PROLONGED COURSE OF LUTEAL ESTRADIOL IN PREPARATION FOR IVF CYCLES REDUCES PREGNANCY RATES

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ABSTRACT

Introduction: Luteal estradiol administered, from day 20 until next cycle day 2, as a pre-treatment to IVF hyperstimulation protocols improves follicle synchronization and retrieval of mature oocytes. As a matter of logistic at the OVO CLINIC, some stimulation protocols were started on day 4 to 9 of the next cycle, to limit the number of oocyte retrieval procedures performed on the same day. We performed a quality control of our procedures by conducting a retrospective comparative cohort study.

Methods: Women aged 25 to 42 years old who consulted at the OVO CLINIC for IVF, who were prescribed a gonadotropin stimulation protocol, either a microdose flare-up protocol or an antagonist protocol and who were given a course of 4 mg oral estradiol-17β daily for a minimum of 5 days were included in the analysis. We analysed 708 IVF cycles performed from August 2007 to November 2010; 303 and 405 cycles in control and treatment groups respectively (stimulation started on day 1 to 3 and on day 4 and more of the subsequent cycle respectively). Positive β-hCG test rate (one value ≥25 mIU/mL) in all cycles was the primary outcome. We compared continuous data using the unpaired Student's t-test and categorical data with Chi-squared and/or Fisher's exact tests, according to the size of the samples. P<0.05 was considered statistically significant.

Results: The groups were comparable with regard to age, day 3 serum FSH, basal antral follicle count and serum AMH. A significant statistical difference was observed between groups for the mean follicle count at last ultrasound (12.77 ± 8.02 vs 11.16 ± 6.42; *P<0.004*), mature oocyte count (7.97 ± 5.44 vs 7.03 ± 4.50; *P<0.02*), and normally fertilized oocyte count (4.78 ± 3.80 vs 4.10 ± 3.19; P<0.02). However, the mean transferred and frozen embryos were equivalent in both groups. The clinical pregnancy rates in all cycles (28.71 vs 21.48 %; *P<0.03*) and in cycles with a transfer (35.37 vs 27.44 %; *P<0.04*) were statistically significantly superior in the control group.

Conclusions: The present study confirmed that a prolonged course of luteal estradiol significantly reduces pregnancy rates. While luteal estradiol pre-treatment coordinates follicular recruitment, hyperstimulation must be started soon in such protocol to maintain IVF success rates.

INTRODUCTION

- Luteal estradiol is known to improve follicle synchronization and retrieval of mature oocytes when administered as a pre-treatment to IVF controlled ovarian hyperstimulation protocols through its inherent suppressive effect on endogenous FSH secretion.
- In IVF cycles with a luteal estradiol protocol, it is normally given from day 20 until next cycle day 2, and the ovarian stimulation protocol is usually started on day 3 of the subsequent cycle.
- In order to limit the number of oocyte retrieval procedures performed on the same day at the OVO CLINIC, some stimulation protocols were started on day 4 to 9 of next cycle.

OBJECTIVE

We performed a quality control of our procedures by conducting a retrospective comparative cohort study to compare IVF outcomes in standard versus prolonged courses of 17β-E2.

METHODS

- Retrospective analysis of 708 IVF cycles performed from August 2007 until November 2010.
- Control group (303 cycles): stimulation started on day 1 to 3 of subsequent cycle. Treatment group (405 cycles): stimulation started on day 4 and more of subsequent cycle.
- Inclusion criteria: Women aged 25 to 42 years old who had an indication for IVF, who were prescribed a gonadotropin stimulation protocol and who were administered 4 mg oral 17β-E2 daily for a minimum of 5 days as a pre-treatment to IVF.
- All patients followed a microdose flare-up protocol ("short" protocol) or an antagonist protocol which consisted of gonadotropins with buserelin acetate or GnRH antagonist respectively.
- IVF cycles were performed according to the OVO CLINIC's standard procedures (transvaginal ultrasound-guided oocyte retrieval 36 hours after hCG injection, embryo transfer under abdominal ultrasound visualization 2 to 3 days later, serum pregnancy test 15 days after oocyte retrieval and ultrasound at approximately 7 weeks of pregnancy to confirm foetal viability).
- Main outcome: positive β-hCG test rate in all cycles.

STATISTICS

- Retrieval and compilation of data by research assistants using *Microsoft Excel* software.
- Data analysis realized using **S***TATA 10 Data Analysis and SISA online statistical analysis* softwares.
- Comparison of continuous data with the unpaired Student's t-test for normally distributed data and of categorical data with the Chi-squared and/or Fisher's exact tests according to the size of the samples studied.
- P<0.05 was considered statistically significant.
- Data validation of 17 elements of 70 randomly selected cycles (10%): obtention of a 2.77 % error rate concerning secondary outcomes (5 % considered acceptable).

TABLE 1. Demographic data in standard and prolonged course of luteal estradiol

Demographic data	Stimulation started on day ≤ 3 of next cycle	Stimulation started on day > 3 of next cycle	p-value[1]
Age (years)	36.34 ± 3.99 (n=303)	36.61 ± 4.02 (n=405)	NS
Day 3 serum FSH (IU/L)	7.89 ± 3.26 (n=246)	8.32 ± 3.33 (n=359)	
Serum AMH (IU/L)	1.30 ± 1.33 (n=70)	1.18 ± 1.08 (n=109)	
Total basal antral follicle count[2]	13.17 ± 7.91 (n=246)	12.75 ± 8.14 (n=341)	

Note: Values are means ± SD. NS = not significant.

[1] Unpaired Student's t-test for normally distributed data. 95 % CI.
[2] An ovarian reserve performed during the previous ≤ 2 years from IVF cycle was considered as reliable.

TABLE 2. IVF stimulation, oocyte and embryo outcome data in standard and prolonged course of luteal estradiol

IVF stimulation, oocyte and embryo outcome data	Stimulation started on day ≤ 3 of next cycle	Stimulation started on day > 3 of next cycle	p-value[1]
Duration of stimulation (days)	11.61 ± 2.12 (n=303)	11.33 ± 2.11 (n=405)	NS
Total gonadotropin dose (IU)	5022.58 ± 1870.51 (n=303)	5144.31 ± 3515.50 (n=405)	NS
Follicle count at last ultrasound	12.77 ± 8.02 (n=301)	11.16 ± 6.42 (n=402)	0.004
Retrieved oocyte count	10.39 ± 6.54 n=269)	9.36 ± 5.89 (n=356)	0.04
Mature oocyte count	7.97 ± 5.44 (n=264)	7.03 ± 4.50 (n=349)	0.02
Normally fertilized oocyte count	4.78 ± 3.80 (n=267)	4.10 ± 3.19 (n=351)	0.02
Fertilization rate (%)	59.35 ± 27.50 (n=263)	57.59 ± 28.58 n=346)	NS
Transferred embryos	1.98 ± 1.16 (n=267)	1.88 ± 1.15 (n=351)	NS
Frozen embryos	0.88 ± 2.08 (n=267)	0.80 ± 1.72 (n=351)	NS

Note: Values are means ± SD. NS = not significant. [1] Unpaired Student's t-test for normally distributed data. 95 % CI.

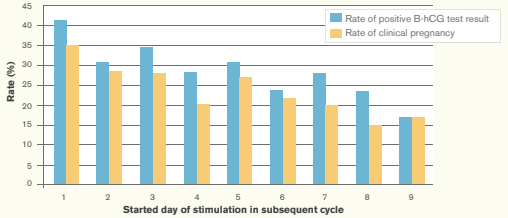
TABLE 3. IVF outcome data in standard and prolonged course of luteal estradiol

IVF outcome data	Stimulation started on day ≤ 3 of next cycle	Stimulation started on day > 3 of next cycle	p-value[1]
Positive β-hCG test rate in all cycles (%)[2]	33.66 (n=102/303)	27.16 (n=110/405)	NS
Positive β-hCG test rate in cycles with transfer (%)[2]	41.46 (n=102/246)	34.70 (n=110/317)	NS
Implantation rate in all cycles (%)	29.70 (n=90/303)	23.21 (n=94/405)	NS
Implantation rate in cycles with transfer (%)	36.59 (n=90/246)	29.65 (n=94/317)	NS
Clinical pregnancy rate in all cycles (%)	28.71 (n=87/303)	21.48 (n=87/405)	0.03
Clinical pregnancy rate in cycles with transfer (%)	35.37 (n=87/246)	27.44 (n=87/317)	0.04
Multiple pregnancy rate in clinical pregnancy (%)	25.29 (n=22/87)	21.84 (n=19/87)	NS
Cancellation rate (%)	11.22 (n=34/303)	12.10 (n=49/405)	NS

Note: Values are means ± SD. NS = not significant.

[1] Chi-squared and/or Fisher's exact tests. 95 % CI.
[2] One β-hCG dosage of ≥25 mIU/mL was considered a positive β-hCG test result.

FIGURE 1. Positive β-hCG test result and clinical pregnancy rates according to the started day of stimulation in subsequent cycle



DISCUSSION

- Hypothesis: a long course of 4 mg oral 17β-E2 daily in preparation for an IVF cycle with gonadotropins did not affect IVF outcomes.
- A significant difference was observed for the mean follicle count at last ultrasound and consequently the mean oocyte count at egg retrieval, the mean mature oocyte count and the mean normally fertilized oocyte count in favor of the control group. A prolonged course of 17β-E2 may have a negative effect on follicular recruitment.
- An absence of difference was found for the mean number of transferred embryos and the mean number of frozen embryos created through IVF cycles. A prolonged course of 17β-E2 did not alter embryo outcomes.
- A significant difference in clinical pregnancy rate in all cycles and in cycles with transfer confirmed that stimulation started later in subsequent cycle combined with a prolonged course of luteal estradiol should be avoided.
- A trend in favor of the stimulation started on day ≤3 of subsequent cycle for positive β-hCG test rate and for implantation rate in all cycles was noted.
- A time graph demonstrated a gradual diminution of the positive β-hCG test rate and clinical pregnancy rate through time, the further the stimulation was started in subsequent cycle. These outcomes reached their paroxysm in cases when stimulation was started on day 1 of next cycle.
- Results confirmed that a prolonged course of estradiol-17β had a significant negative impact on clinical pregnancy rates.
- While luteal estradiol permits coordination of IVF cycles and homogenization of follicular recruitment, controlled ovarian hyperstimulation must be started soon in subsequent cycle in such protocol to maintain IVF success rates.

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