ORAL CONTRACEPTIVES prior to IVF

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Paradox

Treating subfertile patients with a medicine that

is mainly used to prevent conception

Oral Contraceptive Pills

- Developed in the 1950s
- Clinically used in the 1960s
- Used for IVF in mid 1980s

Ingredients

- Synthetic Estrogen
  - Ethynl estradiol
- C-19 steroids with progestational activity

Oral Contraceptives Pretreatment

- Oral Ethynl Estradiol in the early follicular phase
  - Suppression in gonadotropins
  - Lengthening of the follicular phase

Tsai CC,Yen SS, 1971
Vaitukaitis JL et al, 1971

Programming Oocyte Retrieval

- To Prevent the premature LH surge and luteinization
- To Turn oocyte retrieval from an emergency to an elective operation
- Randomized studies have showed the superiority of GnRH-a

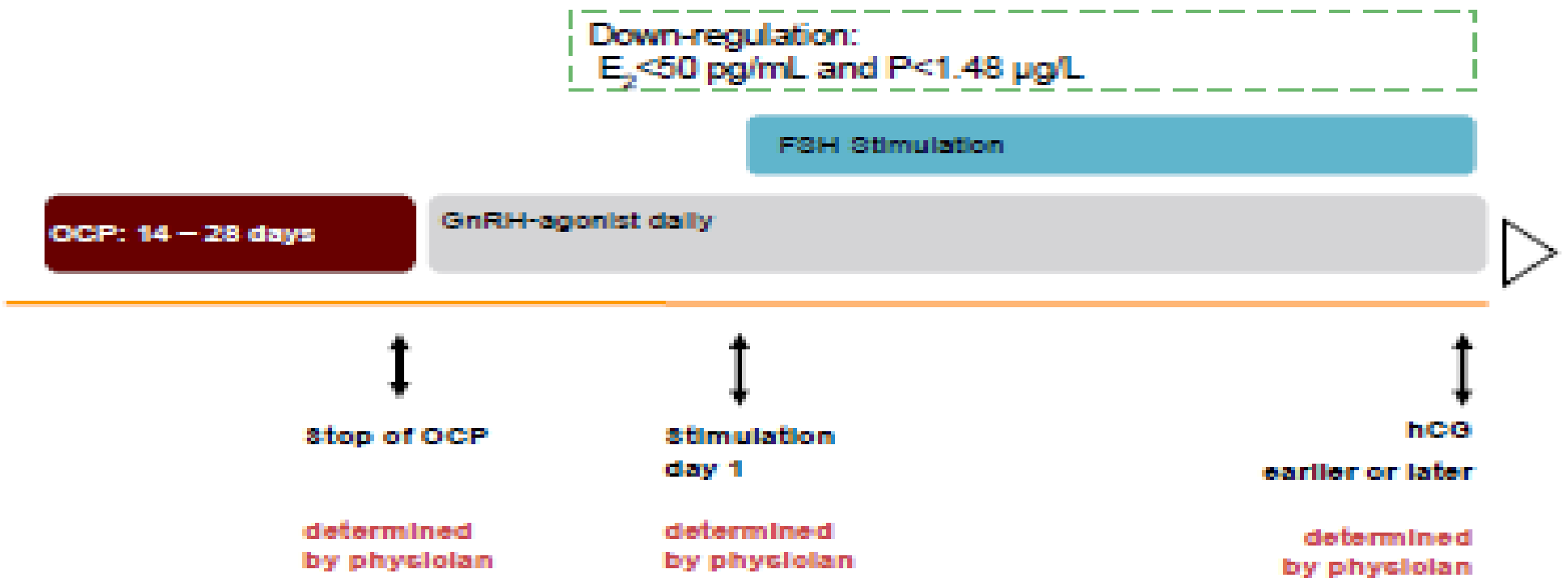
OCs in Ovulation-Induction Programs

Authors	Study design	Sample	Experimental Regimen
Branigan et al 1999	Prospective,non-randomization Observational	38 CC-resistant women	OC followed by repeat CC 100mg for 5 days
Branigan et al 2003	Randomized,controlled	48 CC-resistant women	OC followed by repeat CC 100mg for 5 days
Elkind-Hirsch et al 2003	Prospective,non-randomization	20 PCOS women	OC in COS with r-FSH and GnRH-agonist

OCs in Ovulation-Induction Programs

Authors	Clinical Results	Comments
Branigan et al 1999	↑ Ovulation rate ↑ Pregnancy rate	No randomization No statical analysis No control group
Branigan et al 2003	↑ Ovulation rate ↑ CumulativePregnancy rate	Randomized,controlled design Adequate sample size ↓ 17-ß E2, LH, Androgens
Elkind-Hirsch et al 2003	↑ Ovulation rate ↑ Pregnancy rate ↑ Ongoing Pregnancy rate	No randomization No control group No power analysis Preliminary data

OC pre-treatment in a long agonist protocol



Use of OCs in IVF programs
GnRH-Agonist

- Reversibly supresses pituitary function
- Avoids premature LH peak and luteinization
- Causes functional ovarian cyst formation

OCs and GnRH-agonists in IVF Programs

Authors	Study design	Sample	Experimental Regimen
Damario et al 1997	Retrospective,,non-controlled	73 high responder women	Dual suppression with OC and GnRH-a in IVF-ET cycles
Biljan et al 1998	Retrospective,,non-controlled	31 infertile women	OC prior to GnRH-a in IVF cycles
Biljan et al 1998	Randomized,controlled	83 infertile women	OC prior to GnRH-a in IVFcycles

OCs and GnRH-agonists in IVF Programs

Authors	Clinical Results	Comments
Damario et al 1998	↑ Fertilization rate ↑ Clinical pregnancy rate ↑ Ongoing pregnancy rate	Retrospective analysis No control group
Biljan et al 1998	↓ Functional ovarian cysts ↓ Time to pituitary supression Small sample size	Retrospective analysis No control group
Biljan et al 1998	↓ Functional ovarian cysts ↓ Time to pituitary supression ↓ Ampoules of gonadotropin required ↑ Pregnancy rate	Randomized controlled design Adequate sample size Power analysis

OCs and GnRH-a Combination

- Normalize LH / FSH ratio and reduce ovarian androgen concentrations
- Improved the IVF outcome
- Reduce miscarriage rate in the following pregnancy

Damario MA et al, 1997
Suikkarı AM et al, 2001
Clifford K et al, 1996

- The use of OCs prior to controlled ovarian hyperstimulation (COH) allows for convenient cycle scheduling aswell as for ovulation suppression so that subsequent GnRH-a treatment cannot stimulate residual corpus luteum function.

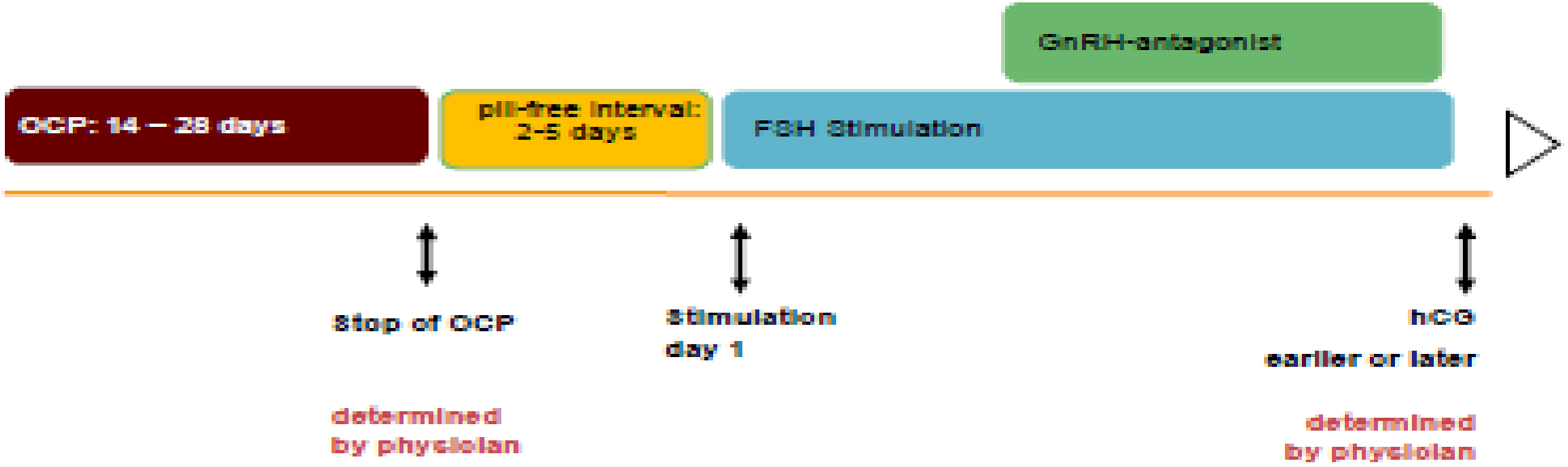
- OCs also can reduce the incidence of functional ovarian cyst formation, shorten the time required to achieve pituitary suppression and decrease gonadotropin requirements .

Biljan MM et al 1998
Barmat LI et al 2006

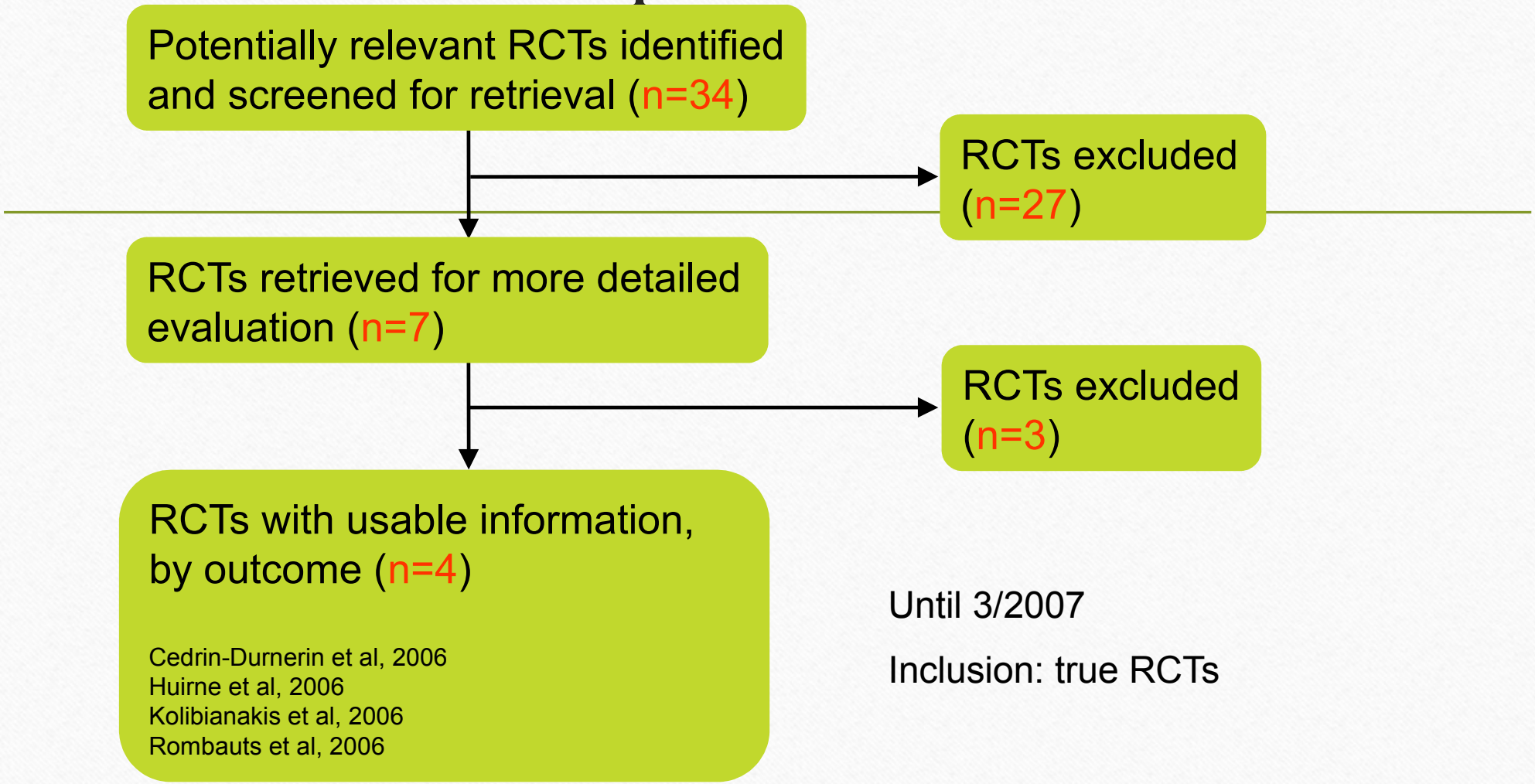
OCs plus GnRH-a protocols

- Since so many positive reports have been published concerning OCs in IVF treatment,combined use of OCs and GnRH-a down regulation has become a standard protocol in IVF therapy

OC pre-treatment in an antagonist protocol



Oral Contraceptive Pill Pretreatment



Until 3/2007

Inclusion: true RCTs

Griesinger et al. *Fertil Steril*. 2008;90:1055.

Effect of OCP Pretreatment

	Effect	*P* Value
Gonadotropin consumption	**+542 IU** 95% CI, +127 to +956	<0.01
Stimulation duration	**+1.41 days** 95% CI, +1.13 to +1.68	<0.01
Number of COCs	**+1.63** 95% CI, –0.34 to +3.61	0.11
OR for ongoing PR per randomized patient	**0.74** 95% CI, 0.53 to 1.03	0.08
Rate difference for ongoing PR	**–5%** 95% CI, –10.0 to +0.4	0.07

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Griesinger et al. *Fertil Steril*. 2008;90:1055.

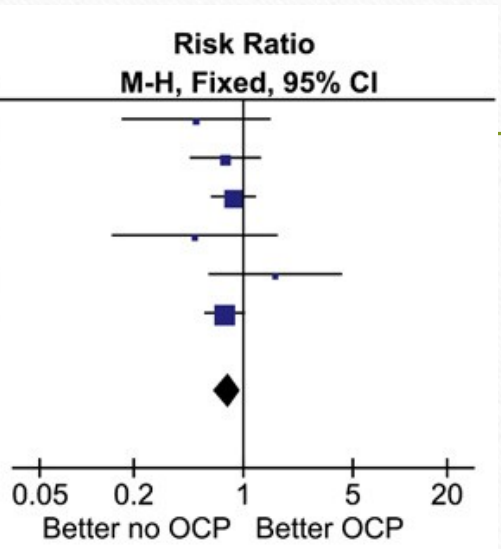
Oral Contraceptive Pretreatment Significantly Reduces Ongoing Pregnancy Likelihood in GnRH Antagonist Cycles: A Meta-Analysis

A

Study or Subgroup	OCP Events	OCP Total	no OCP Events	no OCP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Huirne	4	32	8	32	4.5%	0.50 [0.17, 1.50]	2006
Rombauts	20	117	26	117	14.7%	0.77 [0.46, 1.30]	2006
Kolibianakis	51	250	60	254	33.7%	0.86 [0.62, 1.20]	2006
Cedrin	3	21	7	24	3.7%	0.49 [0.14, 1.66]	2007
Kim	8	27	5	27	2.8%	1.60 [0.60, 4.27]	2009
Tavmergen	55	223	71	219	40.5%	0.76 [0.56, 1.03]	2009
Total (95% CI)		**670**		**673**	**100.0%**	**0.80 [0.66, 0.97]**	
Total events	141		177				

Heterogeneity: Chi² = 3.58, df = 5 (P = 0.61); I² = 0%

Test for overall effect: Z = 2.28 (P = 0.02)



The probability of an ongoing pregnancy per randomized woman was found to be significantly lower in patients who received oral contraceptive pill pre-treatment (RR 0.80, 95% CI: 0.66 to 0.97; *p*=0.02

BUT….

Griesinger et al. Fertil Steril 2010;94:2382-4

Ongoing pregnancy rate per randomized woman

Absolute treatment effects:

-5% in ongoing pregnancy rate
(95% CI: -10 to 1)

Number-needed-to-treat-to-harm

20 (95% CI:10–100)

(e.g., for every 20 patients pretreated with OC, one ongoing pregnancy is missed

Can weekend oocyte pick-ups be avoided by scheduling initation of stimulation?

- NO…..because

- there is a wide range of duration of stimulation
  6-15 days Elonva study (ENGAGE)
  6-18 days phase III antagonist
  7-16 days long agonist (Middle East trial)
- Pre-treatment does not decrease the variation in duratiomn of stimulation

Griesinger & Kolibianakis, RBMonline 2012

- Comparable outcomes are obtained between long agonist and OCP treated antagonist protocols
- RCT (N=115)

Cycle outcome.

	OCP, n (%)	No OCP, n (%)	*P* value	Odds ratio (95% CI)
Biochemical PR	61/115 (53.0)	67/113 (59.3)	.17	0.7 (0.4, 1.3)
Clinical PR	56/115 (48.7)	64/113 (56.6)	.12	0.7 (0.4, 1.2)
Ongoing PR	55/115 (47.8)	61/113 (53.9)	.18	0.8 (0.5, 1.3)
Multiple PR	15/56 (26.7)	18/64 (28.1)	.43	0.9 (0.4, 2.1)
Implantation rate	75/207 (36.2)	80/204 (39.2)	.26	0.9 (0.6, 1.3)
Miscarriage rate	5/56 (8.9)	11/64 (17)	.09	0.5 (0.1, 1.4)
Live birth rate	51/115 (44.3)	53/113 (47)	.35	0.9 (0.5, 1.5)

- Pill-free interval
- Type of estrogen/progesterone

Garcia Velasco et al. Fertil Steril 2011;96:5903

Synchronising the follicular cohort and patient scheduling

- Intention
- I. Distributing workload
- II. Avoiding weekends
- III. (Synchronising follicular cohort)
- Means
- I. Schedule start of ovarian stimulation
- II. Delay hCG or give hCG earlie

Early vs Late hCG

When is the correct moment to induce final oocyte maturation ?

- At least 3 follicles of ≥ 17 mm present in ultrasound
  - *Borm and Mannaerts HR 2000, The Middle East orgalutran study group HR 2001,*
  - *Fluker FS 2001, Kolibianakis FS 2002, 2003*
- At least 3 follicles of ≥ 18 mm present in ultrasound
  - *Garcia - Velasco HR 2001*
- Leading follicle attained 18-20 mm and estradiol levels were indicating satisfactory follicular development
  - *Olivennes HR 1998*
- At least ≥ 1 follicle of ≥ 18 mm and 3 follicles of ≥ 15 mm
  - *de Jong FS 2001*
- At least 1 follicle of ≥ 20 mm and an estradiol level 1200 pg/ml
  - *Albano HR 2000*
- At least 1 follicle of ≥ 20 mm or an estradiol level 1200 pg/ml
  - *Felberbaum HR 2000*

Effect of Delaying hCG by 2 Days

	Early hCG	Late hCG	*P* Value
Duration of recFSH stimulation (d)	9.6 ± 0.2	11.3 ± 0.2	0.001
COCs	11.2 ± 0.5	12.4 ± 0.5	0.07
2PN oocytes	6.4 ± 0.1	7.2 ± 0.3	NS
Embryos transferred	2.0 ± 0.1	2.0 ± 0.1	NS
Mean quality score of transferred embryos	1.6 ± 0.4	1.6 ± 0.4	NS
Ongoing PR	35.6	25.0	0.03

Kolibianakis et al. *Hum Reprod*. 2005;20:2453.

Table III IVF outcomes for ORs conducted on the ideal day of scheduling compared with those advanced or delayed by 1 day from ideal.

	Monday OR		*P*-value	Friday OR		*P*-value
	Ideal Monday OR (n = 221)	Ideal Sunday OR (n = 251)		Ideal Friday OR (n = 207)	Ideal Saturday OR (n = 165)	
Number of days rFSH stimulation	9.66 ± 2.5	10.48 ± 1.9	<0.0001	9.30 ± 2.1	8.35 ± 1.9	<0.0001
Number of oocytes	7.78 ± 5.5	9.88 ± 5.6	<0.0001	9.04 ± 5.7	7.95 ± 5.4	0.0241
Number of embryos	4.78 ± 3.6	5.78 ± 3.9	<0.004	5.32 ± 4.1	4.45 ± 3.5	0.010
Fertilization rate (%)	60.0%	58.0%	0.187	58.01%	55.0%	0.093
Embryos transferred	1.15 ± 0.50	1.23 ± 0.51	0.128	1.27 ± 0.5	1.13 ± 0.5	0.006
Embryos cryopreserved	1.07 ± 1.7	1.51 ± 2.1	0.675	1.19 ± 2.1	0.91 ± 1.7	0.142
Biochemical pregnancy rate (%)	38.91% (86/221)	39.04% (98/251)	0.977	40.0% (83/207)	35.8% (59/165)	0.391
Implantation rate (%)	32.15% (82/255)	29.54% (91/308)	0.503	34.60% (91/263)	31.72% (59/186)	0.523
Live birth rate (%)	30.76% (68/221)	33.06% (83/251)	0.621	35.74% (74/207)	32.12% (53/165)	0.463

Tremellen *et al.,* Hum Reprod, 2010

3. Shifting stimulation start

Scheduling Oocyte Retrieval
Shifting Stimulation Start Day (Day 2 vs Day 3)

- Retrospective analysis of day of oocyte retrieval by stimulation start day (cycle day 2 vs 3) in patients receiving Ganirelix plus Follistim in Engage
  - HCG administration could be delayed by 1 day if necessary
- To reduce weekend oocyte retrieval, stimulation should be initiated on a day the reduces the likelihood of reaching HCG criterion on a Thursday:

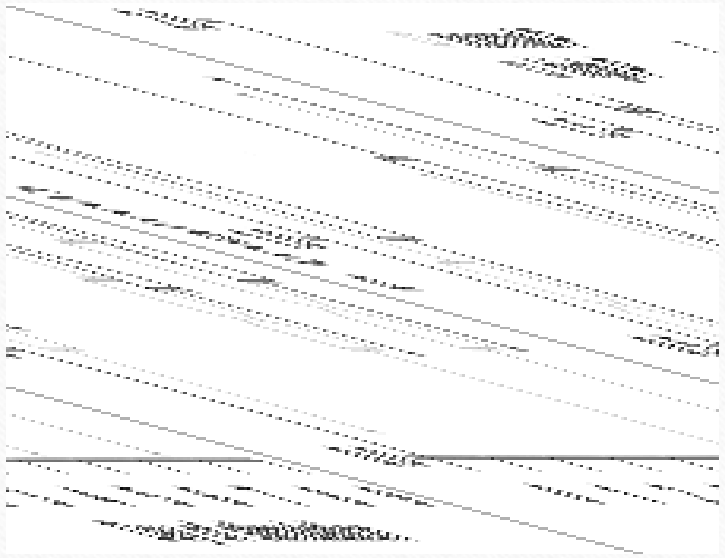
Week Day of Menses	Patients Reaching HCG Criterion on a Thursday, %		Recommended Stimulation Start Day
	Day 2	Day 3	
Sunday	**7.8**	15.2	**2**
Monday	**19.3**	27.4	**2**
Tuesday	**30.2**	38.0	**2**
Wednesday	35.5	**7.2**	**3**
Thursday	3.6	**3.5**	**3**
Friday	0.6	1.9	**2**
Saturday	3.1	6.9	**2**

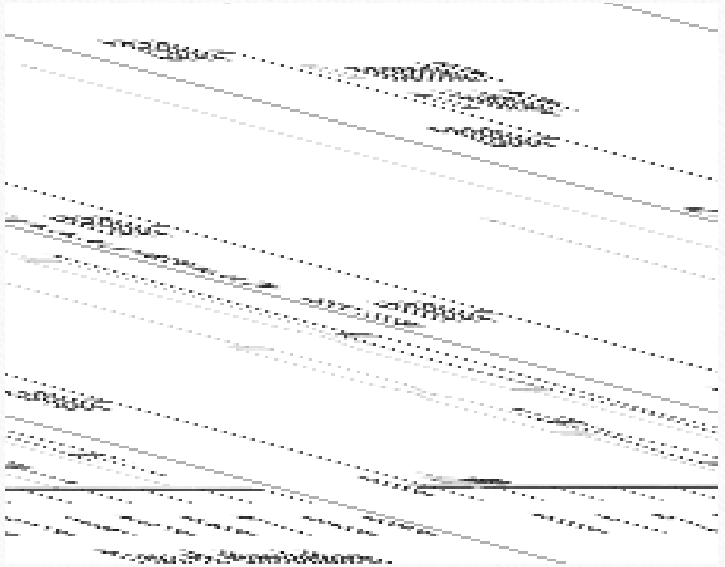
- If this strategy had been implemented in the Engage trial, weekend oocyte retrievals would have been reduced from 25.1% to 9.3%

Levy et al. *Reprod Biomed Online*. 2013;26:50-58.

3. Pretreatment with GnRH antagonists

Laboratory assessment prior to start of stimulation





Kolibianakis *et al.*, Hum Reprod, 2004

	Normal-P	High-P	P-value
Ongoing pregnancy rate			
Per started cycle % (*n*)	31.8 (124/390)	5.0 (1/20)	0.011
Per oocyte retrieval % (*n*)	33.8 (124/367)	6.3 (1/16)	0.026
Per embryo transfer % (*n*)	36.9 (124/336)	6.3 (1/16)	0.014
Ongoing implantation rate % (*n*)	21.1 (151/714)	3.6 (1/28)	0.028

Kolibianakis *et al.*, Hum Reprod, 2004

Administration of a GnRH antagonist before start in case of *elevated* progesterone

Anderson *et al.,* Hum Reprod,1999
Dragisic *et al.*, Fertil Steril, 2005
Von Wolff *et al.*, Fertil Steril, 2009

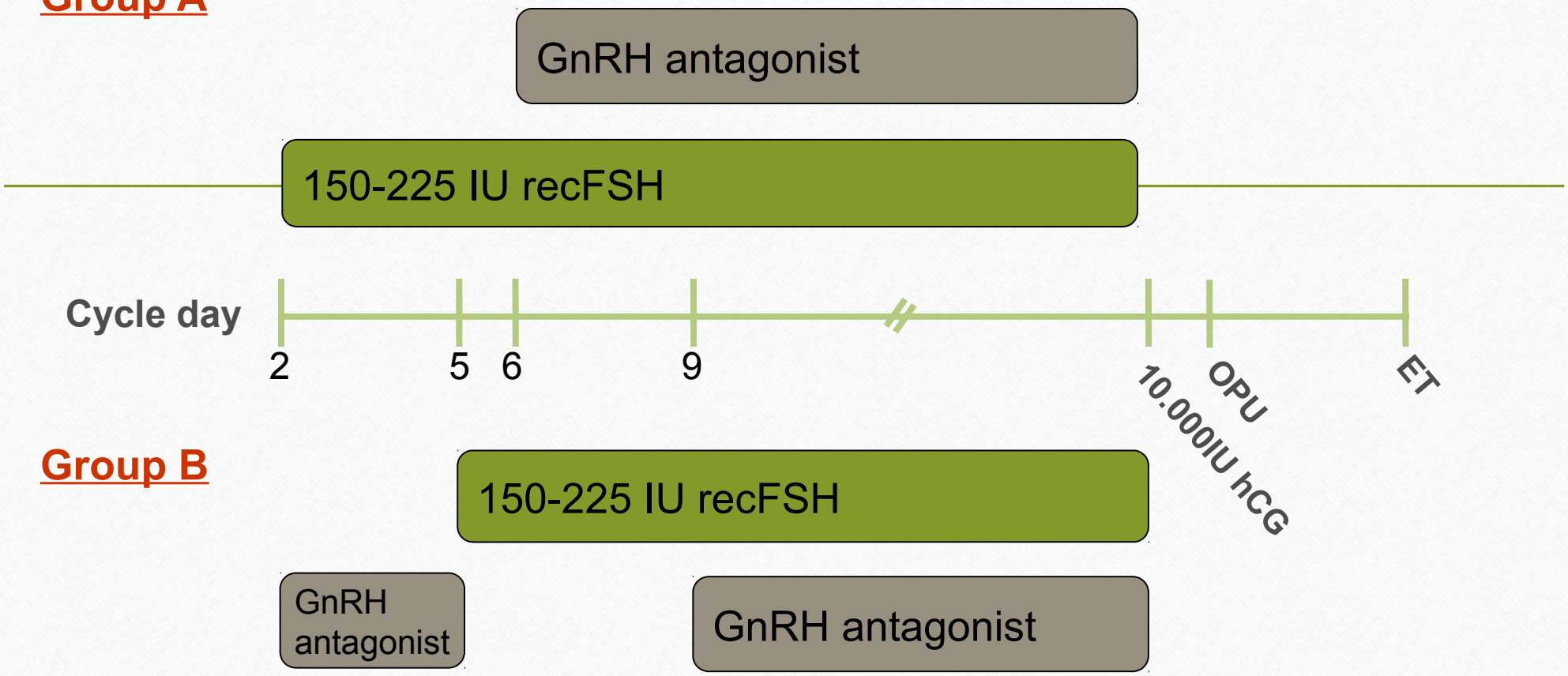
GnRH antagonists before start

	Normal P group (n=454)	High P group (n= 30)	
	On day 2 of the cycle	On day 2 of the cycle	After 3 days of antagonist
P (ng/ml)	0.8 ± 1.0	**3.3** ± 1.5	**0.8** ± 0.4
E_2 (pg/ml)	34.3 ± 17.4	48.4 ± 21.1	19.5 ± 13.8
FSH (IU/L)	7.19 ± 2.7	5.14 ± 2.3	5.92 ± 1.2
LH (IU/L)	5.13 ± 2.5	4.8 ± 2.5	3.5 ± 1.6

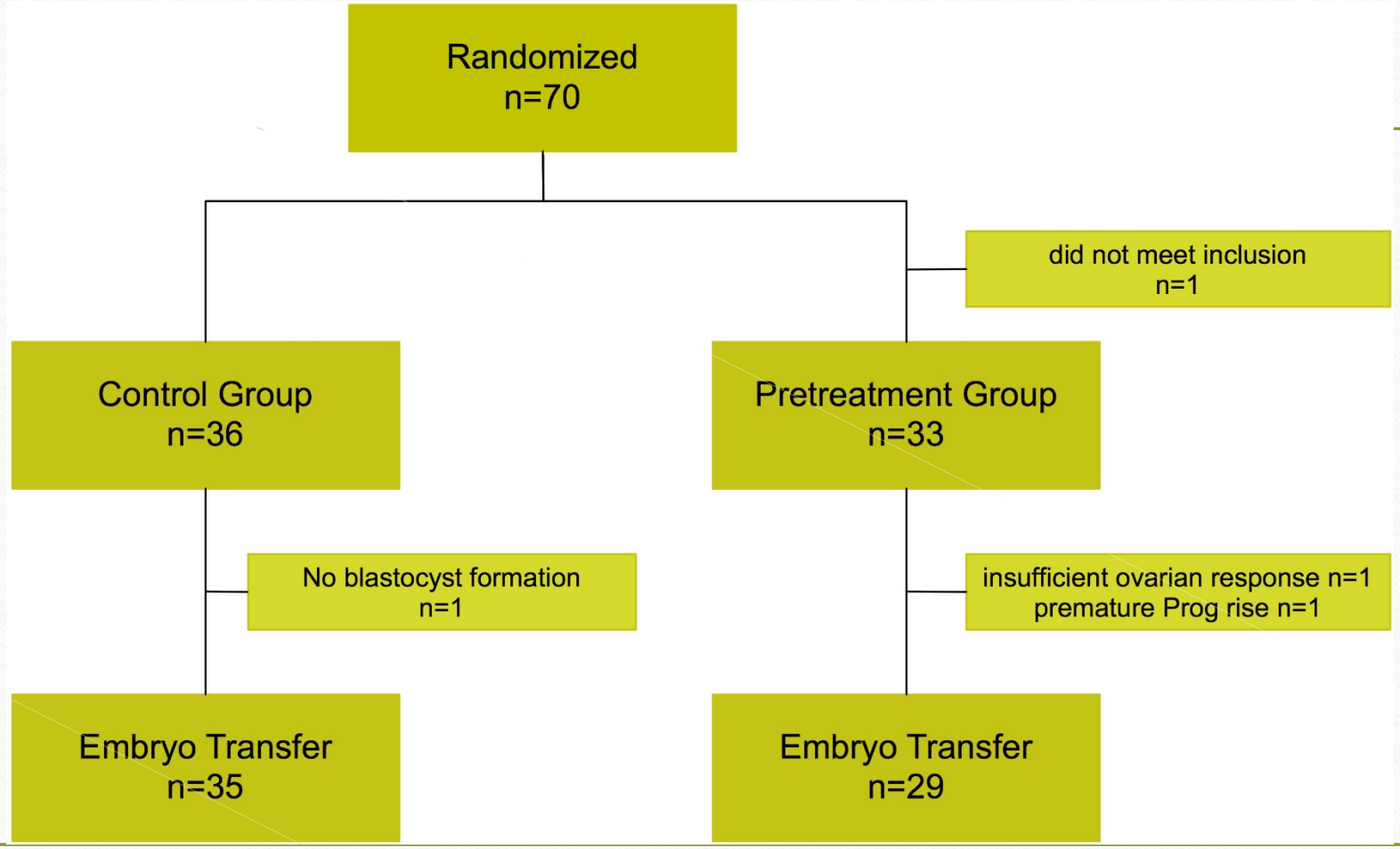
Blockeel *et al.*, Curr Pharmac *Biotech, 2011.*

Administration of a GnRH antagonist before start in case of *normal* progesterone

Treatment of Subjects



Trial profile of the study

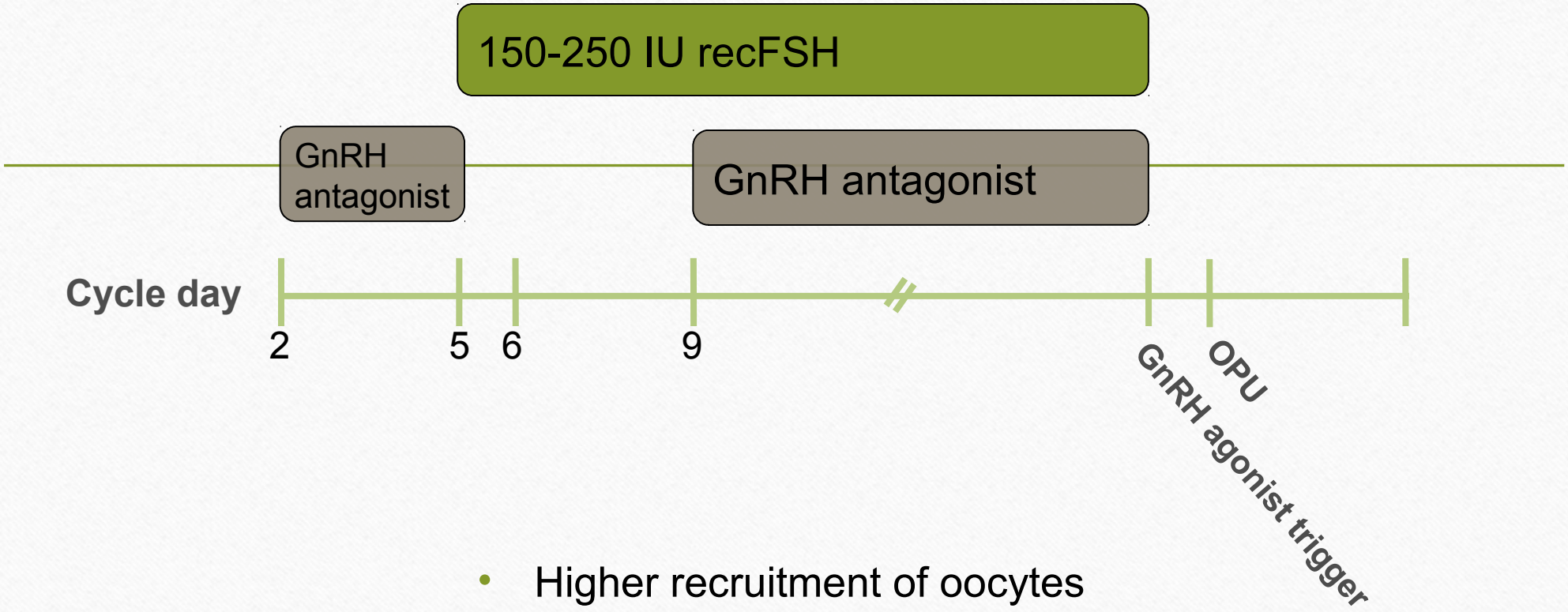


	Control group	Pretreatment group	P - value
Starting dose of rFSH (IU)	177.7 ± 32.3	166.9 ± 22.9	0.125
Days of rFSH stimulation	8.8 ± 1.7	8.8 ± 1.4	1.000
Number of COCs*	9.9 ± 4.9	13.6 ± 7.3	**0.016**
Ongoing pregnancy rate per started cycle % (n)	33.3% (12/36)	42.4% (14/33)	0.596

* Number of COCs per oocyte retrieval

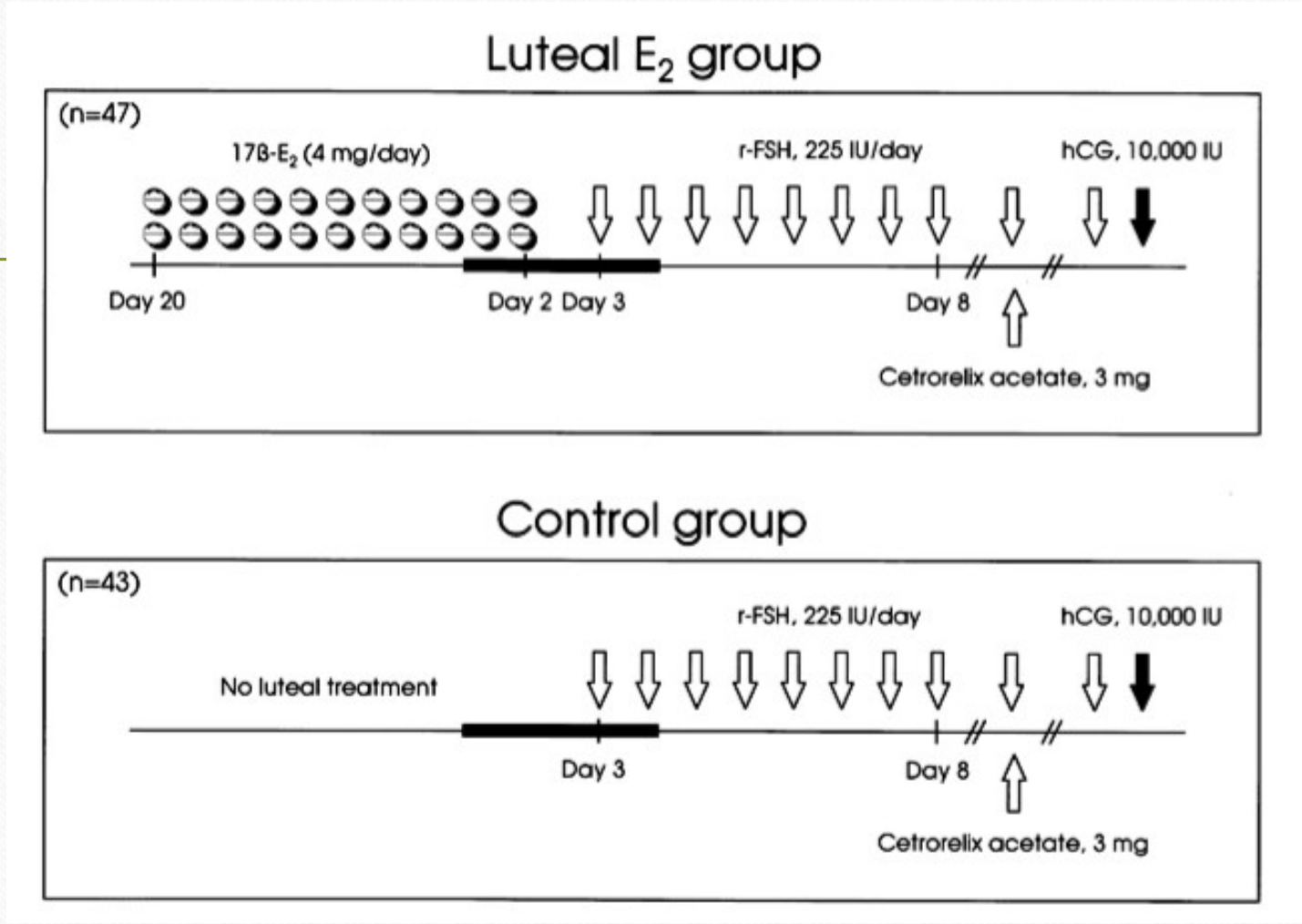
Blockeel *et al.,* Fertil Steril, 2011

Protocol for oocyte donors



- Higher recruitment of oocytes
- No OHSS

4. ESTRADIOL



Fanchin et al. *Hum Reprod*. 2003;12:2698.

Luteal estradiol pretreatment

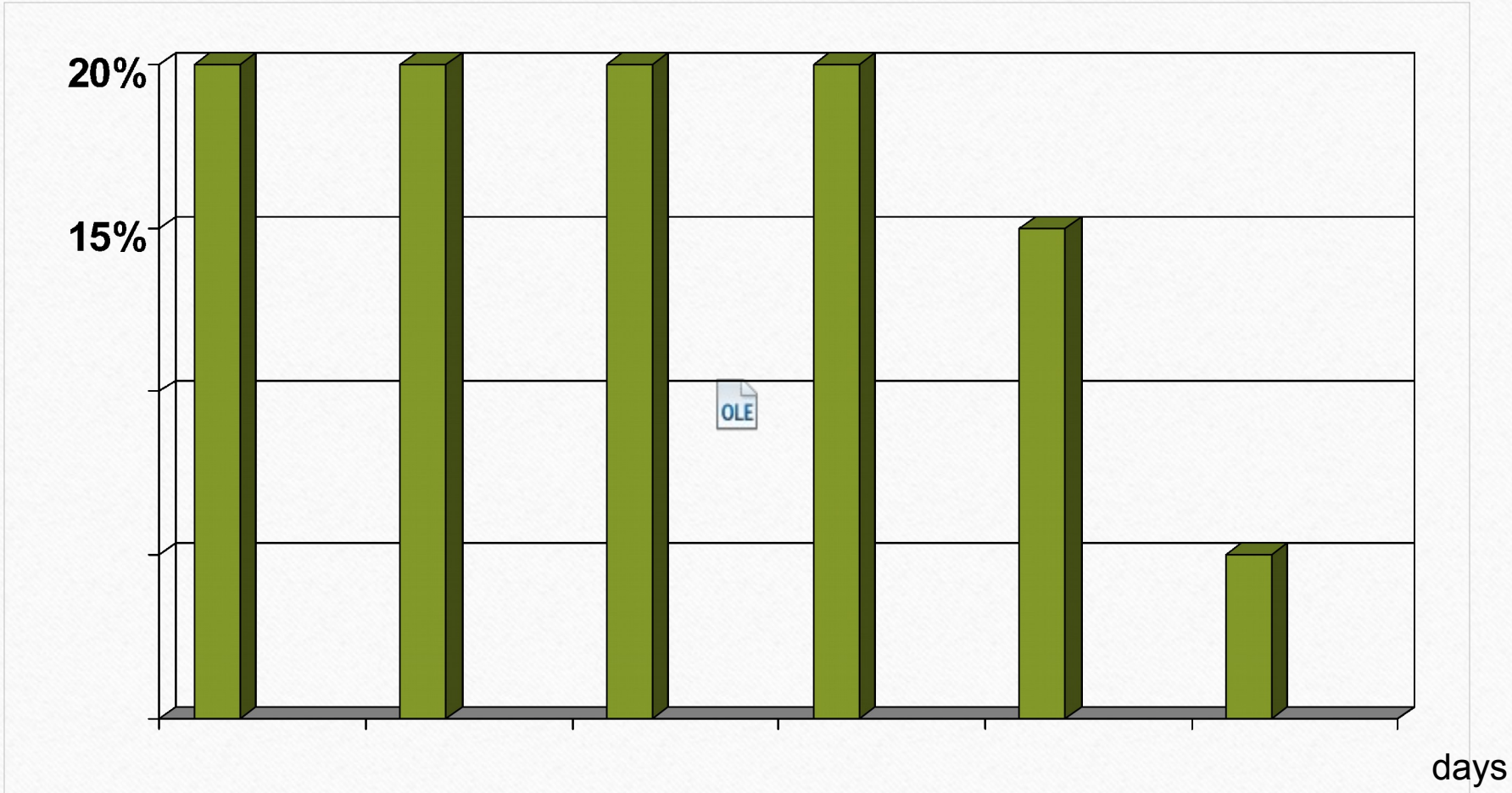
- Suppression of FSH
- Coordination of antral follicle growth (homogeneity - synchronisation)
- More physiological than GnRH agonist or OCP

	Luteal E_2 group	Control group	*P*
No. of follicles >10 mm on day 8	16.4 ± 1.0	16.8 ± 0.9	NS
Mean follicular size on day 8 (mm)	9.9 ± 0.2	11.1 ± 0.3	<0.001
CV of follicular sizes on day 8	0.22	0.26	<0.02
Day of GnRH antagonist administration	9.1 ± 0.2	8.5 ± 0.2	<0.01
Day of HCG administration	11.9 ± 0.2	10.8 ± 0.2	<0.001
No. of follicles ⩾16 mm on day of HCG	9.9 ± 0.5	7.9 ± 0.5	<0.01
No. of mature follicles	9.3 ± 0.7	7.3 ± 0.5	<0.03
No. of available embryos	6.4 ± 0.6	4.6 ± 0.3	<0.01
No. of embryos transferred	2.6 ± 0.1	2.7 ± 0.1	NS
Clinical pregnancy rates/cycle	34%	25%	NS

CV = coefficient of variation.

Fanchin et al. *Hum Reprod*. 2003;12:2698.

Programming of egg retrievals



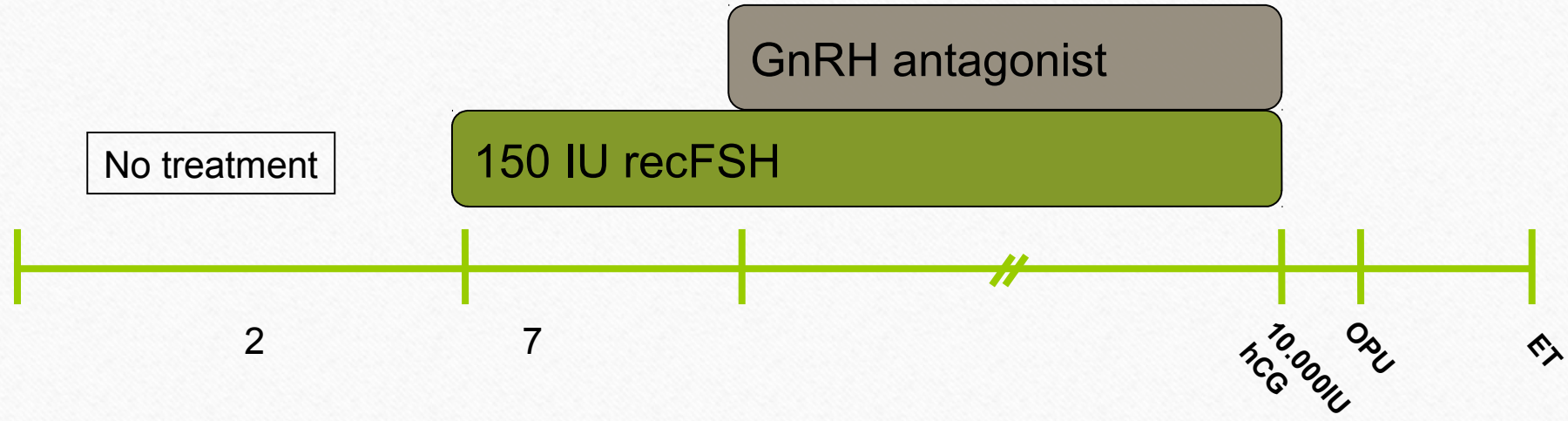
A Guivarc'h - Levêque et al GOF 2010

Results

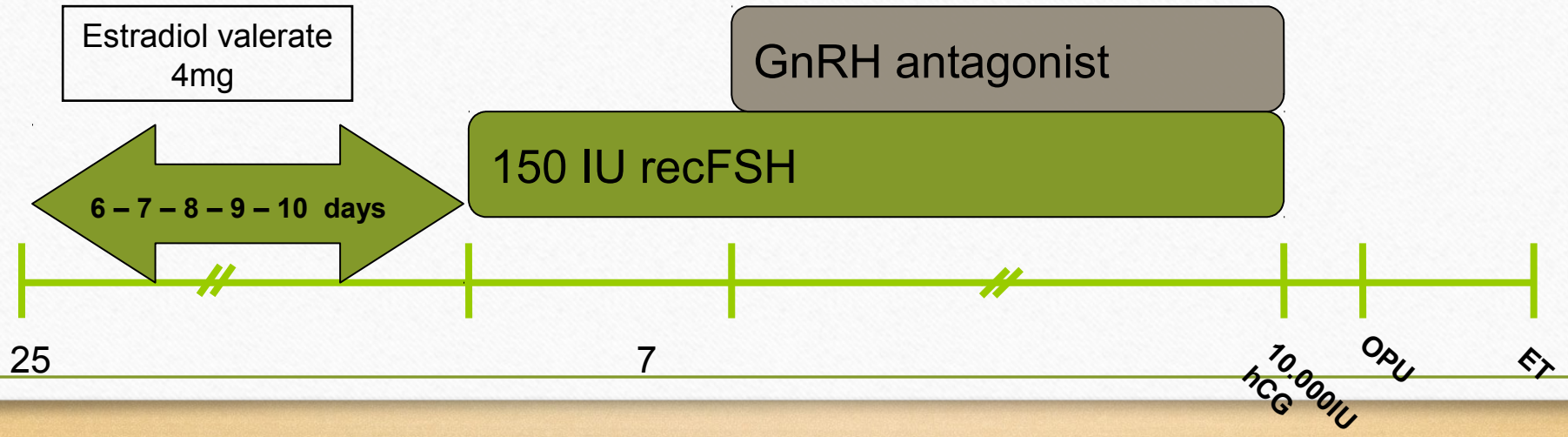
Results	Antagonist	Long Agonist	P
Age (years)	32.5	33.1	
Cycles (n)	426	412	
OPU rate (%)	88%	88%	
Eggs inseminate (mean)	6.8	7.6	< 0.01
Pregnancy rate	29%	28%	NS

A Guivarc'h - Levêque et al GOF 2010

Control Group A



Pretreatment Group B

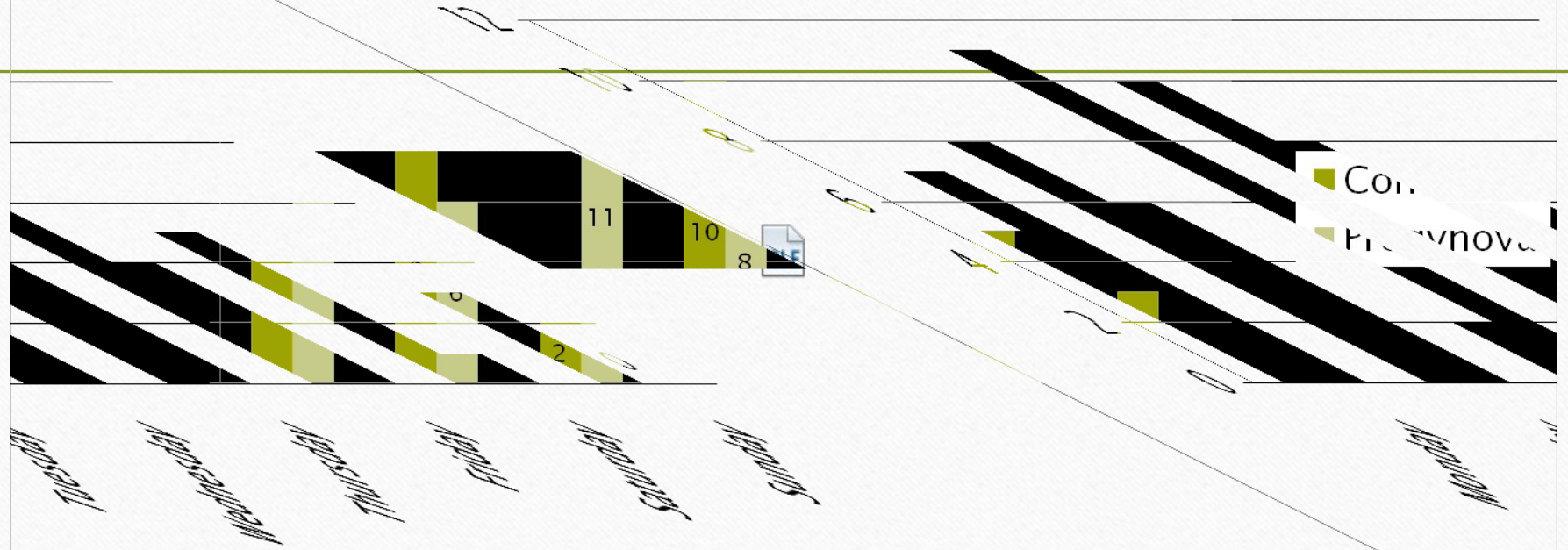


If day 25 is….

- Monday 6 days Progynova 4 mg
- Tuesday 10 days Progynova 4 mg
- Wednesday 9 days Progynova 4 mg
- Thursday 8 days Progynova 4 mg
- Friday 7 days Progynova 4 mg
- Saturday 6 days Progynova 4 mg
- Sunday 6 days Progynova 4 mg

Results

Primary endpoint: proportion of patients undergoing an oocyte retrieval during weekend days



	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Total	%OR during weekend days
Control	5	8	2	10	6	5	3	39	8/39 (20.5%)
Progynova	7	6	11	8	4	1	0	37	1/37 (2.70%)

P=0.029

Stimulation characteristics and embryological data

Results (2)

	Control group (n=39)	Pretreatment group (n=37)	P-value *
Days of rFSH stimulation	8.6 ±1.5	9.6 ± 1.4	**0.004**
Total dose of rFSH consumption, IU	1295.0 ± 254.2	1485.1 ± 248.7	**0.002**
Number of COCs	12.2 ± 8.7	12.2 ± 6.2	1.00
Number of MII oocytes	9.9 ± 7.8	10.0 ± 4.7	0.947
Number of 2-PN oocytes	7.6 ± 6.5	8.4 ± 3.7	0.625

* P-value for Student's *t* test; P-values less than 0.5 are bold

Blockeel et al., RBMOnline, *2012*.

Results (3)

Ongoing pregnancy rates

	Control group	Pretreatment group	P-value *
Ongoing pregnancy rate			
Per started cycle, n (%)	16/42 (38.1%)	16/44 (36.4%)°	0.868
Per pickup, n (%)	16/39 (41.0%)	16/37 (43.2%)°	0.845
Per embryo transfer, n (%)	16/37 (43.2%)	16/35 (45.7%)°	0.833

* P-value for Fisher's exact of Chi-squared test

° pregnancy outcome still awaited for 3 patients in the pretreatment group

Blockeel et al., RBMOnline, *2012*.

E2 Pretreatment vs no-pretreatment in GnRH Antagonist Protocol

Parameter	Estrogen (n=233)	No pretreatment (n=220)	P-Value
FSH starting dose (IU/d)	158 ± 23	156 ± 24	NS
Total FSH dose (IU)	1,557 ± 408	1389 ± 347	<.0001
Oocytes	10.9 ± 5.7	10.2 ± 5.6	NS
Total delivery (n)	62	66	NS

Cédrin-Durnerin *et al.*, Fertil Steril, 2012.

Conclusion

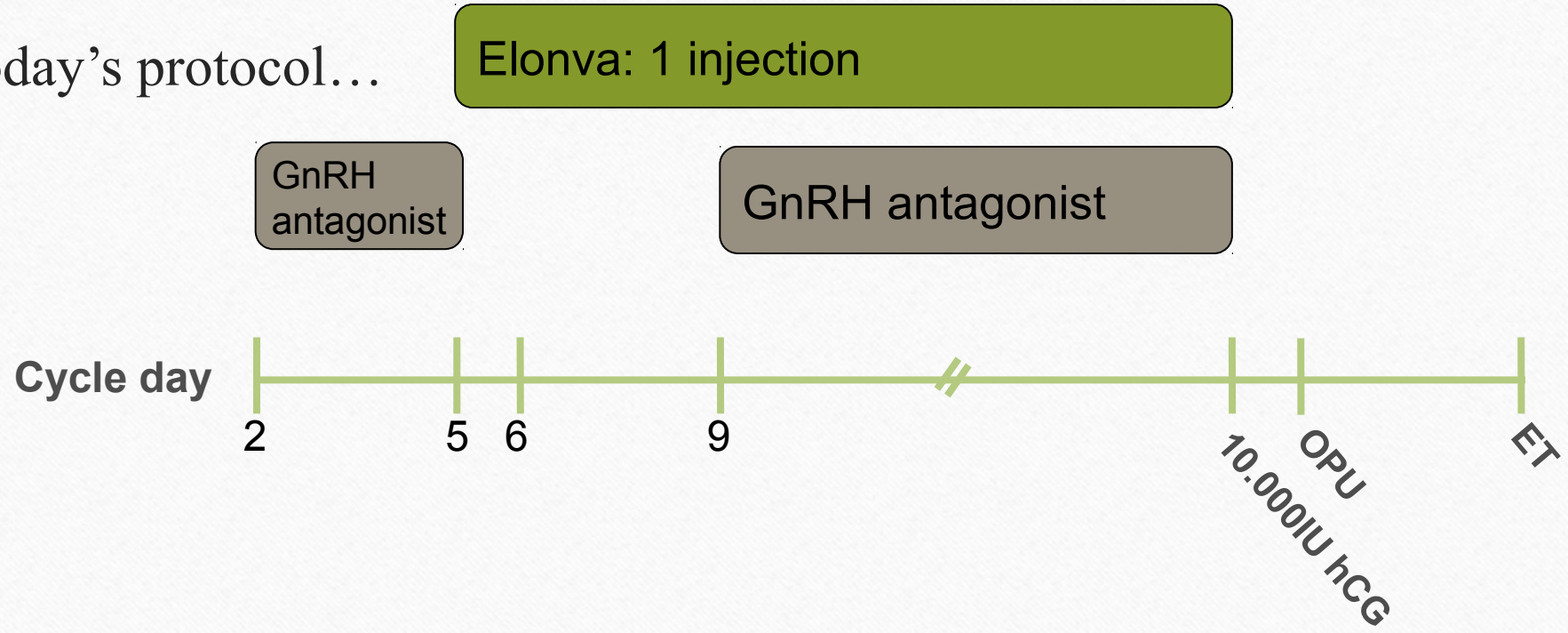
Estradiol valerate pretreatment

- ✓ **allows scheduling** of GnRH antagonist cycles, with a significantly lower proportion of patients undergoing OR during weekend days
- ✓ **without deleterious effects** on the number of oocytes retrieved and the ongoing pregnancy rates

Blockeel et al., RBMOnline, *2012*.

Conclusion: planning is possible!

Today's protocol…



Conclusion: planning is possible!