Early Short Stimulation Modified Natural Cycle IVF With GnRH Agonist Trigger and In Vitro Maturation in a Woman with Polycystic Ovary Syndrome: A Case Report

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Abstract

Background: Gonadotropin-releasing hormone agonist (GnRHa) triggering of final oocyte maturation has been used successfully in GnRH antagonist IVF cycles. It has not been used to date in cycles in which immature oocytes are matured in vitro.

Case: We report here for the first time that GnRHa triggering in a variation on the modified natural IVF cycle can be used as a strategy in the treatment of infertility secondary to polycystic ovary syndrome. In this approach, follicles were stimulated with gonadotropins for three to five days when they were small, and triggering of ovulation occurred when the largest follicles were 10 to 12 mm in diameter. This was followed by retrieval of many immature oocytes that were matured in vitro and subsequently developed to form blastocysts that resulted in a live birth.

Conclusion: This is the first human evidence that GnRHa triggering of ovulation can be used successfully when the aim is in vitro maturation of oocytes.

Résumé

Contexte : Le déclenchement de la maturation finale de l'ovocyte au moyen d'un agoniste de la gonadolibérine (GnRHa) a été utilisé avec succès dans le cadre de cycles de fécondation *in vitro* (FIV) faisant appel à des antagonistes de la gonadolibérine (GnRH). On ne l'a pas utilisé, à ce jour, dans le cadre de cycles faisant appel à la maturation *in vitro* des ovocytes immatures.

Cas : Nous signalons pour la première fois aux présentes que le déclenchement au moyen d'un GnRHa peut, dans le cadre d'une variation du cycle modifié de FIV naturelle, être utilisé à titre de stratégie dans le traitement de l'infertilité attribuable au syndrome des ovaires polykystiques. Dans le cadre de cette approche, les follicules ont été stimulés au moyen de gonadotrophines pendant de trois à cinq jours lorsqu'ils étaient petits et le déclenchement de l'ovulation a été mis en œuvre lorsque les follicules les plus gros atteignaient de 10 à 12 mm de diamètre. Par la suite, nous avons procédé à la récupération de nombreux ovocytes immatures qui ont ensuite fait l'objet d'une maturation *in vitro* et qui en sont subséquemment venus à former des blastocystes ayant donné lieu à une naissance vivante.

Conclusion : Nous avons obtenu les premières données probantes issues d'études menées chez l'homme qui indiquent que le déclenchement de l'ovulation au moyen d'un agoniste de la GnRH peut être utilisé avec succès lorsque la maturation *in vitro* des ovocytes constitue l'objectif visé.

Key Words: In vitro maturation, IVM, GnRH agonist trigger, modified natural cycle, polycystic ovary syndrome, PCOS, ovarian hyperstimulation syndrome, OHSS

Competing Interests: None declared.

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INTRODUCTION

Ovulation is induced by the mid-cycle surge of luteinizing hormone from the pituitary gland. This surge is elicited by a rapid increase in concentrations of serum estradiol in the late follicular phase. More than 50 years ago, exogenous human chorionic gonadotropin was introduced as a substitute for the endogenous LH surge (in a dose of 5000 to 10 000 IU) to induce final oocyte maturation.[1] This substitution was possible because hCG has the ability to bind to LH receptors; LH and hCG share common alpha subunits, and their beta subunits demonstrate homology.[2] Another property of hCG is a long half-life, so that when it is given as an ovulatory dose it will support the development of corpora lutea for seven to 10 days after injection.[3] Interestingly, the significantly longer half-life of hCG (compared with LH) also leads to the development of multiple corpora lutea and an

increase in the levels of serum estradiol, progesterone, and vascular endothelial growth factor throughout the luteal phase.[4] The use of hCG consequently increases the risk of ovarian hyperstimulation syndrome.[5–7] The increased risk of OHSS induced by the triggering of final oocyte maturation with hCG led to the development of alternative triggering methods to achieve final maturation.[8]

Gonadotropin-releasing hormone agonists have been shown to stimulate ovulation effectively and to induce final oocyte maturation when given in cycles in which GnRH antagonists were used to prevent ovulation.[8] The GnRHa injection leads to an initial secretion of LH and FSH (flare-up effect) similar to that seen in the natural menstrual cycle, although of shorter duration.[9] The application of a GnRHa trigger in IVF cycles resulted in a significant reduction in OHSS compared with the use of hCG triggering.[8,10,11] However, the use of GnRHa triggering resulted in lower live birth rates than with hCG triggering.[8] This was attributed to the rapid luteolysis caused by GnRHa, leading to luteal phase insufficiency. Consequently, attempts were made to rescue the luteal phase with a small supplementary bolus of LH-like activity in normal and hyper-responding patients.[12–14] Administration of hCG 1500 IU one hour after oocyte retrieval, after triggering with GnRHa, resulted in normal concentrations of serum progesterone in the mid-luteal phase and normalization of pregnancy rates.[12,13] The risk of severe OHSS in young women with polycystic ovary syndrome or in women with polycystic ovaries is greater than in women with normal ovaries.[15] This increase in risk is likely due to the high number of follicles and higher levels of vascular endothelial growth factor in serum and follicular fluid.[16,17] Recently, many studies have focused on natural and modified natural IVF cycles,[18,19] in vitro maturation,[20,21] and natural cycle IVF combined with in vitro maturation[22] to simplify treatment and reduce the costs and side effects of ovarian stimulation. In natural cycle IVF, no hormonal stimulation is given and hCG is given to trigger ovulation when the leading follicle is $\geq$ 18 mm in mean diameter,[18,19] resulting in the collection of a single mature oocyte. Unfortunately, a premature LH surge and resulting premature ovulation occurs in 30% of these cycles; the pregnancy rate is less than 10% per cycle.[18] In response, "modified natural cycle IVF" has been developed.[18] In this modification, a GnRH antagonist is given daily when the dominant follicle reaches a mean diameter of 14 to 15 mm, and daily injections of human menopausal gonadotropin begin concurrently. When the follicle reaches 18 mm in diameter, hCG is administered to plan oocyte retrieval. This approach reduces the risk of premature ovulation due to an uncontrolled LH surge. The main limitation of this modified natural cycle IVF is that only one mature oocyte can be retrieved; hence, the pregnancy rate is 15% per cycle.[18]

Another reproductive technology requiring minimal or no gonadotropin stimulation is IVM of human oocytes. Initially, in the modified McGill IVM protocol, a single injection of hCG was given when follicles had a mean diameter of $<$ 10 mm.[20,21] However, if the hCG injection was delayed until the leading follicles reached 10 to 12 mm in mean diameter, it was often possible to retrieve a metaphase II oocyte in addition to many germinal vesicle oocytes. As a result the clinical pregnancy rate rose to over 40% per cycle.[23] In women with regular ovulatory cycles, the leading follicle will reach 10 to 12 mm in diameter without stimulation, but this is not the case in anovulatory women with PCOS. Therefore, a short course of gonadotropins may be given in anovulatory women to induce folliculogenesis up to a follicle diameter of 12 mm. This short course of gonadotropins may be administered to induce follicular development after an ultrasound scan on cycle day 8 to 9 shows no evidence of follicular growth.[24] However, this short course of gonadotropins also may be given from day 3 of the cycle to shorten the treatment cycle, save time, and limit the number of ultrasound assessments for patients. We term this treatment approach "early short stimulation (ESS) modified natural cycle IVF." In this protocol, as in the conventional modified natural cycle IVF, low-dose gonadotropin therapy is required for only three to five days (hence "short"). However, this treatment begins early in the cycle when the lead follicle is only 3 to 5 mm in diameter (hence "early"). No administration of a GnRH antagonist is required because oocyte retrieval occurs before any spontaneous LH surge. In addition to the retrieval of one mature oocyte, multiple immature oocytes also are retrieved and can be matured in vitro. This increases the potential number of embryos available for selection, transfer, and cryopreservation for future use. In our experience, this can lead to a clinical pregnancy rate per cycle of 45% in women under 35 years.

ABBREVIATIONS

ESS	early short stimulation
GnRHa	gonadotropin-releasing hormone agonisth
CG	human chorionic gonadotropinh
MG	human menopausal gonadotropin
IVM	in vitro maturation
OHSS	ovarian hyperstimulation syndrome
PCOS	polycystic ovary syndrome