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# NEW DEBATES

# The ISMAAR proposal on terminology for ovarian stimulation for IVF

**G. Nargund[6,1], B.C.J.M. Fauser[2], N.S. Macklon[2], W. Ombelet[3], K. Nygren[4], and R. Frydman[5], for the Rotterdam ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF**

*[1]Department of Reproductive Medicine, St George's Hospital and Medical School, Blackshaw Road, London SW17 0QT, UK; [2]Department of Reproductive Medicine and Gynaecology, University Medical Center, Utrecht, The Netherlands; [3]Department of Obstetrics and Gynaecology, ZOL Campus St Jan, Genk, Belgium; [4]IVF Clinic, Sophiahemmet Hospital, Stockholm, Sweden; [5]Department of Obstetrics and Gynaecology, and Reproductive Medicine, Hôpital Béclère - Sce Gynéco-Obstétrique, 157 rue de la Porte de Trivaux, 92141 CLAMART, France*

[6]Correspondence address. Tel: +44-208-947-9600; Fax: +44-208-944-5800; E-mail: geetanargund@gmail.com

**IVF is performed with oocytes collected in natural and stimulated cycles. Different approaches to ovarian stimulation have been employed worldwide. Following the introduction of GnRH antagonists and strategies to reduce multiple births such as single embryo transfer, there is a genuine scientific interest in the revival of natural cycle and mild approaches to ovarian stimulation in IVF. Recent evidence suggests that application of natural and mild IVF is patient-centred, aimed at reducing the cost of treatment, patient discomfort and multiple pregnancies. However, there seems to be no consistency in the terminology used for definitions and protocols for ovarian stimulation in IVF cycles. Following the recent International Society for Mild Approaches in Assisted Reproduction (ISMAAR) meeting and communication with interested international experts, this article has recommended revised definitions and terminology for natural cycle IVF and different protocols used in ovarian stimulation for IVF. It is proposed that these terms are adopted internationally in order to achieve a consistency in clinical practice, research publications and communication with patients.**

*Keywords:* natural cycle IVF; mild IVF; minimal stimulation IVF; conventional IVF; proposal on terminology

## Introduction

More than 50 peer-reviewed papers have been published in the last 10 years addressing natural and mild approaches in *in vitro* fertilization (IVF). Recent studies have addressed the potential advantages of modified natural cycle and mild IVF in the light of current attempts to reduce patient distress, multiple births and cost of IVF cycles (Pelinck *et al.*, 2006; Heijnen *et al.*, 2007). Several terminologies (Table 1) have been used in the published literature to describe unstimulated or superovulation cycles which has led to confusion among clinicians, research workers and patients.

Following a renewed scientific interest and revival of natural cycle and mild approaches to ovarian stimulation in clinical practice (Fauser *et al.*, 1999; Hojgaard *et al.*, 2001; Pelinck *et al.*, 2002; Baart *et al.*, 2007; Nargund and Frydman, 2007; Pennings and Ombelet, 2007), we feel it is essential to define the terminology and protocols for natural cycle and ovarian stimulation in IVF. An interested group of international experts from International Society for Mild Approaches in Assisted Reproduction (ISMAAR) met recently with an aim of clarifying and proposing a concise terminology in this area. Following extensive discussion followed by personal communication with authors, agreement was reached regarding terminology. In this article, we propose a simplified and revised nomenclature for the different approaches to ovarian stimulation for IVF (Table 2). Detailed descriptions and discussion regarding indications, protocols, cost implications and success rates for each method is beyond the scope of this article and will be the subject of a separate paper.

## Revised definitions

### *Natural cycle IVF*

The term Natural cycle IVF should be used when IVF is carried out with oocytes collected from a woman's ovary or ovaries in a spontaneous menstrual cycle without administration of any

**Table 1:** Terminology

| Recommended | To replace |
|---|---|
| Natural cycle IVF | Unstimulated, spontaneous cycle IVF |
| Modified natural cycle IVF | Semi-natural, controlled natural cycle IVF |
| Mild IVF | Soft, minimal stimulation, 'friendly' IVF |
| Conventional IVF | Standard, routine IVF, controlled ovarian stimulation IVF |

medication at any time during the cycle. The aim of this cycle is to collect a naturally selected single oocyte at the lowest possible cost.

### *Modified natural cycle IVF*

The term Modified natural cycle should be applied when exogenous hormones or any drugs are used when IVF is being performed during a spontaneous cycle with the aim of collecting a naturally selected single oocyte but with a reduction in chance of cycle cancellation. This could include the following scenarios.

(i) The use of human chorionic gonadotrophin (hCG) to induce final oocyte maturation. Luteal support may/may not be administered.
(ii) The administration of gonadotrophin-releasing hormone (GnRH) antagonist to block the spontaneous luteinizing hormone (LH) surge with or without follicle-stimulating hormone (FSH) or human menopausal gonadotrophin (HMG) as add-back therapy. An hCG injection and luteal support are administered.

### *Mild IVF*

A mild IVF cycle is defined as the method when FSH or HMG is administered at lower doses, and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds (anti-estrogens, or aromatase inhibitors) are used (Branigan and Estes 2000), either alone or in combination with gonadotrophins. HCG injection and luteal support are also administered. The aim is to collect between 2 and 7 oocytes (based on clinical experience and results of mild IVF within the ISMAAR consensus group: Heijnen *et al.* (2007). In theory, it may be possible to develop mild IVF protocols using GnRH agonist, but no such data are currently available. Therefore, it makes sense to combine mild approaches to ovarian stimulation with the use of GnRH antagonist and normal start of the menstrual cycle involving high endogenous FSH concentrations during the early follicular phase (Fauser and Devroey 2005).

**Table 2:** Definitions

| Terminology | Aim | Methodology |
|---|---|---|
| Natural cycle IVF | Single oocyte | No medication |
| Modified Natural cycle IVF | Single oocyte | hCG only GnRH antagonist and FSH/HMG add-back |
| Mild IVF | 2–7 oocytes | Low dose FSH/HMG, oral compounds and GnRH antagonist |
| Conventional IVF | ≥8 oocytes | GnRH agonist or antagonist conventional FSH/HMG dose |

### *Conventional IVF*

This term is used to define the following scenarios:

(i) GnRH agonist is used for pituitary down-regulation followed by conventional doses of stimulation with FSH or HMG.
(ii) GnRH agonist is administered in a flare protocol with conventional doses of FSH or HMG.
(iii) GnRH antagonist is used with conventional doses and early start of FSH or HMG.

All of the above methods include the administration of hCG and luteal support.

The aim is to collect eight or more oocytes.

## Brief description of protocols

### *Natural cycle IVF*

This method is currently rarely used due to high cancellation rates and low success rates. However, it is applied in treatment cycles where all types of gonadotrophins are to be avoided (i.e. cancer patients). The cycle is monitored with serial ultrasound scans and/or hormone assays. The timing of oocyte collection may be based on an optimum level of serum estradiol ($E_2$) and LH and/or ultrasound measurement of follicular diameter endometrial thickness (Nargund *et al.*, 2001; Pelinck *et al.*, 2002). Tests may be carried out to detect urinary LH surge prior to oocyte collection. Follicular flushing may be used during ultrasound-directed follicle aspiratio IVF and embryo transfer techniques are similar to those used in stimulated cycles. Luteal support is not used.

### *Modified natural cycle IVF*

This is the more commonly used method for a natural cycle approach in IVF. It is used in women who do not wish to take hormones to produce more than one naturally selected oocyte (Nargund *et al.*, 2001). Recent evidence suggests that it may be useful in poor responders (Feldman *et al.*, 2001; Elizur *et al.*, 2005; Papaleo *et al.*, 2006). The cycle may be monitored with serial ultrasound scans and/or serum $E_2$ and LH levels. With optimum level of $E_2$ and LH levels and follicular and endometrial measurements, GnRH antagonist is administered daily with or without low dose FSH or HMG as add-back therapy (up to 150 IU/day) to compensate for a possible resultant drop in FSH levels and to maintain follicular health (Rongieres-Bertrand *et al.*, 1999). The administration of hCG, oocyte collection, IVF and ET techniques are similar to those used in stimulated cycles. Luteal support is given either in the form of hCG or progesterone.

### *Mild IVF*

This method is likely to increase and possibly even replace the current conventional protocol in the future. A fixed low dose

FSH or HMG (up to 150 IU/day) is administered in a GnRH antagonist co-treatment cycle (Heijnen *et al.*, 2007). Flexible FSH doses may be applied in theory but there is no evidence that this is useful. The treatment cycle is monitored by serial ultrasound scans (in some centres serial serum $E_2$ measurements).

The use of oral compounds such as the anti-estrogens (clomiphene citrate or tamoxifen) or aromatase inhibitors for ovarian stimulation in IVF either alone or in combination with exogenous gonadotrophins (with or without GnRH antagonist co-treatment) should be further evaluated.

The criteria for administration of hCG, IVF and embryo transfer techniques are similar to those applied in other IVF protocols. Luteal support is given either in the form of hCG or progesterone. It may be possible to develop mild IVF protocols using GnRH agonist co-treatment and low dose FSH or HMG. But there are no such published data at the moment. In addition, early suppression of endogenous gonadotrophins will certainly result in the need for higher doses of exogenous FSH or HMG for ovarian stimulation.

### *Conventional IVF*

This is currently the most commonly used protocol. It includes cycles where GnRH agonist is administered either in a long or short protocol with conventional doses of FSH or HMG (up to 600 IU/day) for ovarian stimulation. It also includes GnRH antagonist cycles with conventional doses of stimulation from day 2 of cycle (Macklon *et al.*, 2006). The dose of HMG or FSH used per cycle is higher and/or the total duration of stimulation is longer compared with the 'mild IVF' approach (Heijnen *et al.*, 2007; Hohmann *et al.*, 2003). The administration of hCG, IVF and embryo transfer techniques are similar. Luteal support is administered.

## Discussion

There is an urgent need to adopt definitions for terminology and protocols in IVF practice worldwide. This would not only help to achieve consistency in methodology essential for clinical training and practice, but also to maintain standards in the peer-reviewed scientific literature aiming to further improve stimulation protocols.

Further advances in embryology, ultrasound technology, the clinical availability of GnRH antagonist and the move toward 'single embryo transfer' will make different approaches to stimulation in IVF cycles more relevant in day-to-day clinical practice.

Increasing concerns regarding the patient discomfort, safety, efficacy and cost effectiveness of the conventional high stimulation protocol for IVF, and its extensive use, have prompted a number of research groups to develop novel treatment protocols designed to (i) reduce the risk of ovarian hyperstimulation syndrome and the incidence of multiple pregnancy, (ii) improve oocyte and endometrial quality, (iii) reduce the emotional stress and financial burden to couples. Although many of these protocols are similar, they have been described in the literature by a bewildering array of different terminologies. This ISMAAR consensus statement aims to simplify the definition of protocols into four main categories with clear, intuitive and understandable descriptions. We propose that these terms be adopted internationally in order to end the current confusion. This will be to the benefit of clinical practice and research, and communication with our patients and health policy makers.

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