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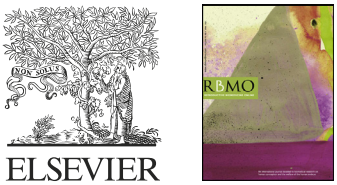

COMMENTARY

Exogenous progesterone for LH surge prevention is redundant in ovarian stimulation protocols

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ABSTRACT

During ovarian stimulation for IVF–embryo transfer treatment, a premature LH surge may lead to progesterone elevation that disrupts endometrial maturation and affects the probability of pregnancy following fresh embryo transfer. Preventing this LH surge and progesterone elevation using gonadotrophin-releasing hormone (GnRH) analogues is considered a standard practice. The same policy applies to cycles in which the 'freeze-all' protocol has been selected from the outset (e.g. donors), but the need for this has not been discussed. Moreover, in 'freeze-all' cycles, exogenous progesterone administration tends to replace GnRH antagonists, without reducing efficacy after embryo transfer in frozen-thawed cycles. Nevertheless, as exogenous progesterone is expected to have the same impact on the endometrium as endogenous progesterone, it is clear that, unlike in fresh cycles, in 'freeze-all' cycles an endogenous LH surge prevention does not seem necessary. Therefore, both GnRH antagonists and exogenous progesterone appear to be redundant in 'freeze-all' cycles, and in this context the indications for the use of GnRH analogues in ovarian stimulation protocols need to be revisited.

It is well known that administration of exogenous FSH in the early follicular phase of the menstrual cycle widens the FSH 'window' and results in the selection of multiple follicles. This leads to various hormonal changes, such as a rapid increase in serum oestradiol concentrations that exceeds the threshold of the positive feedback before full follicle maturation takes place, as well as a significant rise in the bioactivity of gonadotrophin surge-attenuating factor (GnSAF) (*Messinis, 2006*). The combination of these two changes in cycles with only FSH leads to the prevention of the LH surge in about 80% of them, and when the surge occurs it is premature in most cases. When a premature LH surge occurs, even if it is markedly attenuated, luteinization with increased progesterone concentrations can take place. Based on the results of a large meta-analysis including more than 60,000 stimulated cycles, it was shown that elevation of progesterone up to 3 ng/ml decreased the probability of pregnancy only in the fresh and not in the frozen-thawed cycles, suggesting that the elevated progesterone concentrations affect the endometrium rather than the oocytes (*Venetis et al., 2013*). This raises the question of whether ovarian stimulation should be different in cycles with fresh embryo transfer ('fresh' cycles) from cycles in which freezing of all embryos ('freeze-all' cycles) has been pre-decided.

The category of 'freeze-all' cycles is divided into planned or 'elective' and unplanned or 'non-elective' freezing (*Blockeel et al., 2019*). This Commentary deals with 'elective' freezing, which includes women who have medical reasons or express a desire for this before starting any treatment. The 'non-elective' group includes women where the freezing arises for medical reasons in the course of ovarian stimulation. According to *Blockeel et al. (2019)*, cases of women who fall into the category of 'elective' freezing relate to the application of preimplantation genetic testing, the existence of endometriosis and/or adenomyosis and embryo pooling via repeated egg retrievals in poor responders. However, oocyte donors and women requesting fertility preservation also fall into this category, while a new indication may be possible COVID-19

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KEY WORDS

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IVF
Progesterone

infection (*Anifandis et al., 2020*). In this Commentary, an attempt is made to answer the question raised above and suggest an alternative ovarian stimulation practice somewhat different from the one currently in use.

Nowadays, the prevention of the endogenous LH surge during ovarian stimulation in 'fresh' cycles is accomplished using gonadotrophin-releasing hormone (GnRH) analogues (agonists or antagonists). An alternative way is to include in the stimulation protocol clomiphene citrate given for more than 5 days, as its prolonged administration blocks the positive feedback mechanism; as such, it has been used in clinical practice (*Kato et al., 2012*). Despite differences between GnRH agonists and antagonists, in terms of their effect on gonadotrophin secretion (*Janssens et al., 2000*; *Dal Prato et al., 2004*; *Messinis et al., 2005*; *Griesinger et al., 2006*; *Messinis et al., 2010*), the clinical outcome in terms of live birth rate after IVF is similar (*Al-Inany et al., 2016*).

In recent years, the spectacular improvement in embryo cryopreservation techniques has changed the daily practice of IVF. With current practice, what applies to the 'fresh' cycles regarding the prevention of the LH surge also applies to 'freeze-all' cycles, but no one knows if this is necessary or not in the latter. Recently, in such cycles, progesterone/progestins have been included in ovarian stimulation protocols to prevent the endogenous LH surge (*Kuang et al., 2015*). Although progesterone is a physiological trigger of the LH surge (*Dozortsev et al., 2020*), the ability of this steroid and its derivatives to block under certain conditions the positive feedback mechanism of oestradiol has been known for many years (*March et al., 1979*).

Different types of progesterone have been used in clinical studies, such as medroxyprogesterone acetate, micronized progesterone, dydrogesterone and desogestrel. The recommended protocol of progestin priming involves the administration of this compound from cycle day 2 or 3 up to the day before the triggering of final oocyte maturation with a GnRH agonist (*La Marca and Capusso, 2019*). Oocyte recovery takes place as in 'fresh' cycles, but either the 'freeze-all' method is chosen or fresh embryos are transferred to synchronized recipients. Studies published since the introduction of progestins in 2015 include comparisons between a progestin-primed protocol and a short agonist protocol or a natural cycle, or between different doses of the same progestin or between a progestin and a GnRH antagonist (*La Marca and Capusso, 2019*). Depending on the primary end-point, the published studies have shown no significant difference in the number of metaphase II oocytes or the ongoing pregnancy rate when the embryos were transferred to the same women or to recipients in artificial cycles (*Iwami et al., 2018*; *Begueria et al., 2019*; *Martinez et al., 2020*). A recent meta-analysis has shown no difference in live birth rate between a progestin-primed and a GnRH antagonist protocol (*Alexandru et al., 2020*). Concerns have been raised regarding the impact of progestins on the quality of the oocytes; however, a recent meta-analysis has shown no significant difference in the congenital malformation risk between progestins and GnRH antagonists, suggesting the safety of these compounds (*Zolfaroli et al., 2020*).

To date, there are no studies examining the possibility of ovarian stimulation without the use of GnRH antagonists, i.e. with no attempt to prevent the LH surge, although an earlier meta-analysis involving only agonists has shown an advantage over not using them (*Hughes et al., 1992*). Such an investigation might yield interesting results. It would certainly be interesting to look at this separately for 'fresh' and 'freeze-all' cycles. In 'fresh' cycles, ovarian stimulation with only FSH would mean an increased risk of premature luteinization with an impact on maturation of the endometrium. Theoretically, such a protocol would need to monitor whether luteinization occurs, using daily progesterone measurement. Nevertheless, up to now, there has been a lack of consensus in the literature regarding the cut-off concentration of progesterone in blood that defines luteinization. If such a concentration could be set, ovarian stimulation could be attempted in all cycles without the use of GnRH analogues. In a hypothetical protocol, if, during ovarian stimulation, progesterone remained below the cut-off concentration, one would proceed with fresh embryo transfer, while if the cut-off concentration were exceeded, the 'freeze-all' method would be adopted and embryo transfer would be performed in subsequent thawed cycles. However, until such research is carried out, the use of GnRH analogues will continue to be the main choice in 'fresh' cycles.

In contrast to 'fresh' cycles, luteinization is not a problem in 'freeze-all' cycles, as in any case homologous fresh embryo transfer will not take place. Therefore, in such cycles, prevention of the endogenous LH surge is of minor importance and consequently the administration of a GnRH antagonist may be omitted. Indeed, induction of multiple follicular development with exogenous FSH without GnRH analogues can be successfully initiated at any stage during the normal menstrual cycle, under different hormonal environments.

Nevertheless, when ovarian stimulation begins in the early follicular phase, a reservation has been expressed that, without a GnRH antagonist, premature ovulation may take place, but this is rather unlikely for the following reasons. Data in rats have shown that, although only 5% of the gonadotrophin surge is adequate to induce maximal progesterone secretion, at least 85% of the surge amplitude is required for the follicle to rupture (*Peluso, 1990*). Studies in women stimulated with FSH without a GnRH analogue and displaying an attenuated LH surge have confirmed these observations concerning progesterone rise, while ovulation has been detected only occasionally by ultrasonography, but even this can be disputed as at that time only the intra-abdominal route was possible (*Messinis and Templeton, 1986*).

What is interesting in these cycles is the number of follicles measuring 12–15 mm in diameter, which was found to be significantly higher in cases without than with an LH surge (*Messinis and Templeton, 1986*, *1987*). This means that the more intense the degree of ovarian stimulation, the greater the chance of the LH surge being markedly attenuated or completely blocked due to overproduction of GnSAF (*Messinis et al., 1986*; *Messinis 2006*). This is particularly important in 'freeze-all' cycles in which the effort is targeted at intense ovarian stimulation in order to obtain as many eggs as possible with one attempt, and therefore the possibility of premature rupture of follicles, when no GnRH analogues are used, is minimized.

TABLE 1 PROPOSAL FOR A DIFFERENT APPROACH TO OVARIAN STIMULATION IN 'FRESH' AND 'FREEZE-ALL' CYCLES

Parameter	'Fresh' cycles	'Freeze-all' cycles
Importance of premature luteinization	Yes	No
Use of GnRH agonists	Yes	No
Use of GnRH antagonists	Yes	No
Progestin priming	No	No
GnRH agonist triggering	Yes	Yes

'Fresh' = fresh embryo transfer.

'Freeze-all' = freezing of all embryos, decided before the start of ovarian stimulation.

GnRH, gonadotrophin-releasing hormone.

It is evident that, under these conditions, the occurrence of a premature LH surge in 'freeze-all' cycles is not a major issue, as it is in 'fresh' cycles, where the use of GnRH analogues is necessary. Nevertheless, it should be noted that even in 'fresh' cycles, in which women are given a GnRH antagonist, multiple premature peaks of LH have been reported with luteinization in about 30% of cases, although this does not appear to affect the outcome of IVF treatment as, due to the uninterrupted administration of FSH, the follicles continue to grow (*Loumaye et al., 2003*; *Messinis et al., 2005*). Regarding GnRH agonists, they are preferable to human chorionic gonadotrophin in 'freeze-all' cycles for the final trigger in order to avoid ovarian hyperstimulation syndrome (OHSS).

It is interesting that luteinization is not always preceded by an increase in LH (*Dozortsev et al., 2020*). This LH-independent luteinization has been observed when administering GnRH analogues. Whether such a small increase in progesterone independent of LH can also take place in cycles without analogues has not been investigated.

As mentioned above, exogenous progesterone is given in order to prevent the rise of endogenous progesterone by blocking the LH surge. However, with either endogenous or exogenous progesterone, the impact on the maturation of the endometrium is expected to be the same. Therefore, administration of exogenous progesterone in these cases is without any substantial reason and could be abandoned. This view is further supported by data from double ovarian stimulation protocols, in which the second stimulation period starts at a time when the concentrations of progesterone are increasing as a result of the first stimulation and triggering and are maintained at high levels, on average above 10 ng/ml, until the day of the second trigger (*Kuang et al., 2014*). However, regardless of the effect on the endometrium, due to wide individual variations, it should not be taken for granted that elevated progesterone will be able to block the pituitary (*Lawrenz et al., 2018*).

Therefore, as an answer to the original question, it becomes clear from the above discussion that the protocol of ovarian stimulation in 'freeze-all' cycles needs to be differentiated from that in cycles with fresh embryo transfer. This differentiation results from the distinct importance of specific parameters in each of the two types of cycle (TABLE 1), such as premature luteinization, which is important in 'fresh' but not in 'freeze-all' cycles, so consequently GnRH analogues should be used to prevent luteinization only in 'fresh' cycles, unless new research shows otherwise. In addition, progesterone priming is not important for either group, while GnRH agonist triggering is necessary for both types of cycle, as it dramatically reduces the incidence of OHSS.

In conclusion, data from the existing literature seem to indicate the need to establish different principles of ovarian stimulation in 'fresh' and 'freeze-all' cycles. Simplified stimulation with FSH alone is probably sufficient in 'freeze-all' cycles. A consensus meeting to revisit the use of GnRH analogues in ovarian stimulation protocols for IVF could provide interesting results.

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