In Vitro Fertilization Programmed for Weekday-Only Oocyte Harvest: Analysis of Outcome Based on Actual Retrieval Day

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Objective: *Our aim was to assess the effect of the day of ovum retrieval on outcome in an IVF program scheduled for weekday-only ovum retrievals.*
Design: *This was a retrospective study of patients who underwent transvaginal ultrasound-guided ovum retrieval (TVUS-OR) in an IVF program from August 10, 1992, to April 30, 1993.*
Setting: *A university-based tertiary referral hospital center was the setting.*
Participants and Methods: *All patients (n = 501) who underwent TVUS-OR were divided into three groups: (1) patients who underwent TVUS-OR on Monday; (2) patients who underwent retrieval on Tuesday, Wednesday, or Thursday; and (3) patients who underwent retrieval on Friday. All patients were induced by the same controlled ovarian hyperstimulation protocol, which consisted of a GnRH analogue "flare-up" followed by parenteral menotropins, after a scheduled oral contraceptive-induced menses. Patients and cycle characteristics in the three groups were compared and clinical outcome was evaluated.*
Results: *The similarity of patients and cycle characteristics confirmed the uniformity of the three groups. No difference was found in any of the clinical outcomes. However, in the first half of the program, we revealed a trend in which patients at high risk for ovarian hyperstimulation syndrome, requiring freezing all embryos and not allowing transfer during the treatment cycle, occurred more commonly in women whose retrieval occurred on Monday. This trend disappeared in the second half of the analysis.*
Conclusions: *In an in vitro fertilization program in which ovum retrievals occurred only on weekdays, no significant difference in outcome was found in patients undergoing ovum retrieval on Monday or Friday versus midweek. In addition to significant savings by eliminating weekend retrievals, IVF outcome is not compromised.*

KEY WORDS: In vitro fertilization; scheduled oocyte retrieval; controlled ovarian hyperstimulation.

INTRODUCTION

In vitro fertilization and embryo transfer (IVF-ET) is a costly treatment with respect to patients' time, financial resources, and emotional reserve. The medical and technical personnel and laboratory resources required for IVF-ET significantly affect the cost per cycle. Many protocols have emerged to simplify IVF-ET and decrease the associated medical and laboratory costs. Tempelton *et al.* (1) first introduced a fixed regimen of ovulation induction following scheduled menses using norethisterone or oral contraceptives, to limit preovulatory follicle aspiration to weekdays. Many authors have demonstrated the effectiveness of progestogens (2, 3) or oral contraceptives (4, 5) in scheduling oocyte retrieval on weekdays. However, as gonadotropin-releasing hormone analogues (GnRH-a) were not used in these studies, the cancellation rate due to premature luteinization or ovulation was very high (6). With the introduction of GnRH agonist-based protocols for IVF (7), luteinizing hormone (LH) surges are prevented, and the initiation of menotropin administration can be based on the desired day of retrieval. In GnRH-a based protocols, the timing of hCG administration is flexible as well, as several studies have suggested no detrimental effect, and even a potential benefit, of postponing hCG administration on IVF outcome. (8–13).

In order to decrease the costs and inconvenience associated with IVF, we have taken advantage of the flexibility of a GnRH-a "flare-up" protocol and have initiated a "weekday-only" policy for ovum retrieval.

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Concerns that hCG may be administered at a "less than optimum time" due to weekend constraints, thereby adversely affecting outcome in some patients, initiated a retrospective study of outcome in couples undergoing Monday or Friday versus midweek retrievals (on Tuesday, Wednesday, and Thursday). We hypothesized that there would be no significant difference in fertilization or pregnancy rates between the different days of ovum pickup (OPU).

MATERIALS AND METHODS

A retrospective study was performed of all 501 cycles of transvaginal ultrasound-guided ovum retrieval (TVUS-OR) in a university-based IVF program (The Toronto Hospital, Toronto, Canada), from August 10, 1992, to April 30, 1993. Cycles were classified into three groups according to the day of ovum retrieval: retrieval on Monday (possible delayed OPU); retrieval on Tuesday, Wednesday, or Thursday, days which were not constrained by weekends; and retrieval on Friday (possible premature OPU).

Patients in all groups were on oral contraceptives prior to their IVF cycle. Controlled ovarian hyperstimulation (COH) consisted of a "flare-up" protocol, utilizing daily subcutaneous GnRH-a (1 mg leuprolide acetate; Lupron; Abbott Pharmaceutical Company Ltd., Point Claire, Quebec, Canada) and parenteral gonadotropins beginning on the eighth day following the last day of oral contraceptive pill ingestion. The standard protocol began with 2 ampoules of human menopausal gonadotropin (hMG; 75 IU/amp Pergonal; Serono, Mississauga, Ontario, Canada) in women under 35 and 3 ampoules in women over 35. The standard protocol was modified if there was a history of poor response or a risk of hyperstimulation based on menstrual history or prior response.

Daily ultrasound for follicular tracking was performed starting on the third day of gonadotropin administration. Blood samples for measurement of serum E_2, concentration were also drawn daily. Human chorionic gonadotropin (hCG; 5000 IU; Profasi; Serono) was administered when at least two follicles had a diameter $\geq$ 18 mm as detected on TVUS, and the E_2 level was higher than 1000 pmol/L per mature follicle. Based on US findings and serum E_2 levels, hCG was administered on Saturday through Wednesday and ovum retrieval was performed 36 hr later.

On the morning of ovum retrieval, the patient was premedicated with Ativan (Wyeth, Windsor, Ontario, Canada), 2 mg sublingually, and atropine sulfate (Abbott Pharmaceutical Company Ltd.), 0.5 mg iv. Transvaginal ultrasound-guided ovum retrieval was performed after local anesthetic injection (lidocaine benzoate, 0.5%) to both lateral fornices of the vagina (10 ml on each side).

Up to three embryos, and rarely four embryos, were transferred 48 hr following ovum retrieval. Freezing of extra fertilized oocytes, usually at the two-pronuclear stage, was offered to all patients. In women judged to be at very high risk for ovarian hyperstimulation syndrome (OHSS; peak $E_2 > 25{,}000$ pmol/L and multiple intermediate-size follicles 14–16 mm), this risk was diminished by freezing all embryos and thereby avoiding the chance of conception during the treatment cycle. The luteal support protocol consisted of 1500 IU Profasi every third day for 2 weeks, accompanied by progesterone vaginal suppositories. In cases judged at risk for OHSS following embryo transfer, increased progesterone support only was used.

Clinical characteristics evaluated included patient age and infertility diagnosis. Cycle characteristics included duration of oral contraceptive pill ingestion (OCP) before ovulation induction, number of hMG ampoules used for ovarian hyperstimulation, cycle day of hCG administration, and E_2 level and endometrium thickness on the day of hCG administration. Sperm characteristics included number of sperm and motility as achieved after treatment by standard swim-up. Outcome parameters included number of oocytes retrieved per patient, distribution of oocyte maturity as assessed by cumulus/corona cell complex dispersion (14), fertilization rate, number of embryos transferred, clinical pregnancies (positive gestational sac identified on ultrasound), and frequency of ovarian hyperstimulation syndrome.

Statistical Evaluation

The SPSS PC (+) (SPSS Inc.) statistical software package was used for analysis. Data were analyzed by one-way ANOVA, Student *t* test, and chi-square where appropriate. A difference of $P < 0.05$ was considered significant. All values are given as mean $\pm$ SD.

RESULTS

Five hundred one TVUS-OR were performed between August 10, 1992, and April 30, 1993. In 18 cycles (3.6%) no oocytes were retrieved. In 483 cycles one or more oocytes were retrieved. These cycles were included in our study. In 408 cycles at least one egg was

Table I. Cycle Distribution

	Group 1 (Mon.)	Group 2 (Tues./Wed./Thur.)	Group 3 (Fri.)	Total
No. of cycles	110	312	79	501
No. of cycles in which 1 egg or more retrieved	106 (96.3%)	302 (96.8%)	75 (94.9%)	483 (96%)
No egg retrieved[a]	4 (3.7%)	10 (3.2%)	4 (4.1%)	18 (4%) ($P = 0.35$)
No. of cycles in which 1 egg or more fertilized	82 (77.4%)	262 (86.8%)	64 (85.4%)	408 (84%)
No egg fertilized[a]	24 (22.6%)	40 (13.2%)	11 (14.6%)	75 (16%) ($P = 0.069$)
No. of cycles in which 1 fresh embryo or more transferred	76 (92.7%)	258 (98.5%)	64 (100%)	398 (97.6%)
No. of cycles with all embryos frozen[b]	6 (7.3%)	4 (1.5%)	0 (0%)	10 (2.4%) ($P < 0.01$)

[a] No statistical significance was found betwen these groups.
[b] Number of cycles with all embryos frozen on Sunday compared to the rest of the weekdays was significantly different.

Table II. Clinical and Cycle Characteristics

Group 1 (Mon.)	Group 1 (Mon.)	Group 2 (Tues./Wed./Thur.)	Group 3 (Fri.)	Significance (P value)
Mean age (yr)	34.3 ± 3.2	33.3 ± 3.2	34.2 ± 3.5	0.03
OCP (days)	19.4 ± 15.3	20.4 ± 14.2	19.1 ± 15.3	NS
hMG (No. of amps)	24.4 ± 12.5	22.2 ± 10.3	26.4 ± 10.2	NS
Cycle day of hCG	13.4 ± 2.0	13.2 ± 1.6	13.3 ± 1.4	NS
E_2 level at hCG day (pmol/ml)	12,995 ± 7,857	11,947 ± 7,824	10,495 ± 6,832	NS
Endo thickness at hCG day (mm)	9.83 ± 2.7	9.86 ± 2.8	9.72 ± 2.8	NS

fertilized and transferred. In the remained 75 cycles (18.3%) no oocyte was fertilized. There was no difference between groups with respect to failed oocyte retrieval or failed fertilization (Table I).

Table II shows the clinical and cycle characteristics of the three groups. Although the mean age of the patients in group 2 was significantly lower than that in groups 1 and 3 ($P = 0.03$), this does not seem to have any clinical significance. The rest of the parameters were not significantly different between groups. Table III shows the similar distribution of the infertility diagnoses in the three groups.

Sperm characteristics including number of sperm and motility as achieved after treatment by standard swim-up showed no significant difference between groups.

Outcome Parameters

The IVF outcome analysis (Table IV) demonstrated no significant difference with respect to the number of eggs retrieved or their maturity breakdown. No significant difference was found with respect to the fertilization rate, the number of embryos transferred, and the most important parameter, the pregnancy rate.

Ovarian Hyperstimulation Syndrome

Moderate and severe OHSS (15), requiring hospital admission, occurred in 12 of the 408 patients in whom

Table III. Comparison of Diagnosis in the Three Groups[a]

Diagnosis	Group 1 (Mon.)	Group 2 (Tues./Wed./Thur.)	Group 3 Fri.)
Tubal (%)	53	50	50
Normal infertile (%)	15	15	23
Male factor (%)	17	19	13
Endometriosis (%)	10	11	9
Anovulation (PCO) (%)	6	6	5
Others (%)	8	5	4

[a] The cumulative percentage in each group is above 100%, because some couples had more than one diagnosis. No statistical significance was found between these groups ($\chi^2 = 12.5$, $P = 0.81$).

Table IV. The Effect of Retrieval Day on IVF Outcome Parameters

	Group 1 (Mon.)	Group 2 (Tues./Wed./Thur.)	Group 3 (Fri.)	Significance (*P* value)
Total No. of eggs	9.4 ± 6.9	9.4 ± 7.3	8.2 ± 5.2	NS
No. of postmature eggs	1.7 ± 2.0	1.7 ± 2.1	1.1 ± 2.1	NS
No. of mature eggs	2.5 ± 2.8	2.3 ± 2.7	2.2 ± 2.2	NS
No. of intermediate mature eggs	1.9 ± 3.0	2.3 ± 3.6	1.8 ± 2.7	NS
No. of immature eggs	2.1 ± 1.9	2.1 ± 2.3	1.8 ± 1.7	NS
Fertilization rate (%)	56.1 ± 37	54.7 ± 32	56.6 ± 34	NS
No. of embryos transferred	2.6 ± 0.8	2.5 ± 0.8	2.6 ± 0.7	NS
OHSS (%)[a]	3.6	3.0	1.5	NS
Pregnancy rate (% per ET)	27.6 (27/76)	27.4 (69/258)	21.8 (14/64)	NS

[a] Ovarian hyperstimulation syndrome was defined as moderate to severe (15), requiring hospital admission.

embryos were transferred (n = 3, 8, and 1 in groups 1, 2, and 3, respectively). The difference in occurrence rate between groups was not statistically significant.

Ten patients who were felt to be at a very high risk for developing OHSS did not undergo fresh embryo transfer. To avoid OHSS in these high-risk patients, all their embryos were frozen. Six of these 10 were in group 1 and represented 6 of 82 (7.3%) of all group 1 patients with embryos. Four of these 10 were in group 2 and represented 4 of 262 (1.5%) with embryos available for transfer. None of these patients were in group 3.

DISCUSSION

Prior to the introduction of GnRH-a based protocols, approximately 15–30% of all cycles initiated were canceled due to premature LH surge or ovulation (6, 16). These early protocols required the ability to schedule retrievals on any day of the week and, in some cases, at any time of the day or night to "capture" a cycle in which a spontaneous LH surge had occurred. This "24 hr a day, 7 days a week" service increased the expense and inconvenience of IVF.

To decrease the cost and inconvenience of IVF-ET and increase efficiency, several methods of cycle scheduling have been proposed. Initially, cycles were scheduled by using progestogen (1–3)- or oral contraceptive (4,5)-induced withdrawal bleeds to initiate cycles. With the knowledge that most patients are ready for hCG between day 10 and day 12 of the follicular phase, cycles were timed so that most retrievals fell on weekdays. However, since GnRH-a was not used in these studies, the cancellation rate due to premature luteinization or ovulation was 15–30% (6).

Since the original description of the use of GnRH-a to block endogenous gonadotropin secretion, followed by exogenous gonadotropin stimulation of the ovaries (17), numerous studies of the role of GnRH-a in assisted reproduction have been published. In addition to its other beneficial effects (18, 19), GnRH-a has been demonstrated to eliminate the spontaneous LH surge, which greatly reduces the cancellation rate of IVF-ET cycles (18). After pituitary desensitization by GnRH-a administration, initiation of exogenous gonadotropins can be planned, based on average length of cycle stimulation, to avoid ovum retrievals on weekends or holidays (10). Unfortunately, not all patients responded as expected. Initially it was assumed that the timing of hCG is crucial in order to harvest the greatest number of mature oocytes. Several studies have subsequently dispelled this theory. Dimitry *et al.* (11) demonstrated that in association with a long protocol of GnRH-a-based gonadotropin stimulation for IVF-ET, a 1-day delay in hCG beyond what ordinarily would be considered the optimum time does not compromise outcome and, in fact, may be beneficial. Moreover, in a prospective randomized study, Tan *et al.* (12) demonstrated that even a 2-day delay in hCG administration beyond the time that follicular maturity was felt to be reached did not compromise pregnancy rate. A subsequent prospective randomized study by Dimitry *et al.* (13), using a GnRH-a-based down-regulated protocol, demonstrated that further delay of hCG administration to allow oocyte retrieval on as few as 3 of 5 midweek days did not increase the cancellation rate or adversely affect the pregnancy rate. Using a "flare-up" protocol of GnRH-a administration, Abdalla *et al.* (8) demonstrated that a delay of hCG of up to 2 days, limiting retrieval to Monday, Wednesday, Thursday, or Friday, was associated with an equally good outcome. Furthermore, Zorn *et al.* (20) described a combination of using a progestin to induce a scheduled menstrual cycle with the use of a GnRH-a-based "flare-up" protocol to modify further scheduling of IVF retrieval with good success. Although none of these randomized studies demonstrated any significant

difference between protocols, none critically evaluated possible differences between days of retrieval in a given protocol, especially with respect to possible premature retrievals on Fridays.

All reported studies suggest that these methods of programming IVF cycles to allow oocyte retrieval on predictable weekdays decrease both stress and financial cost to the patients and improve cycle efficiency. They also suggest that pregnancy outcome and cancellation rate are not adversely affected. Few studies have looked at the incidence of OHSS as a result of delaying administration of hCG. Those that have suggest no increase in this complication (13).

In order to schedule our IVF program to weekday-only ovum retrieval, we adopted the method of a "flare-up" protocol, utilizing GnRH-a (leuprolide acetate) and parenteral gonadotropin beginning on day 5 following a scheduled oral contraceptive withdrawal bleed. In the present study, we retrospectively analyzed outcome in three groups of IVF patients, which differed only in the day of ovum retrieval. All the groups were similar in terms of diagnosis, OCP treatment duration, and protocol of controlled ovarian hyperstimulation. Although there proved to be a small statistically significant difference in age in group 2, it is unlikely that this small statistical difference was clinically significant. The similarity of day of hCG administration and E_2 level and endometrial thickness on the day of hCG confirms the similarity of the three groups in this retrospective study and justifies the pregnancy outcome analysis.

The cycle outcome in the Monday retrieval group (group 1) showed no deleterious effect, which had been feared due to weekend constraints and possible delay in hCG administration. This confirms results of others (8–13), who showed that a delay in hCG administration of 1 or 2 days did not worsen the outcome. However, although not statistically significant, patients undergoing retrieval on Friday (group 3), who theoretically may be receiving hCG "too early," showed a trend of having a lower pregnancy rate per embryo transfer. The fact that the distribution of egg maturity and the fertilization rate in all groups were similar might suggest that early retrieval can lead to early embryo transfer to immature endometrium with decreased endometrial receptivity. Power analysis determined that a cohort of approximately 4000 cycles is needed to show a significant difference between the groups in terms of pregnancy rate per embryo transfer.

Concerns about OHSS complicating COH by GnRH-a and menotropins were raised in the past (21), and there is much debate with regard to the best way to minimize this complication (22). Since hCG is a known stimulant of ovarian activity, pregnancy has been shown to worsen the severity of OHSS (21). Therefore, it has been suggested that in patients at high risk for OHSS, all resulting embryos should be cryopreserved (23, 24). On the other hand, Wada *et al.* (25) found recently that, although elective cryopreservation of all embryos did not reduce the incidence of OHSS, it reduced the severity of the syndrome.

Six of 10 patients at high risk for OHSS, requiring freezing of all embryos and not allowing transfer during the treatment cycle, occurred in women whose TVUS-OR was delayed for retrieval until Monday, while the other 4 occurred in group 2. Nine of these 10 cases occurred in the first half of the program, and only one occurred in the subsequent half. This suggests that increasing experience with this new protocol allowed this situation to be anticipated and avoided. Transfer of cryopreserved embryos in our program is relatively new, with a pregnancy rate per embryo transfer of approximately 3%. Therefore, by avoiding the need to freeze all embryos, which occurred rarely after experience was acquired, there proved to be no disadvantage to retrieval on any specific weekday.

This study proves that scheduled oocyte retrieval should be used, to decrease IVF expense and inconvenience and improve program efficiency. Larger cohort studies should be performed in order to confirm or refute a possible deleterious effect of early retrievals (on Fridays) on pregnancy rate.

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