prevent follicular maturation and reduce in-vitro fertilization success. Luteinizing hormone support can be provided by recombinant luteinizing hormone or combined with follicle-stimulating hormone in highly

Table 3. Gonadotrophin-releasing hormone agonist protocols

Protocol	Initiation	Duration
Long	In the follicular phase or luteal phase	Minimum 14 days before gonadotrophin stimulation
Short	Day 2 of menstrual cycle	Gonadotrophin stimulation started the following day
Ultra-short	Commenced on the same day as gonadotrophin stimulation	First 3 days of gonadotrophin stimulation

From Nardo et al (2013), Siristatidis et al (2015)

purified urinary human menopausal gonadotrophin. A Cochrane review (Mochtar et al, 2017) showed some evidence that recombinant luteinizing hormone may increase pregnancy rate but had no improvement in live birth rate. There is more evidence to support luteinizing hormone supplementation in those who are known to be deficient in luteinizing hormone such as those with hypogonadotropic hypogonadism (Raju et al, 2013).

Triggering final oocyte maturation

Serial ultrasound, with or without measurement of serum oestradiol levels, is used to monitor stimulation and identify the optimal time for retrieval. A trigger injection is required for final oocyte maturation before retrieval 36 hours later (Al-Inany et al, 2016; Gallos et al, 2017). In a natural cycle the luteinizing hormone surge resumes meiosis to metaphase II, causes rupture of the dominant follicle and formation of the corpus luteum. In in-vitro fertilization this is usually induced by an injection of human chorionic gonadotrophin as it is structurally similar to luteinizing hormone. A review by Youssef et al (2016), comparing recombinant and urinary human chorionic gonadotrophin, showed increased numbers of oocytes were retrieved when recombinant human chorionic gonadotrophin was used. There was no difference in live birth rate or rates of ovarian hyperstimulation syndrome.

Alternatively, in an antagonist cycle, a gonadotrophin-releasing hormone agonist can be used as the trigger. This quickly overcomes pituitary suppression resulting in an endogenous surge of luteinizing hormone and follicle-stimulating hormone. An agonist trigger significantly reduces rates of ovarian hyperstimulation syndrome given the shorter half-life compared to human chorionic gonadotrophin (Gallos et al, 2017). However, this reduced duration of luteinizing hormone may result in a deficient luteal phase and therefore additional luteal support is required (Mascarenhas and Balen, 2017).

Youssef et al (2014) compared human chorionic gonadotrophin *vs* agonist trigger in antagonist cycles. A lower live birth rate and lower pregnancy rate was seen in fresh autologous cycles when an agonist trigger was used. However, there were significantly reduced rates of ovarian hyperstimulation syndrome with the agonist trigger. There was no difference in live birth rate or pregnancy rate in donor–recipient cycles but again reduced rates of ovarian hyperstimulation syndrome. This supports consideration of an agonist trigger for women at increased risk of ovarian hyperstimulation syndrome.

Luteal phase support

In a natural cycle the corpus luteum produces progesterone, inducing endometrial changes in preparation for implantation. Following implantation, trophoblastic tissue secretes human chorionic gonadotrophin supporting the corpus luteum until the placenta takes over at 7 weeks' gestation.

> **“Serial ultrasound, with or without measurement of serum oestradiol levels, is used to monitor stimulation and identify the optimal time for retrieval.”**

In-vitro fertilization is associated with a deficient luteal phase, but the physiology behind this remains unclear. Multiple follicles cause supra-physiological steroid levels resulting in negative feedback on pituitary release of luteinizing hormone. Adequate luteal support is required to support implantation and pregnancy. A review of the agents available concluded progesterone and human chorionic gonadotrophin may increase live birth rate but human chorionic gonadotrophin increased rates of ovarian hyperstimulation syndrome (van der Linden et al, 2015). The National Institute for Health and Care Excellence recommends progesterone up to 8 weeks' gestation and advises against use of human chorionic gonadotrophin because of the increased risks of ovarian hyperstimulation syndrome (National Institute for Health and Care Excellence, 2017).

Challenging patients

Polycystic ovary syndrome

Women with polycystic ovary syndrome are at increased risk of excessive ovarian response and ovarian hyperstimulation syndrome. The use of an antagonist protocol with agonist trigger significantly reduces this risk. Metformin pre-treatment significantly reduces the risk of ovarian hyperstimulation syndrome in women with polycystic ovary syndrome (Tso et al, 2014). It increases pregnancy rate but has no effect on live birth rate when compared to placebo or no treatment. There was no evidence that it increased the number of oocytes retrieved (Tso et al, 2014). It is hypothesized that metformin inhibits release of vascular endothelial growth factor and lowers oestradiol levels. Treatment is recommended for 4 months before in-vitro fertilization, during in-vitro fertilization and up to 12 weeks of pregnancy (Balakumar et al, 2017).

Poor responders

A poor response can be defined as three or fewer oocytes or low oestradiol levels and has an estimated incidence of 9–24% of cycles (Pandian et al, 2010). Both poor and hyper response have been associated with reduced pregnancy rate (Lensen et al, 2017). Cycle cancellation increases with increasing age. Women aged 35–40 years have a 10–15% risk of poor response (Lensen et al, 2017). The Human Fertilisation and Embryology Authority (2014) reported that 29.1% of cycle cancellations were the result of a poor response. This may be because of reduced ovarian reserve or suboptimal gonadotrophins. However, increased doses of gonadotrophins are likely to be effective only when there is adequate ovarian reserve.

A review of interventions for poor responders assessed various downregulation protocols, different gonadotrophins

KEY POINTS

- Controlled ovarian stimulation with gonadotrophins produces multi-follicular development.
- Anti-Mullerian hormone levels are superior to other markers of ovarian reserve.
- Pituitary downregulation with gonadotrophin receptor analogues is essential to prevent premature ovulation.
- The gonadotrophin dose should be based on the patient's age, characteristics and ovarian reserve.
- Luteal phase support is required to support implantation and the early pregnancy.
- Ovarian hyperstimulation syndrome is a serious risk of controlled ovarian stimulation.
- Further evidence is required to make clear recommendations to standardize treatment.

and adjuvant therapies such as progestins and steroids. No specific recommendations could be made because of a lack of high quality evidence (Pandian et al, 2010).

The risks

Ovarian stimulation can lead to ovarian hyperstimulation syndrome which is potentially fatal. Exposure to excess human chorionic gonadotrophin or luteinizing hormone promotes the release of inflammatory mediators, such as vascular endothelial growth factor. This increases vessel permeability resulting in a fluid shift causing ascites and pleural effusions. Resultant hypovolaemia and haemoconcentration increases the risk of thromboembolism and multi-organ failure (Royal College of Obstetricians and Gynaecologists, 2016). Early onset within 7 days of oocyte retrieval results from the exogenous human chorionic gonadotrophin trigger. Late onset, more than 10 days after retrieval, is the result of endogenous human chorionic gonadotrophin from pregnancy (Balakumar et al, 2017). Women at the highest risk are young, have a high level of anti-Mullerian hormone and a history of polycystic ovary syndrome or previous ovarian hyperstimulation syndrome.

Most cases are mild requiring only supportive treatment. However, some patients will experience serious complications. Current estimates of ovarian hyperstimulation syndrome are 0.6–5% of cycles, with 0.01–0.3% requiring hospital admission. Hospitalization increases to 4% if more than 20 oocytes are retrieved (Lensen et al, 2017). The Human Fertilisation and Embryology Authority (2014) reported that 36.1% of cycles were abandoned after egg retrieval, most commonly because of the risk of ovarian hyperstimulation syndrome.

The long-term safety of in-vitro fertilization for patients and their offspring is still debated. Ovulation induction and stimulation has no direct link with cancers, but long-term data on health outcomes are still awaited (Metwally and Ledger, 2011). The National Institute for Health and Care Excellence recommends limiting gonadotrophins to the lowest dose and shortest duration (National Institute for Health and Care Excellence, 2017). There is some evidence that ovarian stimulation may be associated with increased chromosomal aneuploidy in the oocyte (Mascarenhas and Balen, 2017) and may increase the risk of imprinting disorders in offspring (Metwally and Ledger, 2011). Further evidence on the long-term safety is required before clear advice can be given to patients.

Future developments

Electively freezing all embryos avoids exposure to the endogenous human chorionic gonadotrophin of pregnancy, reducing the risk of late ovarian hyperstimulation syndrome. It may also avoid a negative effect of hyperstimulation on the endometrium, improving implantation. A Cochrane report (Wong et al, 2017) found no difference in live birth rate between freeze all strategies and conventional in-vitro fertilization. There was a significant reduction in ovarian hyperstimulation syndrome with elective freeze. However, it is associated with delay to embryo transfer and potentially increases pregnancy complications.

In-vitro maturation involves retrieval of immature oocytes from unstimulated ovaries, with maturation and fertilization in vitro. This avoids the risk of ovarian hyperstimulation syndrome, but is associated with a reduced live birth rate (Reavey et al, 2016). It may be useful in patients with polycystic ovary syndrome or those requiring urgent fertility preservation before treatment for cancer.

Embryonic stem cells from the inner cell mass are pluripotent, thus they can differentiate into any cell type. It is possible that oocytes could be created from embryonic stem cells in women requiring donated oocytes. The nucleus of a somatic cell from the recipient would be transferred to a donor enucleate oocyte before in vitro culture to a blastocyst. The stem cells from the embryonic inner cell mass would be used to create gametes that would be genetically identical to the recipient. Removing the inner cell mass destroys the embryo. One of the main ethical considerations is the status of a human embryo with regards to when it becomes 'human'. Furthermore, there are concerns regarding mutations in the gametes and the potential effects on children born from embryonic stem cells. Clearly further research is required before these can be considered in clinical practice (Whittaker, 2007).

Conclusions

The increase in the success of in-vitro fertilization is partly attributed to improvements in controlled ovarian stimulation. However, there remains significant variation in practice reflecting the lack of a strong evidence base. Tests of ovarian reserve are better than age alone for predicting ovarian response, but these do not necessarily correlate with in-vitro fertilization outcomes. The use of agonists for downregulation remains the most common protocol. However, there may be a move towards antagonist protocols if further evidence supports no

detriment to in-vitro fertilization outcomes. A standard dose of gonadotrophins may be the most appropriate for women with an expected normal response, with dose individualization reserved for those at risk of a poor or hyper response. Clearly further evidence is required before clear recommendations can be made to standardize treatment. Patient safety must always be paramount when planning treatment protocols. **BJHM**

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