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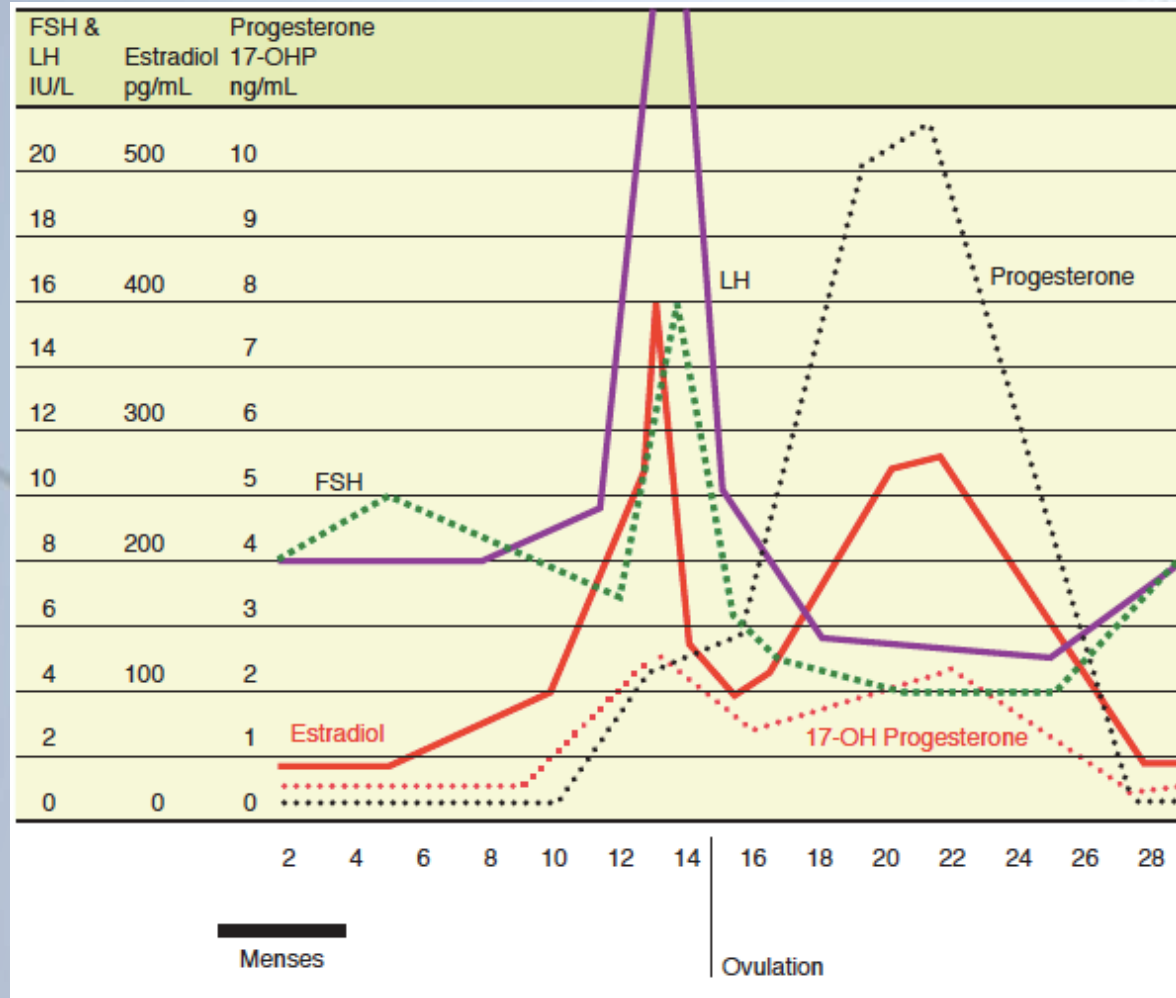
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LPS For Fresh & Frozen Replacement Cycles – State of The ART

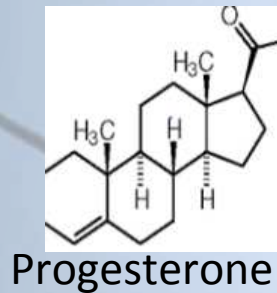


LH and Progesterone-Natural Cycle

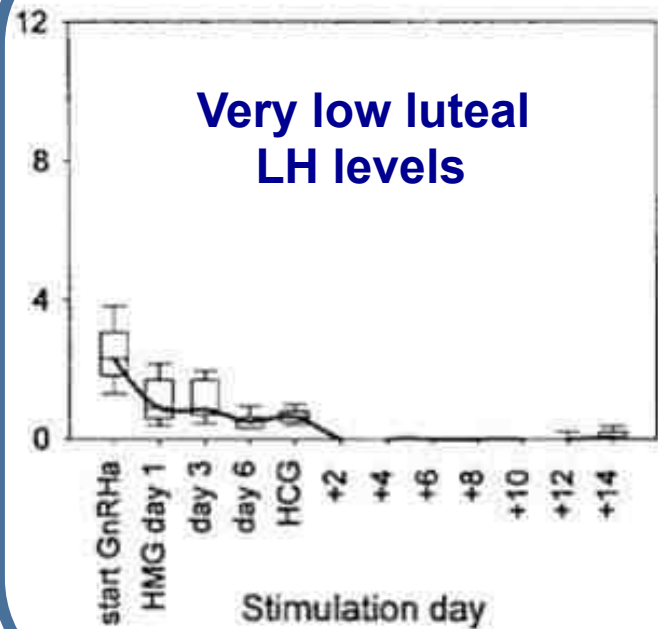


IVF Cycle-Luteal Phase Defect

**Supra-physiological
steroid levels**

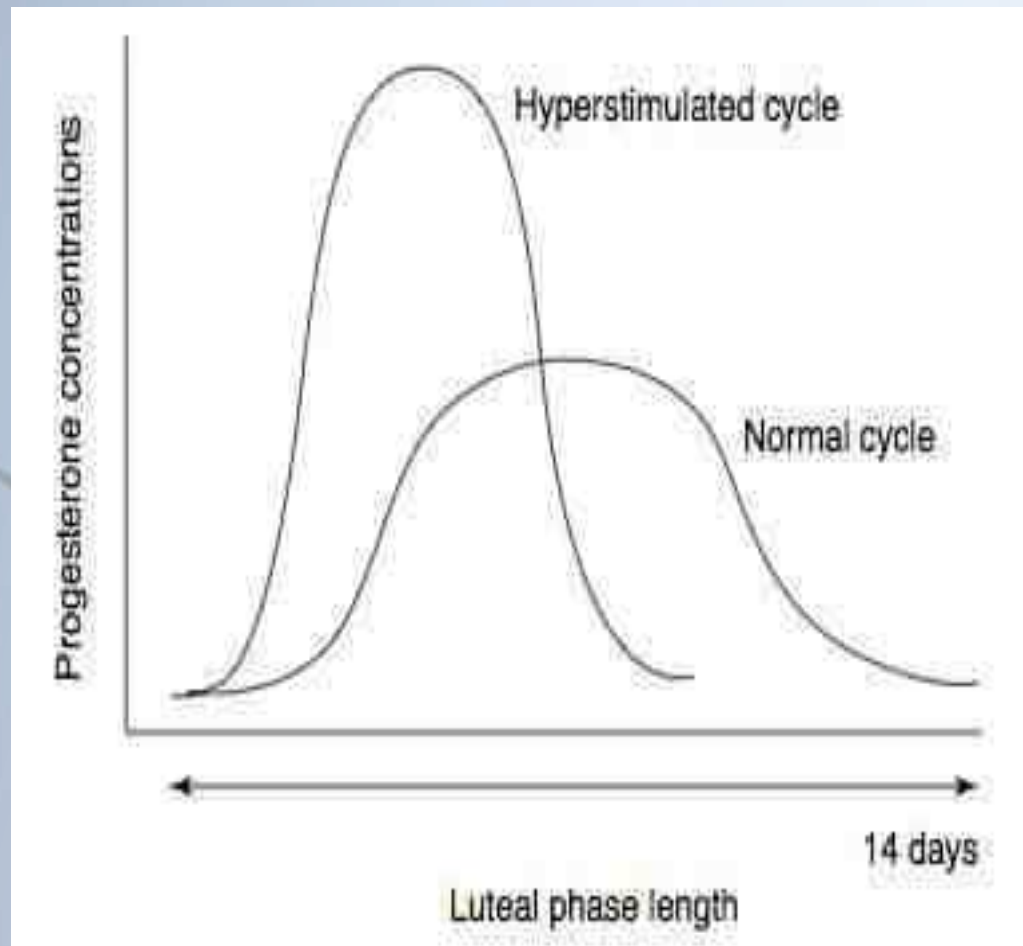


**Very low luteal
LH levels**



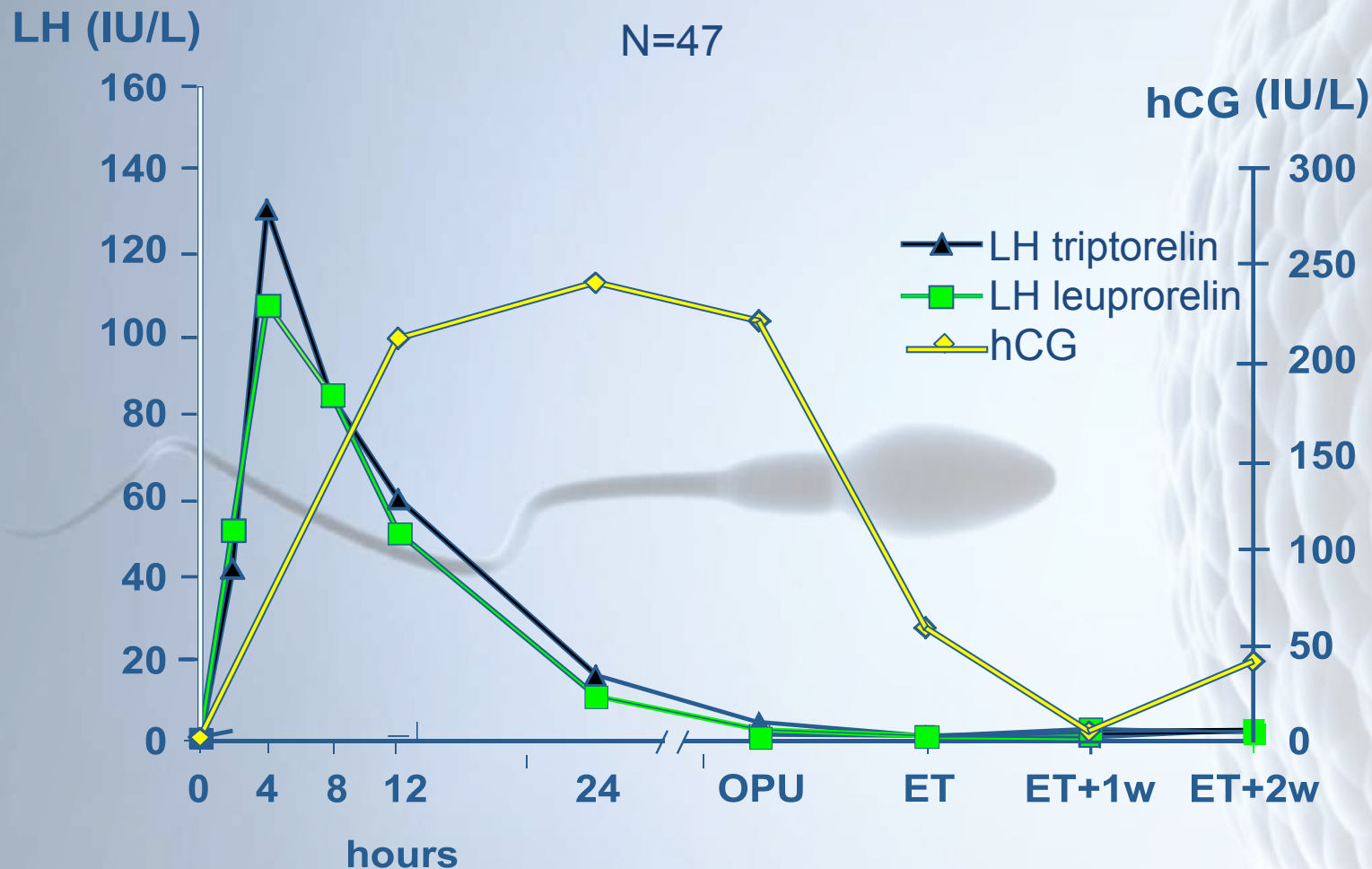
Luteal Phase Defect

Luteal Phase Defect-IVF Sequel of COS..

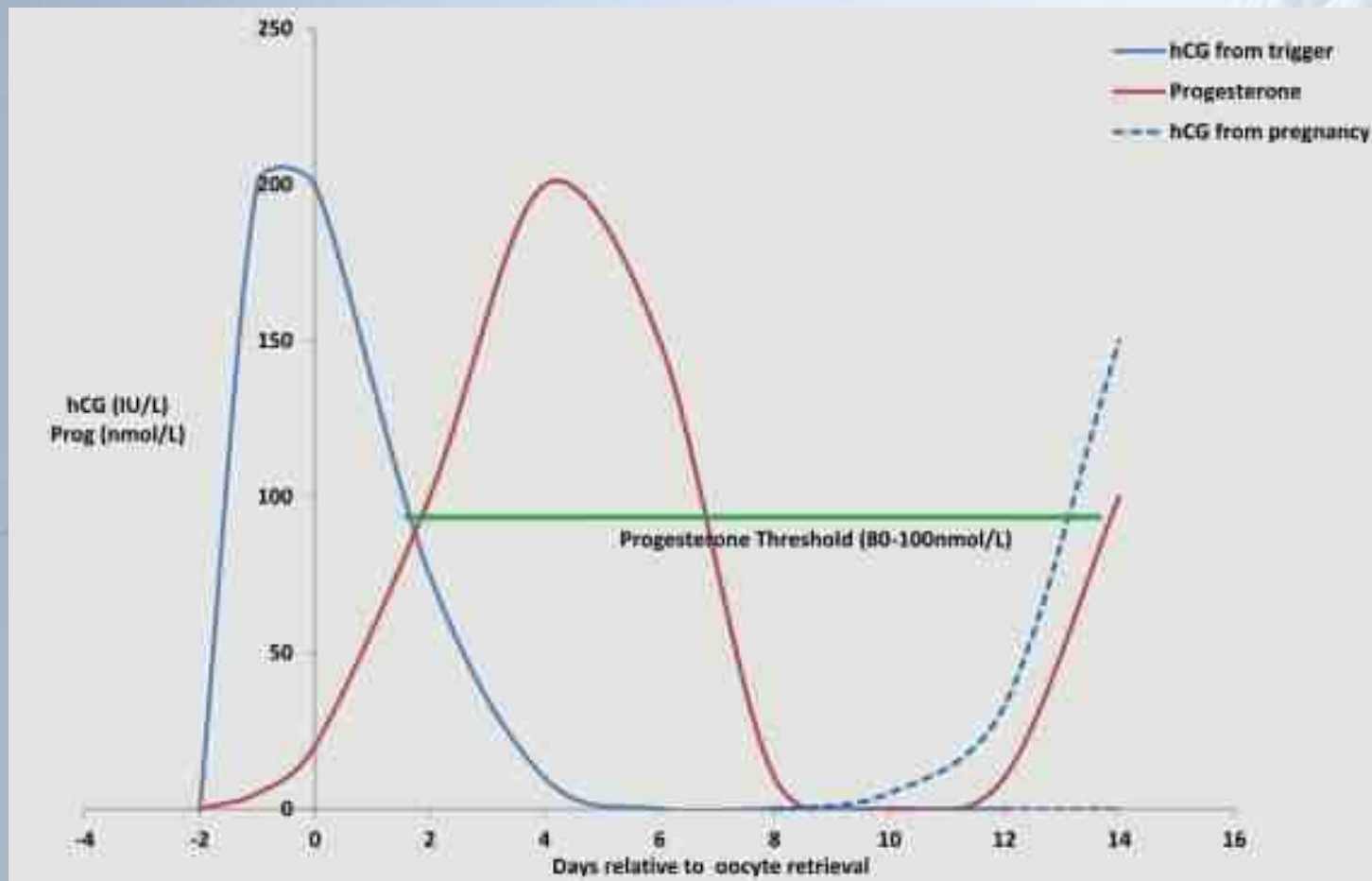


Adapted from Jones-1996 by Fauser and Devroey-2003

GnRH Agonists Triggering: Lower Duration of LH Activity Exposure vs hCG

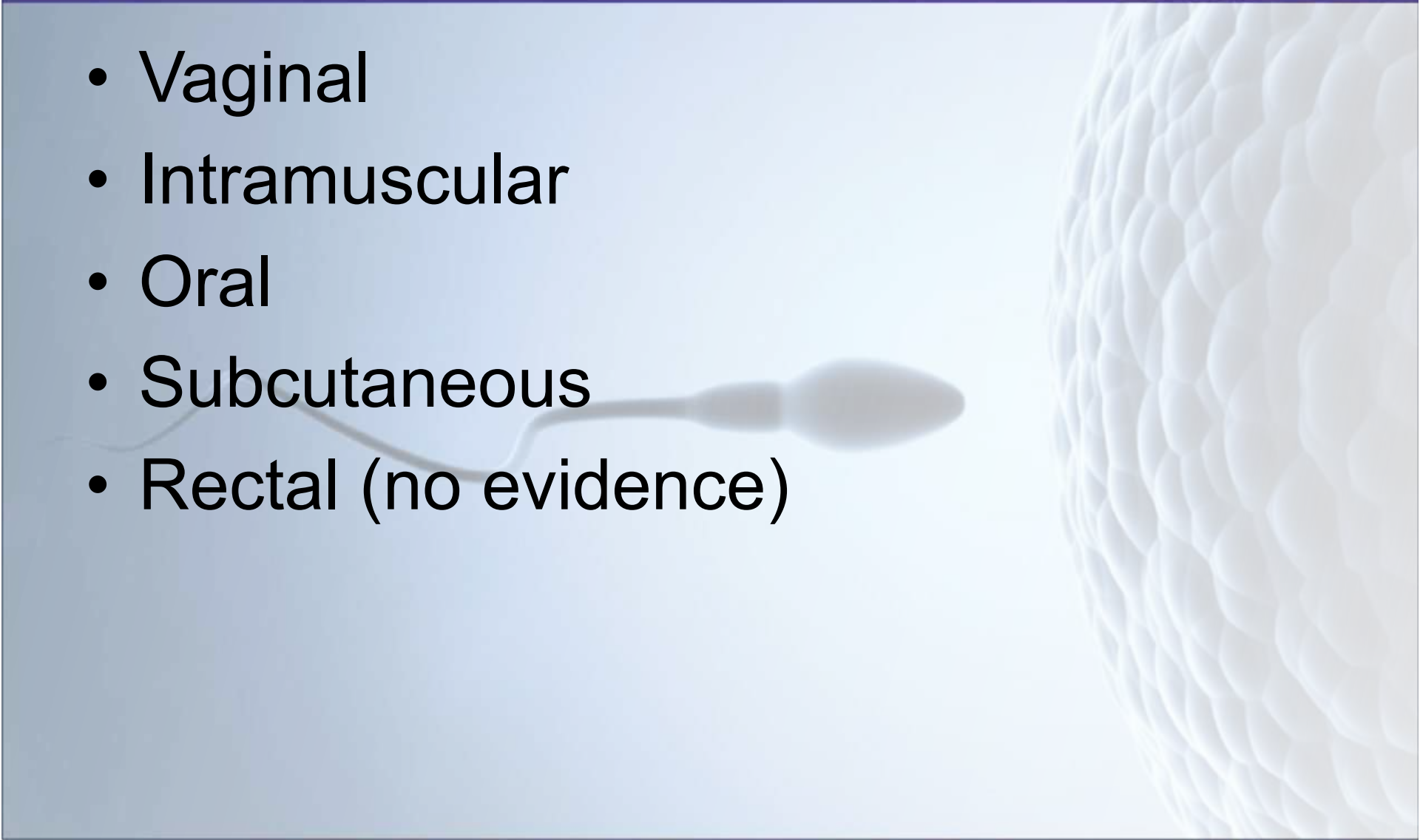


hCG and P levels after hCG trigger until early pregnancy in IVF



Progesterone-Routes

- Vaginal
- Intramuscular
- Oral
- Subcutaneous
- Rectal (no evidence)



Oral Progesterone

- Simple to use
- Drawbacks
 - First pass hepatic metabolism- *Maxon 1984*
 - Low bio-availability of oral micronized progesterone-*Devroey et al 1989 & Bourgain et al-1990*
 - Poor results- *Buvat et al-1990; Licciardi et al-1999; Friedler et al-1999*
- Dydrogesterone (DG)
 - Similar pregnancy rates- *Chakravarty et al-2004; Ganesh et al-2011; Salehpour et al-2013; Tomic et al al-2015; Saharkhiz et al-2015*
 - More large RCT's are warranted

Vaginal vs im Prog.-Fresh autologous cycles



	No. of studies	No. of participants	OR (95% CI)
Live birth or Ongoing pregnancy rate	7	2039	1.37 (0.94-1.99)
Clinical pregnancy rate	13	2932	1.14 (0.97-1.33)
Miscarriage rate	6	1468	0.79 (0.56-1.13)

Similar Efficacy

Vaginal vs im Prog.-Patient satisfaction

- Improved patient satisfaction scores with vaginal P
 - Easier to use
 - Less painful
 - Less time consuming
 - Associated with fewer discomforts

Luteal Bleeding

Vaginal vs im Progesterone

Outcome	Crinone (n=190)	im Progesterone (n=175)	p
Pregnant (%)	128 (67)	112 (64)	0.51
Ongoing/born (%)	86 (67.2)	79 (70.5)	0.39
Luteal bleeding (%)	63 (33.2)	45 (25.7)	0.14
Luteal bleeding among non-pregnant women (%)	35/62 (56.5)	24/63 (38.1)	0.05

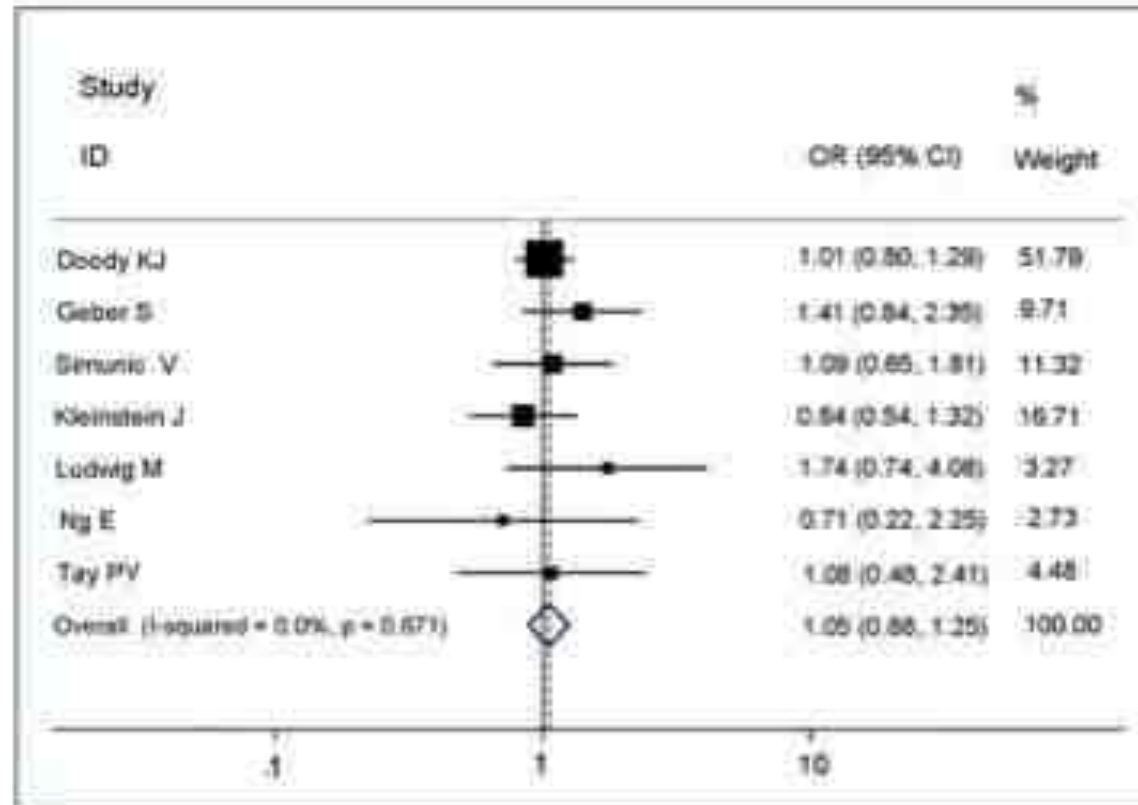
***Which Vaginal Progesterone
and which dose to use?***



Which vaginal Progesterone? Meta-analysis

- 7 trials; 2,447 patients
- P **gel** 90 mg once or twice daily vs
 - 600 mg/d vaginal P **capsules** (utrogestan, utrogest) (4 trials)
 - 200, 400, 600 mg utrogestan and 400 mg/d vaginal P **pessaries** (cyclogest) (1 trial)
 - 100, 200 mg/d vaginal P **inserts** (endometrin) (1 trial)
 - 800 mg/d vaginal P **pessaries** (cyclogest) (1 trial)

Which vaginal Progesterone? Meta-analysis



A. Overall clinical pregnancy

Vaginal P-Low-dose vs high-dose (Fresh autologous cycles)



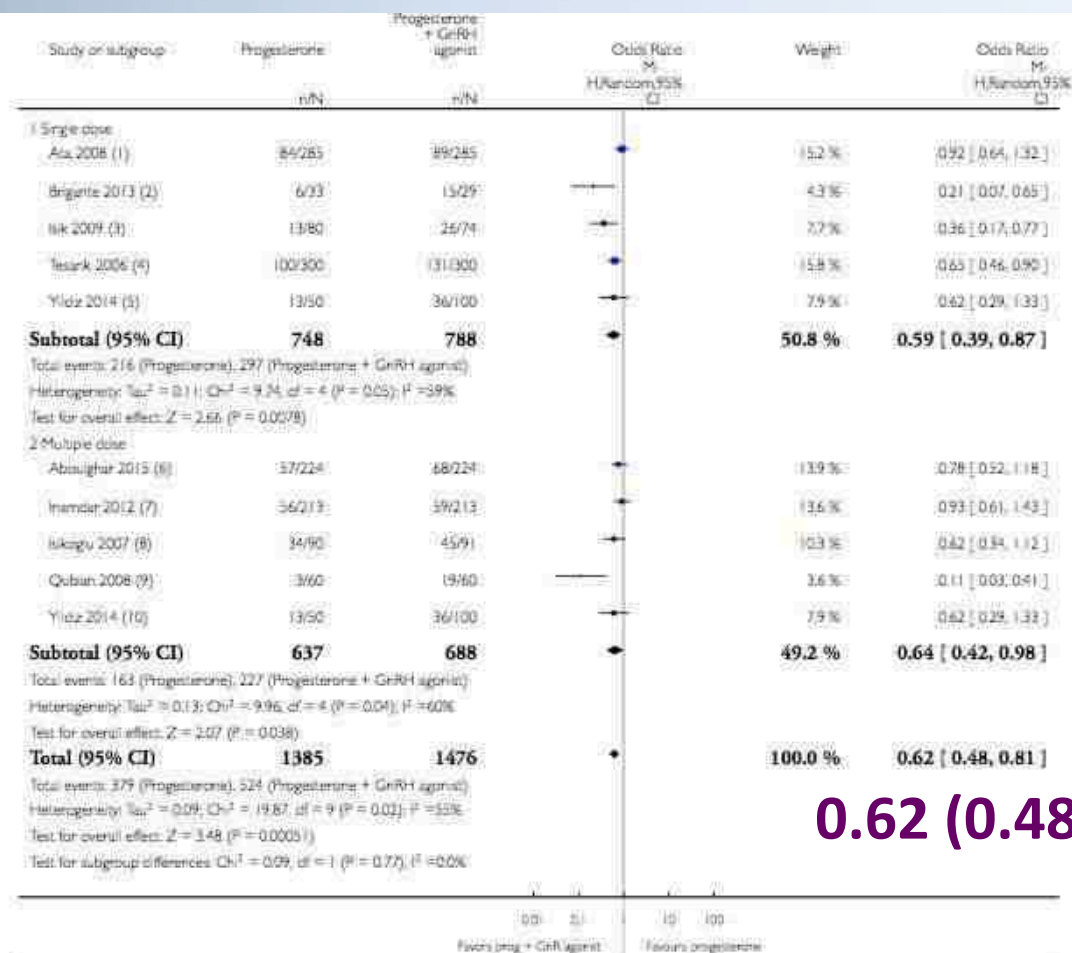
Outcome	No. of studies	No. of participants	OR (95% CI)
Live birth or Ongoing pregnancy	5	3720	0.97 (0.84-1.11)

E₂+P vs P for LPS-Meta-analysis

(15 RCT's; 2406 patients)

	E ₂ +P vs P - RR (95% CI)
Routes	
Per oral	1.18 (0.98-1.41)
Vaginal	1.07 (0.59-1.93)
Transdermal	1.81 (0.53-6.17)
Doses-oral	
6 mg/day	1.12 (0.92-1.36)
4 mg/day	1.19 (0.75-1.89)
2 mg/day	1.24 (0.91-1.69)

GnRH-a + P vs P-only – Live birth or Ongoing pregnancy



0.62 (0.48-0.81)

Adjuvant Treatment

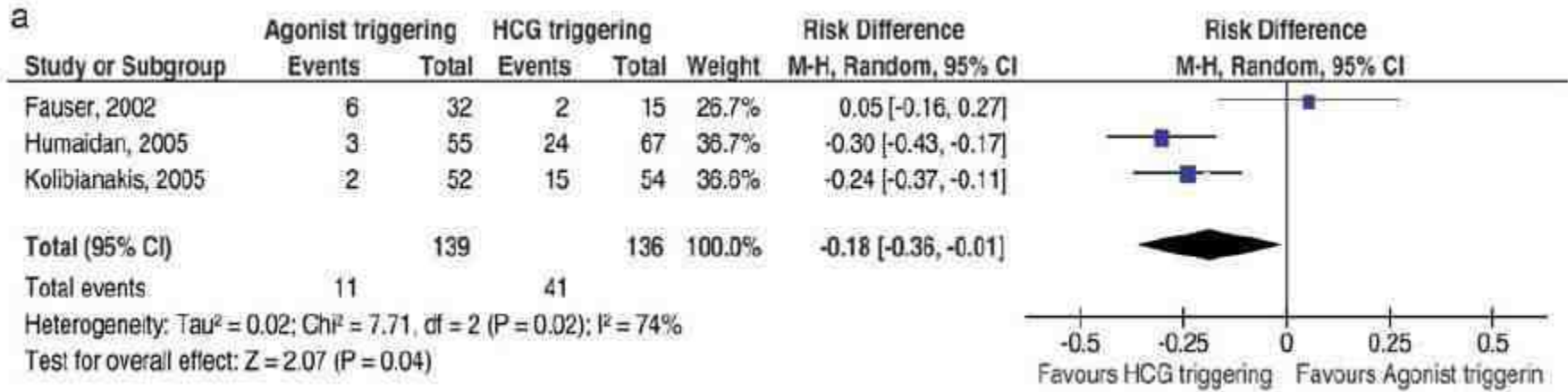
- Immunotherapy
 - IVIG
 - TNF-alpha
 - iv Lipids
 - Corticosteroids
- Vasodilators
 - Nitric oxide and nitroglycerin
 - Sildenafil citrate
- Uterine relaxants
 - Nitroglycerin
- Allergic antagonists
- Heparin

No Evidence !

LPS for GnRH-a triggered cycles



GnRH-a Triggering-Ongoing PRs after Conventional Luteal Support



GnRH-a Trigger-Fresh ET

- Rescue corpora lutea (**“European” Approach**)
 - 1500 IU hCG (OPU +1hr)
- Intensive luteal phase support (ILPS) (**“American” Approach**)
 - Dual trigger (ILPS + 1000 IU hCG) when peak $E_2 < 4,000$ pg/ml (Kummer et al-2011)

Intensive luteal phase E&P support

Pregnancy outcome

- Good

- Engmann et al-2008; DiLuigi et al-2010; Shapiro et al-2011; Imbar et al-2012; Iliodromiti et al-2013

- Poor

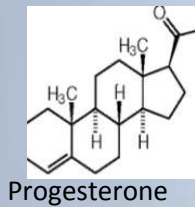
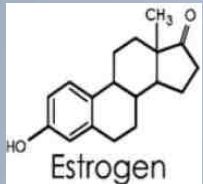
- Babayof et al-2006; Orvieto 2012



LH / hCG & Luteal Phase

LH / hCG

E & P Synthesis



Activation of
uterine
LH receptors



Upregulation of
growth factors and cytokines

IMPLANTATION

1500 IU hCG rescue-Patients at high risk of OHSS-*RCT*

	GnRHa + 1500 IU hCG (n=60)	5000 IU hCG (n=58)
Ongoing preg. per patient	28.3%	25.9%
Implantation rate	35.5%	29.4%
Early pregnancy loss	16.0%	19.0%
OHSS	0	2 (3.4%)

14-25 follicles ≥ 11 mm on the GnRHa trigger day

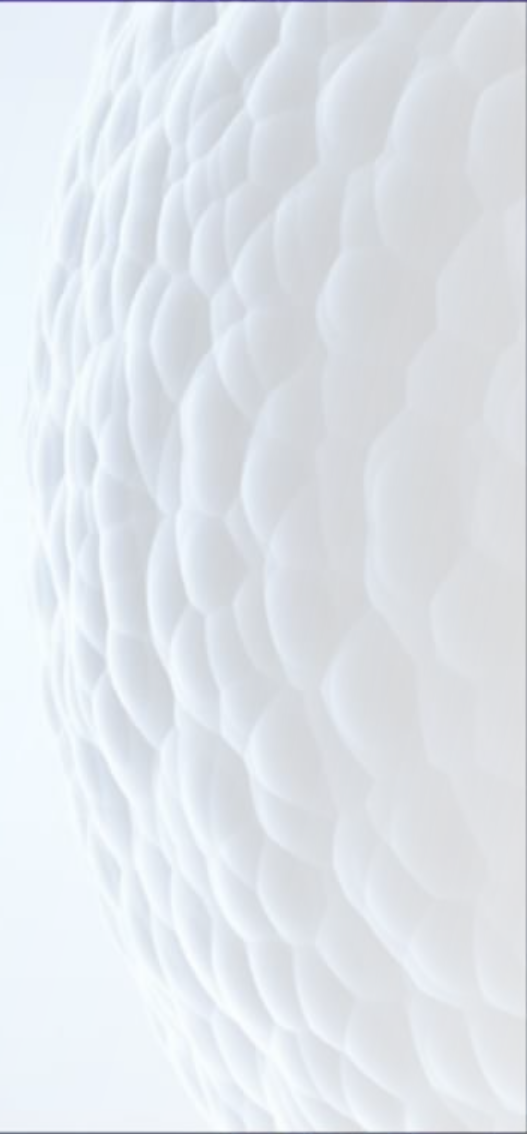
1500 IU hCG rescue

Anatolia Experience (n=157)

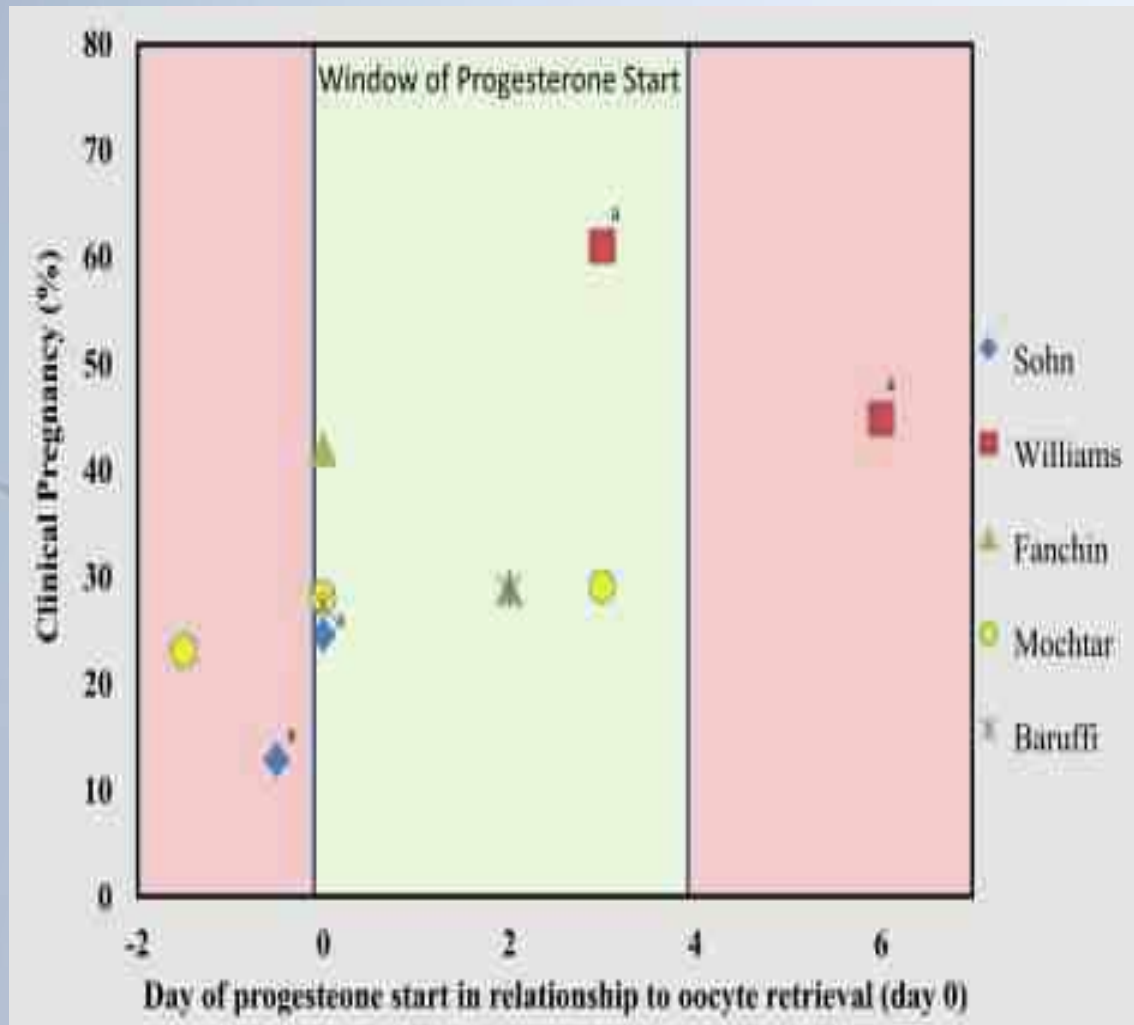
Female age	28.7± 4.4 (19-42)
No. of oocytes	17.2± 5.4 (5-37)
Fertilization rate	73%
Blastulation rate	57%
Day-5 ET rate	71%
No. of embryos transferred	1.6±0.5 (1-2)
Pregnancy rate	89/157 (57%)

GnRH-a Triggering-Other Approaches to Rescue Luteal Phase

- rLH
 - Papanikolaou et al-2011
- Luteal GnRH-agonist-only
 - Pirard et al-2015
- Luteal hCG-only
 - Low-dose daily (125 IU/d)
 - (Andersen et al-2015)



When to start LPS ?



When to stop LPS ?

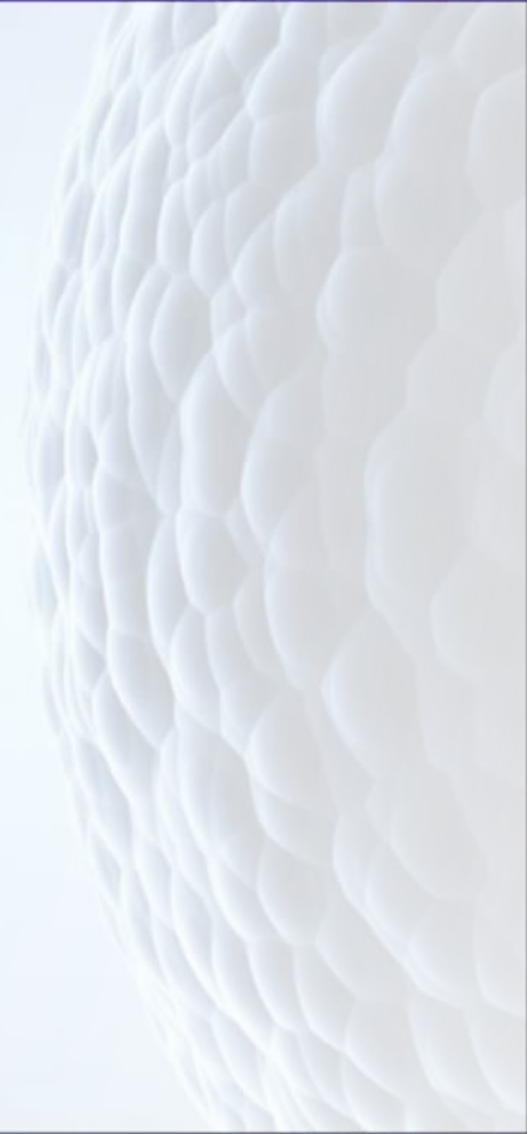
- Day of pregnancy test
 - *Nyboe Andersen et al.-2002; Goudge et al-2010; Kyrou et al-2011*
- First TV-USG (5th-7nd weeks)
 - *Aboulghar et al.-2008; Kohls et al.-2012*

LPS for Frozen Embryo Replacement (FER) Cycles



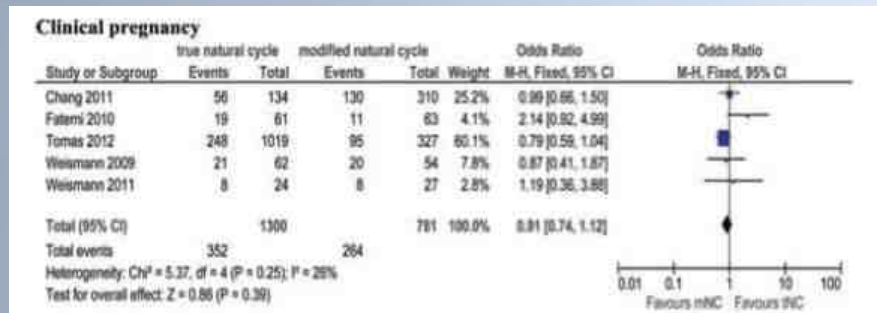
Preparation of endometrium for FER

- Natural cycle (NC)
 - True NC (tNC)
 - with Progesterone support
 - without Progesterone support
 - Modified NC (mNC)
 - with Progesterone support
 - without Progesterone support
- Artificial cycle
 - with GnRH-a suppression
 - without GnRH-a suppression

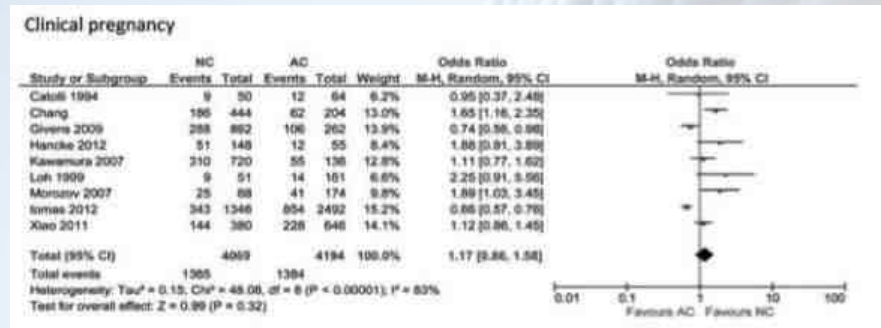


What is the Optimal Protocol to Prepare Endometrium in FER Cycles? (Meta-analysis)

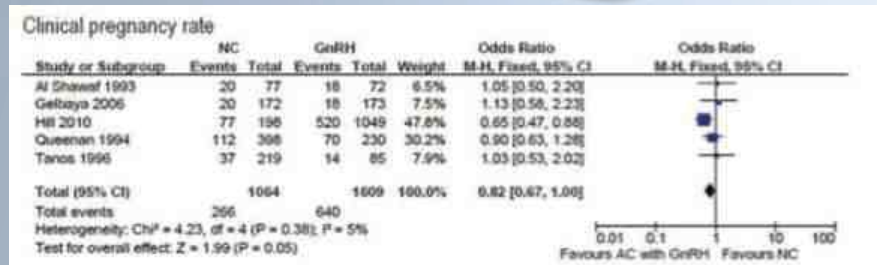
True vs Modified NC



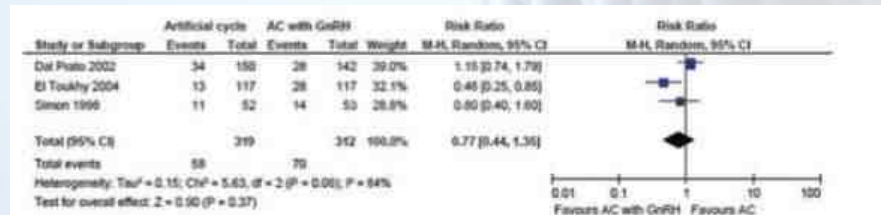
NC vs Artificial Cycle



NC vs AC with GnRH-a

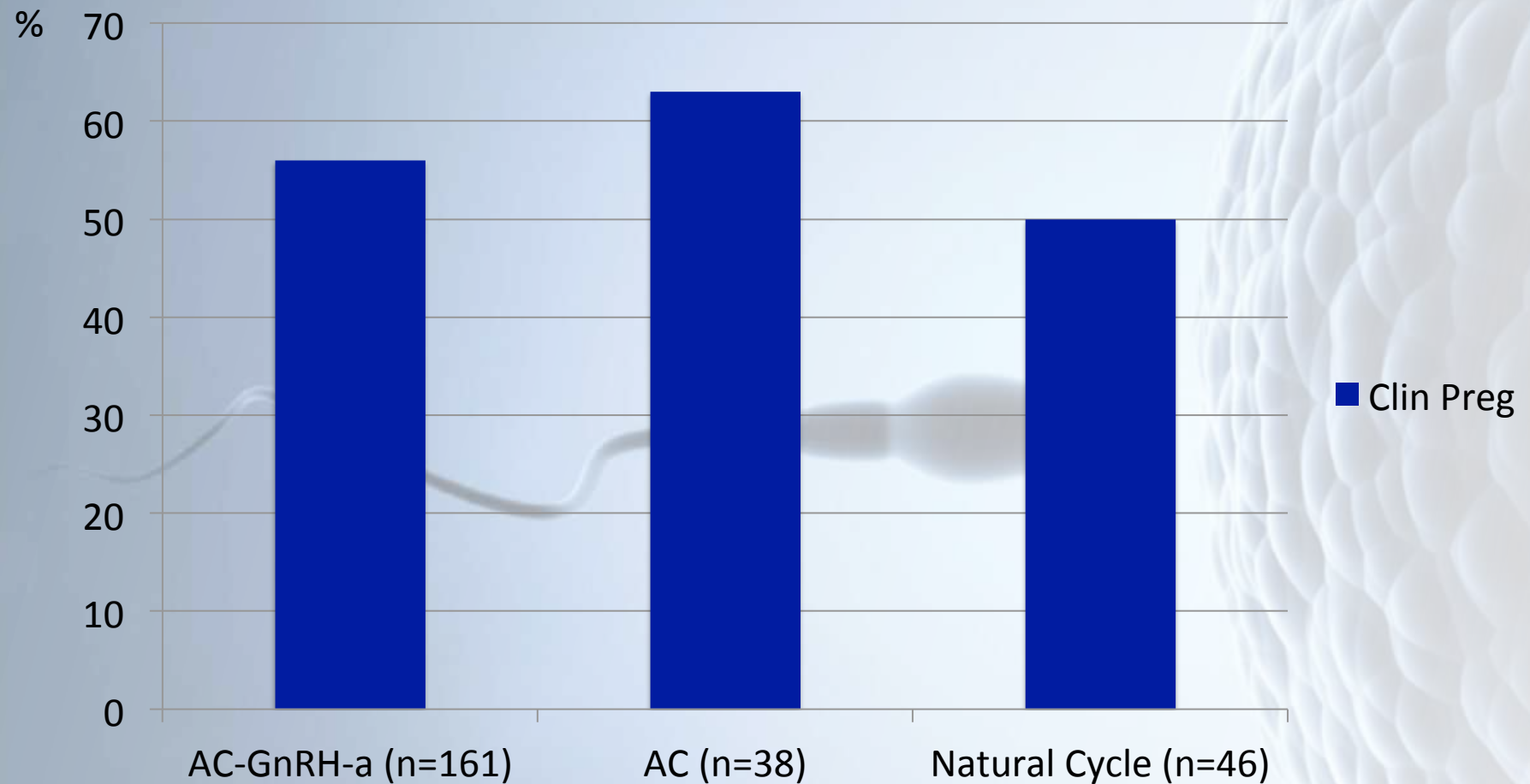


AC vs AC with GnRH-a

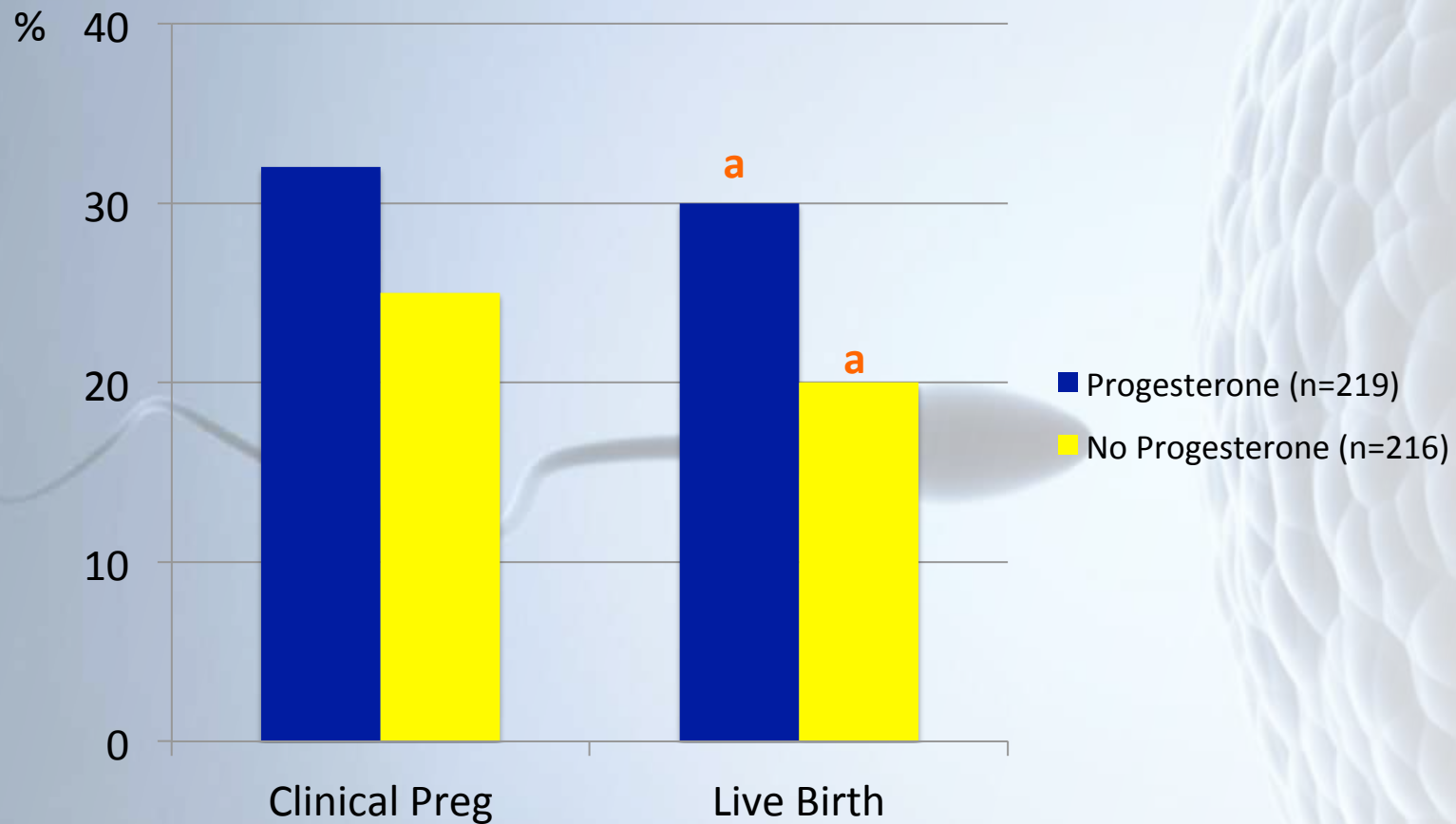


Similar Efficacy

FER Protocols-Anatolia Experience-2015

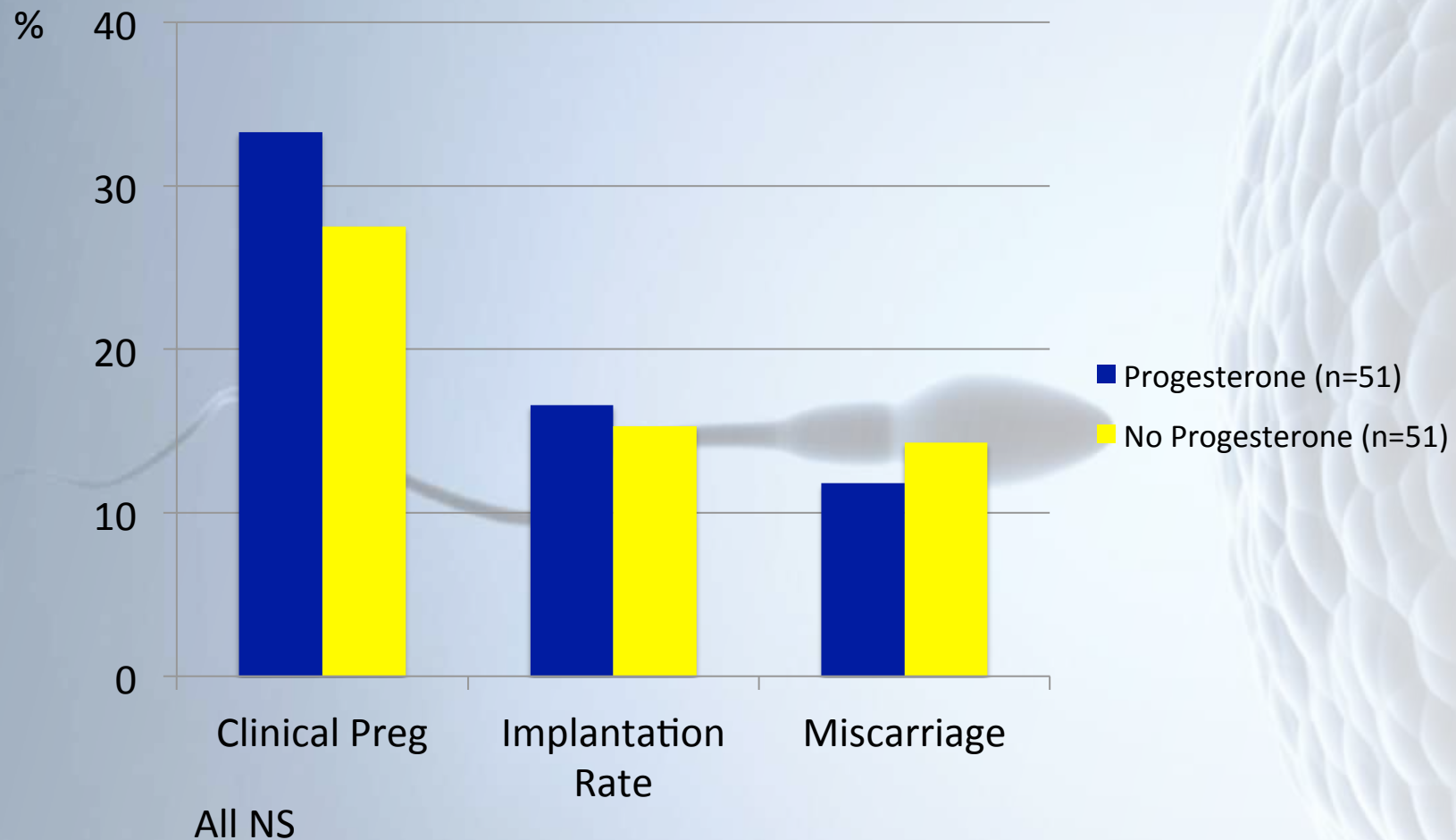


Is Progesterone supplementation needed in true-NC FER cycles? (RCT)



a: $p=0.0272$

Is Progesterone supplementation needed in modified-NC FER cycles? (RCT)



Luteal Support-Natural Cycle

Conclusion

- hCG administration in modified-NC provides luteal support that is comparable to either vaginal or im Prog. in artificial cycles and therefore LPS may not be needed
- True-NC benefit from vaginal Prog.

***Vaginal vs im Progesterone in Artificial
FER Cycles-Any difference?***

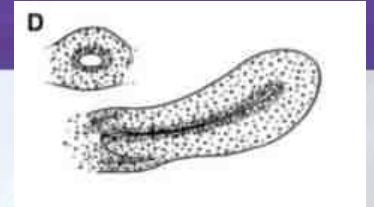


Artificial Cycle-Vaginal vs im Prog.

(Autologous and donor egg cycles)

- Higher live birth rate with im Prog.
 - Haddad et al. JARG 2007; 24: 467-70
 - Heitmann et al. Fertil Steril 2013; 100: S460
 - Kaser et al. Fertil Steril 2012; 98: 1464-9
- Similar live birth rate
 - Gibbons et al. Fertil Steril 1998; 69: 96-101 (RCT)
 - Johanputra et al. Fertil Steril 1999; 72: 980-4
 - Toner. Human Reprod 2000; 15: 166-71.
 - Berger and Phillips. Fertil Steril 2007; 89: S11-2
 - Berger and Phillips. Fertil Steril 2008; 90: S459
 - Williams et al. Fertil Steril 2000; 74: S209
 - Shapiro et al. Human Reprod 2014; 29: 1706-11
 - Leonard et al. J Reprod Med 60: 103-8, 2015 (RCT)
 - Wang et al. Plos One 2015; Jul 29;10(7):e0133027. doi: 10.1371 (RCT)

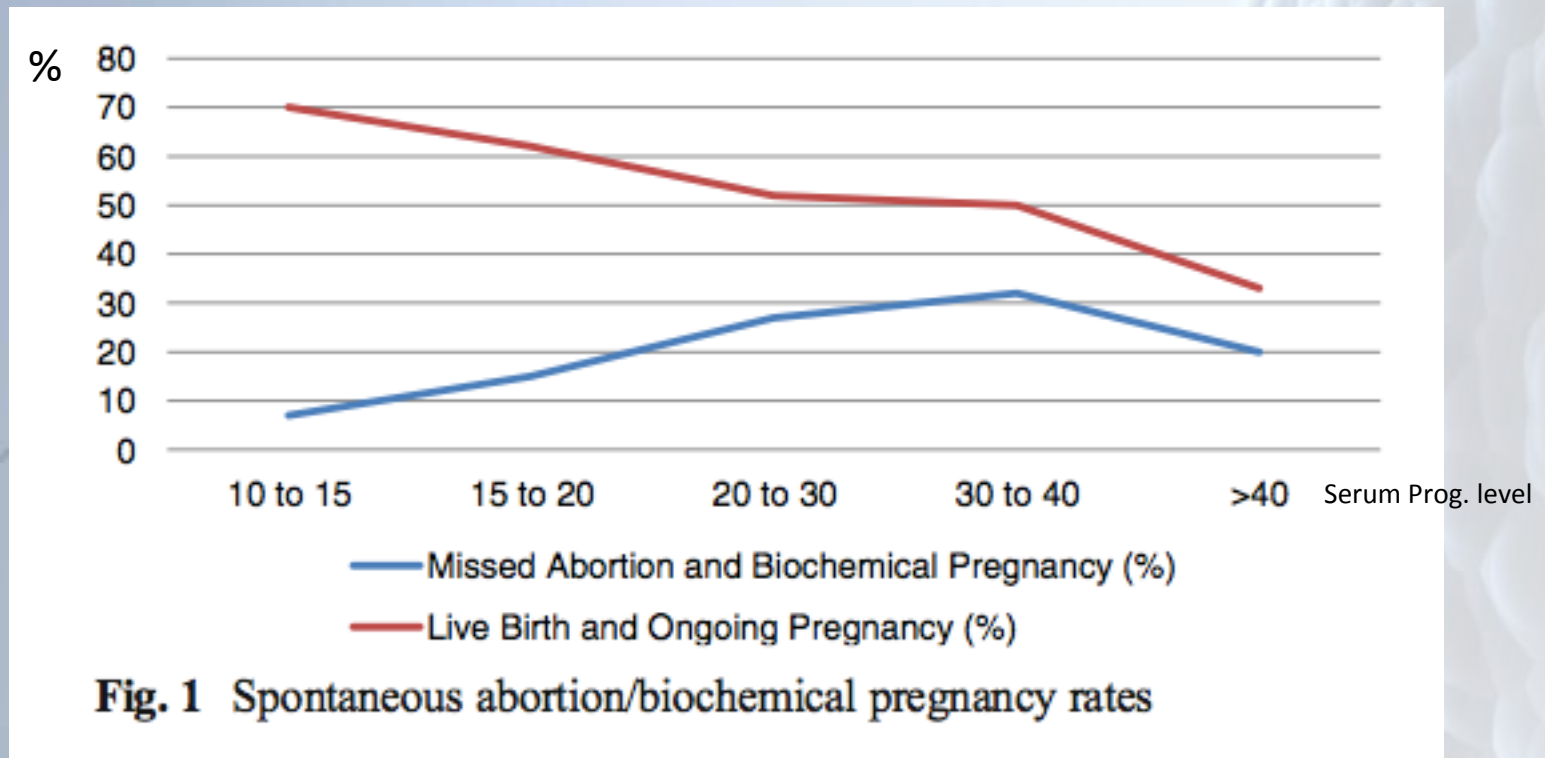
First-pass uterus effect



Circulating vs Endometrial Progesterone Concentrations

- Higher circulating Prog with im route
- Higher endometrial Prog with vaginal route

Higher circulating Prog. Levels may even be detrimental...



FER-Single Euploid Blastocyst ET (n=213); Day-19 Serum Prog levels (Day of ET)

Artificial Cycle-Progesterone Route

Conclusion

- There is absence of superiority of im over vaginal Progesterone
- Patient acceptance, convenience, potential complications and cost should be taken into account



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