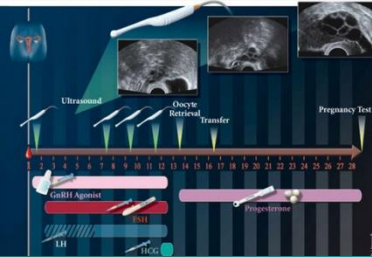# EFFECT OF LENGTH OF STIMULATION ON IVF PREGNANCY RATE

Le Hoang, M.D., Ph.D., Nguyen Thi Lien Huong, M.D.,Ph.D.

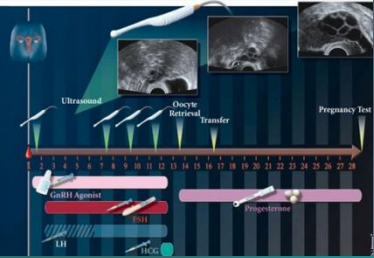**NATIONAL ART CENTER**

REVIEW

- 3 protocols of ovarian stimulation: long or short agonist protocol, antagonist protocol.

- Common length of stimulation: 8-12 days.

- Ovarian follicle development:

- Natural cycle: 1-4 mm/ day, mean: 1,4mm/day.

- Stimulation cycle: 1,7mm/day

- hCG trigger: follicle size reach 16-22mm.

- ≥ 3 follicles 16mm.

- ≥ 3 follicles 18mm.

Does early hCG trigger (day 8) affect on oocyte and embryo quality? May it not allow enough time for endometrial development?

Does length of ovarian stimulation affect IVF oocyte, embryo quality, and pregnancy rate?

Does prolonged duration of stimulation affect on oocyte, embryo quality and pregnancy rate?
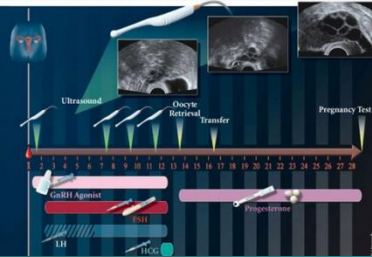
METHOD AND MATERIALS

- Subjects:

    Retrospective analysis of all IVF cycle in National ART center from Janury to August 2015.

- Selection criteria:

    • Stimulation phage length (SPL) 8-12 days.

    • Full informations.

METHOD AND MATERIALS

Sample size: 3 groups, each group was divided into 5 subgroups:

SPL 8, 9, 10, 11, 12 days:

- Group 1: Evaluate oocyte and embryo quality: 2037 cycles.

- Group 2: Evaluate pregnancy rate: 1658 cycles.

- Group 3: Evaluate pregnancy rate of 3 ovarian stimulation protocols (poor prognosis patients are excluded: age> 40, NMTC < 8 or >14mm, IVF thất bại> 3 chu kỳ, abnormal uterine)

- Long protocol: 347 cycles (was divided into 4 subgroup because n SPL 8 days = 1)).

- Short protocol: 624 cycles.

- Antagonist protocol: cycles.

RESULTS

Table 1. Patient characteristics (1)

	SPL					Total
	8	9	10	11	12	
Tubal factors	46	260	270	105	23	704
	37.2%	33.2%	35.2%	33.6%	44.9%	34.6%
Male factors	14	143	117	37	7	318
	11.5%	18.3%	15.2%	12.0%	12.3%	15.6%
Unexplained	55	330	330	144	18	877
	44.2%	42.1%	43.0%	46.2%	34.7%	43.0%
Mixed factors	7	29	35	21	1	93
	5.3%	3.7%	4.5%	6.8%	2.0%	4.5%
Abnormal uterine	1	18	11	4	3	37
	.9%	2.3%	1.4%	1.4%	6.1%	1.8%
Others	0	3	2	0	0	5
	.0%	.4%	.3%	.0%	.0%	.3%
Endometriosis	1	0	2	0	0	3
	.9%	.0%	.3%	.0%	.0%	.2%
Total	124	783	767	311	52	2037
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
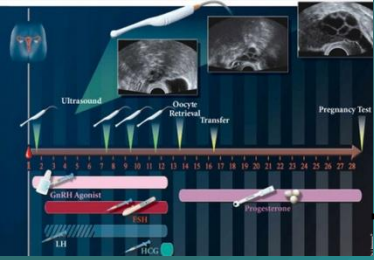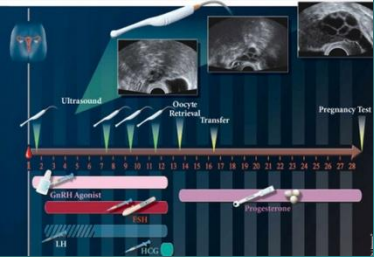
RESULTS

Table 2. Patient characteristics (2)

	SPL					Total
	8	9	10	11	12	
Primary infertility	59	410	394	169	31	1063
	47.2%	52.4%	51.4%	54.3%	59.6%	52.2%
Secondary infertility	65	373	373	142	21	974
	52.8%	47.6%	48.6%	45.7%	40.4%	47.8%
Total	124	783	767	311	52	2037
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
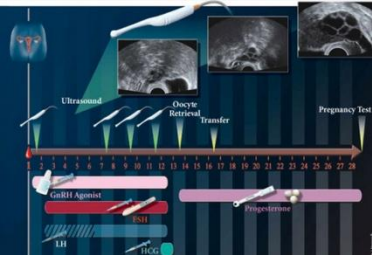
RESULTS

Table 3. Patient characteristics (3)

	SPL					Total
	8	9	10	11	12	
Long protocol	1	60	213	142	12	428
	.8%	7.6%	27.8%	45.5%	23.1%	21.0%
antagonist	51	360	345	110	22	879
	33.4%	45.9%	45.0%	35.5%	42.3%	43.1%
Short protocol	82	363	209	59	18	725
	65.8%	46.5%	27.2%	19.0%	34.6%	35.8%
Total	124	783	767	311	52	2037
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
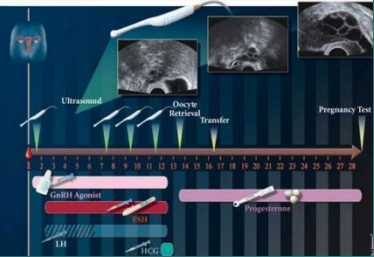
RESULTS

Table 5. Patient characteristics (4)

SPL	Infertility duration	age	IVF cycles	FSH dosages	Total
8	5.15 ± 3.89	32.98 ± 5.83	1.19 ± 0.57	1984.11 ± 749	124
9	5.44 ± 3.83	32.77 ± 5.47	1.28 ± 0.84	2111.12 ± 825	783
10	5.2 ± 3.68	32.25 ± 5.13	1.21 ± 0.64	2205.16 ± 861	767
11	5.49 ± 3.55	32.48 ± 5.2	1.25 ± 0.9	2359.73 ± 932	311
12	5.67 ± 3.76	32.52 ± 5.47	1.25 ± 0.59	2914.42 ± 1084	52
Total	5.35 ±3.73	32.54± 5.33	1.25 ± 0.74	2197.25 ± 873	2037

RESULTS
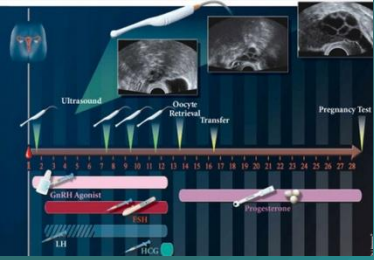
Table 4. No ET cycles in study

|	SPL					Total
	8	9	10	11	12	
No oocyte	0	4	6	2	0	12
	.0%	.5%	.8%	.7%	.0%	.6%
No embryo	0	13	15	6	1	35
	.0%	1.7%	2.0%	2.0%	1.9%	1.7%
Freeze all	15	103	117	53	7	295
	12.2%	13.2%	15.2%	17.0%	13.5%	14.5%
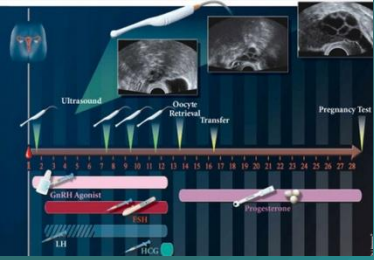
RESULTS

Table 6. Oocyte and embryo quality in study

| SPL	Oocye MII	Oocyte MI+GV	Infertiliza-tion rate	Oocte degenara-tion	Good embryo rate	Oocyte number	Embryo number	Tranfferred emryo number	Total
8	0.85 ± 0.22	0.14 ± 0.22	0.89 0.13	0.07 ± 0.14	0.65 ± 0.33	9.26 ± 6.18	5.98 ± 3.81	2.52 ± 1.23	124
9	0.79 ± 0.28	0.20 ±0.28	0.88 ± 0.19	0.08 ± 0.14	0.7± 0.28	10.86 ± 6.53	7.12 ± 4.06	2.53 ± 1.27	783
10	0.81 ± 0.26	0.18 ± 0.26	0.89 ± 0.15	0.08 ± 0.15	0.72 ± 0.28	12,34 ± 6.77	8.2 ± 4.70	2.45 ± 1.25	767
11	0.76 ± 0.31	0.23 ± 0.31	0.89 ± 0.14	0.08 ± 0.14	0.7 ± 0.28	12.07 ± 7.11	7.85 ± 5.27	2.47 ± 1.54	311
12	0.78 ± 031	0.21 ± 0.31	0.89 ± 0.17	0.08 ± 0.16	0.74 ± 0.28	10.52 ± 7.00	6.85 ± 4.09	2.62 ± 1.28	52
Total	0.8 ± 0.28	0.19 ± 0.28	0.89 ± 0.16	0.08 ± 0.14	0.71 ± 0.28	11.5 ± 6.77	7.56 ± 4.73	2.49 ± 1.3	2037

P MII8*11=0,008, MI+GV=0,007, p oocyte number 8*9; 8*10; 8*11; 9*10; 9*11 <0,01, p emryo number 8*9 ; 8*10,; 8*11; 9*10;10*12<0,01
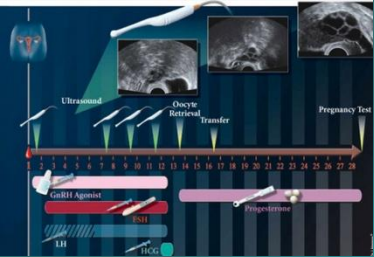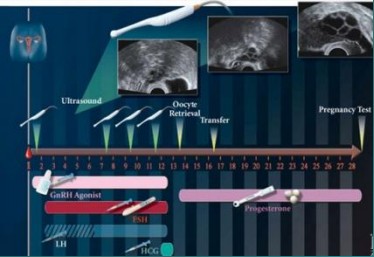
RESULTS

Table 7. Pregnancy rate in study

	SPL					p
	8	9	10	11	12	
0	63	366	321	124	22	p> 0.05/pair
	60.0%	56.5%	51.9%	50.8%	52.4%	P8*11= 0.11
1	42	282	298	120	20	
	40.0%	43.5%	48.1%	49.2%	47.6%	
Total	105	648	619	244	42	
	100.0%	100.0%	100.0%	100.0%	100.0%	
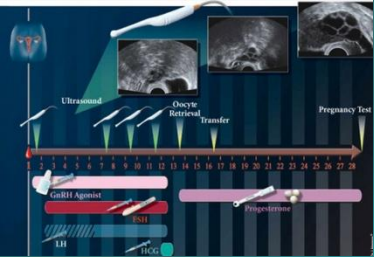
RESULTS

Table 8. Pregnancy rate of long protocol

	SPL				p
	9	10	11	12	
0	20	77	52	4	
	43.5%	44.3%	44.8%	36.4%	
1	26	97	64	7	> 0.05 P11,12= 0,78
	56.5%	55.7%	55.2%	63.6%	
Total	46	174	116	11	

RESULTS

Table 9. Pregnancy rate of antagonist protocol

	SPL					p
	8	**9**	**10**	**11**	**12**	
0	14	123	114	37	8	
	45.2%	47.9%	46.7%	55.2%	44.4%	
1	17	134	130	30	10	> 0.05
	54.8%	52.1%	53.3%	44.8%	55.6%	
Total	31	257	244	67	18	
	100.0%	100.0%	100.0%	100.0%	100.0%	

RESULTS
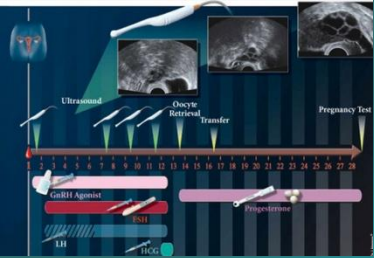
Table 10. Pregnancy rate of short protocol

	SPL					Total
	8	9	10	11	12	
0	47	211	120	27	10	
	66.2%	66.8%	67.4%	57.4%	83.3%	
1	24	105	58	20	2	P > 0.05/pair
	33.8%	33.2%	32.6%	42.6%	16.7%	P11,12=0.33
Total	71	316	178	47	12	
	100.0%	100.0%	100.0%	100.0%	100.0%	

DISSCUSSIONS

Effect of length of stimulation in ART cycles on pregnancy rate

Kristen A. Ivani, Louis N. Weckstein, Denise M. Walker

Objective: Past studies have suggested a negative impact of very long or very short stimulations on pregnancy rate in ART cycles. An excessively long cycle may suggest diminished ovarian reserve, and clinicians often are tempted to cancel these cycles prior to egg retrieval. A very short stimulation may be suboptimal for the development of a receptive endometrium. This study was undertaken to determine the impact of excessively long or short ovarian stimulation on pregnancy rates in ART cycles.

Design: Retrospective analysis of 2223 ART cycles from January 1998 – December 2002 in a private practice setting.

Materials and Methods: Cycles reviewed included all ART cycles in our center for patients under the age of 40, using their own eggs (excludes oocyte donation cycles). Clinical pregnancy rates per embryo transfer were calculated based on the number of days of ovarian stimulation prior to the day hCG was given. Approximately 65% of cycles were Lupron down regulation cycles, 20% were micro dose lupron flare, and 15% of cycles were antagonist cycles. Statistical analysis consisted of measures of association to explore the relationship between stimulation cycle length and pregnancy rates. Nominal logistic regression was also employed to examine the effect of stimulation on pregnancy rates.

Results: Table 1 depicts the relationship between days of stimulation and pregnancy outcomes. As is apparent from Table 1, there seems to be a natural decline of positive pregnancy outcomes once stimulation days exceed 11. From the likelihood ratio statistics (Chi-Square = 29.57, p = 0.005), it is apparent there is a strong linear relationship between stimulation days and pregnancy outcomes.

Conclusions: Cycle stimulation length of 6 – 11 days appeared to be optimal for best pregnancy rates. Surprisingly, very short cycle stimulation of 6 – 7 days was associated with good pregnancy rates. Though short stimulation lengths may not allow much time for endometrial development, patients who stimulate quickly usually have very good ovarian reserve, and thus embryo quality factors may be able to compensate for endometrial factors. Cycle stimulation lengths greater than 11 days are associated with lower pregnancy rates; however pregnancy rates were not unacceptable even with cycle stimulation lengths of up to 15 days. This data may be useful for clinicians faced with making decisions regarding canceling excessively short or long stimulation cycles.
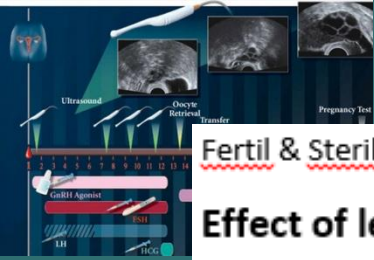
DISSCUSSIONS

Does length of ovarian stimulation affect IVF pregnancy and implantation rates?

M.P. Portmann,L.S. Morrison, D.R. PrinzB. A. McGuirk,R.F. Feinberg, M.J. Tucker

Objective

To determine if day of hCG administration following controlled gonadotropin stimulation affects pregnancy and implantation rates in patients undergoing fresh, non-donor IVF and day 3 embryo transfer.

Design

Retrospective analysis of 154 fresh non-donor IVF cycles during a 16 month period. All cycle starts that occurred on a Friday with subsequent day 3 transfer were included in the study. Three groups were compared; transfers occurring on a Thursday or Friday (9 or 10 day med protocol); transfers occurring on a Saturday or Sunday (11 or 12 day med protocol); and transfers occurring on a Monday, Tuesday or Wednesday (13, 14 or 15 day treatment). All retrievals initiated prior to day 9 and after 15 days of drug treatment were excluded from the study. Pregnancy and implantation rates were compared between the groups using Chi Square Analysis.
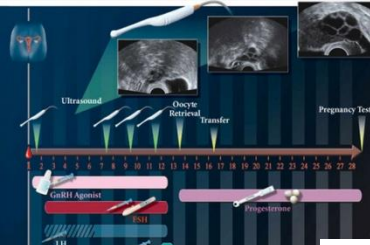
Results

In the 148 cycles analyzed, 352 fresh embryos were AH and transferred (avg. 2.4 embryos/transfer), yielding a clinical implantation rate of 29% and PR of 54.7%. Significant differences in pregnancy and implantation rates were observed between the Sat/Sun and Mon/Tues/Wed transfer groups.

11-12D   13-15D

Conclusion

The observed differences between groups might suggest that optimally timed drug stimulation regimes could yield significant improvements in IVF pregnancy and implantation rates. Although endocrine and ultrasonographic information are useful in the determination of optimal HCG administration, they may not necessarily reflect appropriate nuclear and cytoplasmic maturational synchrony of the oocytes retrieved. In poor and hyper-responders, abnormally short and long treatment regimes may upset the delicate equilibrium of nuclear and cytoplasmic events within an oocyte, i.e. nuclear mature oocytes with post mature granularity and vacuolation that ultimately results in poor embryo development. An 11 or 12-day ovarian stimulation regime may optimally strike a balance between immature, mature, and post mature nuclear and cytoplasmic events leading to optimized results in the form of better quality embryos. However, inherent patient variables (less stress on weekends, better patient compliance), reduced stress levels amongst clinical and laboratory staff, and practice philosophy cannot be ruled out as important prognostic factors.

DISSCUSSIONS

Does the [text obscured]

Brie Alport, B.Sc.[1], [text obscured]

Materials an [text obscured] rwent
IVF. Follicle [text obscured] using
transvaginal u [text obscured] tropin
(hCG) was a [text obscured] hCG.
Oocytes unde [text obscured] were
transferred on [text obscured] ations
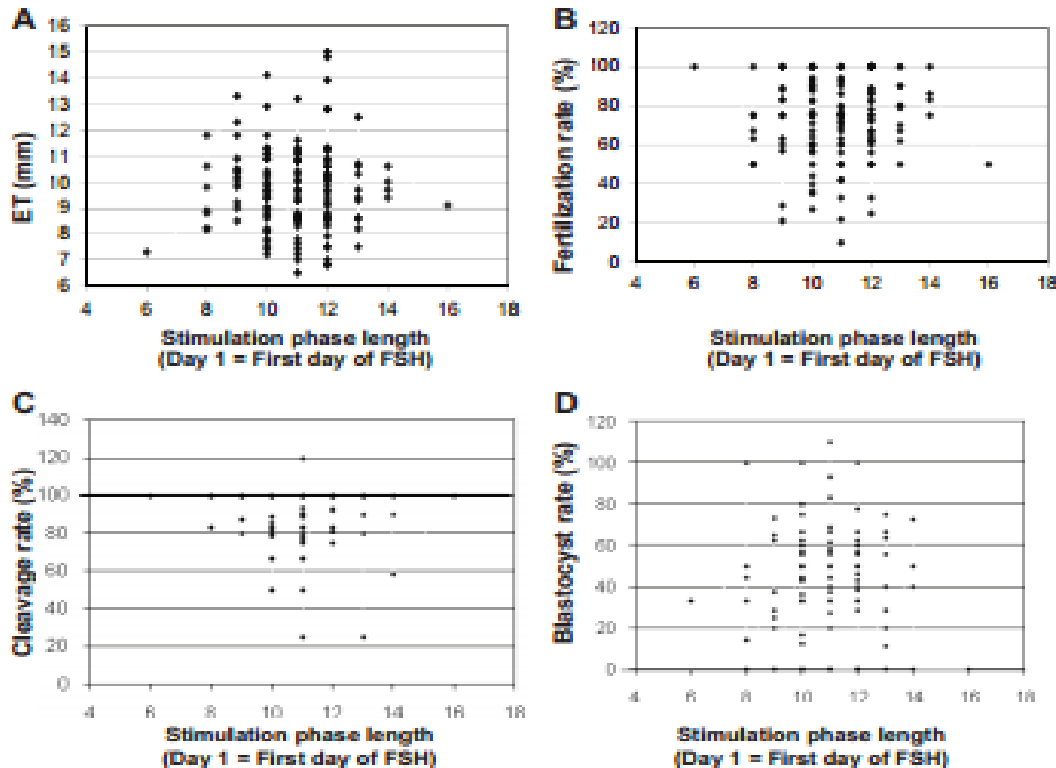between SPL, [text obscured] ersion
17.0; SPSS In [text obscured]

Fig 2: Associations between the stimulation phase length (SPL) and endometrial thickness (ET), fertilization rate (%), cleavage rate (%) and blastocyst rate (%). No regression lines are shown because no associations were detected.

Results: A SPL of 11 days was associated with an optimal number of follicles that developed to ≥ 6 mm, ≥ 10 mm and ≥ 15 mm; serum estradiol concentrations; and number of oocytes collected ($p < 0.05$). Gradual reductions in the number of developing follicles, serum estradiol concentrations and number of oocytes collected occurred with SPL less than or greater than 11 days ($p < 0.05$). The SPL did not influence endometrial, embryo or pregnancy outcomes ($p > 0.05$). Associations between SPL and outcomes were not influenced by age ($p > 0.05$).
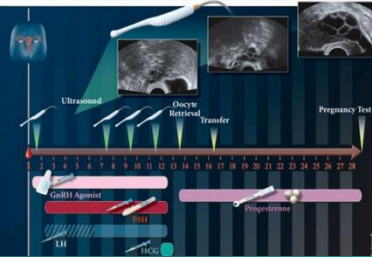
DISSCUSSIONS

- M. Chuang et al. 2013: 794 CK

TABLE. Study characteristics by duration of gonadotropin stimulation

	<10 days, n=100	10-12 days, n=439	>12 days, n=160	P
Age, yrs	34.6 (4.5)	35.5 (4.3)	34.5 (4.2)	0.02
FSH, mIU/ml	7.6 (2.7)	7.7 (2.5)	8.0 (3.0)	0.48
Primary infertility, %	40.0	41.2	51.3	0.07
BMI, kg/m2	26.2 (6.3)	25.4 (5.5)	26.1 (6.0)	0.39
Total dose of gonadotropins, IU	2401 (1188)	3031 (1581)	4319 (2065)	<0.01
Oocytes retrieved	11.3 (6.3)	12.8 (7.1)	11.7 (6.6)	0.06
Embryos transferred	2.6 (1)	2.6 (0.9)	2.5 (0.9)	0.59
Day 5 transfer, %	2.0	9.3	6.9	0.04
Clinical pregnancy, %	36.0	37.8	24.4	<0.01
Live Birth, %	30.0	30.3	18.8	0.02
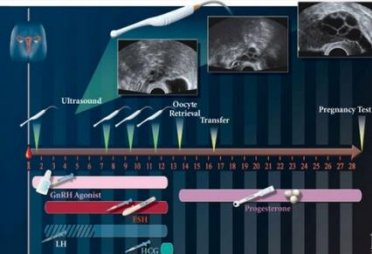
DOES OVARIAN STIMULATION DURATION MAKE ANY DIFFERENCE ON PREGNANCY OUTCOMES IN POOR RESPONDER PATIENTS UNDERGOING IVF-ICSI CYCLES WITH GnRH ANTAGONIST PROTOCOL?

F. Aybar,[a] A. P. Cil,[a] G. Batmaz,[b] S. G. Temel,[c] S. Kahraman.[a] [a]Assisted Reproductive Technologies and Reproductive Genetics Center, Memorial Hospital, Istanbul, Sisli, Turkey; [b]Obstetrics and Gynaecology, Bezmialem Vakif University, Istanbul, Fatih, Turkey; [c]Department of Histology & Embryology, University of Uludag, Faculty of Medicine, Bursa, Turkey.

OBJECTIVE: To determine whether stimulation duration affects IVF-ICSI outcomes in poor responder patients undergoing IVF-ICSI cycles with GnRH antagonist protocol.

DESIGN: Retrospective data analysis.

MATERIALS AND METHODS: Totally 289 poor responder patients undergoing IVF-ICSI cycles with GnRH antagonist protocol from August 2011 to January 2013 were included. Patients were divided into 3 groups:

Comparison of success rates

	ER (n=48)	NR (n=157)	DR (n=84)	p- value	p value after adjustment
Age	36.5	36.2*	38.5*	0.001	
CPR(%)	32.5*	38*·*	19.7*·**	0.041	0.386
OPR(%)	25	30.2	19.7	0.297	0.901
MR(%)	23.1	22.4	0	0.188	
CR(%)	16.7	17.2	28.6	0.088	

*,** İndicates significant difference between groups.
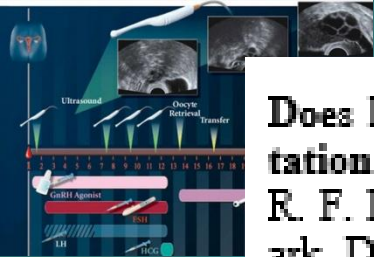
Does length of ovarian stimulation affect IVF pregnancy and implantation rates? M. P. Portmann, L. S. Morrison, D. R. Prinz, B. A. McGuirk, R. F. Feinberg, M. J. Tucker. Reproductive Associates of Delaware, Newark, DE; Georgia Reproductive Specialists, Atlanta, GA.

RESULTS:

Day of Transfer	N	Mean Age	Pregnant	Implanted	# Trans	Preg. Rate	Imp. Rate
Thur / Fri (Day 9 or 10 Trigger)	43	35.2	22	30	103	51.2% [1,2]	29.1% [4,5]
Sat / Sun (Day 11 or 12 Trigger)	77	34.7	49	61	186	63.6% [1,3]	32.8% [4,6]
Mon/Tues/Wed (Day 13, 14 or 15 Trigger)	28	35.6	10	11	63	35.7% [2,3]	17.5% [5,6]
Totals	148	35.2	81	102	352	54.7%	29.0%

Th/Fr vs Sa/Su   [1] $p = 0.1825$ [4] $p = 0.2461$
Th/Fr vs Mo/Tu/We   [2] $p = 0.2011$ [5] $p = 0.0723$
Sa/Su vs Mo/Tu/We   [3] $p = 0.0108$ [6] $p = 0.0033$

OB/GYN) under abdominal ultrasound guidance and performed by the same
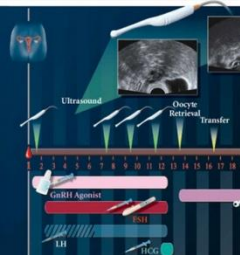
Ovarian stimulation in in vitro fertilization with or without the "long" gonadotropin-releasing hormone agonist protocol: effect on cycle duration and outcome

Ron Beloosesky, M.D., Shahar Kol, M.D., Abraham Lightman, M.D., and Joseph Itskovitz-Eldor, M.D., D.Sc.

Department of Obstetrics and Gynecology, Rambam Medical Center, and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Objective: To study the correlation between stimulation duration of IVF cycles, with and without GnRH agonist (GnRH-a), and cycle outcome.

Design: Retrospective analysis of data.

Setting: University-affiliated IVF clinic.

Patient(s): 998 IVF cycles in which long GnRH-a protocol was used, and 155 cycles with hMG only.

Intervention(s): IVF cycles.

Main Outcome Measure(s): Cycle outcome in number of oocytes and embryos, and pregnancy rate.

Result(s): The mean stimulation duration ($\pm$SD) was 9.6 $\pm$ 1.7 and 6.7 $\pm$ 1.0 for the GnRH-a and the hMG-only cycles, respectively ($P < 0.01$). In the GnRH-a group, no statistically significant correlation between cycle duration and pregnancy rate was found. Interestingly, the patients treated for 9 days had the highest number of oocytes retrieved and the highest pregnancy rate. Stimulation duration was not affected by age in either protocol. GnRH-a cycles yielded a significantly higher number of oocytes and embryos compared to cycles without GnRH-a. The pregnancy rate was similar in both groups.

Prolonged gonadotropin stimulation for assisted reproductive technology cycles is associated with decreased pregnancy rates for all women except for women with polycystic ovary syndrome

Amanda Ryan, Shunping Wang, Ruben Alvero, Alex J Polotsky

Abstract

Purpose

To determine if etiology of infertility modifies the relationship between the duration of ovarian stimulation and success during assisted reproductive technology (ART) cycles.

Methods

A prospectively collected database was analyzed in an academic infertility practice. Eight hundred and twelve infertile women undergoing their initial fresh embryo, non-donor in vitro fertilization (IVF) or Intracytoplasmic Sperm Injection ICSI) cycle between January 1999 and December 2010 were evaluated. Clinical pregnancy was the main outcome measured.

Results

Out of 663 cycles resulting in oocyte retrieval, 299 produced a clinical pregnancy (45.1%). Women who achieved a clinical pregnancy had a significantly shorter stimulation length (11.9 vs. 12.1 days, p=0.047). Polycystic ovary syndrome (PCOS) was the only etiology of infertility that was significantly associated with a higher chance for clinical pregnancy and was a significant confounder for the association of duration and success of treatment. Women with 13 days or longer of stimulation had a 34 % lower chance of clinical pregnancy as compared to those who had a shorter cycle (OR 0.66, 95% CI:0.46-0.95) after adjustment for age, ovarian reserve, number of oocytes retrieved, embryos transferred and PCOS diagnosis.

Conclusion

Prolonged duration of stimulation is associated with decreased ART success for all couples, except for women with PCOS.
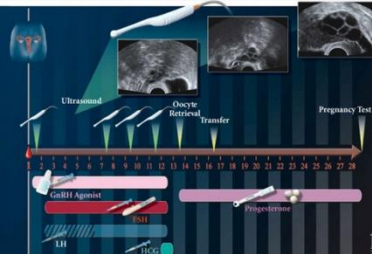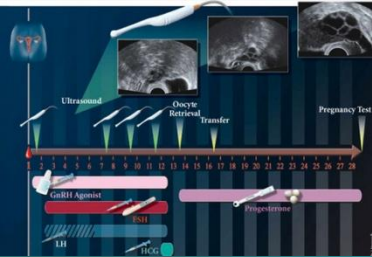
Protocols for COS: GnRH Antagonists vs Agonists

POOR RESPONDERS			
14 RCT (1127 patients); Pu et al. 2011			
Duration of stimulation	Oocytes retrieved	Cycle cancellation	CPR
-1.9 days (-3.6; -0.12)	-0.17 (-2.42; -0.66)	1.01 (0.71; 1.42)	1.23 (0.92, 1.66)

Lainas *et al*. Hum Reprod. 2010;25:683; Pu D *et al*. Hum Reprod. 2011; 26: 2742.

CONCLUSION

- hCG trigger on day 8 SPL not affect on oocyte, embryo quality and pregnancy rate.

- SPL day 8: number of oocytes and embryos significant lower than SPL day 9-12.

- SPL day 10,11: number of oocytes and embryos significant higher than other groups.