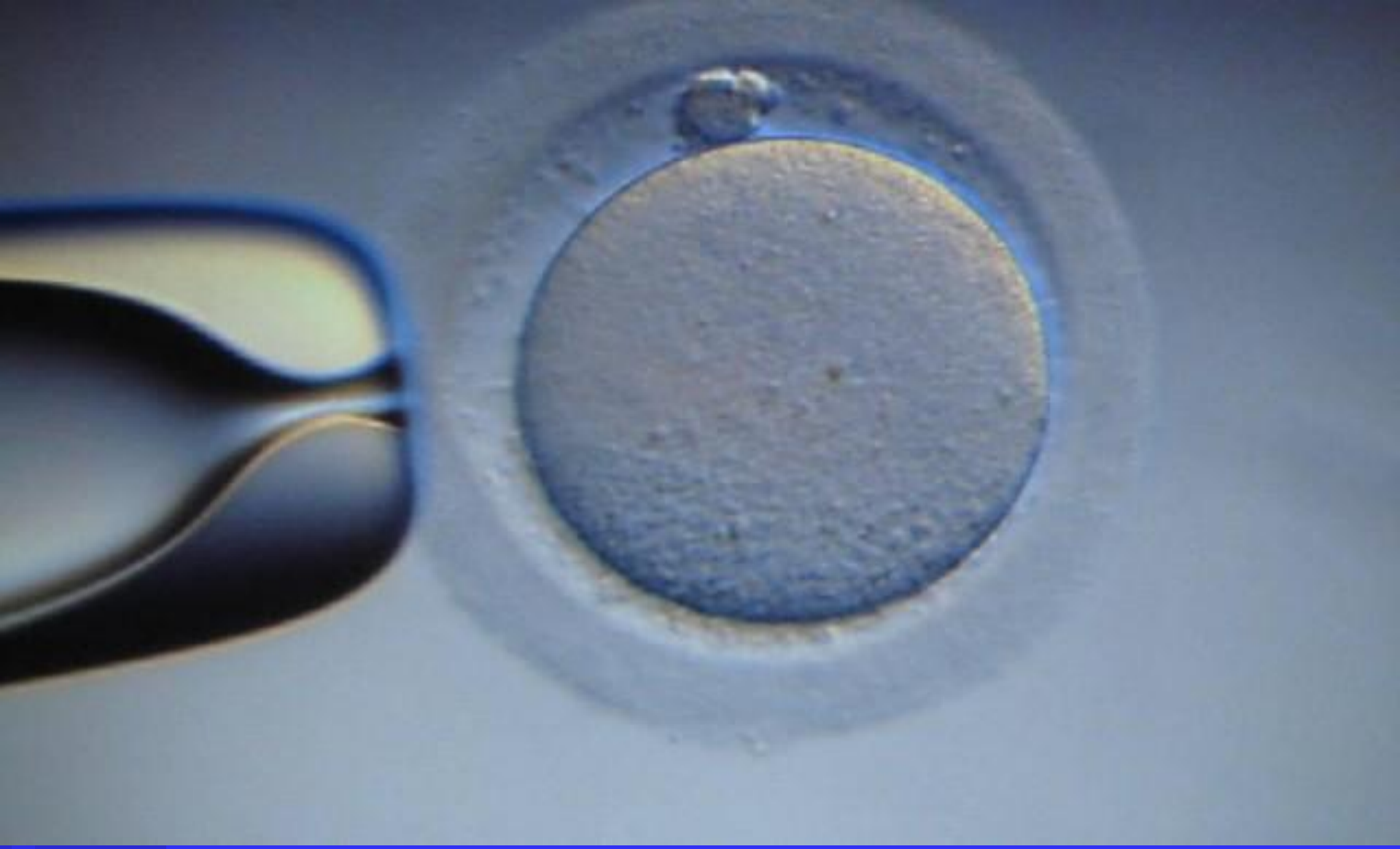


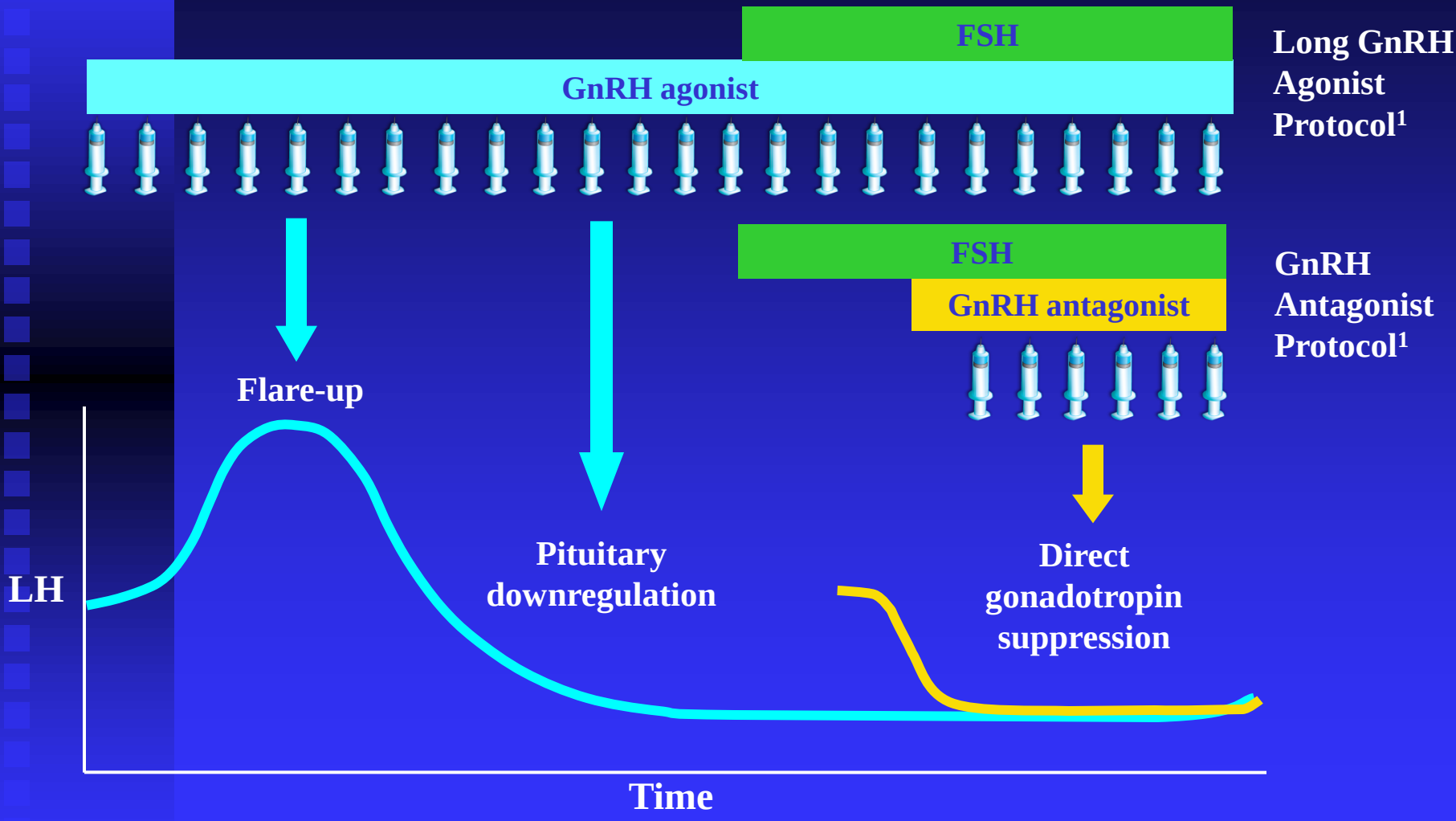
Optimal usage of the GnRH antagonist protocol

Peter Humaidan
The Fertility Clinic, Skive Hospital and Aarhus University, Denmark

Overview

- GnRHa vs GnRH Antagonists
- GnRH antagonist protocols - scheduling
- Modulating cycles with OCP or E2
- Fixed vs Flexible GnRH Antagonist protocol
- FSH dose
- Timing of hCG

GnRH Antagonist Cycle versus Long GnRHa Cycle



1. Adapted with permission from de Greef R et al. *Clin Pharmacol Ther*. 2010;88:79–87.
2. Adapted from Hodgen. *Contemp Rev Obstet Gynaecol*. 1990;35:10–24.

Short vs long protocol

Characteristics of the long GnRHa down-regulation protocol

- Rigid programming
- 5 day working week
- Large numbers of oocytes
- Large numbers of embryos
- Large number of frozen embryos

What do our patients expect from an IVF cycle?

- Rigid programming
- 5 day working
- Large numbers of oocytes
- Large numbers of embryos
- Large number of frozen embryos

- Flexibility
- Convenience
- Enough oocytes for fresh ET
- Rapid completion of cycle
- Low incidence of side effects

GnRH antagonists in ART

- GnRH antagonist versus GnRHa facts:

- Suppression of the endogenous LH level within a few hours
- No flare up effect
- No risk of GnRHa induced cyst formation
- No estrogen deprivation symptoms
- FSH consumption reduced
- Duration of stimulation shortened – less costly
- 21 days shorter treatment duration
- Unintended administration during early pregnancy avoided
- Reduction in **severe** OHSS rate

(Al-Inany et al., 2007;Tarlatzis *et al.*, 2006; Klingmuller *et al.*, 1993; Varney *et al.*, 1993)

GnRH antagonists in ART

- And what about the psychological impact:

Significantly fewer symptoms of depression 1 week after treatment termination in women experiencing failure (two or more trials) after GnRH antagonist treatment as comparerd to long GnRHa treatment (De Klerk et al., 2007)

Significantly lower drop-out rate (Heijnen et al., 2007)

GnRH antagonists in ART

And what about OHSS?

- 39 % relative risk reduction for severe OHSS

  (Al-Inany et al., 2007; Cochrane Review)

- 54 % risk reduction of hospitalization due to OHSS

  (Kolibianakias et al., 2007; Meta-analysis)

GnRH Antagonist versus GnRHa Long Protocol

- Lower risk of OHSS
- Shorter treatment
- Reduced gonadotropin consumption
- Administration only during period needed to suppress endogenous LH surge
- No initial flare-up
- No estrogen deprivation symptoms
- Always the option to trigger with GnRHa

OHSS = ovarian hyperstimulation syndrome.

Reviewed in Devroey et al., 2009

What is the Current Data on Outcomes Between GnRHa vs GnRH Antagonist?

Meta-Analyses of GnRH Antagonists versus GnRHa - Conflicting Results

Systematic Reviews	Year	Conclusion
Ludwig et al[1]	2001	No difference in clinical pregnancy rate
Al-Inany and Aboulgar[2]	2002	Lower clinical pregnancy rate
Al-Inany[3]	2006	Lower ongoing pregnancy and live birth rate
Kolibianakis[4]	2006	No difference in live birth rate

1. Ludwig et al. *Arch Gynecol Obstet*. 2001;265:175-82. **2.** Al-Inany and Aboulgar. *Hum Reprod*. 2002;17:874-85.
3. Al-Inany et al. *Cochrane Database Syst Rev*. 2011;3:CD001750. **4**. Kolibianakis et al. *Hum Reprod Update*. 2006;12:651.

Cochrane Review 2011

Table. Summary of Main Outcome Measures

Measure	No. Trials	No. Participants	Assumed risk GnRH Agonists	Corresponding risk GnRH Antagonists	Odds Ratio (95% CI)
Live birth rate	9	1515	314 per 1000	282 per 1000	0.86 (0.69-1.08)
Ongoing pregnancy rate	28	5014	303 per 1000	277 per 1000	0.88 (0.77-1.0)
OHSS rate	29	5417	66 per 1000	29 per 1000	0.43 (0.33-0.57)

- No statistically significant difference in live birth rate (9 RCTs; OR 0.86, 95% CI, 0.69 to 1.08)
- No significant difference in ongoing pregnancy rate (28 RCTs; OR 0.88, 95% CI, 0.77 to 1.00)
- Significant difference in clinical pregnancy rate in favor of GnRH agonists (41 RCTs; OR 0.84, 95% CI, 0.75 to 0.94)
- Significantly lower incidence of OHSS (29 RCTs; OR 0.43, 95% CI, 0.33 to 0.57)
  - 50% relative reduction

GnRH = gonadotrophin-releasing hormone; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; RCT = randomized, controlled trial.

1. Al-Inany H, et al. *Cochrane Database Syst Rev* 2011; May 11;5:CD001750.

Scheduling Approaches

- OCP
- E2 alone
- Varying FSH start day
- Varying day of hCG trigger

Scheduling Approaches

- OCP studies (Tavmergen et al. 2009) :
  - Lower OPR with OCP
  - 26.3% vs 35.7%; *P*=0.04
- Meta-analysis (Griesinger et al. *Fertil Steril*. 2010)
  - Significantly lower OPR vs no OCP
  - more FSH needed (542 IU 95%)
- E2 Alone: Luteal E2 vs No Pretreatment

Programming in vitro fertilization retrievals during working days after a gonadotropin-releasing hormone antagonist protocol with estrogen pretreatment: does the length of exposure to estradiol impact on controlled ovarian hyperstimulation outcomes?

Anne Guivarc'h-Levêque, M.D.,[a] *Lionel Homer, M.D.,*[a] *Philippe Arvis, M.D.,*[a] *Pierre Louis Broux, M.D.,*[a] *Ludovic Moy, M.D.,*[a] *Gérard Priou, M.D.,*[a] *Jean Vialard, M.D.,*[a] *Daniel Colleu, Ph.D.,*[b] *and Didier Dewailly, M.D.*[c]

[a] Clinique Mutualiste La Sagesse, and [b] Laboratoires de Biologie Réunis, Rennes; and [c] Department of Endocrine Gynaecology and Reproductive Medecine, Hôpital Jeanne de Flandre, C.H.R.U., and Faculty of Medicine of Lille, Université de Lille II, Lille, France

Objective: To verify whether a variable number of days beyond the menses of estrogen (E) pretreatment may impact on controlled ovarian hyperstimulation (COH) outcomes and birth rate using a GnRH antagonist protocol.
Design: Single center, prospective, nonrandomized study.
Setting: Nonacademic fertility unit.
Patient(s): A total of 1,080 women, aged 25–38 years, consecutively included (1,603 cycles).

Programming

TABLE 3

Comparison of hormonal and endometrial data between groups.

	A (n = 283)	B (n = 258)	C (n = 296)	D (n = 272)	E (n = 245)	F (n = 249)	*P* value[b]
E_2 at S1 (pg/mL)	134.9 ± 96.2	161.5 ± 106.9	174.7 ± 109.5	177.4 ± 119.5	188.2 ± 134.1	178.6 ± 101.3	<.0001[c]
LH at S1 (IU/L)	4.2 ± 2.9	4.5 ± 3.7	5.5 ± 4.0	6.2 ± 3.8	7.0 ± 4.0	7.9 ± 3.8	<.0001[c]
P at S1 (ng/mL)	0.57 ± 0.33	0.56 ± 0.29	0.53 ± 0.37	0.51 ± 0.36	0.49 ± 0.23	0.52 ± 0.37	NS
E_2 on the day of hCG (pg/mL)[a]	1,583 ± 788	1,720 ± 903	1,766 ± 876	1,867 ± 924	1,813 ± 909	1,964 ± 901	<.0001[c]
Endometrial thickness on the day of hCG (mm)[a]	10.1 ± 1.8	9.7 ± 1.8	10.1 ± 1.9	10.1 ± 2.0	10.0 ± 1.9	10.1 ± 2.0	NS

Note: Mean values ± SD. Groups were defined according to the number of days under E_2 treatment beyond the first day of menses up to the start of stimulation, in a range of 1–8 days (group A: 1 or 2 days, group B: 3 days, group C: 4 days, group D: 5 days, group E: 6 days, and group F: 7 or 8 days). NS = nonsignificant; S1 = first day of controlled ovarian hyperstimulation.

[a] In the noncancelled cycles (n = 1,419).

[b] By analysis of variance (ANOVA).

[c] See text for post hoc analysis.

Guivarc'h-Levêque. E_2 pretreatment for GnRH antagonist protocols. Fertil Steril 2011.

Giuvarc`h Leveque, Fertil Steril 2011

Programming

TABLE 2

Main outcomes of COH in the different groups.

	A (n = 283)	B (n = 258)	C (n = 296)	D (n = 272)	E (n = 245)	F (n = 249)	*P* value
Cancelation rate (%)	10.6	8.5	10.8	9.9	13.9	15.6	NS[d]
Length of COH (days)[a]	10.50 ± 1.22	10.70 ± 1.14	10.65 ± 1.21	10.61 ± 1.10	10.37 ± 1.16	10.45 ± 1.14	<.0005[b,c]
Cumulated dose of Gn (units)[a]	1,833 ± 748	2,008 ± 822	2,044 ± 826	1,956 ± 818	1,813 ± 690	1,901 ± 672	<.001[b,c]
No. of oocytes retrieved	8.9 ± 7.0	8.9 ± 5.7	8.2 ± 4.9	8.4 ± 5.6	8.2 ± 5.2	8.1 ± 4.9	NS[b]
No. of obtained embryos	4.6 ± 3.9	4.9 ± 3.5	4.5 ± 3.1	4.8 ± 3.5	4.4 ± 3.1	4.7 ± 3.2	NS[b]
No. of transferred embryos	1.7 ± 0.9	1.7 ± 0.7	1.9 ± 0.8	1.9 ± 0.6	1.7 ± 0.7	1.9 ± 0.7	NS[b]
No. of cryopreserved embryos	0.9 ± 1.8	1.0 ± 2.0	0.8 ± 1.5	0.8 ± 1.7	0.7 ± 1.5	0.7 ± 1.7	NS[b]
Ongoing PR/transfer (%)	26.9	31.4	30.0	28.6	30.0	34.8	NS[d]
Delivery rate/transfer (%)	23.1	26.4	23.5	22.4	24.2	29.5	NS[d]

Note: Mean ± SD or %. Groups were defined according to the number of days under E_2 treatment beyond the first day of menses up to the start of stimulation, in a range of 1–8 days (group A: 1 or 2 days, group B: 3 days, group C: 4 days, group D: 5 days, group E: 6 days, and group F: 7 or 8 days). COH = controlled ovarian hyperstimulation; Gn = gonadotropin; NS = nonsignificant; PR = pregnancy rate.

[a] In the noncancelled cycles (n = 1,419).

[b] By analysis of variance (ANOVA).

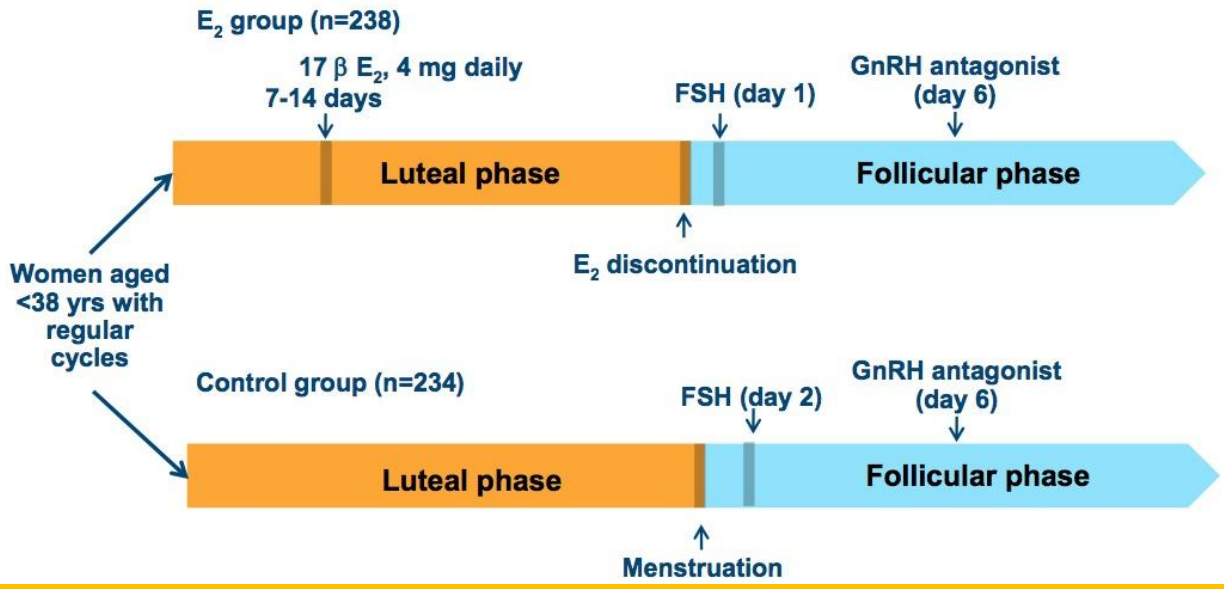
[c] See text for post hoc analysis.

[d] By χ^2 test.

Guivarc'h-Levêque. E_2 pretreatment for GnRH antagonist protocols. Fertil Steril 2011.

Giuvarc`h Leveque, Fertil Steril 2011

Prospective randomized multicenter study to assess effects of E_2 pretreatment compared with no pretreatment



	Luteal E_2 pretreatment (n=238)	No pretreatment (n=234)	*P* Value
FSH consumption (IU)	1557 ± 408	1389 ± 347	<0.0001
Duration of stimulation (days)	10.8 ± 1.4	10.0 ± 1.5	<0.0001
Oocytes (no.)	10.9 ± 5.7	10.2 ± 5.6	NS
Embryos (no.)	5.5 ± 3.7	4.8 ± 3.7	NS
Ultrasound PR per retrieval (%)	35.9	38.2	NS
Delivery rate per retrieval (%)	29	32.3	NS

Cedrin-Durnerin et al. Fertil Steril 2012

Varying the day of stimulation start and trigger

- Stimulation start cd 2, 3, 4 or 5
- Ovulation trigger – follicle size 15,16,17,18

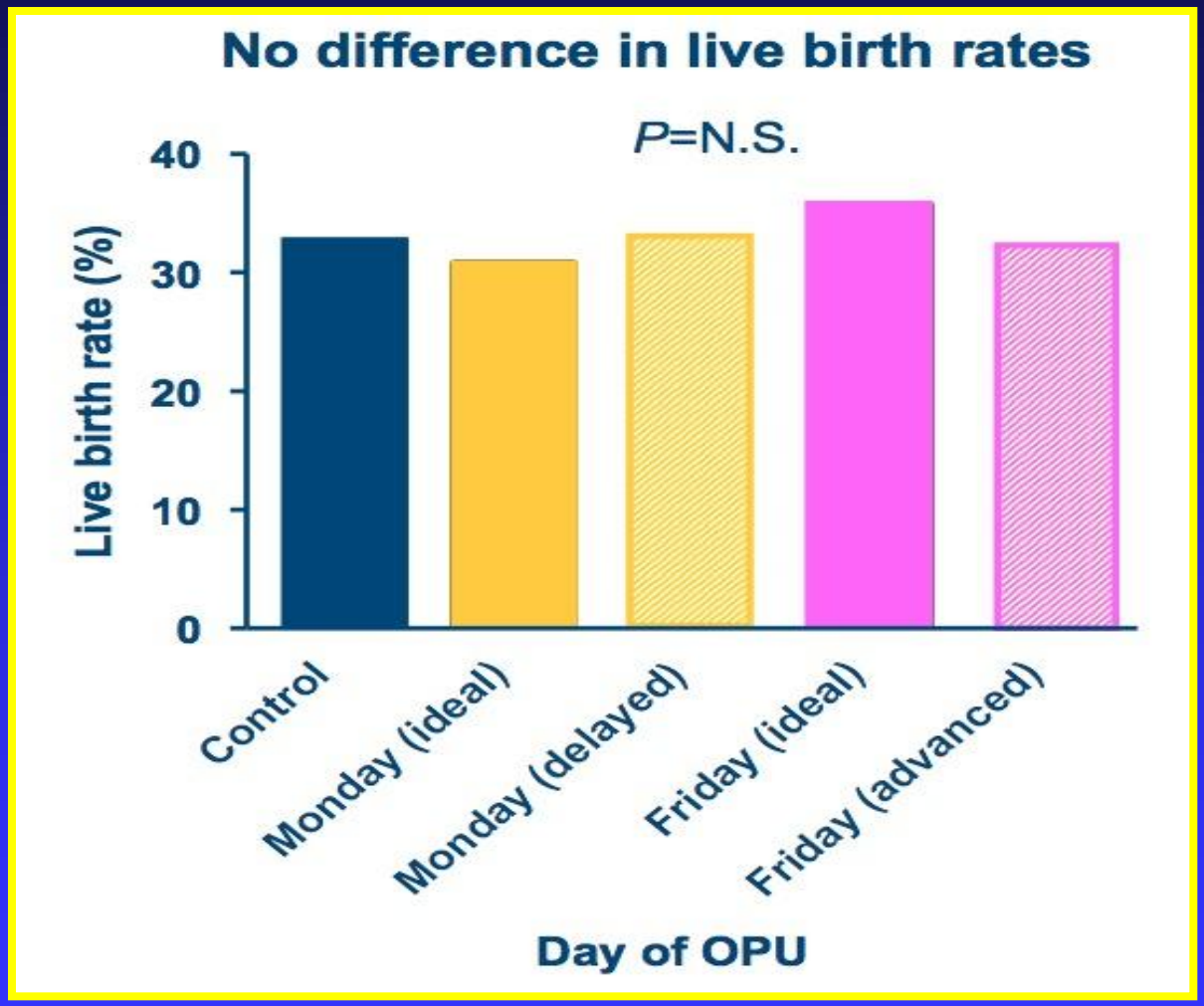
Varying the Day of hCG Trigger

No difference in OPR between triggering immediately vs a 1-day delay

	Corifollitropin alfa		rFSH	
	No delay N=503	1-day delay N=211	No delay N=524	1-day delay N=209
Oocytes	14.1 ± 8.2	14.4 ± 7.0	12.5 ± 6.7	13.3 ± 6.5
GQ Embryos day 3	4.4 ± 4.4	5.4 ± 4.1	4.3 ± 3.8	4.8 ± 4.2
OPR	40.0%	38.9%	37.8%	41.8%

Hillensjo T et al., 2011.

Delaying or advancing the Day of hCG Trigger



Tremellen and Lane, Hum Reprod. 2010

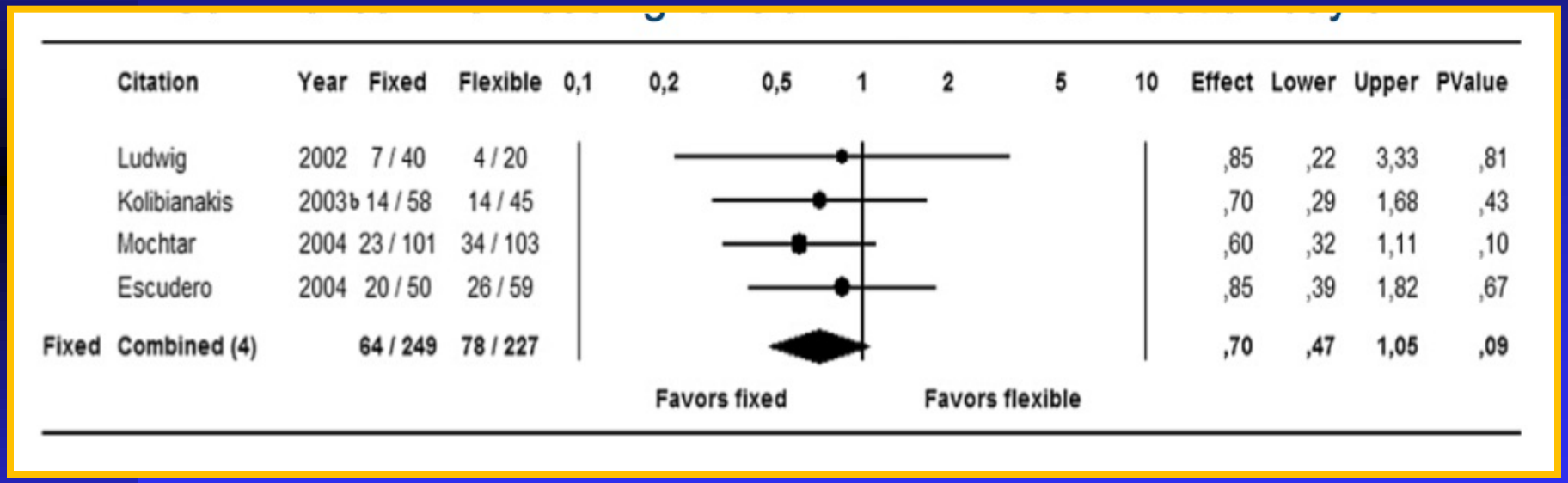
Optimal Timing of GnRH antagonist co-treatment

Fixed: day 5 or 6 of stimulation

Flexible: lead follicle(s) ≥12 mm

When to Start GnRH Antagonist?

Clinical PR in fixed versus flexible protocols



Al Inany et al. *Reprod Biomed Online*. 2005

GnRH antagonists in ART

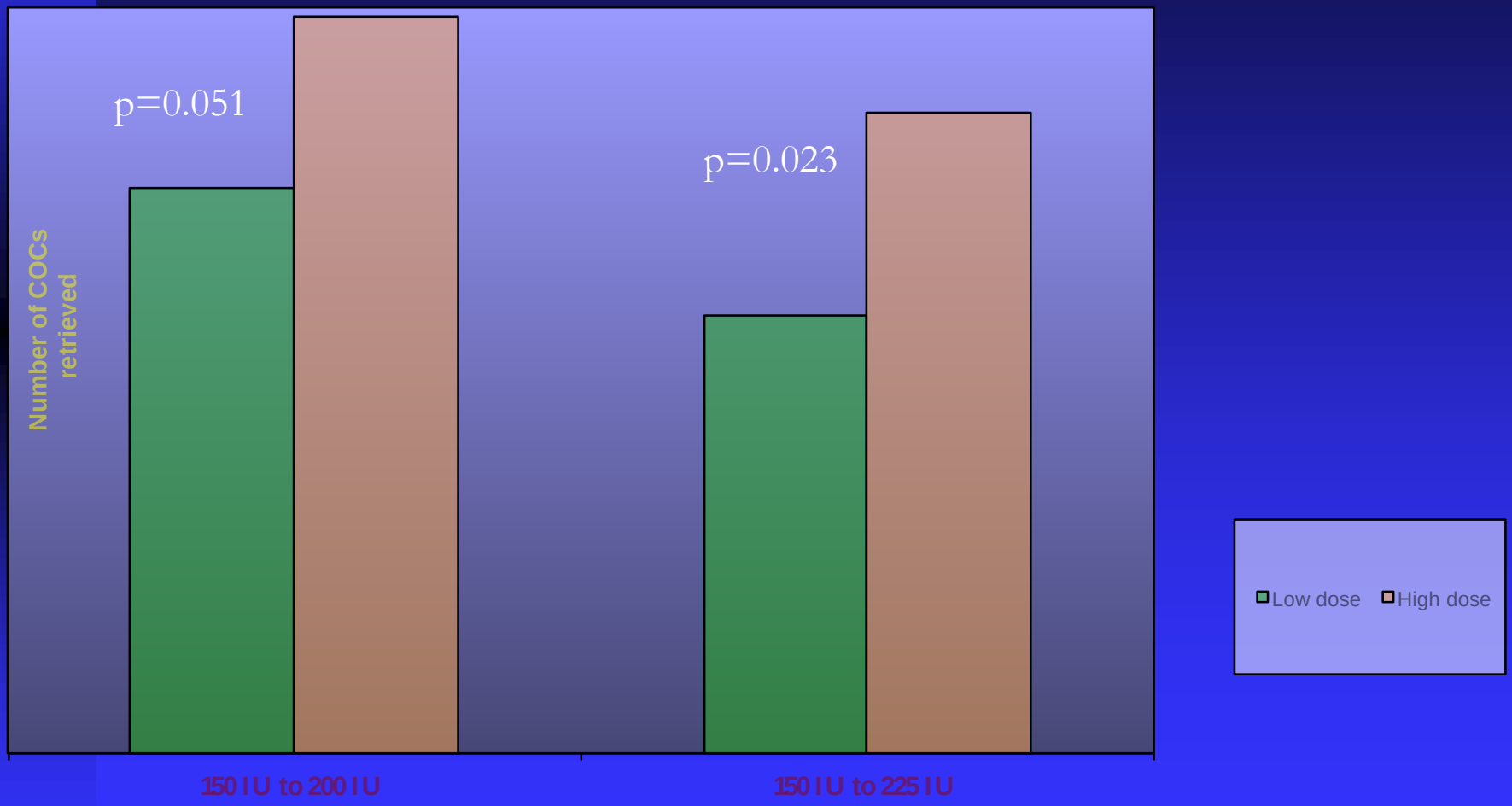
Fixed versus flexible protocol - current recommendation:

- Fixed GnRH antagonist protocol from day 5 or 6 of stimulation
- If flexible protocol - GnRH antagonist co-treatment as soon as follicles are ≥ 12 mm
- The time between the last GnRH antagonist injection and hCG should not exceed 30 h

(Devroey et al., Hum Reprod 2009)

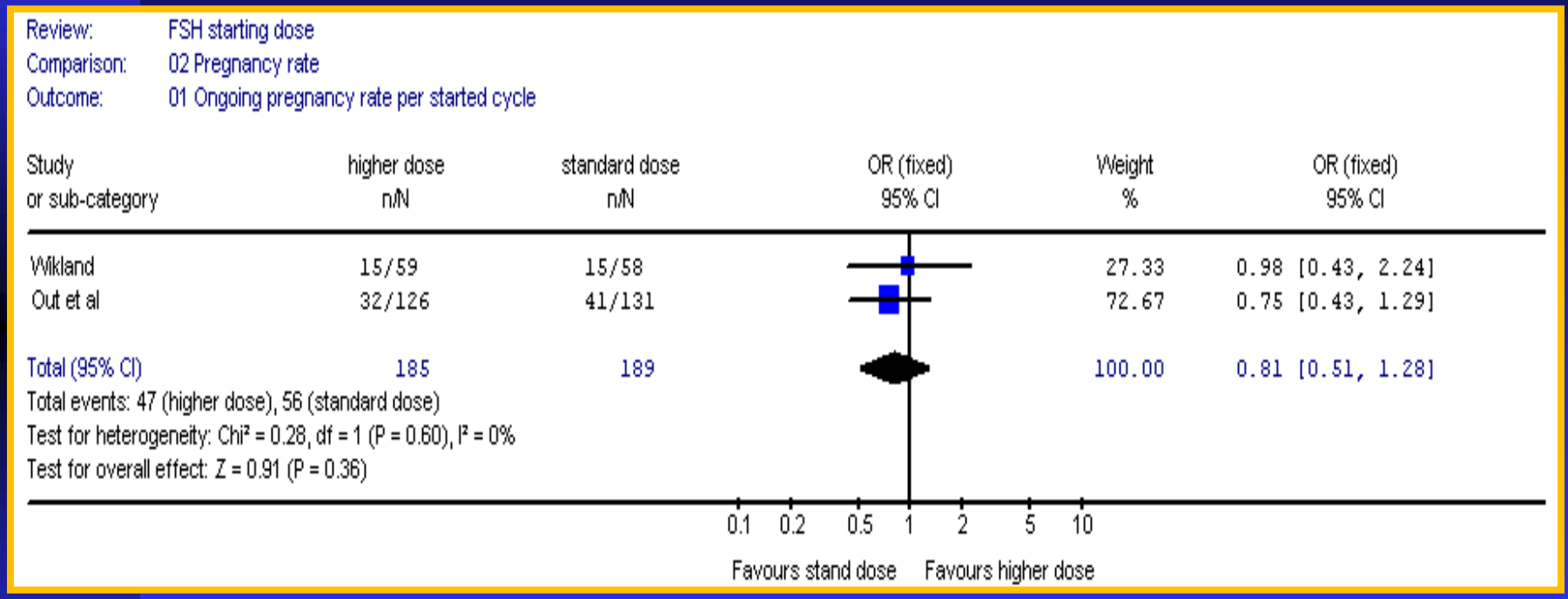
Should we increase the starting dose of gonadotropins in GnRH antagonist cycles?

Should we increase the starting dose of gonadotropins in GnRH antagonist cycles?



Wikland et al 2001 Hum Reprod, Out et al 2004 Hum Reprod

Should we increase the starting dose of gonadotropins in GnRH antagonist cycles?



Wikland et al 2001 Hum Reprod, Out et al 2004 Hum Reprod

Need for LH activity supplementation in the standard patient?

Endogenous LH Levels and Likelihood of Pregnancy in GnRH Antagonist Protocols

Low LH levels on the day of hCG are not associated with pregnancy likelihood	Merviel et al. *Fertil Steril*. 2004
High endogenous LH levels in the follicular phase are associated with a decreased chance of pregnancy	Kolibianakis et al. *Fertil Steril*. 2003
Low LH levels on day 8 are associated with an increased chance of pregnancy	Kolibianakis et al. *Hum Reprod*. 2004

Kolibianakis et al. *Hum Reprod Update*. 2006;12:3.

What about Luteal Phase Support?

luteal support in GnRH antagonist cycles

Fixed dose of rec FSH 150 IU, daily GnRH antagonist at a follicle size of 14mm

At a follicle size of 18mm patients were randomized to trigger with: rec hCG, rec LH or GnRHa

No luteal support

Beckers et al 2004 JCEM

Luteal support in GnRH antagonist cycles

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)
No. patients achieving embryo transfer[b]	9	11	14
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)

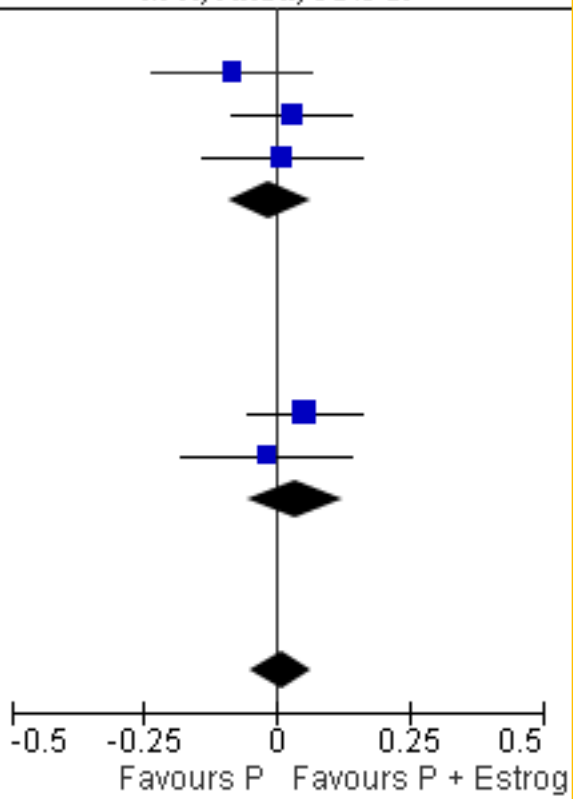
Beckers et al 2004 JCEM

Is estradiol supplementation necessary?

Estrogen for luteal support?

Outcome: live birth

Study or Subgroup	P + E Events	P + E Total	P Events	P Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.4.1 Trully randomized						
Engmann et al., (200	37	84	43	82	17.9%	-0.08 [-0.24, 0.07]
Fatemi et al.,(2006)	24	101	21	100	21.7%	0.03 [-0.09, 0.14]
Serna et al., (2006)	32	79	32	81	17.3%	0.01 [-0.14, 0.16]
Subtotal (95% CI)	**93**	**264**	**96**	**263**	**56.9%**	**-0.01 [-0.09, 0.07]**
Heterogeneity: Chi² = 1.41, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.4.2 Pseudorandomized/not reported						
Karlikaya et al. (20	78	190	44	123	32.3%	0.05 [-0.06, 0.16]
Lewin et al., (1994)	10	50	11	50	10.8%	-0.02 [-0.18, 0.14]
Subtotal (95% CI)	**88**	**240**	**55**	**173**	**43.1%**	**0.03 [-0.06, 0.13]**
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)	**181**	**504**	**151**	**436**	**100.0%**	**0.01 [-0.05, 0.07]**
Heterogeneity: Chi² = 2.28, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.81)						



Kolibianakis et al Hum Reprod 2008

Conclusion GnRH antagonist co-treatment

- Reduces significantly severe OHSS
- Provides similar live birth rates
- Always the option to trigger with GnRHa
- Reduces the treatment burden of the patient

GnRH antagonists in ART

GnRH antagonists - a matter of timing?

- If GnRH antagonists had been approved for inhibition of premature LH surges in 1982 would we be having this discussion?
- Would anyone have suggested GnRHa for this indication?
- Would patients have been willing to change to the “new” long protocols?

Thank You for Your attention