Do not increase the burden for poor responders

Since the introduction of gonadotropins for ovarian stimulation for the purpose of multiple follicular recruitment for in vitro fertilization (IVF), it was recognized that patients respond differently to the same stimulation protocol and dose. Some respond with a large number of eggs, some with moderate, some with low, and some without any developing follicles. There are no universally accepted definitions for these patients. Over the years, multiple approaches have been used to increase the number of eggs in low responders. Most of these approaches involve increasing the dose of medications or adding adjuvant and often expensive therapies. Most of these therapies have not been subjected to well-designed randomized controlled trials. Yet, many of these therapies are still used commonly, mostly in the United States, despite the lack of clear efficacy. The main outcome for these challenging patients is the live birth rate and not the ovarian reserve markers or the number of retrieved oocytes. Converting a low responder to a moderate or high category is not achievable in the large majority of cases. As such, the main aim of treatment for these patients is not to increase the burden of treatment, in terms of cost, stress, and office visits.

We are all too familiar with adjuvant interventions in reproductive medicine, such as human growth hormone (1), which have been proposed to improve response to controlled ovarian stimulation and live birth rates among poor responders. Unfortunately, we have yet to find an adjuvant intervention that provides clear and high-quality evidence demonstrating improvement in live birth rates (2, 3). Considerable research has been conducted comparing stimulation protocols for poor responders with no clear evidence of superiority. It is important to consider circumstances where "less is more," particularly with poor responders. For example, minimal stimulation protocols for poor responders have similar outcomes to standard protocols with significantly lower financial burden for patients (4). Mild/minimal stimulation protocols significantly decrease the cost and allow patients to have repeat stimulations instead of draining their resources with 1 expensive treatment. Despite the endorsement of the Practice Committee of the American Society for Reproductive Medicine for the use of these protocols and providing evidence of similar efficacy to standard protocols, physicians have been slow or resistant to the adoption of these treatments.

Diaz-Garcia et al. (5) present a well-designed randomized controlled trial with parallel assignment of 34 women with poor ovarian response according to the European Society of Human Reproduction and Embryology criteria. Patients were randomized to laparoscopic ovarian fragmentation in only 1 ovary vs. no intervention in the control group. This allowed for women receiving intervention to serve as their own internal controls while being compared with women who did not receive the intervention. After the intervention, ovarian reserve biomarkers were collected biweekly for 6 months. Ovarian stimulation for IVF was initiated after a doubling of antral follicle count (AFC) or at the end of the follow-up period. The primary outcome was number of metaphase II (MII) oocytes. The secondary outcomes included AFC, serum antimüllerian hormone, and reproductive outcomes (e.g., live birth rate). Exploratory outcomes included surgical results and gene expression/protein expression analyses reflecting Hippo pathway inhibition (YAP phosphorylation and expression of YAP target proteins, *CCN* and *BIRC*) (5).

Ovarian fragmentation for follicular activation (OFFA) was associated with statistically significant increases in the intervention ovary compared with the control ovary and total AFC in the OFFA group compared with the control group. Ovarian fragmentation for follicular activation did not improve serum levels of antimüllerian hormone or follicle-stimulating hormone. In the control group, 33 MII oocytes were retrieved, and 18 embryo transfers were performed with pregnancy and live birth rates of 20% and 18.7%, respectively. In the OFFA group, 23 MII oocytes were retrieved, and 11 embryo transfers were performed with pregnancy and live birth rates of 13.3% and 6.7%, respectively. Among those who underwent OFFA, molecular expression analysis confirmed an 18.8% reduction in phosphor-YAP/YAP ratio and *BIRC* and *CCN* overexpression. The study investigators concluded that among women with poor ovarian response, OFFA resulted in an increase in AFC but did not modify IVF outcomes compared with controls.

When considering the findings of this investigation, there are important limitations that warrant discussion. A major limitation in study design is related to differences in time to stimulation. The wait time to start the IVF treatment was on average 2 months earlier in the surgical group compared with that in the control group. Although the investigators stress that this was not statistically significant, it could be clinically significant for the control group because the wait time was 155 days. It is also unclear why the investigators expected an increase in the AFC over time in the control group. The number of mature eggs was lower, although not significant, in the treatment group than in the control group as well as the live birth rate. This study was not adequately powered to detect differences in live birth rate, which is the most important outcome for our patients. Despite known endometriosis being an exclusion criterion, 26% of participants were found to have endometriosis at the time of surgery. It is unclear how this diagnosis could affect ovarian stimulation. Rightfully, the study investigators conclude that this intervention should not be recommended given findings showing lack of benefit.

Ovarian fragmentation for follicular activation involves a complex laparoscopic procedure that requires a high degree of surgical expertise. In addition, this procedure will require the presence of laboratory personnel trained in this new technique. Furthermore, such an intervention exposes patients

to an increased financial cost and risk of surgical complications. Although there are patients who are willing to pay for expensive adjuvant interventions with hopes of improving their fertility treatment outcomes, it may not always be in their best interest. It is our duty as fertility specialists to rigorously evaluate emerging therapies and interventions to provide high-quality, evidence-based care. In this case, we clearly recognize that the benefits of this adjuvant intervention do not justify the potential risks and financial costs. Therefore, it should not be recommended for the improvement of IVF outcomes among poor responders.

Benjamin S. Harris, M.D., M.P.H.
Suheil J. Muasher, M.D.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University Medical Center, Morrisville, North Carolina

https://doi.org/10.1016/j.fertnstert.2022.01.022

REFERENCES

1. Cozzolino M, Cecchino GN, Troiano G, Romanelli C. Growth hormone cotreatment for poor responders undergoing in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril 2020;114:97–109.
2. Kyrou D, Kolibianakis EM, Venetis CA, Papanikolaou EG, Bontis J, Tarlatzis BC. How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril 2009;91:749–66.
3. Sood A, Mohiyiddeen G, Ahmad G, Fitzgerald C, Watson A, Mohiyiddeen L. Growth hormone for in vitro fertilisation (IVF). Cochrane Database Syst Rev 2021;11:CD000099.
4. Practice Committee of the American Society for Reproductive Medicine. Comparison of pregnancy rates for poor responders using IVF with mild ovarian stimulation versus conventional IVF: a guideline. Fertil Steril 2018;109:993–9.
5. Díaz-García C, Herraiz S, Pamplona L, Subirá J, Soriano MJ, Simon C, et al. Follicular activation in women previously diagnosed with poor ovarian response: a randomized, controlled trial. Fertil Steril 2022;117:747–55.