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REVIEW

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The dilemma of the trigger timing in IVF: a review

Hassan Maghraby[1,2], Hesham Saleh[1,2], Ismail L. Fourtia[8], Salah Rasheed[2,3], Mohamed Elmahdy[1,2], Amr S. Abdelbadie[2,4], Federica Di Guardo[5,6*], Panagiotis Drakopoulos[6,7,11], Habib Midassi[9,10] and Ahmed Shoukry[1,2]

Abstract

Background Triggering final oocyte maturation is a pivotal step in modern patient-tailored IVF/ICSI treatment, securing the optimal number of mature oocytes retrieved without compromising fertilization, embryo development, and live birth. Several factors need to be considered when deciding the time of the trigger: the size of the leading follicles, distribution of the follicular cohort, the duration of stimulation, the protocol used for stimulation, and ovarian response status.

Main body The current narrative review aims to appraise all available evidence for determining the proper time for inducing final oocyte maturation following IVF treatment. Moreover, it discusses the impact of the stimulation protocol, follicular size, and magnitude of ovarian response on choosing the proper timing for trigger. Comprehensive literature search of all available articles and relevant articles studying the criteria for timing of final oocyte maturation trigger in IVF/ICSI cycles were included in this review. It was found that leading follicles size of 16–22 mm is associated with the optimum oocyte maturation ratio, size of the remaining cohort of follicles should be ≥ 14 mm, 10–12 days of minimum length of stimulation should be auspicated in normal responders before trigger, and the timing of trigger administration should not depend solely on hormonal levels.

Conclusion In conclusion, the timing of triggering of final oocyte maturation in ICSI cycles should be individualized on a case-by-case basis.

Keywords Final oocyte maturation, Trigger, Criteria, Follicle size, Stimulation phase length, Delaying trigger, Human chorionic gonadotropin, Agonist trigger

*Correspondence:
Federica Di Guardo
fediguardo@gmail.com
[1] Department of Obstetrics & Gynaecology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[2] EFRE (Egyptian Foundation for Reproductive Medicine and Embryology), Alexandria, Egypt
[3] Department of Obstetrics & Gynaecology, Faculty of Medicine, Sohag University, Sohag, Egypt
[4] Department of Obstetrics & Gynaecology, Faculty of Medicine, Aswan University, Aswan, Egypt
[5] Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy
[6] Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan, 101-1090 Brussels, Belgium
[7] School of Medicine, European University Cyprus, Nicosia, Cyprus
[8] Department of Obstetrics & Gynecology, Misrata Infertility Center, Misrata, Libya
[9] IVF Center Ibn Annafis, Sfax, Tunisia
[10] Poseidon Group, Odessa, Ukraine
[11] Institute of Life, IVF clinic, Athens, Greece

Background

The timing of the trigger is an essential part of the successful assisted reproductive technology (ART) cycle. Trigger timing is tailored to retrieve a high proportion of mature and competent oocytes from the available follicular cohort [1]. Nevertheless, limited evidence is available regarding trigger time in different stimulation protocols. In clinical practice, the time of triggering administration mostly depends on the extent of response and follicle size in different protocols [2]. A comprehensive knowledge about pharmacokinetics and pharmacodynamics of the triggering agents is important for answering the following questions: when to end the follicular phase, the ideal triggering agent to be used, its ideal dose, optimal timing of the oocyte retrieval [3, 4].

This review is a comprehensive search of literature regarding the proper timing of administration of the triggering agent in different stimulation protocols and in different patterns of ovarian response to ovarian stimulation.

Comprehensive literature search of all available articles published in English on PubMed and Google Scholar libraries were searched independently from inception till January 2022 using the terms "final oocyte maturation," "trigger," "criteria," "follicle size," "stimulation phase length," "delaying trigger," "human chorionic gonadotropin," and "agonist trigger." Articles which were found to be relevant and studying the criteria for timing of final oocyte maturation trigger in IVF/ICSI cycles were included in this narrative literature review.

Main text

Ovulation trigger in ICSI cycles vs. natural cycles

Stimulated cycles differ from natural cycles in different aspects including supraphysiological follicular and luteal phase steroid levels due to multifollicular development, altered hypothalamic response due to the use of GnRH analogues, and low levels of endogenous gonadotropins during the luteal phase [1]. Moreover, the follicular growth rate is greater during ovarian stimulation cycles (1.69 ± 0.03 mm/day) compared to natural cycles (1.42 ± 0.05 mm/day), and the interval from dominant follicle selection to ovulation was found to be shorter during stimulated cycles (5.08 ± 0.07 days) compared to natural cycles (7.16 ± 0.23 days) [5].

A successful triggering should guarantee an LH exposure adequate for the resumption of meiosis, cytoplasmic maturation, and oocyte competence in harmony with a timely receptive endometrium [6–8]. Optimal triggering means "good yield with minimal or no complications" [9].

Factors influencing the timing of the trigger: when to end the follicular phase?

Timing of the trigger in ICSI cycles has an obvious effect on oocyte competence and endometrium receptivity [10]. Many factors have been studied for the determination of proper timing of trigger administration in ICSI cycles; they include follicle size, serum estradiol (E2) and progesterone levels, peak E2 per follicle, and previous response to ovarian stimulation (COS).

The most important factors influencing the choice of timing of trigger administration in ICSI cycles will be discussed in the current review.

Stimulation Phase Length (SPL)

The duration of gonadotropin stimulation is likely related to oocyte competence and endometrial readiness. Short and long stimulation could compromise ART cycle success [11–15]. In long agonist protocol, there is no clear indication that the duration of stimulation is associated with poor outcome [16–18].

Adding to the complexity of the situation are differential growth patterns of folliculogenesis in poor and normal responders [19–21].

In antagonist protocol, however, a short stimulation phase is associated with poor outcome only in normal responders. Conversely, in low responders, the short stimulation phase was not reported as a disadvantage [22].

A novel concept of "Term Oocyte Maturation" (TOM) has been recently proposed, referring to a minimal essential time to reach oocyte developmental competence [23]. TOM duration of 14 or 15 days could be a safe limit for oocyte competence, just like term pregnancy does for the wellbeing of a child. TOM tends to be shorter in stimulated cycles than in natural cycles due to faster follicular growth rate, higher FSH, and more mural/cumulus granulosa. Interestingly in some studies, deliberately delaying of trigger was not associated with an adverse outcome.

Table 1 displays the main characteristics of studies evaluating the effect of stimulation phase length on ICSI outcomes.

In conclusion, the impact of stimulation phase length on ICSI outcomes could be summarized:

1) A minimum duration of ovarian stimulation is required for oocyte maturation before triggering ovulation (term oocyte maturation).
2) From the best available evidence, a duration of 10–12 days of ovarian stimulation (OS) in normal responder women has been shown to be associated with better success outcomes.

Table 1 Main characteristics of studies evaluating the effect of stimulation phase length on ICSI outcomes

Study/design	Patients	Stimulation protocol	Study groups	Criteria used for triggering ovulation	Statistically significant results ($p < 0.05$)
Martin et al. [16] Retrospective	555 IVF/ICSI cycles from 460 women	Long agonist protocol	G1: 6–9, G2: 10–11 and G3: 12 or more days of stimulation	At least 3 follicles ≥ 18 in mean diameter	Fewer oocytes retrieved in group 3. No diff. in IR, CPR, and OPR
Chuang et al. [17] Retrospective	794 cycles from 545 women	Long agonist, flare, or antagonist protocols	G1: ≤ 9 days, G2: 10–12 and G3: 13 or more days of stimulation	Minimum of 2 follicles ≥ 17 mm in mean diameter	On multivariate analysis, cycles with SPL ≥ 13 days were associated with significantly lower CPR and LBR
Ryan et al. [24] Prospective	663 women	Long agonist, flare, or antagonist protocols	G1: SPL ≥ 13 days G2: SPL < 13 days	hCG was used as a trigger when at least 3 follicles ≥ 18 mm and the majority of the cohort above 14 mm	CPR was dramatically decreased when SPL is 13 days or longer
Alport et al. (2011) [25] Retrospective	140 normal responder women	Long agonist and antagonist protocol	G1: SPL < 10, G2: 10–12 and G3: 12 or more days	When > 3 follicles reached > 17 mm, 10,000 IU u-hCG were administrated	SPL of 11 days was associated with the optimum number of follicles and oocytes. No difference in IR and CPR
Mardesic et al. [18] Retrospective	1448 women	Antagonist	Early responders (received hCG prior to or on day 8) and Normal responders (received hCG after day 8)	hCG was administrated when at least 3 follicles ≥ 17 mm in mean diameter	No difference in the number of oocytes retrieved and OPR between the two groups
Purandare et al. (2016) [26] Retrospective	10,487 IVF/ICSI cycles	Long agonist, flare, or antagonist protocols	Patients arranged from the shortest stimulation period (7 days) to the longest period (16 days)	hCG was administrated when at least 2–3 follicles ≥ 18 mm in diameter	No difference in CPR in both IVF and ICSI cycles with all used protocols
Deepmala et al. (2019) [27] Prospective	136 women	Long agonist and antagonist protocol	Short SPL (< 10 days), medium (10–12 days), and long (> 12 days)	Rec-hCG was administrated when at least 3 follicles ≥ 18 mm in mean diameter	Peak follicles, oocytes retrieved, MII oocytes were found at 11 days of stimulation then falls. No difference in fertilization, implantation, and pregnancy rates

3) Duration of stimulation may have different impacts on women with extremes of ovarian response (hyper and poor responders).
4) Prolongation of ovarian stimulation days to retrieve more oocytes appears to be more beneficial in agonist cycles rather than cycles stimulated with the antagonist protocol.

Sizes of the growing cohort of follicles

Timing of the trigger has been, for more than 3 decades, at least 3 follicles with a diameter of 17 mm or more [28–31].

Table 2 summarizes the main characteristics of the important studies correlating follicular size and several IVF success parameters.

Size of the leading follicle(s) on the day of the trigger

Determination of the follicle size essential for trigger is an important step in COS [37]. Vaginal ultrasound is used during (COS) to monitor follicles of different sizes that grow at different rates, thus adding to the complexity of evaluating their competence [38]. Most specialists tend to agree that oocytes are mainly aspirated from large follicles [28].

This is based on the concept that the cumulus oocyte complex is dissociated easily from the wall of "large follicles" under the effect of hyaluronidase expressed by the hCG trigger [39–43].

Despite this, there is no universal agreement on the minimum follicular size required to obtain a competent oocyte. The cutoff for obtaining a mature M2 oocyte is 16 mm in one view [31], and follicles smaller than 12 mm produce varying stages of oocyte immaturity [39, 44, 45]. Follicles above 22 mm often contain "post-mature" oocytes [31] that demonstrate decreased fertilization rate and impaired developmental competence [46]. To obtain a mature oocyte, an 18-mm cut-off was proposed by some authors [45, 47], 16 mm by others [48]. According to some publications [49, 50], follicles below 14-mm diameter do not contain MII oocytes, both in normal and polycystic ovaries. Moreover, while Dubey et al. [30] observed comparable fertilization rates in oocytes from 16- to 22-mm follicles to those from 22- to 26-mm follicles, Ectors et al. [31] found that follicles of 16–23 mm on the day of oocyte retrieval had higher fertilization rates than those > 23 mm. However, the percentage of good-scored oocytes was demonstrated to increase from 55.4% of follicle size of 16–23 mm to 64.6% of follicles > 23 mm. Knopman et al. tried to find an answer to the question "is bigger better?" [35]. It was found that delaying ovulation trigger to advance follicular growth does not appear to improve IVF outcomes. Indeed, those patients with 2 lead follicles ≥ 20 mm had a reduced (although non-significant) live birth rate (LBR). Although larger follicles are presumed to yield a higher quantity of mature oocytes and subsequently a greater number of resultant embryos, this study suggested that this hypothesis could be flawed as those women with follicles ≥ 20 mm had the lowest ($p = 0.03$) MII oocytes number amongst all women in the study. Moreover, they reported also the lowest 2PN zygotes and blastocyst numbers (although non-significant). Hence, the authors concluded that extension of ovarian stimulation to achieve marked follicular growth should not be done as it was not associated with improved outcomes. Similarly, it was found that a follicular size of 16 mm or more on OPU day is the best predictor of the fertilization potential of oocytes, even superior to the morphological appearance of COC [30]. This finding was also supported by another large study that found that oocytes retrieved from follicles above 18 mm have the best fertilization potential [45]. It can be concluded that follicles 16–22 mm in diameter are associated with the highest chance to retrieve mature oocytes [51], best fertilization protentional, and embryo developmental competence [31, 45].

Size of the cohort of the growing follicles on the day of trigger

The mechanism underlying the individual response of antral follicles to exogenous gonadotropin has not yet been clearly determined [52, 53]. However, it is known that early antral follicles do not necessarily grow coordinately in response to exogenous gonadotropins to reach simultaneous functional and morphologic maturation and that not necessarily all the FSH responding follicles have enough LH receptors to respond to the maturation signal induced by hCG [54, 55].

Moreover, in GnRH antagonist cycles, a physiological increase in the FSH level during the luteal-follicular transition phase provokes a heterogeneous follicular development leading to a slightly lower maturation rate when compared to agonist cycles. During the early follicular phase, early antral follicles present noticeable size heterogeneities that may be amplified during COS [56].

Thus, multifollicular growth may result in heterogeneous size of follicles and variable growth rate and also may cause secondary and tertiary cohorts [57–59].

The follicular size associated with the greatest chance of oocyte yield was studied by Hu et al. [10]. They categorized women treated with antagonist cycles by the proportion of 17 mm/10 mm follicles ratio on the day of trigger, as low (30% ≥ 17 mm), middle (30–60% ≥ 17 mm), or high proportion (> 60% ≥ 17 mm). Oocyte maturation rate in the middle- and high-proportion groups was higher than that in the low-proportion group. Implantation rate, pregnancy rate, and LBR were significantly

Table 2 Main characteristics of the important studies correlating follicular size and several IVF success parameters

Study/design	Patients	Stimulation protocol	Study groups	Criteria used for triggering ovulation	Statistically significant results ($p < 0.05$)
Mohr-Sasson et al. [32] Prospective	640 follicles measured from 204 women	Antagonist protocol	follicles were measured and divided into three groups according to their maximal dimensional size: large: ≥ 16 mm, medium: 15 to 13 mm, and small: < 13 mm	When at least two leading follicles measuring > 17 mm for maximal diameter	Follicles > 13 mm revealed a higher oocyte recovery rate and higher maturity ratio compared to smaller follicles (no diff. between medium and large follicles)
Abbara et al. [33] Retrospective	499 IVF cycles	Antagonist protocol	All follicles > 8 mm were measured, and combinations of follicle sizes were calculated, e.g., number of follicles 8, 8–9, 8–10, 8–11	When two to three follicles reached 17–18 mm in diameter. Trigger was accomplished via either hCG, agonist or kisspeptin	Follicles 12–19 mm on the day of trigger contributed the most to the number of oocytes and mature oocytes retrieved
Hu et al. [10] Retrospective	492 IVF/ICSI cycles	Antagonist protocol	3 groups according to their ≥ 17 mm/ ≥ 10 mm follicles ratio on the day of HCG administration (Low proportion ≤ 30%, Middle proportion 30–60%, High proportion: ≥ 60%)	When at least 3 mature follicles measuring > 17 mm	The number of oocytes retrieved in low proportion group is more than in the other 2 groups. IR, CPR, and LBR in the high proportion group were the highest among the 3 groups
Orvieto et al. (2020) [34] Retrospective	428 follicles measured from 204 women	Antagonist protocol	large: ≥ 24 mm and normal: < 24 mm	When at least two leading follicles measuring > 17 mm for maximal diameter	Non-significant lower oocyte retrieved in the large follicles group. No in-between group differences in MII, fertilization, and TQE rates. Nevertheless, once a zygote (2PN) was achieved, a trend toward a higher TQE rate/2PN was found in the large follicle group
Knopman et al. [35] Retrospective	1577 IVF cycles	Luteal GnRH agonist, antagonist or microdose agonist protocols	Based on the mean diameter of the two largest follicles on the day of trigger: < 18 mm, 18–18.9 mm, 19–19.9 mm, ≥ 20 mm	10,000 units of IM hCG were administered when at least two lead follicles measured 17 mm in diameter	There were no significant differences noted for cycle parameters or outcomes for the 4 groups. However, although LBR was not significantly different, there was a decline noted as lead follicle size increased
Knopman et al. [35] Retrospective	360 follicles measured from 49 IVF/ICSI cycles	Long agonist, flare or antagonist protocols	Group A (mean diameter 12–14.5 mm), group B (mean diameter 15–18 mm) and group C (diameter > 18.5 mm)	When at least two follicles had mean diameters of 20 mm	Significantly higher oocyte recovery rate from large compared to small follicles. In addition, the aspiration of follicles greater than 18 mm. provided the highest probability of retrieving mature oocytes (MII)

Table 2 (continued)

Study/design	Patients	Stimulation protocol	Study groups	Criteria used for triggering ovulation	Statistically significant results ($p < 0.05$)
Dubey et al. [30] Retrospective	2,429 oocytes from 215 patients undergoing 324 stimulated IVF cycles	Long agonist protocol	Large follicles ≥ 16 mm and small follicles ≤ 14 mm	When at least two follicles had a mean diameter of 20 mm, or the E2 level approximated 250 pg/ mL per follicle	Small size follicles are still capable of containing mature oocytes, but their rate of abnormal or no fertilization is high
Ectors et al. [31] Prospective	412 IVF/ICSI cycles from 340 women	Long agonist protocol	Follicles were measured and divided into three groups according to their maximal dimensional size: large: > 23 mm, medium: 16 to 23 mm, and small: < 16 mm	when most large follicles reached 18–20-mm diameter and when serum oestradiol concentration per Introduction developed follicle was ~ 1100 pmol/l	The fertilization rate of all oocytes regardless of morphological type revealed a positive linear correlation with increasing follicle diameter
Das et al. (2013) [36] Retrospective	114 women	Antagonist protocol	According to the leading follicle diameter on the day of trigger: group 1:17–18 mm, group 2: 19–20 mm, group 3: > 20 mm	When ≥ 3 follicles were ≥ 17 mm in diameter	Oocytes from follicles with a mean diameter ≥ 16 mm had significantly higher fertilization rates than did oocytes from follicles with a mean diameter ≤ 14 mm

higher in the high-proportion group compared with the low- and middle-proportion groups.

Another retrospective analysis was conducted by Abbara et al. [33]; they found that follicles with a mean diameter of 12–19 mm have the greatest odds of containing mature oocytes and this finding was noticed with both hCG and GnRH-agonist triggers.

A recent prospective study was conducted by Mohr-Sasson et al. [32] to assess the correlation between follicular size and oocyte and embryo quality. Before oocyte pickup, follicles were measured and divided into three groups according to maximum dimensions: large ≥ 16 mm, medium 13–15 mm, and small < 13 mm. Oocytes were obtained during aspiration from 76.3%, 70.3%, and 55.6% of the large, medium, and small follicle groups, respectively (the difference between medium and large groups was not significant). The mature oocyte (metaphase II) rate was significantly higher in the large ($P=0.001$) and medium ($P=0.01$) compared with the small follicle group. However, no differences were observed in fertilization or top-quality embryo (TQE) rates among mature oocytes regardless of the size of the follicle from which they originated. They reported also that triggering mode (hCG, GnRH agonist, or dual trigger) did not influence oocyte recovery rate in the different follicle size groups.

In conclusion, it appears that the size of follicles (both leading follicles and remaining follicular cohort) at the time of ovulation trigger can influence the likelihood that LH-like exposure can induce oocyte maturation. Most reproductive IVF centers administer the bolus trigger when two to three lead follicles are 17 to 18 mm in diameter provided that follicles grow as a tight representative cohort behind the lead follicle.

In the view of the best available evidence [60, 61], the European Society of Human Reproduction and Embryology (ESHRE) (2020) recommendations about the timing of trigger [62] are as follows: "Most often, final oocyte maturation is triggered at sizes of several of the leading follicles between 16–22 mm as data on specific follicle sizes that are most likely to yield an mature oocyte have predominantly been generated on the day of oocyte retrieval, at which time follicles of 16 to 22 mm are thought to be most likely to yield oocytes" [63].

Hormonal levels as determinants for the timing of trigger

Serum E2 level on the day of trigger administration

Serum estradiol levels during ovarian stimulation greatly vary depending on the size of the growing follicular cohort, the distribution of follicles between different size classes within the growing cohort, and the endocrine situation of the patient and the endocrine milieu of the stimulation cycle [62].

Several observational studies have been conducted aiming to find an association between outcomes of oocyte retrieval in IVF/ICSI cycles and estradiol levels on the day of trigger administration; some studies tried to correlate the estradiol levels (pg/mL) on the day of trigger [64–66] and other studies the effect of estradiol/follicle and estradiol/oocyte ratio as a parameter for triggering ovulation [67, 68].

To the best of our knowledge, there are no interventional studies performed assessing the use of serum estradiol and/or estradiol/follicle as a marker for timing the final oocyte maturation trigger.

Therefore, the guidelines of ESHRE 2020 for ovarian stimulation in IVF/ICSI do not recommend the use of either estradiol level or estradiol/follicle ratio as the sole parameter for the timing of trigger in IVF/ICSI cycles [62].

Serum progesterone (P) level on the day of trigger administration

In spite of the wide use of GnRH analogs during COS for ICSI, a subtle pre-ovulatory rise in the serum progesterone concentration before trigger administration for final oocyte maturation still occurred in 5–30% of COS cycles [69–71]; this phenomenon has been called premature luteinization. It has been recently proposed that "premature luteinization" is not an appropriate term for this condition because premature serum P rise occurs when the serum LH concentration is low. Therefore, excess serum P is unlikely to be produced by the luteinization process and is more probably due to accumulation from a large number of follicles [72–74]. The impact of this "pre-ovulatory" progesterone rise on outcomes of IVF/ICSI remains inconclusive and controversial. The majority of studies have advocated that progesterone rise on the day of hCG trigger adversely affects pregnancy outcome [75–77] due to its harmful effect on the endometrium and implantation process [78, 79] or affecting the quality of the developing oocytes and embryos [80, 81]. An interesting study reported significantly lower LBRs in patients with both low (≤ 0.05 ng/mL) and high (≥ 1.5 ng/mL) progesterone levels on the day of hCG trigger [82]. Nevertheless, other studies showed that progesterone rise does not appear to negatively affect IVF outcomes [72, 83, 84].

A randomized controlled trial showed that if the progesterone level is higher than 1 ng/ml, delaying the administration of hCG by 24 h has no effect on the number of mature oocytes. If the progesterone level is ≤ 1 ng/ml and 30–50% of the follicles have diameters ≥ 18 mm, delaying oocyte maturation by 24 h is advised [85]. However, another RCT [86] describes that even in patients with normal progesterone level (< 1 ng/ml) stimulated

with antagonist protocol, delaying trigger administration by 24 h is not beneficial in any success outcome parameters.

Therefore, there is no sufficient evidence to recommend the use of serum progesterone to determine the timing of trigger administration. However, there are no clear cut-off values for normal and elevated progesterone levels.

Impact of the stimulation protocol on the timing of trigger administration

The question of whether it is better to delay or put forward the time of trigger administration in the different protocols remains elusive [52].

GnRH agonist protocol

In agonist cycles, upon administration of gonadotrophins, follicles are recruited in a backdrop of pituitary suppression, producing a pool of relatively equivalent follicles [87, 88]. In contrast, patients undergoing antagonist protocol maintain pituitary function, whereby endogenous gonadotrophin stimulates a degree of follicular development, augmented with exogenous gonadotrophins. This may induce additional follicle development, resulting in a more heterogeneous cohort of follicles [88].

There is a general agreement that, in GnRH agonist cycles, prolongation of the stimulation phase does not seem to have a detrimental effect on outcomes of IVF/ICSI.

A well-designed RCT by Mochtar et al. [61] investigated the effect of follicular diameter size on ongoing pregnancy rates (OPR) in agonist IVF/ICSI cycles. Women were randomized between timing oocyte collection when the leading follicle had a diameter of 22 mm or when the leading follicle had a diameter of 18 mm. In the 22-mm group, more women reached an ongoing pregnancy in comparison with the 18-mm group with a resulting relative risk (RR) of 1.6 (95% CI = 1.03–2.5). No statistically significant difference was reached for the secondary outcomes: clinical pregnancy rate (CPR) and LBR. The mean days of stimulation were, as predicted, more in the 22-mm group than in the 18-mm group (11.7 vs. 10.7). The mean number of oocytes retrieved and M-II oocytes was significantly higher in the 22-mm group; similarly, the mean number of top-quality embryos was found to be higher in the 22-mm group.

However, it has to be mentioned that to obtain optimal results in ICSI, the real paradigm might not be the stimulation regimens (mild or conventional) themselves but delaying oocyte collection to harvest more oocytes from the growing cohort, which then, in turn, leads to more high-quality embryos [61]. It is important to reiterate that better outcome with larger follicles could be restricted to long agonist protocol because delaying retrieval in antagonist could be associated with a poor outcome [14].

Similarly, another old study suggested that women would benefit from delayed administration of hCG in agonist cycles with proportionately more clinical pregnancies [89].

On the other hand, there are several studies showing no significant advantage of precise timing of hCG trigger in agonist cycles.

A RCT conducted to study different hCG criteria in patients undergoing IVF using the long GnRH-agonist protocol concluded that extending the duration of ovarian stimulation in a long GnRH agonist protocol by 2 days does not affect oocyte retrieval, fertilization, and pregnancy rates [90].

Chen et al. [60] performed a meta-analysis of 7 RCTs; in three trials, women were treated with agonist protocol and in the other four trials with antagonist protocol. Estradiol levels were significantly higher with either 24 h ($p = 0.04$) or 48 h ($p < 0.00001$) delay of hCG administration which reflects relatively more follicles come into maturation. The number of oocytes retrieved in the late hCG group was significantly higher than in the early hCG group (95% CI = 1.11–1.30, $p < 0.00001$), while CPRs and LBRs did not differ between the early and late hCG groups.

In conclusion, delaying the hCG trigger (1–2 days) in agonist ICSI cycles would result in better oocyte yield which in turn may have a positive impact on number of embryos and pregnancy rates; however, this could be associated with increased incidence of pre-ovulatory progesterone rise.

GnRH antagonist protocol

Since antagonist cycles do not involve pituitary desensitization, the ICSI cycle length is shorter than cycles treated with agonists [91].

It was reported that when GnRH antagonists are used, oocyte maturation is obtained at a lower follicle size than when a GnRH agonist is given in the classical "long" protocol [57].

It seems that, in antagonist ICSI cycles, the decision is usually made somewhat earlier than in agonist cycles [85]. In 2006, the Brussels GnRH antagonist Consensus Workshop Group stated that the optimal timing for triggering oocyte maturation when using a GnRH antagonist protocol needed to be explored further [92].

The criteria used for triggering the final maturation of oocytes in GnRH antagonist ICSI cycles are markedly variable between investigators. In the majority of studies, the trigger is administrated when at least 3 follicles ≥ 17 mm in diameter [91, 93–96]. Alternatively, triggering of final oocyte maturation is performed in

the presence of 3 follicles with a maximum diameter of 18 mm [97] or in the presence of 1 follicle of 18 mm and 3 follicles of 15 mm [98]. It would therefore appear that follicles between 15 and 18 mm in diameter have good reproductive potential [99].

A RCT was conducted by Kolibianakis et al. [14] to assess the effect of prolongation of the follicular stimulation phase by 2 days in antagonist ICSI cycles. Patients were randomized to receive the bolus trigger of hCG either as soon as at least three follicles were 17 mm on ultrasound (early-hCG group) or 2 days later after this criterion was met (late-hCG group). A significantly lower OPR rate per retrieval and per transfer as well as a significantly lower ongoing implantation rate was present in the late-hCG as compared with the early-hCG group.

Morley et al. [87] performed a RCT to study the effect of precise timing vs. delayed trigger administration in antagonist cycles. All subjects were monitored daily from day 9 of stimulation until at least three follicles reached a diameter of ≥ 17 mm. Patients were then randomized to receive an injection of 10,000 units of hCG either on that day (group A) or delayed by either 24 h (group B) or 48 h (group C). The pregnancy rates per cycle were not statistically different among the groups.

Tremellen and Lane [99] conducted a retrospective analysis of 1642 IVF cycles to study the effect of advancing or delaying hCG administration by 1 day from the ideal time for the purpose of avoiding weekend oocyte pickups. "Ideal" timing of the hCG trigger administration for the collection of mature oocytes was the presence of two or more follicles ≥ 17 mm in diameter, with the majority of follicles being ≥ 14 mm.

Advancing or delaying trigger had no impact on ICSI outcome. The authors concluded that avoidance of weekend oocyte pickups had no detrimental effect on IVF pregnancy outcomes.

The effect of delaying hCG administration on endometrial development is still a debatable issue [14, 100]. Evidence described that endometrial biopsy taken on the day of oocyte pickup in women administered with hCG either as per normal protocol or with a 48-h delay showed that endometrial development was advanced by up to 3 days in the delayed hCG group [101].

In view of the available evidence, it could be concluded that in antagonist protocol, it seems that triggering oocyte maturation should be more precise (and usually earlier) than in agonist cycles; the timing of trigger should be when at least 3 follicles ≥ 17–18 mm and most of the remaining cohort of follicles are proportionately large follicle (≥ 14 mm) with consideration of appropriate estradiol level (100–400 pg/mL/ oocyte).

Progestin primed ovarian stimulation (PPOS) protocol

Since 2013, different progestins have been used as effective oral surrogates for preventing a premature luteinizing hormone (LH) surge in women undergoing COS. This protocol is called the progestin-primed ovarian stimulation (PPOS) protocol [100, 102, 103]. PPOS has proven effective for patients with a normal response, diminished ovarian reserve, polycystic ovarian syndrome (PCOS), and high body mass index (BMI) [104, 105].

Currently, there are no specific recommended criteria for timing of triggering final oocyte maturation in PPOS; however, the majority of studies investigating this new evolving protocol use dual trigger (a GnRH agonist and different doses of hCG) [106–108], hCG trigger alone [109], or agonist trigger alone [110]. Triggering of final oocyte maturation was performed in most studies when at least there are 3 follicles ≥ 17 mm and the majority of follicles are ≥ 14 mm [100, 102, 103, 106–110].

Influence of the state of predicted response to conventional ovarian stimulation (Normal, poor, or hyper-responders)

The question here "is there a need to also individualize the timing of trigger according to the predicted pattern of ovarian response?" or in other words, does the predicted response to ovarian stimulation affect the trigger timing? There are only a few studies that tried to find a valid answer to this question.

Poor responders

Individualized criteria for timing of ovulation trigger in poor responders are not yet established. Only very few studies tried to find out whether poor ovarian response could impact the timing of ovulation trigger in IVF/ICSI cycles.

Yang et al. [22] studied the effect of ovarian stimulation duration on different IVF population categories. In poor responder women, shorter and prolonged stimulation duration was found insignificant in terms of pregnancy rates.

In a similar study by Kahyaoglu et al. [111], a retrospective analysis of 3194 fresh IVF/ICSI cycles showed that in poor responders, MII oocyte number and fertilization rate were found to be higher with stimulation length between 9 and 12 days. With stimulation length > 12 days, the OPR was significantly decreased.

Aybar et al. [112] investigated if the stimulation phase length could affect IVF outcomes in women with poor ovarian response. They reported that the mean age in women with delayed response (≥ 9 days stimulation) was significantly higher compared to women with stimulation duration 6–8 days. CPR in delayed responders was significantly lower compared to others. However, when

adjusted for age, the number of stimulation days did not have any significant effect on CPR and OPR.

Therefore, it was suggested that women with normal ovarian reserve and poor responder women cannot be judged in the same way during ovarian stimulation, considering early follicular recruitment, follicular growth rate, endometrial receptivity, and the stimulation durations. An optimal FSH stimulation duration together with follicular size criteria, serum estradiol, and progesterone levels are important parameters in determining trigger timing to balance between oocyte maturity and endometrial receptivity.

High responders (PCOS)

There is no absolute consensus on the best time for triggering ovulation in women with PCOS [52]. To the best of our knowledge, there are no interventional studies investigating specific criteria for the timing of final oocyte maturation for PCOS women. There are only a few studies investigating the effect of the duration of ovarian stimulation in PCOS women separately.

It has been hypothesized by some authors that it might be preferable, for example, to administer the trigger earlier in high responders than in normal and poor responders to avoid premature progesterone rise and consequently poor outcomes [2].

As aforementioned, Ryan et al. reported that stimulation longer than 13 days was not associated with decreased ART success for women with PCOS [24, 111].

These findings came in line with the results of a meta-analysis of 793 cycles with PCOS and 1116 matched controls which demonstrated that the duration of stimulation was 1.2 days longer in the PCOS group than in controls [113]. In another relevant study of Lin et al. [52], a new concept of proportion of dominant follicles (PDF) was investigated as a valid criterion for timing of trigger administration in PCOS women with different stimulation protocols. PDF was calculated by dividing the number of ≥ 18 mm follicles/number of ≥ 10 mm follicles on the hCG day. Cycles were divided into three sub-groups according to PDF in the GnRH agonist long protocol and the GnRH antagonist protocol, respectively: group A: PDF below 20%; group B: moderate PDF between 20 and 40%; group C: PDF of more than 40%. Top-quality embryos, implantation rate, and CPR were comparable among the three groups. However, there was a statistically significant increase in moderate and severe ovarian hyperstimulation syndrome (OHSS) with increased PDF. For GnRH antagonist cycles (347/718), the number of fertilized oocytes, available embryos, implantation rate, CPR, and moderate and severe OHSS were comparable between the three groups. From this study, it could be concluded that a PDF of 20 to 40% may be recommended in PCOS either in GnRH agonist long protocol or GnRH antagonist protocol in order to balance the risk of OHSS and the clinical pregnancy.

Conclusions

According to the currently available evidence, we could conclude that:

1. The timing of triggering of final oocyte maturation in ICSI cycles (stimulation phase length) should be individualized on a case-by-case basis.
2. The decision of administration of the trigger in ICSI cycles is multifactorial and many factors should be considered while making such decision as:

    i. Leading follicles size (16–22 mm) is associated with the optimum oocyte maturation ratio.
    ii. Size of the remaining cohort of follicles should be proportionally large follicles (≥ 14 mm).
    iii. The protocol used for ovarian stimulation:

    a) For GnRH agonist protocol: most of the available evidence suggested that prolongation of stimulation 24–48 h in agonist cycles would result in higher oocyte yield and more mature oocyte and in turn better outcomes.
    b) For GnRH antagonist protocol: according to the best knowledge; such a prolongation of stimulation beyond the precise timing (criteria) of trigger seems to have no added benefits in case of poor and high responders.

Abbreviations

ARTs	Assisted reproductive technologies
CPR	Clinical pregnancy rate
COS	Controlled ovarian stimulation
COC	Cumulus oocyte complex
ESHRE	European Society of Human Reproduction and Embryology
GV	Germinal vesicle
IVF/ICSI	In vitro fertilization/intracytoplasmic sperm injection
LBR	Live birth rate
MI	Metaphase I
MII	Metaphase II
OPR	Ongoing pregnancy rates
OS	Ovarian stimulation
PCOS	Polycystic ovarian syndrome
PPOS	Progestin primed ovarian stimulation
PDF	Proportion of dominant follicles
RCT	Randomized controlled trial
RR	Relative risk
SPL	Stimulation phase length
TOM	Term oocyte maturation
TQE	Top-quality embryos

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HS, AS, and HS wrote the first draft of the manuscript. SR and ME contributed to the design and data collection. ASA and FDG contributed to the revision process improving the quality of the paper. PD is responsible for the main concept. All authors discussed the results and contributed to the final manuscript with the specific support of PD.

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Competing interests
PD has been a consultant to Merck Healthcare KGaA (Darmstadt, Germany) from April 2021 till June 2023 and is a Merck employee (Medical Director, Global Medical Affairs Fertility) with Merck Healthcare KGAaA (Darmstadt, Germany) since July 2023. He declares honoraria for lecturing from Merck KGaA, MSD, Organon, and Ferring. The other authors declare that they have no competing interests.

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