

A Successful Pregnancy by Utilization of Gradually Increasing Low Dose Gonadotrophin Stimulation in a Modified Natural Cycle in Vitro Fertilization Procedure: Case Report

Serkan KAHYAOĞLU¹, Ayşe Seval ERDİNÇ¹, Nafiye KARAKAŞ YILMAZ¹, Mahmut Nedim ÇİÇEK¹

Ankara, Turkey

The modified natural cycle in vitro fertilization (MNC-IVF) treatment can be a promising method for poor responder patients especially in young patients with poor ovarian reserve. A 34-year-old primary infertile woman presented with a history of poor ovarian response and cycle cancellation following controlled ovarian hyperstimulation during an IVF-ET procedure two months ago. During MNC-IVF treatment with intracytoplasmic sperm injection (ICSI), gradually increasing doses of hMG for three days (totally 675 IU) have been administered accompanied by daily 0,25 mg cetrorelix. Following ovulation triggering, one oocyte was picked up and a good quality (grade 1) embryo was transferred on day 2. A clinical pregnancy was established with ultrasonography on sixth weeks of gestation. Acceptable pregnancy rates per embryo transfer, low medication cost, relatively low risk of complications and higher patient acceptability are the main advantages of MNC-IVF treatment as a feasible treatment option especially for poor responder patients.

Key Words: Modified natural cycle, Poor responder, In vitro fertilization

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Introduction

Historically, the first pregnancy achieved by an in vitro fertilization-embryo transfer (IVF-ET) procedure was performed in a natural cycle. The evolution of IVF-ET treatment has moved towards the controlled ovarian hyperstimulation (COH) protocols that utilize high dose gonadotrophins to increase pregnancy rates by retrieval of high number of oocytes. Although high dose gonadotrophins are administered, it usually results with retrieval of low number of oocytes for poor responders during COH. Frequently, when a poor responder patient is offered assisted reproduction treatment, the stimulation regimens utilizing high gonadotrophin doses that increase the cost of the treatment results with disappointing outcome for oocyte yield retrieved. As mentioned by the International Society for Mild Approaches in Assisted Reproduction (IS-MAAR); the term natural cycle IVF defines the treatment strategy conducted with the oocytes collected following a woman's own menstrual cycle without using any ovulation induction agent (Table 1).¹ The natural cycle IVF is currently rarely used due to high cancellation rates and low success

rates except patients with malignancies sensitive to gonadotrophins.²⁻³ Ata et al. compared natural and stimulated assisted reproduction treatment cycles in poor responders and they concluded that natural cycle IVF may be a reasonable and patient-friendly treatment choice yielding an acceptable outcome for women who are known or anticipated poor responders to ovarian stimulation.⁴ The term modified natural cycle (MNC) should be used when IVF is being performed during a spontaneous menstrual cycle to achieve a naturally selected dominant follicle by limited utilization of exogenous gonadotrophins and/or any other fertility drugs with a lower risk of cycle cancellation than natural cycle IVF.⁵ MNC-IVF treatment cycle can also include the use of human chorionic gonadotrophin (hCG) for ovulation triggering and GnRH-antagonists for preventing spontaneous LH surge accompanied by low dose and cost FSH and/or hMG utilization that is administered for dominant follicle support. Unlike natural cycle IVF, luteal support can be a part of the MNC-IVF treatment. The MNC-IVF is different from the mild IVF cycles because single oocyte is intended to be achieved as the outcome of the MNC-IVF treatment cycle. During a mild IVF treatment cycle, the aim is to collect between 2 and 7 oocytes by using FSH or HMG administration at lower doses, and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral medications (anti-estrogens, or aromatase inhibitors) are used, either alone or in combination with gonadotrophins. The MNC-IVF treatment can be a promising method for poor responder patients especially in young patients with poor ovarian reserve. We report a successful MNC-IVF cycle treatment of a poor responder patient following a conventional IVF cycle cancellation.

¹Department of Assisted Reproductive Medicine, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara

Address of Correspondence: Serkan Kahyaoğlu
Serhat Mah. 1292. Sok. Nevbahar
Botanik 2 Konutları C Blok No: 7/49
Yenimahalle, Ankara
mdserkankahyaoglu@gmail.com

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Table 1: Definitions of various in vitro fertilization treatment modalities*

Treatment	Intended endpoint of treatment	Medications used
Natural cycle IVF	Single oocyte	No medication/ No luteal phase support needed
Modified natural cycle IVF	Single oocyte	Low dose FSH and/ or hMG administration accompanied by GnRH antagonist plus hCG for ovulation trigger plus luteal phase support
Mild IVF	2-7 oocytes	Low dose FSH and/ or hMG administration and/or antiestrogens and/ or aromatase inhibitors accompanied by GnRH antagonist plus hCG for ovulation trigger plus luteal phase support
Conventional IVF	≥8 oocytes	Conventional FSH and/ or hMG administration accompanied by GnRH agonist or antagonist plus hCG for ovulation trigger plus luteal phase support

*: The information within the Table 1 is prepared from the reference number 1

Case Report

A 34-year-old primary infertile woman presented with a history of poor ovarian response to COH during an IVF-ET procedure two months ago that resulted with cycle cancellation following COH by utilization of totally 3525 IU gonadotrophins for nine days. Her day 3 FSH and E2 levels were 9.5 IU/L and 120 pg/mL respectively and her antral follicle count was 5 totally. Her past reproductive history was uneventful except four unsuccessful ovulation induction and intrauterine insemination procedures conducted and an ovarian surgery performed for a benign ovarian cyst. Her partner's spermogram parameters were within the normal limits according to the WHO 2010 criteria. She has been offered to have a MNC-IVF treatment with intracytoplasmic sperm injection (ICSI) with regard to our clinical practice to increase the fertilization rate. She was evaluated with transvaginal ultrasonography on day 3 to exclude any ovarian cystic structure. On day 6 of the natural menstrual cycle, transvaginal ultrasonographic examination revealed 5 antral follicles with diameters of 12, 7, 7, 6 and 5 mm respectively and 150 IU hMG (Menogon; Ferring, Istanbul, Turkey) was initiated subcutaneously. When the leading follicle size was measured 14 mm in diameter on day 7 and 16 mm on day 8, 225 IU and 300 IU hMG have also been administered respectively accompanied by daily GnRH antagonist cetrorelix 0,25 mg (Cetrotide; Merck Serono, Istanbul, Turkey). Following 3 days of mild ovarian stimulation by totally 675 IU gonadotrophins, on day 9, we achieved 5 follicles with 18, 13, 8, 7 and 6 mm diameters and 10.000 IU hCG (Pregnyl; Ferring, Istanbul, Turkey) was administered intramuscularly to induce ovulation. Her serum E2 and progesterone levels were 459 pg/mL and 0,5 ng/mL on hCG day. One oocyte was picked up during oocyte retrieval procedure that was performed 36 hours later. Intracytoplasmic sperm injection of this oocyte resulted with a good quality (grade 1) embryo which was transferred to the patient on day 2. Vaginal progesterone gel (Crinone 8% gel; Merck Serono, Istanbul, Turkey) twice daily and 3 doses of

1.500 IU human chorionic gonadotrophin (hCG) every 3 days were recommended for luteal phase support. A serum pregnancy test performed after 12 days following embryo transfer revealed a successful pregnancy and a clinical pregnancy represented by fetal heart beat detection on sixth weeks of gestation was established on ultrasonography.

Discussion

Basically, following the advances in embryology, the clinical availability of GnRH antagonists and the increasing popularity of the "single embryo transfer" strategy to decrease multiple pregnancy rates resulting from IVF-ET treatment regimens based on COH made mild stimulation regimens like natural cycle IVF safer and acceptable treatment choices for patients. When the probability to achieve high number of oocytes for IVF-ET is low regarding previous poor ovarian responses to COH, it seems reasonable to stimulate patients with poor ovarian reserve mildly at the expense of achievement of only one oocyte that grows within a more physiological hormonal milieu. Two prospective studies with historical controls (failed cycles with poor response in the same patients) revealed lower cancellation rates and comparable pregnancy rates for natural cycle IVF treatment.^{2,3} The only randomised controlled study about this issue was conducted by Morgia et al. who have compared natural cycle IVF with microdose GnRH analog flare ovarian stimulation protocol among 129 poor responder patients.⁶ Similar pregnancy rates per cycle and per embryo transfer were established besides a significantly higher implantation rate achieved with natural cycle IVF. Paulson et al. have first described MNC-IVF to enhance the efficacy of unstimulated natural cycle by administration of late follicular gonadotrophins and GnRH antagonists to overcome the relatively frequent drawbacks of natural cycle IVF like cycle cancellation and premature LH surge.⁵ In a preliminary report about 44 MNC-IVF cycles in 33 young normal responder patients, embryo transfer was performed in 50% of the group with acceptable clinical pregnancy rates per transfer and

per retrieval of 32% and 17.5% respectively.⁷ However, MNC-IVF treatment that results with single oocyte yield achievement at best has not gained popularity among IVF treatment cycles except for poor responder patients. Recent evidence suggests conflicting results about recommendation of MNC-IVF treatment in poor responder patients.⁸⁻¹⁰ Kolibianakis et al. found no ongoing pregnancies with the use of 78 MNC-IVF treatment cycles among 32 poor responder patients. Embryo transfer was performed in 19 (43.2%) out of 44 cycles in which oocytes were retrieved.⁹ The only randomised controlled trial evaluating the efficacy of MNC-IVF treatment was performed by Kim et al.¹¹ They compared the treatment outcome of 45 conventional GnRH antagonist cycles with 45 MNC-IVF cycles among poor responder patients. Despite the number of oocytes retrieved, mature oocytes, fertilized oocytes, grade 1 and 2 embryos and embryos transferred were all significantly lower in the MNC-IVF group; live birth rates and clinical pregnancy rates per cycle initiated and per embryo transfer were found to be similar between the two treatment groups. Rongieres- Bertrand et al. described low dose FSH or hMG administration up to 150 IU/ day during late follicular phase of the menstrual cycle to maintain follicular requirement.⁷ For mimicking menstrual physiology, we gradually increased hMG dose starting with 150 IU on day 6, proceeding with 225 IU on day 7 and finally 300 IU on day 8 concurrently with GnRH antagonist for the last two days of stimulation and accompanied by serum estradiol (E₂) levels of 176.228 and 297 pg/mL respectively. Serum E₂ level on hCG day was 459 pg/mL which was assumed to be within physiological hormonal limits related to the developing single dominant follicle.

Despite resulting with a low cost of medication and being a safe treatment alternative especially for poor responder patients, low efficiency of the procedure forestalled the widespread use of MNC-IVF treatment. Previous studies evaluating the outcome of MNC-IVF treatment revealed that, the likelihood of retrieving an oocyte is between 45-80%, likelihood of succeeding an embryo transfer is 50% and likelihood of achieving a pregnancy is around 5% (0%-20%) depending on the maternal age and current ovarian reserve.^{8-10,12} Kadoch et al. suggested that MNC-IVF treatment should be considered as the first approach in young poor responder patients.¹³

Among poor responder patients, an ovarian stimulation regimen that mimics natural ovulation process can be advantageous in favor of the oocyte quality and endometrial receptivity. In this case report; by retrospectively reviewing the ovulation induction regimen of the patient who have succeeded to achieve a clinical pregnancy resulting from a grade 1 quality embryo transfer, we suggested a gradually increasing dose of gonadotrophin (hMG) administration for days 6-8 accompanied by concurrently started daily GnRH antagonist in-

jections when the leading follicle size measurement reaches 14 mm in diameter, mimicking physiological late menstrual follicular phase LH increase. Acceptable pregnancy rates per embryo transfer, low medication cost, relatively low risk of complications and higher patient acceptability are the main advantages of MNC-IVF treatment as a feasible treatment option over conventional COH treatment for IVF especially for poor responder patients.

Kademeli Olarak Artan Düşük Doz Gonadotropin Verilerek Yapılan Bir Modifiye Doğal Siklus in Vitro Fertilizasyon İşleminde Başarılı bir Gebelik: Olgu Sunumu

Modifiye doğal siklus in vitro fertilizasyon tedavisi (MDS-İVF) tedaviye kötü cevap veren hastalar için, özellikle de kötü ovaryan rezerve sahip genç hastalar için daha etkin bir metod olabilir.

Otuzdört yaşındaki primer infertil bir kadın iki ay önceki bir İVF-ET işlemi esnasında yapılan kontrollü ovaryan hiperstimülasyona kötü over cevabı ve siklus iptali hikayesi ile başvurmuştur. İntrasitoplazmik sperm enjeksiyonu ile birlikte yapılan MDS-İVF tedavisi esnasında, eşlik eden cetorelix tedavisine ek olarak üç gün boyunca dereceli olarak artan dozlarda hMG (toplam 675 İU) uygulanmıştır. Ovulasyon tetiklemesini takiben, bir oosit toplanmış ve hastaya iyi kalitede bir ikinci gün embriyosu transfer edilmiştir. Altıncı gebelik haftasında ultrasonografi ile bir klinik gebelik tespit edilmiştir.

Özellikle stimülasyona kötü cevap veren hastalar için uygun bir tedavi şekli olarak MDS-İVF tedavisinin temel avantajları embriyo transferi başına kabul edilebilir gebelik oranları, düşük ilaç bedeli, göreceli olarak düşük komplikasyon riski ve yüksek hasta kabul edilebilirliğidir.

Anahtar Kelimeler: Modifiye doğal siklus, Kötü cevap verenler, İn vitro fertilizasyon

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