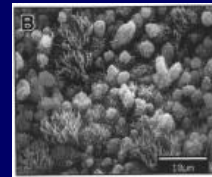


# Support of the Luteal phase: What is the evidence?

Zeev Shoham, M.D.

*IVF Unit, Kaplan Medical Center Rehovot, Israel*

Cross communication



Optimizing the endometrium for implantation

The normal luteal phase.

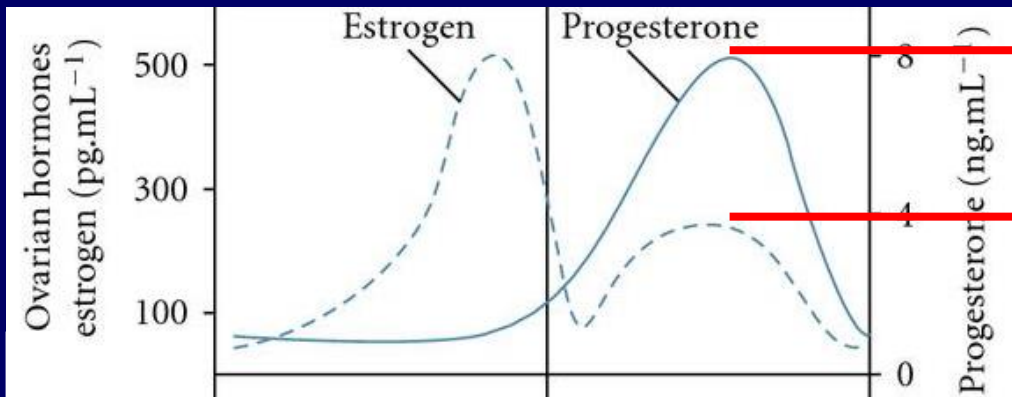
Luteal phase in ART cycles: Do we need luteal phase support?

What can we add to the current protocol? (GnRH agonist)

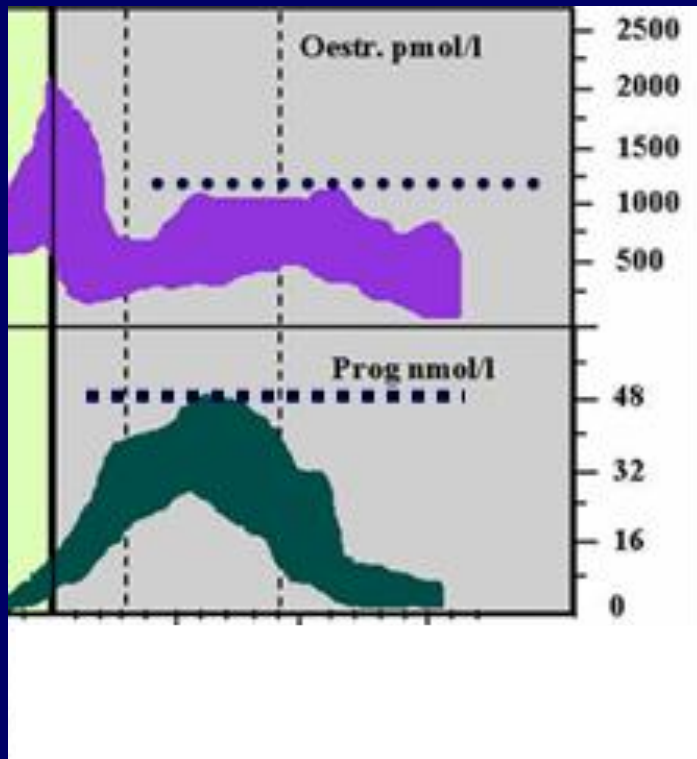
When to start when to stop? (World survey)

# The Normal Luteal Phase

# The normal luteal phase



Serum level - 20 ↑



E production: 0.6 mg/day

Daily production is (40-fold)

P production: 25 mg/d

# Do we need luteal phase support in ART ?

Nosarka S, Kruger T, Siebert I, et al. Luteal phase support in in vitro fertilization: **Metaanalysis** of randomized trials. *Gynecol Obstet Invest.* 2005;60:67–74.

van der Linden M, Buckingham K, Farquhar C, et al. Luteal phase support for assisted reproduction cycles. **Cochrane Database** of Syst Rev. 2011

Van der Linden M, Buckingham K, Farquhar C, et al. Luteal phase support for assisted reproduction cycles. **Cochrane Database** Syst Rev. 2015

Luteal support promotes the successful outcome of the  
IVF procedure.

# What do we need for implantation

**Progesterone**



**Estrogen**



Sufficient to produce the conditions needed for  
pregnancy

# Success of donor egg programs

Lutjen et al. Nature 307:174, 1984

Feichtinger and Kemeter, Lancet 2:722, 1985

Navot et al. N Eng J Med 314:806, 1986

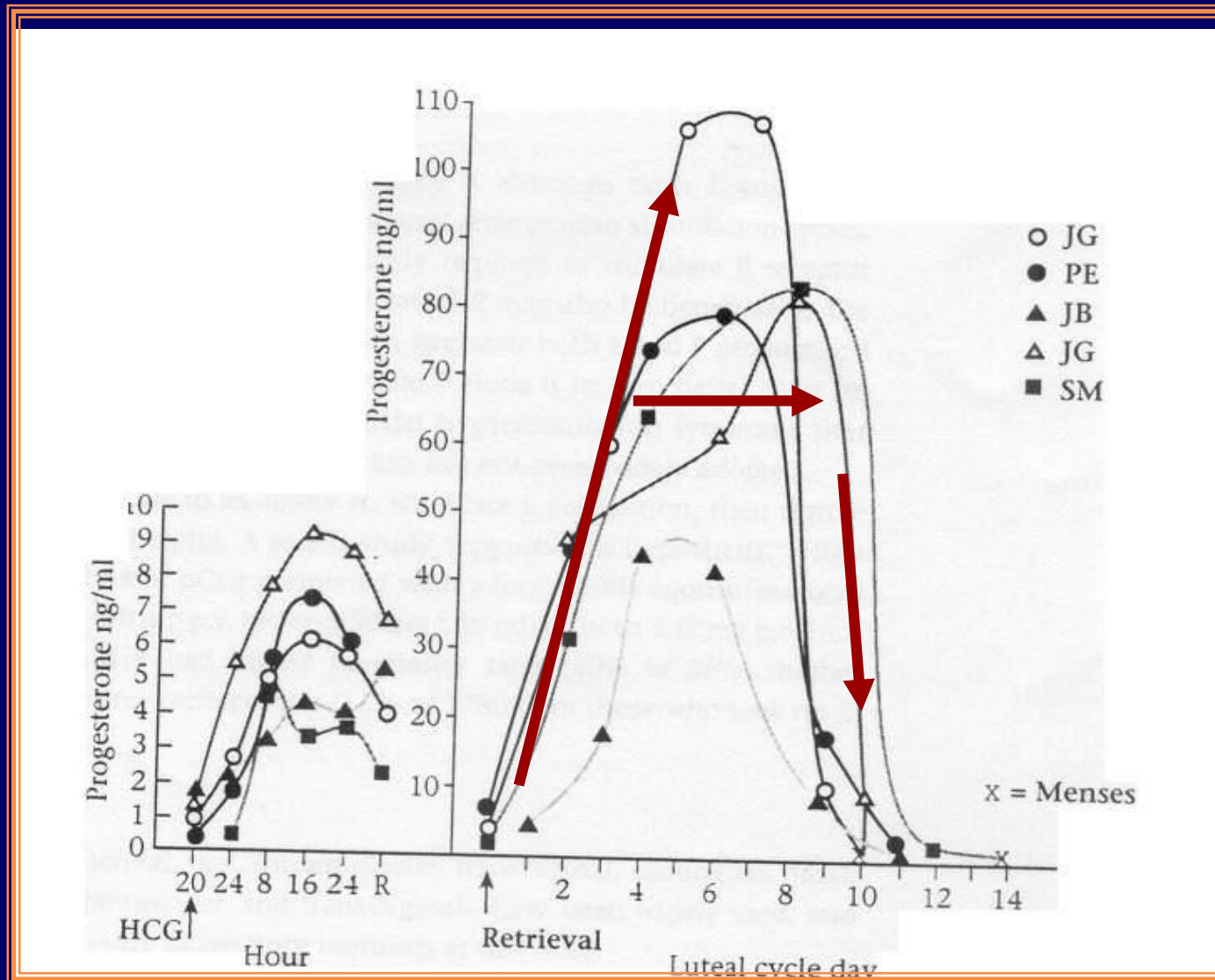
# The Luteal Phase in ART Cycles

Is it defective?

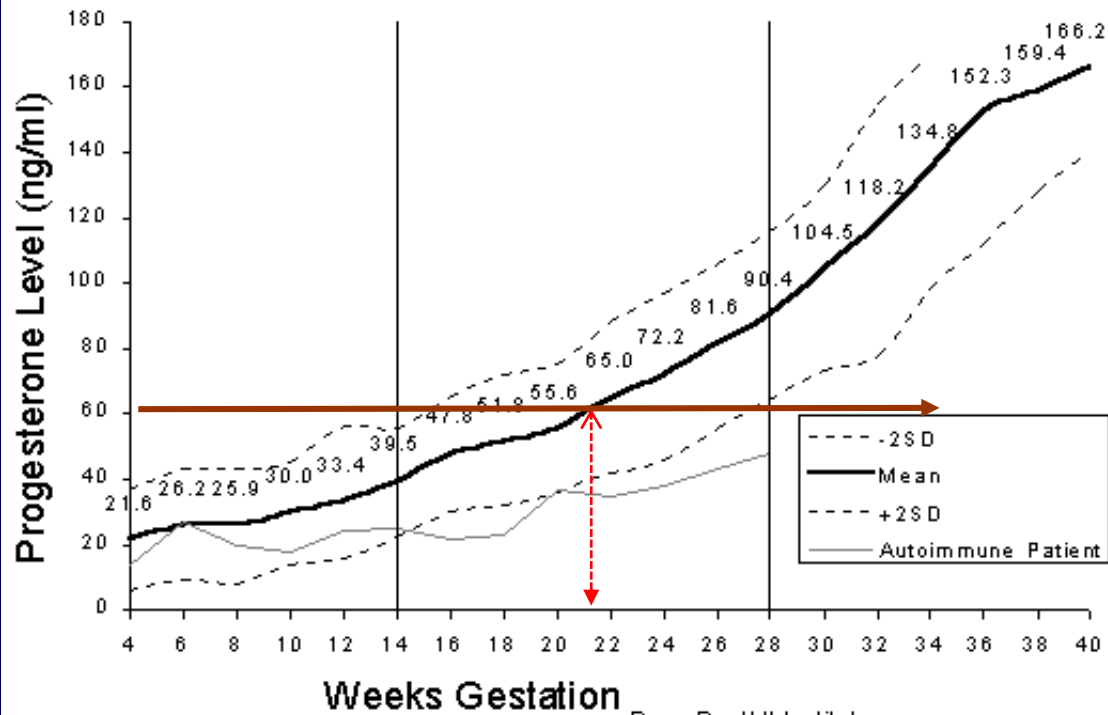
Yes



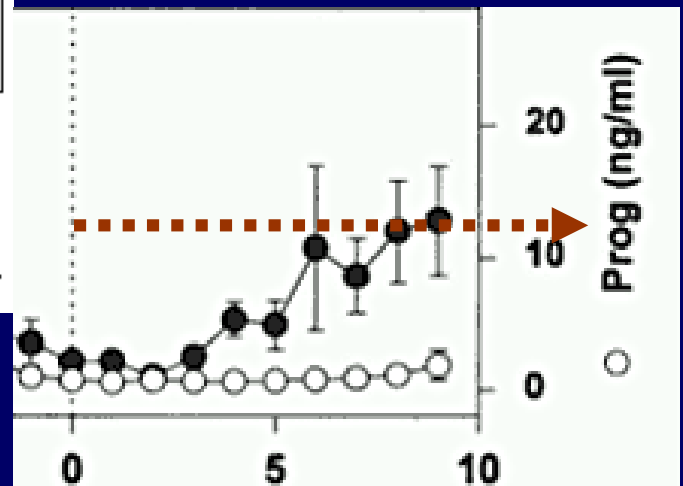
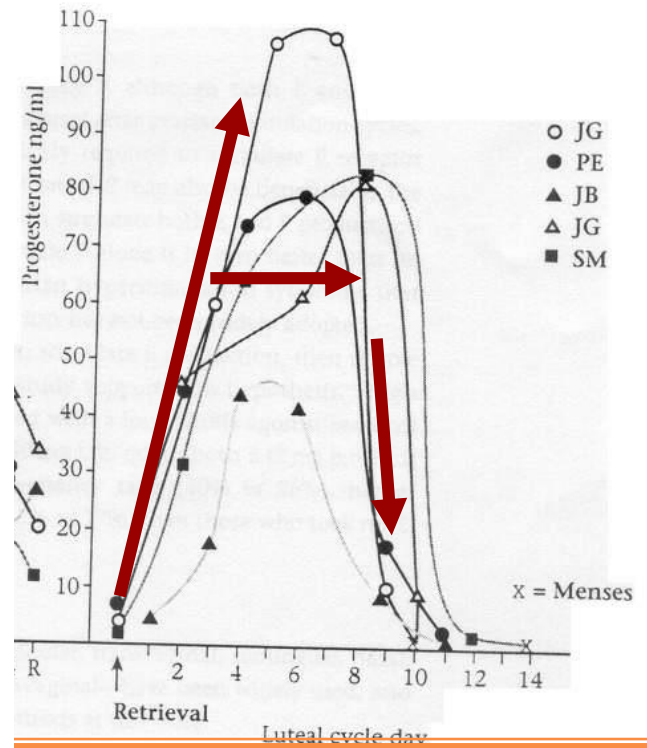
# The luteal phase in ART cycles:



## Progesterone Levels in Pregnancy



Pope Paul VI Institute  
National Reproductive Hormone Laboratory



# The special problem of programmed cycles

- **Stroma more advanced than glands  
(dyssynchrony)**



Stroma development



↑ P concentration

Glandular development



Duration of exposure



Steroid production

Endometrial development

Defective

(Drugs, Protocols)

*Sterzik et al, Fertil Steril 1988;50;457-62*

GnRH protocols → LH ↓

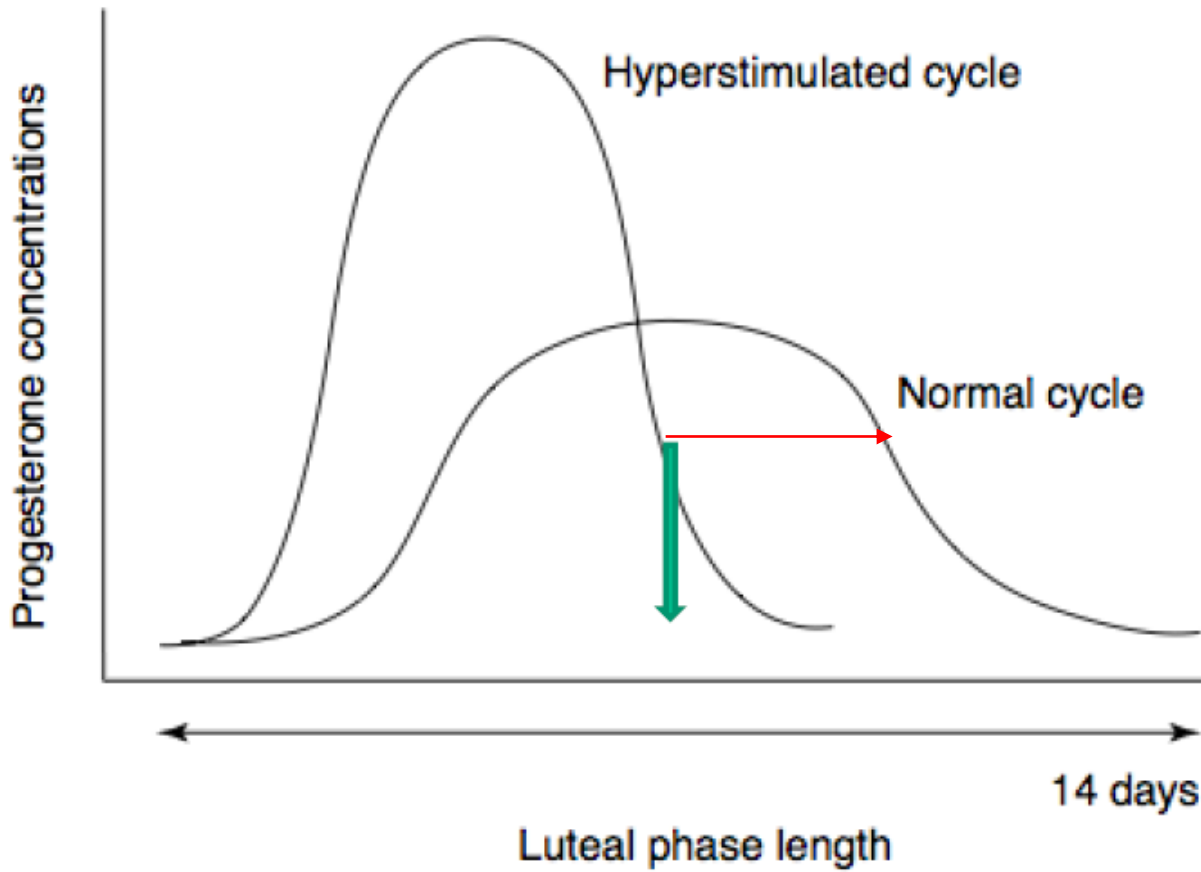
Aspiration of  
granulosa cells



Insufficient  
Corpus luteum

Luteal phase defect

50% delayed endometrium development > 2 days



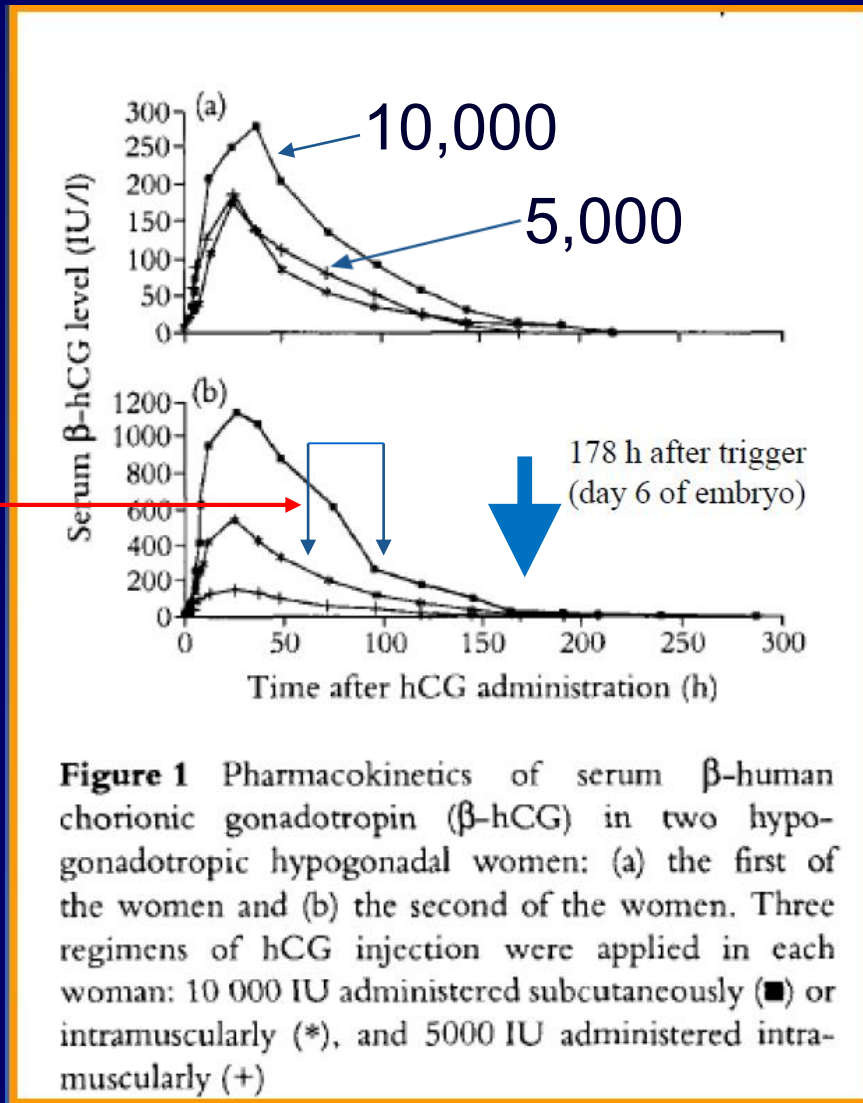
*TRENDS in Endocrinology & Metabolism*

# Timing of Luteal Support in ART Cycles

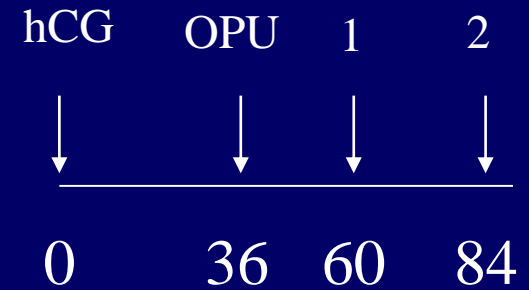
- At the time of hCG admin.
- At the time OPU
- One day post OPU
- At the time of ET
- 6 days post OPU



# Pharmacokinetics of hCG administration



Time to start P support



Sohn et al. Fertil Steril 1999

Williams et al. Fertil Steril 2001

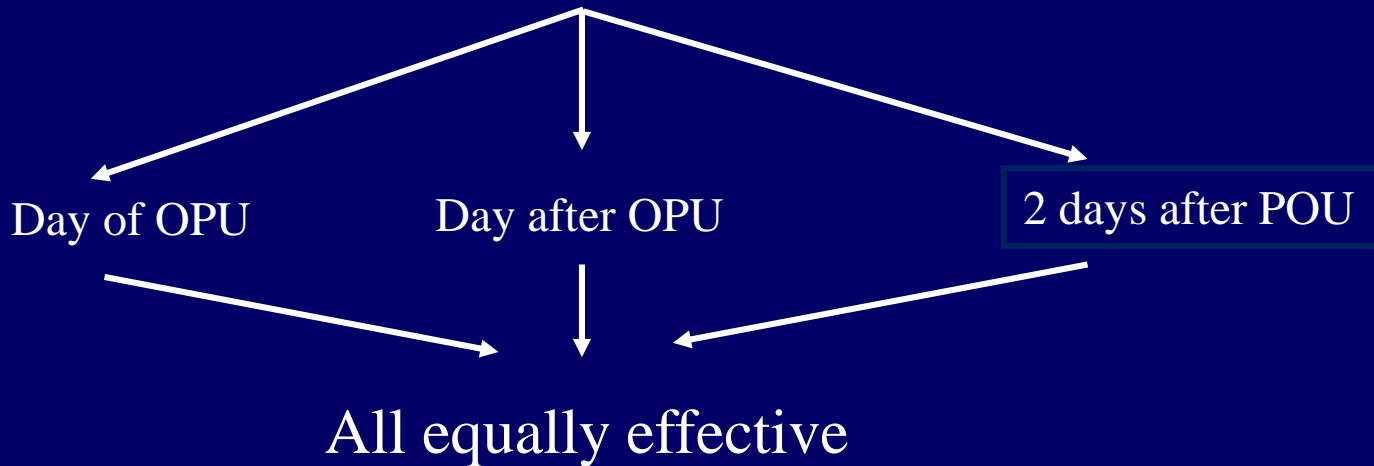
Baruffi et al J. Assit Rep Genetics 2003

Mochtar et al. Hum Reprod 2006

Feichtinger et al. J Reprod Endocrinol 2011  
( Pros Rand study om 1111 IVF cycles)

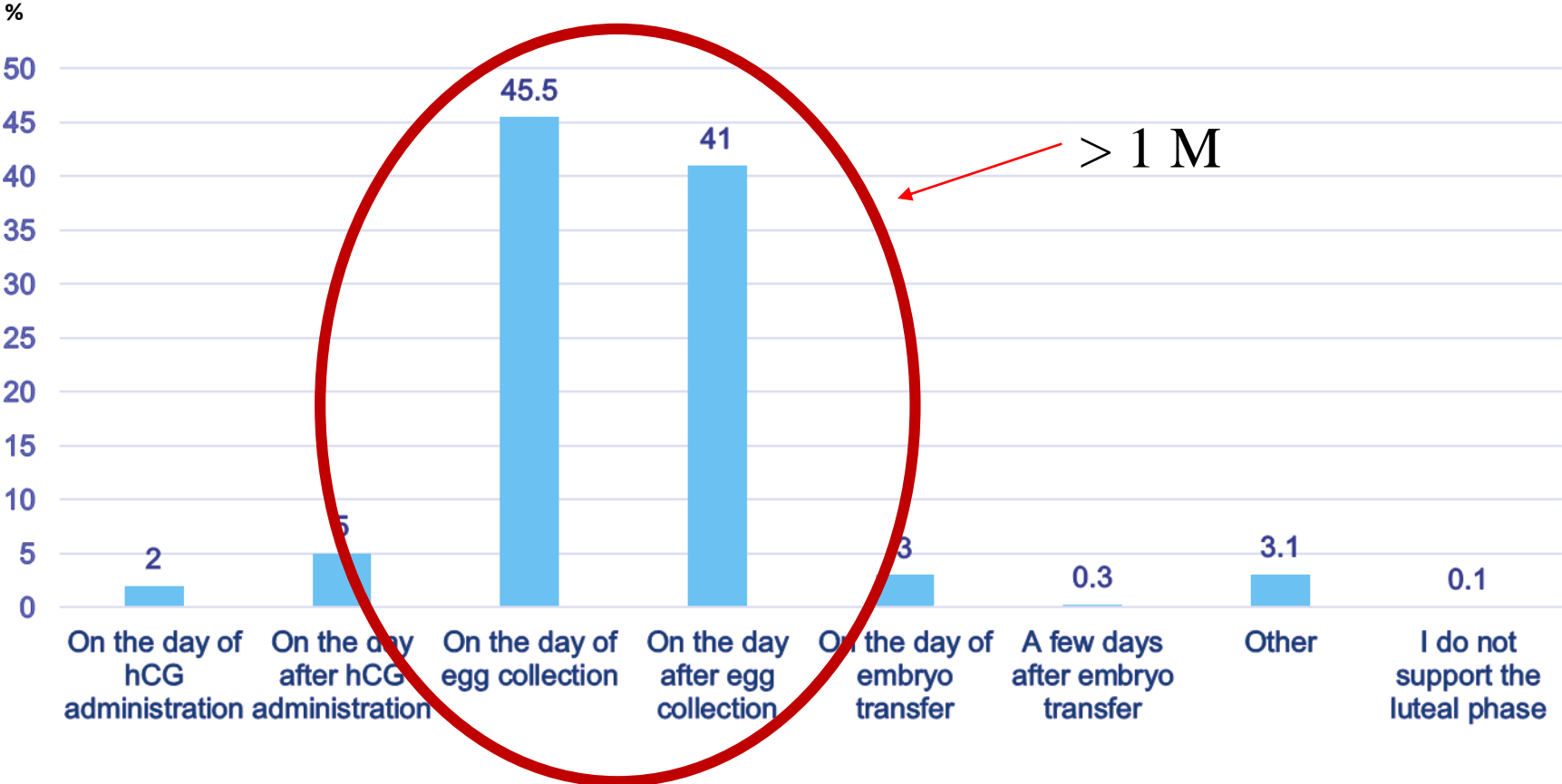


## When to start the LPS?



Initiating LPS on the day of or day after oocyte retrieval,  
has now become a routine practice in ART

# If you support the luteal phase, when do you start the regimen you use?



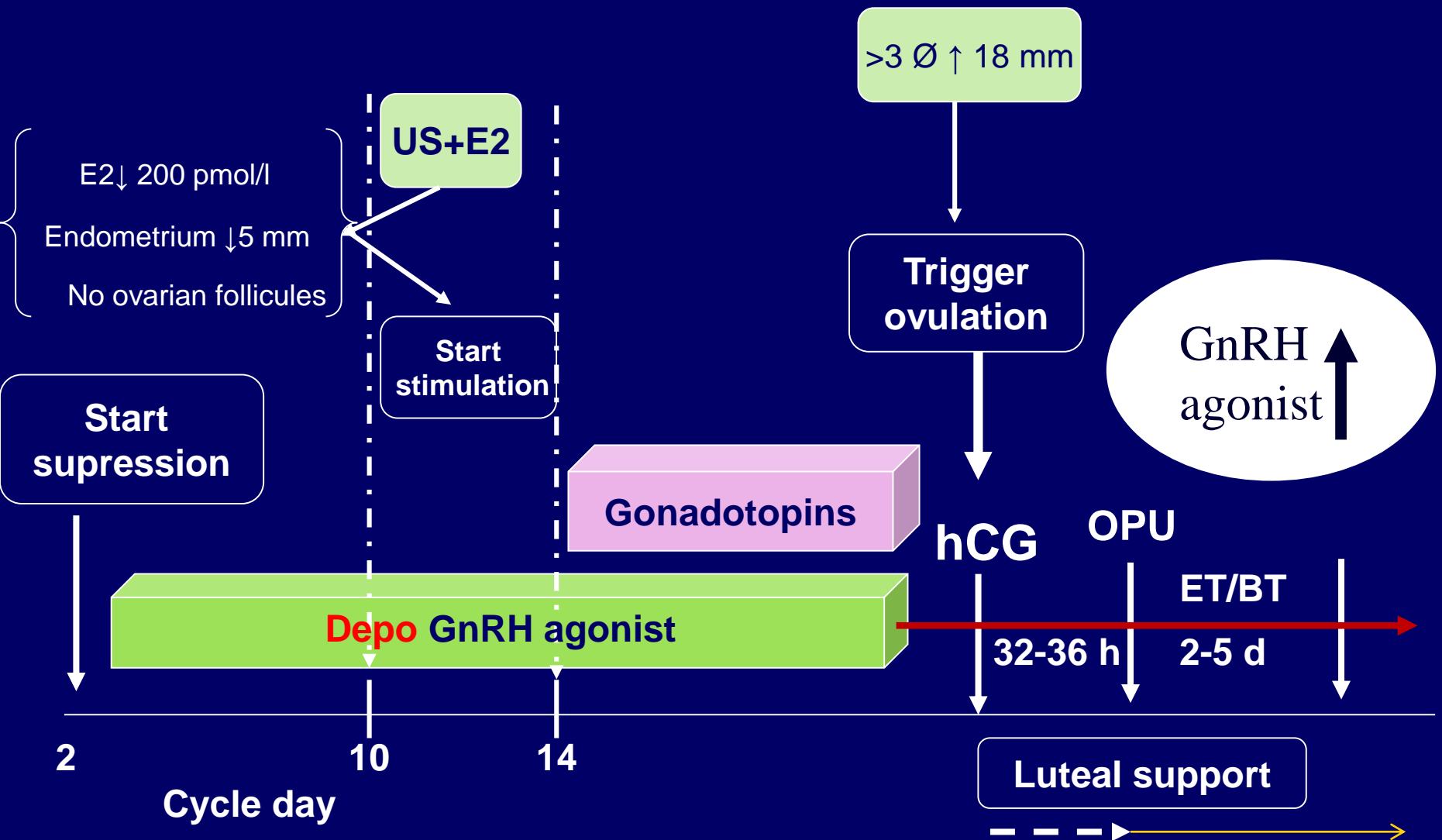
# Elements of luteal support

Estrogen

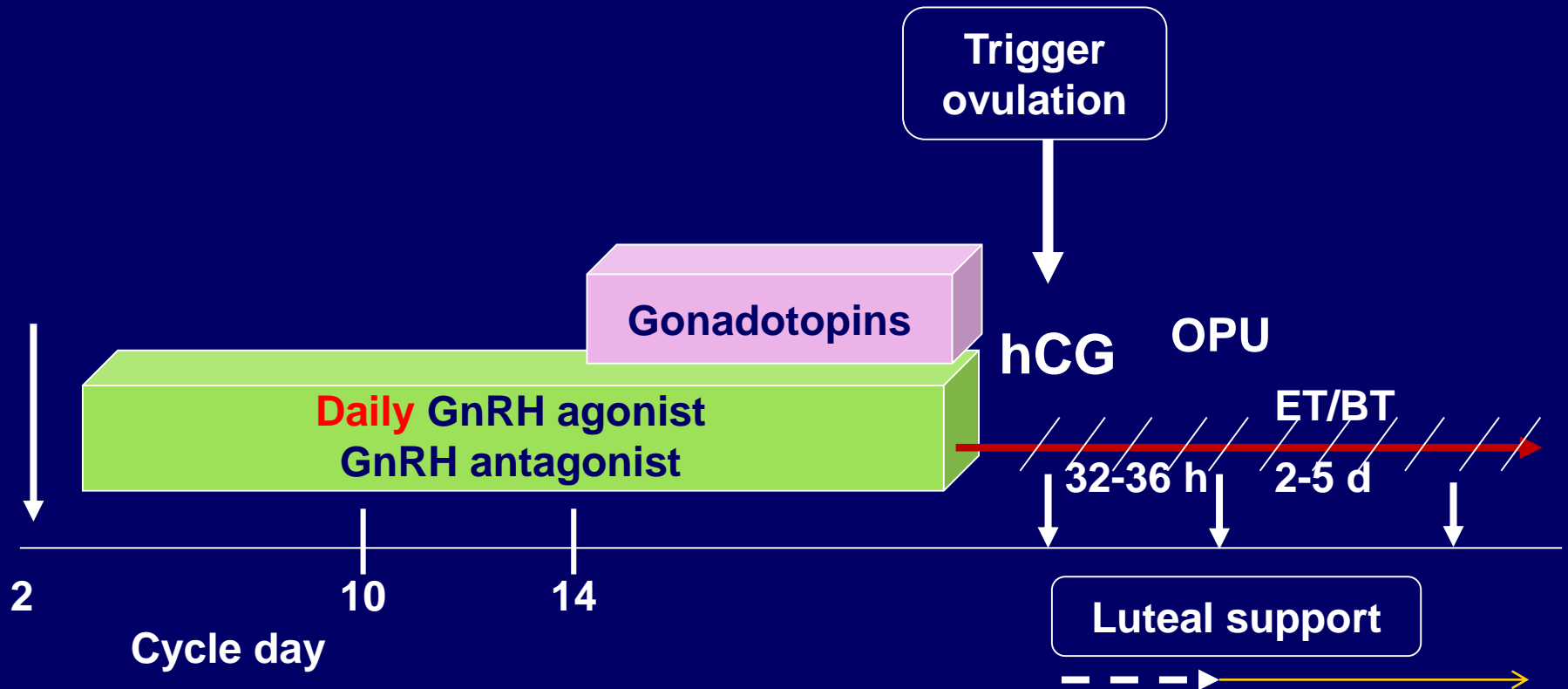
Progesterone

GnRH agonist

# GnRH agonist long protocol (Follicular phase)

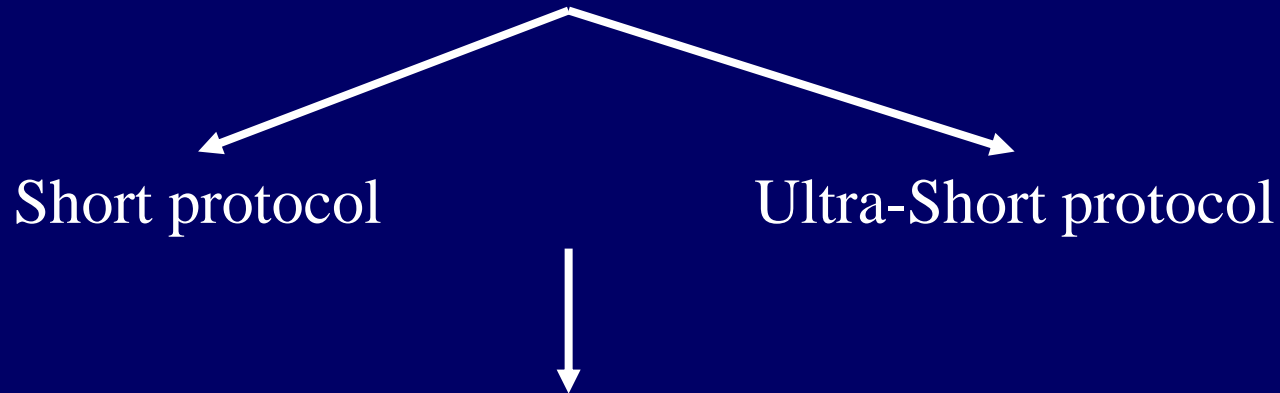


# GnRH agonist long protocol (Follicular phase)



## Common knowledge

The high pregnancy rate of the GnRH-a long protocol compare with:



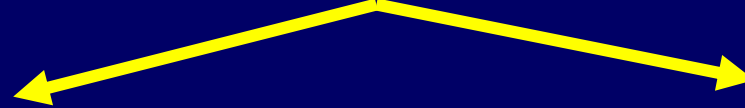
Synchronization of follicles development

High level of GnRH agonist at the time of implantation and embryo development

Cultured Murine embryos



GnRH receptor



Placenta secretes decapeptide

Present in the developing embryos.

Cultured Murine embryos



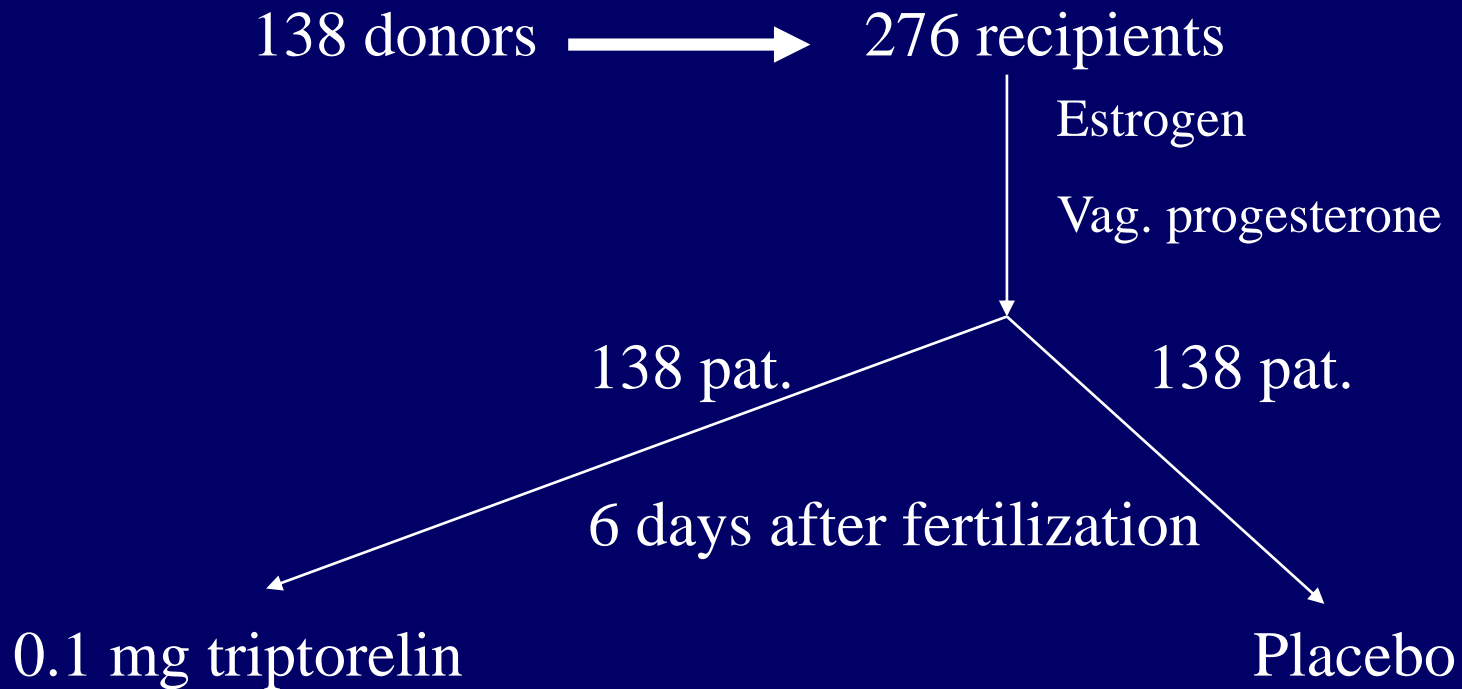
Blastocyst

GnRH-agonist

GnRH-antagonist

GnRH agonist - Enhanced embryonic development.

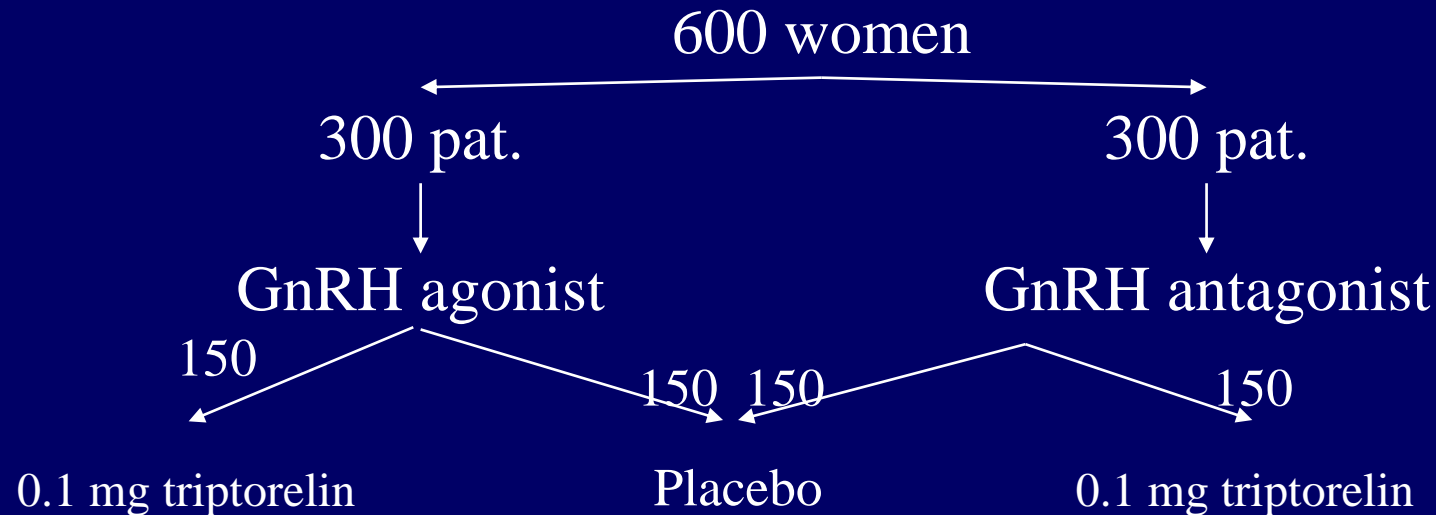
# Oocyte donation program



Group	E.T.	Gestational sacs	Implantation rate	p
GnRH -a	331	122	36.9	<.05
Control	335	84	25.1	



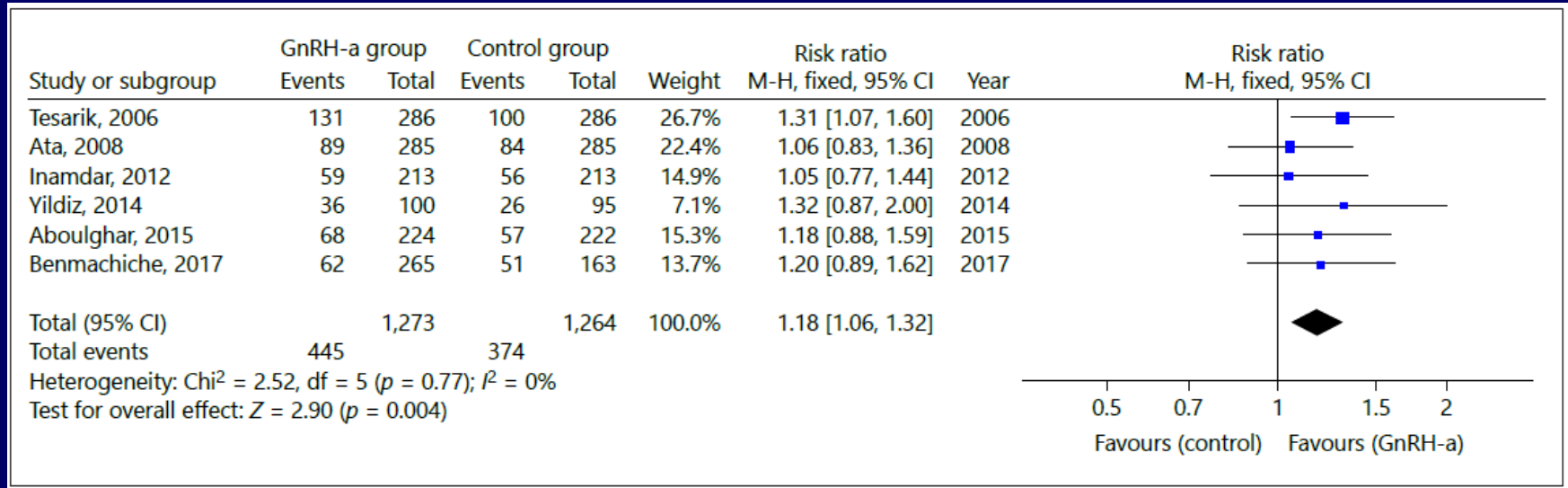
# IVF program - prospective randomized study



Group	Clinical PR	Group	Clinical PR
GnRH - agonist	29.8%	GnRH - Antagonist	27.1%
Placebo	18.2%	Placebo	17.4%
p	<0.05		<0.05

# Effect of Gonadotrophin-Releasing Hormone Agonist Addition for Luteal Support on Pregnancy Outcome in vitro Fertilization/Intracytoplasmic Sperm Injection Cycles: A Meta-Analysis Based on Randomized Controlled Trials

Xiaoling Ma et al. Gynecology and Obstetrics Investigation 2019



## Ongoing pregnancy rate based on 6 studies

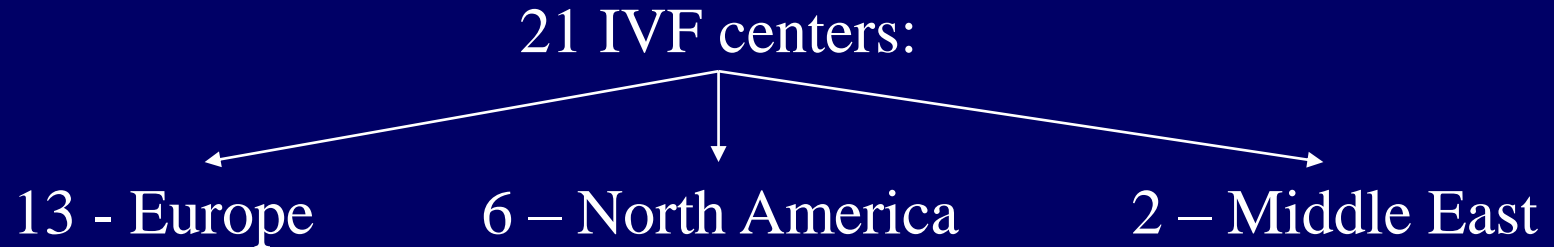
The ongoing pregnancy rate of GnRH-a group was significantly better than that of control group (RR 1.18; 95% CI 1.06–1.32;  $p = 0.004$ ),

How long do you continue progesterone supplementation if the patient conceives?



- At the time of pregnancy test
- At the time of 1<sup>st</sup> US (6W)
- At 8 W
- At 10-12 W

# For How long?



**Day of hCG – 8 centers**

FHR - 4 centers

FHR + 2 weeks (7-9 w) – 6 centers

10-11 weeks of gestation - 2 centers

As instructed – 1 center

The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a **meta-analysis**  
Liu1 et al. Reproductive Biology and Endocrinology 2012

The currently available evidence suggests that progesterone supplementation beyond the first positive hCG test after IVF/ICSI might generally be unnecessary.

# Ongoing pregnancy rate

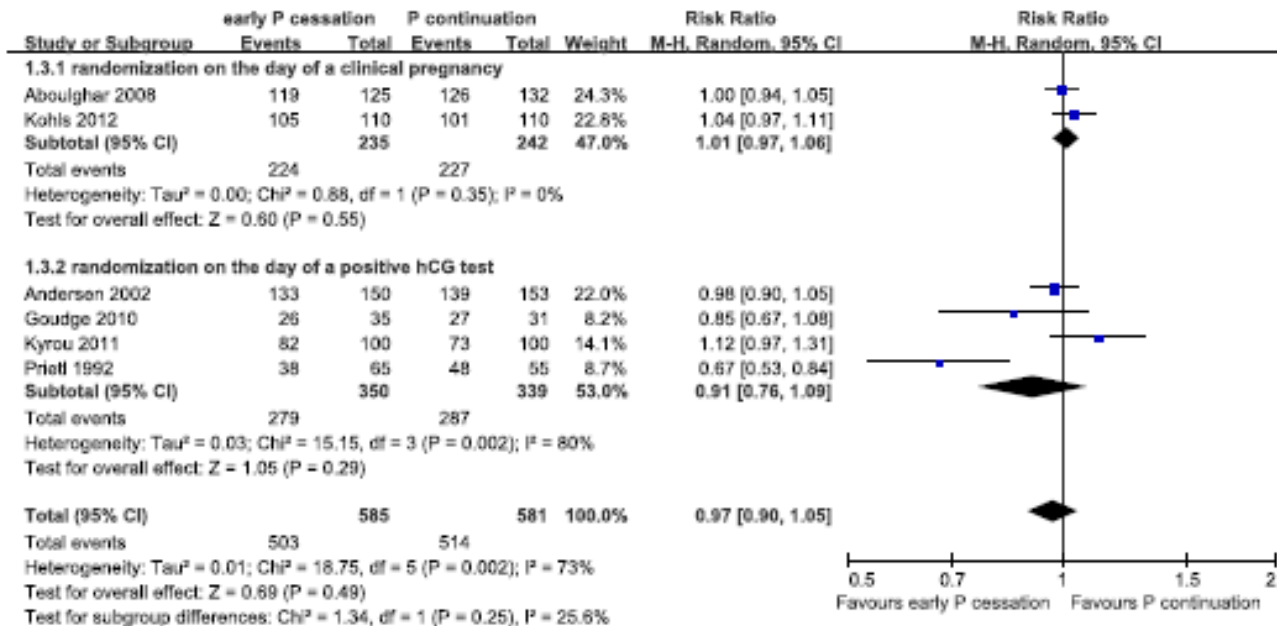


Figure 6 Ongoing pregnancy rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

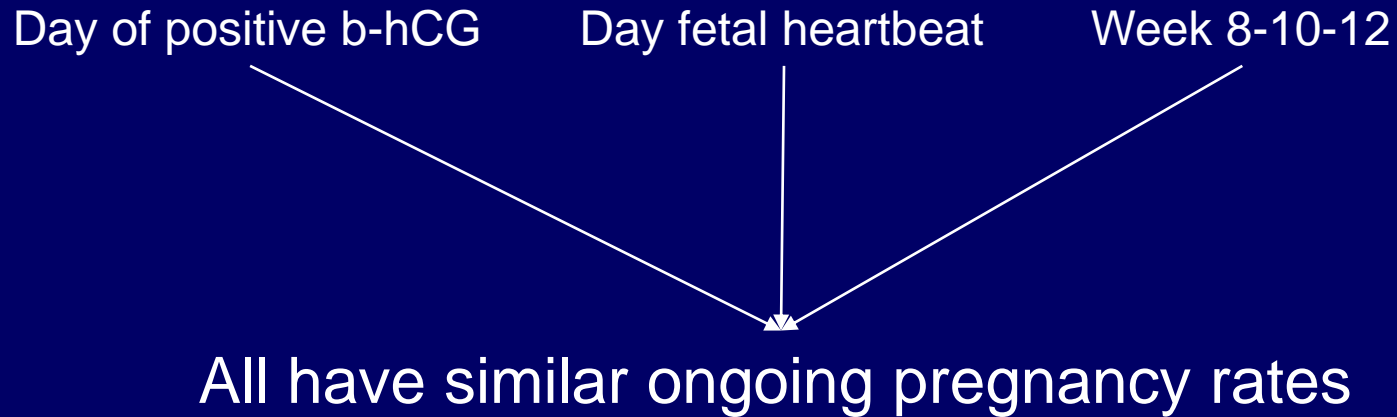
There was no statistically significant difference between the early P cessation and P continuation groups.

# Live birth rate



Figure 4 Live birth rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

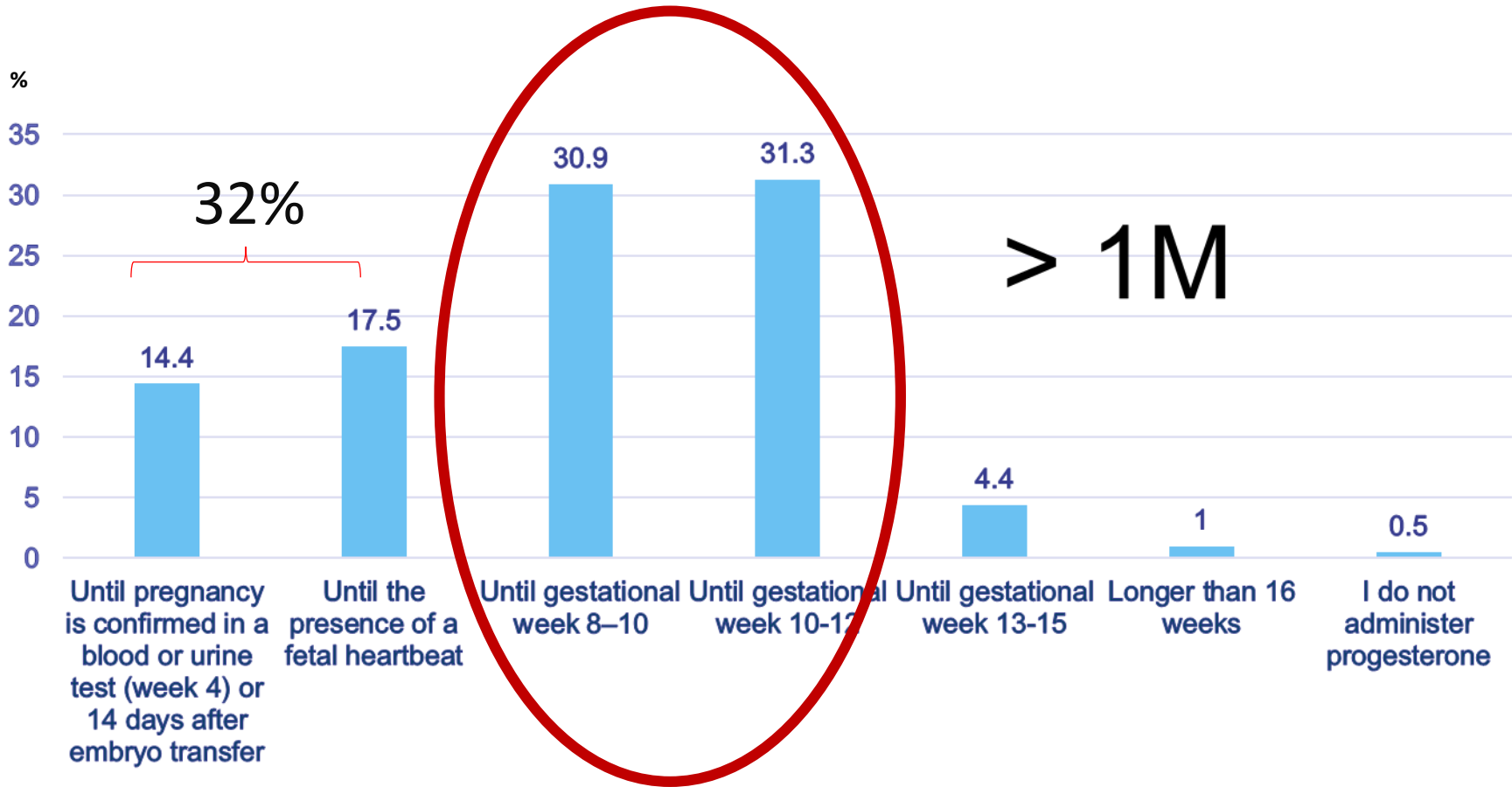
# When to stop LPS?



This should encourage treatment teams to discontinue LPS  
on the day of positive  $\beta$ -hCG



# How long do you continue progesterone supplementation if the patient conceives?



# Fetal Safety of Dydrogesterone Exposure in the First Trimester of Pregnancy

Koren<sup>1</sup> et al. Clinical Drug Investigation 2019

Follow up fetal outcome after gestational exposure to dydrogesterone (Duphaston)

- 2.5 million patient database.
- Congenital malformations among babies exposed in utero during the first trimester of pregnancy to dydrogesterone. 1999 – 2016
- Compared to a group not receiving this medication.

777,422

8508 children exposed to dydrogesterone

4417 males, 4091 females

Increased risk for hypospadias

Overall cardiovascular malformations

Spina bifida

Hydrocephalus

Frozen thawed embryo

## Follicular and Luteal Phase

Hormonal support (E+P)

Natural cycle (if possible)

Replacing one blastocyst.

Analyzing our data base, during the last 2 years.

Significant reduce rate of miscarriage if the frozen thawed embryo was replaced in natural cycle vs hormonal replacement cycle.

Artificial cycle for frozen embryo transfer is associated with increased miscarriage rate compared to natural/stimulated cycle: a large multicenter cohort study (14421 cycles)

Vinsonneau et al. France, ESHRE abstract 2019

9 centers in France  
Retrospective study

Results were significant

# Conclusions

LPS is necessary in ART because CL support by LH is deficient

It is recommended to start LPS around the time of OPU.

It is recommended to add GnRH agonist at the time of implantation.

It is recommended to stop luteal support in between gestational week 5-7.

In general: we should prevent giving drugs unless showed direct correlation to treatment success.

