Can we modify assisted reproductive technology practice to broaden reproductive care access?

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One of the barriers to access to fertility care is the relative complexity of fertility treatments. If these can be simplified, more patients may be able to take advantage of these treatments. In this overview, we review the potential benefits of simplifying ovarian stimulation by the means of four distinct methods: 1) using mild stimulation for IVF cycles; 2) using in vitro maturation to allow for the retrieval of oocytes that are not yet fully mature yet have the potential to result in live births; 3) conducting IVF in modified natural cycles which use no exogenous FSH stimulation; and 4) allowing embryo culture to take place in a novel intravaginal incubation system. These methods are considered to be somewhat unconventional, yet they have all been shown to lead to live births. In the era of individualized patient care, these techniques present viable alternatives to standard treatment. As experience and outcome data accumulate, they may prove to be not just alternatives to standard treatment, but potentially first-line treatment choices. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: ART, Mild stimulation, IVM, natural cycle IVF, intravaginal culture

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There are many factors that limit patient access to fertility care. In countries where insurance does not cover the treatment, cost is often a primary barrier. However, even in countries where cost is not an issue, patients frequently do not avail themselves of care they need due to its perceived complexity, physical stress, and the emotional toll that fertility treatment entails.

Many modifications of fertility treatment have been proposed over the past 30 or so years. In this article, we present an overview of four such modifications: mild stimulation for in vitro fertilization (IVF), in vitro maturation (IVM) as an alternative to stimulation, the modified natural cycle for IVF (which includes IVM), and intravaginal culture as an alternative to standard laboratory incubators and embryo culture. These techniques are as yet unconventional, but they have the potential to make IVF accessible to patients who would otherwise not be able to take advantage of this technology. This can be due to lower cost, less stress, and/or lower physical trauma to the patient.

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MILD APPROACHES IN IVF: IMPROVING ACCESS TO CARE BY REDUCING COST, BURDEN OF TREATMENT AND COMPLICATIONS

IVF history books tell us that the very first IVF pregnancy occurred after ovarian stimulation with the antiestrogen clomiphene citrate. However, that pregnancy ended in a miscarriage. Professor Bob Edwards subsequently speculated regarding the possible involvement of abnormal corpus luteum function due to ovarian stimulation for IVF. The first live birth took place in 1978 after IVF in a completely natural cycle. In subsequent years, clomiphene citrate stimulation for IVF was developed in the early 1980s in Australia and the use of exogenous gonadotropins for IVF was reported shortly thereafter in the USA. GnRH agonists were subsequently used to prevent premature luteinization due to ovarian stimulation interfering with

steroid feedback at the hypothalamic-pituitary level. In addition, oral steroid pretreatment has been widely used to schedule the IVF cycle, as reviewed by Macklon et al. (1).

It seems justified to conclude that currently used ovarian stimulation regimens have become extremely complex and expensive, with substantial concern regarding patient compliance, as well as inducing the need for frequent hospital visits and ovarian response monitoring. For example, in the Netherlands, costs associated with ovarian stimulation are equal to the cost of the IVF procedure itself.

Ovarian stimulation is used to initiate the IVF procedure with multiple oocytes, to compensate for suboptimal laboratory performance regarding oocyte fertilization, embryo development and selection, and embryo transfer and implantation. It is generally thought that a large number of oocytes is required for optimal IVF outcomes. Based on cross-sectional national data analysis, the optimal oocyte number is thought to be ≥ 15 (2). However, such analyses only assess pregnancy rates per cycle following conventional IVF in splendid isolation, disregarding other associated features such as cost, patient discomfort, and burden of treatment (giving rise to drop-outs from subsequent IVF treatment and therefore reducing cumulative pregnancy rates involving multiple IVF cycles), and risk of complications.

Overall, clinicians associate low oocyte numbers being retrieved with poor IVF outcome. Poor ovarian response to maximum stimulation represents a distinct sign of ovarian ageing (3). Under those circumstances, poor IVF outcome is due to a patient factor which is completely unrelated to ovarian stimulation per se.

We advocated more than 15 years ago (4) that the paradigm of maximum ovarian stimulation was in need of revision, based on the above-mentioned arguments. We have subsequently undertaken a series of prospective randomized studies, demonstrating that the generation of fewer oocytes after mild ovarian stimulation gives rise to improved embryo quality and implantation (5), an increased proportion of euploid embryos (6), improved embryo implantation rates at lower oocyte numbers (7), and reduced drop-out rates (8). When live birth rates per started treatment (involving multiple IVF cycles) was used as the primary end point, mild ovarian stimulation resulted in similar live birth rates (9). Mild ovarian stimulation as a realistic alternative in IVF has recently been reported by other independent investigators (10, 11). Moreover, stimulating growth of more ovarian follicles with higher doses of exogenous FSH does not result in increased live birth rates (12). Recent data suggest that fewer oocytes are required for success when mild ovarian stimulation is used (presumably 10 rather than 20 oocytes to generate a single live birth). Owing to recent improvements in cryopreservation technology, fresh transfer can be restricted to a single embryo only without sacrificing the chances of success from the entire harvest of oocytes from a single stimulation cycle.

It is generally acknowledged that great individual variability exists in ovarian response to stimulation, in relation to female age and ovarian reserve markers such as the antral follicle count and antimüllerian hormone concentrations. The challenge is to first assess what would be the optimal number of oocytes to be retrieved, which we have speculated in the past to be somewhere around five to eight (13, 14). Subsequent prospective studies should be designed with the use of different drugs and doses to develop the preferred stimulation protocol to achieve the optimal balance between IVF success, burden of treatment, complications, and cost (14, 15).

Future studies should focus on improved access to care (directly related to health economics of IVF) and reducing burden of treatment (16) in influencing overall success rates per started treatment.

IN VITRO MATURATION OF OOCYTES

In vitro maturation is a technique that differs from conventional in vitro fertilization treatment in two major ways: absence of controlled ovarian hyperstimulation; and collection of immature oocytes that are cultured in vitro until they reach the metaphase II (MII; mature) stage. Robert Edwards, the pioneer of IVF, thought that recovery of immature oocytes followed by IVM would be a potentially useful treatment for women with infertility (17, 18). IVM was first used successfully in humans in 1991 in an unstimulated donor cycle (19), and the first successful use of IVM in patients with polycystic ovary syndrome (PCOS) occurred in 1994 (20).

There is no universal protocol for performing IVM. One approach recommends administration of FSH at a dose of 100 IU/d for 3 days followed by 10,000 IU hCG, with immature oocyte pick-up 36 hours after hCG. The collected oocytes can then be classified into two groups based on their maturity level at collection. Germinal vesicle (GV) and metaphase I (MI) stage oocytes are cultured in a human tubal fluid medium that is supplemented with FSH 7.5 IU/mL, hCG 100 IU/mL, growth hormone 1 IU/mL, and 10% patient serum for 20 hours. MII-stage oocytes are inseminated on the same day. All mature oocytes are then inseminated with the use of intracytoplasmic sperm injection.

IVM has a number of advantages over conventional IVF, including safety (elimination of ovarian hyperstimulation syndrome [OHSS] in PCOS), low cost (owing to the lack of the stimulation requirement), and convenience (less patient stress, lower medication use, and fewer controls). However, there are also a number of concerns about IVM. The first of these relates to success rate. In patients with PCOS, initial reports showed a pregnancy rate of 21.9%–29.9% (21, 22). However, more recent data show that the success rate of IVM has improved, with pregnancy and delivery rates of 32%–44% and 22%–29%, respectively (23, 24). One study reported that, with single-blastocyst transfers after IVM in PCOS patients, the live birth rate could be as high as 42.4% per oocyte collection (25). The most recent analysis of IVM versus IVF in PCOS patients was a retrospective case-control study of 121 subjects who underwent 178 treatment cycles (26). The results showed no difference in clinical pregnancy rates for fresh or frozen embryo transfer (FET) cycles between the IVM and IVF groups, although the cumulative pregnancy rate was lower in the IVM group. In addition, significantly fewer live births resulted from IVM treatment for both fresh and cumulative cycles, but there was no