İZMİR UNIVERSITY
MEDICAL CENTER

Luteal Phase Support in ART Cycles

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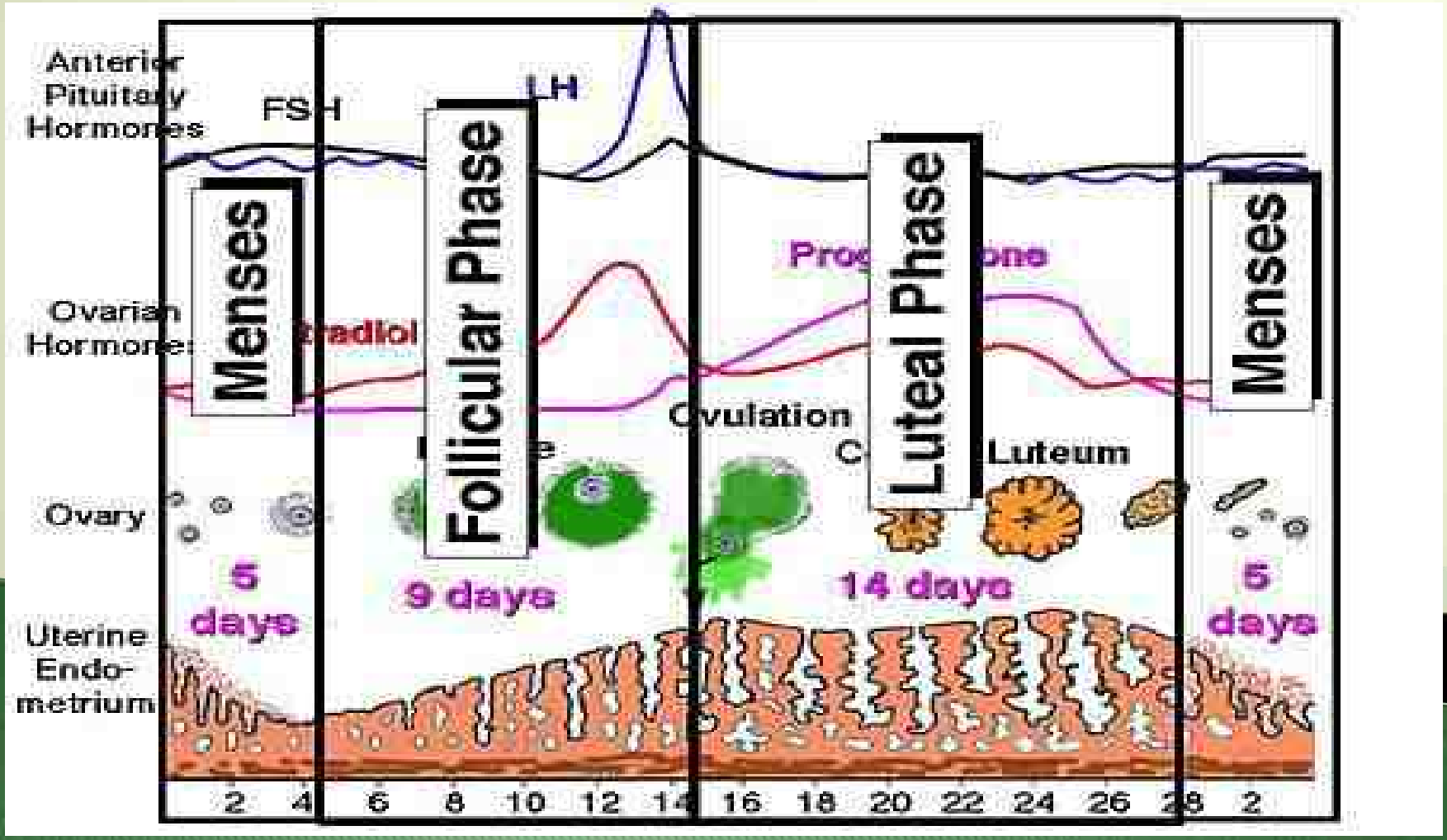
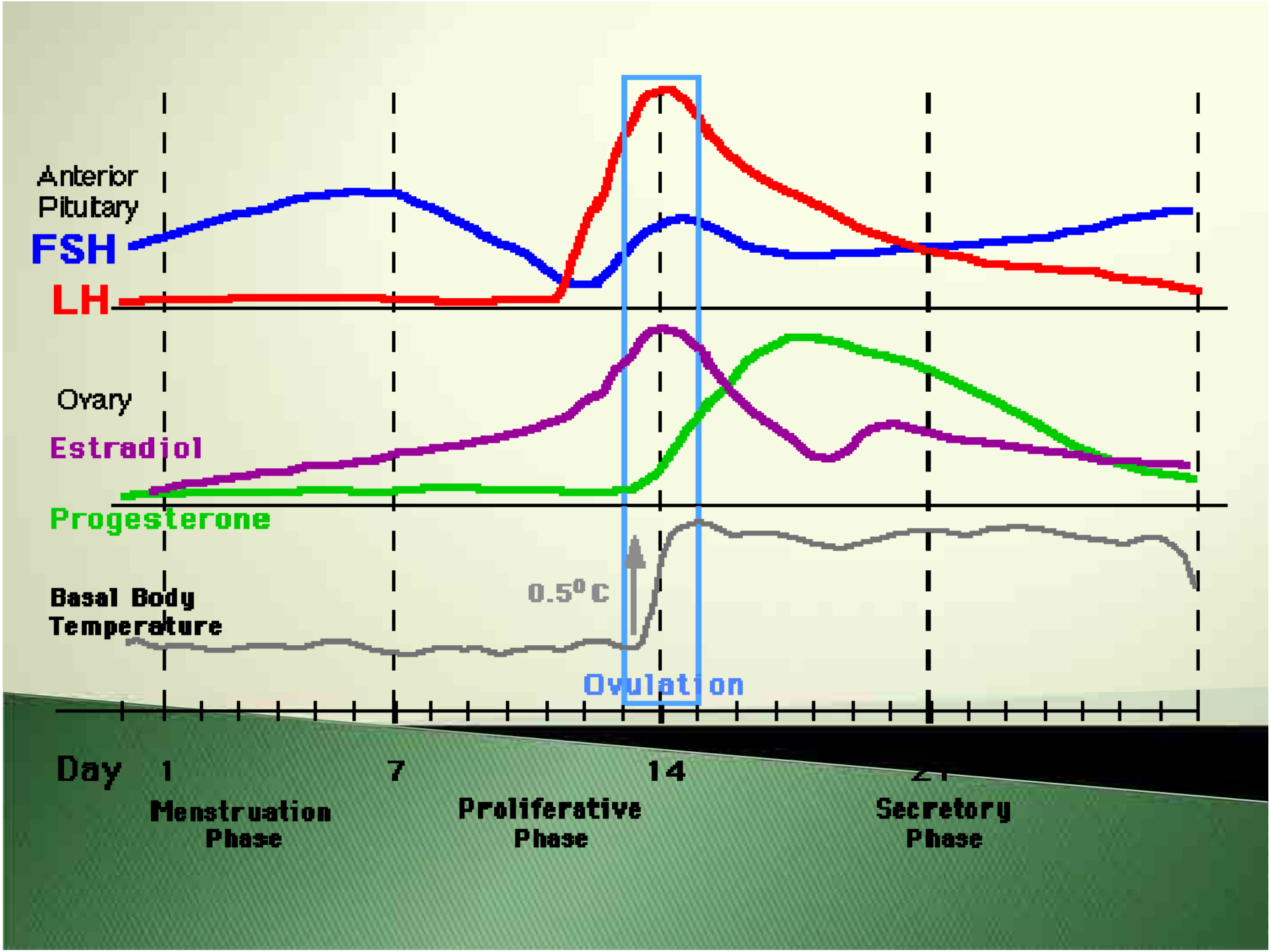
Menstrual Cycle




Anterior Pituitary
FSH
LH
Ovary
Estradiol
Progesterone
Basal Body Temperature
0.5°C
Ovulation
Day
1
7
14
21
Menstruation Phase
Proliferative Phase
Secretory Phase

Luteal Phase

- Twelve to sixteen days time period between ovulation and aftercoming menses or detection of pregnancy is called as luteal phase.
- Following ovulation steroid hormones (E2,P4) secreting corpus luteum is formed and endometrium is transformed to secretory phase
- If conception and implantation occurs hCG secreted by blastocyst maintains the secretions of corpus luteum
- Luteoplacental shift occurs 7 weeks after the first day of last menstrual period . (Scott 1991)

What is the importance of a normal luteal phase ?

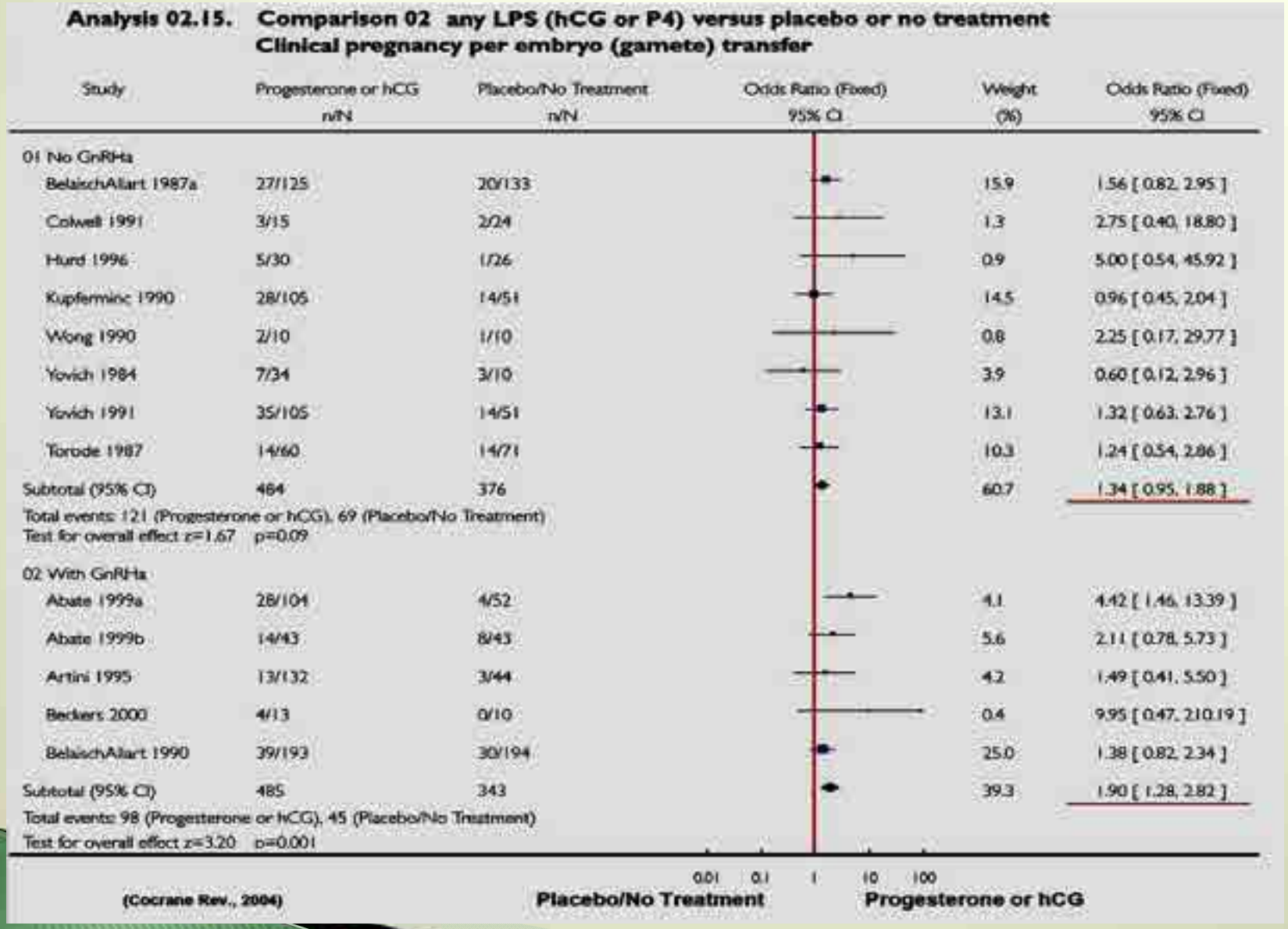
- A receptive (functional) endometrium is a must for a successful implantation in spontaneous or induced cycles
- A normal luteal phase characterised by
  - **A normal hormonal milieu,**
  - **Sufficient progesterone secretion from corpus luteum**
  - **Sufficient secretory endometrial transformation** (1)
- Corpus luteum function is dependent on LH and LH secretion is dependent on GnRH secretion (2,3,4)

1. Tavaniotou A et al. Impact of ovarian stimulation on corpus luteum function and embryonic implantation. J Reprod Immunol. 2002; 55:123-130.
2. Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab. 2003; 14:236-242.
3. McCracken JA et al. Luteolysis: a neuroendocrinemediated event. Physiol Rev 1999; 79:263-323.
4. Filicori M et al. Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion. J Clin Invest 1984; 73:1638-1647.

- Is it necessary to support luteal phase in COH cycles ?

- From the early phase of assisted reproduction, it has been clear that the luteal phase in ART is not sufficient, although the underlying mechanism is unclear (Edwards 1980).
- Long term suppression of hypophysis by GnRH analogs leads to verly low luteal LH and progesterone levels and short luteal phases in ART cycles. (Smitz 1988 -1992)
- Necessity of luteal phase support in GnRH analog utilising IVF cycles has been established in several meta analysis. (Prittz 2002, Daya 2004, van der Linden 2011)

Significantly low pregnancy rates in patients without luteal phase support



Analysis 02.15. Comparison 02 any LPS (hCG or P4) versus placebo or no treatment
Clinical pregnancy per embryo (gamete) transfer

Study	Progesterone or hCG n/N	Placebo/No Treatment n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 No GnRHa					
BelaischAllart 1987a	27/125	20/133		15.9	1.56 [0.82, 2.95]
Colwell 1991	3/15	2/24		1.3	2.75 [0.40, 18.80]
Hurd 1996	5/30	1/26		0.9	5.00 [0.54, 45.92]
Kupferminc 1990	28/105	14/51		14.5	0.96 [0.45, 2.04]
Wong 1990	2/10	1/10		0.8	2.25 [0.17, 29.77]
Yovich 1984	7/34	3/10		3.9	0.60 [0.12, 2.96]
Yovich 1991	35/105	14/51		13.1	1.32 [0.63, 2.76]
Torrode 1987	14/60	14/71		10.3	1.24 [0.54, 2.86]
Subtotal (95% CI)	484	376		60.7	1.34 [0.95, 1.88]
Total events: 121 (Progesterone or hCG), 69 (Placebo/No Treatment)					
Test for overall effect z=1.67 p=0.09					
02 With GnRHa					
Abate 1999a	28/104	4/52		4.1	4.42 [1.46, 13.39]
Abate 1999b	14/43	8/43		5.6	2.11 [0.78, 5.73]
Artini 1995	13/132	3/44		4.2	1.49 [0.41, 5.50]
Beckers 2000	4/13	0/10		0.4	9.95 [0.47, 210.19]
BelaischAllart 1990	39/193	30/194		25.0	1.38 [0.82, 2.34]
Subtotal (95% CI)	485	343		39.3	1.90 [1.28, 2.82]
Total events: 98 (Progesterone or hCG), 45 (Placebo/No Treatment)					
Test for overall effect z=3.20 p=0.001					

0.01 0.1 1 10 100

(Cochrane Rev., 2004)

Placebo/No Treatment

Progesterone or hCG

Analysis 2.2. Comparison 2 Progesterone versus placebo or no treatment, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 2 Clinical Pregnancy Rate

Study or subgroup	Progesterone n/N	Placebo/no treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Abate 1999 (1)	14/43	8/43		13.5 %	2.06 [0.79, 5.41]
Abate 1999a (2)	28/104	4/52		18.6 %	3.23 [1.42, 7.34]
Artini 1995 (3)	13/88	4/44		10.8 %	1.65 [0.56, 4.85]
Belaisch-Allart 1987 (4)	27/141	20/145		32.2 %	1.47 [0.79, 2.75]
Hurd 1996 (5)	5/30	1/26		4.4 %	3.73 [0.69, 20.06]
Kupferminc 1990 (6)	16/54	14/51		17.7 %	1.11 [0.48, 2.58]
Wong 1990 (7)	3/10	1/10		2.8 %	3.28 [0.39, 27.75]
Total (95% CI)	**470**	**371**		**100.0 %**	**1.83 [1.29, 2.61]**

Total events: 106 (Progesterone), 52 (Placebo/no treatment)

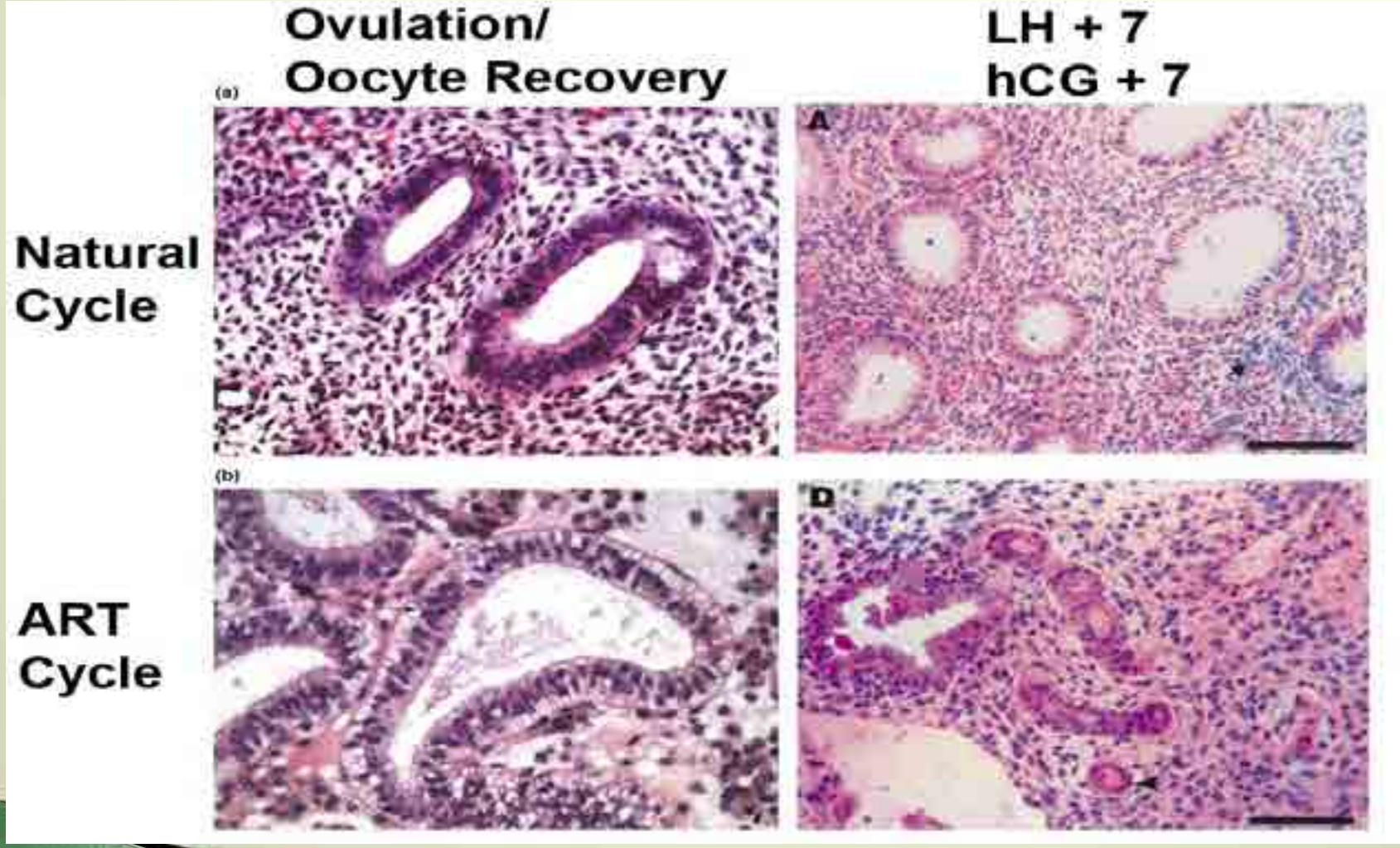
Heterogeneity: $Chi^2 = 4.70$, $df = 6$ ($P = 0.58$); $I^2 = 0.0\%$

Test for overall effect: $Z = 3.35$ ($P = 0.00081$)

(7) IM progesterone 50 mg daily

(Continued . . .)

COH leads to advanced endometrial development in early luteal phase and delayed endometrial development in mid luteal phase. In addition to this COH changes endometrial gene expressions.



(Hum. Reprod., 2001; Trends Endocrinol. Metabol., 2004)

Luteal phase in IVF cycles

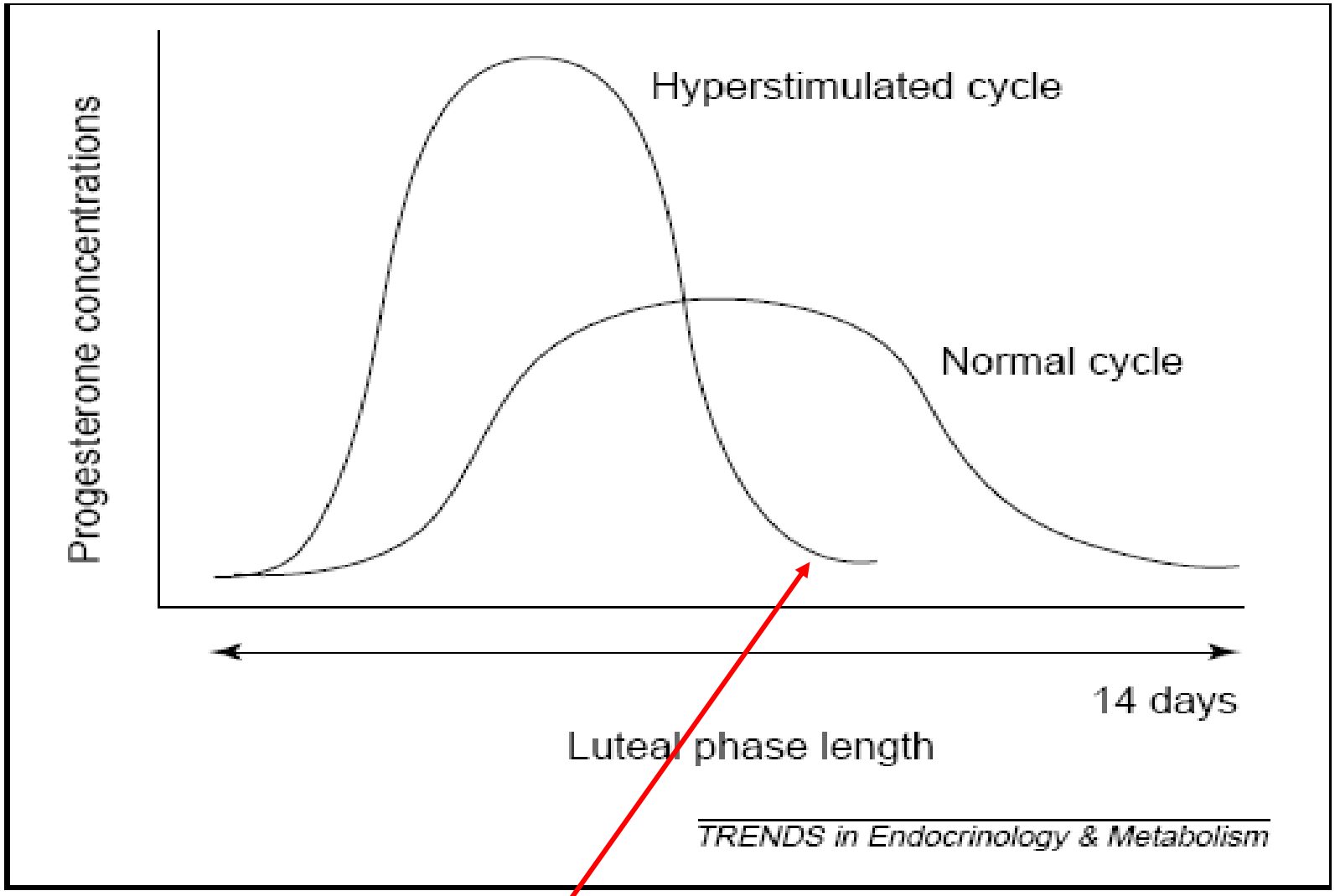
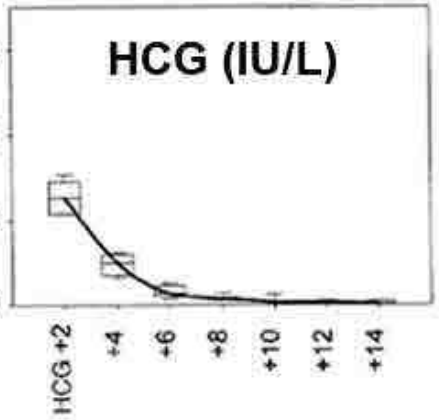


Fig. 2. Abnormal corpus luteum function following ovarian stimulation for *in vitro* fertilization. Abnormally raised progesterone levels during the early luteal phase coincide with premature luteolysis. Adapted, with permission, from [48].

GnRHa +HMG +HCG

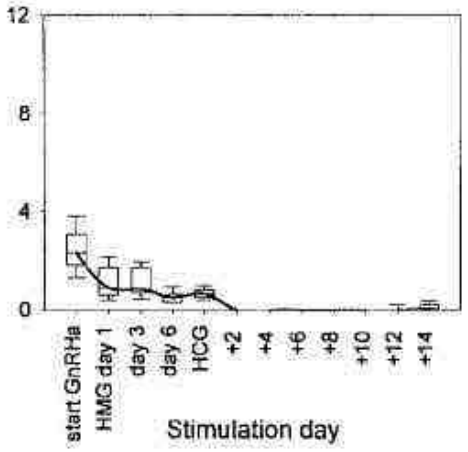


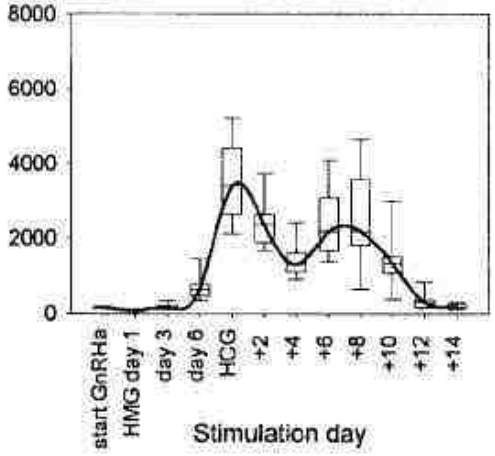
GnRHa+HMG+HCG:
supraphysiologic E_2/P_4 in early luteal phase; premature luteolysis during midluteal phase.
The duration of ovarian steroid production is shorter than normal by 1-3 days.

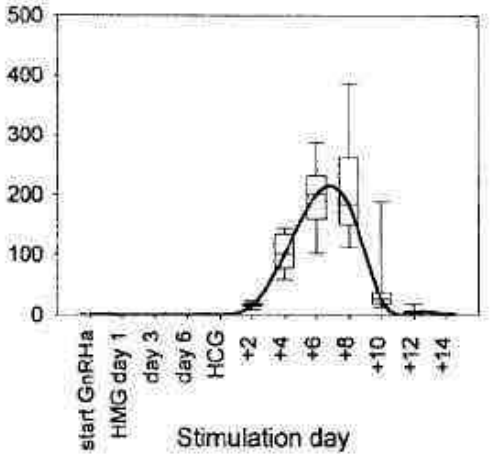
(Hum. Reprod., 2000)

LH (IU/L) **E_2 (pmol/L)** **P_4 (nmol/L)**

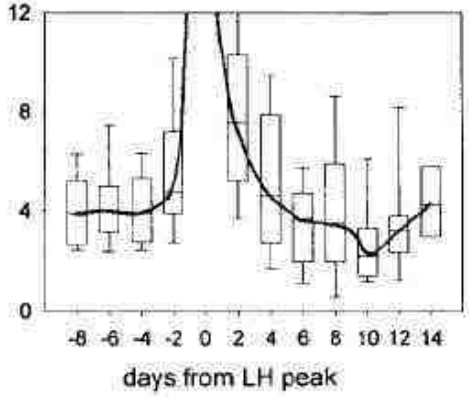
GnRHa +HMG +HCG

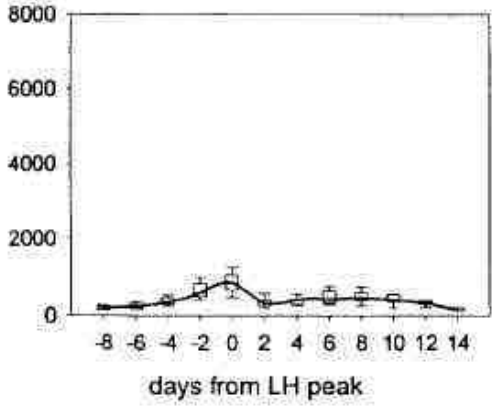


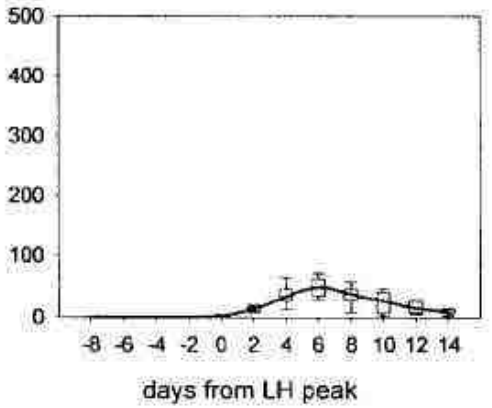




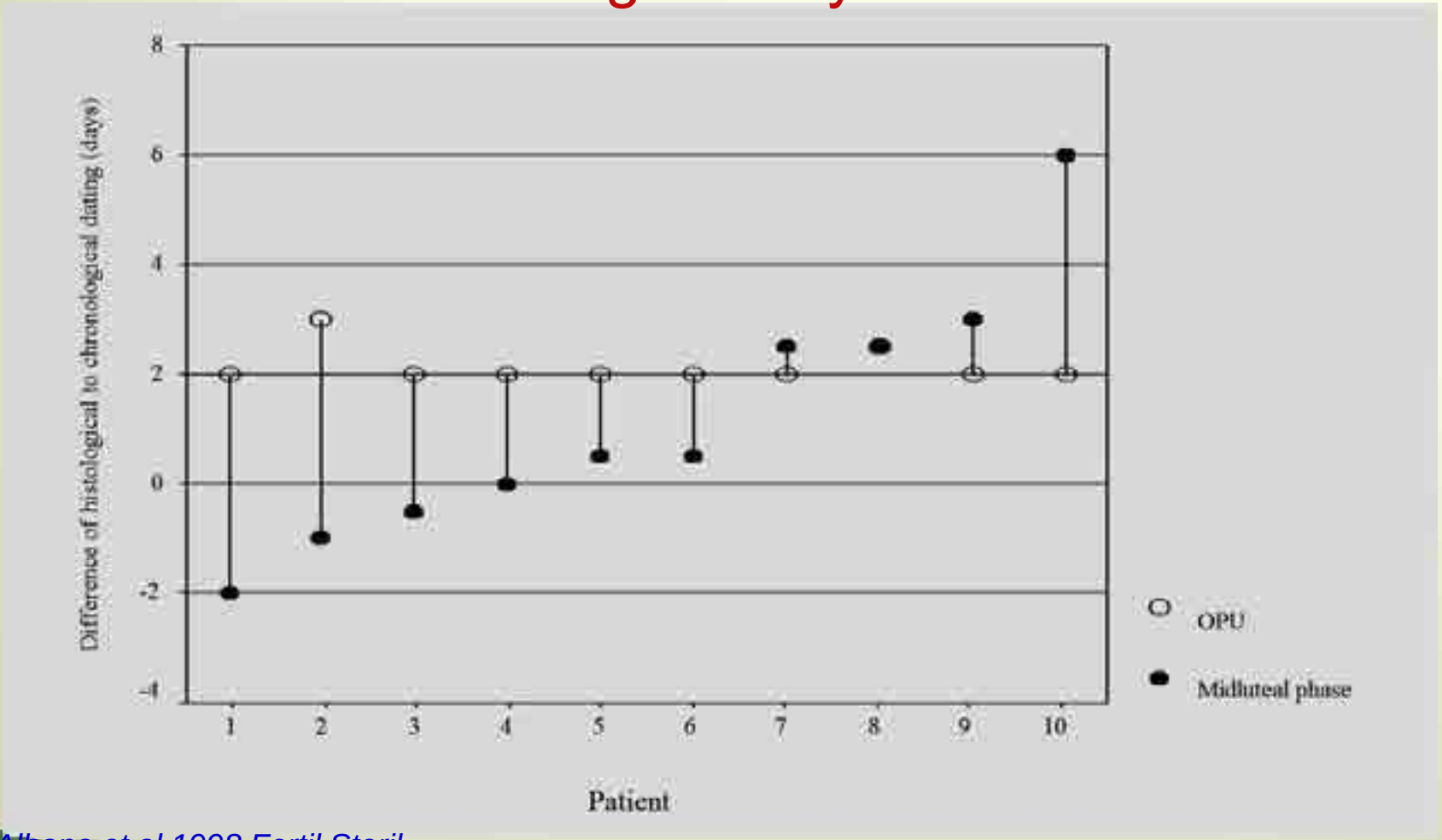
Normal Control







Endometrial dating is also abnormal in GnRH antagonist cycles



Albano et al 1998 Fertil Steril

Kolibianakis et al 2003 Fertil Steril

Luteal phase is defective in GnRHant **cycles too.** Luteolysis is prematurely begins due to "negative feedback. For that reason it seems to be mandatory to support luteal phase.

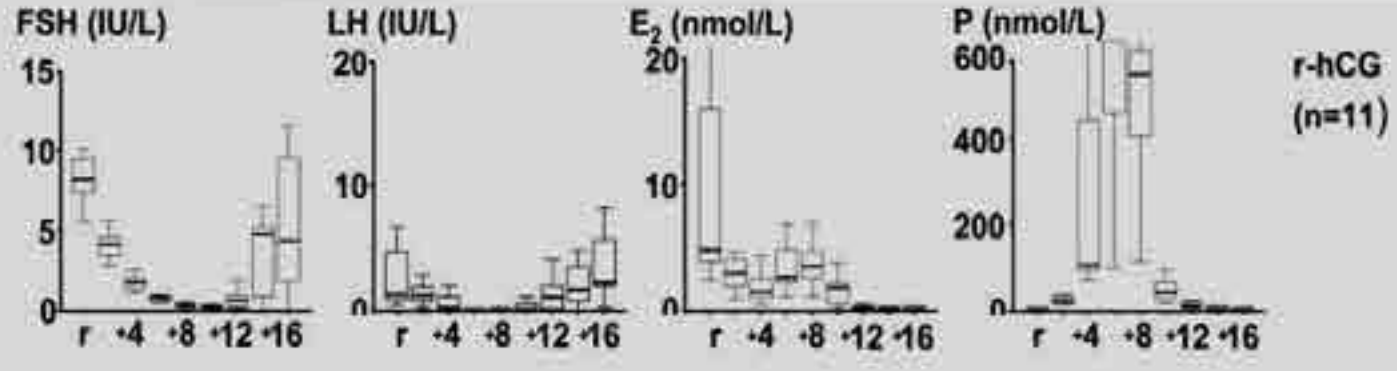
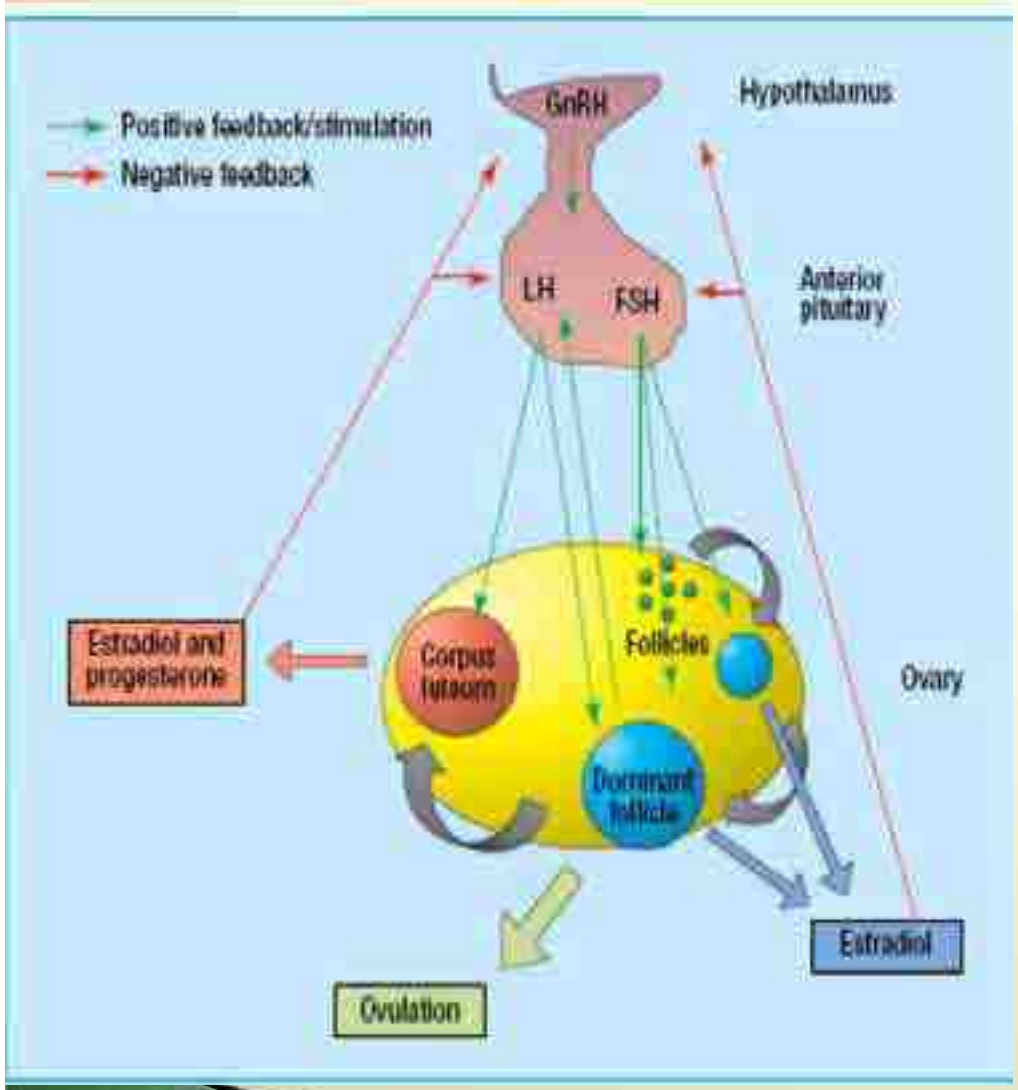


TABLE 1. Follicular and luteal phase characteristics (median and ranges) of 39 subjects undergoing ovarian stimulation using r-hFSH/GnRH antagonist, randomized for three different strategies for the induction of final oocyte maturation

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)	*P* value[a]
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)	0.9
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)	1.0
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)	0.8
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)	0.9
No. achieving embryo transfer[b]	9	11	14	0.4
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)	0.8
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)	0.3
$LH_{(day\ of\ oocyte\ retrieval)}$ (IU/liter)	1.3 (0.3–2.9)	50.6 (3.7–54.1)	5.5 (2.0–9.6)	<0.001
Day of $P_{maximum}$	6 (6–8)	4 (4–6)	4 (4–6)	<0.001
Day of decrease of P	8 (6–8)	4 (4–8)	4 (4–8)	<0.001

Beckers et al. J. Clin. Endocrinol. Metab., 2003)



Multifollicular development

Supraphysiologic serum progesterone and estradiol levels

Long-loop feedback mechanisms

Decrease in LH secretion

Luteal phase defect

Premature luteolysis

Short luteal phase

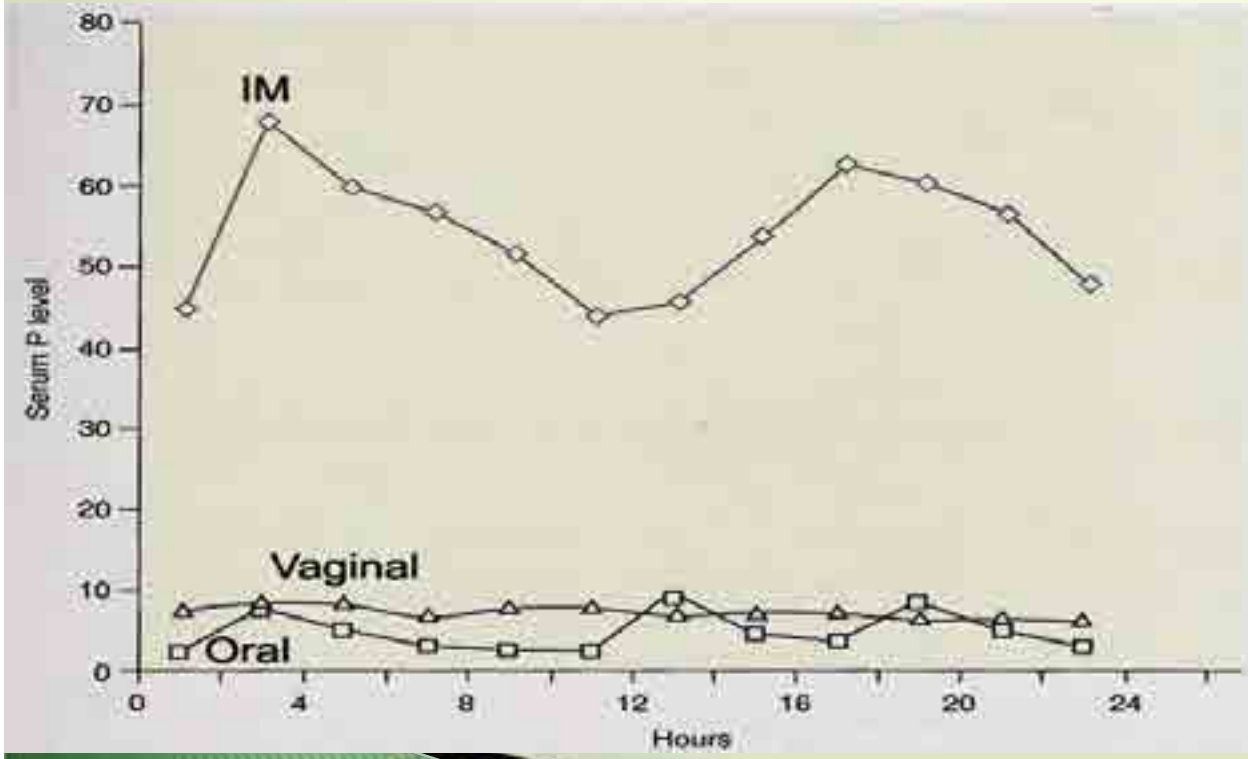
Progesterone support routes

Oral : Only 10% of oral dose of P4 is active in circulation due to first pass effect of liver. It causes dizziness.

Vaginal: "First Uterine Pass Effect (FUPE)" leads to more physiologic endometrium. Associated with increased vaginal irritation and secretion.

Intramuscular: Higher serum P4 levels. Painful, risk of sterile abcess formation and allergic response.

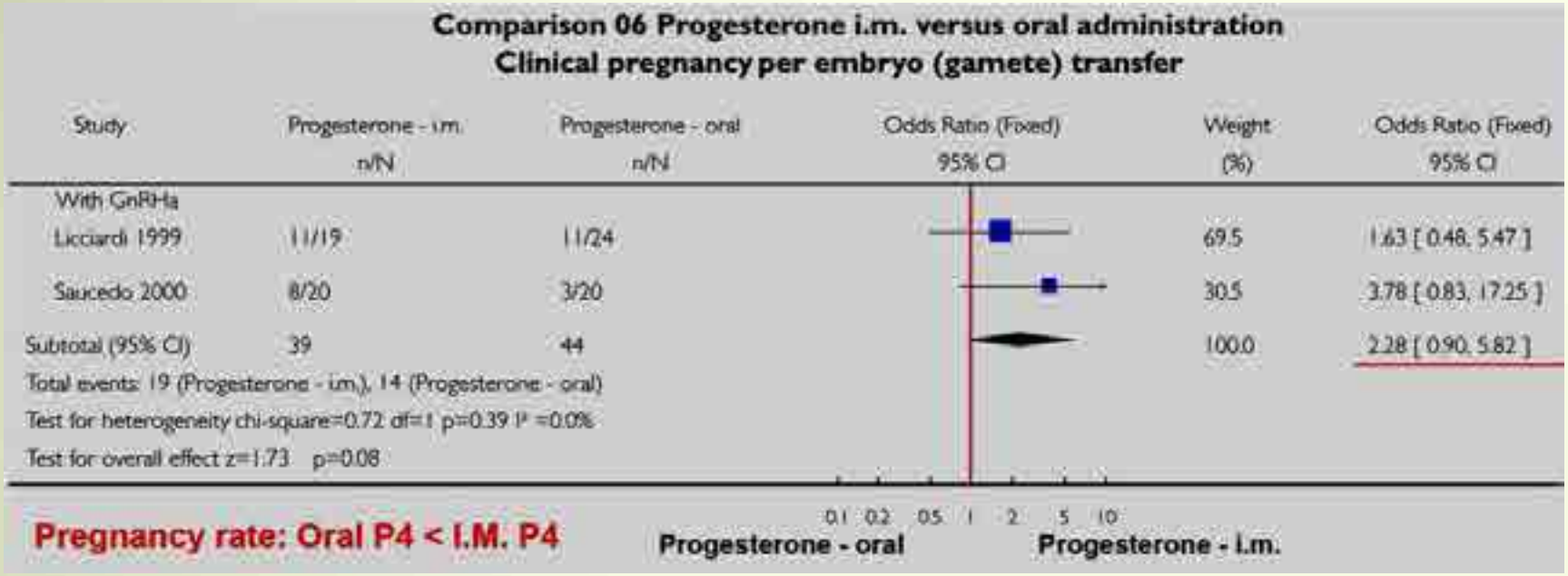
Subcutaneous: Promising, allergic skin reaction.

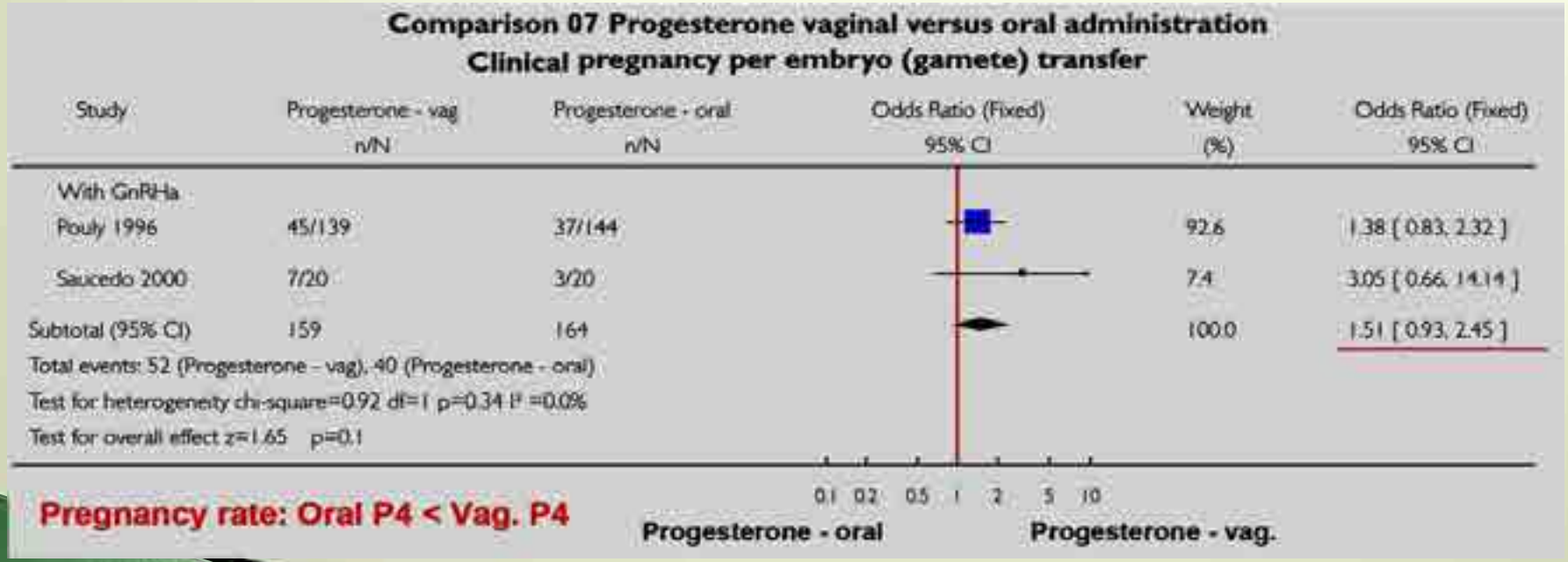


IM (50 bid)
Oral (100 tid)
Vaginal (100 tid)

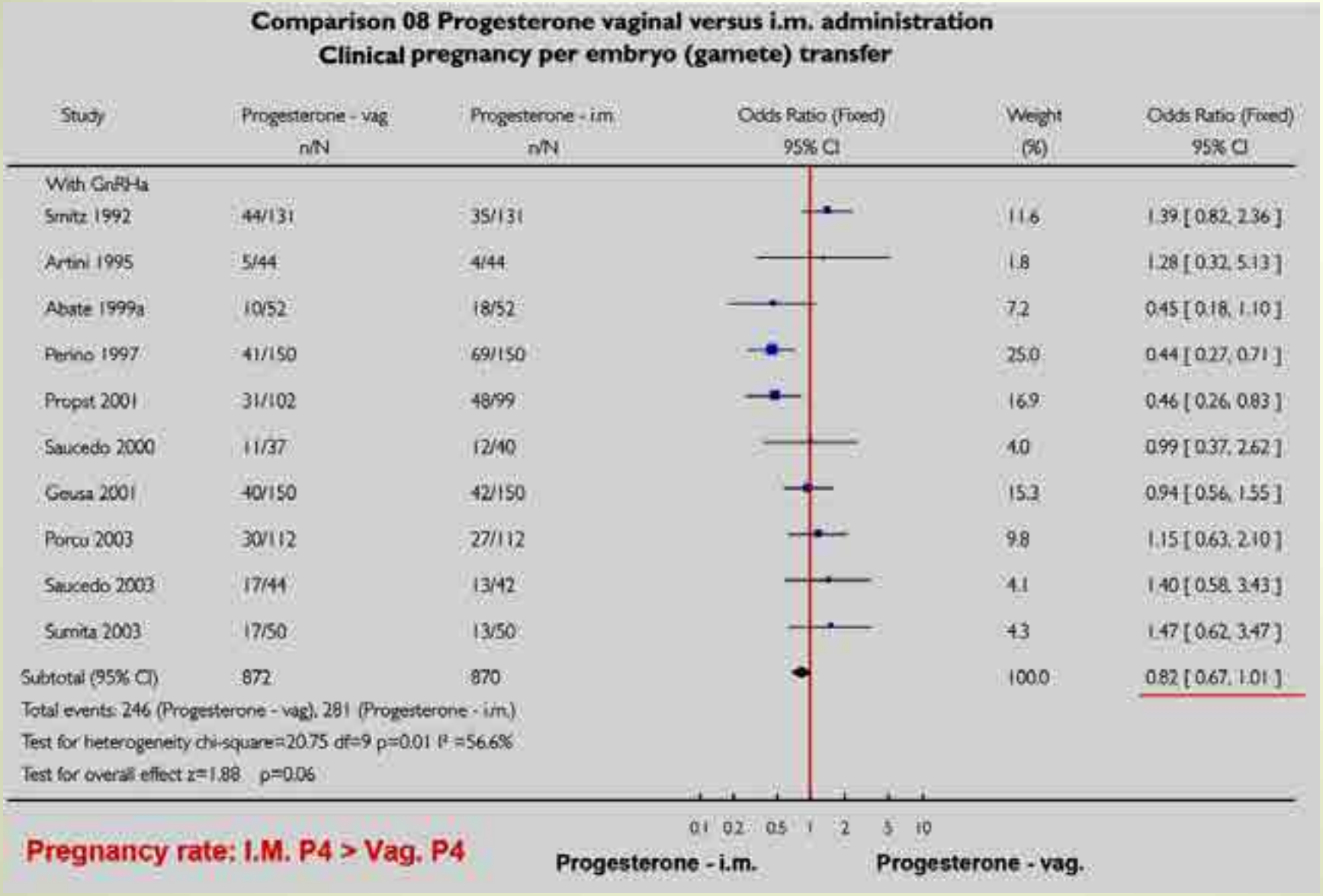
Route	> 2 days out of phase	Exactly in phase
Oral	100% (16/16)	0% (0/16)
IM	6% (2/31)	19% (6/31)
Vaginal	0% (0/28)	36% (10/26)

(Textbook of ART, 2nd Ed., 2004)





(Cochrane Rev., 2004)



Pregnancy rate: I.M. P4 > Vag. P4 > Oral P4

(Cochrane Rev., 2004)

Comparison of oral dydrogestrone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study

Ashalatha Ganesh, M.B.B.S., M.M.S.T., Ph.D.,[a] Nishant Chakravarty, M.B.B.S., M.M.S.T.,[a] Rashmi Mukherjee, M.Sc.,[a] Sourendrakanta Goswami, M.B.B.S.,[b] Koel Chaudhury, Ph.D.,[a] and Baidyanath Chakravarty, M.B.B.S., M.D.[b]

[a] School of Medical Science and Technology, Indian Institute of Technology, Kharagpur; and [b] Institute of Reproductive Medicine, Salt Lake, Kolkata, West Bengal, India

TABLE 2

Demographic data of patients randomly subjected to three different luteal supplementation protocols.

Demographic parameter	Oral dydrogesterone protocol, group A (n = 422)	Micronized vaginal P gel, group B (n = 482)	Vaginal P capsules, group C (n = 469)
Mean age (y)	32 ± 4.53	32 ± 4.65	33 ± 4.59
Mean BMI (kg/m^2)	23.71 ± 3.59	23.88 ± 3.45	23.85 ± 3.49
FSH (mIU/mL)	6.36 ± 1.76	5.98 ± 1.79	6.40 ± 2.01
LH (mIU/mL)	5.48 ± 2.64	5.24 ± 1.94	5.44 ± 2.40
E_2 (pg/mL)	47.73 ± 27.70	48.14 ± 29.36	46.07 ± 30.55
Basal antral follicle	14.50 ± 12.85	13.88 ± 7.61	12.20 ± 7.22
Endometrial thickness	9.47 ± 1.99	8.79 ± 2.28	8.96 ± 2.23
Pregnancy rate	28.67 (121/422)[a]	28.63 (138/482)[a]	22.65 (104/459)[a]
Miscarriage rate	11.57 (14/121)[a]	15.94 (22/138)[a]	18.26 (19/104)[a]

Note: Data presented as mean ± SD or percentage (number).
[a] Not significant.

Ganesh. Oral dydrogesterone as luteal support. Fertil Steril 2011.

Iran J Reprod Med Vol. 11. No. 11. pp: 913-918, November 2013
Original article

Comparison of oral dydrogesterone with suppository vaginal progesterone for luteal-phase support in in vitro fertilization (IVF): A randomized clinical trial

Saghar Salehpour M.D., Maryam Tamimi M.D., Nasrin Saharkhiz M.D.

Duphaston 10 mg 4x1 vs cyclogest 400 mg vaginal 2x1

Two groups – n=40 each

Similar pregnancy rates but side effects and bleeding episodes were more in Duphaston.
Oral synthetic progesterone can be an alternative to vaginal route.

Fertil Steril. 2010 Mar 26.

- **Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study.**

Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M.

- **RESULTS:** Crinone vaginal jel is equally effective in luteal phase support with IMP in IVF and better tolerated than IMP by patients.
- (in normoresponders patients)

Fertil Steril. 2010 May 25.

- Patterns of luteal phase bleeding in in vitro fertilization cycles supplemented with Crinone vaginal gel and with intramuscular progesterone-impact of luteal estrogen: prospective, randomized study and post hoc analysis.

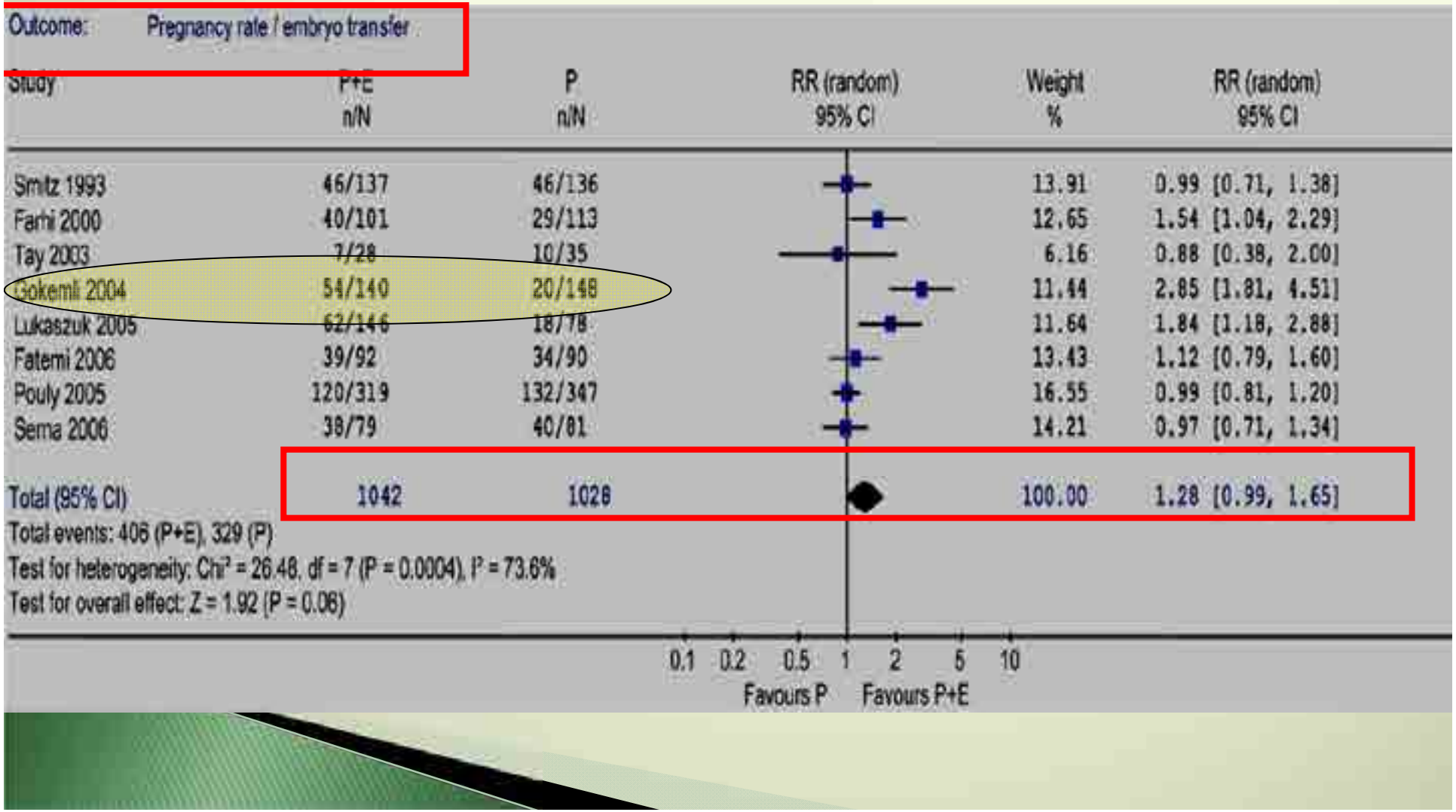
  Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M.
- RESULTS: In only non-pregnant patients there were more bleeding episodes in luteal phase with Crinone gel support. IMP without changing the pregnancy rates delayed the time of menses in non-pregnant group. Similarly luteal estrogen support delayed menses without significantly changing the outcome.

Different routes of progesterone support

- Linden 2015- When routes of progesterone administration were compared, no conclusive findings be gathered.
- The analysis for the miscarriage rate suggested benefit derived from low-dose vaginal progesterone.
- No evidence revealed differences between low-dose and high-dose groups for the other outcomes.
- A new method consists of a weekly progesterone ring, for which we also conducted a comparison. No evidence favoured the vaginal ring or gel.

Luteal phase support – E_2

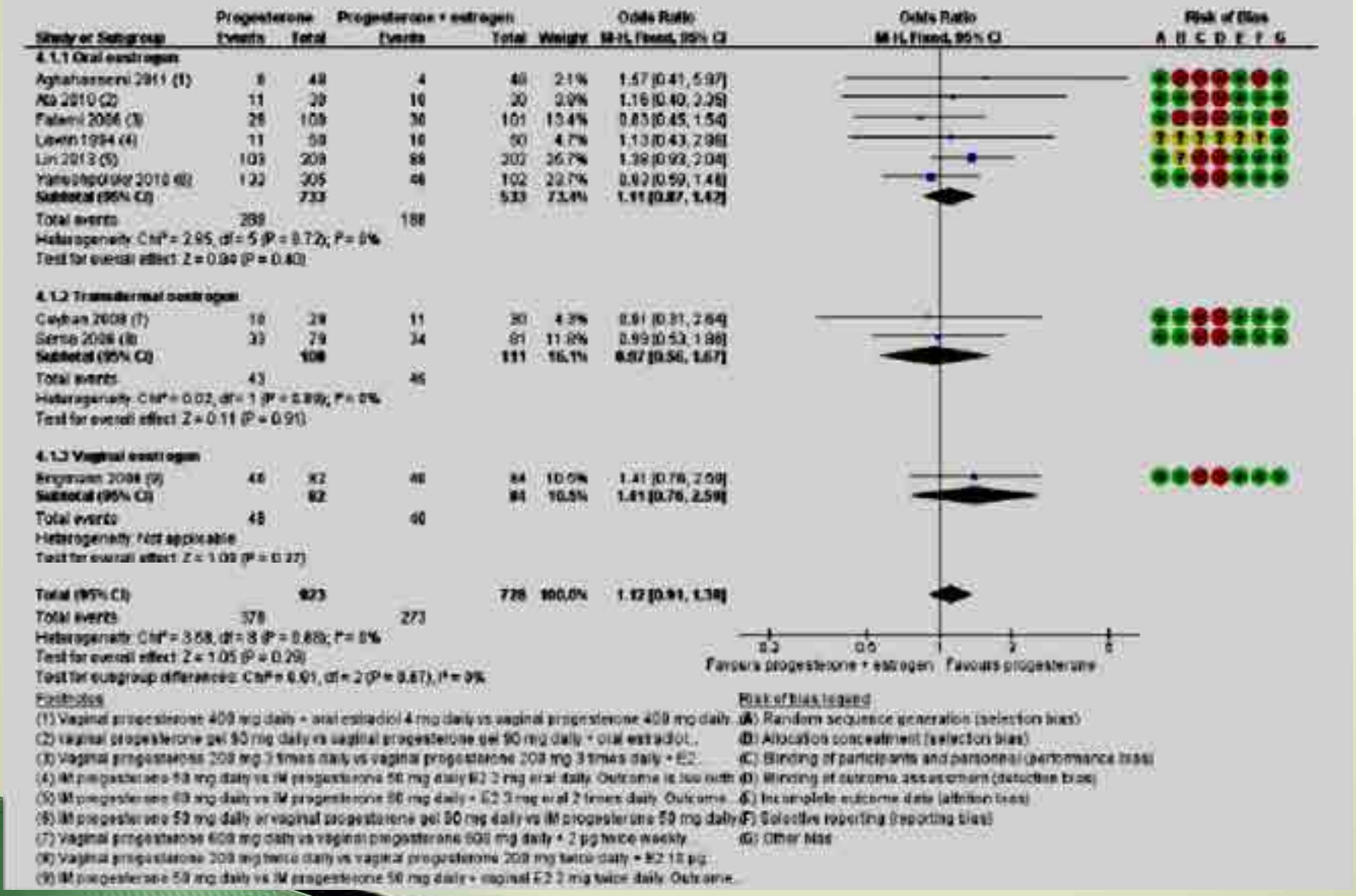
Gelbaya, *et al.*, 2008



Luteal support - E2

- Kolibianakis et al, 2008- meta analysis
- Conclusion: In IVF cycles with GnRH a + Gonadotropins the necessity of luteal E2 support in addition to P4 could not be established
- Linden 2015- No evidence of difference of in live birth rate with P4+ E2 vs P4 only.
- In subgroup analysis in clinical pregnancy rate transdermal E2 group is better than P4 only group with very low quality of evidence

Figure 11. Forest plot of comparison: 4 Progesterone vs progesterone + oestrogen, outcome: 4.1 Live birth/ongoing pregnancy rate.

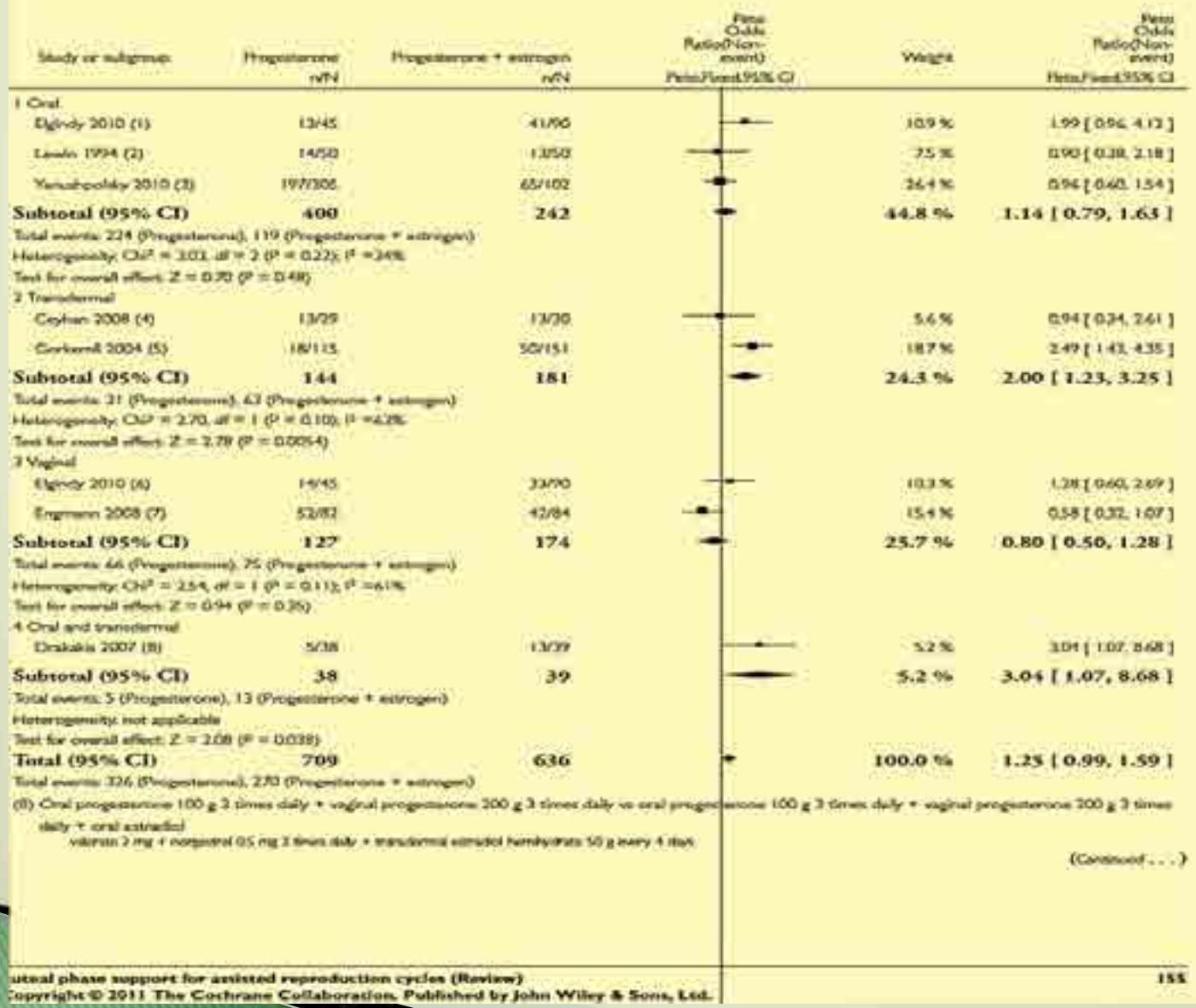


Analysis 4.2. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

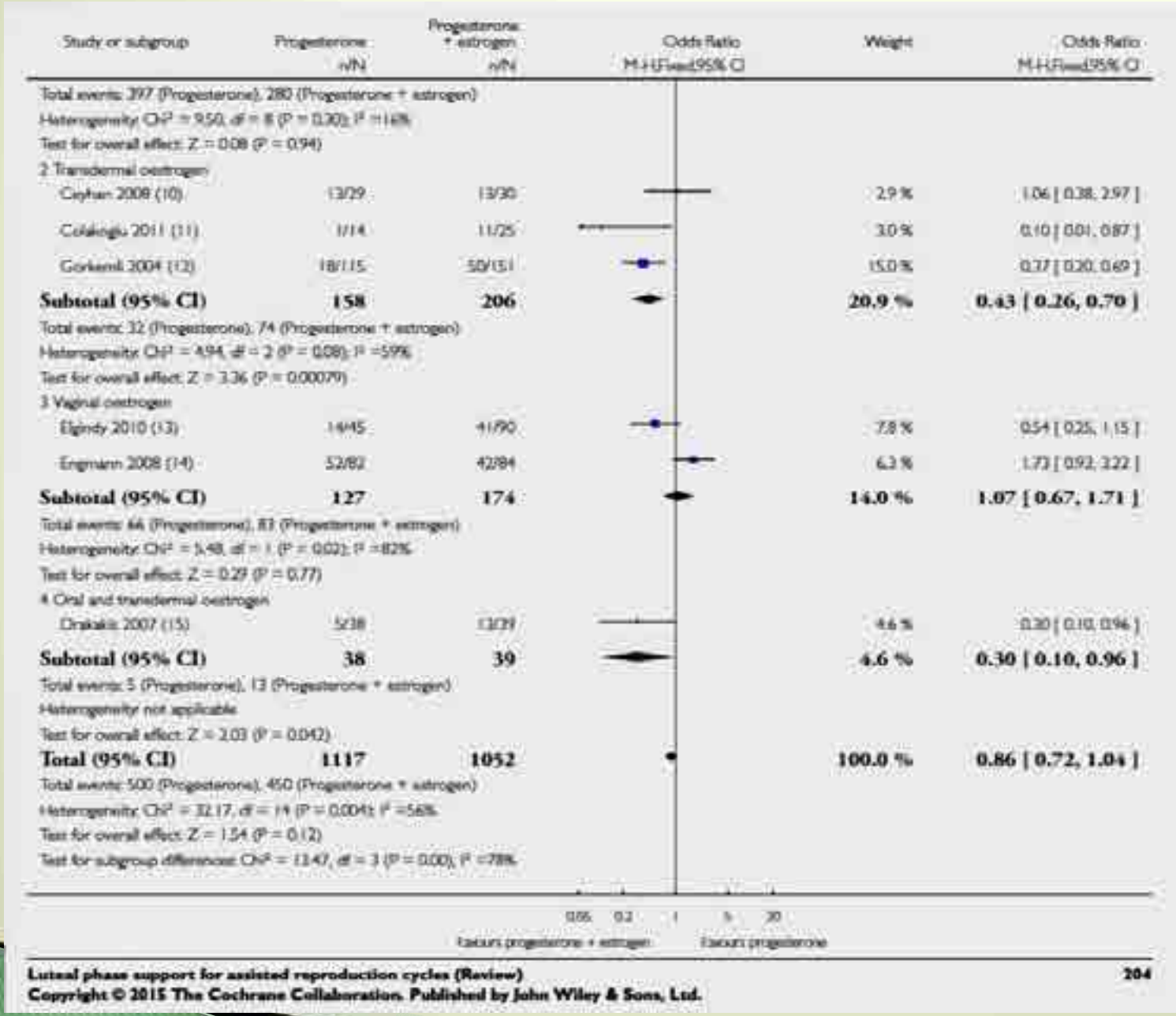
Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 2 Clinical Pregnancy Rate



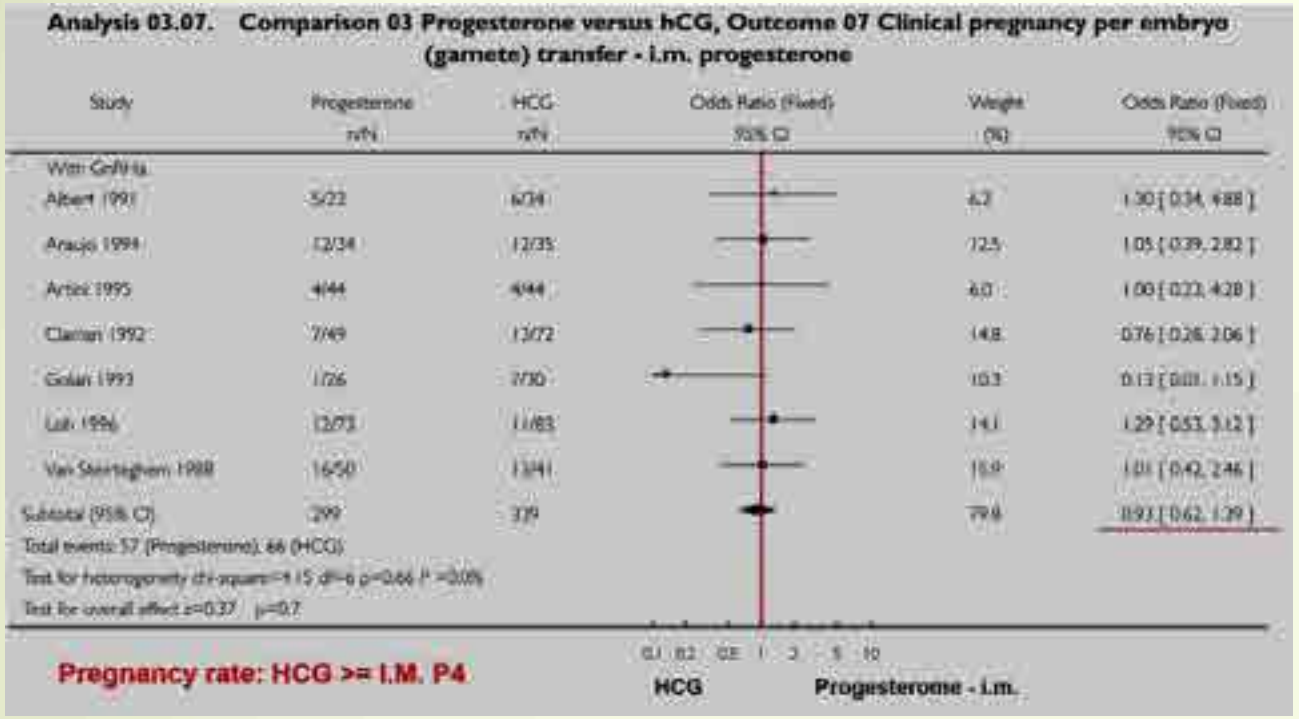
(8) Oral progesterone 100 g 3 times daily + vaginal progesterone 200 g 3 times daily vs oral progesterone 100 g 3 times daily + vaginal progesterone 200 g 3 times daily + oral estradiol valerate 2 mg + norgestrel 0.5 mg 3 times daily + transdermal estradiol hemihydrate 50 g every 4 days

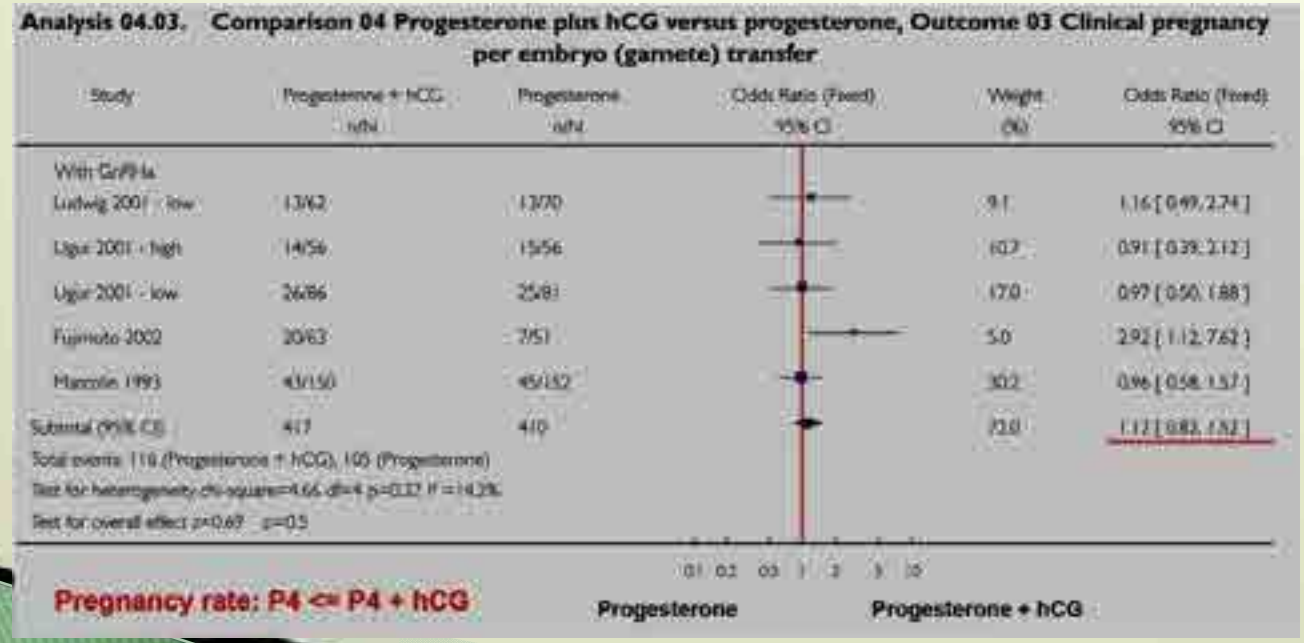
(Continued . . .)



Luteal E2 support in poor responder patients

- Kutlusoy F (2014)- prospective randomized study – P4 gel(1) vs 2mg E2 + gel(2) and 6mg E2 + gel (3)
- All patients were poor responders
- In the 2nd group there was significantly higher pregnancy and clinical pregnancy rates in comparison to other groups.





(Cochrane Rev., 2004)

HCG in Luteal Phase Support

- Meta Analysis
- hCG increased the risk of OHSS at least 2 times. İt should be used cautiously in all patients. (Ludwig ve Diedrich 2001)
- 2002 Pritts ve Atwood- Similar effect with P4 only.
- 2005 Nosarka- Better than P4 only.
- 2011 van der Linden M, No difference between P4 and HCG. In subgroup analysis P4 only is better than P4+HCG and there is significantly increased risk of OHSS.
- 2015 van der Linden M. No difference in any parameter analysed.

A comparison of the effects of three different luteal phase support protocols on in vitro fertilization outcomes: a randomized clinical trial

Turgut Var, M.D., Esra Aygin Tonguc, M.D., Melike Doganay, M.D., Cavidan Guleroman, M.D., Tayfun Gungor, M.D., and Leyla Mollamahmutoglu, M.D.

Zekai Tahir Burak Woman's Health Education and Research Hospital, Assisted Reproduction Unit, Ankara, Turkey

TABLE 2

In vitro fertilization cycle characteristics of the three treatment groups.

Characteristic	Group 1 (E_2 + P), n = 96	Group 2 (hCG + P), n = 95	Group 3 (P only), n = 97	*P* value
No. of oocytes retrieved	9.1 ± 3.9	9.5 ± 3.9	9.5 ± 1.8	.65
No. of embryos transferred	2.7 ± 1.0	2.6 ± 0.6	2.7 ± 0.4	.28
Implantation rate (%)	16.7 ± 22.7	20.0 ± 21.6	7.9 ± 15.4	.001[a]
Clinical PR, % (no.)	40.6 (39/96)	38.9 (37/95)	21.6 (21/97)	.01[a]
Miscarriage rate, % (no.)	12.8 (5/39)	13.5 (5/37)	38 (8/21)	.02[a]
Multiple-pregnancy rate, % (no.)	2.3 (2/96)	14.7 (14/95)	0 (0/97)	.001[b]

Note: $P < .05$ was considered to be statistically significant. Data are expressed as mean ± SD or as percentage and number.

[a] Group 3 versus group 1 and group 2.

[b] Group 2 versus group 1 and group 3.

Var. Three different luteal phase supports. Fertil Steril 2011.

Possible mechanisms of action of GnRH analogs in luteal phase support

- Unintentional exposure to GnRHa in luteal phase appeared not to destyroy a conception and even made the implantation better in patients prepared for a long protocol IVF cycle.

- GnRH receptors were found to be expressed in human preimplantation embryos, endometrium and corpus luteum. For that reason GnRHa may have direct effects on these targets.

- It was established that GnRHa increased hCG production in trophoblasts.

Beneficial Effect of Luteal-phase GnRHa on Embryo Implantation in GnRHa-treated Ovarian Stimulation Cycles

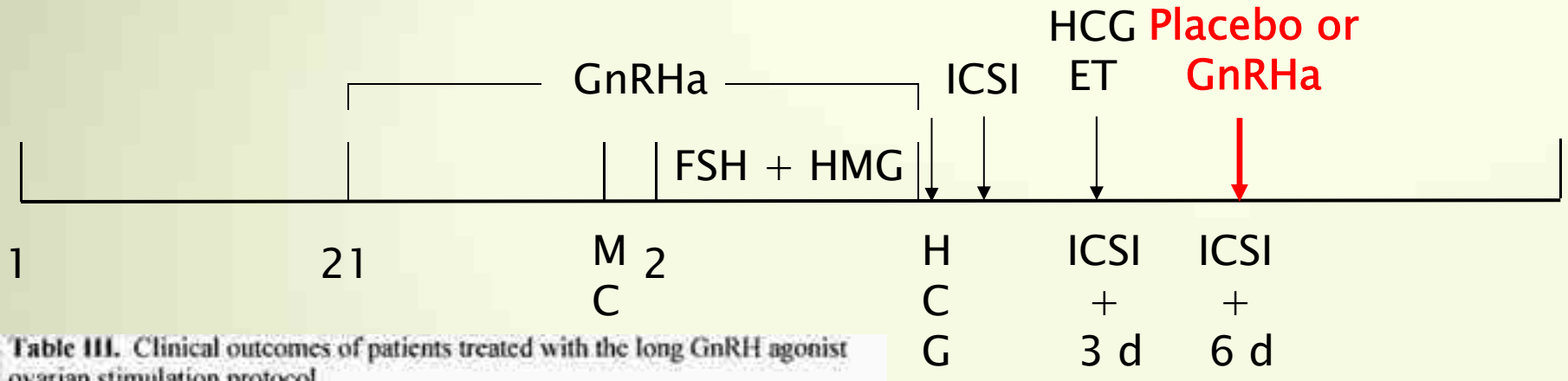


Table III. Clinical outcomes of patients treated with the long GnRH agonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Intention to treat	150	150
Transfer procedures	141	142
Embryos transferred	325	330
Embryos per transfer[a]	2.3 ± 0.5 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer[a]	2.0 ± 0.4	2.0 ± 0.5 (2.0)
Clinical pregnancy rate		
Per embryo transfer	51.1% (72/141)	41.5% (59/142)
Per intention to treat	48.0% (72/150)	39.3% (59/15
Clinical implantation rate	29.8% (97/325)[b]	18.2% (60/330)
Ongoing pregnancy rate		
Per embryo transfer	46.8% (66/141)	38.0% (54/142)
Per intention to treat	44.0% (66/150)	36.0% (54/150)
Live birth rate	27.4% (89/325)[b]	18.2% (60/330)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

Luteal-phase GnRHa
(Triptorelin 0.1 mg 6 d after ICSI) **enhances** embryo implantation and live birth rates

Tesarik et al. (Hum. Reprod., 2006)

Beneficial Effect of Luteal-phase GnRHa on Embryo Implantation in GnRHant-treated Ovarian Stimulation Cycles

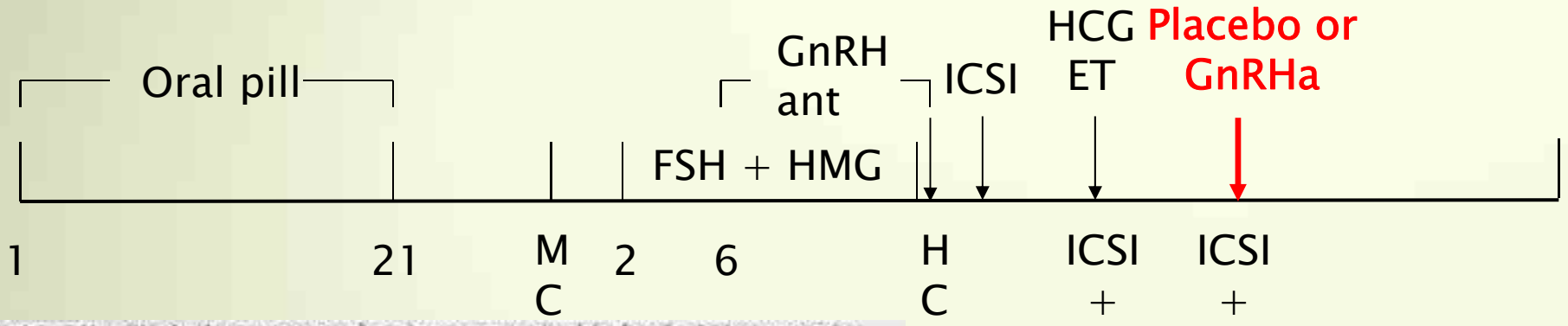


Table VI. Clinical outcomes of patients treated with the GnRH antagonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Transfer procedures	145	144
Embryos transferred	317	328
Embryos per transfer[a]	2.2 ± 0.4 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer	1.9 ± 0.4 (2.0)	2.0 ± 0.4 (2.0)
Clinical pregnancy rate		
Per embryo transfer	47.6% (69/145)	37.5% (54/144)
Per intention to treat	46.0% (69/150)	36.0% (54/150)
Clinical implantation rate	27.1% (86/317)[b]	17.4% (57/328)
Ongoing pregnancy rate		
Per embryo transfer	44.8% (65/145)[b]	31.9% (46/144)
Per intention to treat	43.3% (65/150)[b]	30.7% (46/150)
Live birth rate	25.2% (80/317)[b]	14.6% (48/3328)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

Luteal-phase GnRHa (Triptorelin 0.1 mg 6 d after ICSI) enhances embryo implantation and live birth rates

Tesarik et al.(Hum. Reprod., 2006)

RBMOnline - Vol 19. No 4. 2009 472–477 Reproductive BioMedicine Online; www.rbmonline.com/Article/4036 on web 19 August 2009

Article

Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study

Dr A Zeki Isik obtained his medical degree in 1988 from Hacettepe University Faculty of Medicine, Turkey. After completing his obstetrics and gynaecology residency, he worked as a research fellow in New York Hospital-Cornell Medical Center. He has published more than 40 articles in the field of assisted reproductive technology.

Dr A Zeki Isik

AZ Isik[1], GS Caglar[2,3], E Sozen[1], C Akarsu[1], G Tuncay[1], T Ozbicer[1], K Vicdan[1]

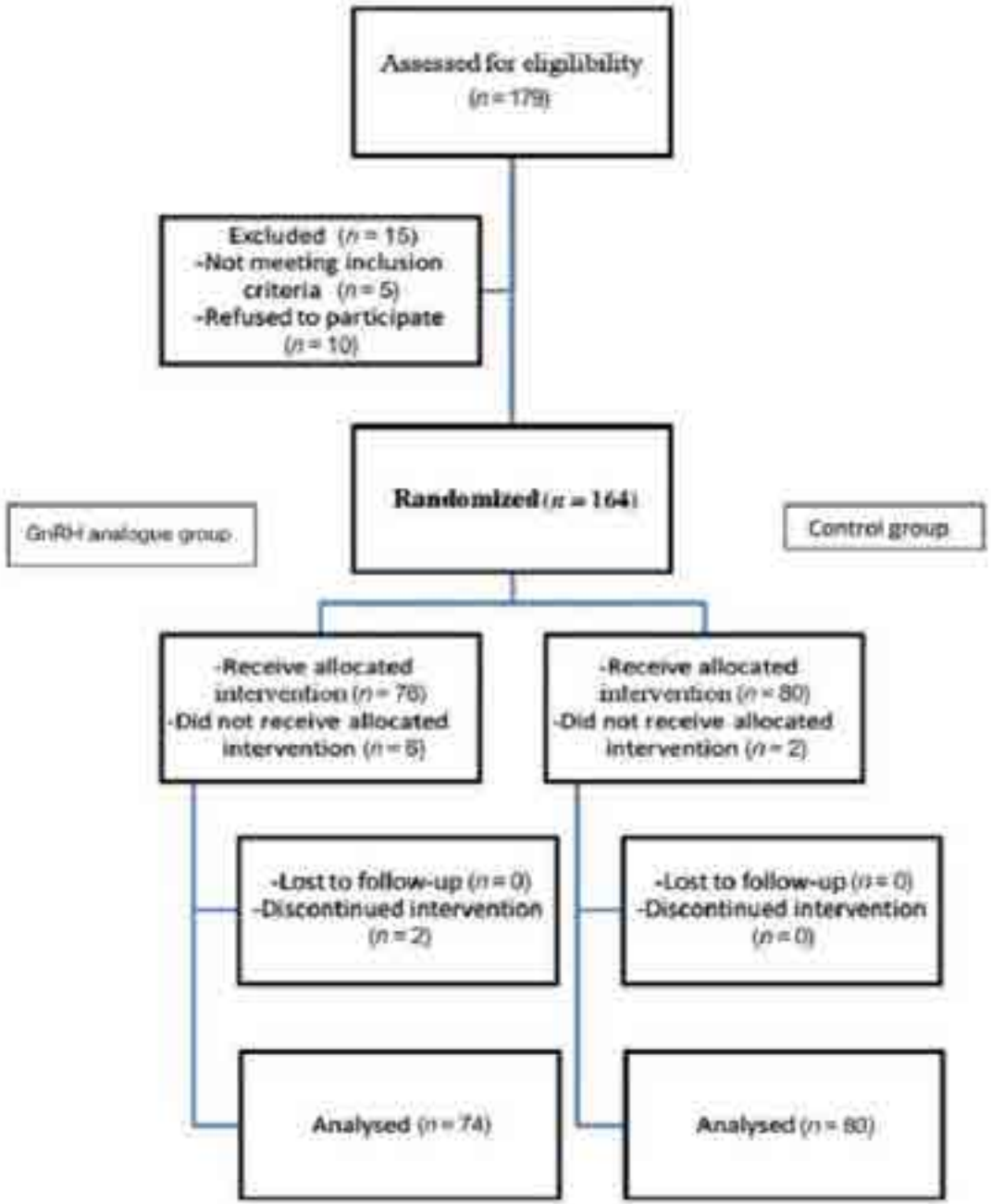


Figure 1. Patient flow through the randomized trial. GnRH = gonadotrophin-releasing hormone.

Table 1. Patient and cycle characteristics.

Parameter	*GnRH agonist (+) (n = 74)*	*Control (n = 80)*
Age (years)	35.56 ± 4.46	35.59 ± 5.54
Basal FSH (mIU/ml)	7.73 ± 2.29	7.7 ± 2.27
Duration of infertility (years)	10.0 ± 6.6	9.9 ± 5.5
Duration of stimulation (days)	9.9 ± 2.2	9.9 ± 2.2
Daily gonadotrophin dosage (IU)	452.2 ± 102.2	411.11 ± 135.5
Total gonadotrophin dose (IU)	3882.2 ± 1598.0	3871.1 ± 1273.3

Values are means ± SD. GnRH, gonadotrophin-releasing hormone. There were no statistically significant differences between the two groups.

Table 2. Cycle characteristics.

Parameter	*GnRH agonist (+) (n = 74)*	*Control group (n = 80)*
Oocytes retrieved	10.00 ± 7.74	10.07 ± 8.87
MII oocytes	7.71 ± 5.57	7.77 ± 6.63
Fertilized oocytes	5.58 ± 4.45	5.53 ± 4.49
Embryos transferred	2.27 ± 1.15	2.23 ± 1.15
Grade-1 embryos transferred	1.14 ± 1.18	1.16 ± 1.17

Values are means ± SD. GnRH, gonadotrophin-releasing hormone; MII, metaphase II. There were no statistically significant differences between the two groups.

Table 3. Pregnancy outcome.

Parameter	*GnRH agonist (+) (n = 74)*	*Control (n = 80)*	*P-value*
βHCG positive	32 (43.2)	23 (28.8)	NS
Implantation rate	54/204 (26.5)	21/227 (9.3)	<0.0001
Clinical pregnancies	30 (40.5)	16 (20.0)	0.0055
Multiple pregnancies	17 (56.7)	3 (18.8)	0.0145
Live birth/embryo transfer	26/74 (35.1)	13/80 (16.3)	0.007

Values are number (percentage); GnRH, gonadotrophin-releasing hormone; NS, not statistically significant.

Eur J Obstet Gynecol Reprod Biol. 2014

The addition of gonadotrophin releasing hormone agonist to routine luteal phase support in intracytoplasmic sperm injection and embryo transfer cycles: a randomized clinical trial.

Yıldız GA[1], Sükür YE[2], Ateş C[3], Aytaç R[2].

[1]Ankara University School of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey.

- No difference in implantation rates. (A- single dose GnRHa (leuprolide 1 mg 6 days after ICSI + vaginal P4 -20.7% B- Two doses of GnRHa- D3 and D6- 25.8% C- control group 13.3%, p=.099).
- Clinical pregnancy and miscarriage rates were similar.
- Ongoing pregnancy rates in control group was 27.4 %, 36 % in group A, 42.9 % in group B (p=.093).
- No difference in OHSS rate.
- Significantly higher multiple pregnancy rate was found in group A and B in comparison to control group. (12% ve 17.9% vs. 4.2%;respectively p=.014).

Analysis 5.1. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 1 Live Birth Rate

Study or subgroup	Progesterone n/N	Progesterone + GnRH agonist n/N	Peto Odds Ratio(Non-event) Peto,Fixed,95% CI	Weight	Peto Odds Ratio(Non-event) Peto,Fixed,95% CI
1 Single dose					
Isik 2009 (1)	13/80	26/74		31.8 %	2.70 [1.31, 5.57]
Subtotal (95% CI)	**80**	**74**		**31.8 %**	**2.70 [1.31, 5.57]**
Total events: 13 (Progesterone), 26 (Progesterone + GnRH agonist)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.68 (P = 0.0073)					
2 Multiple dose					
Ikkoglu 2007 (2)	34/90	45/91		48.6 %	1.60 [0.89, 2.88]
Qublan 2008 (3)	3/60	19/60		19.7 %	5.85 [2.33, 14.69]
Subtotal (95% CI)	**150**	**151**		**68.2 %**	**2.33 [1.42, 3.82]**
Total events: 37 (Progesterone), 64 (Progesterone + GnRH agonist)					
Heterogeneity: Chi^2 = 5.40, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 3.35 (P = 0.00081)					
Total (95% CI)	**230**	**225**		**100.0 %**	**2.44 [1.62, 3.67]**
Total events: 50 (Progesterone), 90 (Progesterone + GnRH agonist)					
Heterogeneity: Chi^2 = 5.51, df = 2 (P = 0.06); I^2 =64%					
Test for overall effect: Z = 4.28 (P = 0.000019)					
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%					

(1) Vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU vs vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU + sc leuprolide acetate 0.5 mg on day 6 after ET

(2) Progesterone 50 mg im daily vs progesterone 50 mg im daily + GnRH agonist 0.25 mg sc daily for 12 days

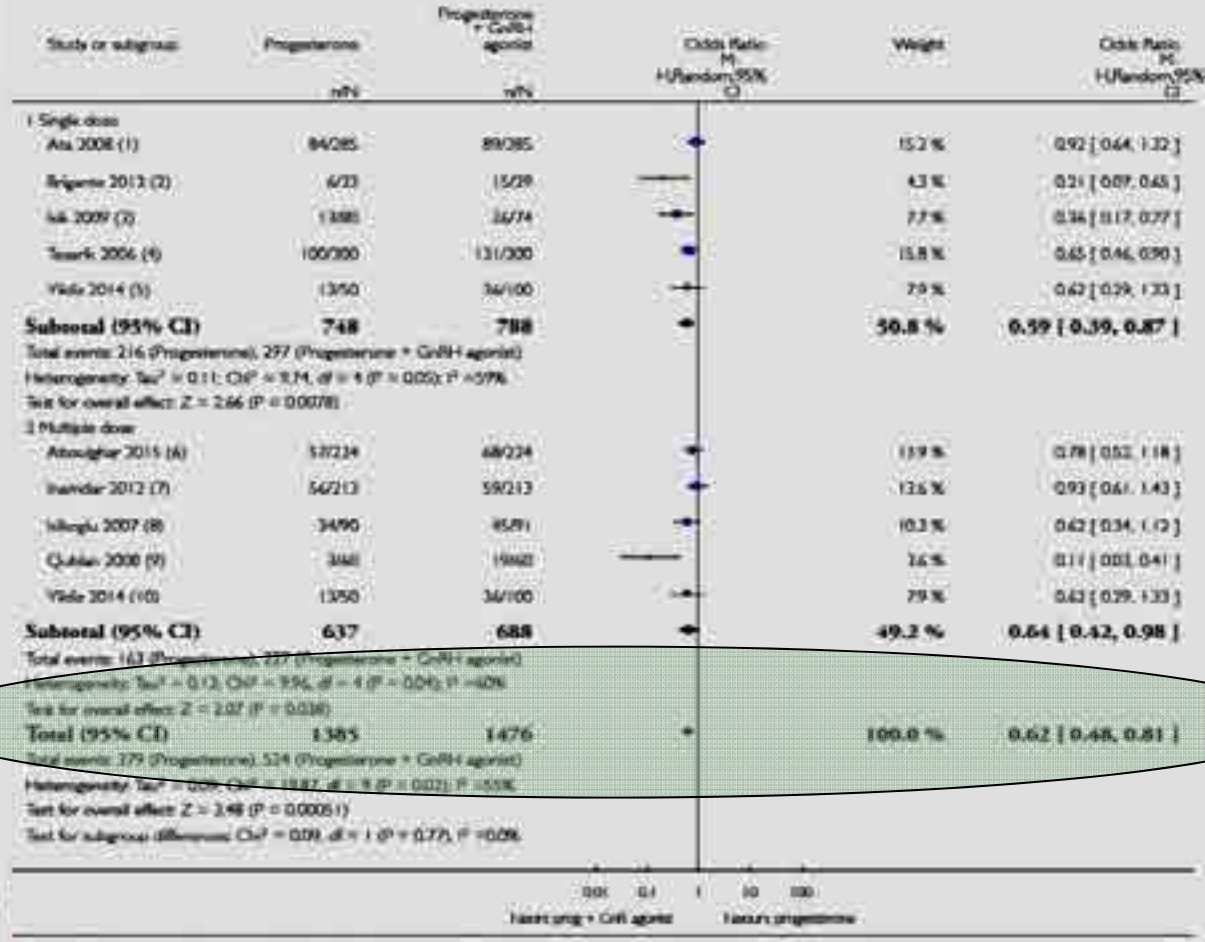
(3) Cyclogest (not defined) + placebo vs Cyclogest (not defined) + sc triptorelin 0.1 mg 3 times

Analysis 5.1. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 1 Live birth or ongoing pregnancy rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone vs progesterone + GnRH agonist

Outcome: 1 Live birth or ongoing pregnancy rate



Timing of Luteal Phase Support

1- Two days after ovulation triggering can be ideal time for start progesterone support.

2- On the other hand no statistically significant differences were found between P4 start at day of hCG, oocyte retrieval or ET.(Linden 2015)

3- It can be stopped at the day of positive b-HCG or at the time of the detection of fetal heart beat. (Aboulghar 2008)

Table 48.1 Relationship between the duration of P treatment before embryo transfer and the subsequent pregnancy rate.[12]

# days after P started	"Cycle day"	*n*	Implantation rate (%)	Pregnancy rate (%)
2	16	18	0	0
3	17	25	3.5	12
4	18	40	14.1	40
5	19	60	15.8	48
6	20	49	5.6	20

(Textbook of ART, 2nd Ed., 2004)

Fertil Steril. 2012 Jun

Early progesterone cessation after in vitro fertilization/intracytoplasmic sperm injection: a randomized, controlled trial.

Kohls G, Ruiz F, Martínez M, Hauzman E, de la Fuente G, Pellicer A, Garcia-Velasco JA. IVI Madrid, Madrid, Spain.

DESIGN:
Prospective, randomized, controlled trial.
PATIENT(S):
A total of 220 patients with intrauterine pregnancy demonstrated by transvaginal ultrasound after IVF/ICSI.
INTERVENTION(S):
Luteal phase support with micronized vaginal P was suspended at week 5 or at week 8.
RESULT(S):
Progesterone levels were similar on the day of the first pregnancy ultrasound exam (149 ± 108 vs. 167 ± 115 ng/mL). Significantly more bleeding episodes were observed in early suspension group (18.0 ± 2.6 vs. 7.2 ± 1.3 episodes). Miscarriage rate in singleton pregnancies were similar in both groups (5/80 vs. 6/79).
Conclusion:
After IVF/ICSI vaginal P4 support can be suspended safely at 5th week of pregnancy as the outcome is similar with 8th week suspension.

Luteal phase support in freeze-thaw cycles

- Fertil Steril. 2012 Dec;98(6):1464-9.
- Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer.
- Kaser DJ[1], Ginsburg ES, Missmer SA, Correia KF, Racowsky C.
- RESULT(S):
- IMP (n = 440) and Crinone (n = 298) recipients were similar for all demographic characteristics and cycle parameters assessed. Although implantation rates did not differ significantly between the two groups (Crinone vs. IMP: 19.6% vs. 30.4%), women supplemented with Crinone had significantly lower rates of clinical pregnancy (36.9% vs. 51.1%) and live birth (24.4% vs. 39.1%) compared with those on IMP.

Reprod Biomed Online. 2013 Feb;26(2):133-7.

Increasing vaginal progesterone gel supplementation after frozen-thawed embryo transfer significantly increases the delivery rate.

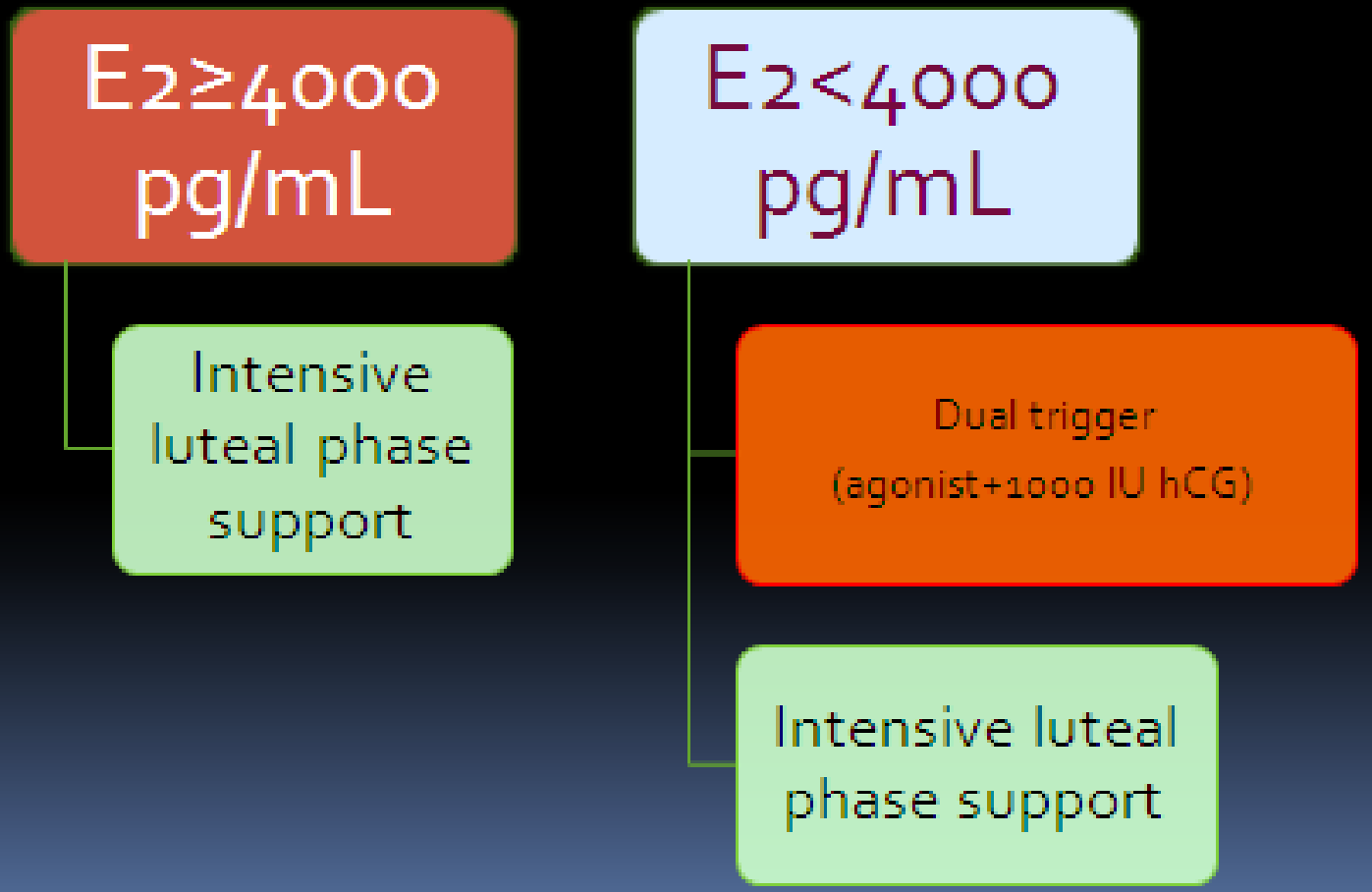
Alsbjerg B[1], Polyzos NP, Elbaek HO, Povlsen BB, Andersen CY, Humaidan P.

The vaginal progesterone dose was changed from 90 mg (Crinone) once a day to twice a day and the reproductive outcome during the two periods was compared. The pregnancy rate increased significantly after doubling of the progesterone dose (26.7% (90 mg) versus 38.4% (180 mg); P=0.021). Moreover, the early pregnancy loss rate decreased significantly (67.4% versus 43.7%, respectively; P=0.014), which significantly increased the delivery rate (8.7% versus 20.5%, respectively; P=0.002).

Luteal phase support in anolog trigger cycles

- HumanReproduction,Vol.28,No.9pp.2529–2536,2013
- Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-riskpatients after GnRHagonist triggering and modified luteal support: a retrospective multicentre study
- StamatinaIliodromiti, Christophe Blockeel, KeltonP.Tremellen, Richard Fleming, HermanTournaye, PeterHumaidan and Scott M.Nelson
- Multicenter retrospective case series with 275 high risk patients for OHSS. Only 2 cases of sOHSS with 41.8 % clinical pregnancy rate . In one hour time after OPU 1500 IU HCG was administered and luteal phase was supported by Crinone gel 8% 1x1 and 3x2 200 mg micronised vaginal P4 plus 4 mg oral E 2/day .

Maintaining optimal conception rates



Engmann L. et. al. Fertil Steril 2012

Intense luteal support

- **50 mg IM Progesterone (daily)**
- **0.3 mg transdermal E2 patch (every other day)**
- **Till 10 weeks of pregnancy**
- **Serum E2 ve P4 levels monitorization (day 3-7) and weekly**
- **P>20 ng/mL**
- **E2>200 pg/mL**
- **P max 75mg/day**
- **E2 max 0.4 mg patch and additional 4mg oral micronised**

- **%52.9 live birth rate with this approach**

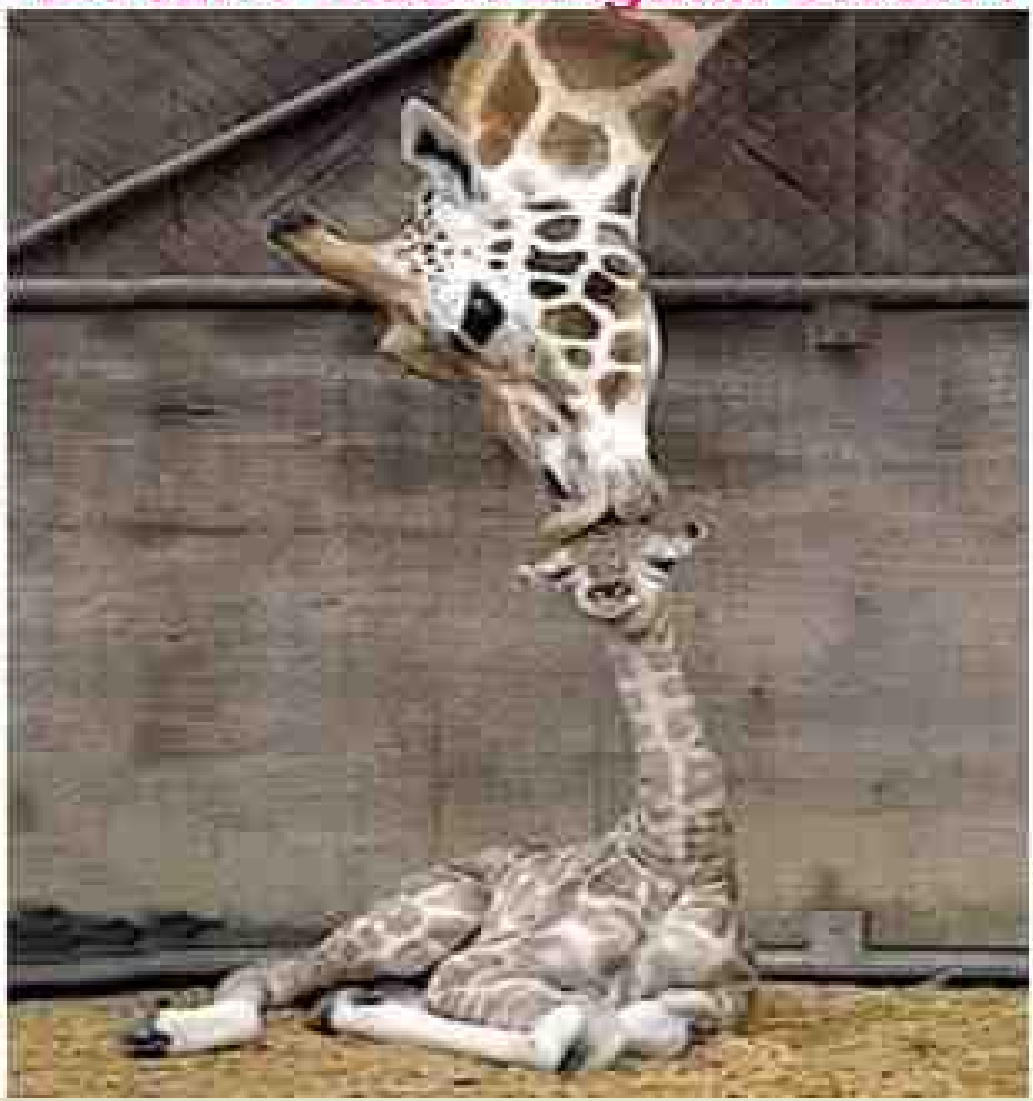
Vaginal P4 ring and subcutaneous P4

- Weekly vag P4 ring found to be similar with vag gel (Stadtmauer 2013)
- Multicenter phase III single blind prospective randomised trial n: 1297
- de Ziegler D 2013- Subcutaneous 25-50 mg dose finding study
- Similar endometrial histological effect
- Baker VL 2014- Multicenter randomised controlled trial Endometrin 100 mg 2x1 vag vs 25 mg Prolutex (s.c.) n; 800
- Pregnancy rates and side effects similar.

CONCLUSION

- In COH cycles there is defective luteal phase mainly due to the supression of hypophysial LH which is the result of supraphysiological steroid hormone levels secreted by multiple follicles.
- İ.M. and vaginal progesterone routes seem to be equivalent Synthetic oral progesterone (dihydrogesteron) and s.c. route can be alternatives.
- In freeze-thaw cycles the P4 dose can be increased.
- Adding E2 to P4 in luteal support seems to be not necessary but in patients with bleeding episodes and in recurrent failure, poor responder and anolog trigger (intense luteal support) cases especially the transdermal form can be used successfully.
- Progesteron plus GnRH a significantly increased the live birth rate (low quality evidence).
- Due to increased OHSS risk extreme caution should be taken in utilising the HCG in luteal support.

Bir tane olsun sağlıklı olsun !



One is better and healthier