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Title:

Extending Ovarian Stimulation in Patients Who are Slow to Respond: Does Persistence Pay Off?

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Objective:

IVF patients with decreased ovarian response often require controlled ovarian hyperstimulation (COH), resulting in late ovulation trigger and VOR on or after cycle day 16. Patients who require lengthier COH are often viewed as having a poor prognosis, although it is not well established how, independent of oocyte age and ovarian reserve, differences in stimulation duration are predictive of cycle outcome.

Design:

Retrospective cohort analysis

Materials and Methods:

Patients who underwent COH with blastocyst-staged embryo transfers from September 2002 to April 2016 were included. Donor oocyte and male factor infertility cases were excluded. COH was initiated on cycle day 3. Criteria for ovulation trigger was ≥ 2 mature follicles ≥ 18 mm in size. Patients were stratified by whether ovulation was triggered before vs. on and after cycle day 14. Outcomes of COH (estradiol at surge, oocytes retrieved, fertilization, blastulation and aneuploidy rates) and embryo transfer (ET) in a fresh or frozen (FET) cycle (implantation and early pregnancy loss) were analyzed. A sub-analysis restricted to euploid embryo transfers was performed. Data was analyzed using student's T test, chi square, linear and binary logistic regression.

Results:

COH was performed in 7839 IVF cycles, with 4850 concurrent ETs in the stimulation cycle and 2786 FET's in subsequent cycles. Patients triggered <day 14 (n=6749) vs. \geq day 14 (n=1090) were compared according to patient demographics, cycle characteristics and clinical outcome (Table 1). For every year increase in age, there was a 0.05 increase in days of COH (p<0.0001). Controlling for age and day 3 FSH, each increase in cycle day of ovulation trigger corresponded



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with decreased ovarian response (-63.3 pg/ml estradiol at trigger), oocytes retrieved (-1.1), fertilized (-0.06), blastocysts developed (-0.4) and available for trophectoderm (TE) biopsy (-0.4) and the number of euploid embryos (-0.1) ($p < 0.0001$). Increased cycle day of ovulation trigger was associated with increased odds of not meeting criteria for oocyte retrieval (OR 1.5 [95% CI 1.3-1.7]), < 4 oocytes retrieved (OR 1.3 [95% CI 1.2-1.3]), and failed fertilization (OR 1.1 [95% CI 1.1-1.2]) ($p < 0.0001$), with decreased odds of having a blastocyst available for biopsy (OR 0.9 [95% CI 0.8-0.9]) or transfer (OR 0.9 [95% CI 0.8-0.9]) ($p < 0.0001$). However, cycle day of trigger did not influence the odds of having no euploid blastocysts when biopsy was performed (OR 1.0 [95% 0.9-1.1], NS). Controlling for age, number of embryos transferred and ploidy, odds of implantation and early pregnancy loss did not vary with timing of ovulation trigger in the COH cycle.

Conclusions:

Patients who require COH past cycle day 14 are a poor prognosis group, as they are at increased risk of not reaching retrieval, fertilization or blastulation. However, it is encouraging that if these hurdles are overcome, overall embryo quality and competence is not hindered. Based on this data, clinicians can counsel slow-responding patients regarding their IVF prognosis, while reassuring them that blastocysts eligible for biopsy and/or transfer are not an increased risk for failed implantation.

Support:

None

Table 1:

Cycle day of ovulation trigger	<14	≥ 14	P value
Cycles	6749	1090	
Patient age	36.5 \pm 4.7	38.3 \pm 4.4	<0.0001
BMI	24.2 \pm 11.3	26.2 \pm 6.5	NS
Day 3 FSH	6.2 \pm 2.8	6.5 \pm 4.1	NS
E2 at surge (pg/ml)	2244.8 \pm 1148.8	1638.2 \pm 976.7	<0.0001
Cumulative gonadotropin dose	3295.7 \pm 1229.4	5353.5 \pm 1329.1	<0.0001
Oocytes retrieved	15.4 \pm 9.5	9.7 \pm 7.4	<0.0001
Mean number of day 5 blastocysts	5.1 \pm 4.7	2.9 \pm 3.7	<0.0001
Mean number of blastocysts biopsied	5.1 \pm 4.4	3.5 \pm 3.3	<0.0001
Aneuploidy rate	50.3%	49.1%	NS



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Total Fresh ETs	4350	500	
Mean number of fresh embryos transferred	2.1 ± 0.8	1.9 ± 0.9	<0.0001
Fresh ET Implantation rate	53.4% (2322/4350)	48.8% (244/500)	NS
Fresh ET Early pregnancy loss rate	19.4% (845/4350)	20.6% (103/500)	NS
Total FETs	2533	253	
Mean number of frozen embryos transferred	1.6 ± 0.8	1.3 ± 0.5	<0.0001
FET Implantation rate	51.2% (1296/2533)	56.1% (142/253)	NS
FET Early pregnancy loss rate	21.8% (551/2533)	19.4% (49/253)	NS