

MODIFIED NATURAL CYCLE

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The first successful in vitro fertilization (IVF) treatment was performed in a natural, unstimulated menstrual cycle (Steptoe and Edwards, 1978). In those days, oocyte harvesting was done by laparoscopy, necessitating general anaesthesia and was often unsuccessful. Timing of oocyte retrieval was based on the LH surge, requiring intensive cycle monitoring, and untimely ovulations often occurred. In the laboratory, in-vitro fertilization was not very efficient, especially in cases with suboptimal semen quality.

Thus, IVF in the natural cycle was largely replaced by IVF with controlled ovarian hyperstimulation (COH) in order to obtain a larger number of growing follicles, making oocyte retrieval more efficient and increasing the oocyte yield and number of embryos available for transfer.

The use of COH and the practice of multiple embryo transfer led to an increase in pregnancy rates, but along with it to an increase in complications and costs. Complications occurring after COH are the ovarian hyperstimulation syndrome (OHSS), bleeding and infection of the ovaries after oocyte retrieval and multiple pregnancies. The most important complication, related to the practice of transferring multiple embryos, is the occurrence of multiple pregnancies, which are associated with increased adverse maternal outcome, poor neonatal outcome and high costs (Fauser *et al.*, 2005). Evidence is increasing however, that also singleton pregnancies derived from COH-IVF are associated with poor neonatal outcome as compared to spontaneous pregnancies (Helmerhorst *et al.*, 2004).

The growing awareness of the risks and long-term consequences of multiple pregnancies, gave room for a change in approach in IVF treatments, with more focus on patient (dis)comfort and prevention of multiple pregnancies.

Elective single embryo transfer was introduced as a means to prevent multiple pregnancies (Gerris *et al.*, 1999). Milder stimulation regimens, with less patient discomfort and shorter duration per treatment cycle were proposed as an alternative for COH (Heijnen *et al.*, 2007).

The development of GnRH-antagonists has renewed interest in the use of the natural cycle for IVF (Rongières-Bertrand *et al.*, 1999). GnRH-antagonists are able to block LH-surges while allowing for the development of one single dominant follicle. Since the occurrence of untimely LH-rises were an important cause of the lack of efficacy in natural cycle IVF, GnRH-antagonists are expected to be able to raise its efficacy.

The approach in which treatment is aimed at the use of the one dominant follicle in the natural cycle, using a GnRH-antagonist for prevention of LH-rises, together with gonadotrophins for substitution, is called modified natural cycle (MNC)- IVF (Nargund *et al.*, 2007).

MNC-IVF offers several advantages. Since gonadotrophins are administered in a low dose and only one or few follicles develop, the risk of the ovarian hyperstimulation syndrome (OHSS) is negligible. Since usually no more than one single embryo is available for transfer, it is associated with a low chance of multiple pregnancies. MNC-IVF is also a patient-friendly treatment since medication is administered for a few days only, causing few side effects, and the duration of a treatment cycle is considerably shorter than standard IVF with COH. Since usually only one follicle is aspirated, oocyte retrieval is easy and short-lasting and can be performed without analgesia (Ramsewak *et al.*, 1990). As opposed to COH-IVF, in MNC-IVF no resting cycle is necessary after a failed treatment cycle and treatments are easily repeated in consecutive cycles.

The low-risk and patient-friendly profile of MNC-IVF make it worthwhile to investigate its efficacy.

In our center, we did several cohort studies exploring the efficacy of MNC-IVF. Inclusion criteria for these studies were: female patient age 18-36 years, first IVF treatment ever or first IVF treatment after a pregnancy, the presence of a regular and proven ovulatory menstrual cycle with a length of 26-35 days and BMI (kg/m²) of 18-28. Indications for IVF were tubal pathology, unexplained subfertility, male factor, endometriosis, cervical factor or failed artificial inseminations with donor semen (AID). Patients were not included in the studies in case an endometriosis cyst was seen on ultrasound. Patients requiring ICSI were not included in this study.

Protocol: the unstimulated menstrual cycle was monitored by ultrasound. When a dominant follicle (diameter ≥ 14 mm) was observed, daily injections of 0.25 mg of the GnRH antagonist cetrorelix together with 150 IU recombinant FSH were started. Ovulation triggering was achieved by 10 000 IU of HCG when a follicle with a diameter of ≥ 18 mm was observed and/or plasma E2 levels were ≥ 0.8 nmol/l. Oocyte retrieval was performed 34 h after ovulation triggering. Embryo transfer was performed on the third day after oocyte retrieval. For luteal support, HCG 1500 IU was given 5, 8 and 11 days after oocyte retrieval.

In our studies we found:

- a rather high rate of cancellation of oocyte retrieval (13-18% of cycles), due to either lack of development of a dominant follicle, or the occurrence of untimely LH-rises and ovulations, despite the correct use of medication.
- failure of oocyte retrieval in in 23-27% of cases.
- embryo transfer rate per cycle of 37-44%.
- ongoing pregnancy rate per (single) ET of 21-33%.
- ongoing pregnancy rate per started cycle of 8-14%, with a low twin pregnancy rate (2-6%).
- no difference in pregnancy rates according to cause of subfertility.
- a cumulative clinical pregnancy rate of 44% after a maximum of nine cycles of MNC-IVF, with a twin pregnancy rate of 3%.
- a cumulative ongoing pregnancy rate of 57% after sequential treatment consisting of MNC, followed by COH-IVF if MNC was unsuccessful, with an overall twin pregnancy rate of 8%.

These results will be presented along with a cost-effectiveness analysis and a report on perinatal outcome.