



Quick Response Code

Have we finally written the obituary for conventional IVF?

About the Author



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INTRODUCTION

The psychological, physical, emotional, and financial stress experienced by a couple undergoing *in vitro* fertilization (IVF) treatment is very high. Mild stimulation represents a patient-friendly alternative to conventional IVF. If the patient is anxious about the side effects of hormones, she will be greatly relieved if she is offered minimal stimulation instead of the conventional aggressive regimen. A major advantage of a milder form of stimulation is the reduced risk of ovarian hyperstimulation syndrome (OHSS). The current rate of severe as well as mild OHSS can be brought down significantly using the minimal stimulation regimens – 1.4 versus 3.7% in mild and standard groups, respectively, as reported by Ledger in 2007.^[1] The second main advantage is a significantly lower risk of multiple pregnancies – 0.5 versus 13.1% in mild and standard groups, respectively.^[1]

Although the first pregnancy obtained by IVF was in a natural cycle, this method was soon abandoned in favor of gonadotropin-stimulated protocols to improve pregnancy rates. Over the last two decades, easier and less expensive stimulation treatments have been largely replaced by more complex and more demanding protocols. Since the mid-90s, long-term gonadotropin-releasing hormone agonist stimulation protocols have been

widely used. Such lengthy expensive regimens are not free from short- and long-term risks and complications. Mild stimulation protocols reduce the mean number of days of stimulation, the total amount of gonadotropins used and the mean number of oocytes retrieved, and have the possibility of repetition each month at a much lower cost. The proportion of high-quality and euploid embryos seems to be higher compared with conventional stimulation protocols and the pregnancy rate per embryo transfer is comparable. Recent findings suggest that the magnitude of ovarian stimulation affects the proportion of euploid embryos.^[2] There is an ever-increasing trend in reproductive medicine to reduce the intensity of ovarian stimulation for IVF and to restrict the number of embryos that are transferred into the uterine cavity. Conventional IVF aims at increasing the pregnancy rate by replacing several embryos. The milder form of IVF treatment recommends replacing fewer embryos because of the higher quality of the embryos produced using this treatment.^[3]

Due to the high costs of assisted reproductive technology (ART) procedures, there is widespread concern about equity in access to reproductive health care. In India and other developing economies in South East Asia and Africa, the economic status of the patient is an important factor determining access to infertility treatment. In 2008,

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we established India's first budget IVF center, Rotunda Blue where, with minimal stimulation IVF (msIVF), we could bring down the cost by over 40% per cycle by using lesser amount of urinary gonadotropins per cycle without compromising on quality or results. Fewer oocytes translated to reduction in the use of laboratory disposables and expensive culture media. As the number of oocytes and embryos to handle per patient was much lower in the milder treatment, it reduced the workload of the embryologist substantially. Next, we started a combination of clomiphene citrate, human menopausal gonadotropins (hMG), and cetrorelix cycles to decrease costs further while achieving similar pregnancy rates. Reducing costs in developing countries can be mainly dictated by reducing the usage of gonadotropin in ART cycles. These milder stimulation cycles with a flexible antagonist protocol helps us achieve comparable pregnancy rates with a very substantial cut in cost. The reduction in cost enables patients to attempt more cycles, thus increasing cumulative rates of success. If the cost is reduced by 40%, then even the lower economic groups will have almost equal access to infertility treatments and IVF pregnancy would be more widely available.

DISCUSSION

Conventional IVF (IVF) today is being challenged by simpler methodologies. These include:

- Natural cycle IVF (nIVF)^[4-6]
- msIVF^[7-9]
- IVF Lite {msIVF + [vitrification + accumulation of embryos (ACCU-VIT)] + remote embryo transfer (rET)}^[10]

nIVF

Controlled ovarian stimulation with exogenous gonadotropins and gonadotropin-releasing hormone (GnRH) analogues enables the collection of multiple oocytes and subsequent development of multiple embryos. However, interference with the natural hormonal milieu may decrease the probability of successful embryo implantation due to effects on oocytes and/or endometrium. To provide a fair comparison of embryo implantation rates between natural cycles and stimulated cycles, bias caused by the presence of multiple embryos available for transfer in stimulated cycles should be avoided. A retrospective study by Ata *et al.*, analyzed embryo implantation rates in cycles in which only a single embryo was available for transfer in 304 women who had responded poorly to ovarian stimulation in the previous cycle.^[11] Embryo implantation rates with different stimulation protocols were as follows:

Natural cycle: 20% (6/30); gonadotropin only: 5.6% (3/54); long GnRH protocol: 3.8% (2/52); co-flare protocol: 1.9% (1/52); microdose flare-up: 15.4% (4/26); GnRH antagonists: 14.4% (13/90). Although the difference was not statistically significant, there was a trend toward higher rates of implantation with natural cycles in this group of women. nIVF maybe a reasonable and patient-friendly choice of treatment yielding an acceptable outcome for women who are known or anticipated poor responders to ovarian stimulation.

Gordon *et al.*, recently reported the utilization and outcomes of natural cycle (unstimulated) IVF as reported to the Society of Assisted Reproductive Technology (SART) in 2006 and 2007.^[12] The main outcome measures of this paper were the utilization of nIVF, description of patient demographics, and comparison of implantation and pregnancy rates between unstimulated and stimulated IVF cycles. During 2006 and 2007, a total of 795 unstimulated IVF cycles were initiated. Rates of success were age dependent, with patients <35 years of age demonstrating clinical pregnancy rates, per cycle, of start, retrieval, and transfer of 19.2, 26.8, and 35.9%, respectively. Implantation rates were statistically higher for unstimulated compared with stimulated IVF in patients who were 35 to 42 years old. Unstimulated IVF represents <1% of the total IVF cycles initiated in the United States. The rates of pregnancy and live birth per initiated cycle were 19.2 and 15.2%, respectively, in patients <35 years old. The implantation rates in unstimulated IVF cycles compared favorably with stimulated IVF. The study concluded that nIVF may be considered in a wide range of patients as an alternative therapy for the infertile couple.^[12]

nIVF and its variants offer the benefit of minimal consumption of drugs and the practical absence of side effects. It virtually eliminates the occurrence of multiple pregnancies. Its efficiency is however limited and is characterized by a high number of cancellations. The cumulative pregnancy rate per embryo transfer is comparable with the pregnancy rate of conventional stimulation protocols.^[4-6,11,12]

The use of modified natural cycle IVF (mncIVF) by adding an agonist trigger is a valuable alternative to IVF in young poor responders and should be considered in patients who demonstrate endocrinologic evidence of ovarian aging and in those who have had one or two canceled controlled ovarian hyperstimulation cycles.^[5]

A Japanese group in 2008 described three successful cases involving patients of advanced age from whom

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dominant follicles were retrieved during the natural cycle.^[4] All patients had failed to bear children through stimulated IVF. In case 1, a follicle was retrieved after a GnRHa was used to induce luteinizing hormone surge. In cases 2 and 3, pregnancy was achieved via completely natural cycles. One embryo was transferred every 16 cycles. The authors concluded that retrieval of mature oocytes followed by natural rather than stimulated IVF might be a potential treatment for patients of advanced age when stimulated IVF has been repeatedly unsuccessful.^[4]

In a retrospective cohort trial by Polyzos *et al.*,^[13] 164 consecutive patients undergoing 469 nIVF between 2008 and 2011 were included. Patients were stratified as poor and normal responders: 136 (390 cycles) were poor ovarian responders according to the Bologna criteria, whereas 28 women (79 treatment cycles) did not fulfill the criteria and were considered as normal responders. The trial suggested that although nIVF is a promising treatment option for younger normal responders, its potential is very limited for poor ovarian responders as described by the Bologna criteria, irrespective of the age of the patient.^[13]

In an analysis of 500 consecutive nIVF cycles, oocytes were found in 391 cases (78.1%), and cleaving embryos suitable for transfer were obtained in 285 cycles (57.0%).^[6] Pregnancy was observed in 49 cases, with a pregnancy rate of 9.8% per cycle, 17.1% per transfer, and 16.7% per patient. The authors concluded that in poor responder patients, nIVF is an effective treatment, especially in younger women.^[6]

Costs of medication for nIVF and mncIVF were 96.3 and 97.5%, respectively, lesser than for the least expensive conventional IVF cycle. Pregnancy rates per embryo transfer are acceptable for these treatment modalities, the cost for medication is low, risks of complications are reduced dramatically, and the treatments maybe more psychologically acceptable to the patients.^[14]

Birth weights of mncIVF singletons found in the study of Pelinck *et al.*, are higher than standard IVF singletons, suggesting that ovarian stimulation maybe a causative factor in the occurrence of low birth weight in standard IVF.^[15]

msIVF

The introduction of msIVF adds to the repertoire of fertility treatments. However, its place is still novel and is

contested within the literature. An msIVF cycle is defined either as a stimulation regimen in which gonadotropins are administered at a lower-than-usual dose and/or for a shorter duration throughout a cycle in which a GnRH antagonist is given as cotreatment, or a stimulation in which oral compounds (e.g, antiestrogens) are used either alone or in combination with gonadotropins and GnRH antagonists. The indications for msIVF that began with poor or low responders have now extended to older women, women with previous IVF failures, hyper-responders, and now even young normoresponders.

Merviel *et al.*, described mild stimulation as the administration of low doses (150 IU/day) of FSH, continuously, from the fifth day of the cycle, associated with the administration of GnRH antagonists.^[16] Despite the lower number of oocytes collected during mild stimulation, they are better for pregnancy rates with an endometrium mimicking that of a natural cycle, and reducing the risk of ovarian hyperstimulation. Although the number of IVF and intracytoplasmic sperm injection (ICSI) attempts is limited to four in France, they proposed msIVF in young women, those with a polycystic ovary syndrome or 'low responder' women.^[16]

Teramoto *et al.* proposed clomiphene citrate – based msIVF protocols and published one of the largest series in the literature.^[7] Fifty mg clomiphene citrate was initiated on cycle day 3, and from day 8, patients received 150 IU of FSH every other day. When the size of the dominant follicle and the estradiol concentration reached the predefined values, GnRHa was administered to induce follicular maturation. Oocytes were retrieved 32-35 hours later. Of all the 43,433 cycles initiated, the rates for oocyte retrieval and embryo cleavage were 83 and 64%, respectively. The mean number of oocytes retrieved was 2.2. The rates for live births, miscarriages, and ectopic pregnancies, in relation to initiated cycles, including cases of frozen-thawed transfer, were 11.1, 3.4, and 0.2%, respectively.^[7]

Craft *et al.*, included poor responders as well as hyper-responders in their msIVF protocols.^[8] Group I included 18 poor responders (24 cycles) with no live birth in 23 previous IVF cycles with GnRH agonists. Group II included seven hyper-responder patients (seven cycles) with polycystic ovaries. The treatment protocol involved a daily dose of clomiphene citrate 100 mg for five days and gonadotropin injections from cycle day 2. Cetorelix 0.25 mg/day was started when the leading follicle reached 14 mm. The outcome in both groups was favorable compared to previous treatment with GnRH agonists.^[8]

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Lin *et al.*, corroborated the experience of Craft *et al.*, and concluded that the clomiphene citrate/hMG/cetrorelix protocol is an acceptable alternative protocol for hyper-responders.^[9]

The use of a GnRH antagonist in controlled ovarian hyperstimulation improves the outcome of the pregnancy of patients with a history of multiple failure of IVF/ICSI embryo transfer in a GnRHa protocol, most likely due to improvement in the quality of the blastocysts generated.^[3] Forty women with no live births after conventional IVF/ICSI and subsequent blastocyst transfer (BT) with a GnRHa long protocol entered this study. The treatment protocol consisted of a daily dose of clomiphene citrate 100 mg for five days and gonadotropin injections daily from cycle day 4 onward. Cetrorelix, 0.25 mg/day, was started when the leading follicle reached 14 mm. Induction of ovulation was triggered with human chorionic gonadotropin (hCG) ($n = 36$) or GnRHa ($n = 4$). It was possible to perform BT in 38 patients. Takahashi *et al.*, surmised that the msIVF antagonist-based protocol gave them improved embryo (blastocyst) quality.^[5]

The experiences of msIVF women have received minimal attention. The aim of the study of Payne *et al.*, was to explore the perspectives of women regarding msIVF.^[17] In this qualitative thematic analysis study, 17 women and two partners were interviewed regarding their perceptions of 'mild' cycle IVF. Data were thematically analyzed to identify the key aspects of the perceptions of participants. Participants reported that 'mild' cycle IVF offered a number of positive aspects, including the reduction in the intrusion of IVF procedures in the lives of women, the short time frame spent in awaiting the results, and the manner in which the mild cycle worked with natural hormonal cycles of women. 'Mild' cycle IVF was perceived positively by the participants, particularly in terms of time frames and the impact on their physical and emotional well-being.

IVF LITE (MSIVF + ACCUVIT + RET)

The evolution of IVF Lite began with nIVF and unfolded over 15 years with variations of mncIVF, msIVF, or mild IVF to the present day 'mini-IVF'^[18] or 'IVF Lite'.^[10] This protocol requires a reliable and cheap method for embryo cryopreservation such as vitrification, because of the negative impact of clomiphene citrate on the endometrium and because cryopreserved embryo transfers with this protocol have yielded much higher pregnancy rates than fresh transfers.^[10,18] The backbone of the successful Rotunda IVF Lite program are the ACCU-VIT and the rET protocols that we have inculcated in our standard operating

procedures.^[10] IVF Lite includes ACCU-VIT over a few cycles for poor responders and older women. For women with previous IVF failures and hyper-responders, we can complete the ACCU-VIT segment in one cycle. Since 2011, we have expanded the indications of IVF Lite to:

- Women with low ovarian reserve (poor responders)
- Women with previous multiple IVF failures
- Women above the age of 40
- Women with previous OHSS and polycystic ovary syndrome patients (hyper-responders).

Zhang *et al.*,^[18] described an msIVF + vitrification + rET protocol christened 'mini-IVF'. In this series, the patients were not denied treatment based on their day-3 FSH value or ovarian reserve.^[18] Yet, very acceptable pregnancy rates were achieved (20% for fresh embryo transfers and 41% for cryopreserved rETs).^[18] These results strengthen the argument for IVF Lite as an alternative to standard conventional IVF stimulation protocols.

CONCLUSIONS

Gentle IVF protocols, such as 'IVF Lite', have several potential advantages over conventional IVF protocols, including less medication and fewer injections, producing fewer eggs, but eggs of higher quality. Patient acceptability of the milder stimulation protocols is better. With vitrification as the cornerstone of IVF Lite, we get pregnancy rates comparable to conventional IVF in patients with a normal ovarian reserve. IVF Lite provides much better pregnancy rates than conventional IVF in older patients, patients with previous conventional IVF failures, poor responders, and hyper-responders. In cost-conscious environments, IVF Lite is definitely helping us write the obituary for conventional IVF.

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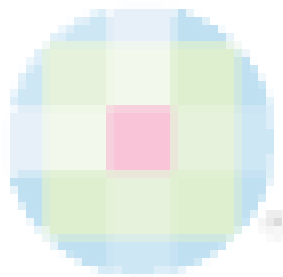
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