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Alteration of final maturation and laboratory techniques in low responders

Lan N. Vuong, M.D., Ph.D.[a,b]

[a] Department of Obstetrics and Gynecology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam; and [b] HOPE Research Center, My Duc Hospital, Ho Chi Minh City, Vietnam

The number and quality of embryos generated from the limited number of oocytes retrieved from low responders are important aspects of infertility treatment for these patients. This article focuses on 5 aspects relating to final maturation and laboratory techniques: follicular size at trigger, dual trigger, artificial oocyte activation (AOA), blastocyst transfer, and the role of preimplantation genetic testing for aneuploidy (PGT-A). There is lack of data regarding the role of follicular size, specifically in low-responder patients, but consideration should be given to using broader follicular size criteria when retrieving oocytes in this patient group. Use of dual trigger seems to be a good strategy in low-responder patients on the basis of initial evidence. Use of AOA with calcium ionophore may improve fertilization, embryonic development, and outcomes in cases with previous developmental problems. There is lack of data for low responders, but this promising technique deserves further study. In unselected patients, clinical trial data on blastocyst transfer are conflicting, and no high-quality studies have evaluated whether the live birth rate is higher after blastocyst transfer than after cleavage-stage embryo transfer in low responders. Specific evidence for PGT-A in low-responder patients is also lacking. Preimplantation genetic testing for aneuploidy should be considered in POSEIDON group 2 patients, especially those aged >38 years. Overall, applying the limited data available in combination with patient preference and individual patient characteristics will ensure a patient-centered and evidence-based approach that should optimize fertility outcomes for low responders. (Fertil Steril® 2022;117:675–81. ©2022 by American Society for Reproductive Medicine.)

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Assisted reproductive technology (ART) strategies for low-responder patients have typically focused on ovarian stimulation and how to increase the number of oocytes obtained. However, in addition to the absolute number of embryos, the quality and number of embryos generated from the limited number of oocytes retrieved from low responders are important aspects of infertility treatment in these patients, because these factors are directly related to patient-centered outcomes, such as the live birth rate.

This article in a series devoted to low-responder patients presents data and recommendations relating to 5 aspects of final maturation and laboratory techniques: follicular size at trigger, dual trigger, artificial oocyte activation (AOA), blastocyst transfer and the role of preimplantation genetic testing for aneuploidy (PGT-A) in the setting of low oocyte numbers.

SIZE OF FOLLICLE AT TRIGGER

In theory, oocyte competence and maturity after stimulation and trigger depend on the size of the follicle that contains it. This would mean that follicles with larger diameters would yield oocytes with greater competence and maturation ability, as described in early studies (1–4). However, if ovarian follicles grow too large, they may not be competent for fertilization (5). These observations and the need to define an optimal follicular size are probably related to the fact that preovulatory follicles in natural cycles reach diameters of 17–25 mm (6). However, smaller follicles may still result in competent oocytes. A better understanding of the relationship between follicular size and oocyte competence and maturation potential is relevant for the treatment of low-responder patients who have smaller numbers of follicles from which to obtain oocytes.

Data from in vitro maturation studies can provide some guidance about the size of follicles from which mature oocytes can be retrieved. Follicles as small as 4 mm in diameter have been shown to contain mature oocytes, and mature oocytes from follicles with a diameter ≤10 mm after human

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Correspondence: Lan N. Vuong, M.D., Ph.D., Department of Obstetrics and Gynecology, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang Street, District 5, Ho Chi Minh City, Vietnam (E-mail: lanvuong@ump.edu.vn).

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chorionic gonadotropin (hCG) priming were associated with fertility outcomes similar to those of oocytes retrieved from larger follicles (7). However, a positive correlation between the size of the dominant follicle and the number of in vivo-matured oocytes retrieved has been reported (8, 9).

Wirleitner et al. (10) evaluated oocyte maturity and blastocyst development in 1,493 individually aspirated follicles based on follicular diameter and volume (8–12 mm/0.3–0.9 mL [small], 13–23 mm/1–6 mL [medium], and ≥24 mm/>6 mL [large]). Although the rate of oocyte recovery from small follicles was significantly lower than that from medium and large follicles ($P<.001$), both fertilization (85.1% vs. 75.3% and 81.4%, respectively) and blastocyst (40.5% vs. 40.6% and 37.2%, respectively) rates per metaphase II (MII) oocyte did not significantly differ between groups with different follicle sizes (10). In addition, the live birth rate actually tended to be higher in pregnancies achieved with the use of oocytes from small vs. medium or large follicles (54.5% vs. 42.0% or 42.7%). These findings suggest that small follicles (8–12 mm in diameter) should be aspirated, because the oocytes obtained have the potential for normal development and may contribute to the achievement of live birth (10). Similarly, another single-center study showed that the fertilization rates and the numbers of top-quality embryos from mature oocytes were not related to the size of the follicle from which they were obtained (11). Thus, despite the fact that the proportion of mature (MII) oocytes was significantly higher among those obtained from large (≥16 mm) or medium (13–15 mm) vs. small (<13 mm) follicles, once the follicle was mature, follicle size had no influence on fertility outcomes (11).

No significant benefit of later triggering (and, therefore, increased follicle size) was found in a meta-analysis of data from 7 randomized controlled trials (RCTs) (1,295 in vitro fertilization [IVF] cycles) (12). Although delaying hCG triggering by 48 hours was associated with a higher fertilization ratio, the ongoing pregnancy rate per oocyte pick-up and the rates of miscarriage and live birth were similar in patients treated with standard trigger timing and those treated with triggering delayed for 24 or 48 hours (12).

In a retrospective analysis of data from IVF cycles, follicles 12–19 mm in diameter on the morning of triggering were the most likely to yield a mature oocyte (13). However, this finding may not be relevant to subsequent fertility outcomes if the outcomes are equivalent for all mature embryos regardless of the size of the follicle they were obtained from (10, 11). In addition, with the trend toward single embryo transfer, obtaining large numbers of mature oocytes may be less relevant (14).

The findings of a recent study suggest that the importance of follicular size may vary according to the type of ART used (15). In Japanese women undergoing treatment for infertility, the fertilization rate among those undergoing conventional IVF was lower for oocytes from small follicles because of a lower proportion of mature oocytes (15). However, for oocytes fertilized with the use of intracytoplasmic sperm injection (ICSI), the development potential (to blastocyst stage) of oocytes from small follicles was similar to that of oocytes from larger follicles (15). These results indicate that even oocytes from small follicles can grow into blastocysts if they can be fertilized. Furthermore, both the blastocyst formation rate and pregnancy rate were not affected by follicular size, as also reported previously (10, 15). However, differences in the influence of follicle size based on the type of ART need to be studied further.

Currently available data are reflected in the 2019 European Society of Human Reproduction and Embryology guidelines on ovarian stimulation for IVF/ICSI, which state that the use of follicle size as a triggering criterion has not been sufficiently studied in any population (16). Therefore, "physicians may choose the follicle size on which final oocyte maturation is triggered on a case to case basis."

Perspectives

Overall, although there are not yet any studies evaluating the role of follicular size specifically in low-responder patients, the overall body of current evidence suggests that consideration should be given to using broader criteria related to follicular size when retrieving oocytes in this patient group. In addition, studies conducted in low-responder populations are required to provide evidence that can be used to inform guidelines facilitating more individualized care for these patients.

DUAL TRIGGER

Exposure to luteinizing hormone (LH) is required to initiate the process of oocyte maturation, and LH-like exposure is a critical step in IVF, enabling the retrieval of mature oocytes. This "trigger" is usually provided through the use of either hCG or a gonadotropin-releasing hormone agonist (GnRHa) (17). Human chorionic gonadotropin was the gold standard for inducing final follicular maturation for a long time. It provides a pharmacologic surrogate for the natural midcycle LH surge. Human chorionic gonadotropin is sufficiently similar to LH that it activates the LH receptor, providing only LH-like activity (17). However, hCG has a substantially longer half-life than LH, and the sustained luteotropic activity that occurs after the administration of hCG trigger has a number of undesirable consequences, including contributing to the development of ovarian hyperstimulation syndrome (17).

Gonadotropin-releasing hormone agonists have a number of potential advantages over hCG trigger. These include stimulating the release of both LH and follicle-stimulating hormone from the pituitary gland, producing a gonadotropin surge similar to that in the natural cycle (17). However, the duration of the LH surge is shorter than that in natural cycles, which results in a dysfunctional luteal phase, increased early pregnancy loss, and lower ongoing pregnancy rates in the presence of standard luteal phase supplementation (18–20). Therefore, in recent years, a "dual trigger" approach has become more popular, combining a small dose of hCG with GnRHa. This approach is thought to be more effective for overcoming impairments in follicular function, oocyte meiotic maturation, and cumulus expansion (21). Retrieving even one more oocyte in poor responder patients has the potential to enhance reproductive outcomes (22).

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Normal Responders

A recent double-blind RCT in normal responder patients undergoing IVF compared oocyte maturation and pregnancy outcomes after dual trigger with outcomes after hCG trigger (23). Patients who received dual trigger for final oocyte maturation had significantly better outcomes for all parameters assessed, including the numbers of oocytes retrieved, MII oocytes, blastocysts, and top-quality blastocysts, and the rates of clinical pregnancy and live birth. The authors concluded that more widespread use of dual trigger might contribute to better IVF outcomes (23). Similar results were reported in an open-label randomized study that also included normal responder patients (24).

Both of the above trials (published in 2020) build on earlier studies that investigated the same question (25–29). The results of these studies had some inconsistencies, but with one exception, all reported some significant differences in favor of dual trigger over hCG trigger alone (28). Most commonly, the implantation and pregnancy rates were significantly higher after dual trigger than after hCG trigger; however, one study reported higher numbers of embryos after dual trigger, without any difference in pregnancy rates (25–29).

Poor Responders

A small number of studies have investigated the utility of a dual trigger approach in patients with diminished ovarian reserve or poor response. In a retrospective cohort study of patients with diminished ovarian reserve, cycles triggered by hCG + GnRHa had significantly higher numbers of retrieved oocytes, mature (MII) oocytes, fertilized oocytes, cleavage-stage embryos, and top-quality cleavage-stage embryos (all $P<.001$ vs. hCG alone) (30). In addition, the clinical pregnancy and live birth rates were significantly higher in the dual-trigger group than in the hCG group (23.1% vs. 8.7%, $P=.004$, and 17.5% vs. 5.4%, $P=.006$, respectively) (30). Higher rates of fertilization, clinical pregnancy, and live birth with dual trigger than with hCG trigger were also reported in another retrospective analysis, although the mean numbers of retrieved oocytes and MII oocytes were similar in the 2 groups (31).

The value of a dual trigger approach was specifically investigated in a pilot study of poor responder patients undergoing IVF (32). Patients meeting the Bologna criteria for poor response were randomly assigned to 1 of 3 different trigger treatments and timings: hCG 36 hours before oocyte pickup (hCG group), GnRHa 36 hours before oocyte pickup + hCG on the day of oocyte pickup (GnRHa group), or GnRHa at 40 hours before oocyte pickup + hCG at 34 hours before oocyte pickup (dual trigger group) (32). The number of top-quality embryos obtained in the dual trigger group (1.1 ± 0.9) was significantly higher than those in the hCG and GnRHa groups (0.3 ± 0.8 and 0.5 ± 0.7, respectively; $P<.02$). Although the between-group differences did not reach statistical significance, the ongoing pregnancy rate was highest in the dual-trigger group (18.2%), followed by the hCG trigger group (9.1%); no ongoing pregnancies occurred in the GnRHa group (32). Although this study was limited by the small number of patients in each group, it provides preliminary evidence for a benefit of dual trigger in poor responder patients and supports further investigation in this area.

Perspectives

The results of a recent meta-analysis aggregated data from the clinical studies highlighted above and confirmed the benefit of dual trigger in terms of oocyte number and quality as well as clinical pregnancy and live birth rates (33). However, the level of evidence was low to moderate, highlighting the need for additional research.

Although the dual trigger approach appears to be a good strategy, there is a lack of data about the value of this approach in low-responder populations. Nevertheless, the ability of combined trigger with hCG and GnRHa to improve both a variety of oocyte parameters (such as the number of oocytes retrieved and oocyte quality) and IVF outcomes (including live birth rate) suggests that it could be ideally suited to implementation in low-responder patients if preliminary data are supported by future robust clinical trial findings.

ARTIFICIAL OOCYTE ACTIVATION

In vivo, a sperm-borne phospholipase C-zeta (PLCz) has been identified as the physiologic trigger of oocyte activation (34). Phospholipase C-zeta enters the ooplasm and cleaves membrane-bound phosphatidylinositol biphosphate 2, yielding diacylglycerol (which initiates zona reaction) and inositol triphosphate (IP3). Inositol triphosphate subsequently binds to receptors located in the endoplasmic reticulum, which causes calcium release from this internal store (35). The resulting calcium ion (Ca^{2+}) flux presents in an oscillatory mode. Any deficiency in these crucial biochemical substances (i.e., PLCz, phosphatidylinositol biphosphate 2, and IP3) will automatically result in a reduction in intracellular calcium, in particular an absence of Ca^{2+} oscillations. These issues can be compensated for by artificially increasing calcium in the oocyte and, thus, inducing oocyte activation.

Successful fertilization requires oocyte activation, which depends on a proper interaction between the gametes, and activation failure results in poor fertilization rates (36–39). An RCT conducted by Fawzy et al. (40) evaluated the effects of artificial oocyte activation with calcium ionophore after ICSI for couples with male factor infertility linked to abnormal sperm morphology or those who had previous ICSI cycles with unexplained low fertilization or inadequate fertilization associated with impaired oocyte morphology. The results showed that artificial oocyte activation with calcium ionophore was superior to ICSI alone with respect to the rates of ongoing pregnancy (36% vs. 23%; $P=.023$) and live birth (33% vs. 18%; $P=.012$) (40).

A prospective multicenter study reported improved embryonic development and pregnancy outcomes after artificial oocyte activation with calcium ionophore (41). The study included couples with complete embryo developmental arrest in a previous cycle (no transfer), complete developmental delay (no morula or blastocyst on day 5), or reduced

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blastocyst formation on day 5 ($\leq$15%); immediately preceding cycles in the same patients constituted the control cycles (41). Although the fertilization rate did not differ between artificial oocyte activation and the control cycles (75.4% vs. 73.2%), further cleavage to the 2-cell stage occurred in significantly more treatment than control cycles (98.5% vs. 91.9%; $P<.001$). In addition, significantly more blastocysts formed on day 5 in the treatment than in the control group (47.6% vs. 5.5%; $P<.05$), and this was associated with significantly higher rates of implantation (44.4% vs. 12.5%), clinical pregnancy (45.1% vs. 12.8%), and live birth (45.1% vs. 12.8%; all $P<.01$) (41).

Perspectives

To date there have been few trials investigating the use of calcium ionophore for improving fertilization and embryonic development, and there is a lack of data on low responders. However, when the total number of oocytes is limited, this technique has promise for improving fertilization and the quality of available embryos.

BLASTOCYST TRANSFER

Blastocyst transfer could be advantageous in ART, because the timing of the embryo's reaching the endometrial cavity is more consistent with what occurs in a natural cycle. As embryo culture systems have improved, there has been a steady shift to blastocyst transfer. However, the results of blastocyst transfer in unselected patients remain controversial. A recent Cochrane meta-analysis of data from 27 RCTs found a higher live birth rate per transfer after fresh blastocyst transfer than after transfer of cleavage-stage embryos (odds ratio 1.48, 95% confidence interval [CI] 1.20–1.82), without any evidence for between-group differences in the rates of miscarriage, multiple pregnancies, or high-order multiple pregnancies (42). However, this analysis included only 539 patients and was not powered to identify subgroups of patients who might benefit from a cleavage-stage embryo transfer. Another systematic review and meta-analysis of reproductive outcomes after blastocyst vs. cleavage-stage embryo transfer included data from 12 studies enrolling 1,200 women undergoing blastocyst transfer and 1,248 women undergoing cleavage-stage embryo transfer (43). Low-quality evidence found no significant difference between blastocyst and cleavage-stage embryo transfer with respect to live birth or ongoing pregnancy (relative risk [RR] 1.11, 95% CI 0.92–1.35; 10 RCTs, 1,940 women, $I^2 = 54\%$), clinical pregnancy (RR 1.10, 95% CI 0.93–1.31; 12 RCTs, 2,418 women, $I^2 = 64\%$), cumulative pregnancy (RR 0.89, 95% CI 0.67–1.16; 4 RCTs, 524 women, $I^2 = 63\%$), and miscarriage (RR 1.08, 95% CI 0.74–1.56; 10 RCTs, 763 pregnancies, $I^2 = 0\%$) (43). There was moderate-quality evidence for a decrease in the number of women with surplus embryos after blastocyst transfer compared with cleavage-stage embryo transfer (RR 0.78, 95% CI 0.66–0.91). Overall, the quality of the evidence was limited by the quality of the included studies and by unexplained inconsistency between studies (43).

Perspectives

The use of blastocyst transfer in unselected patients remains controversial. For patients with a good prognosis, there is now a consensus that it is beneficial to transfer a blastocyst rather than a cleavage-stage embryo. However, for low responders, many clinicians offer transfer of cleavage-stage embryos to reduce the rate of cycle cancellation due to failure of embryos to develop to the blastocyst stage. A non-inferiority RCT is under way to compare blastocyst transfer with cleavage-stage embryo transfer in patients with a poor prognosis undergoing IVF (44). If blastocyst transfer is shown to be non-inferior to cleavage-stage embryo transfer, the adoption of blastocyst transfer for low responders would result in a higher rate of single embryo transfers, reduce the number of multiple pregnancies, and simplify laboratory protocols.

PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY

The risk of fetal aneuploidy appears to be increased in patients with poor vs. normal ovarian reserve, even in younger women (45–48). In addition, the incidence of aneuploid blasts has been found to be higher in women with diminished ovarian reserve, including those with recurrent pregnancy loss (49, 50). However, not every study has shown a higher risk of aneuploidy in older women who have a poor response to ovarian stimulation during IVF (51).

The only currently available clinical strategy that can avoid the transfer of aneuploid embryos is PGT-A. This process involves analysis of the whole karyotype (comprehensive chromosome testing) of an embryo biopsy specimen, and it can use several techniques, including quantitative polymerase chain reaction, array-comparative genome hybridization, single nucleotide polymorphisms array, and/or next-generation sequencing (52, 53). The trophectoderm biopsy of blastocysts is currently the most robust and reliable source of embryonic DNA for PGT-A (53).

If aneuploid embryos are identified, they can be excluded from transfer so that only euploid embryos are transferred, thus reducing the reproductive risks associated with transfer of aneuploid embryos (54). However, PGT-A is only a tool for embryo selection, and the achievement of pregnancy and fertility outcomes depends on a wide variety of factors, of which aneuploidy is only one (54). Preventing the implantation of aneuploid embryos can contribute to a shorter time to pregnancy, lower risk of miscarriage, and minimal residual risk of chromosomal syndromes, but fertility outcomes may not always be improved (54). In a retrospective study of IVF cycles from an academic fertility center, the use of PGT-A in poor ovarian responders with $\leq$4 oocytes retrieved had no effect on the live birth rate (6.6% in the PGT-A group vs. 5.4% in the non-PGT-A group), despite a lower rate of miscarriage in the PGT-A group (55).

The majority of studies evaluating the role of PGT-A in ART have shown that this approach enhances embryo selection, improves the implantation rate, and decreases the miscarriage rate per transfer. However, most of these studies were conducted in subjects with an adequate ovarian response who therefore had at least a moderate number of

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blastocysts available for PGT-A (56–59). This may not be the case for patients with poor ovarian response, who may not have blastocysts available for PGT-A. In addition, there is a lack of data on PGT-A outcomes per retrieved oocyte, which is a relevant metric when seeking to apply this technique in poor responders.

Other issues relating to PGT-A include the cost of the procedure and the time it requires (55). Data from one study suggested that 31 PGT-A procedures would need to be performed to prevent one miscarriage, meaning that this approach may not be not cost effective (55). In addition, the success rate per cycle might be decreased because of the loss of viable embryos due to the need for extended culture, biopsy, and freezing as well as misdiagnosis (55). These factors are especially relevant in poor responder patients who already have a low oocyte yield. In a recent retrospective study, 86.3% of poor ovarian response patients who had ≤4 oocytes retrieved and underwent PGT-A did not obtain a euploid blastocyst for transfer, resulting in an overall live birth rate per retrieved oocyte of 6.6% (55). However, when one euploid embryo was obtained and transferred, the live birth rate per transferred embryo was 50% (55).

When should PGT-A be used?

Recommendations for the use of PGT-A suggest using this technique primarily in the setting of advanced maternal age, recurrent implantation failure, recurrent pregnancy loss, severe male infertility, or elective single embryo transfer (60, 61). Looking specifically at non-responders, it has been suggested that PGT-A should be considered in POSEIDON group 2 patients, especially those aged >38 years (62). The findings of a recent meta-analysis of studies comparing outcomes in patients treated and not treated with the use of PGT-A (63) provide some guidance in the absence of any other data. Overall, the available data showed that PGT-A of blastocyst-stage embryos from women aged >35 years might improve clinical outcomes and live birth rates (63). There was no clear evidence of the use of PGT-A in younger patients, and the majority of the benefit appeared to be in women aged >35 years, in whom PGT-A decreases the miscarriage rate and, therefore, improves the chance of sustaining a pregnancy leading to live birth (63). The fact that PGT-A improved the live birth rate in older but not younger women may reflect the fact that aneuploidy rates are lower in younger women, and therefore, there is no benefit to performing PGT-A in younger women (64–67). It is the higher rates of aneuploidy in older women that make the risk-benefit ratio for PGT-A more favorable.

The use of PGT-A may decrease the number of embryo transfers needed to achieve a live birth over time (cumulative approach) by identifying and excluding aneuploid embryos (63). Meta-analysis data showed that PGT-A cycles in which at least 1 euploid embryo was identified and that proceeded to embryo transfer appeared to show higher live birth rates compared with non-PGT-A cycles, primarily in the older age group (>35 years) (63).

Although it is obvious that PGT-A cannot be implemented in the absence of blastocyst-stage embryos (which is more likely to be an issue in poor responders), there are no data to indicate whether there is a minimum adequate number of embryos that are required for the optimal application of PGT-A. The current American Society for Reproductive Medicine guidelines propose a single embryo transfer after PGT-A, regardless of the patient's age, because this may result in live birth rates that are similar to those after double embryo transfer without PGT-A (14, 56).

Perspectives

The primary goal of using PGT-A in an ART cycle is to identify embryos for transfer that maximize implantation potential while minimizing the risk of pregnancy loss (63). More research is needed to determine the characteristics of couples most likely to benefit from PGT-A, although evidence suggests that this technique is best used in older women in whom the risk of aneuploidy is higher. The lack of robust evidence on which to base recommendations for or against PGT-A is especially relevant for poor responders. Thus, there is an unmet need for additional research in this area. An individualized treatment plan based on the best currently available data is the preferred approach. A decision to use PGT-A in poor responder patients with a low number of oocytes needs to be made in consultation with the couple undergoing ART, taking account of the potential outcomes of each decision. This will ensure a patient-centered and evidence-based approach that should optimize fertility outcomes for this challenging group of patients.

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