DEBATE

The possible role of natural cycle and modified natural cycle in IVF

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1. Natural cycle

The first successful pregnancy and live birth resulting from IVF were achieved during an unstimulated natural cycle (1). Soon thereafter, natural IVF was replaced by stimulated IVF because of the very high cancellation rates of natural cycles, and stimulated treatment became the standard in IVF. However, ovarian stimulation is not free from negative consequences and risks, including ovarian hyperstimulation syndrome (OHSS), which affects up to 5–10% of IVF cycles and can be life-threatening (2). Multiple pregnancies occur in approximately 30% of pregnancies in patients who undergo the COH protocol and this phenomenon is related to increased risks of pregnancy loss, obstetrical complications, prematurity and neonatal morbidity with long-term damage. The long-term side effects however remain largely unknown. Ovarian cancer and gestational trophoblastic disease may be associated with the chronic use of gonadotrophins (3). Nevertheless, the interest in natural IVF cycle treatment has been renewed in recent years because of the increased efficiency of IVF technology. With the increasing awareness of side effects of ovarian stimulation and better understanding of ovarian physiology in relation to ovarian follicular growth and maturation, IVF in natural cycles has gained great attention and interest for both normal responder and poor responder patients (4).

1.1. Advantages

Natural IVF cycles are simple, inexpensive and rapid and side effects associated with ovarian stimulation are eliminated. Natural cycle offers a more physiological, less drug-oriented, lower risk and more patient-friendly approach (4). Natural IVF cycles might be more efficient for obtaining ideal embryos. It can be repeated on a monthly basis, and the overall chances of success are therefore higher. Some patients might prefer several successive natural IVF cycles instead of stimulated IVF cycles, which can only be repeated once a month (5). It has been reported that the clinical pregnancy rate with stimulated IVF has reached approximately 25–30% (6). However, repeated stimulated cycles should span over several months to allow for the ovaries to recover. Further, if stimulated IVF cycles are repeated, the pregnancy rate will obviously decrease.

1.2. Disadvantages

Problems related to natural IVF cycles include an increased risk of untimely LH surge and the possibility that no oocyte is retrieved and no embryo is available for transfer (5). The efficacy of natural IVF is hampered by the high incidence of oocyte retrieval failure (16.7–71.4%) and the relatively low pregnancy rate per embryo transfer (ET) cycle (0–23.5%) (4). Natural IVF cycles resulted in an ongoing pregnancy rate of approximately 7% per started cycle and approximately 16% per ET (7).

1.3. Natural cycles in poor responders

Previous studies found that the natural cycle works at least as well as the COH in poor responder women who failed previous ovarian hyperstimulation (8). In poor responder patients, only very few follicles can be recruited and very few oocytes can be retrieved after stimulation despite the high dose of gonadotropins administered or repeated stimulated cycles performed and their management remains a challenge in assisted reproduction. The majority of poor responder women had advanced reproductive age, diminished antral
follicle count, elevated day-3 FSH concentrations or previous failed cycles. In the context of a poor responder woman, the natural cycle could yield better quality oocyte by natural follicle selection and allow transfer on endometrium whose receptivity has not been distorted by stimulation.

The combination of natural cycle IVF with IVM of immature oocytes (natural cycle IVF/IVM) has successfully resulted in pregnancy for infertility and has been looked upon with an increasing interest as a novel treatment (9). Natural cycle IVF/IVM treatment for poor responders may be a reasonable and effective treatment alternative to ovarian stimulation because of its easy, monthly repeatability and because of the more oocytes retrieved compared with natural cycle IVF. This treatment maximizes the treatment efficacy by combining the advantages of natural cycle IVF and IVM, especially desirable for women with poor-responding who has only very few follicles recruited and very few oocytes retrieved after stimulated cycles (8).

### 1.4. Natural cycles in advanced age

Treatment via natural IVF cycles may assist patients of advanced age who have failed to become pregnant after treatment via stimulated IVF cycles and who have regular ovulatory cycles (5).

### 1.5. Evaluation

The cumulative pregnancy and live birth rates might be as high as 46% and 32%, respectively (10). Cumulative pregnancy rates are more relevant than pregnancy rates per started cycle to evaluate the effectiveness of the natural cycle because of the monthly, patient-friendly and easy repeatability. It has been reported that the cumulative ongoing pregnancy rate was 34.0% after three cycles of minimal stimulation IVF (11), 43% and 42% after three and five natural oocyte pickup cycles (12) and 46% after four started natural cycles.

### 2. Modified natural cycle

The trend towards single embryo transfer and increasing focus on ‘patient friendly’ IVF has lately led to a growing interest in modified natural cycle IVF (MNC-IVF) and mild IVF (M-IVF). Several countries now have legislation regulating the number of embryos transferred per treatment cycle, and population studies of children born after IVF clearly show the health benefits from treatments leading to deliveries of singletons (13). MNC-IVF and M-IVF are both treatment modalities involving less medical intervention, leading to a reduced number of oocytes retrieved. The International Society for Mild Approaches to Assisted Reproduction published guidelines for terminology and description of protocols. Treatment strategies for MNC-IVF and M-IVF include FSH stimulation, clomiphene citrate and the use of gonadotrophin-releasing hormone (GnRH) antagonists, as well as luteal phase support administered both vaginally and as injections. In the modified natural cycle IVF, the one follicle that spontaneously develops to dominance is used for IVF. A GnRH antagonist is administered in the late follicular phase of the natural cycle to prevent unwanted LH-surges and ovulations. Together with the GnRH antagonist, gonadotrophins are used to substitute for an expected fall in estradiol levels (14).

#### 2.1. Advantages

MNC-IVF offers several advantages (15). It is a patient-friendly approach due to minimal use of medication, easy oocyte retrieval and negligible risk of OHSS. Treatment is easily repeated in consecutive cycles and no resting cycle is necessary in between. Since in most cases only one embryo is available for transfer, the multiple pregnancy rate is low, which is advantageous considering the many problems associated with multiple pregnancies. For patients who, for ethical or religious reasons, are opposed to the generation of spare embryos, MNC-IVF forms an attractive alternative to IVF with controlled ovarian stimulation (COS), and legal problems associated with cryopreserved embryos are avoided. It forms a valuable treatment modality prior to, or as an alternative to, standard IVF with COS. Per cycle, MNC-IVF is cheaper than COS-IVF due to the minimal use of hormonal medication and in terms of costs per live birth, MNC-IVF may be cost-effective compared with COS-IVF (16). In a recent study, birthweights of singletons conceived by MNC-IVF and COS-IVF were compared. A significantly higher mean birthweight was found in the MNC-IVF group, whereas patient characteristics in both groups were similar(17). This should be confirmed in further studies. It is a valuable treatment option preceding standard IVF with COS, even if pregnancy rates per cycle are lower than those obtained with COS-IVF.

#### 2.2. Disadvantages

Low pregnancy rates of 0.0–18.3% per started cycle have been found in several studies on MNC-IVF and ICSI (15). Obviously, a higher number of MNCs will be required to obtain pregnancy rates comparable to those obtained with COS-IVF. A major concern for mnc-IVF is the cancellation rate. The cancellation rate prior to oocyte retrieval was 31% in the MNC-IVF group, and 46.5% of the started mnc-IVF cycles reached embryo transfer.

#### 2.3. Mnc-IVF in low responders

The results from both MNC-IVF and M-IVF indicate that these treatment modalities are less attractive for older patients (18). No pregnancies were observed in the mnc-IVF group among patients >38 years and a marked difference in ongoing pregnancy rate per embryo transfer between younger and older patients (30.6 versus 17.5%) was observed using 38 years as a cut-off threshold. MNC does not offer a realistic chance of parenthood in patients with high levels of FSH on day 3 of the cycle and previous poor response to ovarian stimulation, when offered as a last resort prior to oocyte donation (19).
The best outcome definition of success after IVF is the live birth rate per started treatment consisting of consecutive cycles (15). When MNC-IVF is applied before COS-IVF, the outcome parameter would be the cumulative live birth rate after sequential treatment with MNC-IVF, if necessary followed by COS-IVF. Since the CPR after MNC-IVF is 40.6% and many of those not conceiving with MNC proceeded with COS-IVF, the overall CPR per patient probably will be favourable. In applying sequential treatment with MNC-IVF followed by COS-IVF, those patients conceiving with MNC-IVF will not be exposed to the risks and burden of COS-IVF. The optimal number of treatment cycles per patient remains unclear. Considering the advantages of MNC-IVF, the very low multiple pregnancy rate and negligible risk of OHSS in particular, MNC-IVF offers a valuable treatment modality for patients requiring IVF.

References


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The first IVF pregnancy was in a natural cycle (1). The results of IVF were poor because oocyte pickup techniques were rather primitive. However, natural IVF cycles or Clomid IVF cycles were used in different centres with reasonable results. Natural cycle IVF has over the last couple of decades been held up as the ideal for simplicity, economy (2) and safety (3). However, the complete natural cycle has had limited success (4). Patients undergoing natural cycle IVF are more likely to have abandoned cycles to clomid IVF cycles which resulted in 18% per ET in a small series (5).

Natural cycle treatment has been abandoned following the extensive use of ovarian stimulation by exogenous FSH in an attempt to obtain more oocytes. This has resulted in fewer abandoned cycles and improved pregnancy rates, especially when combined with down-regulation with gonadotrophin-releasing hormone analogues prior to ovarian stimulation. However stimulated cycles posed significant problems such as huge cost, problems of Ovarian hyperstimulation syndrome (OHSS), problems of multiple pregnancy and disposal of extra embryos may cause ethical and religious dilemmas (3).

Natural cycle IVF includes completely natural cycle, natural cycle with hCG to trigger ovulation and modified natural cycle with GnRH antagonist and hMG of FSH. Natural cycle