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EDITORIAL

IVF Lite: Is this the Future of Assisted Reproduction?

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Introduction

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-nineties, long-term gonadotropin-releasing hormone (GnRH) agonist stimulation protocols have been widely used. Such lengthy expensive regimens are not free from short- and long-term risks and complications. The use of controlled ovarian stimulation to obtain multiple eggs for Assisted Conception has resulted in a compromise.

- In terms of the risk of Ovarian hyperstimulation syndrome (OHSS) [1].
- Expense [1].
- Multiple pregnancies [1].
- Wastage of or the need for cryopreservation of surplus embryos [1].
- Even some women with apparently normal menstrual cycles might become "poor responders" when administered with follicular stimulants [1].
- Incidence of oocyte aneuploidy is artificially raised after stimulation [2].

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Consequently, with evolution of patient-friendly Assisted Conception procedures, routine IVF (IVF), is being challenged by simpler methodologies. These include:

- Natural cycle IVF (nIVF) [2].
- Minimal stimulation IVF (msIVF) [3, 4].
- IVF Lite (minimal stimulation IVF + vitrification + accumulation of embryos + remote embryo transfer) (msIVF + ACCUVIT + rET) [5].

A minimal stimulation IVF cycle is defined either as.

(a) 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 GnRH antagonist is given as co-treatment [6, 7], or
(b) a stimulation in which oral compounds (e.g., anti-estrogens) are used either alone or in combination with gonadotropins and GnRH-antagonists [8, 9].

Mild stimulation protocols reduce the mean number of days of stimulation, the total amount of gonadotropins used and the mean number of oocytes retrieved [3]. 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 [2]. Moreover, the reduced costs, the better tolerability for patients, and the less time needed to complete an IVF cycle make mild approaches clinically and cost effective over a given period of time. However, further prospective randomized studies are needed to compare cumulative pregnancy rates between the two protocols. Natural cycle

IVF(nIVF), with minimal stimulation, has been recently proposed as an alternative to conventional stimulation protocols in normo- and poor-responder patients [2, 10, 11].

Natural Cycle IVF (nIVF)

A Japanese group recently described three successful case studies involving patients of advanced age from whom dominant follicles were retrieved during the natural cycle [2]. 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 mature oocyte retrieval followed by natural rather than stimulated IVF might be a potential treatment for patients of advanced age when stimulated IVF has been repeatedly unsuccessful [2].

In an analysis of 500 consecutive natural cycle IVF, oocytes were found in 391 cases (78.1 %), and cleaving embryos suitable for transfer were obtained in 285 cycles (57.0 %). 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, natural cycle IVF is an effective treatment, especially in younger women [10].

Low-dose, post-trigger NSAID was administered in a non-randomized way in cycles at higher ovulation risk where an imminent LH surge was detected on triggering day [11]. NSAID use was associated with a significantly lower risk of premature ovulation (3.6 vs. 6.8 %) and higher embryo transfer rate (46.8 vs. 39.5 %) per scheduled cycle. Clinical pregnancy (39.1 vs. 35.9 %) and live birth rates per embryo transfer (31.3 vs. 31.4 %) were comparable. In this retrospective series, short-term low-dose NSAID application positively influenced nIVF cycles by diminishing the rate of unwanted premature ovulations and increasing the proportion of cycles reaching embryo transfer [11].

Minimal Stimulation IVF (msIVF)

Minimal stimulation IVF initially was introduced for women with low ovarian reserve [3, 7], with previous multiple IVF failures [4], and over the last 5 years, the indications have expanded to older women [6] and hyper-responders [13]. Weghofer et al. [7] published a study to determine whether minimal stimulation with short-term application of low-dose recombinant follicle-stimulating hormone (FSH) together with a GnRH antagonist represents a cost-effective treatment regimen for patients with elevated FSH levels, aged 40 and above. Eighty-five IVF cycles using minimal ovarian stimulation and 85 cycles with a standard long-stimulation protocol in women aged 40 and above who had slightly increased FSH levels were included. Patients on the long protocol underwent standard cycle monitoring and stimulation. In contrast, women with minimal stimulation had transvaginal sonography initiated on day 8 of the menstrual cycle and at a follicle size of 13 mm. They administered 0.25 mg of GnRH antagonist and 75 IU recombinant FSH daily until ovulation induction. Minimal stimulation cycles resulted in a clinical pregnancy rate of 8.2 % per started cycle and 10 % per embryo transfer (ET), whereas the control group yielded a clinical pregnancy rate of 10.6 % per started cycle and of 10.7 % per ET (not statistically significant). The authors concluded that in women aged 40 and above with abnormal FSH levels, minimal stimulation protocol achieves pregnancy rates similar to those of a standard protocol, and thus represents a cost-effective alternative [7].

In a prospective multicenter cohort study, minimal stimulation IVF was offered to 350 patients [6]. All indications for conventional IVF were included. A total of 336 patients completed 844 cycles (2.5 per patient). The overall ongoing pregnancy rate per started cycle was 8.3 % [95 % confidence interval (CI) 6.4–10.2 %]. The cumulative ongoing pregnancy rate after three cycles was 20.8 % (95 % CI 16.4–25.3 %) per patient. No differences were found according to indication for IVF. Owing to the low-risk and patient-friendly nature of this protocol, it seems to be a feasible and promising treatment option for patients requiring IVF [6].

Mohsen and El Din [8] compared the IVF outcomes of letrozole/antagonist and microdose GnRH agonist flare up protocols in poor ovarian responders undergoing intracytoplasmic sperm injection with a randomized controlled trial. The clinical pregnancy rate per cycle was similar in both groups (13.3 vs. 16.6 %; OR = 0.769; 95 % CI = 0.185, 3.198). The doses of used gonadotropins and the number of stimulation days were significantly lower in the letrozole/antagonist protocol. The peak E2 level on the day of hCG, the endometrial thickness, the retrieved oocytes, the number of fertilized oocytes, the number of transferred embryos, and the cancelation rate were statistically similar in both groups.

40 women with no live births after conventional IVF/ICSI and subsequent blastocyst transfer (BT) with a GnRHa-long protocol were enrolled in Takahashi et al.'s study [12]. The treatment protocol consisted of a daily dose of clomiphene citrate 100 mg for 5 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 hCG ($N = 36$) or GnRHa ($N = 4$). It was possible to perform BT in 38 patients. Takahashi et al. concluded that the use

of a GnRH antagonist in controlled ovarian hyperstimulation improves the outcome of pregnancy of patients with a history of multiple failure of IVF/ICSI-ET in a GnRHa protocol, most likely due to improvement of the quality of the blastocysts generated.

Craft et al. [13] extended the indications of msIVF to Hyper-responders. 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 5 days and gonadotropin injections from cycle day 2. Cetrorelix 0.25 mg/day was started when the leading follicle reached 14 mm. The outcome in both groups was favorable compared with previous treatment with GnRH agonists.

A total of 7,244 infertile patients did 20,244 cycles with a clomiphene-based minimal stimulation or natural cycle IVF protocol [14]. Following oocyte retrieval, fertilization, and embryo culture, a total of 10,401 fresh or frozen single embryo transfer procedures were performed involving cleavage-stage embryos or blastocysts. Successful oocyte retrieval rate (78.0 %) showed no age-dependent decrease until 45 years. Fertilization (80.3 %) and cleavage (91.1 %) rates were not significantly different between age groups. Blastocyst formation (70.1–22.8 %) and overall live birth rates (35.9–2 %) showed an age-dependent decrease. Frozen–thawed blastocyst transfer cycles gave the highest chance of live birth per embryo transfer (41.3–6.1 %). Kato et al. [14] concluded that an elective single embryo transfer program based on a minimal ovarian stimulation protocol yields acceptable live-birth rates per embryo transfer in infertile patients up until their mid-forties. However, in very advanced age patients (equal or higher 45 years old) success rates fall below 1 %.

IVF Lite (Minimal Stimulation IVF + Vitrification + Accumulation of Embryos + Remote Embryo Transfer) (msIVF + ACCUVIT + rET)

Zhang et al. [5] described a minimal stimulation protocol christened "mini-IVF." This protocol requires a reliable method for embryo cryopreservation such as vitrification, because of the negative impact of clomiphene citrate on the endometrium and since cryopreserved embryo transfers with this protocol have yielded much higher pregnancy rates than fresh transfers. In this series, patients were not denied treatment based on their day 3 FSH value or ovarian reserve [5]. Yet very acceptable pregnancy rates were achieved (20 % for fresh embryo transfers and 41 % for cryopreserved embryo transfers) [5]. These results strengthen the argument for a mini-IVF protocol and vitrification as an alternative to standard conventional IVF stimulation protocols.

The IVF Lite protocol, similar to the "Mini-IVF" protocol [5] based on minimal stimulation protocols including clomiphene citrate and hMG, vitrification, and cryopreserved remote Embryo Transfers (rET), has yielded much higher pregnancy rates than fresh transfers (Unpublished Data). IVF Lite includes embryo accumulation and vitrification (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. We have since 2011 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 PCOS patients (Hyper-responders).

Conclusions

Gentle ovarian stimulation 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. IVF Lite gives pregnancy rates (PRs) comparable with conventional IVF in patients with a normal ovarian reserve. IVF Lite gives PRs much better than conventional IVF in older patients, patients with previous conventional IVF failures, poor responders, and hyper-responders. Further prospective randomized studies are needed to compare cumulative pregnancy rates between the two protocols. In cost-conscious environments, IVF Lite is probably the type of IVF that is going to be the feasible option in the future.

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