Does Progesterone/oocyte ratio effect pregnancy?

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Introduction

- A subtle increase in serum P levels at the end of COH may be observed
- differs from the so-called “premature luteinization” induced by an uncontrolled LH surge
- Incidence; 5%-35% of cycles with GnRH agonists and 20%-38% of cycles with GnRH antagonists*

*Hugues J et al. Fertil Steril 2011;96:600–4.

Introduction

- The effect of serum P4 increase on cycle outcomes still controversial topic
- Negative effect, no effect, even positive effect
- Differences between agonist vs antagonist cycles?
- Differences between recFSH/HMG ?
- Differences between IVF populations? (poor-normo-high responders)

Introduction

- Several studies suggest that there is no association between progesterone levels and pregnancy rates*
- whereas others have shown that the pregnancy rate is inversely corelated to serum progesterone levels on the day of hCG administration**

*Edelstein et al., 1990; Silverberg et al.,1991; Check, 1994; Check et al., 1994; Givens et al., 1994; Bustillo et al., 1995; Levy et al., 1995; Ubaldi et al., 1995; Abuzeid and Sasy, 1996; Hofmann et al., 1996; Miller et al., 1996; Moffitt et al., 1997; Doldi et al., 1999; Urman et al., 1999; Martinez et al., 2004; Venetis et al

** Check et al., 1993; Fanchin et al., 1993; Harada et al., 1995; Shulman et al., 1996; Fanchin et al., 1997a; Bosch et al., 2003

Possible impact of PPR on egg/embryo quality

- Donor cycles: shown no detrimental effect
- FET cycles: shown no detrimental effect
- No detrimental effect of progesterone elevation on oocyte quality, fertilization rates and embryo quality

Hofmann et al., 1993; Legro et al., 1993;Check et al., 1994; Fanchin et al., 1996; Shulman et al., 1996; Moffitt et al., 1997; Bosch et al.,2003, Martinez et al., 2004, Venetis et al.2013

The effect of PPR on endometrium

- Likely to influence endometrial maturation
- May lead to asynchrony between the endometrium and the developing embryo (Achache and Revel, 2006, Kolibianakis 2004)
- advanced endometrial histological maturation (Saadat et al., 2004)
- differential endometrial gene expression (Labarta et al., 2011; Li et al.,2011, Van Vaerenbergh et al., 2011) has been shown which might be related to implantation failure

Pathogenesis?

- Premature LH peak despite GnRH supression*
- Increase of total granulosa cell activity by FSH stimulation
- Multiple follicular growth (excess number of follicles and granulosa cells)
- Prolongation of follicular phase (prolongation of stimulation, high dose FSH)

*Hofmann et al.1993, Ubaldi et al.1995, Albano et al.2000

Pathogenesis?

- Increased LH sensitivity with poor ovarian responce (De Ziegler et al.2003)
- Increased LH sensitivity of granulosa cells due to high exposure of FSH
- Adrenal gland? is the major source?(Judd et al.1992, De Geyter et al.2002)

Possible factors related with P rise

- the total FSH dose
- the duration of treatment,
- Peak E2 levels
- the number of follicles or oocytes are significantly correlated with serum P increase in both GnRH agonist and antagonist regimens Hugues ,Venesis 2007

Exits;

- Cryopreserving embryos and transfer in a subsequent frozen-thawed cycle*
- Administer hCG at an earlier time in the follicular phase**
- Blastocyst transfer ***

*Silverberg et al.1991, Legro et al. 1993, Silverberg et al, 1994
**Harada et al, 1996
***Papanikolaou et al.2009

Cut-off values

- lack of consensus on the threshold values (differed from 0,8 to 3 ng/ml)
- huge variability among assays used for P determination

Study	protocol	definition	incidense
Silverberg et al.,1991	GnRHa	>0.9 ng/ml	12,4%
Martinez et al., 2004	GnRHa	>0.9 ng/ml	52.3%
Edelstein et al.,1990, Fanchin et al.,1993, Givens et al.,1994, Ubaldi et al.,1995	GnRHa	>0.8-2 ng/ml	5-35%
Younis et al. 2001, Ou et al.,2007	GnRHa	P/E2>1	41%
Ubaldi et al., 1996	antagonist	>1.1 ng/ml	20%
Bosch et al.,2003	antagonist	>1.2 ng/ml	38.3%
Sims et al., 1994	Flare up	>1.0 ng/ml	85%

Objective;

- The value of P levels on HCG day is still debated. Different cut-off levels of progesterone were determined. Controversies continue about the effects of progesterone elevation on pregnancy rates

- Our purpose was to determine effect of peak progesterone levels per oocytes on ART outcomes.

Material and Methods;

- Design:Retrospective cohort analysis
- Single Center-Ege University IVF Center
- A total of 424 ICSI/fresh ET cycles which have been performed during January-September 2013 were analyzed

Material and Methods;

- Progesterone, E2,LH consentrations were measured on the day of hCG administration in all cycles
- The main outcome measure was clinical pregnancy rate
- No exclusion criteria was performed

Material and Methods;

- Hormone levels were determined at a single laboratory
- Immunofluorometric assay was used (Access Immunoassay Systems-Beckman Coulter UniCel DxI System)
- Detection limits for P analysis were 0,1-40 ng/ml

Parameters

- Age
- Basal hormone levels
- Total dosage of gonadotropins
- Progesterone, E2,LH levels on the day of hCG
- Total oocyte
- MII oocyte
- Number of transferred embryos
- Progesterone/oocyte ratio
- Clinical pregnancy and live birth rates

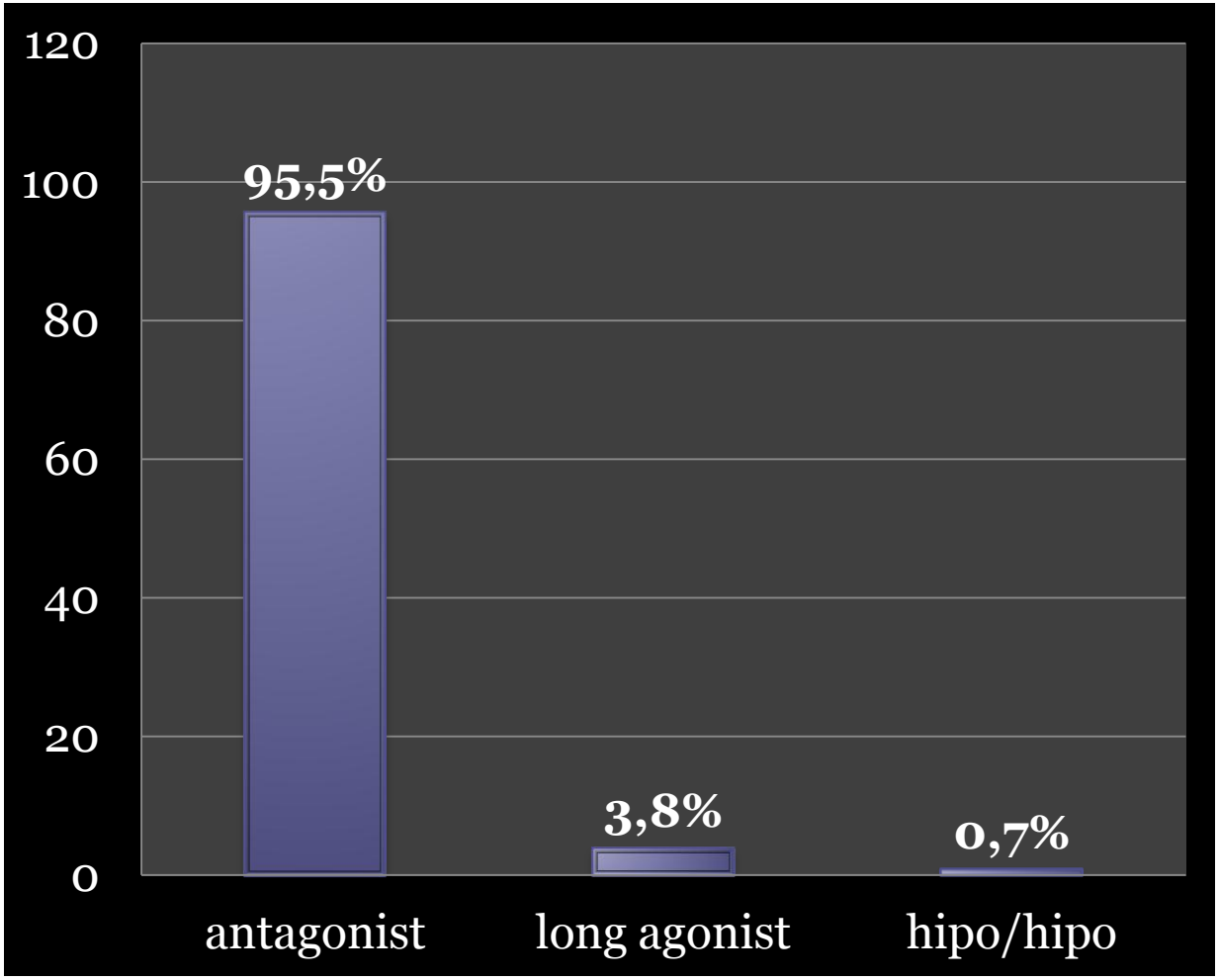
Material and Methods;

- Statistical analysis was performed with SPSS version 16.0.
- Data were presented as mean±SD
- ROC analysis was performed for the cut-off value for progesterone/oocyte
- Student t test, qi-suare test, multiple logistic regression and pearson correlation analysis were used. $P<0.05$ considered significant

Table I: Patient and cycle characteristics

	Mean	Range
Age	33,2 ±5,6 years	19-49
Basal FSH	9,9 ±5,1 iu/ml	1-42
Daily dose of FSH	253±63 IU	75-450
Total dose of FSH	1860 ±619 IU	625-5400
E2 on HCG day	1451±1129pg/ml	64-4836
P4 on HCG day	1,28 ±1 ng/ml	0,1-10
P4/oocyte	262±382 pg/ml	20-4200
E2/oocyte	183±103 pg/ml	16-840
No of oocytes	8,8 ±6,6	1-40
No of MII oocytes	5,9±4,8	0-25
No of transferred embryos	1,3±0,4	1-2
Day of et	2,6±0,6	2-5

Results


120
100
80
60
40
20
0
95,5%
3,8%
0,7%
antagonist
long agonist
hipo/hipo

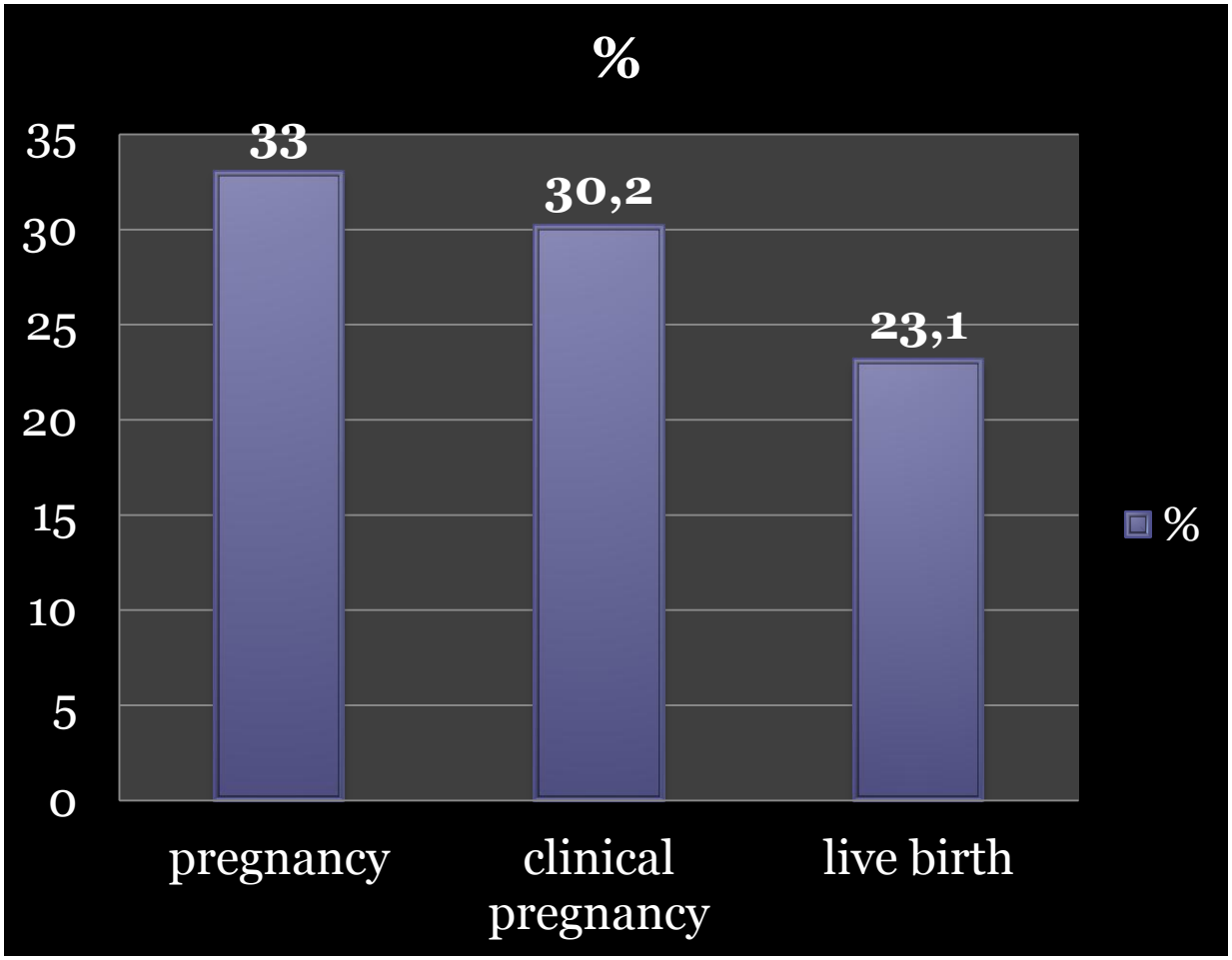
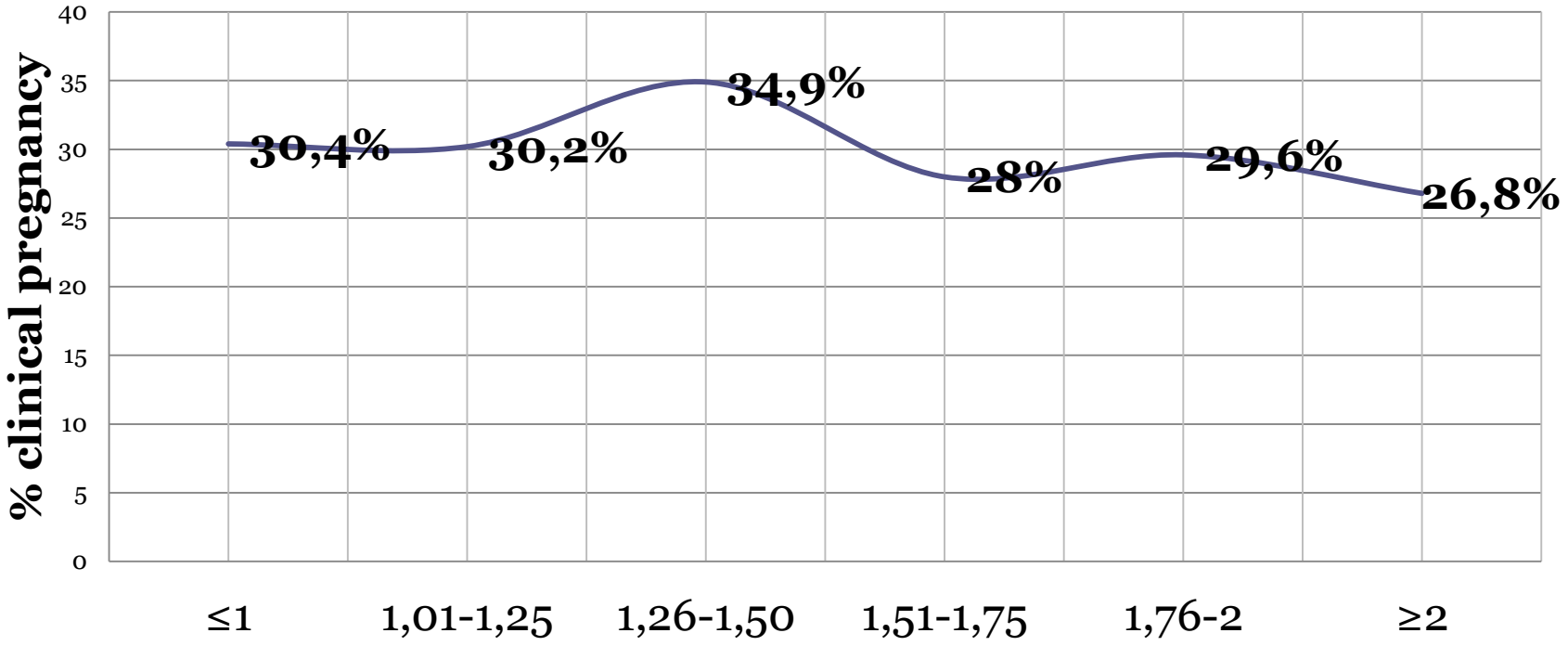

%
35
30
25
20
15
10
5
0
33
30,2
23,1
pregnancy
clinical pregnancy
live birth
%

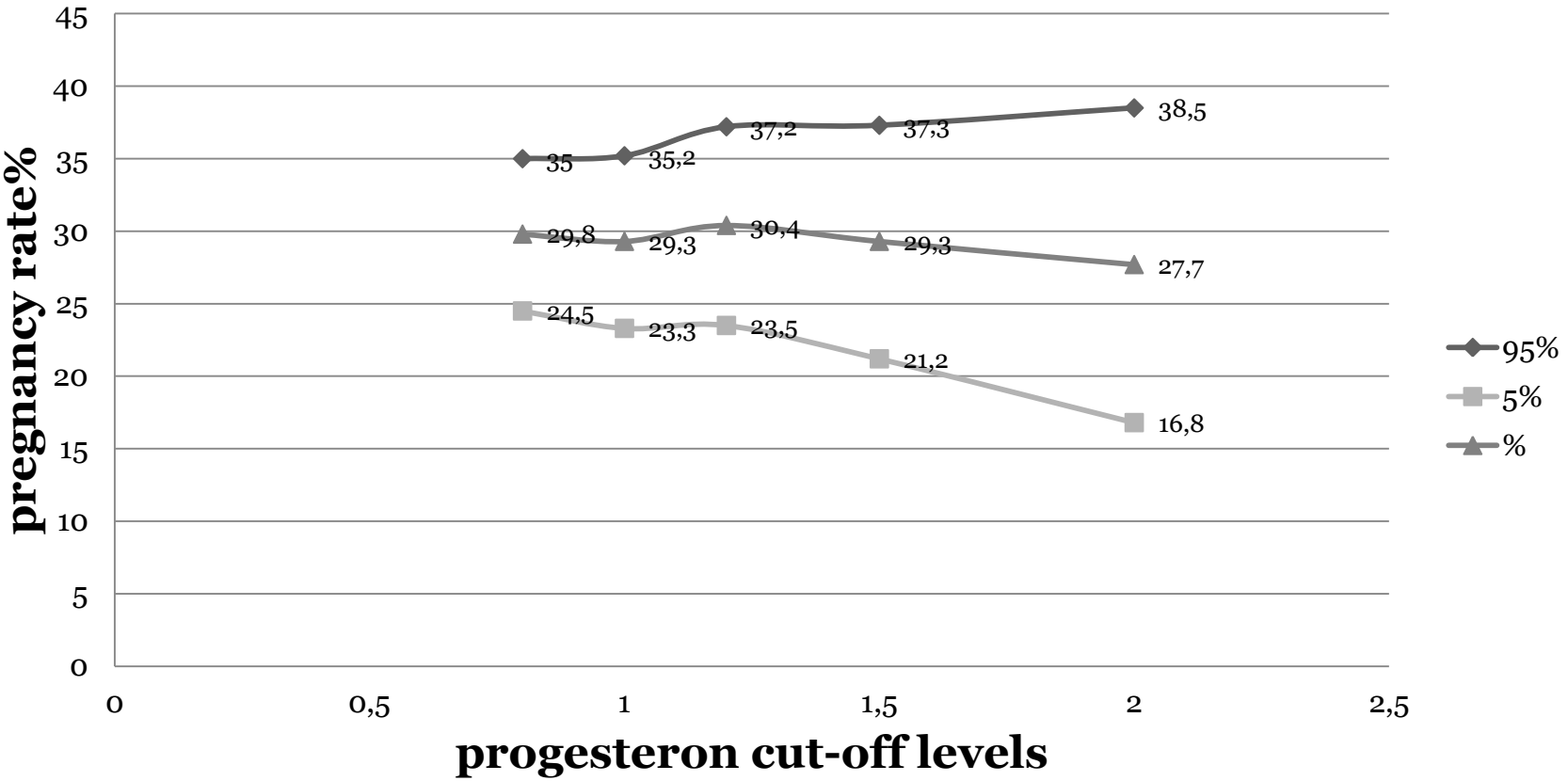
Table II:Stimulation characteristics of cycles with and without pregnancy

	Clinical pregnancy- (n=296)	Clinical pregnancy+ (n=128)	p
Age	33,7±5,7	31,9±5	0,002
Basal FSH	10,1±5,3	9,2±4,5	NS
Total dose of FSH	1889±655	1792±527	NS
Stimulation day of hCG	8,8±1,8	9±2	NS
E2 on HCG day	1412±1156	1541±1061	NS
P4 on HCG day	1,29±1	1,27±1,1	NS
LH on HCG day	4,2±4,1	3,7±3,5	NS
Peak P4/oocyte	289±420	199±266	0,02
Peak P4/E2	1,9±4,8	1,3±1,6	NS
No of oocytes	8,3±6,8	9,8±5,9	0,04
No of MII oocytes	5,7±4,9	6,6±4,4	NS
Day of embryo transfer	2,6±0,6	2,7±0,6	NS
No of transferred embryos	1,3±0,4	1,4±0,5	0,04

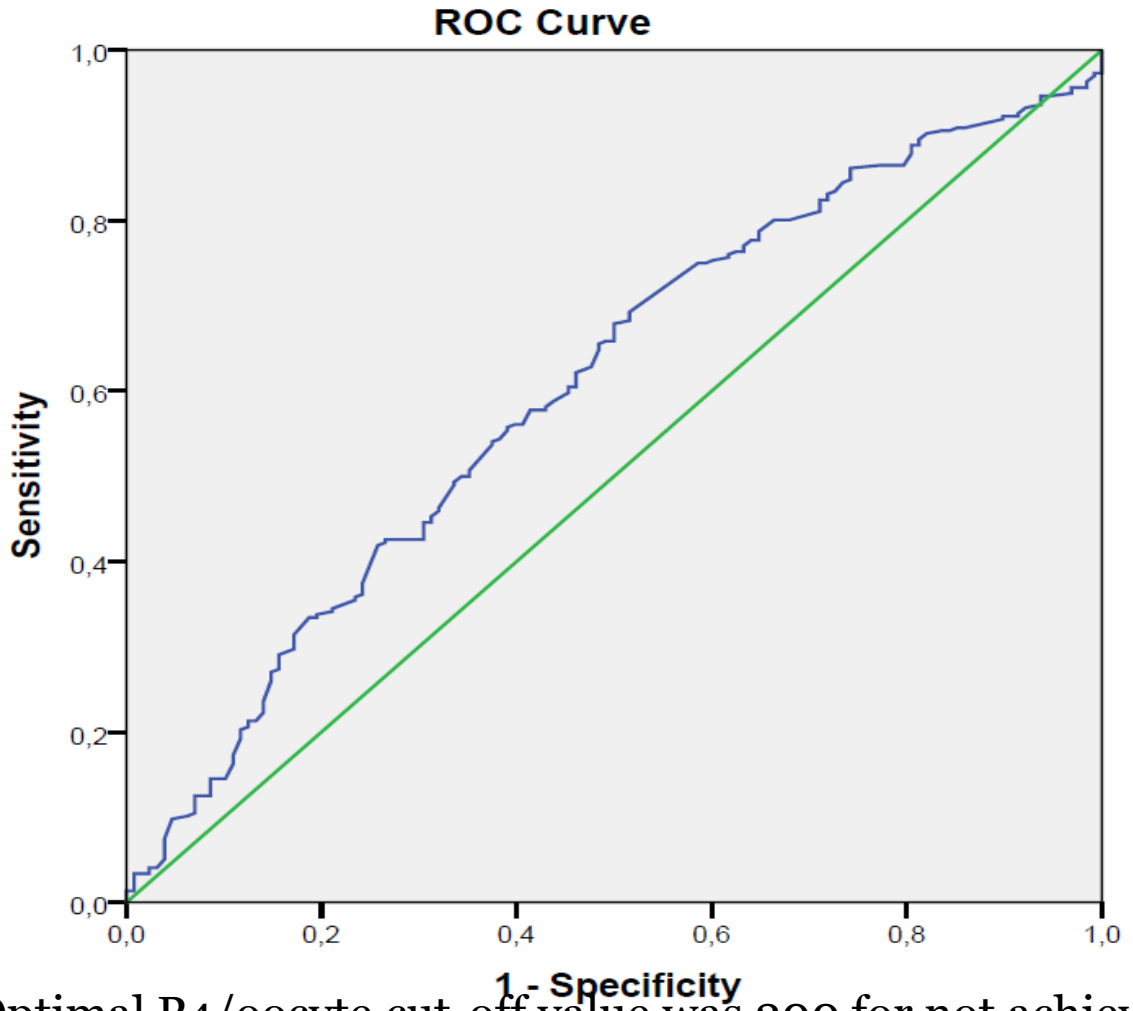
Pregnancy rates for different peak P4 values



n=230	43	43	25	27	56
% 54,2	10,1	10,1	5,9	6,4	13,2


45
40
35
30
25
20
15
10
5
0
pregnancy rate%
0
0,5
1
1,5
2
2,5
progesteron cut-off levels
35
35,2
37,2
37,3
38,5
29,8
29,3
30,4
29,3
27,7
24,5
23,3
23,5
21,2
16,8
95%
5%
%

ROC analysis



Optimal P4/oocyte cut-off value was 200 for not achieving pregnancy which had a sensitivity of 38% and specifity of 78%, PPV:78%, NPV:34.4%

Area Under The Curve was 0,604

Progesterone level/oocyte=200 cut-off value

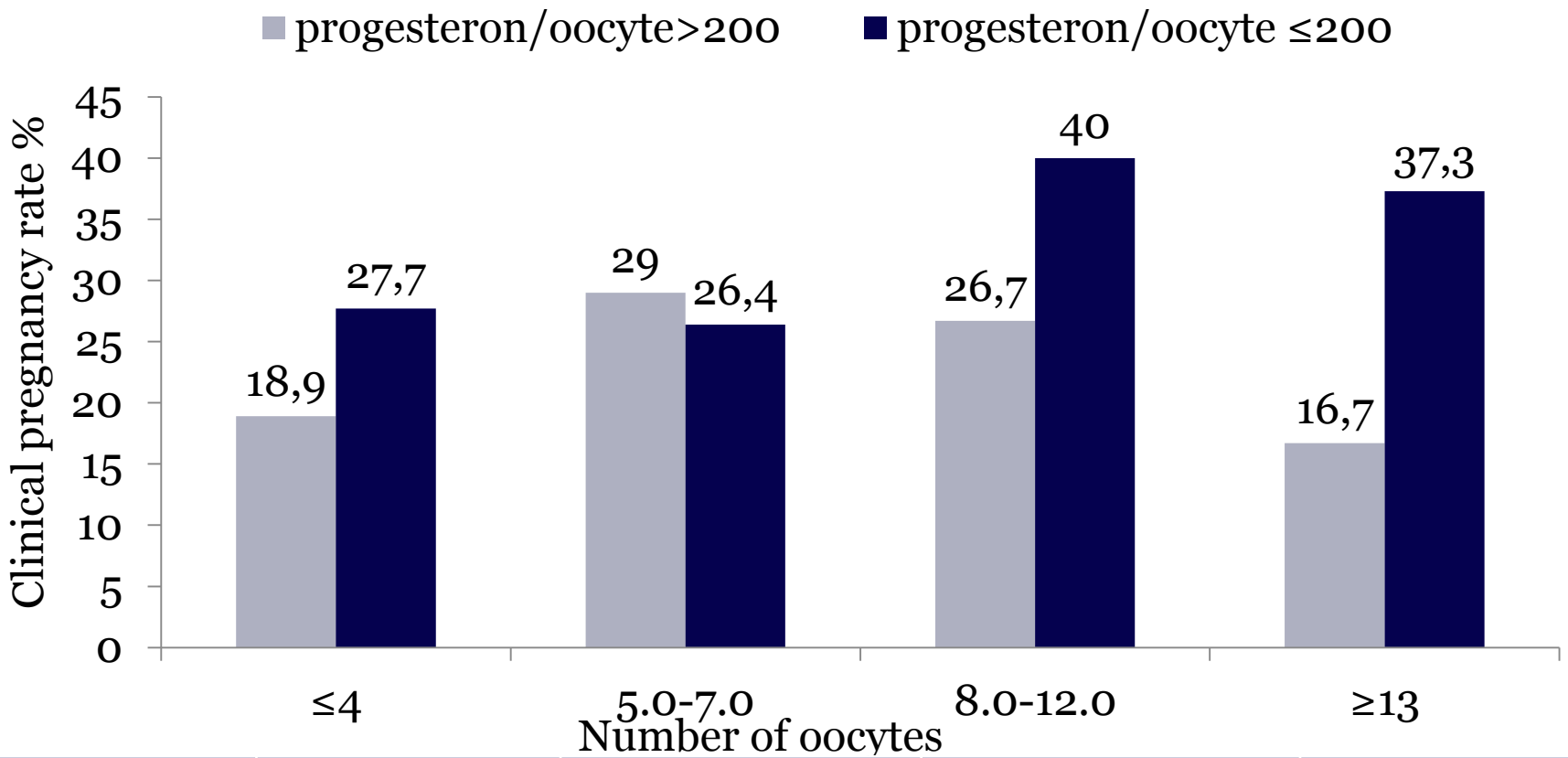
Progesterone/oocyte	Clinical pregnancy rate no	(%)	
≤200	97/282	34.4%	**p=0.008**
>200	31/142	21.8%	

Progesterone/oocyte	Live birth rate no	(%)	
≤200	76/282	27 %	**p=0.008**
>200	22/142	15.5%	

Analysis of correlations with peak P4, Peak P4/ oocyte and Peak E2/oocyte

	Age	Basal FSH	Total dosage	No of Oocytes
Peak P4	NS	r=-.123 p<0.05	NS	*r*=.253 p<.0001
Peak E2	*r*=-.343 p<.0001	*r*=-.393 p<.0001	*r*=-.233 p<.0001	*r*=.782 P<.0001
Peak P4/oocyte	*r*=.224 p<.0001	*r*=.270 p<.0001	*r*=.146 p<.0001	*r*=-.404 P<.0001
Peak E2/oocyte	NS	NS	*r*=.143 p<.0001	r=-.254 P<.0001
Peak LH	r=.154 p<.005	r=.262 p<.0001	NS	r=-.154 p<.005

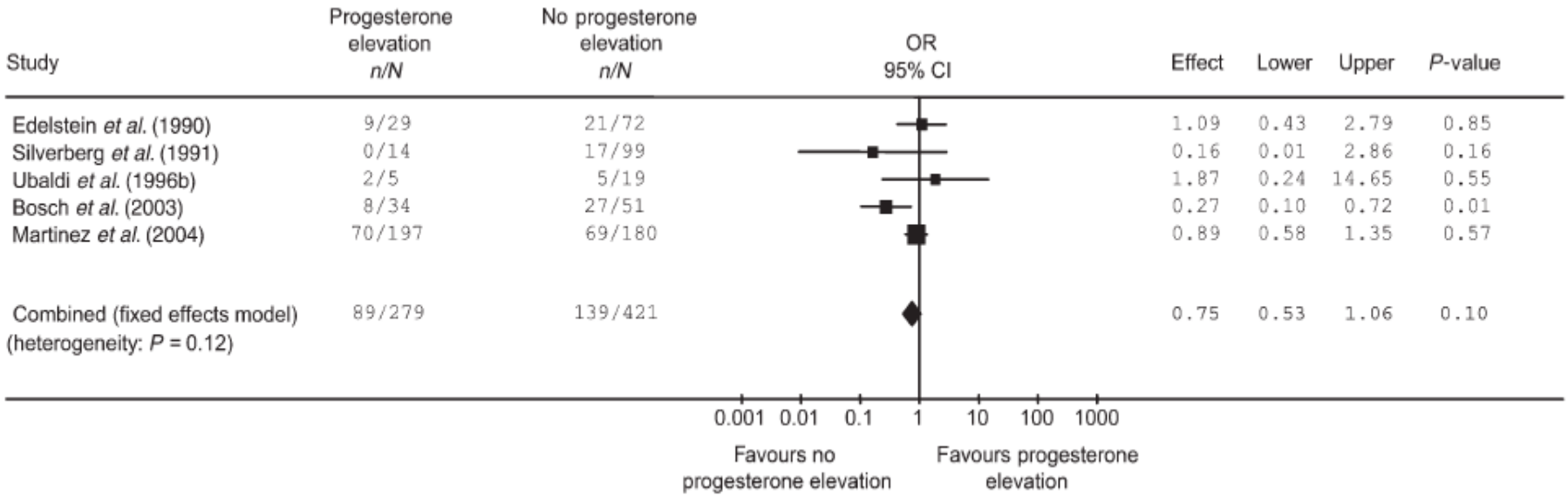
Clinical pregnancy rates by number of oocytes and P/oocyte value



Total 424	n=137	n=84	n=95	n=108
Pregnancy n, %	30 (21,8%)	23 (27.4%)	36 (38%)	39 (36%)
NN	610	…	340	130
P/oocyte>200	90 (65,6%)	31 (37%)	15 (15,8%)	6 (5.5%)

Discussion and conclusion

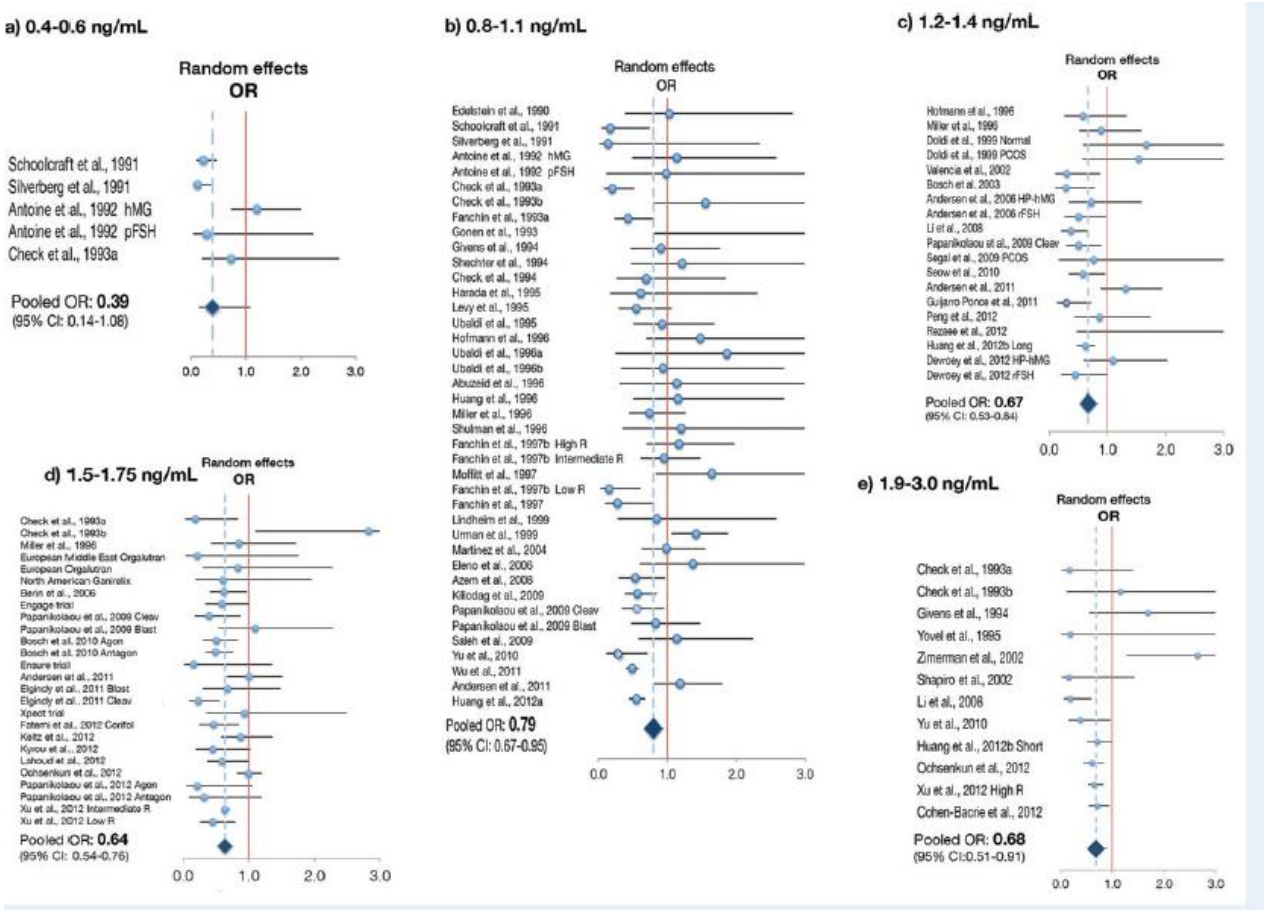
- Venetis et al. (2007) meta-analysis; 12 studies (10 were retrospective). 5 study provided data on clinical pregnancy; no statistically significant association OR:0.75, 95%CI (0,53-1,06 p=0,1)



Discussion and conclusion

- Venetis et al.(2013) meta-analysis; 68 studies, more than 60 000 cycles (55 199 fresh, 7229 frozen, 1330 donor cycles)
- In fresh cycles decreased probability of pregnancy in women with PE (when using a thresold ≥0.8 ng/ml)
- No adverse effect present in frozen and donor cycles

Discussion and conclusion
Venetis et al. meta-analaysis 2013



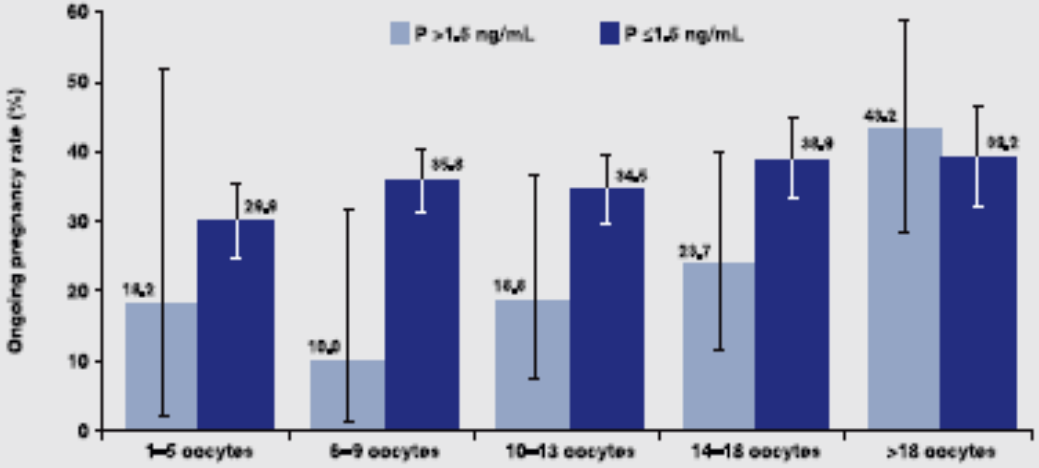
- GnRH antagonist protocol assosiated with a decreased PE when compared with agonist protocol
- No significant effect of PE rates considering the type of gonadotrophins
- E2 levels and number of COCs retrieved were significantly increased in PE group
- In high responders, the effect of PE on pregnancy is exhibited when reached 1.9-3 ng/ml levels

Progesterone elevation does not compromise pregnancy rates in high responders: a pooled analysis of in vitro fertilization patients treated with recombinant follicle-stimulating hormone/gonadotropin-releasing hormone antagonist in six trials

Georg Griesinger, M.D.,[a] Bernadette Mannaerts, Ph.D.,[b] Claus Yding Andersen, D.M.Sc.,[c] Han Witjes, Ph.D.,[b] Efstratios M. Kolibianakis, M.D.,[d] and Keith Gordon, Ph.D.[e]

[a] Department of Reproductive Medicine and Gynecologic Endocrinology, University Clinic of Schleswig-Holstein, Luebeck, Germany; [b] MSD, Oss, the Netherlands; [c] Laboratory of Reproductive Biology, University Hospital of Copenhagen, Copenhagen, Denmark; [d] Unit for Human Reproduction, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece; and [e] Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey

In contrast with low and normal responders the chance of ongoing pregnancy
İs not compromised in high responders, in whom elevated Poccurs most frequently



Ongoing pregnancy rate per embryo transfer and associated 95% confidence interval by number of oocytes retrieved and serum P level on the day of hCG.

Griesinger. Elevated P and ongoing pregnancy. Fertil Steril 2013.

Discussion and conclusion

- Marked variation in the incidence of PPR: explanation is not clear;
  Discrepancies in population characteristics and/or treatment protocols?
- Different cut-off values: Mostly arbitrarly
- Lack of well designed prospective studies

Discussion and conclusion

- Increased number of COC's with higher mean E2 levels in cycles with PPR were shown in previous meta-analyses and number of studies
- P/oocyte ratio might be get some clues
- Each clinic should establish its own ranges and defined cut-off values for specific populations
- Further research is warranted
- Our study on this topic continues

Venetis et al.,2007, Kolibiniakis et al.2012, Venetis et al.2013,