ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Low-dose human chorionic gonadotropin alone can complete follicle maturity: successful application to modified natural cycle in vitro fertilization

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Objective: To investigate the feasibility of utilizing low-dose hCG alone to complete follicle maturity in a natural cycle, without the need for antecedent exogenous FSH stimulation.
Design: Case series.
Setting: Academic fertility program.
Patient(s): Normally ovulatory women with infertility thought to be predominantly due to male factor.
Intervention(s): Modified natural IVF cycles were conducted as follows: natural ovulatory cycles were monitored with serial ultrasound examinations and serum E_2 determinations. When the lead follicle reached preovulatory status according to cycle day, ultrasound, and E_2 levels, 0.25 mg of the GnRH antagonist ganirelix acetate was administered along with 200 IU of hCG. These medications were repeated daily for 2 to 3 days with further serial monitoring. A trigger dose of 10,000 IU of hCG was followed by follicle aspiration, IVF, and ET in a standard manner.
Main Outcome Measure(s): Follicle maturity, live births, documentation of the feasibility of this new approach.
Result(s): In all cases, E_2 levels rose and the dominant follicle continued to increase in size in response to low-dose hCG after GnRH antagonist administration. Follicle aspiration yielded one or more mature oocytes. In vitro fertilization and ET resulted in live births.
Conclusion(s): Low-dose hCG can be used to complete follicle maturity in a natural cycle without the need for antecedent exogenous FSH stimulation. This finding may have strong clinical utility in modified natural cycle IVF. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: hCG boost, IVM, low-dose hCG, modified natural cycle IVF, natural cycle IVF

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The first live birth achieved with the technique of IVF took place in a purely natural cycle (1). However, the relative inefficiency of the laparoscopic approach to follicle aspiration pushed investigators towards controlled ovarian stimulation, to increase the number of follicles and oocytes available and thus increase the per-cycle efficiency of the process. Within a relatively short period controlled ovarian stimulation became the standard of treatment, and it remains so to this day. The advent of ultrasound-guided transvaginal follicle aspiration in the late 1980s significantly reduced the trauma to the patient and increased the efficiency of follicle aspiration, and therefore several programs started to reinvestigate the option of IVF in a cycle without follicular stimulation (2, 3). Subsequent attempts to optimize natural cycle IVF utilized hCG triggering of ovulation;

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this method allowed for more accurate scheduling of follicle aspiration. However, premature ovulation continued to be a problem, and cycle cancellations further hampered the overall efficiency of natural cycle IVF (4, 5).

In the early 1990s antagonists of GnRH first became clinically available. The antagonist could be administered in the late follicular phase of a natural cycle to prevent premature ovulation; however, suppression of the LH surge also blocked the endogenous FSH stimulation of the follicle. Therefore, for follicular development to continue, gonadotropins (typically hMG) had to be administered (6, 7). This approach proved successful and became known as the "modified natural cycle" in the context of its application to IVF. Virtually all subsequent published series have utilized this approach (8–10). The advantage of a decreased cancellation rate is clear. However, the utilization of hMG adds cost, in addition to the inconvenience of additional injections.

Previous studies have demonstrated that hCG alone may be used to complete follicle maturation in cycles using controlled ovarian stimulation (11, 12). In these studies, ovaries were stimulated with exogenous FSH until the lead follicle reached 12 mm. At that point FSH was discontinued and subsequent follicular development achieved with the use of low-dose hCG (200 IU) alone. We reasoned that it might be possible to utilize this approach in conjunction with the modified natural cycle IVF. Furthermore, because a single vial of hCG is substantially less expensive than multiple vials of gonadotropin preparations containing FSH (such as hMG), this modification would have the additional benefit of a decrease in the overall cost of the procedure.

The purpose of this report is to document the feasibility of this approach.

MATERIALS AND METHODS

The protocol for modified natural cycle IVF was approved by the institutional review board of the University of Southern California Keck School of Medicine (HS-10-00090). Modified natural IVF cycles were conducted as follows: natural ovulatory cycles were monitored with serial transvaginal ultrasound examinations and serum E_2 determinations. When the lead follicle reached preovulatory status according to cycle day, ultrasound, and E_2 levels (4, 5), 0.25 mg of the GnRH antagonist ganirelix acetate (GA) was administered along with 200 IU of hCG ("hCG boost"). Both medications were self-administered by patients SC. Patients were asked to return daily for continued serial monitoring with ultrasound and serum E_2 determinations. Both medications were repeated daily until follicle maturity criteria were reached. These criteria were previously established by our program as a guideline for the timing of ovulation triggering (4) and used a combination of follicle size and E_2 levels (>20 mm and >200 pg/mL, or >18 mm and >250 pg/mL, or >15 mm and >300 pg/mL for mean follicle diameter and serum E_2 levels, respectively). When these maturity criteria were reached, a trigger dose of 10,000 IU of hCG was administered. Follicle aspiration, fertilization in vitro, and ET were subsequently performed as previously described (5, 13).

The three cases described here all presented with infertility that was thought to be primarily due to severe male factor. Patient 1 subsequently turned out to have very poor response to ovarian stimulation. Patients 2 and 3 wanted to avoid ovarian stimulation. All had normal ovulatory cycles with normal FSH levels.

RESULTS

Case 1

The patient was a 39-year-old whose infertility was primarily due to oligospermia. She underwent two IVF cycles with controlled ovarian stimulation, in which she demonstrated a poor response to stimulation and poor embryo morphology. In a subsequent cycle, she was monitored during the follicular phase of a natural cycle (Table 1). On cycle day 12, she was found to have a leading follicle of 18.6 mm in mean diameter and serum E_2 level of 139 pg/mL. She was judged to be at risk for ovulation, and a dose of GA 0.25 mg was administered along with "hCG boost." The E_2 level rose and the follicle diameter increased by the next day, and the medications were repeated. On day 14, follicle maturity criteria were reached (Table 1). The patient self-administered a trigger dose of 10,000 IU of hCG, and oocyte retrieval took place 34 hours later. The dominant oocyte was successfully retrieved and fertilized with intracytoplasmic sperm injection (ICSI). A single embryo was transferred 3 days later, resulting in an intrauterine pregnancy and subsequently a live birth at term.

Case 2

A 31-year-old nulligravida with male factor infertility was monitored during a natural cycle, as described in Table 2. In the late follicular phase, growth of the dominant follicle was controlled with a combination of GA and hCG boost as in case 1. After ovulation trigger with 10,000 IU of hCG, the dominant follicle was successfully aspirated. In addition the remaining small follicles were aspirated, yielding a total of 12 oocytes, of which 2 were mature and the rest were immature. Both mature oocytes underwent ICSI, and one fertilized successfully. The resulting embryo was cultured until transfer on day 3 after oocyte retrieval. Embryo transfer resulted in an intrauterine pregnancy and a live birth at term. Of the 10 remaining immature oocytes, 3 underwent in vitro maturation (IVM) by overnight incubation in a culture dish. Two of the three fertilized with ICSI. However, their subsequent embryo

TABLE 1

Patient 1 cycle details.

	Cycle day					
Parameter	**9**	**10**	**11**	**12**	**13**	**14**
Lead follicle (mm)	15.1		16.0	18.6	19.8	21.2
Serum E_2 (pg/mL)	46		111	139	141	218
Ganirelix acetate (mg)				0.25	0.25	0.25
hCG dose (IU)				200	200	10,000

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