Modified natural-cycle in vitro fertilization should be considered as the first approach in young poor responders

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The use of modified natural-cycle in vitro fertilization (IVF) is a valuable alternative to controlled ovarian hyperstimulation in young poor responders and should be considered in patients who require IVF and demonstrate endocrinologic evidence of ovarian aging and in those who have had one or two canceled controlled ovarian hyperstimulation cycles. (Fertil Steril® 2011;96:1066–8. ©2011 by American Society for Reproductive Medicine.)

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Although the first pregnancy obtained by in vitro fertilization (IVF) with embryo transfer was achieved with a natural cycle—and indeed natural-cycle IVF was the method of choice for the first few years of IVF treatment (1)—this procedure was soon abandoned in favor of gonadotropin-stimulated protocols in controlled ovarian hyperstimulation (COH). The use of COH allowed an increase in the number of recruited oocytes and an increase in the pregnancy rates associated with IVF (2). It also has permitted excess embryos to be cryopreserved in the event that the IVF attempt fails to result in a pregnancy or when the patient desires additional sibling attempts without a need for further ovarian stimulation. However, due to the additional costs, risks, and complexity of ovarian stimulation, both the patient and the caregiver feel the pressure to increase the chances of the patient becoming pregnant; therefore, it has become standard to transfer more than one embryo.

In some patients, the induction of multiple follicular growth is not achieved with IVF in a stimulated cycle. Diminished ovarian reserve is the main reason for poor ovarian response in these patients. Some tests are considered as primary markers of poor ovarian response: an increased serum baseline follicle-stimulating hormone (FSH) level, a decreased value of antimüllerian hormone (AMH), or a significant reduction in the antral follicle count.

Over time, oocyte quality decreases in parallel with progressive follicle loss. The combination of decreases in both the quality and number of oocytes explains declining fecundity in females. The diminution of follicle count in women younger than their midthirties is the main limiting factor, and quality is preserved.

In a natural cycle, several follicles are recruited initially, but it is only one that attains dominance and goes on to ovulate. Being able to control ovulation was one of the reasons why natural-cycle IVF was replaced with stimulated-cycle IVF; the first oocyte retrievals had to be performed according to the natural leuteinizing hormone (LH) surge, which resulted in collecting the oocyte at any time of the day or night before ovulation.

A mounting interest in natural-cycle IVF has challenged the medical community to better understand the mechanisms controlling the follicular phase and ovulation in particular, in an effort to optimize this procedure and its outcome. Improvements in laboratory techniques and methods of follicular aspiration have created renewed interest in natural-cycle IVF. Gonadotropin-releasing hormone (GnRH) antagonists induce a reversible medical hypophysectomy, which prevents the occurrence of premature LH surges and thus increases the likely success of a cycle of natural-cycle IVF (3). Indomethacin use during the late follicular phase has also been shown to decrease the rate of spontaneous ovulation and hence provide a higher oocyte retrieval success rate in modified natural-cycle IVF (4).

In fact, the use of modified natural-cycle IVF minimizes physical and emotional stress for the patient and significantly reduces the cost of drugs and laboratory tests for the assisted reproduction unit. Although modified natural-cycle IVF does not reach the levels of pregnancy rate that can be obtained by transferring multiple embryos after ovarian stimulation, we believe that it can be a useful, easy, and cheap tool in the treatment of young poor responders. The benefits of modified natural-cycle IVF are obvious: the increasing problem of multiple pregnancy is removed, the patients do not need to inject themselves with large quantities of expensive medications, and the less invasive nature of the procedure (no sedation or anesthesia is used for the oocyte collections) allows patients to have a cycle each consecutive month. Therefore, as with intrauterine insemination, patients can have three cycles of modified natural-cycle IVF consecutively with minimal impact on their life schedules.

In our center, modified natural-cycle IVF protocol is performed as follows. A baseline transvaginal ultrasound scan is performed on day 3 of menses to exclude ovarian cysts and to ensure that the endometrial lining is <5 mm thick. Serial ultrasound examinations are started on day 6. The follicular diameter is established by SonoAVC (Voluson E8), calculating automatically the mean value. Subsequently, the patient is monitored until the leading follicle reaches a diameter >14 mm. Clinicians, therefore, use surrogate markers of follicular maturation such as estrogen production and follicular size. As soon as the dominant follicle reaches a mean diameter of 15 mm and the endometrium a thickness of 6 mm, the patient receives 0.25 mg SC of GnRH antagonist (Ganirelix, Orgalutran; Merck Canada). Indomethacin (Indocid; Merck Frosst) at a dosage of 50 mg orally three times a day is also started on the same day to prevent spontaneous ovulation. Both are continued until the human chorionic gonadotropin (hCG) is administered. Human menopausal gonadotropin (hMG, Repronex; Ferring Canada), 150 IU

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SC, is administered daily at the time of the first injection of GnRH antagonist to prevent a fall in the estradiol concentration on the following day, and it is repeated thereafter until hCG administration. When the follicle has a diameter of 17 mm, the patient receives 5,000 IU IM of hCG (Pregnyl; Merck Canada) to achieve final follicular maturation. Transvaginal oocyte retrieval is scheduled 34 hours after hCG administration.

Modified natural-cycle IVF has recently received renewed attention and has been used for patients who have shown a poor response in previous attempts with COH. It has been suggested in recent years that natural-cycle IVF may be a promising alternative for poor responders (5, 6). The biological advantages of natural-cycle IVF may provide a single oocyte of better quality and thus allow the transfer of a healthier embryo into a more receptive endometrial environment (7). Overall, these data suggest that poor responders may benefit from natural-cycle IVF, and it should be offered in those young patients with a diminished ovarian reserve. In our clinical experience, modified natural-cycle IVF should be considered as a first approach and not as a consequence of a previous treatment failure. Unfortunately, modified natural-cycle IVF is rarely proposed and only then as a last chance after previous standard attempts have failed. Reasonable pregnancy rates have been reported in several prospective studies where modified natural-cycle IVF was performed in poor responder patients (8–10). Although no large controlled prospective studies are available, we achieve a relatively satisfactory pregnancy rate per cycle compared with studies focused on poor responder patients undergoing different protocols for multiple ovulation induction. Better embryo quality as a consequence of natural oocyte selection, better endometrium receptivity, and monthly repeatability of the procedure can balance the relatively low chance of obtaining an embryo transfer.

For practical reasons, the advancement of the follicular phase in the menstrual cycle is commonly timed according to the onset of last menses. Shorter cycles in poor responders can be explained by the intercycle basal FSH signal. Efforts should be diverted toward controlling when it takes place, either with exogenous estrogen or with oral contraceptives (11). Practically, the prescription of ethinyl estradiol, 4 mg orally, during the 2 or 3 first days of the menstrual cycle can be useful in these conditions to delay follicular maturation and to synchronize with the endometrium.

While laboratory researchers are trying to find the best method to select an embryo or embryos with the best developmental potential for embryo transfer, perhaps the role of natural selection of follicles should be considered. Further research is necessary to verify whether the aneuploidy rate or gene expression of cumulus cells in natural-cycle embryos are improved over embryos resulting from stimulation cycles.

Because there is only one follicle in natural-cycle IVF, there is a greater risk of cycle cancellation than in stimulated cycles, even in younger patients. This is an area of natural-cycle IVF that needs more attention and research, as there is certainly less chance of an embryo transfer after the commencement of a natural-cycle IVF cycle when compared with a stimulated IVF cycle.

The number of women over 35 years of age attempting to conceive has increased significantly in the last decade. Although it is well established that a woman's reproductive success dramatically declines with age, the underlying physiologic changes responsible for this phenomenon are not well understood. Many studies show that the risk of childlessness increases at higher ages as a consequence of ovarian aging. It is well known that the considerable increase in aneuploidy in embryos from older women contributes to these women's inability to conceive, increasing both implantation loss and pregnancy failure (12, 13). Many studies have shown that oocyte quality has the greater impact on the reduction of fertility than oocyte number. The concept of using natural-cycle IVF for older patients has been previously suggested and has had very poor outcomes (14).

Because the pregnancy rate from modified natural-cycle IVF is lower (15), it appears that the benefits of transferring more than one embryo are increased in patients over the age of 35 years. Furthermore, in older patients, achievement of multiple follicle growth remains a challenge. Indeed, poor ovarian responses are commonplace after the age of 35 years in any assisted reproduction unit. The management of these patients is a challenge, and whatever protocol is used their clinical outcome remains poor compared with both young patients and those with normal response. The overall pregnancy rates achieved with modified natural-cycle IVF in older patients are low, and they are reduced with the transfer of a single embryo.

Apart from oocyte donation, there is no established intervention to improve the pregnancy outcome of older patients. Although the factors responsible for diminished oocyte quality remain to be elucidated, recent data focus on the potential role of mitochondria dysfunction in reproductive aging (16). In this context, the use of coenzyme Q10 as a mitochondria energy substratum has been proposed to reduce the aneuploidy rate and enhance the prognosis of modified natural-cycle IVF in older poor responders. This is an area currently under investigation in our clinic's program.

The use of modified natural-cycle IVF is a valuable alternative to COH in young poor responders and is in line with the increasing interest in single-embryo transfer and the resultant reduction in multiple pregnancies. This alternative should be considered in patients who require IVF, who demonstrate endocrinologic evidence of ovarian aging, and who have had one or two canceled COH cycles. Hence, we suggest that modified natural-cycle IVF should be considered as a first approach in young poor responders. Furthermore, the increasing interest in the concept of the potential rejuvenation of ovarian reserve in mammalian females poses the question as to whether modified natural-cycle IVF could become a future option for older patients who have reduced ovarian reserve.

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