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A simple and practical approach to elective egg freezing to control costs and expand access to care

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Abstract

Social elective egg freezing (EEF) is now widely used globally but in many countries is unaffordable to many women because of high costs and lacking insurance coverage. Efforts to reduce costs, therefore, are of importance. Surprisingly, a simple, well-defined and practical approach ensuring optimal outcomes for EEF has, however, so-far not been published. We, therefore, conducted a narrative review of the literature for relevant articles regarding the different steps of ovarian stimulation (OS) in the EEF process, in order to define such a standard protocol. This review revealed that in order to maximize oocyte yields with minimal number of OS cycles - while ensuring patient safety - a multiple-dose GnRH antagonist protocol with a daily gonadotropin dose of 300 IU appears best, unless patients demonstrate a polycystic ovarian phenotype, suggestive of likely high responses. The initial gonadotropin should be recFSH, while LH supplementation should be co-administered with the addition of GnRH antagonist. Final follicular maturation should be triggered by GnRH agonist trigger, with a dual trigger (1000–1500 IU hCG) considered for suboptimal responders to GnRH agonist trigger, optionally with Cabergoline to mitigate ovarian hyperstimulation syndrome (OHSS) in high responders.

Keywords IVF, Ovarian stimulation, Gonadotropin daily dose, Elective egg freezing, Mature oocytes

Introduction

Since the endorsement of social elective egg freezing (EEF) by the American Society for Reproductive Medicine (ASRM) in 2018, EEF has globally become routine [1]. Very active promotion of social EEF by social and traditional media and a rapidly growing fertility preservation industry on the margins of traditional infertility practice, moreover, succeeded in producing significant emotional pressure on women to cryopreserve their oocytes in timely fashion [2]. Especially vulnerable to psychological pressure were women desirous of a traditional family structure but still lacking a partner and fearing to become victims of their declining fertility with advancing age [3].

The initial motivation for social EEF was, however, somewhat different: The hypothesis was that EEF would

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avert age-related increased embryos aneuploidy and the consequential age-related fertility decline, and – by doing so - aid women in postponing pregnancies for educational and career purposes and, thereby, allow them to achieve reproductive autonomy [4].

Studying the sociodemographic characteristics of women undergoing EEF revealed, however, that most were well-educated professionals who were motivated to pursue EEF for a very different reason: Approximately 85% of these women undertook EEF because they – simply - had been unable to find a suitable male partner. They either were single, divorced, had recently broken up a longstanding relationship, had been deployed overseas, or were single mothers. Career planning was, surprisingly, the least common motivation for EEF [5].

They, moreover, attributed their partnership problems to women's higher expectations, men's lower commitments, skewed gender demography in certain locations, and self-blame [6]. And one, of course, can also not ignore financial considerations, considering that EEF is mostly excluded from public insurance coverage and, of course is quite costly. This established obvious access problems for substantial portions of the female population and discriminates against lower socio-economic groups by establishing substantial barriers to care [2].

Though these cost-barriers to care have been recognized, surprisingly little has been done to overcome them. On the medical front, for example, the literature still lacks a "preferred" ovarian stimulation (OS) protocol for EEF cycles that safely minimizes the number of needed IVF cycles attempts, by maximizing the oocytes yield per cycle. Since costs for SEC, of course, increase with every additional EEF cycle required, defining a "preferred" protocol – obviously recognizing that EEF cycles, like all other IVF cycles, may require individualization – appears like a sensible goal. Prompted by these challenges, this narrative review of the literature aimed to offer a simple and practical approach to the uncomplicated young patients requiring EEF (Fig. 1).

What is the number of cryopreserved oocytes sufficient to achieve live birth(s)?

Analyzing the hitherto published studies on patients, with mean age at cryopreservation of 37.2 (±0.8) years, undergoing social EEF has revealed a probability of 2.75% live birth per thawed oocytes [7]. Moreover, Goldman et al. [8] provided an evidence-based model to predict the probability of woman, with uncompromised ovarian reserve, having at least one live birth based on her age at egg retrieval and the number of mature oocytes frozen. According to this model women age 35, 38 or 41y would have to freeze 20, 40 and 80 oocytes, respectively, to have a 90% likelihood of having at least one live birth. Correspondingly, the live birth per thawed oocytes in women age 35, 38 or 41y would be 5%, 2.5% and 1.25%, respectively.

The rational for varying ovarian stimulation protocols

Mainly to prevent a premature rise in luteinizing hormone, the two most commonly used protocols for OS incorporate GnRH-agonists and antagonists co-treatment. Unfortunately, cycle outcome reporting has been inconsistent for live births (LBR) [9]. In our analysis of the literature, the multiple-dose GnRH antagonist protocol appears to offer certain advantages, including shorter treatment duration, lower gonadotropin requirement, and reduced risk of severe ovarian hyperstimulation syndrome (OHSS) [10].

A recently introduced option in IVF cycles using the "freeze - all" strategy is progestin-primed ovarian stimulation. In this approach, progesterone is used as alternative to GnRH antagonist for suppressing premature LH surges during ovarian stimulation [11]. While this strategy may help reduce overall costs, additional research is necessary to fully establish its broad clinical efficacy [12, 13].

Determining the dose of gonadotropin used

As in all assisted reproductive technology (ART) cycles, OS protocols, including medication dosages, must be individualized and, therefore will vary. A few constant issues, however, deserve to be noted: While it is well established that the cumulative live-birth rate (CLBR) increases with the number of retrieved oocytes, the maximal LBR in fresh IVF/ICSI has been reported with oocytes yields in the 10–15 range [14], with younger women requiring fewer and older women more eggs. However, for EEF patients, the desired goal shifts from maximal LBR to maximizing oocyte yields, though with minimal risk of OHSS.

When the ESHRE SIG guideline on OS for IVF/ICSI discussed the role of daily gonadotropin dose, they concluded that for normal responders the optimal response level, in terms of oocytes, a daily dosage of 150 to 225 IU is mostly considered as standard, while in predicted poor responders a gonadotropin dose higher than 300 IU is not recommended [15].

A prospective randomized study by Wikland et al. [16] confirmed that in young normal responders (ages 20–39 yrs), starting with a daily dose of 225 IU rFSH, combined with the multiple dose of 0.25 mg cetrorelix from stimulation day 6, resulted in significantly more oocytes compared to a starting dose of 150 IU rFSH. Similarly, another prospective randomized study by Yong et al. [17] demonstrated that 225 IU yielded more oocytes than 150 IU in young women. Various models for determining the optimal daily FSH doses needed to obtain an optimal oocyte yield (10–15 oocytes) have also shown that higher

First IVF cycle attempt

1. **Protocol Choice:**
   - Multiple-dose GnRH antagonist protocol.
   - Daily gonadotropin dose: 300 IU, adjusted to 200 IU for expected high responders with PCOM.
2. **Gonadotropin Preparation:**
   - Initiate with recombinant FSH (recFSH).
   - Add LH supplementation (rec LH or HP-hMG) with GnRH antagonist.
3. **Final Follicular Maturation Trigger:**
   - Use GnRH agonist trigger as standard.

Expected suboptimal responses to GnRH- agonist trigger (Normal responders)

- Consider dual trigger (1000-1500 IU hCG)

Expected suboptimal responses to GnRH- agonist trigger (High responders)

- Consider dual trigger (1000-1500 IU hCG) with Cabergoline to mitigate OHSS risk.

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Second IVF cycle attempt

4. **Protocol Choice:**
   - Adjust daily gonadotropin dose according to the published calculator.
5. **Gonadotropin Preparation:**
   - Adjust according to patient's response to the different gonadotropin preparations in the first IVF cycle attempt.
6. **Final Follicular Maturation Trigger:**
   - Use GnRH agonist trigger as standard.
   - Consider double trigger (GnRH agonist 40 hours and standard hCG 34 hours prior to oocyte retrieval, respectively) in patients with unexpected suboptimal response in the first IVF cycle attempt.

Fig. 1 Clinical approach to ovarian stimulation in patients requiring EEF

doses can lead to increased oocyte yields, but may carry a higher risk of OHSS [18], which is not the case in EEF patients triggered by GnRH-agonist.

Gonadotropin doses in social EEF women may be on purpose higher than in routine IVF cycles, where the goal shifts to maximizing oocyte yield with minimal OS cycles, while still ensuring safety and cost-effectiveness. Typically, young EEF patients in first ART cycle receive a daily gonadotropin dose of 300 IU [19]. This dosage, however, should be adjusted upwards for more advanced age and lower ovarian reserve, or alternatively downwards in conjunction with minimal stimulation, according to the experience of the treating physician experience. Moreover, in women with a diagnosis of polycystic ovary syndrome (PCOS) or, simply, excessively high anti-Müllerian hormone (AMH) levels, the daily dose should not exceed 200 IU.

In a study of women undergoing social EEF [19], the initial OS attempt with a daily gonadotropin dose of 300 IU yielded 8–9 mature oocytes. Moreover, increasing the daily gonadotropin dose above 300IU was also shown to result in higher mature oocytes yield. However, when analyzing the data according to the number of oocytes retrieved in the second - as compared to the first – cycle attempt, an increase, and no change or reduced oocyte yield in the second cycle was observed regardless of the daily gonadotropin dose in the second cycle attempt (whether increased, unchanged, or decreased compared to the first attempt).

Using logistic regression for individual patients to determine the daily gonadotropin dose needed to increase the oocyte yield in the successive cycle, a study developed two equations (Table 1), with an AUC of 0.85 and simplified dosage determination by inputting the

Table 1 Equations calculating the daily gonadotropin dose needed for maximal oocytes' yield

Step 1: Calculate X using the first equation (a):

X=-0.514 + 2.87*A1 + 1.733*A2–0.194* (E2/1000)

If the number of oocyte retrieved in the first cycle is < 7: A1 = 1 and A2 = 0.

If the number of oocyte retrieved in the first cycle is between 8–12: A1 = 0 and A2 = 1.

And If the number of oocyte retrieved in the first cycle is > 13, A1 = 0 and A2 = 0.

E2 is the estradiol level (pmol/L).

Step 2: After calculating the X value, it should be placed in the following logistic model (b):

P = EXP(X) / [1 + EXP(X)]

If *P* > 0.5 then the suggested daily gonadotropin dose in the successive cycle should be 450IU, while if *P* < 0.5 it should be 300IU.

number of retrieved oocytes and peak E2 levels from the first cycle into a published calculator [20].

Determining the type of gonadotropin used

Another issue of relevance is the type of gonadotropin used in such patients. Studies investigating the role of LH supplementation in patients undergoing ART highlight variations in LH bioactivity-containing preparations, daily doses, and mode of administration. A literature review of studies reporting on IVF/ICSI treatment outcome following OS using either hMG or recFSH+recLH revealed, however, no significant differences in OS variables and clinical pregnancy and live birth rates, when comparing the use of hMG with recLH [21].

A subsequent cross sectional study of patients who underwent two consecutive IVF cycles - one including rFSH+rLH and the other HP-hMG, - however, demonstrated that, while the rate of mature oocytes was not different between the two treatment cycles, mean numbers of mature oocytes retrieved and mean numbers of fertilized oocytes were higher in the rFSH+rLH cycles compared with HP-hMG cycles [22]. Higher mature oocytes yield demonstrated in rFSH+rLH treatment cycles, may be the consequence of greater effectiveness of the rFSH isoform compared to urinary FSH, rather than the result of effects induced by rLH, as it is well-established that, compared to HP-hMG, rFSH leads to higher follicular recruitment (23–24).

Despite initial differences in fertilized oocytes, both treatments, moreover, showed similar outcomes in terms of the number and the rate of top-quality embryos per retrieved oocyte [22]. This underscores that, while rFSH+rLH enhances follicular genesis and oocyte yield, HP-hMG may favor embryonic maturation, and aligns with findings from previous trials that demonstrated a higher proportion of top-quality embryos in the HP-hMG arm (23–24).

Based on these insights, we recommend initial stimulation with recombinant FSH (recFSH), optionally with recombinant LH (recLH), and added LH supplementation (rec LH or HP-hMG) when starting GnRH antagonist therapy.

Triggering final follicular maturation

The final issue to be addressed is the triggering of follicles. Ovarian stimulation that combines GnRH antagonist co-treatment and GnRH agonist trigger has become a common tool in eliminating severe early OHSS and to support the concept of an OHSS-free clinic (25–26).

It is noteworthy that previous studies have indicated that patients receiving a GnRH-agonist trigger alone for final follicular maturation with post-trigger LH < 15 mIU/mL, were more likely to have suboptimal response to the GnRH- agonist trigger, that manifests in low recovery and high immature oocyte rates [27–30]. These patients typically exhibited lower FSH and LH levels on day 2 and lower LH on the day of trigger (LH < 0.5 IU/L at the initiation of ovarian stimulation and at the trigger day). They also required longer stimulation and more gonadotropins, and were more likely to have irregular menses or to have used long-term oral contraceptives (24–25). To mitigate suboptimal responses, we recommend considering a dual trigger approach with low-dose hCG (1,000–1,500 IU) (32–33).

For patients at risk for developing severe OHSS, characterized by rapidly rising E2 levels, peak E2 levels exceeding 3,500 pg/mL, and/or the emergence of a large number of intermediate sized follicles [31], and expected suboptimal responses, the dual trigger approach with low-dose hCG should be offered with close monitoring and cabergoline (0.5 mg/day) from day of trigger or day of oocytes retrieval for 8 days are advised [34].

Moreover, in cases where patients *unexpectedly* respond suboptimal to the GnRH agonist trigger, a double- trigger approached should be offered [33]. The double-trigger approach (GnRH agonist at 40 h and standard hCG added at 34 h prior to oocyte retrieval) was previously offered to two groups of patients showing abnormal final follicular maturation despite normal response to OS: those with < 50% oocytes retrieved per number of dominant follicles > 14 mm in diameter on day of hCG administration [35], and those with < 66% mature/metaphase-II (MII) oocytes per number of oocytes retrieved [36]. In both groups the double-trigger approach resulted in significantly higher number of oocytes retrieved, higher recovery rate, significantly higher number of MII oocytes, and larger proportion of MII oocytes per number of oocytes retrieved.

Conclusion

Figure 1, thus, summarizes the clinical approach to OS in patients requiring EEF:

Patients should embark on the *multiple-dose GnRH antagonist protocol*, with a daily gonadotropin dose of 300 IU, unless they are expected to be unusually high responders, when the daily gonadotropin dose should not exceed 200 IU.

The initial *gonadotropin preparation* should include recFSH, and with the addition of the GnRH antagonist, a LH supplementation should be co-administered (recLH or HP-hMG).

Final follicular maturation trigger should consist of GnRH agonist, unless a suboptimal response to GnRH-agonist trigger is expected. In the latter cases, a dual trigger with 1000–1500 IU of hCG should be administered (with or without Cabergoline in high risk patients to ameliorate the risk of OHSS).

In the second ART cycle attempt, the daily gonadotropin dose should be determined according to the suggested calculator [20].

Moreover, those who unexpectedly responded suboptimal to the GnRH agonist trigger, the double-trigger approach should be offered.

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Declarations

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