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

Daniel Bodri, M.D., M.Sc., Ph.D., Satoshi Kawachiya, M.D., Masae Kondo, M.Sc., Ryutaro Kato, M.Sc., and Tsunekazu Matsumoto, M.D., Ph.D.

Kobe Motomachi Yume Clinic, Kobe, Japan

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 renewed 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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Reprint requests to: Daniel Bodri, M.D., M.Sc., Ph.D., Kobe Motomachi Yume Clinic, 3F Miyuki Building, Akashimachi 44, Chuo-ku, Kobe 650-0037, Japan (E-mail: bodridaniel@gmail.com).

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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 (presurge: 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 μg), 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 μL 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;

TABLE 1

Oocyte retrieval scheduling according to spontaneous LH surge.

Group	Presumed stage of LH surge	Hormonal status on scheduling day	GnRH agonist triggering	Time of oocyte retrieval	Timing ranges
1A–1B	Presurge or surge start	LH <10 or LH 10–30 IU/L, P < 1.0 ng/dL	11:00 PM–12:00 AM	2 d later in the morning (between 8:00 AM and 10:00 AM)	30–36 h[a]
2	Ascending slope	LH 30–53 IU/L, P < 1.0 ng/dL	Triggering immediately	1 d later in the morning/afternoon (until 5:00 PM)	17–31 h[b]
3	Peak	LH 30–140 IU/L, P < 1.0 ng/dL	Nothing	1 d later in the morning/afternoon (until 5:00 PM)	15–28 h[b]
4	Descending slope	E_2 and LH decreasing, P ≥ 1.0 ng/mL	Nothing	Same day (until 5:00 PM)	1–2 h[b]

[a] Between triggering and oocyte retrieval.
[b] Between blood drawing and oocyte retrieval.

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these were compared among subgroups (1A, 1B, 2, 3, and 4). The effect of female age, infertility type, cycle rank, follicular size, serum E_2 level, and the presumed stage of LH surge on oocyte recovery rate was evaluated by multivariate logistic regression analysis. Additionally, overall and age-specific live birth rates were also presented. Metric variables were analyzed by one-way analysis of variance, and nominal variables were analyzed by the χ^2 test. A P value of $<.05$ was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Approximately 58% of our patients were older than 38 years at start of treatment. Mean (±SD) body mass index was low (20.8 ± 2.3 kg/m^2), as expected in the Japanese population. Most patients had primary infertility (67%) and were nulliparous (87%). Among infertility causes Bologna poor responders (29%) were overrepresented. Only few patients (20%) did not have any previous fertility treatment, and most of them (55%) had already undergone conventional and/or minimal IVF treatment cycles at other centers. Baseline patient characteristics are summarized in Supplemental Table 1 (available online).

Main Outcomes According to Different LH Surge Stages

Follicular size and hormonal levels (E_2, LH, and P) on scheduling day, as well as timing intervals according to different surge subgroups, are represented in Figure 1 and Supplemental Table 2. Differences were statistically significant for each variable, which was especially marked for LH levels and timing intervals.

In 61% of the cycles oocyte retrieval was schedule before or just at the start of the LH surge (groups 1A and 1B), whereas in the remaining cases (39%) it was scheduled after LH surge had already started. Overall premature ovulation and successful oocyte recovery rates were 4% (45 of 1,138) and 78% (887 of 1,138), respectively. The proportion of cycles with an inseminated oocyte, fertilized oocyte, and cleaved embryo was 67%, 57%, and 56%, respectively. Main outcomes according to LH surge subgroups are presented in Table 2. The proportion of cycles with successfully recovered (range, 71%–86%), inseminated (range, 61%–78%), fertilized oocytes (range, 47%–68%), and cleaved embryos (range, 45%–66%) was not significantly different among subgroups.

Overall ET and Live Birth Outcomes

Cleavage-stage embryos were transferred in 109 cycles, which resulted in 23 live births (21%). In the remaining 502 cycles cleavage-stage embryos were submitted to prolonged culture, yielding a good-quality blastocyst in 177 treatment cycles (35%). Of these, to date, 146 blastocysts were used (mostly frozen–thawed embryo transfer), resulting in 51 live births (35%). For the entire cohort live birth rate per ET and scheduled oocyte retrieval was 29% (74 of 256) and 6.5% (74 of 1,138), respectively. A detailed flow chart of study events is presented in Figure 2. Age-specific live birth rates per scheduled oocyte retrieval were 22% (29 of 134), 10.5% (16 of 153), 7.7% (18 of 233), and 4.2% (10 of 326) for <35-, 35–37-, 38–40-, and 41–43-year-old patients, respectively. No live births were obtained in infertile women aged ≥44 years.

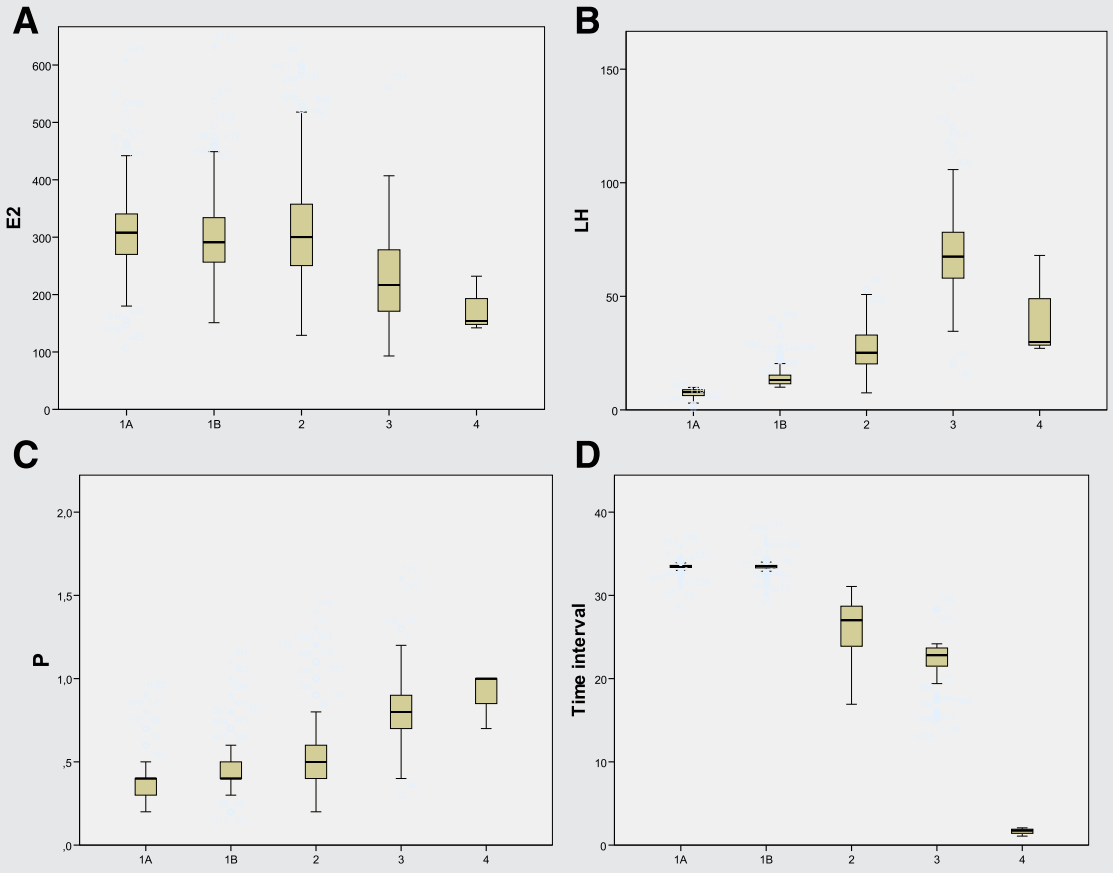
Multivariate Analysis

In a multivariate analysis successful oocyte retrieval was not associated with female age (adjusted odds ratio [aOR] 0.98, 95% confidence interval [CI] 0.94–1.03, $P=.48$), follicular size (aOR 0.96, 95% CI 0.88–1.04, $P=.27$) and serum E_2 level on scheduling day (adjusted OR 1.0, 95% CI 1.0–1.0, $P=.90$), or cycle rank (adjusted OR 1.03, 95% CI 0.99–1.07, $P=.20$). On the other hand, patients with endometriosis had a lower chance of successful oocyte retrieval (aOR 0.40, 95% CI 0.17–0.94, $P=.04$). In Bologna poor ovarian responders a similar almost significant trend was observed (aOR 0.51, 95% CI 0.26–1.02, $P=.06$). After adjusting for the above variables, compared with group 1A (pre-LH surge) group 1B (LH surge start) was associated (aOR 1.64, 95% CI 1.10–2.44, $P=.02$) with a significantly higher whereas group 3 (peak) (aOR 1.90, 95% CI 0.96–3.75, $P=.07$) with an almost significantly higher chance of retrieving an oocyte.

DISCUSSION

Our large, retrospective study showed that in ncIVF treatment oocyte retrieval timing based on the occurrence of

FIGURE 1



Hormonal levels and timing intervals according to LH surge subgroups. (A) E_2, (B) LH, (C) P, (D) time interval.

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spontaneous LH surge is feasible and permits the management of a large natural cycle IVF program on a 7-days-per-week basis within working hours. Moreover, acceptable oocyte recovery, fertilization, and embryo cleavage rates could be reached in concordance with previously published results on the efficacy of ncIVF treatment.

An extensive review that analyzed the efficiency of ncIVF treatment in 20 studies published between 1989 and 2001 involving 1,800 cycles showed that successful oocyte recovery rate varied greatly among studies (30%–96%). The timing of oocyte retrieval was mostly done with exogenous hCG but with cancellation of the cycle if LH surge occurred prematurely (5). Only very few groups planned the oocyte retrieval according to the spontaneous LH surge only. In the retrospective study of Zayed et al. (7) involving 162 cycles the oocyte retrieval rate per planned cycle was 89%. A subsequent retrospective review from the same authors compared the outcome of ncIVF treatments based on whether scheduling was performed according to the occurrence of spontaneous LH surge or with the use of a terminal hCG injection. In the LH surge group (534 cycles) eggs were collected in 81% of the scheduled cycles, whereas in the hCG group (241 cycles) this rate was slightly lower, 76%. The authors concluded that compared with twice-daily LH monitoring the administration of hCG did not have any benefit with respect to eggs collected or pregnancies obtained (12).

Another, more widely published and used protocol is the modified natural cycle IVF protocol (mncIVF), whereby GnRH antagonist cotreatment (with 150 IU/d FSH add-back) is introduced to prevent the spontaneous LH surge and to facilitate oocyte retrieval scheduling with exogenous hCG (2). The largest published series on mncIVF by Pelinck et al. (13), reporting the outcome of 1,048 cycles, found a 66% oocyte retrieval rate per scheduled retrieval. This suggests that the use of GnRH antagonists did not substantially improve the outcome compared with a completely GnRH antagonist–free protocol. However, in a more recent randomized trial from the same group the rates of successful oocyte retrieval were increased to 73% (from 68%) by the use NSAIDs to prevent premature ovulation (14).

In our study groups 1A (presurge) and 1B (surge start) were scheduled using the same strategy involving agonist triggering around midnight and OR scheduled at a fixed 33–34-hour interval 2 days later. Outcomes seemed to be somewhat better for subgroup 1B, in which the LH surge had already started (84% vs. 78% oocyte retrieval rate). In both of these subgroups the triggering agent was administered several hours after the last examination; however, this

TABLE 2

Outcomes according to LH surge stage.

Parameter	Total	Study group 1A	1B	2	3	4	*P* value
Scheduled ORs, n (%)	1,138	347 (31)	347 (30)	343 (30)	98 (8.6)	3 (0.3)	–
Patient age (y), median ± SD	40.3 ± 4.3	40.7 ± 4.4	40.2 ± 4	40.1 ± 4.2	40.2 ± 5	43 ± 3.5	.224[a]
Cycle rank, median ± SD	3.4 ± 4.4	3.7 ± 4.6	3.4 ± 4.5	3.2 ± 4.1	2.8 ± 3.6	1.7 ± 2.1	.264[a]
Ovulated cycles, n (%)[b]	45 (4)	10 (2.9)	18 (5.2)	12 (3.5)	5 (5.1)	0 (0)	.58[c]
Cycles with retrieved oocyte, n (%)[b]	887 (78)	265 (76)	292 (84)	243 (71)	84 (86)	3 (100)	.59[c]
Cycles with inseminated oocyte, n (%)[b]	768 (67)	226 (65)	255 (74)	209 (61)	76 (78)	2 (67)	.49[c]
Fertilization rate (%)	83	85	87	77	88	100	.9[c]
Cycles with fertilized (two pronuclei) oocyte, n (%)[b]	644 (57)	193 (55)	222 (64)	160 (47)	67 (68)	2 (67)	.11[c]
Cycles with cleaved embryo, n (%)[b]	633 (56)	192 (55)	219 (63)	155 (45)	65 (66)	2 (67)	.09[c]
Cycles with embryo transfer, n (%)[b]	256 (22)	79 (23)	88 (25)	64 (19)	24 (24)	0 (0)	.46[c]
Cycles with live birth, n (%)[b]	74 (6.5)	24 (6.9)	27 (7.8)	14 (4.1)	9 (9.2)	–	.25[c]

[a] One-way analysis of variance.
[b] Per scheduled oocyte retrieval.
[c] χ^2 test.

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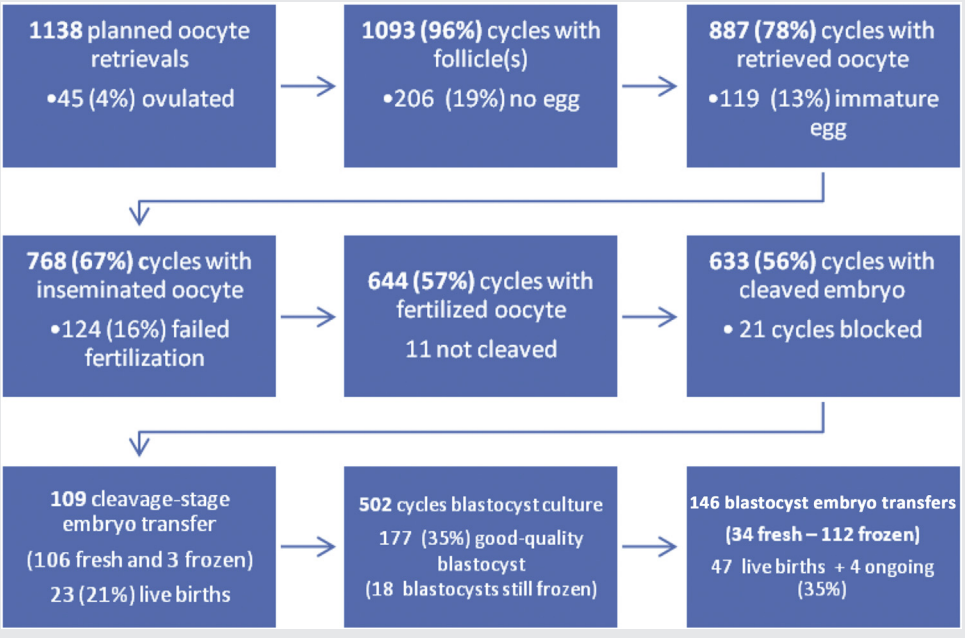
did not seem to affect outcome negatively. Probably in those cycles in which spontaneous LH surge started during this time period the protective effect of NSAIDs prevented the follicle from rupturing and an oocyte could be still retrieved. Group 2 (ascending slope) performed the worst, with the lowest oocyte retrieval rate of 61% in the cohort. This might indicate that some cycles were timed too early (at 24–29 hours). In contrast, the highest oocyte retrieval rate of 86% was reached for group 3 (peak), which suggests that with more advanced LH levels OR was scheduled (anticipated) correctly. Finally only very few cases were in group 4 (descending slope), indicating that with frequent monitoring every other day (and the corresponding center's opening hours 7 days per week) most ncIVF cycles (61%) could be scheduled before or at the start of the spontaneous LH surge.

Follicular flushing was not used in our study, mainly owing to specifics of the very fine (21–22 G) oocyte retrieval needle used (which had an extremely small dead space) but also for practical reasons (to avoid anesthesia and to ensure of rapid turnover of procedures). Nonetheless, in a recent study from a Swiss group involving 164 monofollicular IVF cycles multiple flushing (up to three times) was found to be beneficial by increasing the oocyte yield from 45% to 81% (15).

FIGURE 2



Flow chart of study events.

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A multivariate analysis in our study did not show any significant impact of female age or cycle rank on the chance of retrieving an egg after ncIVF. On the other hand, among infertility diagnoses patients, those with endometriosis had a significantly lower (odds ratio 0.40, 95% CI 0.17–0.94, $P=.04$) possibility of retrieving an oocyte, which might be related to destruction of ovarian tissue by endometriomata and/or previous surgery. Similarly, Bologna poor ovarian responders had a marginally lower chance (odds ratio 0.51, 95% CI 0.26–1.02, $P=.06$) of successful oocyte retrieval. This is in contrast with a recent retrospective review from the Brussels group in which oocyte retrieval rates between Bologna patients and controls were not significantly different (75% vs. 78%). However, in their study live birth rates per started cycle were still much lower among Bologna poor responders (2.6% vs. 8.9% in controls), and the authors concluded that these patients are not benefitting from an ncIVF approach (16).

Similarly to a previous United Kingdom study (12), the large ncIVF program managed at our center implicated a 7-day-per-week working schedule, and the oocyte retrievals were fit in a 9-hour interval (between 8:00 AM and 5:00 PM) within the day. However, most of the procedures were performed in the morning hours (8:00 AM to 10:00 AM) by establishing a very rapid turnover of procedures (every 5 to 6 minutes). This was only feasible by an extremely well-organized flow of patients and by using a very thin (21–22 G) retrieval needle that permitted the avoidance of any anesthesia.

As a part of our center's ncIVF protocol short-term, low-dose NSAIDs were routinely used to reduce the rate of premature ovulations. The effectiveness of this approach during ncIVF treatment was already suggested by previous small-scale studies (17, 18). In a large retrospective analysis of our group involving 1,865 cycles with an imminent LH surge on triggering day (10–30 IU/mL) NSAID use was associated with a significantly lower risk of premature ovulation (aOR 0.24, 95% CI 1.06–1.61) (4). In a recent placebo-controlled, randomized clinical trial performed in the setting of modified natural cycle treatment a Dutch group has found similar encouraging results, even if statistically significant findings (aOR 8.29, 95% CI 1.63–42.3, $P=.009$) were only found in a subgroup of patients without an LH surge (14). In our practice we encourage the routine use of NSAIDs in all stages of ncIVF treatment (before and after spontaneous LH surge has occurred), owing to a good safety profile and potential beneficial effects.

Although overall live birth rates per scheduled OR were low (6.5%) in our series in younger age groups (<38 years), they were more acceptable. Success rates in our series were greatly affected by the fact that blastocyst culture was performed in most (79%) treatment cycles. Probably because of a high proportion of >38-year-old patients this turned out to be counterproductive owing to a high proportion of cycles (65%) that did not reach the blastocyst stage. On the other hand, in another study from our group with a large series of 1,865 ncIVF cycles in which embryos were transferred earlier at day 2 to 3, the rate of cancelled cycles was much lower, and more cycles reached ET (43% vs. 22%), with acceptable live birth rates (14.7% vs. 6.5%) per scheduled cycles, underlining the increased efficiency of cleavage-stage ET compared with blastocyst-stage transfer. Another main limitation of our study is related to its retrospective nature; however, we included only consecutive patients treated with the same protocol, therefore any selection bias might be limited considerably.

In conclusion, in ncIVF treatment OR timing based on the occurrence of spontaneous LH surge yields acceptable oocyte recovery and fertilization rates 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-day-per-week basis within working hours.

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SUPPLEMENTAL TABLE 1

Baseline patient characteristics (n = 365).

Female age (y), mean ± SD	38.4 ± 4.3
28–34 (%)	21
35–37 (%)	21
38–40 (%)	24
41–44 (%)	27
45–52 (%)	7
Body mass index (kg/m^2)	20.8 ± 2.3
Female infertility (%)	
Primary	67
Nulliparous	87
Bologna poor responders	29
Tubal	13
Endometriosis	5.2
PCOS	3.3
Uterine	2.5
Mixed	4.7
Basal FSH ≥12 (IU/L)	33
Basal FSH ≥20 (IU/L)	11
Duration of marriage (y), mean ± SD	6.6 ± 4.1
ART history	
No previous treatment (%)	20
Previous IUI (%), no. of cycles (mean ± SD)	66, 4.8 ± 3.6
Previous IVF (conventional) (%), no. of cycles (mean ± SD)	41, 2.7 ± 2.0
Previous IVF (mild) (%), no. of cycles (mean ± SD)	28, 4.1 ± 4.7
Previous IVF (total) (%), no. of cycles (mean ± SD)	55, 4.1 ± 4.0
Partner age (y), mean ± SD	40.5 ± 5.7

Note: ART = assisted reproductive technology; PCOS = polycystic ovary syndrome.

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SUPPLEMENTAL TABLE 2

Baseline cycle characteristics according to LH surge stage.

	Study group					
Parameter	**1A**	**1B**	**2**	**3**	**4**	***P* value**[a]
Scheduled ORs, n (%)	347 (31)	347 (30)	343 (30)	98 (8.6)	3 (0.3)	–
Leading follicle (mm)	18 (17–19)	17 (16–19)	18 (16–19)	17 (16–19)	17	.001
E_2 (pg/mL)	308 (270–341)	291 (256–334)	300 (250–358)	217 (171–279)	154	<.0001
LH IU/L	8 (6–9)	13 (12–15)	25 (20–33)	68 (58–78)	30	<.0001
P ng/dL	0.4 (0.3–0.4)	0.4 (0.4–0.5)	0.5 (0.4–0.6)	0.8 (0.7–0–9)	1.0	<.0001
Timing interval (h)	33.5 (33.3–33.6)[b]	33.5 (33.3–33.6)[b]	27 (23.9–28.7)[c]	22.8 (21.5–23.7)[c]	1.8[c]	<.0001

Note: Values are medians (quartiles) unless otherwise noted.
[a] One-way analysis of variance.
[b] Between triggering and oocyte retrieval.
[c] Between blood drawing and oocyte retrieval.

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