Fewer medications for in vitro fertilization can be better: thinking outside the box

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The practice of using ovarian stimulation with gonadotropins for in vitro fertilization (IVF) was started by Dr. Georgeanna Seegar Jones and the Norfolk IVF program in 1981. This led to the birth of Elizabeth Carr, the first IVF baby born in the United States, on December 28, 1981. At the time, the stimulation protocol consisted of administering 150 IU hMG IM daily, starting on the third day of menstruation and continuing for an average of 7 days, after which 10,000 IU hCG was administered IM followed by laparoscopic egg retrieval ~36 hours later (1, 2). We recall that the average number of eggs retrieved was 2–3, and we remember well how all of the IVF team and the patient were extremely happy when more than three eggs were retrieved. In the early days of IVF, it was extremely uncommon to retrieve more than ten oocytes, multiple pregnancy was rather uncommon, and ovarian hyperstimulation syndrome (OHSS) was somewhat rare.

Obviously, the practice of IVF and stimulation protocols are very different now from the earlier years. Two main reasons contributed to the increase in the dose of gonadotropins used: 1) An increase in the dosage has been attempted for low responders to decrease the cancellation rate and increase the number of oocytes; and 2) the advantage of obtaining multiple oocytes was clear and preferable to patients as embryo cryopreservation became available. A third, equally important, reason was the introduction of GnRH agonists for suppression of the pituitary reproductive hormones before treatment, which led to increase in the dosage and the duration of treatment. Later on, dual suppression with oral contraceptives and GnRH agonists resulted in a further increase in the dosage of gonadotropins used. In addition, transferring multiple embryos (in many cases more than three) resulted in higher success rates. With improvements in all aspects of IVF methodology, including stimulation protocols, culture conditions, and embryo transfer, success rates improved significantly and, as a result of higher implantation rates, multiple pregnancy became a prime concern. Over the last 10 years, a reduction in the number of embryos transferred has dramatically decreased the incidence of high-order multiple pregnancies (triplets or higher) without compromising overall success rates. The current standard practice is to transfer only one or two embryos in favorable-prognosis patients and to limit the number to three in others (3). The purpose of the present editorial is to question the appropriateness of using aggressive ovarian stimulation protocols in IVF, with its associated increased cost and higher risk of OHSS in some patients, and to point out the many advantages of mild stimulation protocols. It is time to pause, and to think outside the box.

Mild stimulation protocols refer to the use of “soft” or low-dose medications to produce more than one oocyte but not necessarily a high number (more than ten). Gonadotropins, in the dose of 100–150 IU per day, can be used starting in the early follicular phase with a GnRH antagonist added after 5–7 days to prevent an LH surge. In a recent publication, using low-dose gonadotropins, 150 IU per day starting on the fifth day of the cycle, resulted in a lower number of oocytes obtained compared with a conventional protocol, but a significantly higher implantation rate (4). Heijnen et al. (5), in an elegant randomized study, demonstrated similar cumulative live birth rates over 1 year of treatment with a mild gonadotropin/antagonist protocol and single embryo transfer compared with a conventional long GnRH agonist protocol and transfer of two embryos. Clomiphene citrate in the dose of 100 mg per day, from cycle day 3 to 7, can be used with the addition of low-dose gonadotropin (100–150 IU per day) starting on cycle
day 8 and GnRH antagonist starting on cycle day 10 or 11. This protocol of using clomiphene citrate/low-dose gonadotropin/±GnRH antagonist compared very favorably with a long suppression protocol with GnRH agonist regarding pregnancy rates per fresh transfer (6).

The advantages of mild stimulation are many and include a much lower cost of medications, fewer days of monitoring with ultrasound and blood assays, and a much reduced risk of OHSS. The number of days of injections (in the case of clomiphene citrate/gonadotropins) is much less, and the total dose of gonadotropins used is significantly less compared with conventional protocols. In addition, many patients do not elect to cryopreserve excess embryos (owing to the lack of insurance coverage or ethical and moral issues) and thus find mild stimulation protocols to be an attractive option. In clinical practice, it has always seemed awkward to retrieve 20 oocytes, for example, and end up with 10–15 embryos of good quality only to discover that the patient does not want to cryopreserve the excess embryos. Even though cryopreservation of excess embryos offers many advantages to patients in terms of cost and convenience, and is discussed with patients before the start of treatment, some patients change their mind and elect not to proceed with cryopreservation. In some cases, the cost of minimal-stimulation IVF compares favorably with the cost of freezing, thawing, and transfer of cryopreserved embryos.

Pregnancy rates per transfer with mild stimulation protocols compare very favorably with conventional protocols, especially because the number of embryos transferred is usually limited to two or three (7). In a prospective randomized clinical trial, mild stimulation produced a significantly lower rate of aneuploidy with preimplantation genetic screening (PGS) and a higher ongoing pregnancy rate per transfer compared with a conventional protocol (8). In a recent large prospective study (n = 806), increasing the dose of gonadotropins resulted in a lower cycle cancellation rate but also a significantly lower pregnancy rate, possibly owing to adverse effects on the endometrium (9).

The advantages of mild stimulation protocols particularly apply to low-responder patients regarding cost, convenience, and success rates. Historically, the starting dose of gonadotropins was increased in low responders in the late 1980s without a significant increase in pregnancy rates (10). To our knowledge, there has not been a large randomized prospective study conducted that demonstrates a better ongoing pregnancy rate in low responders with increasing the gonadotropin dose to 300 IU per day or more. Klinkert et al. (11), in a small (n = 52) randomized prospective study in patients with poor ovarian reserve (antral follicle count <5), reported no differences in success rates with a starting dose of gonadotropins of 300 IU per day compared with 150 IU. In addition, a prospective randomized study (n = 145) in low responders demonstrated higher pregnancy and implantation rates with a mild stimulation protocol (clomiphene citrate/gonadotropins/GnRH antagonist) compared with a conventional protocol (GnRH agonist suppression/gonadotropins) with much higher doses of medications (12). We are always intrigued in reviewing stimulation protocols of low responders who failed IVF and cannot help noticing that the total dose of gonadotropins often exceeds 4,000 IU, with an associated higher cost. We believe that the practice of using high doses of gonadotropins provides “a comfort level” for physicians and patients, “that they are doing everything possible,” but without a proven significant effect on IVF outcome in low responders.

Mild stimulation should also be an attractive option for high responders. Patients who have anovulation due to polycystic ovarian syndrome, good ovarian reserve as demonstrated by the antral follicle count by ultrasound or cycle day 3 FSH and LH levels, and peak E2 levels >3,000 pg/mL, and/or retrieval of >15 oocytes in an earlier IVF treatment, need to be stimulated with minimal medications to reduce the risk of OHSS. This is one of the most dreadful complications of IVF and we believe that the incidence of this complication is generally underreported, especially in high responders. We believe that it is wrong to aim to recruit more than ten oocytes in a patient, with very few exceptions. High-responder patients generally do very well with a dose of gonadotropins in the range of 100–150 IU per day as well as with a clomiphene citrate/gonadotropin protocol. We believe that mild stimulation should be discussed as an option with these patients before treatment is started, because the risk of severe OHSS is reduced to a minimum with this approach (13).

The aim of ovarian stimulation for IVF is the recruitment of multiple fertilizable oocytes. In the early days of IVF, stimulation protocols were simple (only one form of gonadotropins was available) but pregnancy rates were also generally low. Over the years, success rates have continuously increased owing to improvements in all aspects of the IVF technology, such as the availability of GnRH analogues to prevent a premature LH surge, better culture conditions with blastocyst transfer in some patients, and improvement in transfer techniques. The stimulation process, however, remains as the most stressful experience for the patient, with multiple injections, blood drawings, and ultrasounds. The cost of medications also adds, sometimes significantly, to the overall high cost of the treatment. With so many conventional stimulation protocols available to us, we (physicians as well as patients) sometimes forget that the object of IVF is to have a healthy live birth, and not necessarily to obtain an excessive number of eggs in a given cycle. The time has come to challenge the concept that the more eggs, the better. We fondly remember our mentor, Dr. Georgeanna Seegar Jones, who, when occasionally she did things that seemed unconventional and we questioned her about it, would respond: “The party line is not always correct.” She was often correct.

REFERENCES