Dipartimento di Neuroscienze, Scienze Riproduttive ed Odontostomatologiche

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Tecniche di sincronizzazione ovocitaria. La sincronizzazione follicolare

Carlo Alviggi

The rational of Follicular synchronization and IVF

- Scheduling IVF treatment to meet the organizational needs of both patients and IVF centers, might have important economic and practical implications

- To reduce follicular size discrepancies and to enhance ovarian response in recombinant FSH protocol

- Endogenous FSH suppression before starting ovarian stimulation is an efficient way to schedule ovarian stimulation

Erik E Hauzman *et al.*, Reprod Biol Endocrinol 2013
Fanchin *et al.,* Hum Reprod 2003

GnRH-AGONIST

GnRH-ANTAGONIST

GnRH agonists vs GnRH antagonists

Gonadotrophin-releasing hormone antagonists for assisted reproductive technology (Review)

73 RCTs, 12,212 participants

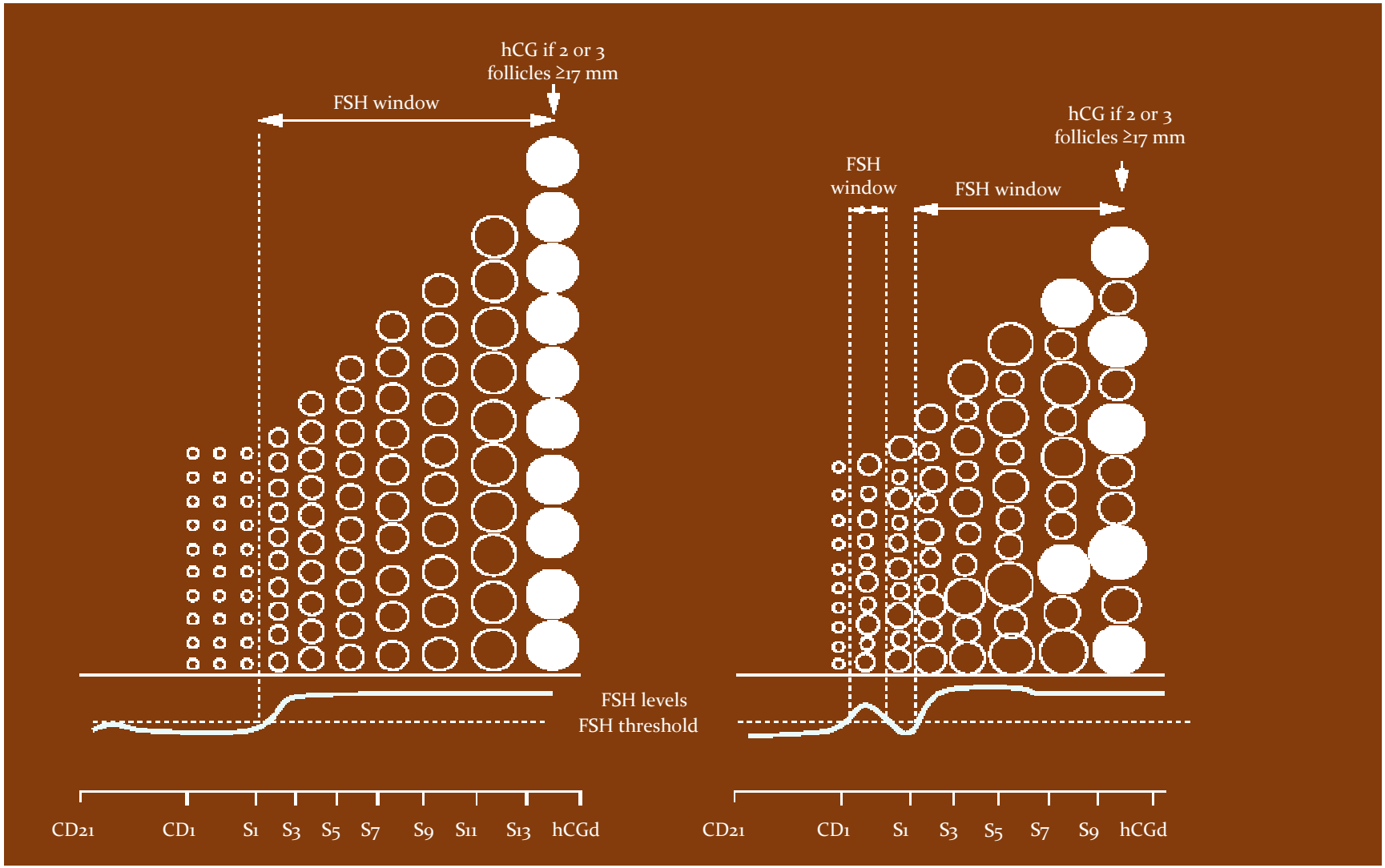
Endpoints:

Comparable Live birth: OR 1.02, 95% CI 0.85 to 1.23; p = NS

Increased OHSS after agonist: OR 0.61, 95% C 0.51 to 0.72; p < 0,05

Al Inany et al (2016) Cochrane Database Syst Rev

GnRH agonist versus GnRH antagonist: Follicular growth dynamics



Huirne et al. (2007) Hum Reprod; 22: 2805–13

Follicular Syncrhonization and IVF: Strategies

- **GnRH antagonist**
  - **Oral contraceptive**
  - **Estradiol**
  - **Progestins and Progestatives**

Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques (Review)

Cochrane Library

Selection criteria

Systematic review and meta-analysis of randomised controlled trials of hormonal pre-treatment in subfertile women undergoing IVF/ ICSI

Intervention

- Combined OCP
- Progestogen
- Estrogen

Conclusion: No evidence of effect was found with regard to the number of live births when using a pre-treatment

Smuders *et al.*, Cochrane Database Syst Rev 2010

Use of OCs for follicles sychronization

Kind of OCs used :

• Ethinyl estradiol 30 µg + 150 µg desogestrel (Cédrin-Durnerin 2007; Kolibianakis 2006; Obruca 2001; Raoofi 2008; Rombauts 2006)

•Ethinyl estradiol 30 µg + 150 µg levonorgestrel daily (Huirne 2006a; Huirne 2006b)

•Ethinyl estradiol 35 µg and 2 mg cyproterone acetate (Hwang 2004)

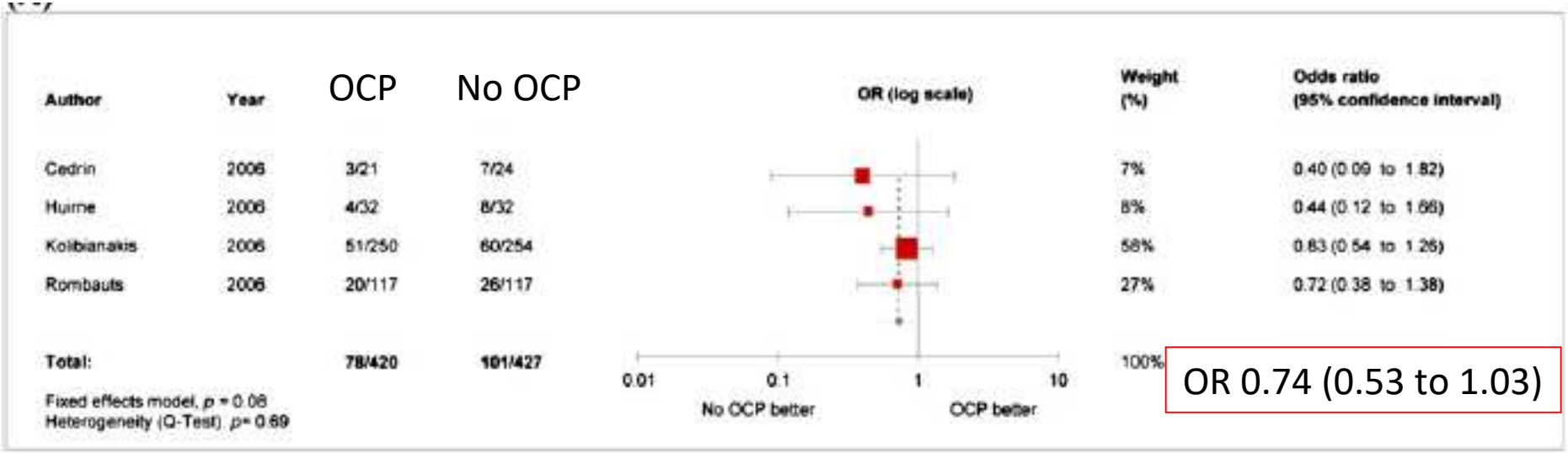
Starting day:

Among trials the starting days of pre-treatment varied from cycle day one to five

Is oral contraceptive pill pretreatment associated with the probability of ongoing pregnancy?

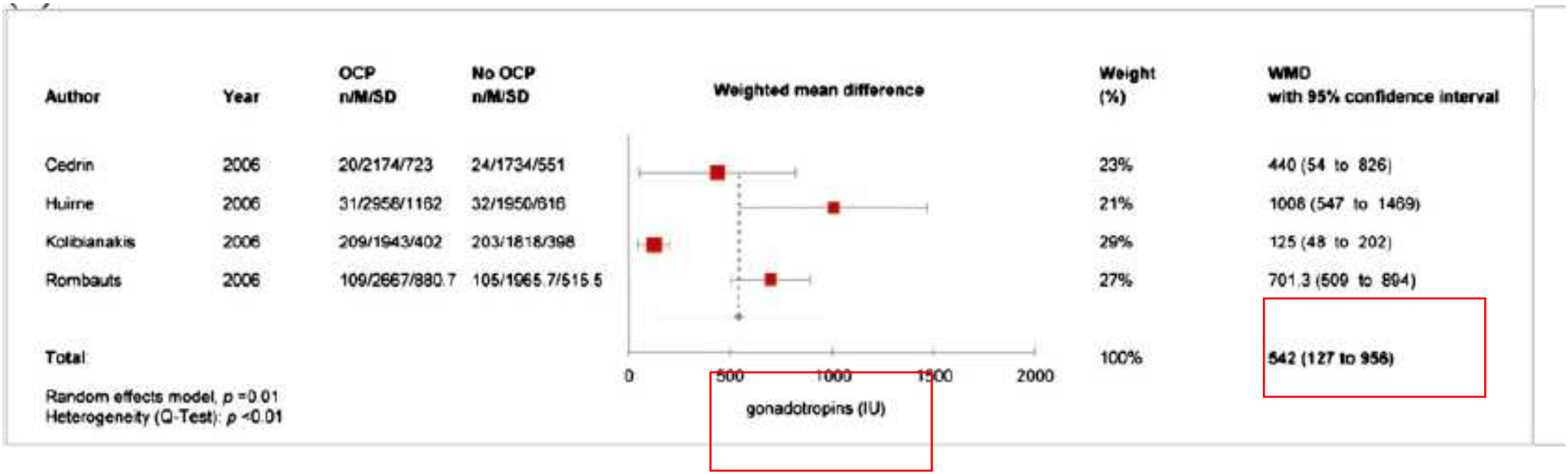
A meta-analysis of RCTs in which comparative data could be retrieved regarding ongoing pregnancy in GnRH antagonist ovarian stimulation after OCP pretreatment versus no OCP pretreatment

No statistically significant difference in terms of ongoing pregnancy rate was found



Griesinger *et al.,* Fertil Steril 2008

Duration of gonadotropin stimulation and gonadotropin consumption were significantly increased after OCP pretreatment



Griesinger *et al.,* Fertil Steril 2008

… Higher Gns consumption and more stim days were observed in pretreat OCP vs no treatement…

a) Amount Gns

Study or subgroup	Combined OCP N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 COCP + Ant vs Ant							
C drin-Dumerin 2007	21	2174 (723)	24	1734 (551)		3.4 %	440.00 [60.24, 819.76]
Huirne 2006b (1)	31	2958 (1162)	32	1950 (616)		2.3 %	1008.00 [546.62, 1469.38]
Kolibianakis 2006 (2)	209	1943 (402)	203	1818 (398)		81.3 %	125.00 [47.75, 202.25]
Rombauts 2006 (3)	109	2667 (880.7)	105	1965.7 (515.5)		13.1 %	701.30 [508.80, 893.80]
Subtotal (95% CI)	**370**		**364**			**100.0 %**	**231.14 [161.50, 300.78]**

b) Days of stimulations

Study or subgroup	Combined OCP N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 COCP + Ant vs Ant							
Huirne 2006b (1)	31	11.6 (2.1)	32	8.7 (1.6)		9.4 %	2.90 [1.98, 3.82]
Kolibianakis 2006 (2)	209	9.7 (2)	203	9.1 (2)		54.0 %	0.60 [0.21, 0.99]
Rombauts 2006 (3)	109	11.7 (1.9)	105	9.4 (1.6)		36.5 %	2.30 [1.83, 2.77]
Subtotal (95% CI)	**349**		**340**			**100.0 %**	**1.44 [1.15, 1.72]**

Smuders *et al.*, Cochrane Database Syst Rev 2010

Follicular Syncrhonization and IVF

How to do?

- Oral contraceptive
- Estradiol
- Progestins and Progestatives

Use of Estrogen for follicles sychronization

Kind of Estrogen used :

Micronized 17-E2 (Cédrin-Durnerin 2007; Fanchin 2003)

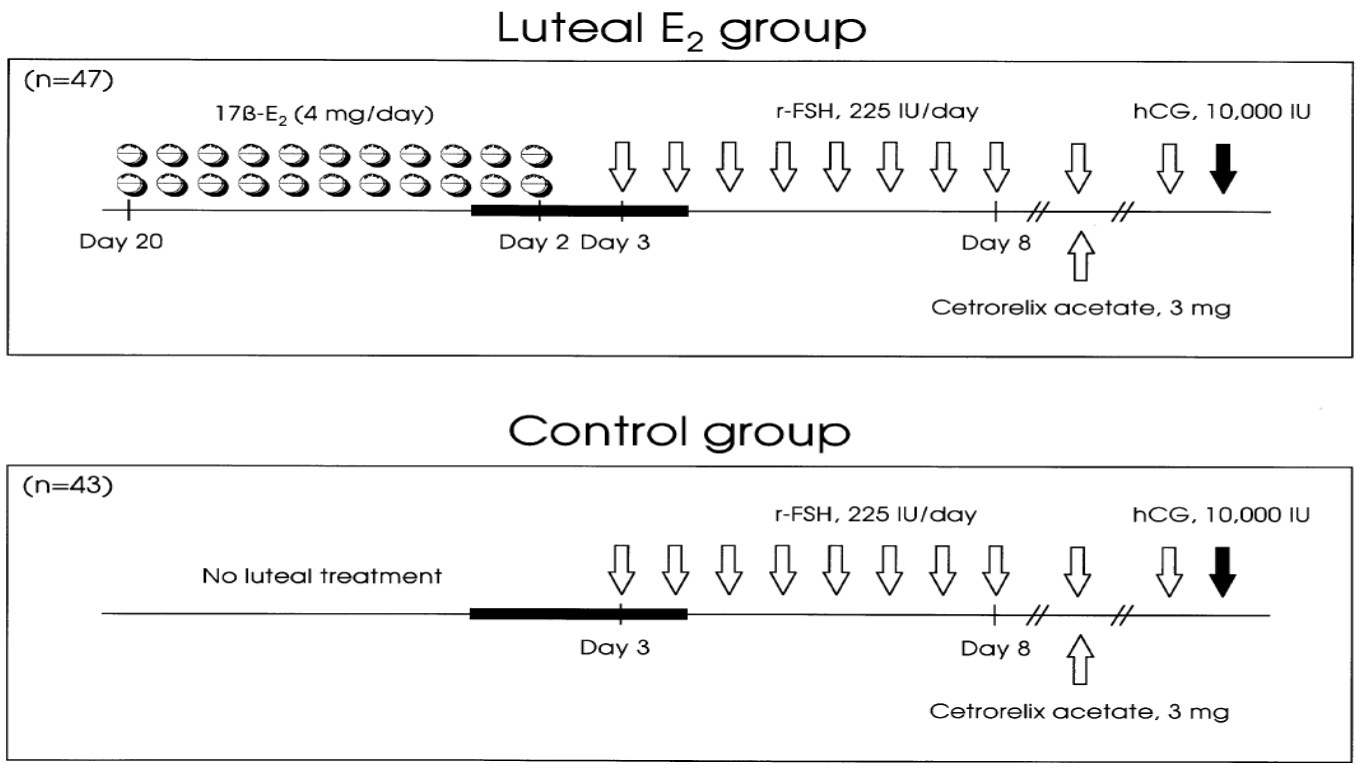
Estradiol valerate (Franco Jr 2003; Blockeel 2012)

Starting day:

The starting days of pre-treatment among trials varied from cycle day 15 to 21

Luteal estradiol pre-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists

An RCT involved 90 IVF-embryo transfer candidates who were randomly pre-treated with 17-beta-E_2 (4 mg/day) from day 20 until next cycle day 2 (*n* = 47)
- Control group: on day 3, all women started r-FSH treatment (*n* = 43)



Fanchin *et al.,* Hum Reprod 2003

Luteal E2 administration reduces the pace of growth, improves size homogeneity of antral follicles on day 8 of r-FSH treatment and increases the number of follicles reaching maturation

Endpoints assessed:

On day 8, follicles were smaller ($P < 0.001$) and their size discrepancies attenuated ($P < 0.001$) in the E_2 group compared with the control group. More >or=16 mm follicles, mature oocytes and embryos in the E_2 group

Table I. Follicular development and embryological results in women pre-treated or not with E_2 during the luteal phase

	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

Fanchin *et al.,* Hum Reprod 2003

Pretreatment with valerate estradiol modifies reproductive outcomes in IVF?

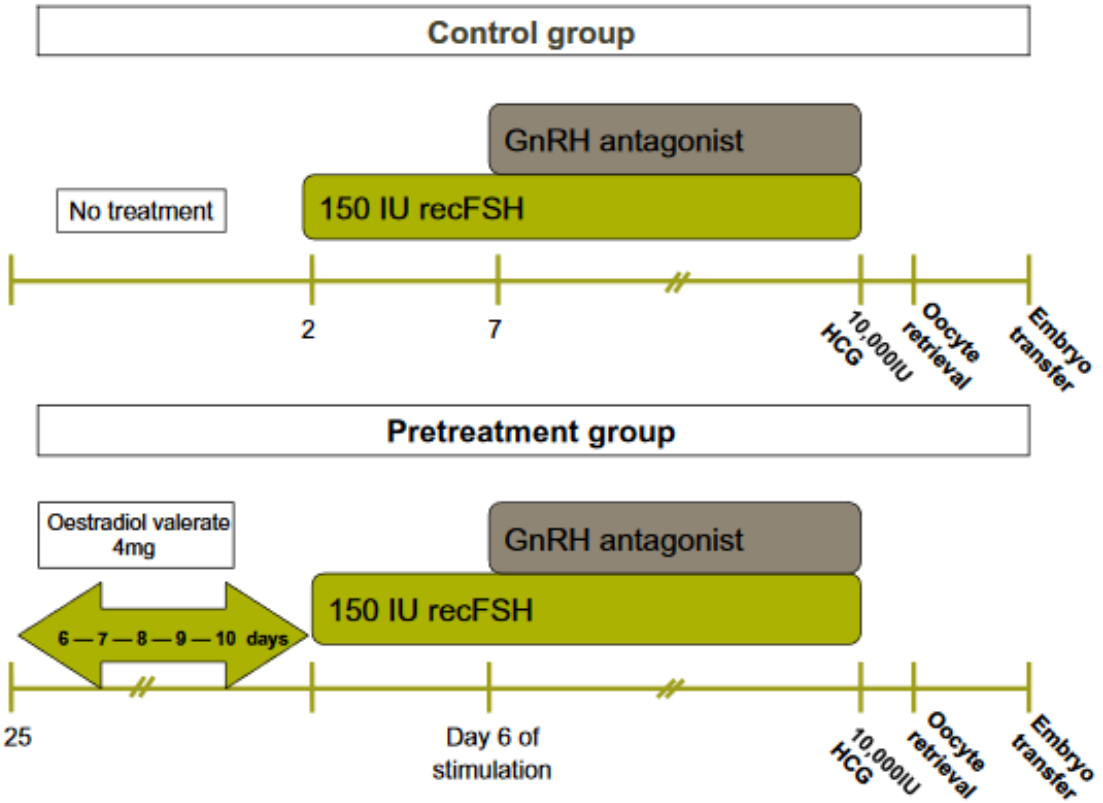
Population:

Eighty-six women undergoing ovarian stimulation for IVF/intracytoplasmic sperm injection

Methods: 86 women undergoing ovarian stimulation for IVF/intracytoplasmic sperm injection were

The control group (*n* = 42) received a standard ovarian stimulation protocol

The pretreatment group (*n* = 44 received oestradiol valerate at a daily dose of 2 m from day 25 of the preceding cycle onwards, during 6–10 consecutive days, depending on the day of the week



Blockeel C *et al.*, Reprod Biomed Online 2012

The proportion of patients undergoing oocyte retrieval during a weekend day which was significantly lower in the pretreatment group but clinical pregnancy rates per started cycle were similar

	Control group	*Pretreatment group*	*Between-group difference (%)*
Patients undergoing oocyte retrieval during a weekend day (primary end point)	8/39 (20.5)	1/37 (2.7)	−17.8 (−31.5 to −4.1)[a]
Positive HCG			
Per started cycle	20/42 (47.6)	19/44 (43.2)	−4.4 (−25.5 to 16.6)
Per retrieval	20/39 (51.3)	19/37 (51.4)	0.1 (−22.4 to 22.6)
Per embryo transfer	20/37 (54.1)	19/35 (54.3)	0.2 (−22.8 to 23.3)
Outcome for patients with positive HCG test			
Biochemical pregnancy	2/20 (10.0)	1/19 (5.3)	−4.7 (−21.3 to 11.8)
Miscarriage	2/20 (10.0)	1/19 (5.3)	−4.7 (−21.3 to 11.8)
Clinical pregnancy	16/20 (80.0)	17/19 (89.5)	9.5 (12.8 to 31.8)
Clinical pregnancy rate			
Per started cycle	16/42 (38.1)	17/44 (38.6)	0.5 (−20.0 to 21.1)
Per retrieval	16/39 (41.0)	17/37 (45.9)	4.9 (−17.4 to 27.2)
Per embryo transfer	16/37 (43.2)	17/35 (48.6)	5.4 (−17.7 to 28.3)

Values are *n*/total (%). Absolute between-group difference = pretreatment-group value − control-group value. Fisher's exact or chi-squared test were used for testing absolute difference between groups. HCG = human chorionic gonadotrophin.
[a]$P = 0.029$.

Blockeel C *et al.*, Reprod Biomed Online 2012

Estrogen vs no pre-treatment in GnRH antagonist cycles is associated more oocytes retrieved but a higher amount of gonadotrophin therapy required

a) n.oocytes retrieved

Study or subgroup	Estrogen N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Estr + Ant vs Ant							
C drin-Dumerin 2007 (1)	22	13.1 (7)	24	9.9 (5.4)		0.5 %	3.20 [-0.44, 6.84]
Fanchin 2003a (2)	47	9.3 (0.7)	43	7.3 (0.5)		99.5 %	2.00 [1.75, 2.25]
Subtotal (95% CI)	**69**		**67**			**100.0 %**	**2.01 [1.76, 2.25]**

b) amount of gonadotropin consumed

Study or subgroup	Estrogen N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Estr + Ant vs Ant							
C drin-Dumerin 2007 (1)	22	1700 (524)	24	1734 (551)		1.6 %	-34.00 [-344.71, 276.71]
Fanchin 2003a (2)	47	2674 (91)	43	2463 (100)		98.4 %	211.00 [171.37, 250.63]
Subtotal (95% CI)	**69**		**67**			**100.0 %**	**207.08 [167.77, 246.39]**

Smuders *et al.*, Cochrane Database Syst Rev 2010

Follicular Syncrhonization and IVF: Strategies

How to do?

- Oral contraceptive
- Estradiol
- Progesterone and derivates

Use of Progestins for follicles sychronization

Kind of progestins used:

- Norethisterone 10 mg/day (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Ditkoff 1996; Engmann 1999; Hugues 1994)

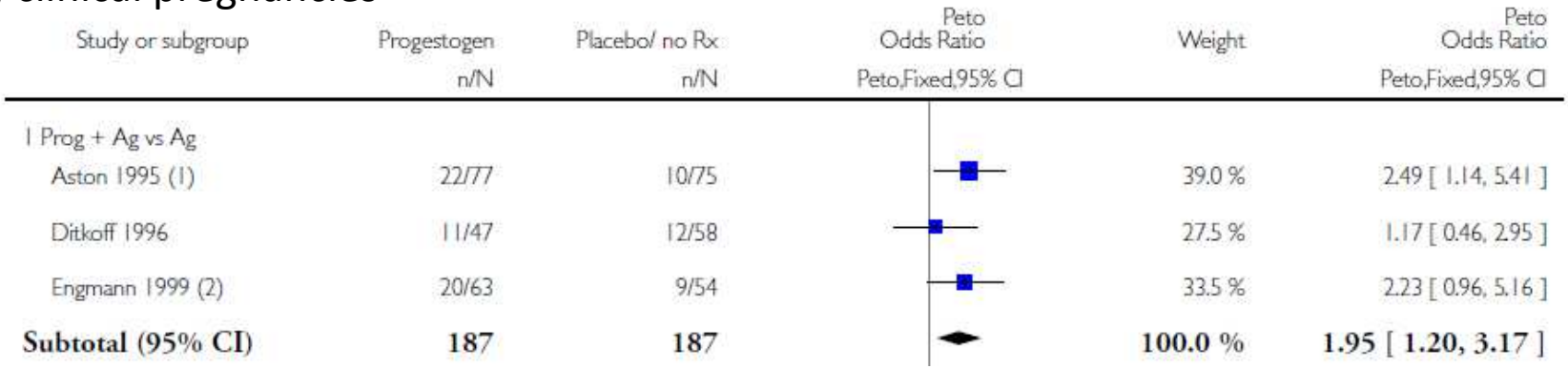
- Medroxyprogesterone acetate 10 mg daily (Aston 1995)

Starting day:

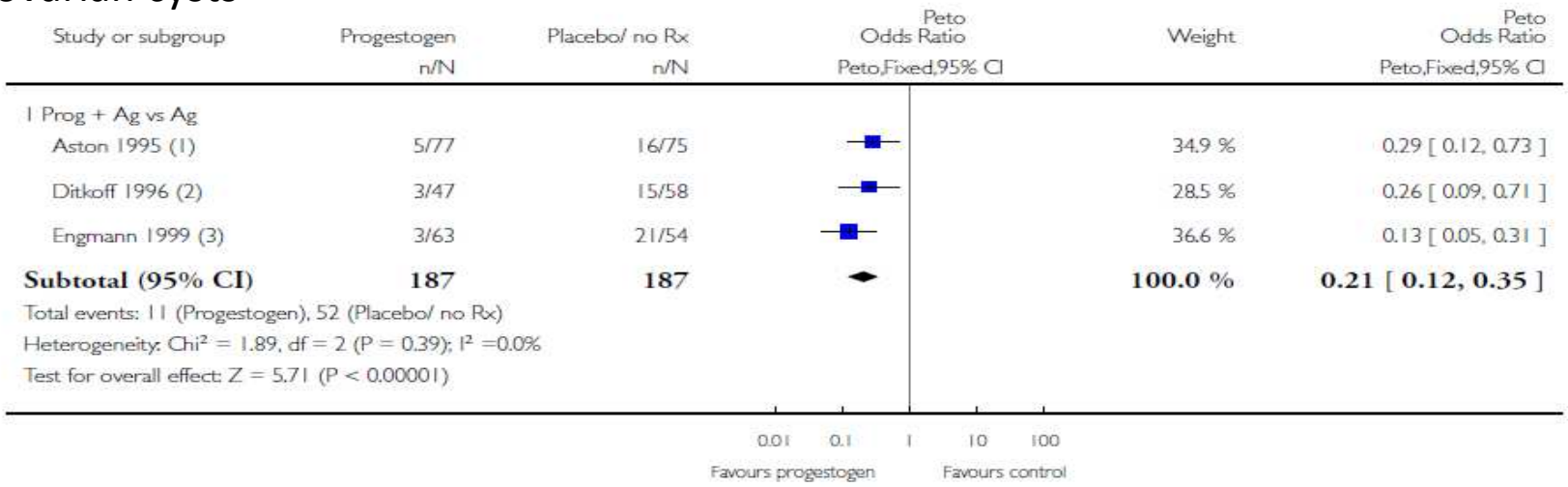
Among trials the starting days of pre-treatment varied from cycle day one to nineteen

Progesterone pre-treatment vs placebo or no pre-treatment in GnRH agonist cycles is associated with more clinical pregnancies (Peto OR 1.95, *P* = 0.007) and fewer ovarian cysts (Peto OR 0.21, *P* < 0.00001)

a) clinical pregnancies



a) ovarian cysts



Smuders *et al.*, Cochrane Database Syst Rev 2010

Follicular Syncrhonization and IVF

How to do?

- Oral contraceptive
- Estradiol
- Progestins

Is there a better method?

Are there differences in ongoing pregnancy rates between GnRH antagonist IVF cycles scheduled with OCPs or E2 valerate?

RCT : 100 women were included in the study, randomized and assigned to either the OCP or E_2 pretreatment arms in 1:1 ratio

- the OCP group started with the pill (30 µg of ethinyl E_2 plus 150 µg of levonorgestrel on day 1 or 2 of menses prior the IVF cycles
- E_2 valerate group started with 4 mg/die orally for 5–12 days, on day 20 of the cycle preceding the IVF/ICSI until the day before the initiation of ovarian stimulation

Erik E Hauzman *et al.*, Reprod Biol Endocrinol 2013

There were **no statistically significant differences in ongoing pregnancy rates** between pretreatment with OCP and E_2

Parameters	OCP (n = 50)	E_2 (n = 50)	Risk difference (%) (95% CI)	P value
Implantation rate[a]	43.5% (30/69)	47.4% (27/57)	3.9 (−13.4 to 21.1)	0.79
Pregnancy rate per cycle	56.0% (28/50)	52.0% (26/50)	−4.0 (−23.1 to 15.4)	0.84
Clinical pregnancy rate per cycle	50.0% (25/50)	48.0% (24/50)	−2.0 (−21.3 to 17.4)	0.99
Early clinical miscarriage[b] *rate per pregnancy*	7.1% (2/28)	7.7% (2/26)	0.6 (−16.4 to 18.3)	0.66
Ongoing pregnancy rate per cycle	46.0% (23/50)	44.0% (22/50)	−2.0 (−21.2 to 17.3)	0.99
Live birth rate per cycle	42.0% (21/50)	40.0% (20/50)	−2.0 (−21.0 to 17.1)	0.99

Significantly more days of pretreatment with OCP compared to E_2 (14.5 ± 1.7 vs. 7.8 ± 1.9 days, P <0.001) were necessary before starting stimulation

Limitation of the study is its sample size. In fact, with 50 patients in each arm of the study, only a difference of >26% could have been detected with 80% power, at a 0.05 significance level

Erik E Hauzman *et al.*, Reprod Biol Endocrinol 2013

Advantages of E_2 pre-treatment compared to OCP

-Pretreatment **is shorter** with E_2 than with OCPs

-Using E_2, GnRH antagonist cycles can be started in a scheduled manner even in patients who have **objections to or present contraindications for taking OCPs** even for a short period

-Avoiding OCP pretreatment, we can give them one more **chance to get pregnant spontaneously in the cycle preceding IVF**

Erik E Hauzman *et al.*, Reprod Biol Endocrinol 2013

Effects of oral contraceptive, synthetic progestogen or natural estrogen pre-treatments on the hormonal profile and the antral follicle cohort before GnRH antagonist protocol

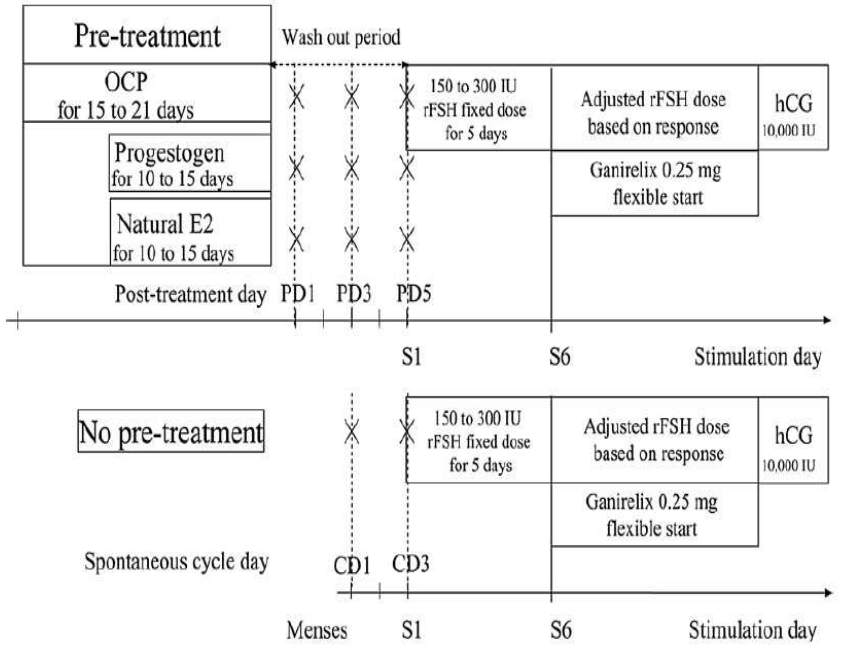
Multicenter RCT involving 93 women undergoing an IVF/ICSI cycle

Group A: 21 COCs ethinyl estradiol 30 µg + desogestrel 150 µg

Group B: 23 norethisterone 10 mg/day

Group C: 25 micronized 17-βE_2 2 mg twice a day

Group D: No pretreatment



C Durnerin et al. 2007

No differences with respect of live birth rate, number of embryos and number of oocytes was observed between groups

Heterogeneous follicular cohort was observed in natural estrogen or no pre-treatment groups, however estradiol pretreatment was associated with lower FSH consumption

Table III. Ovarian stimulation and cycle outcome

	OCP (*n* = 21)	Progestogen (*n* = 23)	Estrogen (*n* = 22)	Control (*n* = 24)	*P*
Starting FSH dose (IU)	212 ± 43	214 ± 56	195 ± 44	188 ± 26	NS
At S6					
E_2 (pg/ml)	679 ± 388	500 ± 238	1030 ± 477	720 ± 352	<0.001
Follicle size (mm)	11.3 ± 2.7	11.5 ±1.5	14.4 ± 2.2	14 ± 1.9	<0.001
Number of follicles >10 mm	6.6 ± 5.3	6.5 ± 7.1	8.1 ± 4.9	5.6 ± 3.3	NS
Cancelled cycle (*n*)	1	2	3	0	
Antagonist starting day	7.5 ± 1.5	7.3 ± 1.4	6.3 ± 0.7	6.7 ± 1.2	0.01
Antagonist duration	3.6 ± 1	3.2 ± 1.3	4 ± 1	3.3 ± 2.1	NS
HCG day	11 ± 1.7	10.6 ± 0.9	10.1 ± 0.9	10.1 ± 1.9	0.04
FSH dose (IU)	2174 ± 723	2010 ± 670	1700 ± 524	1734 ± 551	0.04
Retrieval (*n*)	20	20	19	24	
Number of oocytes	14 ± 8.3	12.6 ± 7.3	13.1 ± 7	9.9 ± 5.4	NS
Number of embryos	8.1 ± 4.7	6.4 ± 5.4	6.9 ± 3.5	6 ± 3.6	NS
Transfer (*n*)	18	18	15	24	
Transferred embryos	2.1 ± 0.5	2 ± 0.5	2.2 ± 0.4	2 ± 0.6	NS
Positive pregnancy test (*n*)	5	7	4	12	
PR per oocyte retrieval	25%	35%	21%	50%	NS
LB (*n*)	3	5	3	6	
LB per oocyte retrieval	15%	25%	15.8%	29.2%	NS
Live babies (*n*)	5	6	3	8	

C Durnerin et al. 2007

Take home messanges

- Although synchronization of follicles is improved comparing with antagonist regimens, in agonist regimens an increased risk OHSS is well documented
- Synchronization in antagonist cycles aim to reduce follicular size discrepancies and to enhance ovarian response in recombinant FSH protocol
- No evidence of effect was found with regard to the number of live births when using a pre-treatment before stimulation
- At moment there is no a preferred method (COCs, progestins and estradiol) in terms of Live birth rate
- Compared with no treatment:
  - Estradiol Is associated with reduced FSH consumption
  - Progestins are associated with increased clinical pregnancy and reduced ovarian cyst
  - COCs are associated with increased FSH consumption and duration of stimulation
- Estradiol pretreatment was associated with reduced FSH consumption and days of stimulation but increased heterogeneity in follicular cohort.

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