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Weekend-free scheduled IVF/ICSI procedures and single embryo transfer do not reduce live-birth rates in a general infertile population

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Key words
Ovum pickup, pregnancy rates, live births, single-embryo transfer, assisted reproductive technology, in vitro fertilization, intracytoplasmatic sperm injection

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Abstract

Introduction. Scheduling of ovum pickup only on weekdays may result in cases of apparently suboptimal timing for human chorionic gonadotropin and ovum pickup. This study aimed to assess whether live-birth rates were reduced in women with a potentially suboptimal day for human chorionic gonadotropin and ovum pickup to avoid weekend work, according to ultrasonographic data on the day of human chorionic gonadotropin planning. *Material and methods.* An evaluation of the optimal human chorionic gonadotropin priming date was performed in treatment protocols of 1000 consecutive patients undergoing their first in vitro fertilization/intracytoplasmatic sperm injection with single-embryo transfer. An ideal ovum pickup day was characterized by human chorionic gonadotropin-scheduling when three or more follicles reached 17 mm (day 0) or with one day of delay (day +1) (n = 760). A non-ideal ovum pickup was either early (day −1, −2, −3) (n = 24) or delayed (day +2, +3, +4) (n = 216). Live-birth rates in the ideal and non-ideal ovum pickup groups was set as primary outcome measure. *Results.* Early-ovum pickups were excluded as they were infrequent. No differences between ideal and delayed ovum pickup groups were found regarding number of oocytes retrieved (9.87 vs. 9.78, p = 0.990), pregnancy rates (28.3% vs. 29.6%, p = 0.701) or live-birth rates (26.2% vs. 25.9%, p = 0.939). However, sub analyses indicated that treatment with gonadotropin releasing hormone antagonists resulted in significantly lower clinical pregnancy rates in delayed ovum pickups (odds ratio 0.46, p = 0.014), compared with agonist treatments. *Conclusions.* Weekend work may not be needed for in vitro fertilization/intracytoplasmatic sperm injection single-embryo transfer treatments. However, in gonadotropin releasing hormone antagonist cycles, delaying ovum pickup more than one day may result in unfavorable outcomes.

Abbreviations: BMI, body mass index; COS, controlled ovarian stimulation; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; ICSI, intracytoplasmatic sperm injection; IVF, in vitro fertilization; OPU, ovum pickup; SET, single embryo transfer.

Introduction

It remains uncertain whether there is a need to perform ovum pickup (OPU) on weekends in connection with in vitro fertilization/intracytoplasmatic sperm injection (IVF/ICSI) treatment. Weekday-only surgical procedures reduce the pressure on staff members through regular weekend-time off and result in decreased maintenance and operating costs (1).

In gonadotropin releasing hormone (GnRH) agonist protocols, a favorable flexibility in planning the OPU date has been sufficiently demonstrated, with a clear feasibility of planning OPUs only on weekdays. Delaying OPU for 24 h did not negatively affect IVF outcomes as estimated by fertilization and pregnancy rates as demonstrated in early reports (2,3). Furthermore, when advancing the day of OPU from a Saturday to a Friday or delaying it from a Sunday to a Monday, no negative effects on IVF outcomes were observed (4,5). Notably, a two-day delay in OPU is associated with stable pregnancy rates and one early randomized controlled study even described an increased pregnancy rate outcome after a two-day delay (6).

However, with the introduction of GnRH antagonist protocols, the timing of OPU raised concern (7). As the onset of gonadotropin administration in antagonist cycles is dependent on spontaneously occurring menses, less flexibility in OPU scheduling than that allowed by agonist treatments has been recognized. Hence, programming the cycle start with exogenous estrogen or progesterone receptor activating compounds has been proposed to advance or delay treatment initiation and therefore the planned date for OPU (1,8,9). In GnRH antagonist treatments, advancement or delay of human chorionic gonadotropin (hCG) administration for just one day does not seem to have a negative impact on pregnancy or live-birth rates (9). However, prolongation of OPU for two days was associated with a reduction in pregnancy rates (7).

Efforts have thus been made to achieve more precise cycle scheduling of antagonist protocols, such as pretreatment with oral contraceptive pills which, used for scheduling in women with regular menses, were suggested to have a residual adverse effect on outcomes after fresh embryo transfer (8,10). However, the use of oral contraceptive pills for GnRH antagonist cycles remains controversial (11). Notably, even with oral contraceptive pill scheduling, weekend work cannot be completely avoided (12,13).

Two previous randomized studies have investigated the effect of delaying OPU in IVF/ICSI treatments, in both agonists (14) and antagonist cycles (15). According to the power analyses reported, both studies failed to recruit a sufficient number of patients. No significant negative effects of postponing hCG administration were found as regards pregnancy or live-birth rates, in which multiple embryos were replaced (14,15).

At many centers, including that of the present study, OPU and embryo transfer are routinely planned only on weekdays, regardless of the stimulation protocol used. In clinical routine, it can be necessary to delay the day of OPU to avoid Saturdays and Sundays, with OPUs scheduled on Mondays, rather than advancing the oocyte retrieval day to Fridays. The aim of the present study was to determine whether scheduling OPUs and embryo transfers only on weekdays, which could result in apparent suboptimal days for hCG and OPU, would reduce the chances of pregnancy and live-birth rates in a general infertile population undergoing single embryo transfer (SET) during their first IVF/ICSI treatment cycle.

Material and methods

The stimulation protocols and treatment outcome of 1000 consecutive women who underwent their first IVF/ICSI treatment cycle with SET at Reproductive Medicine, Karolinska University Hospital between 1 January 2009 and 31 December 2010 were analyzed. The sample size was determined by statistical power analysis (see below in Methods). All treatment-related data were prospectively collected in the clinic's online electronic registry database (Linnefiler, Fertsoft AB, Uppsala, Sweden). The analyses were performed retrospectively, at a time-point when all couples had reported their follow-up results after IVF/ICSI treatments, including data on births and perinatal outcomes. Excluded from the analysis were all treatment cycles involving preimplantation genetic diagnosis, cycles with transfer of two embryos, treatments using donor oocytes, as well as those that required discontinuation of gonadotropins (coasting) for ovarian hyperstimulation syndrome prophylaxis. According to Swedish regulations, assisted reproductive technology treatments are offered free of charge within the tax-funded healthcare system, which includes couples with primary infertility, a female

Key Message

Scheduling of ovum pick-up and single embryo transfer only on weekdays did not result in reduced live-birth rate in IVF/ICSI treatments using single embryo transfer. However, delaying ovum pickup for two days or longer in antagonist cycles might result in unfavorable outcomes.

age limit not exceeding 39 years and male partner upper limit of 56 years.

Two senior reproductive medicine specialists (K.R.W. and P.O.K.) categorized stimulation protocol charts into ideal and non-ideal OPU days. The evaluation was aimed at determining if the hCG trigger had been administered on an ideal day, according to ultrasonographic follicle size criteria including the assumption of a follicle growth of 2 mm/day, or if the trigger was advanced or delayed to avoid weekend OPU or embryo transfer procedures. An ideal day for scheduling OPU was defined by the administration of hCG on the day when at least three follicles reached the size of 17 mm, or with one day of delay (protocol charts 0 and +1), regardless of the type of protocol used, as supported by previous reports (3,9). An early scheduled OPU day was defined as the day before the ideal day of hCG administration (−1, −2, −3), and a delayed day as the opposite (+2, +3, +4 days after the ideal day).

Additional clinical data were masked, including patient's age, menstrual cycle length, antral follicle count, hormone determinations including baseline serum analysis of follicle stimulating hormone or anti-Müllerian hormone levels, and the names of the clinicians involved in the treatments.

The main outcome measure was live-birth rate per OPU. Secondary outcomes included the number of collected oocytes, fertilization rates, and number of supernumerary embryos cryopreserved. Outcomes were compared between the ideal and non-ideal OPU-groups. Subgroup analyses according to the type of protocol used (GnRH agonist or antagonist) were performed to evaluate the impact of the chosen protocol on primary and secondary outcomes.

The women underwent controlled ovarian stimulation (COS) for IVF/ICSI via either a long protocol, using a nasal GnRH agonist [(nafarelin 800 μg daily; Synarela; Pfizer) or buserelin 1200 μg daily; Suprecur (Sanofi)] or a short protocol, using a GnRH antagonist [ganirelix, Orgalutran, (MSD)]. None of the women was administered oral contraceptive pills for synchronizing the menstrual cycle; hence the choice of treatment protocol depended solely on the stage of the patient's self-reported first day of menstrual bleeding, which determined the time of planning an available time-point for treatment within the clinic's schedule.

In long protocol cycles, GnRH agonist nasal spray administration started in the mid-luteal phase, on approximately cycle day 21. Down-regulation status was investigated routinely by assessment of serum estradiol levels and, if demonstrated, daily gonadotropin stimulation was initiated using either recombinant follicle stimulating hormone [Gonal-F (Merck), Puregon (MSD), or hMG (Menopur; Ferring)]. In the antagonist protocol, ovarian stimulation was routinely initiated on menstrual cycle day 2. The dose for COS (75–450 IU) was individualized according to patient's age, menstrual cycle length, antral follicle count, and anti-Müllerian hormone levels. When the GnRH antagonist protocol was used, 0.25 mg Orgalutran (MSD) once-daily s.c. administration was initiated routinely on the fifth day of COS. Ovarian follicular growth tracking was performed by transvaginal ultrasound examinations routinely performed on stimulation days 6–8 and repeated on days 9–11 at the time of planning hCG administration.

Final oocyte maturation was triggered by administration of 250 μg s.c. recombinant hCG [Ovitrelle (Merck)] or 10 000 IU of hCG [Pregnyl (MSD)]. Oocyte retrieval was carried out by transvaginal ultrasonography-guided follicular puncture 37 h after hCG administration. Embryos were classified according to morphological criteria (16) and single-embryo transfer was performed in all cases. The day of embryo transfer was scheduled on a weekday depending on the day of pick-up, i.e. when oocyte retrieval was performed on a Monday, Tuesday or Wednesday, a day-2 embryo transfer was planned. In cases of oocyte retrieval on a Friday, a day-three embryo transfer was planned for the next Monday and OPUs were not generally scheduled on Thursdays. Luteal-phase support was provided by daily administration of vaginal micronized progesterone for two weeks [400 mg × 3 (Apoteksbolaget AB, Sweden), or 90 mg vaginal gel (Crinone, Merck)] until confirmation of pregnancy by a urine pregnancy test, after which it was suspended. Clinical pregnancy was confirmed by vaginal ultrasound at the seventh gestational week.

Statistical analyses

Based on previous published studies (4) and clinical routine we assumed that about 76% of women undergo OPU on an ideal day and thus only a minor proportion would undergo OPU on non-ideal days. Accounting for this expected imbalance in group sizes we calculated that 820 patients (623 in the ideal OPU group and 197 in the non-ideal OPU group) would be needed to demonstrate a 10% difference in live-birth rates between the groups, with a power of 80% and a two-sided significance level of 5%.

For group comparisons, differences in continuous variables were tested using non-parametric tests depending on the normality of data distribution (the Mann–Whitney *U*-test or the Kruskal–Wallis test) and summarized by means ± standard deviations. Pregnancy rates, live-birth and miscarriage rates were assessed using univariate regression models. The results are presented as odds ratio

and 95% confidence intervals. All analyses were performed using SPSS software version 20 (IBM Corp., Armonk, NY, USA). The level of significance was set at $p < 0.05$, two-sided.

Ethical approval

This study was approved by the Regional Ethics Committee in Stockholm (Dnr 2011/1758-31/2).

Results

Of the 1000 consecutive treatment protocols included, 557 (55.7%) utilized a GnRH agonist and 443 (44.3%) a GnRH antagonist. An ideal day of OPU was identified in 760 cases, with 339 on ideal day 0 and 421 on day +1. A delayed OPU-day was found in 216 cases, with 194, 20 and 2 cases of OPU on days +2, +3 and +4, respectively. An early OPU-day was found in only 24 cases. Because of this small number, the cases having an early day of OPU were excluded from further analyses.

Comparison of ideal vs. delayed OPU day

Of the 976 IVF/ICSI treatment protocols included in the final analyses, 77.9% had an ideal OPU-day and 22.1% a delayed OPU-day. There were no significant differences between the two groups concerning women's age, body mass index (BMI), use of IVF or ICSI and cause of infertility. The proportions of treatments using agonists or antagonists were also similar in both groups (Table 1).

Reproductive outcomes per OPU by ideal vs. delayed groups are presented in Table 2. The numbers of retrieved oocytes, fertilization rates and the proportion of women that had undergone embryo transfer were similar in both groups. Pregnancy rates and live-birth rates did not differ significantly between the groups. The numbers of supernumerary embryos obtained and those that could be frozen were also similar and did not differ between the two groups, as well as the proportion of normo vs. poor responders with fewer than five oocytes retrieved ($p = 0.281$).

Subgroup analyses as regards use of agonist or antagonist

In the OPUs found as ideally scheduled, treatment with agonists resulted in a significantly higher number of retrieved oocytes compared with antagonists (Table 3). However, the number of embryos obtained, supernumerary embryos frozen, pregnancy rates and live birth rates were similar and did not differ significantly between agonist vs. antagonist treatments of ideal OPU-day. Nevertheless, in the delayed OPU-group, women treated with antagonist protocols showed a trend towards lower live-birth rates ($p = 0.068$) and a significantly lower chance of achieving clinical pregnancy (odds ratio 0.46, $p = 0.014$) compared with women treated in the agonist protocol (Table 3).

Table 1. Patient demographics, cause of infertility, use of IVF/ICSI and type of protocol used in the treatment of patients scheduled for OPU in the ideal day (day 0) or with one day of delay (day +1), combined into the group denoted ideal day, or in a day that was judged as 2, 3 or 4 days delayed, denoted delayed OPU-day (day +2, +3 or +4).

	Treatment protocols		*p*-Value ideal vs. delayed OPU day
	Ideal OPU day	Delayed OPU day	
Patients	760 (77.9%)	216 (22.1%)	
Age	33.1 ± 3.8	33.6 ± 3.9	0.06
BMI	23.8 ± 4.1	24.2 ± 3.9	0.20
Infertility diagnosis			
Unexplained	260 (34.2%)	84 (38.8%)	0.20
Male factor	143 (18.8%)	39 (18.1%)	0.80
Anovulation	83 (10.9%)	18 (8.3%)	0.27
Tubal factor	52 (6.8%)	14 (6.5%)	0.85
Endometriosis	33 (4.3%)	9 (4.2%)	0.91
Other	189 (24.9%)	52 (24.1%)	0.81
IVF/ICSI	494/266 (65%/35%)	142/74 (65.7%/34.3%)	0.84
GnRH agonist/GnRH antagonist protocol	423/337 (55.7%/44.3%)	124/92 (57.4%/42.6%)	0.64

Data are presented as *n* (%) or mean ± SD.
BMI, body mass index; OPU, ovum pickup.

Table 2. Comparison of treatment outcomes per ovum pickup (OPU) between the groups ideal OPU-day (day 0 or +1) vs. delayed OPU-day (days +2, +3 or +4).

	Ideal day (n = 760)	Delayed day (n = 216)	p-Value (OR, 95% CI)
Retrieved oocytes	9.87 ± 5.57	9.78 ± 5.19	0.99
Fertilization rate	58.03%	57.89%	0.90
Embryos obtained	5.74 ± 4.20	5.75 ± 4.05	0.87
Embryos frozen	1.39 ± 2.04	1.59 ± 2.20	0.29
Pregnancy rate	35.1% (n = 267)	33.3% (n = 72)	0.62 (0.92; 0.67–1.27)
Clinical pregnancy rate	28.4% (n = 216)	29.6% (n = 64)	0.73 (1.06; 0.76–1.48)
Live-birth rate	26.2% (n = 199)	25.9% (n = 56)	0.93 (0.99; 0.70–1.39)
Miscarriage rate	25.5% (n = 68)	22.2% (n = 16)	0.48 (0.81; 0.46–1.44)
Cycles resulting in embryo transfer (SET)	91.5% (n = 688)	89.9% (n = 192)	0.48 (1.19; 0.73–1.95)

Data are presented as mean ± SD.

Table 3. Comparison of treatment outcomes by treatment protocol used (agonist vs. antagonist) within the ideal ovum pickup (OPU)-day and delayed OPU-day groups.

	Ideal OPU day			Delayed OPU day		
	GnRH agonist (n = 423)	GnRH antagonist (n = 337)	Comparison agonist vs. antagonist p-value (OR, 95% CI)	GnRH agonist (n = 124)	GnRH antagonist (n = 92)	Comparison agonist vs. antagonist p-value (OR, 95% CI)
Retrieved oocytes	10.31 ± 5.67	9.33 ± 5.41	0.007	9.90 ± 5.22	9.62 ± 5.18	0.674
Fertilization rate	57.82%	58.29%	0.726	57.12%	58.91%	0.464
Embryos obtained	5.88 ± 4.22	5.57 ± 4.16	0.290	5.79 ± 3.90	5.68 ± 4.25	0.615
Embryos frozen	1.49 ± 2.13	1.27 ± 1.92	0.115	1.73 ± 2.21	1.40 ± 2.19	0.163
Pregnancy rates	35.9% (n = 152)	34.1% (n = 115)	0.604 (0.92; 0.68–1.25)	37.9% (n = 47)	27.2% (n = 25)	0.099 (0.61; 0.34–1.10)
Clinical pregnancies	28.6% (n = 121)	28.2% (n = 95)	0.900 (0.98; 0.71–1.35)	36.3% (n = 45)	20.7% (n = 19)	0.014 (0.46; 0.25–0.85)
Live-birth rates	26% (n = 110)	26.4% (n = 89)	0.900 (1.02; 0.74–1.41)	30.6% (n = 38)	19.6% (n = 18)	0.068 (0.55; 0.29–1.05)
Miscarriage rates	27.6% (n = 42)	22.6% (n = 26)	0.289 (0.76; 0.46–1.27)	17% (n = 9)	24% (n = 7)	0.922 (1.05; 0.38–2.94)

Data are presented as mean ± SD.

Discussion

It has not been previously reported whether delaying hCG administration and OPU may affect treatment outcomes by IVF/ICSI in women receiving SET, which has become a standard in many assisted reproductive technology centers worldwide to reduce multiple births and maternal and perinatal comorbidity (17). Our results indicate that hCG administration may be delayed, with the aim of scheduling OPU on weekdays-only in women receiving SET. However, subgroup analysis by type of protocol used showed that GnRH agonist treatments might be more flexible regarding weekday OPU scheduling, whereas delaying OPU in antagonist protocols for two days or longer might have negative effects on the IVF/ICSI treatment outcome.

In the present study population, onset of stimulation in antagonist treatments was exclusively dependent on spontaneously occurring menses, and the antagonist was initiated routinely on the fifth day of COS. Thus, the negative effects observed in this study might be associated to these facts and not necessarily be present in antagonist treatments that are scheduled using cycle programming that allows a planned treatment start or when antagonist

initiation is determined by ultrasonographically estimated follicle size and estradiol levels. However, a previous randomized study supports that delaying the start of GnRH antagonist treatment may be equally effective as early initiation, making possible the programming of antagonist cycles as well (18).

Although the programming of the treatment cycle is easier in GnRH agonist treatments, weekend OPUs cannot be completely avoided (13). Compared with women treated in the GnRH agonist protocol, women in the antagonist protocol showed a significantly reduced chance of pregnancy in the present study when their OPUs were delayed for two days or longer (odds ratio 0.45), however, the live-birth rate was only marginally affected. There remains a lack of sufficiently numbered randomized controlled trial studies on the effect of advancing or delaying OPU for more than one day (either in GnRH agonist or antagonist protocols) on reporting outcomes on live-birth rates (14,15).

Of note, the present data revealed that it was predominantly chosen to delay rather than advance the day for OPU, and because of the small number of treatments planned for early hCG administration, the effect of scheduling for early OPU could therefore not be investigated. However, previous investigations have shown that when considering cycles using GnRH antagonists, advancement of OPU by one day, implying a shortened period of stimulation, may be associated with a lower number of retrieved oocytes and embryos obtained (9,19); however, findings in these studies did not detect a reduction in pregnancy or live-birth rates.

Data presented herein are in agreement with a previous study that showed reduced pregnancy rates after delaying hCG administration by up to two days in GnRH antagonist treatments (7). The postulated effect seems to be dependent on a shift of the implantation window in COS protocols for IVF/ICSI. Notably, it has been suggested that this effect can be mediated via progesterone elevations in late follicular phase during gonadotropin stimulation treatment, as measured on the day of hCG administration, which could impair implantation in fresh cycles, and a "freeze-all" strategy has been suggested (20). However, in the presence of residual bias as only retrospective studies have addressed this question, management of late follicular progesterone elevations in fresh IVF cycles remains to be determined.

Although endometrial histology and hormone assays have demonstrated an advancement in its development in women receiving GnRH agonists (21) and those receiving antagonists (22), the endometrium seems to undergo slower advancement in GnRH agonist cycles when compared with cycles stimulated with antagonists. Thus, GnRH agonist treatments may be affected less by the potentially negative effects of late OPU, and consequently late embryo transfer, than are antagonist treatments (23). The results of the present study are in agreement with the available evidence suggesting that, in an GnRH antagonist cycle, deferring hCG to avoid a weekend oocyte retrieval should be minimized to one day.

It is recognized that one of the shortcomings of the present study is the retrospective design, but it was considered ethically problematic to enroll a large number of patients in a randomized prospective trial of IVF/ICSI outcome that could potentially result in apparent suboptimal OPU-days to test the hypothesis. In previous randomized studies no significant reduction in pregnancy rates was observed, although notably, the sample size of the previous studies did not reach the number desired according to power analysis calculations (14,15). Therefore, a retrospective evaluation of prospectively collected data of 1000 consecutively treated women scheduled for SET was chosen to reach an adequate sample size in both the ideal-day and delayed-day groups with sufficient power to demonstrate differences in pregnancy and live-birth rates between the groups. The completeness of our center's database in reported obstetrical outcomes was high and was close to 99% during the study period investigated.

In summary, findings presented herein indicate that avoiding weekend OPUs by delaying hCG administration does not result in reduced live-birth rates in an unselected population of infertile couples undergoing their first IVF/ICSI and receiving SET. Notably, to maintain optimal treatment outcomes, a delay of more than one day in hCG induction of final oocyte maturation in treatment cycles using GnRH antagonists, is not advised.

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