

Oocyte retrieval timing based on spontaneous luteinizing hormone surge during natural cycle in vitro fertilization treatment

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Objective: To determine the efficiency of oocyte retrieval (OR) timing based on the occurrence of spontaneous LH surge during natural cycle IVF (ncIVF) treatment.

Design: Retrospective cohort study. The cohort was divided into five subgroups according to the presumed stage of spontaneous LH surge on scheduling day (1A: before onset; 1B: surge start; 2: ascending slope; 3: peak; and 4: descending slope).

Setting: Private infertility clinic.

Patient(s): Three hundred sixty-five infertile patients who underwent 1,138 ncIVF treatment cycles during 2008–2011.

Intervention(s): Drug-free ncIVF treatment.

Main Outcome Measure(s): Rate of successfully retrieved, fertilized oocytes, cleaved embryos, and live births per scheduled oocyte retrieval.

Result(s): In 61% of the cycles OR was scheduled before or just at the start of the LH surge (groups 1A–1B), whereas in the remaining cases it was scheduled after the surge had already started (groups 2–4). The proportion of cycles with successfully recovered (range, 71%–86%), inseminated (range, 61%–78%), fertilized oocytes (range, 47%–68%), cleaved embryos (range, 45%–66%), and live births (range, 4.1%–9.2%) was not significantly different among subgroups.

Conclusion(s): In ncIVF treatment OR timing based on the occurrence of spontaneous LH surge is feasible, yielding acceptable oocyte recovery, fertilization, and embryo cleavage rates. This strategy combined with a rapid and low-risk OR procedure permits the management of a large ncIVF program on a 7-days-per-week basis within working hours. (Fertil Steril® 2014;101:1001–7. ©2014 by American Society for Reproductive Medicine.)

Key Words: Natural cycle IVF, LH surge, GnRH agonist triggering, in vitro fertilization

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Although the first successful IVF treatment was performed in an unstimulated cycle (1), it was quickly abandoned in favor of controlled ovarian hyperstimulation, which has become the standard of care. In recent years, however, a re-

newed interest has emerged in patient-friendly, low-risk, cost-effective IVF treatments, and natural cycle IVF (ncIVF) was "rediscovered" (2).

Natural cycle IVF treatment is greatly hampered by losses occurring at each step of the process, from oocyte

retrieval scheduling until ET. These include the risk of cancellation due to premature LH surge and ovulation, empty follicles, immature eggs, or fertilization failure. This was underlined by a recent registry-based study from the United States reporting the outcome of 795 unstimulated IVF cycles performed between 2006 and 2007, showing that ET rate per started cycle was gradually decreasing, from 54% to 23% in patients aged <35 and >42 years, respectively (3). Whereas the risk of premature LH rise and ovulation might be diminished by GnRH antagonist cotreatment (2) or nonsteroidal anti-inflammatory

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drug (NSAID) use (4), successful oocyte retrieval is greatly influenced by the way it is timed. In the absence of an LH rise, triggering usually is performed by administering exogenous hCG at a fixed interval between 31 and 36 hours (5). However, in some centers oocyte retrieval (OR) timing is based on the occurrence of a spontaneous LH surge, which is a far more challenging approach (6, 7).

Since 1994 Kato Ladies Clinic in Tokyo has pioneered the development of mild IVF approaches in Japan. At Kato Ladies Clinic and at its other affiliate branches (including our center), ncIVF treatments represented a significant proportion of all cycles, and considerable experience was gathered in their optimal management (4). The aim of the present retrospective study was to analyze the effectiveness of oocyte retrieval scheduling based on the occurrence of spontaneous LH surge during ncIVF treatment.

MATERIALS AND METHODS

Study Patients

All 365 consecutive infertile patients who underwent 1,138 ncIVF treatment cycles during 2008–2011 at our center (Kobe Motomachi Yume Clinic, Kobe, Japan) were included in this retrospective review. After obtaining informed consent, ncIVF was routinely offered to normally cycling (26–35 days) infertile women who ovulated, according to their basal body temperature charts (8). Natural cycle IVF was usually proposed as a first, drug-free, and cost-effective treatment option before starting a series of clomiphene-based minimal stimulation cycles in case no pregnancy was achieved (9). Patients were not selected, and this treatment option was offered over a wide age range. Institutional review board approval was not required for the present study owing to its retrospective nature. In our center's Institutional Review Board approval is not necessary in the case of analysis of retrospective data.

ncIVF Treatment Protocol

After obtaining normal results on baseline ultrasound scan and hormonal profile on cycle day 3, monitoring usually started on day 8–10. Every other day follicular size was measured by two-dimensional transvaginal ultrasound scan together with serum hormonal level determinations (E_2 , LH, and P), with results available in-house within 1 hour. In the ncIVF protocol no GnRH antagonists were used to block the spontaneous LH surge. The center's opening times were such that patient examination and blood collection could be performed between 8:00 AM and 6:30 PM, and oocyte retrieval could be scheduled between 8:00 AM and 5:00 PM on any day of the week (the entire staff followed a 6-day-per-week working schedule, with a variable free day).

Oocyte Retrieval Scheduling

The scheduling strategy during ncIVF treatment is summarized in Table 1. When the leading follicle reached 16–20 mm with a concomitant E_2 level of approximately 200–250 pg/mL, oocyte retrieval was scheduled according to the presumed stage of the spontaneous LH surge. For groups 1A (pre-surge: LH <10 IU/L) and 1B (surge start: LH 10–30 IU/L)

triggering was performed at approximately 11:00 PM to 12:00 AM, and OR was scheduled 2 days later in the morning (with a 30–36-hour interval between triggering and OR). For triggering a GnRH agonist was used exclusively in the form of a nasal spray (busereline 600 μ g), and hCG was avoided completely. With ascending LH levels (30–140 IU/L) OR was anticipated (for the next day performed during morning or afternoon working hours) and scheduled between 15 and 31 hours after the examination. The GnRH agonist triggering dose was either administered immediately after the examination (group 2: ascending slope), or in the case of even higher LH levels (group 3: peak) it was omitted. In very few cases if the spontaneous LH surge was already on its descending side by detecting increased LH with a marked decline in E_2 and rising P (group 4), oocyte retrieval could even be scheduled for the same day of the examination (1 to 2 hours later). With the exception of group 4 in all subgroups low-dose NSAIDs were systematically used every 6 hours before oocyte retrieval to diminish the risk of premature ovulation (4). The retrospective cohort was divided into five subgroups according to the presumed stage of spontaneous LH surge on scheduling day (1A: before onset; 1B: surge start; 2: ascending slope; 3: peak; and 4: descending slope).

Oocyte Retrieval, Fertilization, Embryo Culture, and ET Cycles

In our center oocyte retrievals could be scheduled for any day of the week between 8:00 AM and 5:00 PM, and the whole procedure usually only took 5 to 6 minutes. Transvaginal ultrasound-guided oocyte retrieval was performed without anesthesia using a very thin 21–22-G needle (Kitazato), which has virtually no dead space, and hence follicular flushing was not considered useful. After oocyte retrieval any immature (metaphase I or germinal vesicle) oocytes were observed during a maximum of 12 hours until most of them matured spontaneously. Mature (metaphase II) oocytes were inseminated by conventional IVF or intracytoplasmic sperm injection. Normally fertilized two-pronuclei zygotes were cultured individually in 20 μ L of cleavage-stage medium until day 2 or 3 and in a majority of cases subsequently cultured from day 4 to 6 until blastocyst stage in water jacket small multigas incubators (Astec). Most blastocysts were vitrified electively for subsequent use in frozen-thawed blastocyst transfer cycles. Details of the vitrification method using the Cryotop (Kitazato) were described previously (10). Single embryo transfer was performed in all IVF treatment cycles. The procedure was performed using transvaginal ultrasound guidance by precisely placing a single embryo to the mid-uterine cavity (11). In fresh cycles luteal support in form of oral dydrogesterone tablets (30 mg/d) was administered during 2 weeks after ET and continued in case of pregnancy. Frozen-thawed embryo transfers were performed in spontaneous natural or hormonal replacement cycles.

Outcome Measures and Statistical Analysis

Main outcome measures were the rate of cycles with successful oocyte recovery, fertilized oocytes, and cleaved embryos;

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