When is the right time to stop autologous in vitro fertilization treatment in poor responders?

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Declining oocyte quality and quantity with age are the main limiting factors in female reproductive success. Age of the female partner, ovarian reserve, the patient's previous fertility treatment outcomes, and the fertility center's pregnancy success data for specific patient profiles are used to predict live birth rates with in vitro fertilization (IVF) treatment. The chance of finding a euploid blastocyst or achieving live birth after the age of 45 is close to zero. Therefore, any IVF cycle using autologous oocytes after the age of 45 can be accepted as futile and should be discouraged. The number of mature eggs retrieved and the number of embryos available for transfer are the second most important predictors of pregnancy and live birth after female age. For patients aged ≤45 years, the recommendation for attempting IVF should be given considering the patient's age and the expected ovarian response. Before the start of the IVF cycle, patients with a very poor prognosis must be fully informed of the prognosis, risks, costs, and alternatives, including using donor oocytes. Alternative treatments to improve oocyte quality and decrease aneuploidy have the potential to change how clinicians treat poor responders. However, these treatments are not yet ready for clinical use. (Fertil Steril® 2022;117:682–7. ©2022 by American Society for Reproductive Medicine.)

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Many patients who undergo fertility treatment have a reasonable chance of succeeding in their goal of having their biologic child. However, older, low-responder patients have a very low, or in some cases, nonexistent, chance of becoming pregnant with their autologous eggs. Patients receive most information regarding their treatment options and outcomes from their physicians. Physicians ultimately define what is a reasonable outcome of fertility treatment for their patients and determine when these treatments are "futile" or have a "very poor prognosis." The American Society for Reproductive Medicine Ethics Committee defines "futility" in the treatment of infertility as a chance of live birth of <1% and differentiates futility from "very poor prognosis," which is defined as a live birth rate between 1% and 5%, because these terms may have different clinical implications (1). Physicians use the patient's age, ovarian reserve, and previous fertility treatment outcomes and the fertility center's pregnancy success data for specific patient profiles to predict the chance of live birth for a patient (1). Although it may be straightforward to determine that fertility treatment is futile for a patient with ovarian insufficiency, many low responders do not fall into this category, and when IVF with the patient's autologous eggs should be discouraged remains a controversial issue.

MATERNAL AGE IS THE MOST IMPORTANT DETERMINANT OF IVF TREATMENT SUCCESS

Declining oocyte quality and quantity with age are the main limiting factors in female reproductive success. The age-related decline in oocyte quality is mainly due to the onset of meiosis in the oocyte during fetal life, with the consequent need to maintain chromosomal integrity for decades until meiosis resumes at the time of ovulation. With aging, chromosome segregation errors during meiotic division are increasingly common and lead to the production of oocytes with an incorrect number of chromosomes, a condition known as aneuploidy. Aneuploid embryos typically fail in development and implantation, resulting in early pregnancy loss or a child with

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congenital birth defects. Trophectoderm biopsies of >15,000 blastocysts have shown that the rate of aneuploidy steadily increases after age 31 and reaches 85% at age 43 (2). As expected, miscarriage rates increase with age and exceed 50% in women aged ≥44 years (3). Therefore, a woman's age is viewed as the most important prognostic factor in determining IVF success.

Defining the cutoff age beyond which an IVF attempt should be discouraged remains a controversial issue in assisted reproductive technology. Many practitioners argue that IVF treatment in women >43 years of age is simply futile and recommend proceeding with egg donation (4, 5). However, studies suggest that the age at which IVF treatment using autologous oocytes should be considered futile should be higher (6, 7).

In an early study to determine the age-based chance of achieving a live birth in women aged ≥40 years (n = 2,705, ranging from 40–49 years, with mostly day 3 embryo transfers), the live birth rate per cycle start was 14% at the age of 40, declining to 1%–2% at the age of 44–45, and to 0 over the age of 45 (8). In the same study, the cumulative live birth rate (with an average of 2.3 IVF cycles) was 28% for IVF starting at age 40, declining to 2%–5% for IVF starting at the age of 44–45, and to 0 for IVF starting ≥45 years of age (8). The overall cancellation rate due to poor response was as high as 29% in the oldest patient population (8). Similar IVF outcomes were observed in another study focusing on women ≥42 years of age (range, 42–47 years; n = 843) (9). The live birth rates per cycle were 4.2%, 3.3%, and 0.6% for women 42, 43, and 44 years old, respectively, and there were no live births in women ≥44 years of age (9). In a study examining even older women (range, 45–49 years; n = 1,078), 12% of the patients did not start the planned treatment because of high follicle-stimulating hormone levels or the presence of ovarian cysts, and 29% cancelled their treatment before egg retrieval due to lack of response (7). In this study, although the pregnancy rate per embryo transfer was reasonable (19%), the live birth rate was only 3% per egg retrieval due to a high miscarriage rate (82%) (7). More importantly, among patients 45 years of age, only those with a reasonable response (at least 4 mature oocytes retrieved) achieved a live birth (7).

In more recent studies, similar low pregnancy rates (0–2% live births per cycle start) were observed in women aged 44–45, and no live birth was reported after the age of 45 (10, 11). Although the live birth rate improved somewhat after a large number of cleavage-stage embryos were transferred (five to eight day 3 embryos) at the age of 43 and 44 (the live birth rates per transfer were 14% and 9%, respectively), no clear improvement was seen in the 45-year-old group, with a 1.3% rate of live births per transfer (12).

The studies also used preimplantation genetic testing for aneuploidy to examine the chance of finding a euploid embryo in older women (2, 6). In a multicenter longitudinal observational study, the rate of cycles with euploid blastocysts at the age of 44 and 45 was 18% and 5%, respectively (6). The live birth rate was 57% per single frozen embryo transfer (6). The rate of live births per fresh IVF cycle (freeze all) and preimplantation genetic testing for aneuploidy followed by frozen embryo transfer was 10% at the age of 44 and 2% at the age of 45. These more optimistic results should be interpreted with caution, because patients with <3 antral follicles were excluded (6). Therefore, these results may only be applicable in women with good ovarian reserve and the potential to produce a good number of oocytes after ovarian stimulation. In the same study, no euploid embryo was found in patients aged >45 years (6). Although finding euploid embryos at the age of 46 was reported previously, the study population was limited (n = 4) and had high ovarian reserve for age (the average number of retrieved oocytes was 12) (2).

OVARIAN RESERVE IS A CRITICAL DETERMINANT OF IVF SUCCESS, ESPECIALLY IN OLDER WOMEN

In an IVF cycle, the possibility of obtaining a high-quality euploid blastocyst and a live birth increases as a function of the number of mature oocytes obtained (6, 13–15). Therefore, ovarian reserve represents a very important factor for IVF success, especially in older patients with a low euploid rate. For example, in young women in their early 30s, obtaining even a very small number of mature oocytes (1 to 3) per cycle can still result in a reasonable cumulative live birth rate (21%) (14). In contrast, according to a predictive model using 4,570 women with infertility aged ≥38 years, 4 mature oocytes could result in a cumulative live birth rate per fresh IVF cycle of only 16% in women aged 38–39, 12% in women aged 40–41, 5% in women aged 42–43, and 1% in women aged ≥44 years (13). As expected, according to the same model, an increase in the number of mature oocytes in an IVF cycle improves cumulative live birth rates (13). Specifically, having 12 mature oocytes improves the cumulative live birth rate to 36% in women aged 38–39, 24% in women aged 40–41, and 12% in women aged 42–43 (13). However, in women aged ≥44 years, a cumulative live birth rate of 3% could never be reached, regardless of the number of oocytes retrieved (13).

In 2016, the POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) group introduced a new metric of IVF success, namely, the ability to obtain the number of oocytes needed to achieve at least 1 euploid blastocyst for transfer (16). Subsequently, a calculator was developed that uses a woman's age and sperm source to predict the minimum number of metaphase II oocytes required to obtain at least 1 euploid blastocyst for specified probabilities of success (17). This calculator is intended to be a counseling tool for shaping patients' expectations and preparing them both emotionally and financially for IVF treatment. However, to use this calculator, the "reasonable" success rate still needs to be determined by the physician and the patient.

WHEN IS THE RIGHT TIME TO STOP AUTOLOGOUS IVF TREATMENT IN POOR RESPONDERS?

In all published studies, the chance of finding a euploid blastocyst or achieving live birth after the age of 45 is close to zero. This is strong evidence that the age of 45 can be used

as a maximum threshold for oocyte reproductive competence and fertility in women. Therefore, any IVF cycle using autologous oocytes after the age of 45 should be accepted as futile and be discouraged. The number of mature eggs retrieved and the number of embryos available for transfer are the most important predictors of pregnancy and live birth after female age. For patients aged ≤45 years, the recommendation for attempting an IVF cycle should be given considering the patient's age and the expected ovarian response. The limited data suggest that at least 3–4 embryos are needed to have a chance of live birth at the age of 44 or 45 (7, 18). Therefore, the approach of accumulating embryos with multiple IVF cycles to improve the chance of live birth can be adopted. However, this approach may still not be successful in most of the older low-responder patients and may create great financial and emotional burdens.

The decision to initiate, continue, or stop IVF treatment in poor-responder patients with "very poor prognosis" is more complex than in cases of futility. On the one hand, patients are willing to do anything they can to have a child, even when the chances are very low, and have an interest in making autonomous decisions about their fertility care. On the other hand, the clinician's professional duty is to provide treatment that offers a reasonable chance of success to create a pregnancy. Giving up genetic maternity and moving on to egg donation can be a very difficult personal decision. The patient may have an emotional need to believe that all reasonable treatments for having a child have been tried. However, the number of IVF cycles that is reasonable or adequate before stopping further autologous IVF cycles and moving forward with egg donation is not known and can be different in various scenarios. In younger poor responders, because cumulative live birth rates are higher, it is not inappropriate to try more IVF treatments before recommending egg donation. However, if the patient has had several previous IVF cycles without embryo creation due to failed follicular growth, fertilization, or embryonic development, it is appropriate to stop autologous IVF treatment independently of age.

Clinicians may be concerned about providing care with a very low likelihood of success and must factor in the physical risks that are posed by IVF treatment. For patients with a very poor prognosis, the American Society for Reproductive Medicine Ethics Committee suggests that clinicians may only proceed with the patient's preferred treatment on a limited basis if they determine that the chances of physiologic or psychologic benefit are sufficient to make IVF treatment risks acceptable (1). In addition, before starting the IVF cycle, patients must be fully informed of the prognosis (including high cancellation rates), risks, alternatives, and costs of treatment.

Disagreements or conflicts may arise when patients seek to initiate or continue treatment regarded by clinicians as having either a very low or a virtually nonexistent chance of success. To avoid these conflicts, fertility practices can develop patient-centered policies to guide clinicians' decisions about initiating or stopping treatment due to a futile or very poor prognosis (1). Policies should inform couples of any medical criteria used to accept patients to proceed with IVF. The evidence-based medical reasoning of these criteria should also be clearly communicated to the patient. As an example, the policy may state that autologous IVF treatment will not be offered or continued when it has never resulted in a live birth at the clinic for a particular patient profile (1). As an alternative approach, clinicians can make futility determinations as a team. This may result in easier acceptance of the bad news for some patients because it is the consensus of several clinicians (1). After a poor-responder patient begins IVF treatment, it is important to reevaluate the patient's IVF success with new clinical data and to set (or reset) goals periodically. Frequent discussions may be needed about the steps that will be taken if certain events occur or fail to occur during IVF treatment, and about the decisions regarding when it will be time to stop IVF treatment and examine other options, such as using oocyte donors. These discussions may need to be very specific to avoid misunderstandings.

Although almost all couples prefer to conceive a child with genetic links to both parents, this may not be a practical goal in women of very advanced maternal age or with significantly diminished ovarian reserve (poor responders). The clinician's recommendation to stop autologous IVF treatment when faced with very poor or futile prognoses may help patients by encouraging them to consider alternative ways of achieving parenthood. Because live birth rates per embryo transfer are correlated with the age of the egg donor, rather than the intended parent, and exceed 50% per embryo transfer in many centers, using an egg donor during an IVF cycle can be presented to poor-responder patients as a successful alternative (19).

PROPOSED ALTERNATIVE TREATMENTS TO IMPROVE OOCYTE QUALITY AND DECREASE ANEUPLOIDY

A number of cellular dysfunctions affecting egg quality and the process of meiosis have been implicated in the generation of aneuploidy, including impaired mitochondrial metabolic activity and shortening of telomeres (20). Strategies to correct these dysfunctions to improve oocyte quality and overcome aneuploidy have been attempted, with varying degrees of success.

Mitochondrial Enrichment

Poor oocyte quality has been related to mitochondrial dysfunction and/or low mitochondrial count, as these organelles are crucial for acquiring oocyte competence (21). Therefore, mitochondrial enrichment has been proposed as a potential therapeutic option in patients with infertility to improve oocyte quality and subsequent IVF outcomes (21). Different options are available for mitochondrial enrichment treatments, with 2 main approaches: heterologous and autologous.

In the heterologous approach, mitochondria come from an external source, typically a young, healthy oocyte donor. Heterologous mitochondrial enrichment can be performed by transferring healthy cytoplasm into the patient's oocyte (partial cytoplasmic transfer) or replacing the whole compromised cytoplasm by nuclear transfer of the patient's oocyte into an enucleated donor oocyte (total cytoplasmic transfer).

Partial cytoplasmic transfer was performed by either electrofusion of the donor's enucleated cytoplasm with the recipient oocyte or injection of the donor's enucleated cytoplasm at the same time as the spermatozoon during the intracytoplasmic sperm injection procedure (22, 23). After the first human pregnancy following partial cytoplasmic transfer was reported in 1997, this technique was used in patients with a very poor prognosis (22, 24). In 2001, the Food and Drug Administration suspended the use of this procedure due to ethical and technical concerns, as the introduction of foreign cytoplasm leads to mitochondrial heteroplasmy in the patient's oocyte, which may lead to unpredictable consequences not only for the developing embryo but also for the offspring's subsequent long-term health (25).

Total cytoplasmic transfer was proposed to avoid mitochondrial heteroplasmy in the offspring and its potential unknown consequences. Germinal vesicle (GV), spindle, and pronuclear blastomere transfer are different ways of relocating the genetic material from a patient's compromised oocyte to a healthy cytoplasm. However, while reducing mitochondrial heteroplasmy, these techniques were not able to eliminate it.

In 1999, the first GV transfer in humans was performed (26). In subsequent studies, human oocytes reconstituted with GV nuclei were shown to undergo maturation, fertilization, and early embryonic development (27). No live births and healthy offspring have been described with GV transfer in humans so far, probably due to the currently poor efficiency of the in vitro maturation technique.

In spindle transfer, nuclear genetic material, assembled in a spindle structure in the metaphase of the second meiosis, is transferred from the patient's oocyte to an enucleated healthy oocyte of the same developmental stage. The first human live birth by spindle transfer was reported in 2017 in a woman with Leigh syndrome, which is caused by mutations in the mitochondrial deoxyribonucleic acid (28). After spindle transfer, the patient successfully gave birth to a boy with low levels of mutation (28). In 2020, a proof-of-concept study was published showing the feasibility of spindle transfer to overcome embryonic developmental arrest due to poor oocyte competence in a mouse model (29). Pronuclear transfer involves relocating the 2 pronuclei from the compromised zygote to an enucleated healthy zygote. This technique was previously used to overcome early developmental arrest in human embryos and resulted in pregnancy in a woman with infertility (30). In 2015, the United Kingdom approved reduction of the risk of mitochondrial deoxyribonucleic acid disease transmission by means of spindle transfer and pronuclear transfer techniques (31). However, these techniques need to be further optimized and their safety needs to be further studied before they are offered to patients with infertility.

Autologous mitochondrial transfer arose as a new methodologic approach, termed oocyte rejuvenation, to eliminate the unpredictable detrimental consequences of mitochondrial heteroplasmy. In autologous germline mitochondrial energy transfer technology, ovarian germline stem cells were used as an autologous source of high-quality mitochondria (32). In this technique, the patient undergoes laparoscopy for ovarian cortex retrieval to isolate oocyte precursor cells by flow cytometry with the human VASA analogue DDX4 antibody (28). Then autologous mitochondria obtained from these cells are injected into the patient's oocyte at the time of intracytoplasmic sperm injection, along with the spermatozoon. Although initial studies demonstrated promising results (32, 33), a randomized, controlled trial did not show improvement in the clinical outcomes of patients with poor prognosis with the use of this technique (34).

Reactivation of Telomerase Activity

Sufficient telomere length is pivotal for accurate chromosomal alignment as well as adequate function of the meiotic spindle during meiosis, both of which prevent aneuploidy in embryos (35). In addition, telomere attrition can be involved in embryonic fragmentation and developmental arrest (36). In aging oocytes, the significant causes of telomere attrition are the accumulation of reactive oxygen species (37) and loss of telomerase activity (38). In murine models, reactivation of telomerase activity in mice lacking telomerase restored the number of pups and improved fertility (39). However, reactivation of telomerase activity has not been used successfully in human oocytes.

Other Investigational Strategies

One of the proposed techniques to treat trisomy is the use of the CRISPR/Cas9 system to eliminate targeted chromosomes (40). This approach was able to eliminate the extra chromosome in aneuploid mouse embryonic stem cells and human induced pluripotent stem cells with trisomy 21 (40). Another focus is to generate human oogonia from induced pluripotent stem cells in vitro (41). However, these techniques have not been sufficiently developed to ensure the efficacy and safety needed for use in patients with infertility.

CONCLUSION

In conclusion, the reality of reproductive success rates clashes with the high expectations of many patients undergoing IVF treatment, particularly in poor responders. The decision of when to stop autologous IVF treatment is not straightforward for many poor responders, and this decision should be made collectively with the patient after adequate counseling. The woman's age and the anticipated number of mature eggs or embryos are the most important factors affecting this decision. Autologous IVF after the age of 45 can be accepted as futile for poor responders and should be discouraged. For patients aged $\leq$45years, the physician should be fully transparent about the success rate of IVF as determined by the woman's age, expected ovarian response, and previous fertility treatment outcomes. If the patient believes that this expected success rate, as poor as it may be, is "reasonable" for her, IVF treatment can be attempted. If the patient has recurrent failure of follicle growth, fertilization, or embryonic development, it is appropriate to stop autologous IVF treatment independently of age and to offer alternatives, including using donor oocytes. In the future, alternative treatments to improve oocyte quality and decrease aneuploidy have the

potential to change how clinicians treat poor responders. However, these treatments are not yet ready for clinical use.

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