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Textbook of Minimal Stimulation IVF

Milder, Mildest or Back to Nature

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3 Mild Approaches: A Whole Different Philosophy in IVF Approaches—An Overview

Alejandro Chávez-Badiola

INTRODUCTION

Over the last 25 years, several protocols for ovarian stimulation have been developed for *in vitro* fertilization (IVF) treatment, aiming to produce enough oocytes that will result in a reasonable cohort of embryos to select from at the time of embryo transfer. However, increasing concerns are being raised about stimulation protocols, which seem to have become too extreme and too expensive.[1]

Current ovarian stimulation is physically and emotionally demanding. Furthermore, these protocols carry the risk for potentially serious complications for patients and their offspring, such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies, complications that are usually underestimated.[2]

Success rates are now use to attract the potential patient, which sometimes translate into treatment denial to patients with a poor prognosis [older patients and those with "high" follicle-stimulating hormone (FSH) levels], high number of embryos being transferred, risking multiple pregnancies, and long high-dose stimulation regimens being prescribed as daily injections regardless of the discomfort patients have to go through. In other words, nowadays, standard IVF protocols seem to have shifted from being patient-driven to becoming statistic-driven treatments.

In response to all of the above, milder approaches to IVF have been suggested, aiming to reduce treatment complexity, costs and other burdens imposed on patients. These so-called "patient friendly approaches" are mainly focused on reducing the total dose of stimulation drugs, retrieving fewer but the best quality oocytes in each cycle, and transferring fewer (usually one) embryos.

In this chapter, we will focus on natural cycle IVF and minimal stimulation IVF, defined as an IVF cycle where minimal ovarian stimulation is applied, aiming to retrieve few best quality oocytes in the hope to give patients the best chance of a singleton pregnancy while limiting the burdens imposed by standard IVF approaches, offering risk minimization and maintaining cost-effectiveness.

CLINICAL DISCUSSION

Minimal stimulation IVF relies on small doses of medications given for a few days only, causing few side effects and lesser interference with the ovarian physiology. There are several protocols for minimal stimulation that vary from the cycle preparation to the medication used for stimulation and ovulation induction. The most important protocols recently published in literature are presented in Table 3.1.

Clomiphene citrate

Clomiphene is an estradiol antagonist that targets receptors at the hypothalamus and thus, results in FSH elevation and ovarian stimulation. Furthermore, the continuation of Clomiphene administration for a long time during stimulation has proven to effectively suppress spontaneous ovulation.[3]

As described by Teramoto and Kato[3] in the largest trial on minimal stimulation (44,345 IVF cycles) published yet, this protocol aims to produce 3 to 8 follicles and, although with close attention to detail and great flexibility, it follows these basic steps:[3,4]

- Clomiphene is started on day 3 (50 mg/day), and continued until the day before ovulation triggering [relying on clomiphene's potential to successfully inhibit the premature luteinizing hormone (LH) surge].
- FSH is started on day 8 (150 IU every other day) and continued until the day before ovulation induction, provided more than two follicles develop.
- Gonadotropin-releasing hormone (GnRH) agonist nasal spray (250-600 μg) is used for final oocyte maturation when the dominant follicle has reached 18 mm in size.
- Oocyte retrieval is performed 32-35 hours following GnRH agonist nasal spray administration.

Overall, the live-birth rate (LBR) published in this paper was 11% per started cycle when patients over 45 years were included and 28% per started cycle when only patients under

Table 3.1: Minimal stimulation protocols presented according to the main drug used for stimulation

Clomid	*Letrozole*	*FSH*	*GnRH antagonist*	*Ovulation induction*
D3	-	D8 (EOD)	-	GnRHa (NS)
-	D1	D5 (QD)	LF 14 mm (SC/QD)	hCG (IM)
-	-	D5 (QD)	LF 14 mm (SC/QD)	hCG (IM/SC)

D = day; EOD = every other day; QD = once a day; SC = subcutaneous; IM = intramuscular; NS = nasal spray; LF: leading follicle.

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30 years were considered.[3] Similar results have been achieved by other authors using a Clomiphene-based protocol, where pregnancy rates (PR) as high as 35% per started cycle have been reported in patients less than 35 years.[5]

Premature ovulation, a major concern in minimal stimulation cycles, is kept at a very low rate when this protocol is followed, supporting the effectiveness of Clomiphene in the suppression of ovulation. However, close surveillance on LH levels is required in order to identify those cases of premature LH surge and further reduce the rather high rate of started cycles in which no oocytes are collected (around 19%).[3,6]

Letrozole

Letrozole is a nonsteroidal aromatase inhibitor, which seems to increase FSH production and FSH receptors within the ovary,[7, 8] achieving effective ovarian stimulation.[9]

One of the few published protocols using Letrozole for young patients in an IVF setting has shown encouraging results (27% ongoing PR per started cycle). This protocol can be summarized in the following keypoints:[9]

- Previous cycle preparation with oral contraceptives (OCP)
- Letrozole (5 mg/day) for 5 days, starting from day 4 since stopping OCP.
- Human menopausal gonadotropin (hMG), (150 IU/day) from the last day of Letrozole administration and until the day before ovulation triggering.
- GnRH antagonist (Cetrotide, 0.25 mg) daily injections when the leading follicle reaches 14 mm.
- Human chorionic gonadotropin (hCG), (10,000 IU), single dose, when leading follicle reaches 18-20 mm.
- Oocyte retrieval performed 35 hours following hCG injection.

A previously published paper, presented during an American Society for Reproductive Medicine (ASRM) meeting, with serious deficiencies in methodology, stated an increased risk of malformation rate with the use of Letrozole as an ovulation inducing agent.[10] However, larger and better designed studies have been unable to confirm these dubious results.[11]

Gonadotropins

Based on the use of lower doses of FSH and a shorter stimulation period, these protocols mainly vary in the timing to start ovarian stimulation. Protocol schedules are presented in the following key points:

- FSH (150 IU), starting on day 5 of cycle.[12] Alternatively, FSH is started when the leading follicle reaches 14 mm.[6]
- GnRH antagonist (Orgalutran 0.25 mg) cotreatment, started as daily injections when the leading follicle reaches 14 mm.
- hCG (10,000 IU), administered as a single dose, when leading follicle reaches 18 mm.
- Oocyte retrieval 34-35 hours following hCG injection.

A remarkable result was published in one of these studies, suggesting that the total number of chromosomally "healthy" embryos was the same (1.8) for both, standard stimulation and minimal stimulation protocols despite the lower number of oocytes retrieved and available embryos in the minimal stimulation group of patients.[12]

RESULTS

Results in IVF should be assessed more completely than they are today, since pregnancy rates are no further good enough as exclusive outcome measures. It is not only important to achieve acceptable live birth rates (LBR) but it is also important to lower the incidence of associated complications to reduce the overall burden for patients (reducing drop-out rates), and to provide cost-effective treatment.

Pregnancy Rates

Mild approaches not only focus on ovarian stimulation but also tend to be offered along with single embryo transfer (SET). This is especially important when comparing results against conventional IVF treatments, where multiple embryo transfer is common practice.

Published reports on success rates with minimal stimulation protocols range from 11% (LBR in all age groups) to 37% pregnancy rate (PR) per started cycle.[3, 5,9,13] When put in perspective, these results do not deviate much from the results of standard IVF (16-67% PR per embryo transfer).[14]

Since replacing a higher number of embryos would yield a higher pregnancy rate, traditional IVF protocols tend to transfer a higher number of embryos, promoting a higher incidence of multiple pregnancies, which should not be considered as successful treatment. A recently published study adjusted success rates for IVF programs by removing triplets and higher order multiple pregnancies from the statistics. By recalculating the live-birth rates taking these into account, the results decrease by around 10-15% from the initially reported results, which are closer to those obtained with minimal stimulation protocols.

It has been suggested that the best parameter of IVF treatment outcome is the live birth rate per started treatment cycle or the live birth rate after a given period of time. Since the duration of a minimally stimulated treatment cycle is short and there is no need to wait before starting a new cycle, these protocols provide an extra advantage over standard stimulated protocols as treatments can be repeated in consecutive cycles,[13,15] offering attractive cumulative pregnancy rates over a timeframe.

When considering the reported incidence of complications associated with minimal stimulation protocols, namely ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy rates, a great difference becomes apparent.

Complication Rates

Minimal stimulation protocols have successfully achieved a decrease in the incidence of IVF-related complications, namely OHSS and multiple pregnancy rates.

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Ovarian hyperstimulation syndrome is rarely reported in women undergoing minimal stimulation (<1%), and though it can be considered as an unusual complication of standard stimulation protocols, the reported incidence of moderate-severe OHSS with these regimens is still 3-8% [Royal College of Obstetricians and Gynecologists (RCOG)], which let us not forget, is a potentially fatal complication of ovarian stimulation.

The reported incidence of multiple pregnancies following mild IVF approaches ranges from 4 to 11.5% for twin pregnancies and 0-0.04% for triplets,[3,5] which represent a much lower risk when compared to standard IVF approaches with reported multiple pregnancy rates around 25% and with programs reporting up to 40% of triplets alone.[14,16]

As recently concluded by Grunfeld et al.[14] the aim of IVF treatment should shift from maximizing the pregnancy rate per treatment cycle to optimizing the number of healthy deliveries achieved per patient.[14] Reducing iatrogenic multiple pregnancy rates becomes paramount and minimal stimulation protocols successfully achieve this goal.

Dropout Rate

Dropout from IVF impacts on the overall success of an IVF program. Dropout rates have been estimated around 25% after an unsuccessful IVF cycle, with a cumulative dropout rate of 54% after two cycles.[17,18] Although most of the dropouts might be attributed to failure to conceive, it is also possible that this rate could be reduced by reducing stress, side effects and treatment complications.

As suggested by Verberg et al.[19] in a recent study, minimal stimulation protocols seem to be able to significantly impact on reducing the dropout rates related to anxiety by greater than 50%.[19] By having more patients undergo more attempts, the overall cumulative live birth rate per couple enrolling in IVF could also increase.[15]

Cost-effective Treatment

Several papers have shown the cost-effectiveness of minimal stimulation over standard stimulation when assessing the costs per live birth.

After comparing the cumulative live birth rates following one year of treatment, Elijkemans et al.[20] reported similar success rates for both minimal stimulation and standard protocols (43% vs. 44%, respectively). However, the overall costs were significantly reduced in the minimal stimulation protocol by nearly 23%.[20]

In a comparative study between a minimal stimulation IVF center and two conventional IVF centers in the same geographical region, Zhang and colleagues[5] showed a cost reduction per live birth of up to 66% when using minimal stimulation protocols and all these, before even considering the costs associated with the management of OHSS and multiple pregnancies, which are far more frequent with standard IVF approaches.[5]

Drawbacks

Mild stimulation approaches for IVF have a number of relative drawbacks, including the risk of a premature LH surge, need for constant monitoring, failed egg retrievals and a lower embryo transfer rate.

One major concern during minimal stimulation protocols is to lower the rate of cycles in which no eggs are collected, including those that have spontaneous premature ovulations. For this, several interventions have been suggested with apparent success, and include the following:

- Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. Indomethacin[21]
- Continued administration of Clomiphene to suppress the premature LH surge[3]
- GnRH antagonists[9,12]

Patients should be counseled about cancellation rates, being advised that these might be less dramatic because of the low financial, physical and emotional burdens in minimal stimulation.[15]

CASE STUDIES

Minimal stimulation protocols seem to be suitable for all indications for conventional IVF,[6] although their benefits become more evident when treating "difficult" cases (i.e. poor responders and patients at risk of OHSS).

Patients with Poor Ovarian Reserve

Patients with previous poor response to standard stimulation protocols, those with high FSH levels and older patients, namely poor responders, are usually refractory to any stimulation protocol despite the high doses of gonadotropins administered.[22] If these patients are going to produce one or two follicles at the most no matter how aggressive the stimulation protocol is, it is only logical to start them on minimal stimulation considering that this approach will produce the same outcome with regard to the retrieved oocytes, but at a lower cost,[5,23] with lesser discomfort, and lesser disruption of the endocrine environment.

As opposed to standard stimulation regimens, in minimal stimulation protocols, no resting cycle is necessary and treatment can be repeated in consecutive cycles, allowing for more favorable pregnancy rates per time spent by patient,[6] which is paramount in these groups of patients, who are pretty much in a run against time.

Polycystic Ovary Syndrome (PCOS) and Patients at Risk of OHSS

Taking into consideration the negligible risk of OHSS associated with minimal stimulation protocols, patients with a history of OHSS might benefit from these protocols over standard ovarian stimulation. "Soft IVF" approaches could even be combined with techniques such as *in vitro* maturation (IVM) of oocytes, maximizing the number of available eggs while reducing the risks for OHSS.

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The use of a GnRH agonist[4] to induce the needed LH surge towards final oocyte maturation could further reduce the risk of developing OHSS in these patients when a minimal stimulation approach has been pursued.

Furthermore, patients opposed to the generation of spare embryos, or even those living in countries where regulations control the number of oocytes to be fertilized, could benefit from mild stimulation protocols since these will not only reduce costs, but will also allow for treatment during consecutive cycles should the initial treatment cycle fail to achieve a pregnancy.

RECENT ADVANCES

Vitrification

Vitrification is a relatively novel cryopreservation technique, which has proven a dramatic increase in survival rates for embryos and oocytes when compared against the standard slow freezing methods. From several available vitrification technologies, the Cryotop method of vitrification has shown the most consistent results throughout published studies with reported survival rates of 100% for pronuclear stage embryos and 98% for four-cell embryos.[24,25]

Milder approaches to IVF might yield lower pregnancy rate per started cycle if only fresh embryo transfers are considered. However, since most patients will receive single embryo transfers (SETs), there are good chances that these patients will have surplus embryos of top quality available for cryopreservation. Therefore, minimal stimulation is unthinkable without a reliable freezing technique.

Based on its high survival rates, and with pregnancy rates reported at 40-50% per frozen embryo transfer (four-cell stage embryo transfer and blastocyst transfer, respectively),[3] minimal stimulation IVF can offer cumulative pregnancy rates of up to 37% per started cycle, while maintaining a low multiple pregnancy rate (4%),[5] when coupled with embryo vitrification.

Genetics

Ovarian stimulation regimens may result in embryo aneuploidy.[12] Although the exact mechanisms underlying aneuploidy are still unknown, it has been proposed that high levels of estrogens may damage maturing oocytes and distort chromosomal segregation.[1,12] If this were true, lower pharmacologic interference might induce a higher proportion of developmentally competent oocytes and healthy embryos.

In a methodologically well-designed and randomized study conducted by Baart et al.[12] the impact of conventional stimulation protocols and a minimal stimulation approach on the competence of oocytes and embryos for proper chromosomal segregation was prospectively tested by preimplantation genetic screening (PGS) of embryos. Overall, chromosomal abnormality rates for embryos were 55% for mild stimulation and 73% for conventional stimulation. In other words, minimal stimulation resulted in significantly fewer oocytes and embryos, but with a higher rate of "healthy" embryos, which was translated in no difference in the average total number of chromosomally normal embryos (1.8) obtained per patient.[12]

These results are important when counseling patients about IVF since, as previously stated, the number of retrieved oocytes and available embryos is not an outcome measure in IVF and emphasis should be placed on healthy live births.

CONCLUSION

Final success for all assisted reproductive technologies should be redefined as a singleton (or twin) live birth rate.[14] This measure of success should also probably be assessed within a time frame rather than per started cycle.

Minimal stimulation protocols seem to be suitable for all indications for conventional IVF, offering comparable pregnancy rates against conventional IVF, while significantly reducing IVF-associated complications, the emotional, physical and financial burdens imposed on patients, and demonstrating a better cost-efficiency profile than standard IVF stimulation protocols. By achieving all of the above, minimal stimulation protocols also seem to reduce the drop-out rates, enabling couples a better chance of achieving a pregnancy once enrolled in an IVF program.

Standard ovarian stimulation protocols have become too aggressive and too expensive. Beyond associated risks (e.g. OHSS), such aggressive hormonal interventions seem not only to impact on the endometrial and ovarian environments, but also on chromosomal segregation and the chromosomal integrity of embryos. This information should be made available to patients when counseling them about the different IVF approaches.

By redefining success in IVF, the way IVF programs are perceived would change, and patients would potentially have a better marker of identifying their chance of achieving true success at each individual IVF center.[14]

Mild approaches to IVF, such as minimal stimulation IVF, should be further appraised and promoted as major infertility treatment procedures due to their safety and cost-efficiency profiles.[5]

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