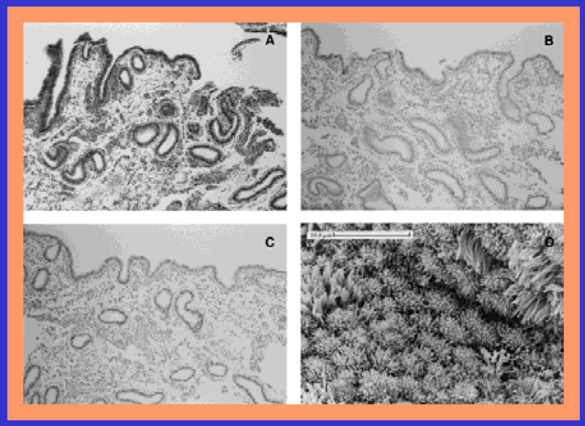
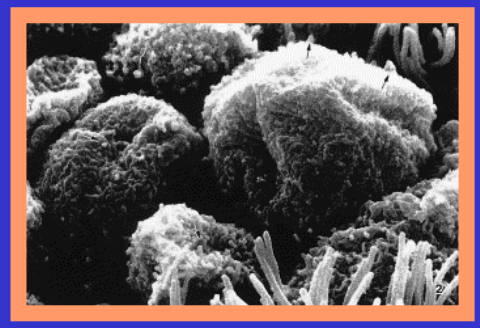
Morphology



Ultrastructue



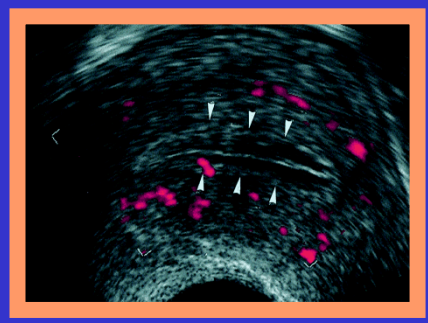
UTZ

The uterus and IVF

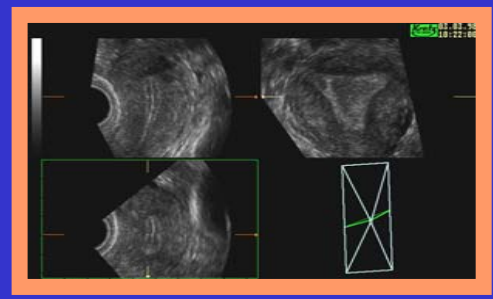
Embryo → Pregnancy

Contractility

Doppler



3D



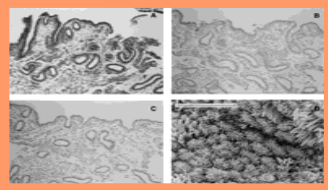
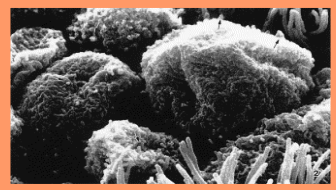
E2 and P4 effects: The donor-egg IVF lesson

Luteal E2

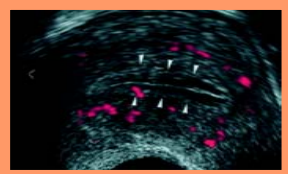
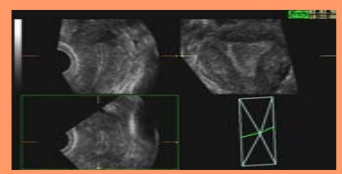
Late follicular P↑

Practical measures to optimize endometrial receptivity:

Biology of endometrial **Embryo** receptivity


The uterus and IVF

→ **Pregnancy**

Before IVF
Minimize A
Fluid in endom
Too thin end.
Contractility

Intercourse and endom. receptivity

Uterine contractility

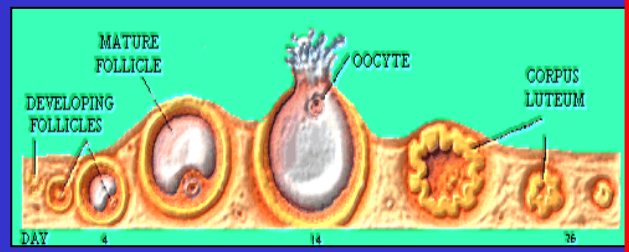
Androgens

Donor egg IVF: A model to study the endometrial effects of E2 and progesterone

E2 and P4 effects the donor-egg IVF lesson

The menstrual cycle

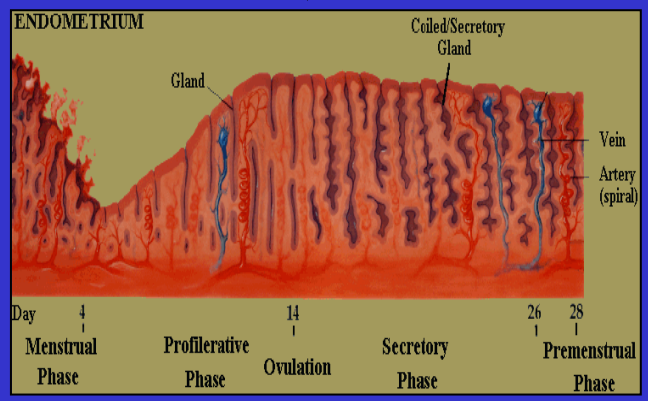
The oocyte donor

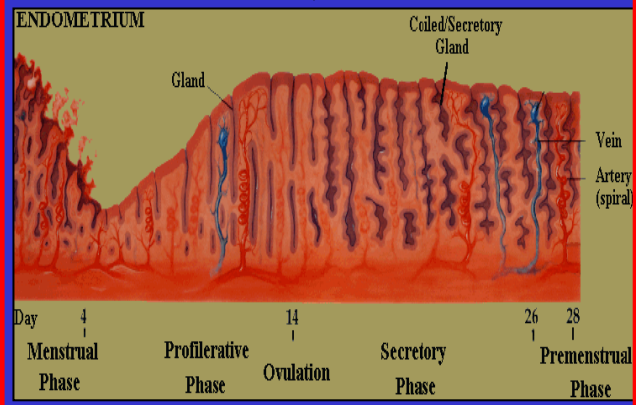


The recipient

Estrogen and Progesterone treatment

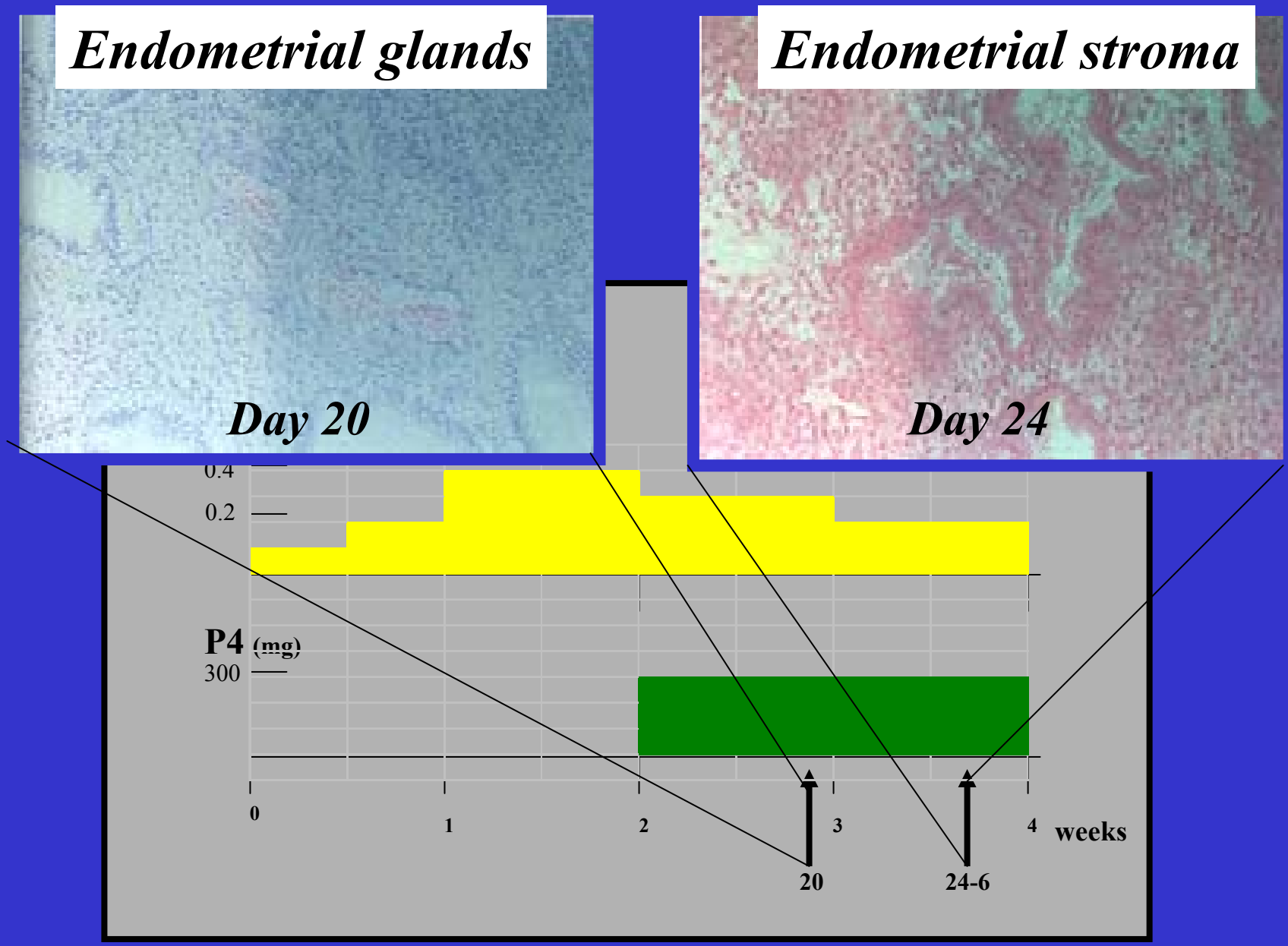
A model to study the effects of E2 and P





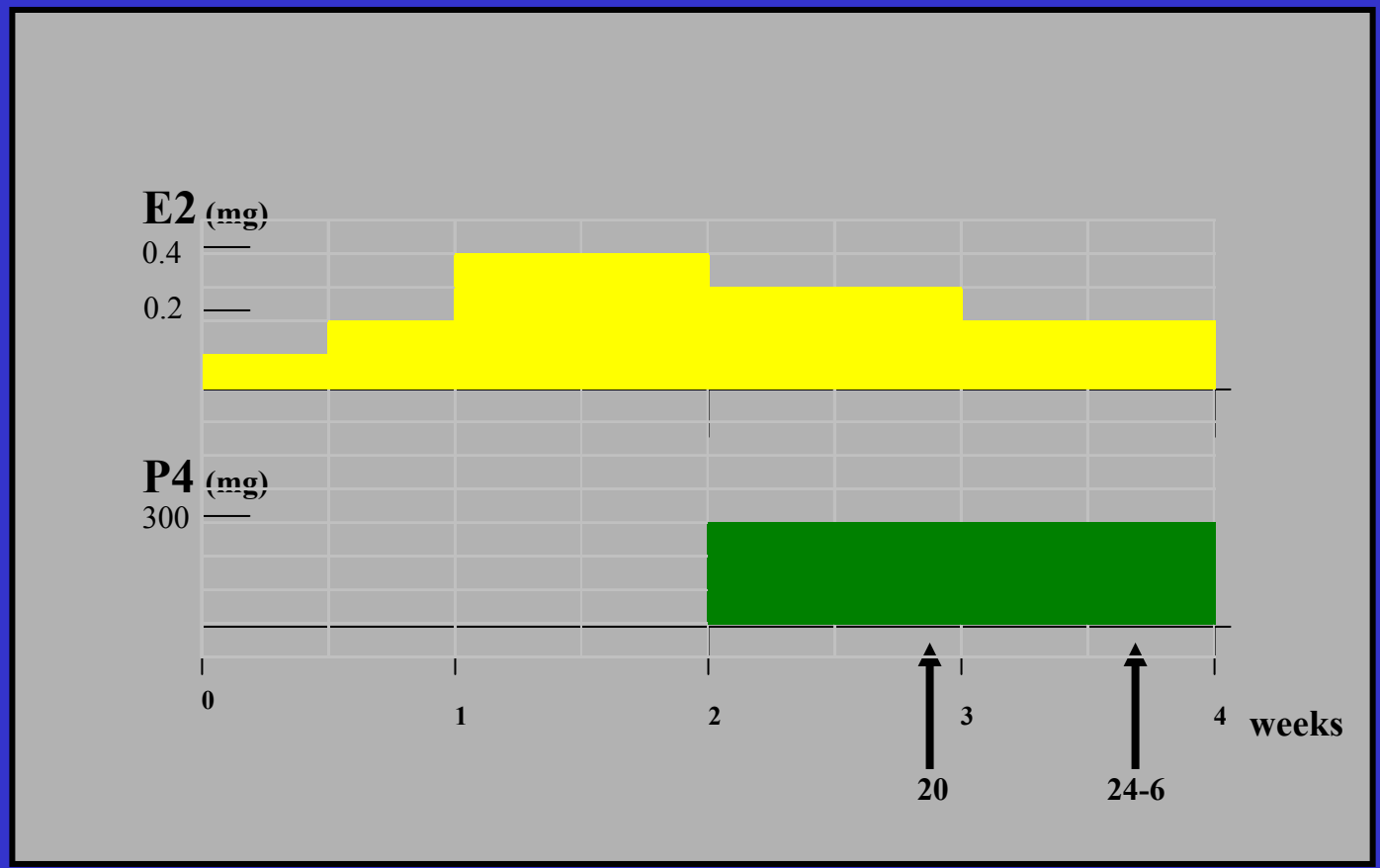
E2

Progesterone



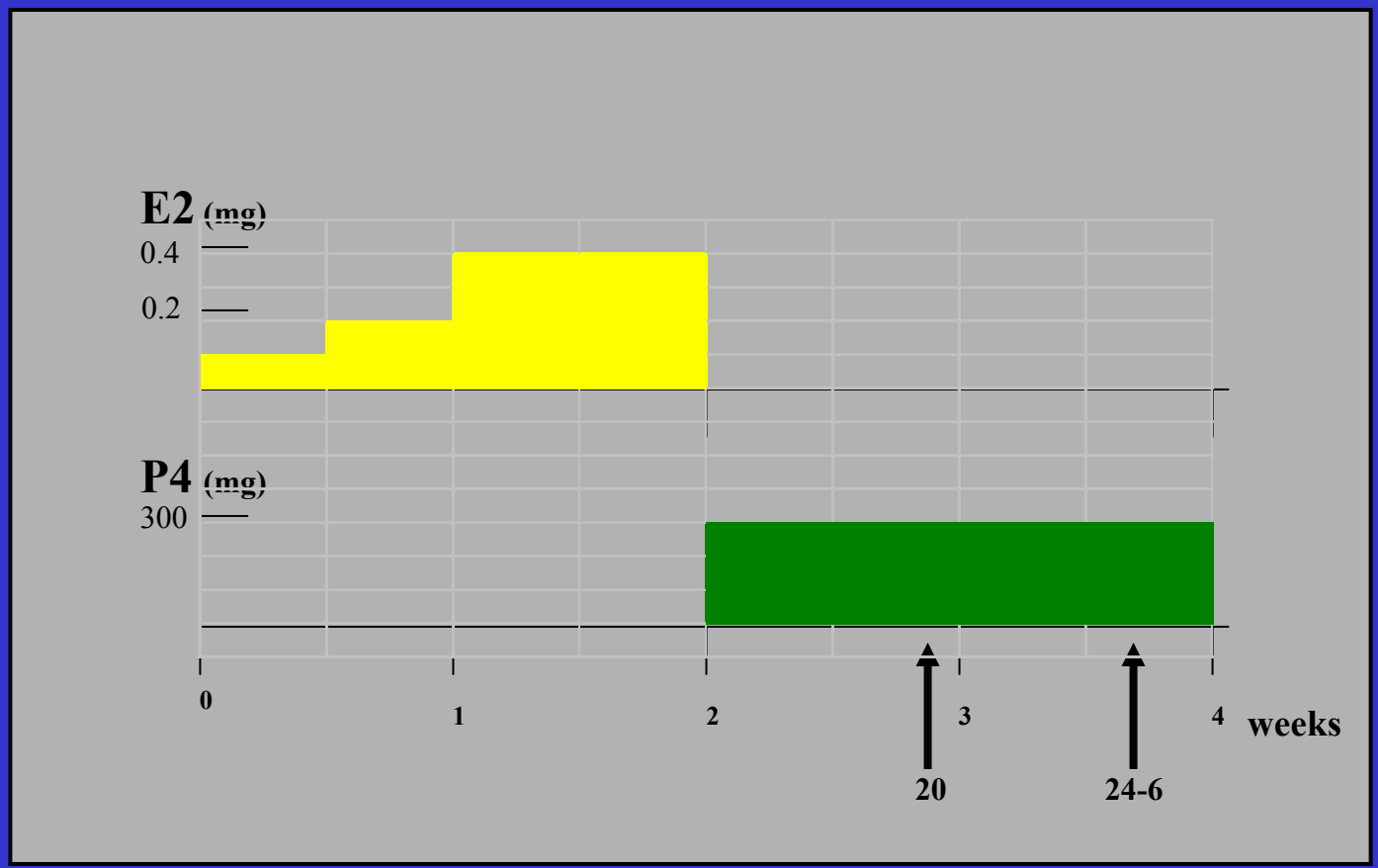
de Ziegler et al J Clin Endocrinol Metab, 1992:74:322-31.
de Ziegler et al, Fertil Steril 1991;56:851-5.

E2/progesterone
effects on endometrial morphology



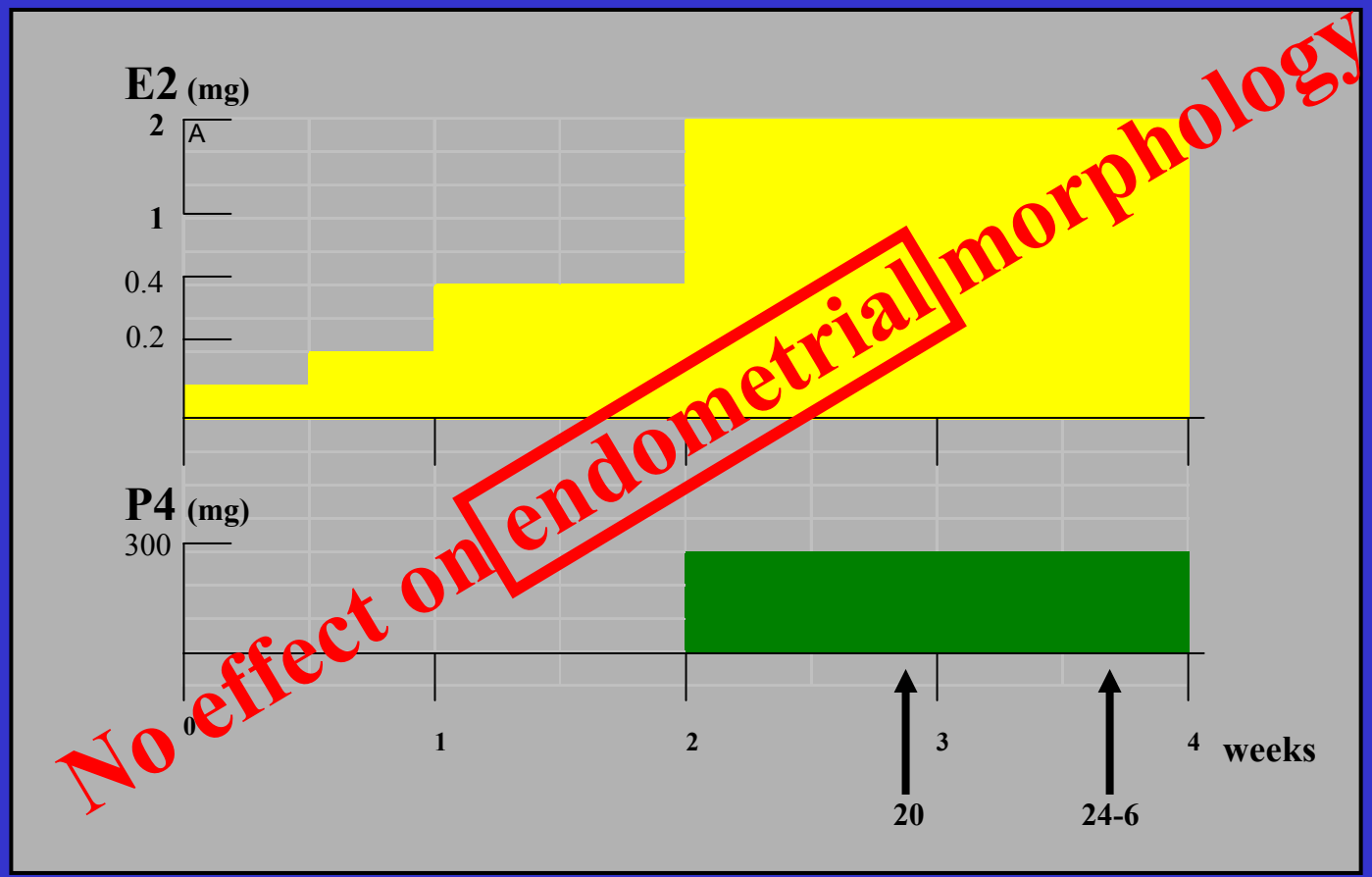
de Ziegler et al J Clin Endocrinol Metab, 1992:74:322-31.
de Ziegler et al, Fertil Steril 1991;56:851-5.

E2/progesterone ↘
effects on endometrial morphology



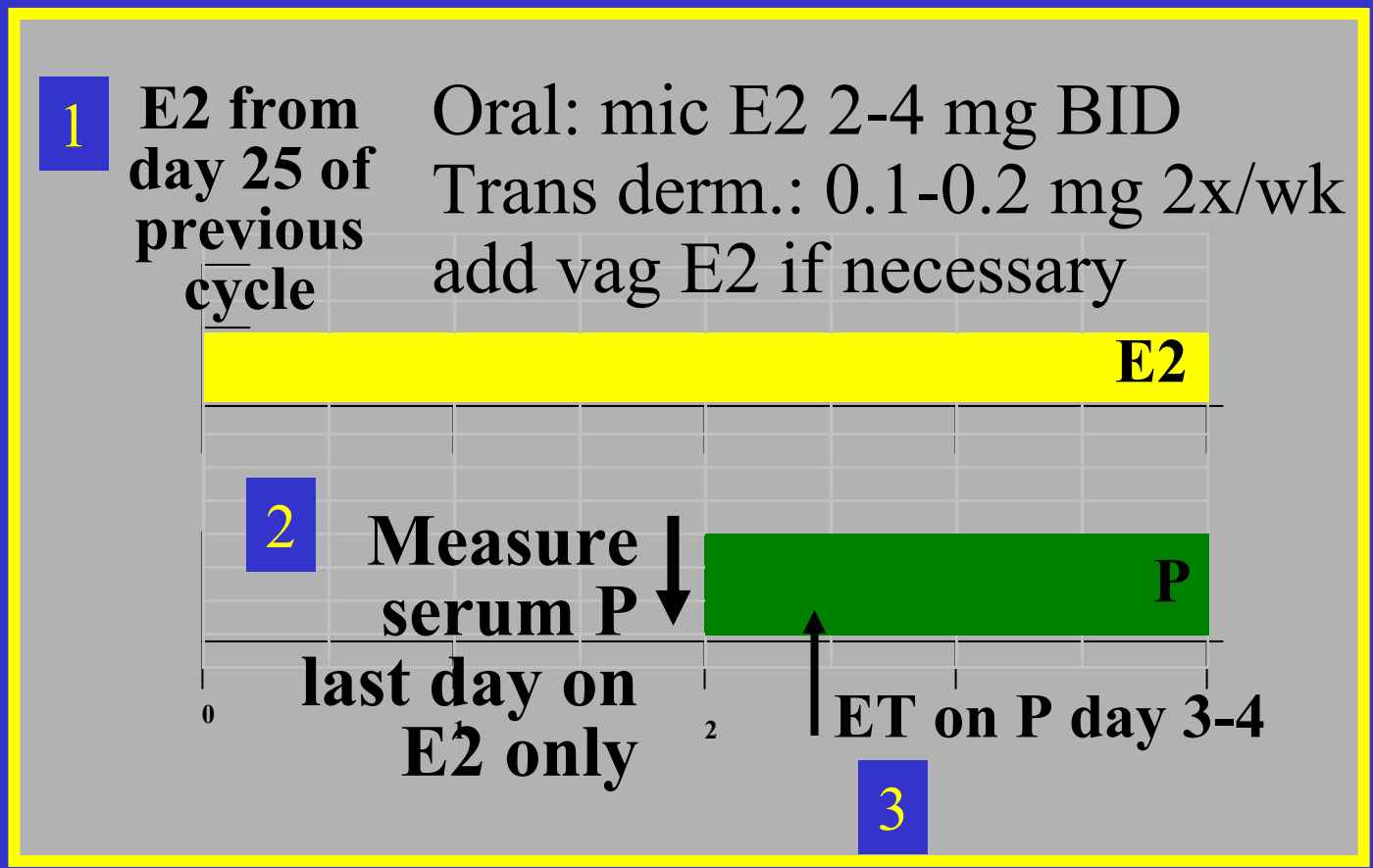
de Ziegler et al J Clin Endocrinol Metab, 1992:74:322-31.
de Ziegler et al, Fertil Steril 1991;56:851-5.

E2/progesterone ↗
effects on endometrial morphology



de Ziegler et al J Clin Endocrinol Metab, 1992:74:322-31.
de Ziegler et al, Fertil Steril 1991;56:851-5.

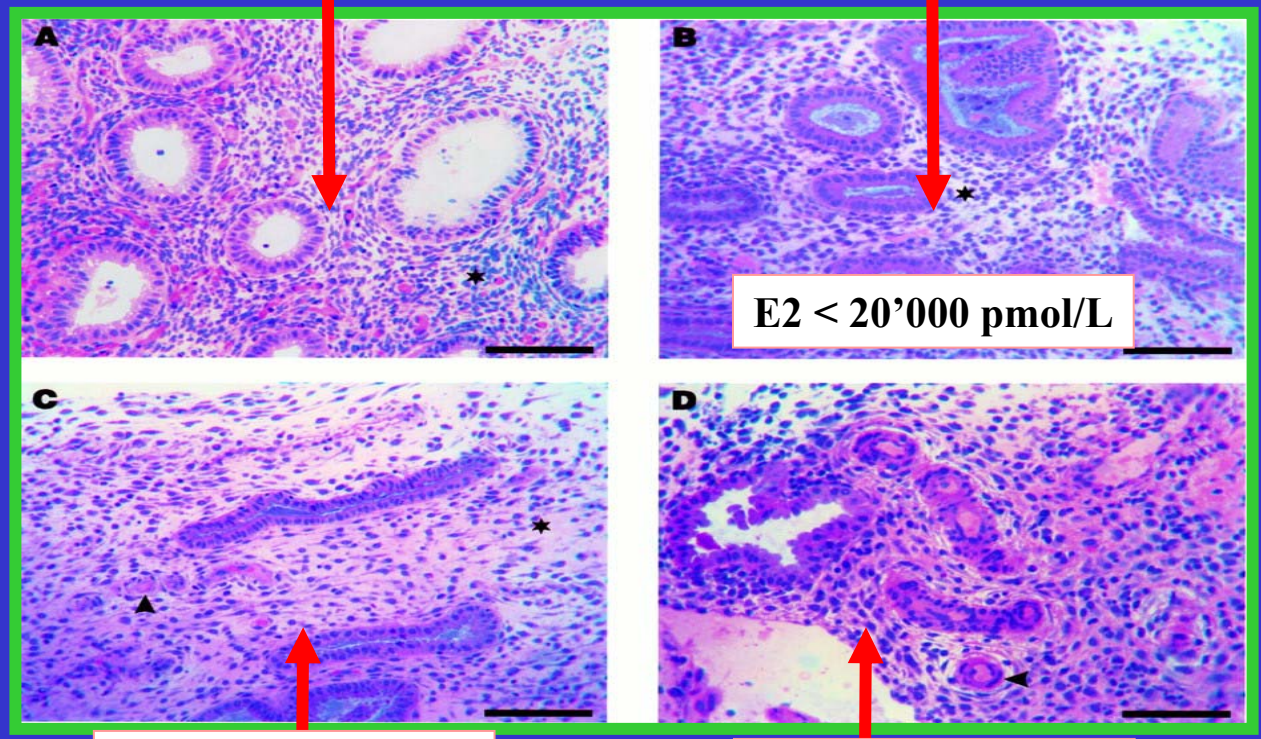
Donor-egg IVF:
a model for priming frozen embryo transfers



Lelaidier C. Fertil Steril. 1995;63:919-21.
Simon A. Fertil Steril. 1999;71:609-13.

Morphometric analysis of endometrium in case of high E2 levels

Basir GS *et al.*
Human Reprod
2001;16:435-40.



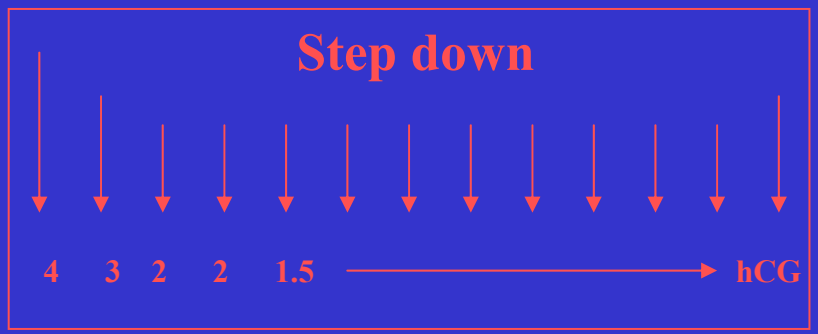
High responders w/
gland-stromal dyssinchrony:
Delayed glandular development
Oedematous stroma

Detrimental effects of E2 ?

Simon C. et al.
Fertil Steril 1998;70:234-9

86 High responders
previous failed IVF
>3 good quality embryos

- 24 Step down
- 62 Regular protocol



	Step-dn	*Std*	*P*
Age	31.6	33.9	NS
Amps	22.4	31.6	NS
E2	1919	5271	0.001
Oocytes	18.1	23.1	0.001
E.Trans.	3.3	3.4	NS
E. frozen	2.5	3.1	NS
PR	64.2	24.2	<0.001
Impl R	29.3	8.5	0.02
OHSS	0	12.9	0.04

Luteal E2

Supplementing luteal E2 ?

Not supported by donor-egg IVF data (mock cycles).

de Ziegler D. J Clin Endocrinol Metab, 1992:74:322-31.
Younis JS. Fertil Steril 1994;62:103-7.

Not supported by early IVF data

Smitz J. Human Reprod 1988;3:585-90
Smitz J. Human Reprod 1992;7:168-75
Smitz J. Human Reprod 1993;8:40-5

Motivated by fear of mid-luteal drop in E2 levels

Hung E. Human Reprod 2000;15:1903-8 *Trend only*
Sahara F.I. Human Reprod 1999;14:2777-82

Are IVF results better when hCG is used for luteal support?

Yes: Hutchinson-W KA Fertil Steril 1990;53:495-5001 Not R, n = 70

No: Martinez F. Gynecol Endocrinol 2000;14:316-20 PRS, n = 310

Supplementing luteal E2 ?

Farhi et al.

Fertil Steril 2000;73:761-6

Prospective randomized study in 271 IVF patients whose E2>2500pg/ml

E2 Micronized E2 (2mg BID), starting 7 days after ET

P4 50mg im Q day +50 mg vag BID

	P	*P+E2*
n patients	142	129
n cycles	149	136
long GnRH-a	113	101
short GnRH-a	36	35
emb transf	3.8	3.7
PR	23.4	33.8
long GnRH-a	25.6	39.6*
Impl rate	9.6	14

Supplementing luteal E2 ?

Jung H and Roh HK *J Assist Reprod Genet 2000;17:28-33*

Prospective randomized study in 81 IVF patients (85 cycles)

E2 Micronized E2 (2mg BID), starting day3 of menses until luteal phase

	Controls (n = 27)	E2 (n = 58)
PR	25.90%	48.30%
IR	10%	26%

No impact on fertilization rate

Late follicular P↗

Late luteal elevation of plasma progesterone

P elevation associated with IVF poorer outcome

Schoolcraft W. Fertil Steril. 1991;55:563-6.
Mio Y. Fertil Steril. 1992;58:159-66.
Dirnfeld M. J Assist Reprod Genet. 1993;10:126-9.
Fanchin Fertil Steril. 1993;59:1090-4.

P elevation only affects the endometrium

Fanchin Fertil Steril. 1996;65:1178-83.

P elevation has no impact on IVF outcome

Silverberg KM. J Clin Endocrinol Metab. 1991;73:797-803.
Givens CR. Fertil Steril. 1994;62:1011-7.
Hofmann GE. Fertil Steril. 1996;66:980-6.
Abuzeid MI. Fertil Steril. 1996;65:981-5.
Lindheim SR. J Assist Reprod Genet. 1999;16:242-6.

Late follicular P↗

Late luteal elevation of plasma progesterone

	Weak	Intermediate	Strong
P > 0.9 ng/ml	3.20%	30%	34%
P < 0.9 ng/ml	23%	31%	30%
P	*< 0.05*	*NS*	*NS*

Fanchin R et al. Fertil Steril 1997;68:799-805

Pathophysiology :

Which are the respective roles of FSH, LH and hCG on P and androgen elevation during the late follicular phase?

The designated suspect, LH, was not the culprit, FSH.

Androgens

FERTILITY AND STERILITY

Fanchin et al.
Fertil Steril
1995, 1997, 2000

P, Androgens
T & D4

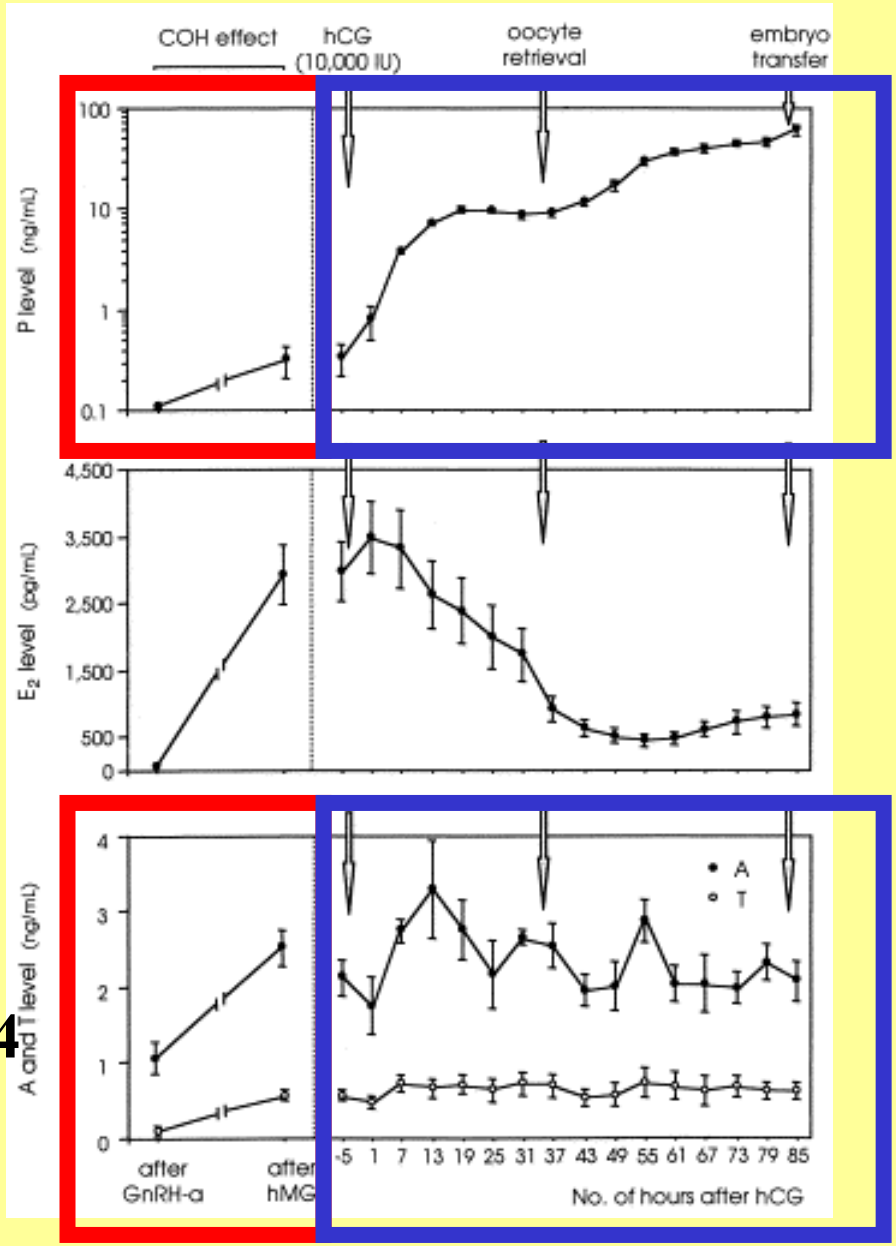
Effects of FSH

Effects of hCG

P

D4

T



FSH rather than LH increases late foll. P4 and A.

Luteinizing hormone increases estradiol secretion but has no effect on progesterone concentrations in the late follicular phase of in vitro fertilization cycles in women treated with gonadotropin-releasing hormone agonist and follicle-stimulating hormone

Adonakis G. et al. Fertil Steril 1998;69:450-3.

George Adonakis, M.D., Nalinee Deshpande, M.R.C.O.G., Robert W.S. Yates, F.R.C.O.G., and Richard Fleming, Ph.D.*

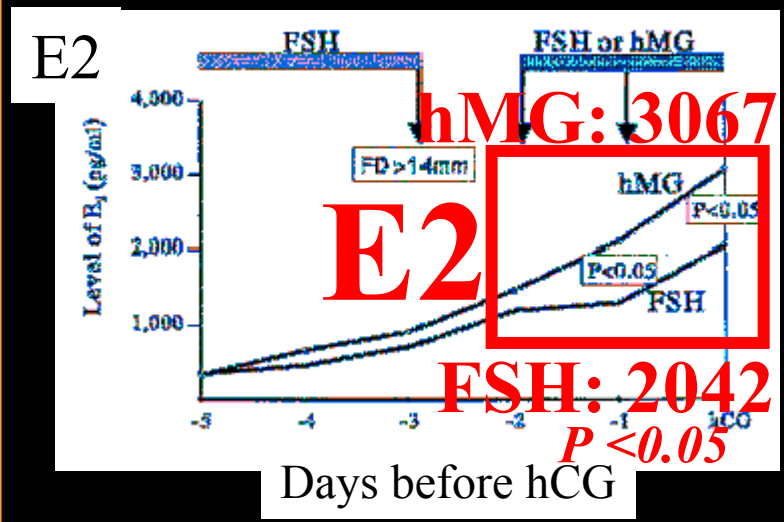
University Department of Obstetrics and Gynaecology, Royal Infirmary, Glasgow, United Kingdom

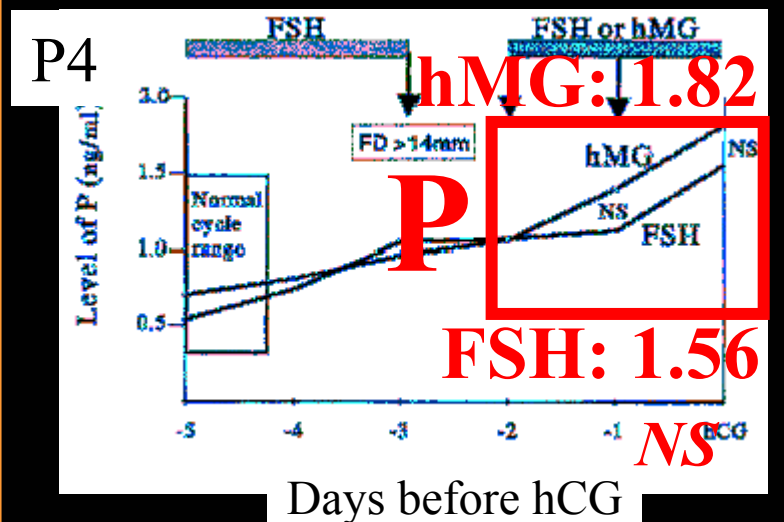
Prospective randomized: (n = 40)

COH with GnRH-a and FSH 300 IU/day until foll. ≥ 15 mm

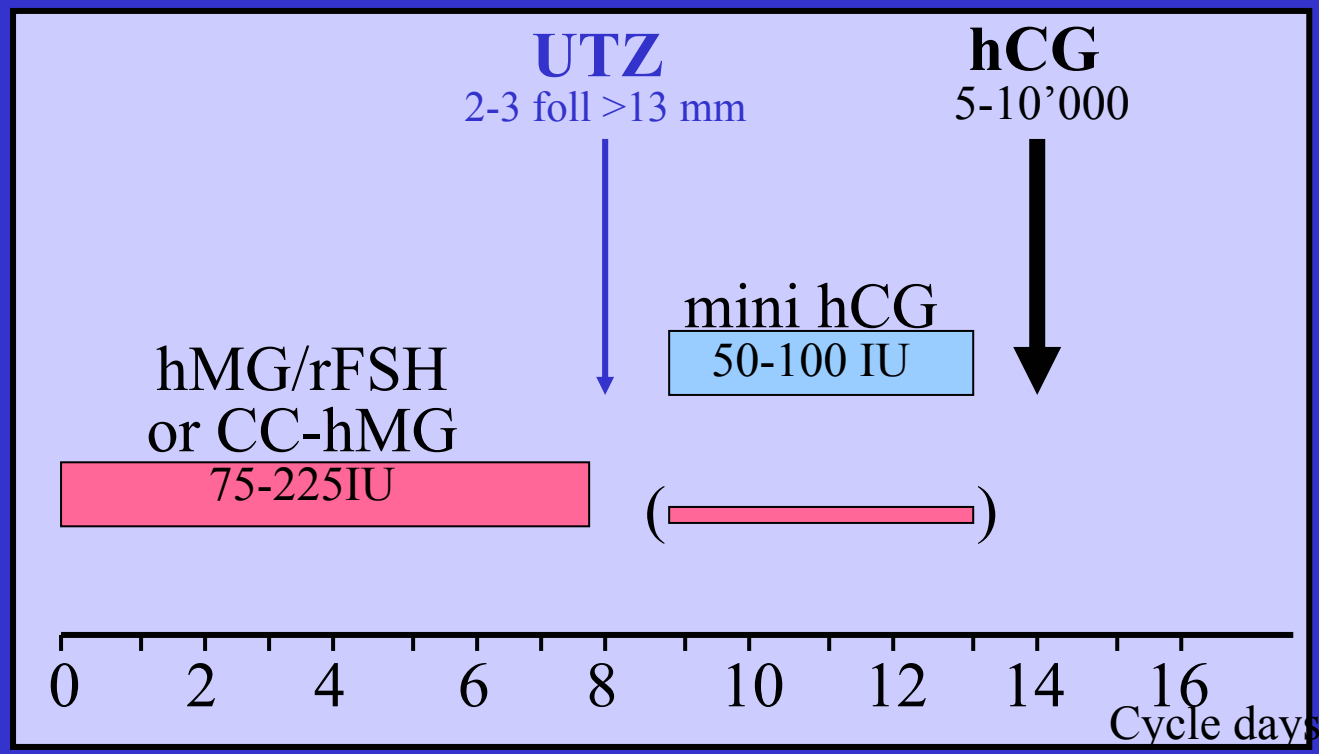
Then, either:

- FSH 225 IU
- hMG 225 IU





Sequential hMG/rFSH - mini hCG regimen



Used when OHSS is feared (PCOD)
Experience on 18 patients
No premature P elevation, normal E2 rise
Cx mucus and endom. unchanged,
Good oocytes, embryo and PR:
IVF 3/5(60%), IUI 4/13(31%), No OHSS

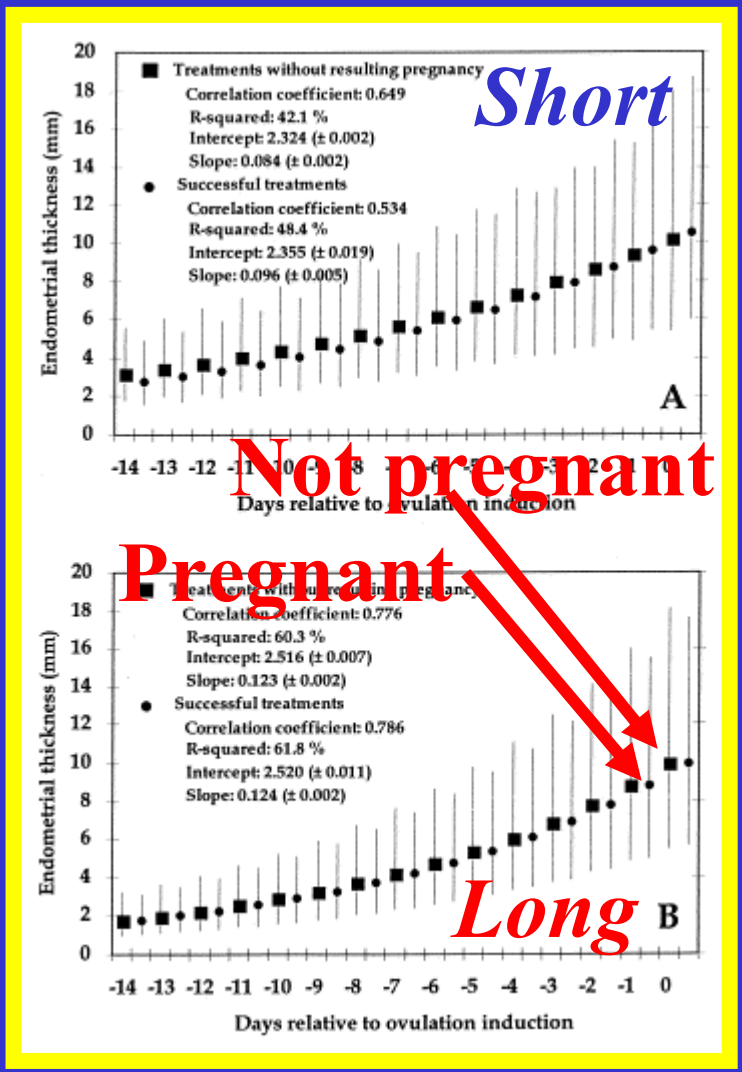
Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women

De Geyter et al., Fertil Steril 2000;73:106-13.

- 539 IUI: cl PR 19.7%
- 712 IVF:cl PR 25.4%

Endom. thickness correlated w/ E2

Odd Ratio for pregnancy only marginally affected by endometrial proliferation



Endometrial echogenicity

Early hyperechogenic changes are of poor prognosis

Renato Fanchin, M.D., Claudia Righini, M.D., Jean-Marc Ayoubi, M.D., François Olivennes, M.D., Dominique de Ziegler, M.D., and René Frydman, M.D.

Department of Obstetrics and Gynecology and Reproductive Endocrinology, Hôpital Antoine Béclère, Clamart, France

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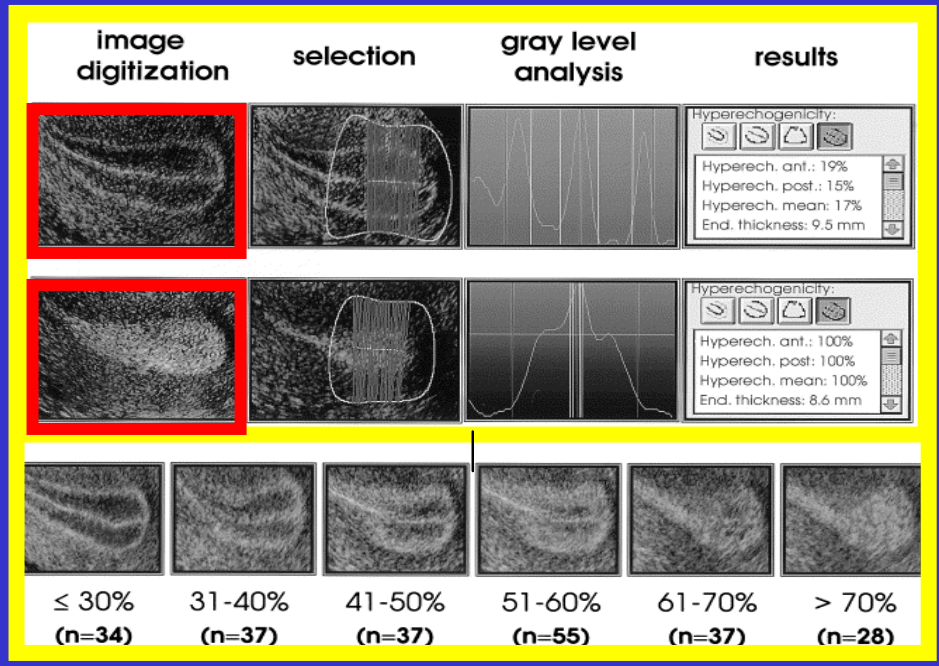
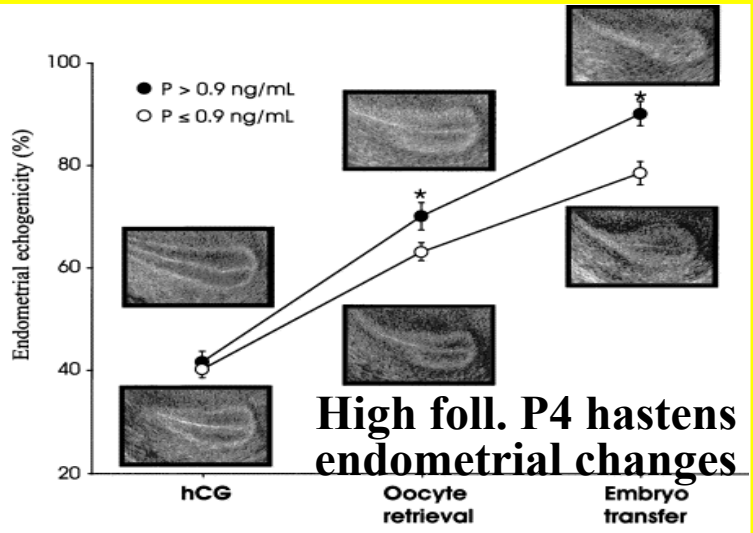
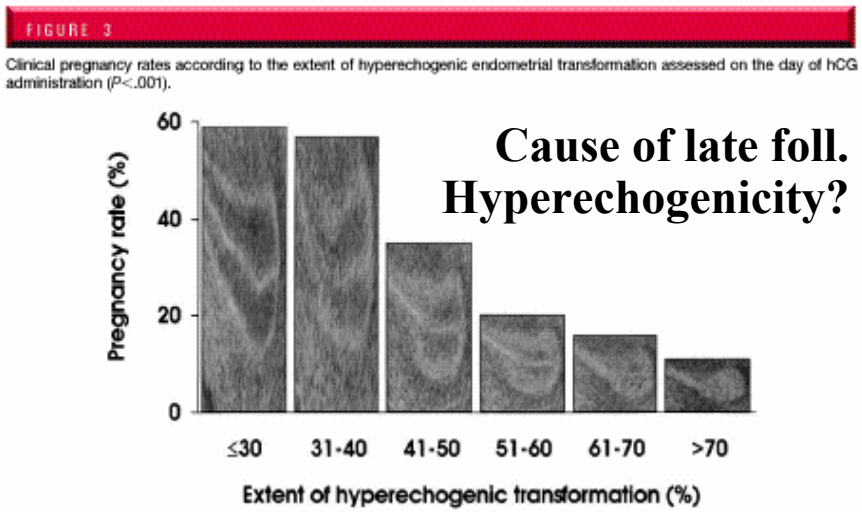




High foll. P4 hastens endometrial changes



Cause of late foll. Hyperechogenicity?

Endometrial echogenicity

Early hyperechogenic changes are of poor prognosis

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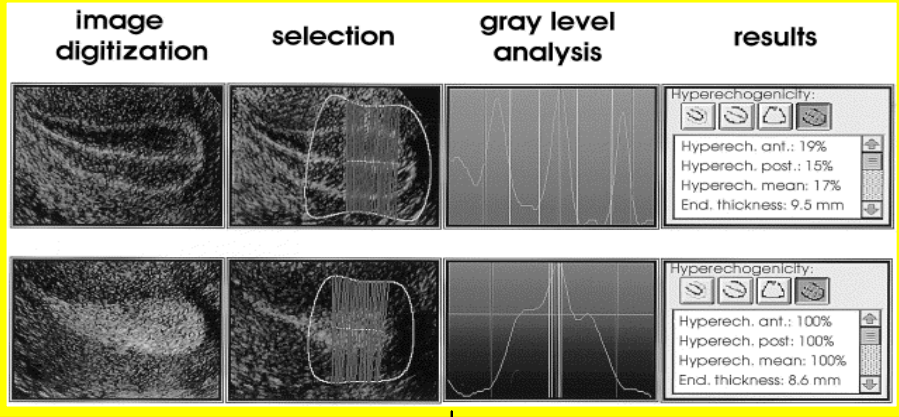
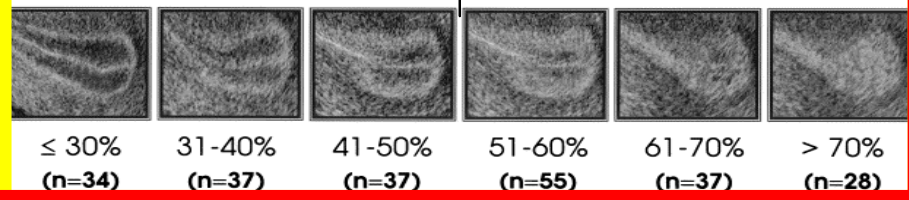
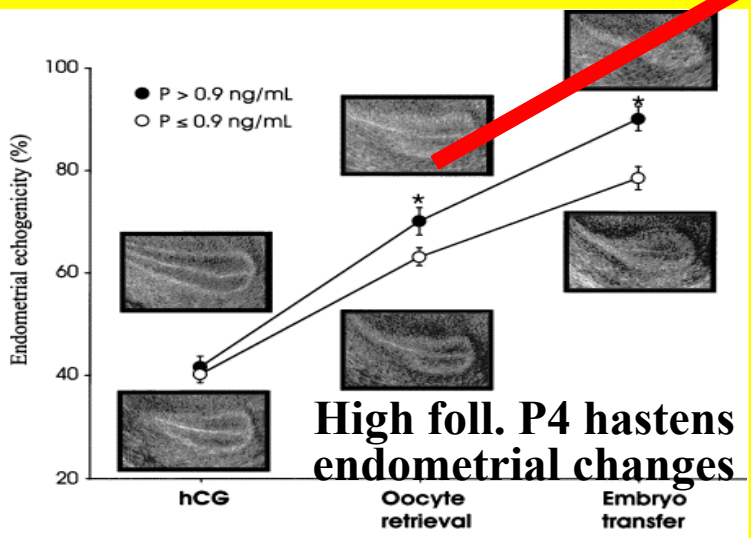


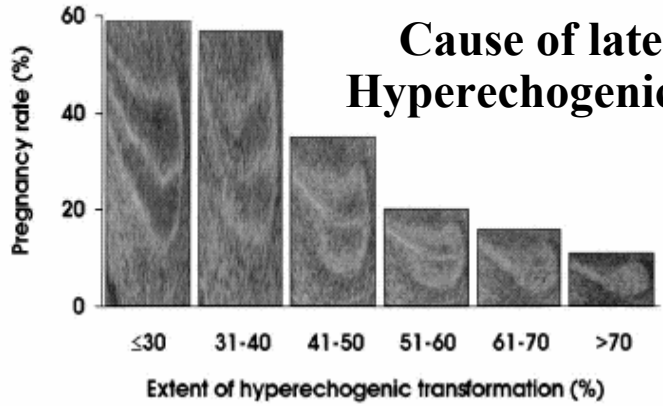




High foll. P4 hastens endometrial changes

FIGURE 3

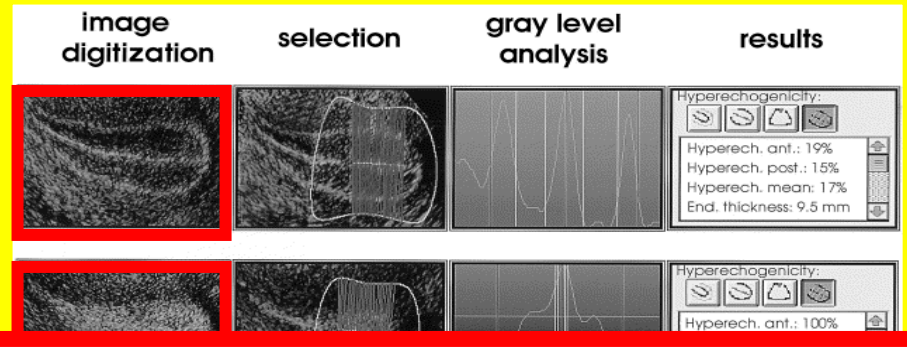
Clinical pregnancy rates according to the extent of hyperechogenic endometrial transformation assessed on the day of hCG administration ($P<.001$).



Cause of late foll. Hyperechogenicity?

Endometrial echogenicity

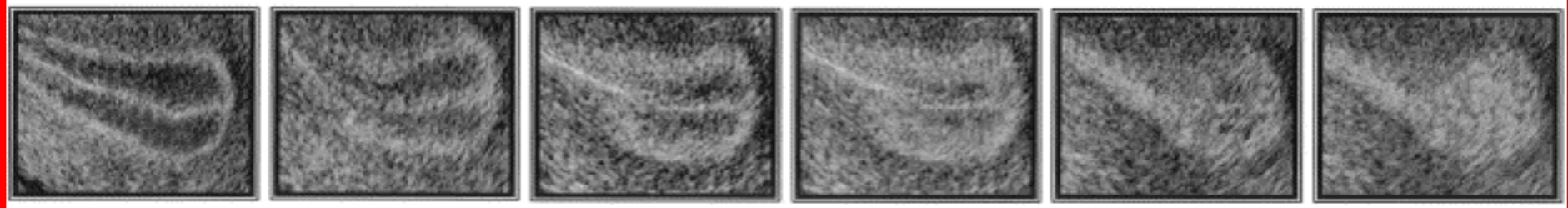
Early hyperechogenic changes



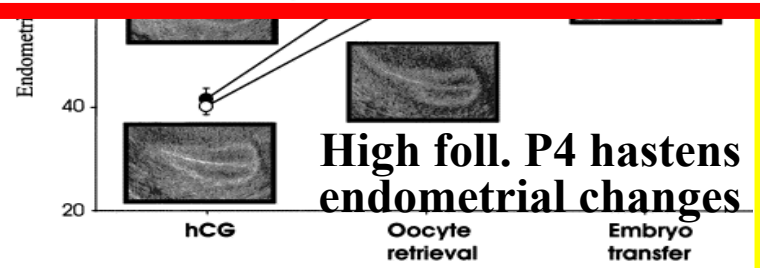
6 echogenicity groups:

Extent of hyperechogenic transformation

Endometrial thickness



≤ 30%	31-40%	41-50%	51-60%	61-70%	> 70%
(n=34)	**(n=37)**	**(n=37)**	**(n=55)**	**(n=37)**	**(n=28)**



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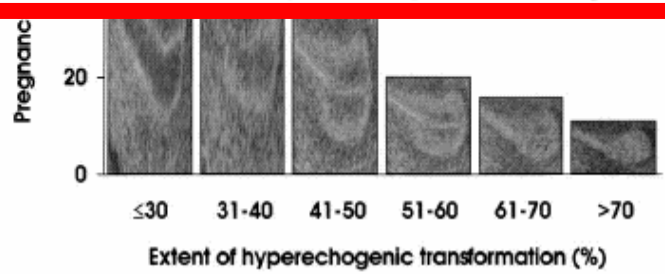

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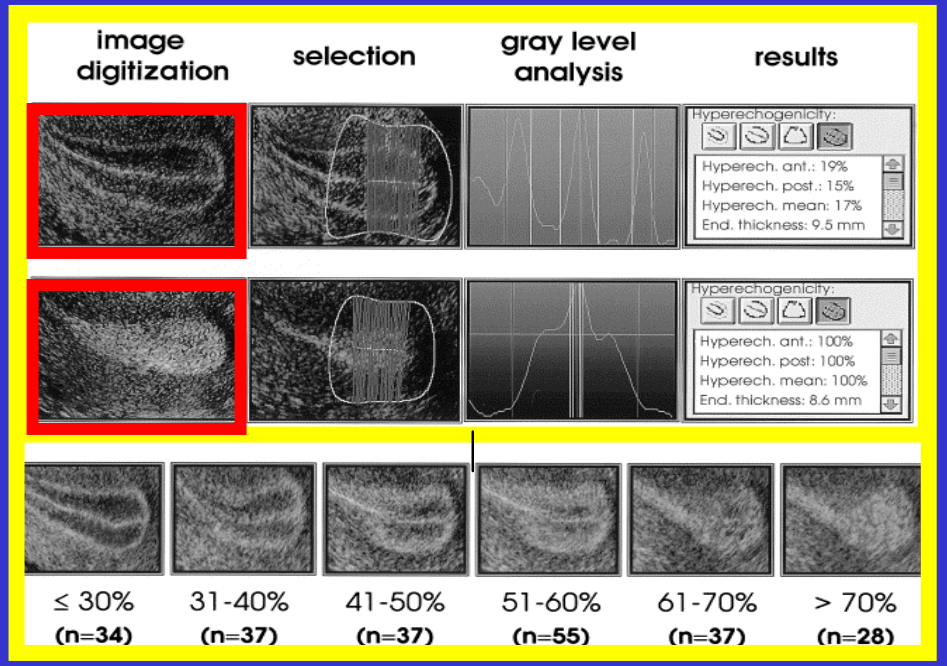

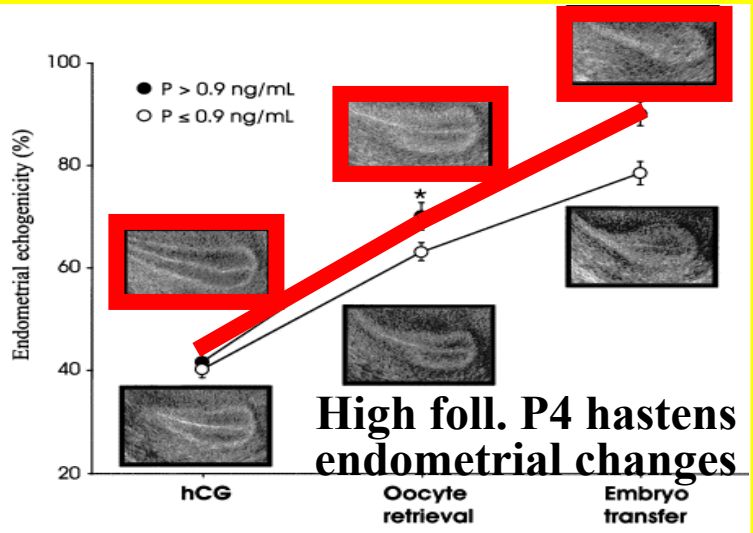

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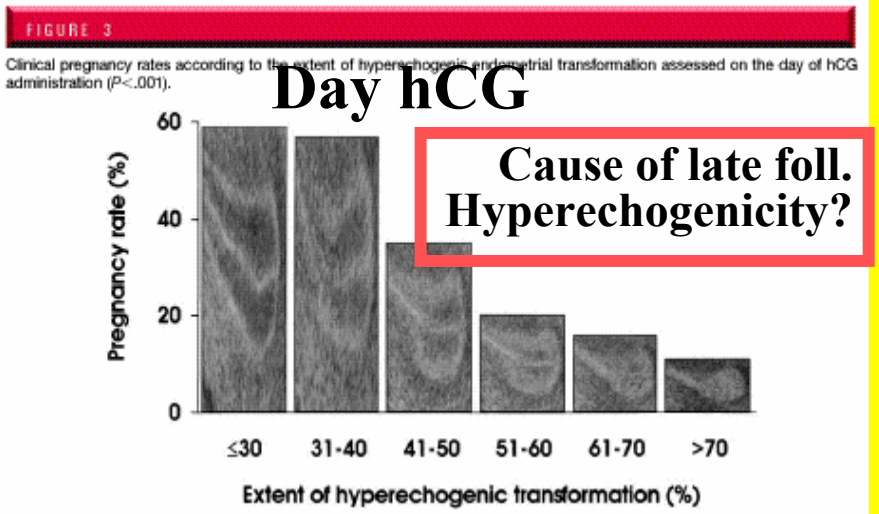
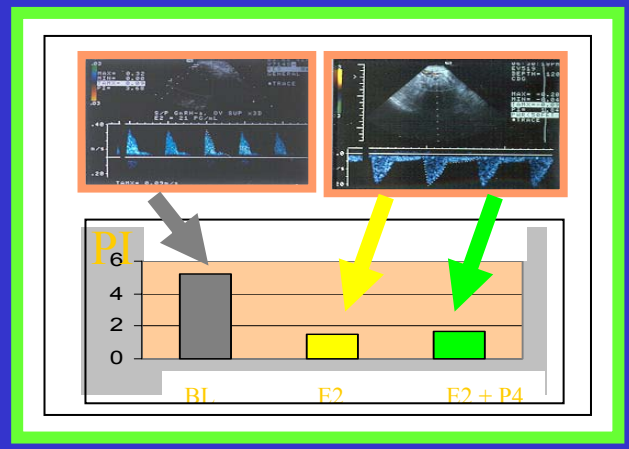


Day hCG

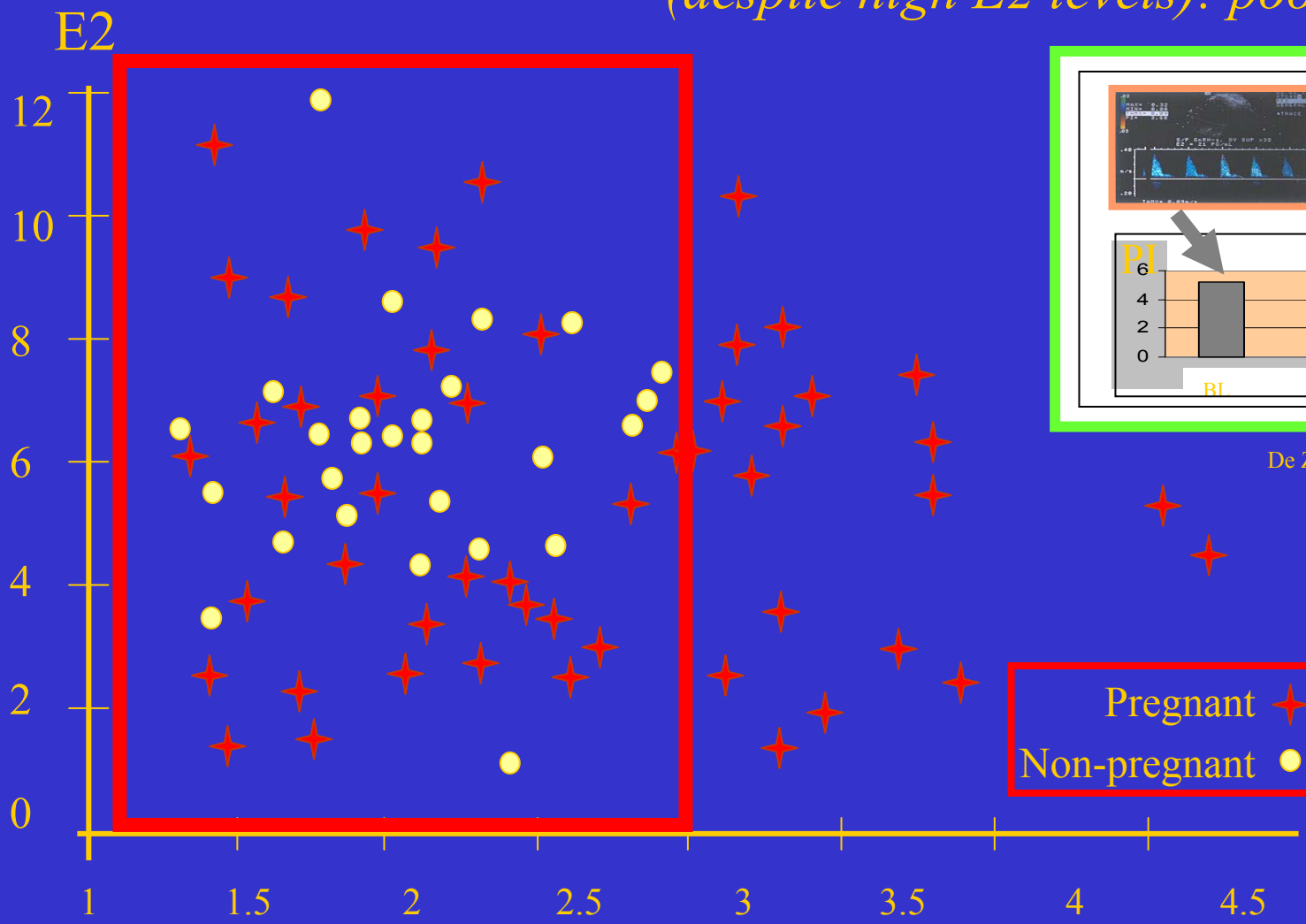
Cause of late foll. Hyperechogenicity?

Uterine Doppler and endometrial receptivity

Early data: PI elevated in a fraction of pts (despite high E2 levels): poor prognosis.



De Ziegler et al. Fertil Steril 1991



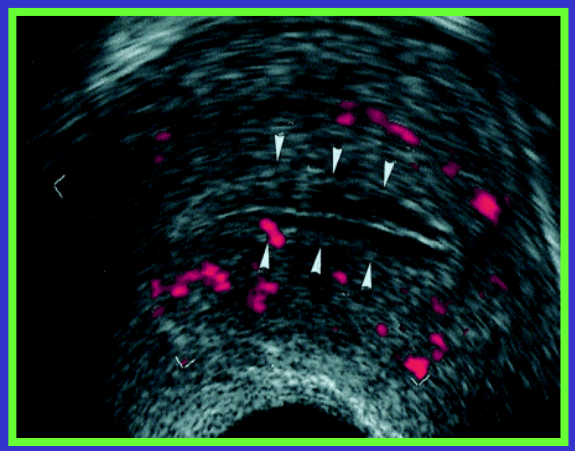
From: Steer et al., Fertil Steril 1992;57:372-6.

Yuval et al., Human Reprod 1999;14:1067-71.

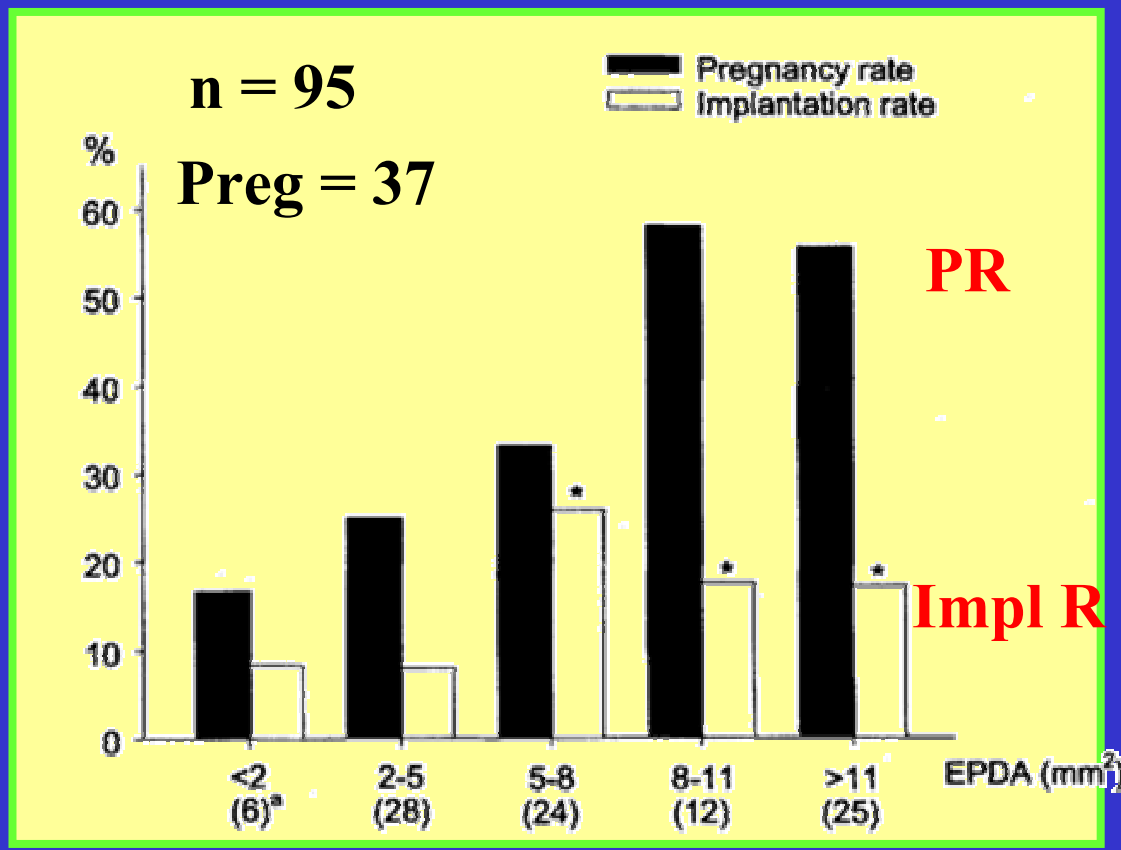
Recent PI data: Low values across the board

	Preg (31)	*Not Preg (125)*	
age	32.1	33.1	NS
E2	1897	1837	NS
oocytes	14.2	11.7	NS
emb.	4.8	3.9	NS
endom th.	10.7	10.9	NS
PI (ret)	0.98	0.99	NS
PI (ET)	1.09	1.1	NS

Yang et al. Human Reprod 1999;14:1606-10



Sub-endometrial and endometrial blood flow Computer assisted assessment of Endometrial Power Doppler Area (EPDA)



Schild RL et al. Fertil Steril 2001;75:361-6.

Neither Doppler of the spiral or uterine arteries nor endometrial thickness or volume was predictive of IVF outcome

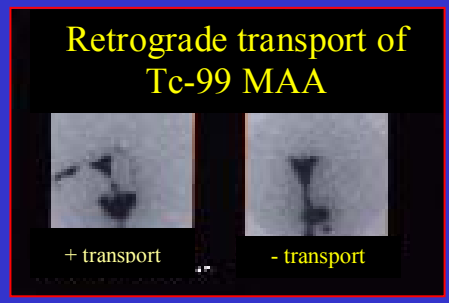
Uterine contractility

Contractility of the non-pregnant uterus

End follicular phase

4-5 UC/min

Mainly retrograde
Involved in sperm transport
Sub-endometrial layers

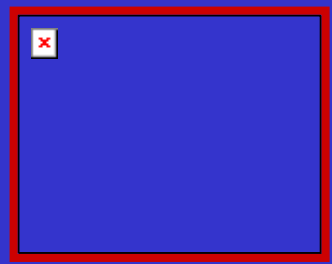


Study displacement of ut content

Mid luteal phase

<2.5 UC/min

Utero-quiescence
Mild biderectional UC

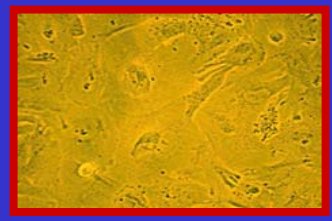


Frequency is primary parameter, UTZ is appropriate

Luteo-follicular transition

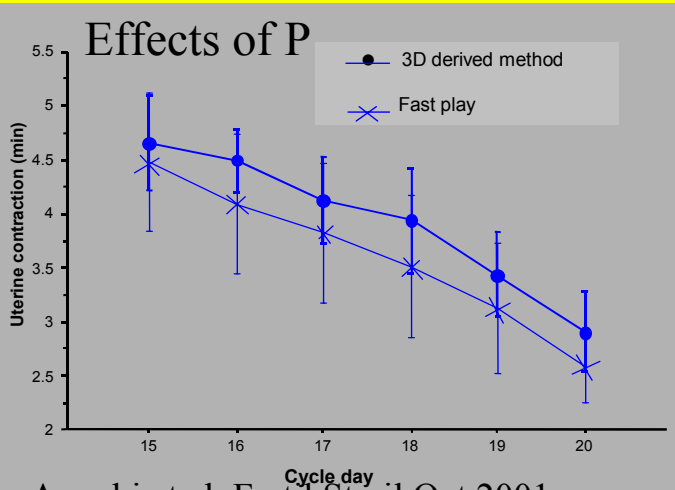
2-3 UC/min

Antegrade
All layers involved
Often painful

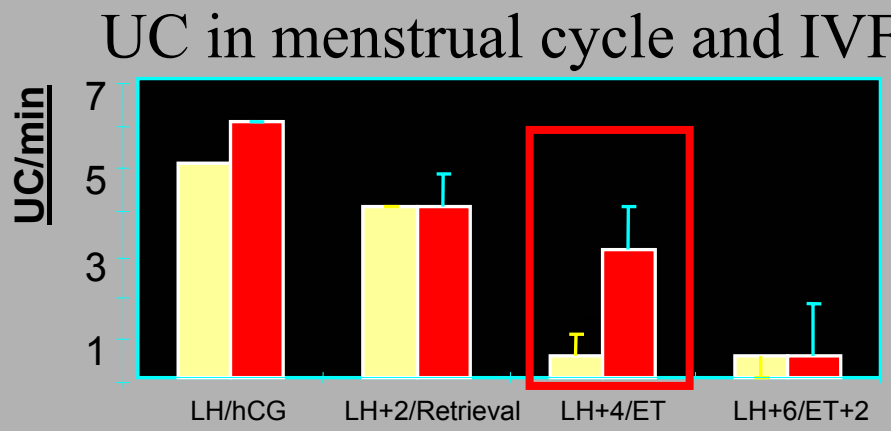


IUP or collection of endometrial debris.

Uterine contractility and IVF

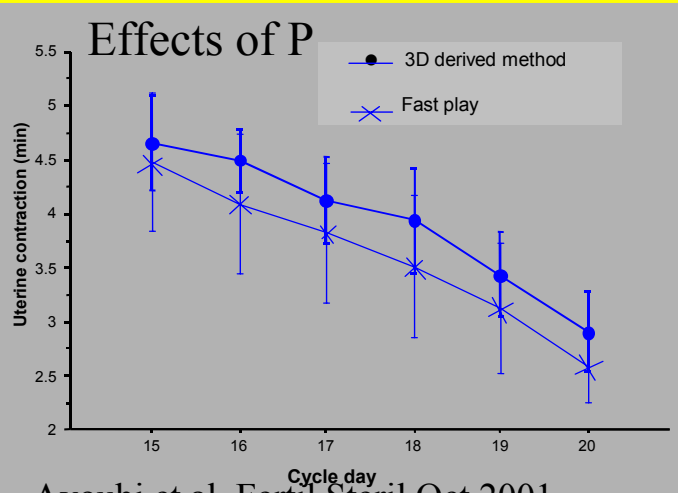


Ayoubi et al. Fertil Steril Oct 2001

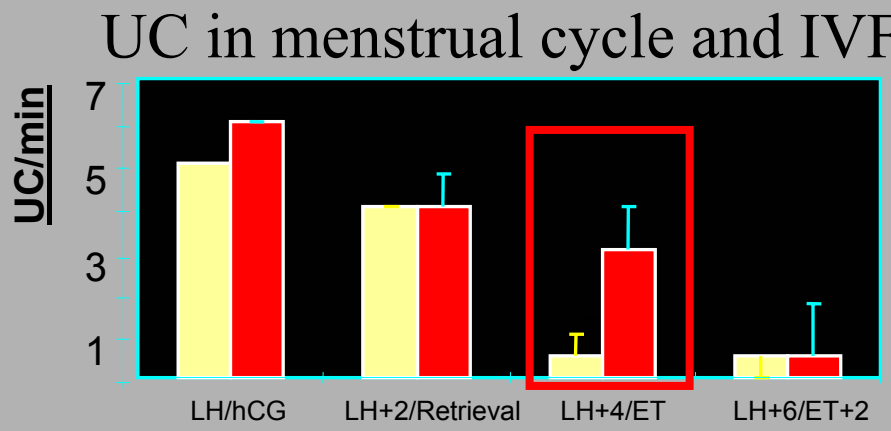


Epiney et al. ASRM 2000

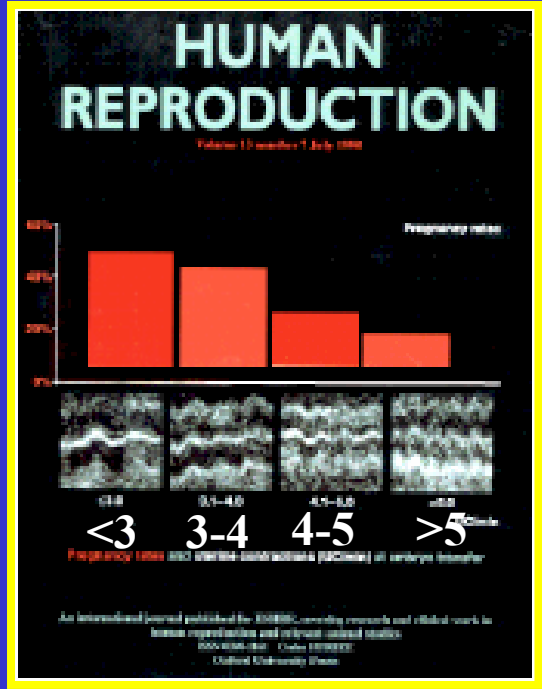
Uterine contractility and IVF

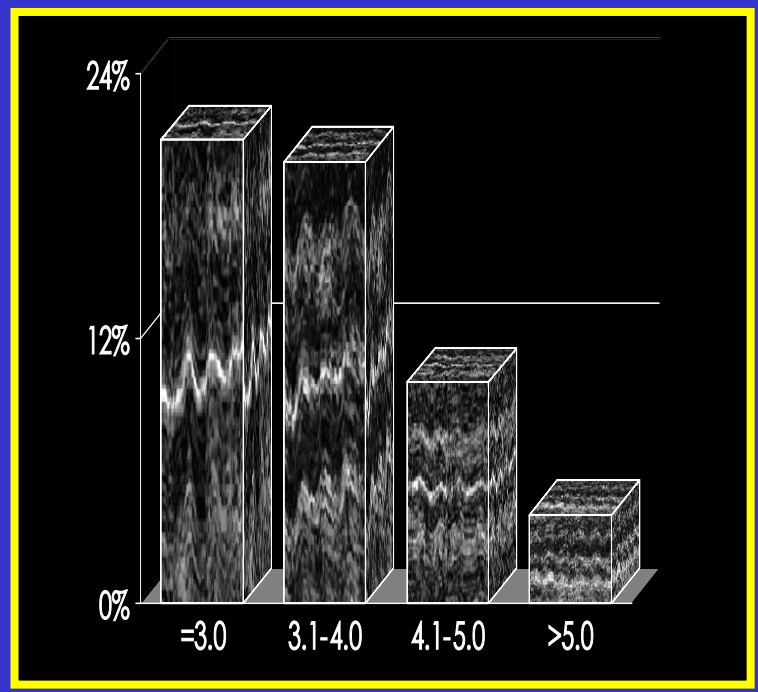


Ayoubi et al. Fertil Steril Oct 2001



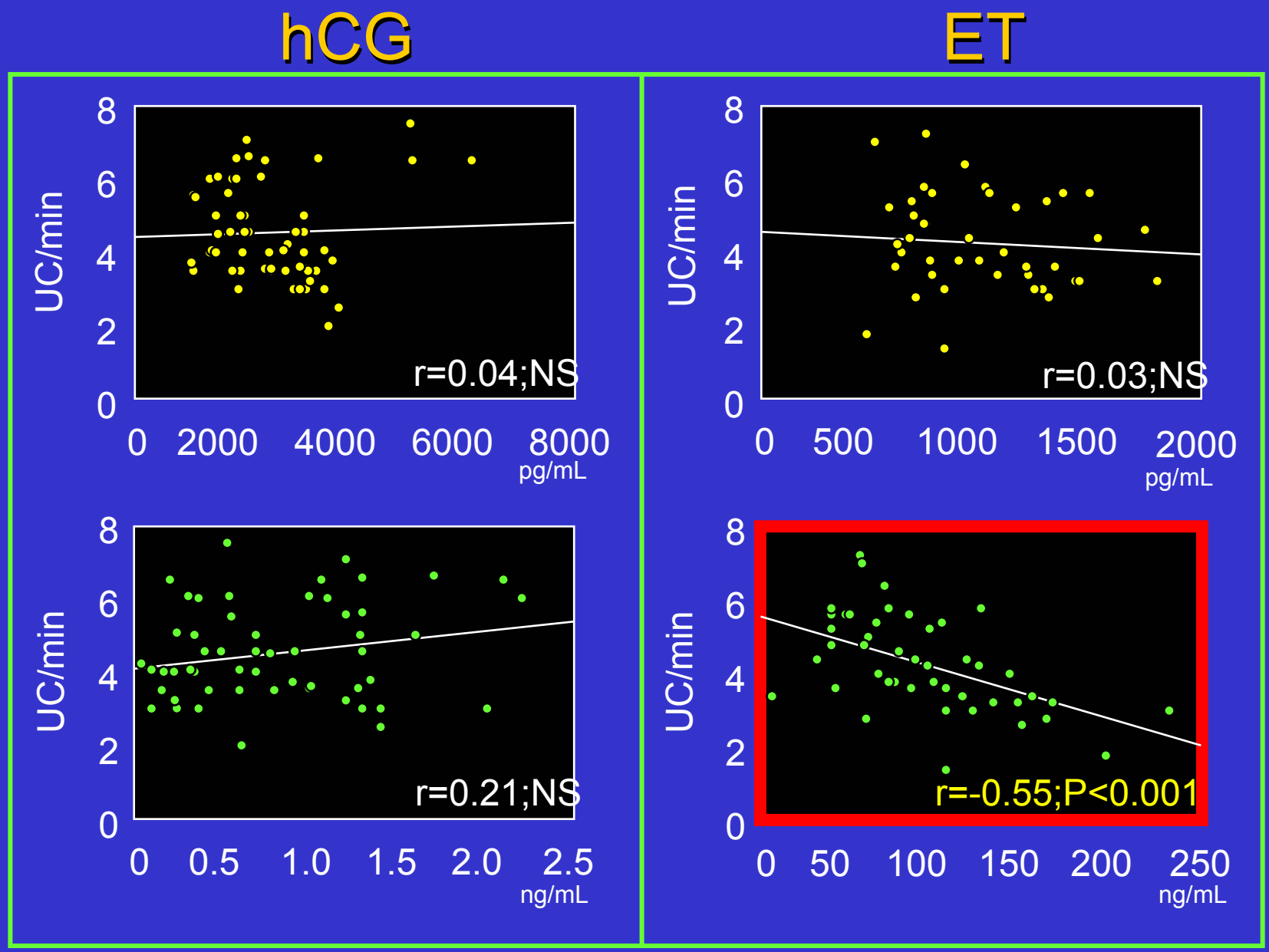
Epiney et al. ASRM 2000





In IVF, high E2 levels induce a relative resistance to the uteroquiescent properties of P4

Uterine contractility and hormonal levels



Uterine contractility and IVF

Woolcrott and Stanger Human Reprod 1997;12:963-6.

Potentially important variables identified by transvaginal UTZ-guided embryo transfer

Endometrial movement was obvious in 36.4% (44/121) of cases

	active movment	no movement seen
Preg.	45.4%(20/44)	15.6%(12/77)

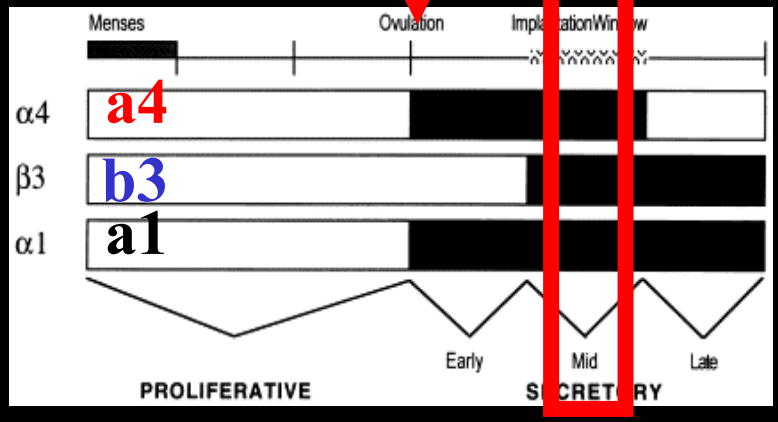
Biology of endometrial receptivity

e g r I n s

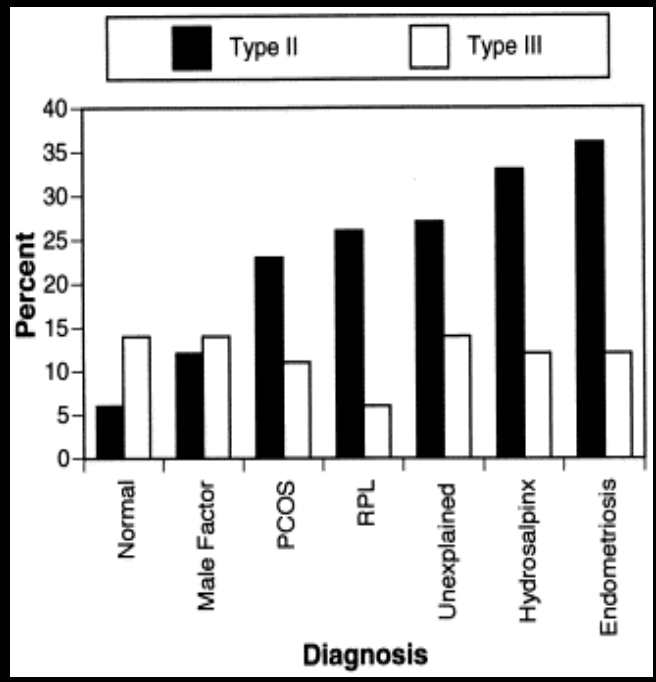
Ovulation

Implant.

n=1050



Lessey et al. Fertil Steril 2000;73:77987

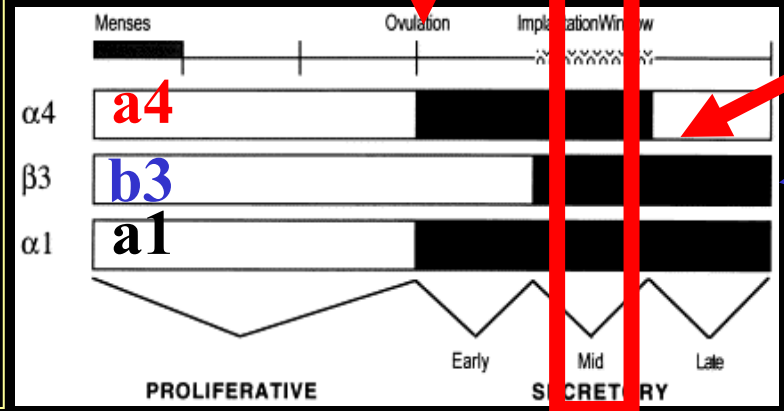


Biology of endometrial receptivity

e g r I n s

Ovulation

Implant.



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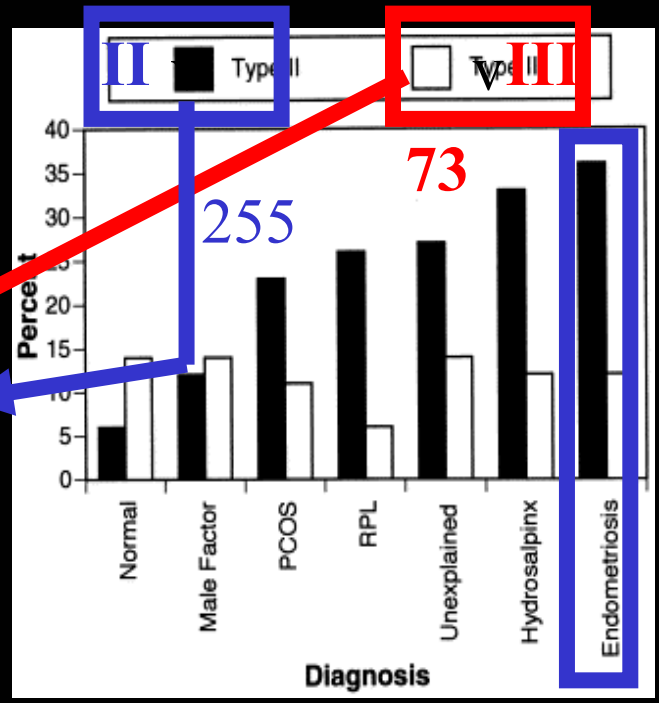
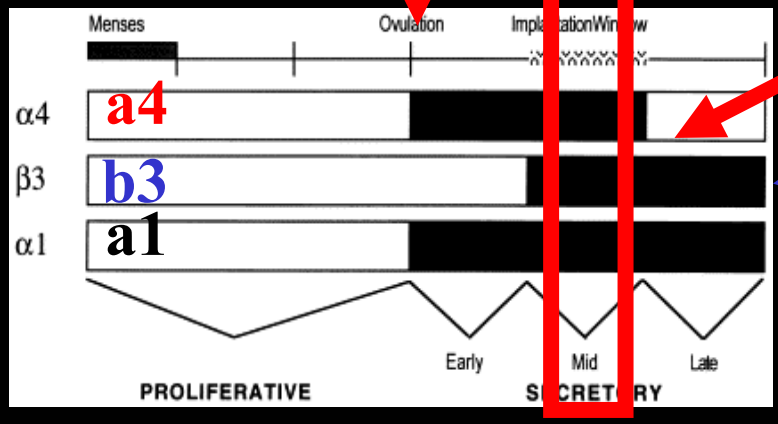


Biology of endometrial receptivity

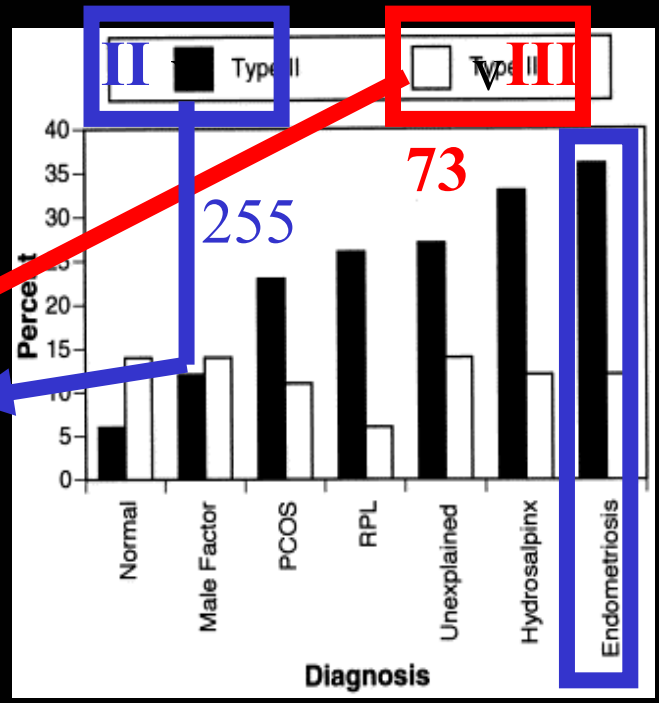
e g r I n s

Ovulation

Implant.

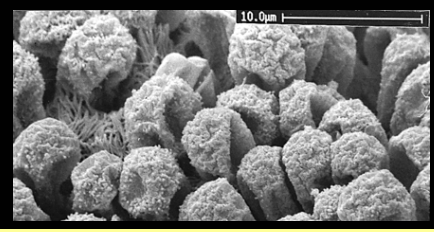


Lessey et al. Fertil Steril 2000;73:77987



Endometrial ultra structure

Pinopodes



	pinopodes	PR	
Nat cycle	20-21	20	Acosta et al. FS 2000;73:788-98
COH	18-19	19	Deveioglu et al. FS 1999;71:1040
E2/P	22	21-22	

Effects of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity

Raymond EG et al. Human Reprod 2000;15:2351-5

Population

19 women underwent a control and study cycle

Treatment

On day of LH surge:
100 mg EE
1 mg norgestrel

EMB 9 ds after LH surge

	Yuzpe	Control	P
	(n = 19)	*(n = 19)*	
Ultrasounds			
Endom. Thick.	**7.58**	9.79	**0.001**
Edometrium (HSCORE)			
b3 integrins	1.75	1.19	NS
Glycodelin	2.39	3.32	NS
LIF	2.33	2.05	NS
MUC-1	**2.30**	3.16	**0.05**
ER	**1.58**	0.82	**0.009**
PR	0.01	0.02	NS
Serum			
E2 (pg/ml)	**102.89**	140.14	**0.007**
P (ng/ml)	13.12	13.65	NS
Glycodelin (mcg/ml)	3.65	3.65	NS

Serum CA 125 concentrations as predictor of pregnancy

CA 125: glycoprotein also produced in the endometrium and measurable in peripheral blood. Could it predict endom. receptivity?

⊕ Predictor of pregnancy

Tavmergen E *et al*. Human Reprod 2001;16:1129-34.

	Non-pregnant	Pregnant	P
n = 75	40(53.3%)	35(46.7%)	
day hCG -2	6.04	14.4	<0.001
day hCG -1	5.92	14.26	<0.001
day retrieval	5.9	15.94	<0.001

Miller KA *et al*. Fertil steril 1996;65:1184-9.
CA 125 > 16IU/ml day hCG, best predictor of P

Chryssikopoulos A *et al*. Fertil Steril 1996;66:599-603.
Elevation of CA 125 in serum
but not in foll fluid

⊖ Predictor of pregnancy

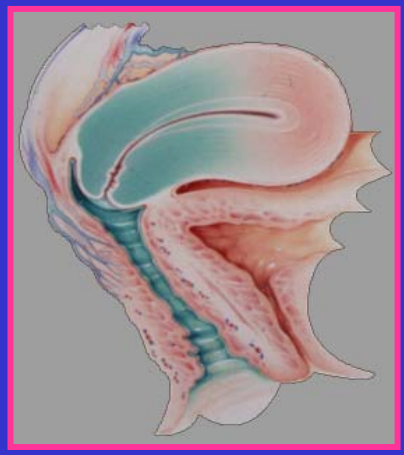
Brandemberger AW *et al.* J Assist Rprod Genet 1998;15:390-4.

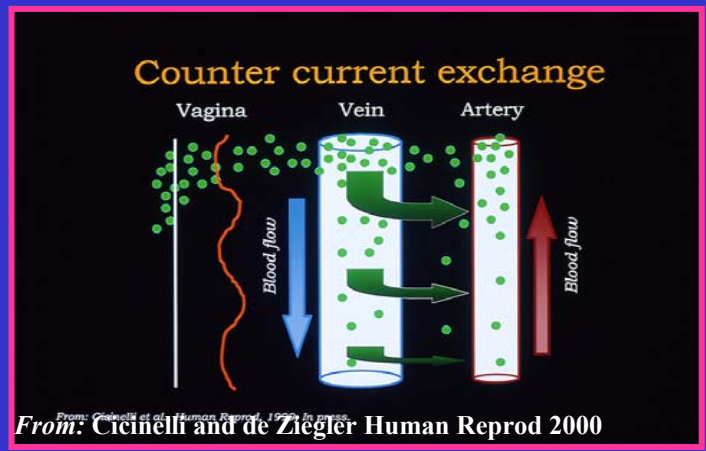
Noci I *et al.* Human Reprod 1999;14:1773-6.

Unkila-Kallio L *et al.* Fertil Steril 2000;74:1125-32.

Explanation for the discrepancy may lie in assay specificity

Intercourse and endom. receptivity





From: Cicinelli and de Ziegler Human Reprod 2000

Tremellen *et al.* Human Reprod 2000;15:2653-8.

	Frozen emb transfers		Fresh IVF	
	intercourse	no ointercourse	intercourse	no ointercourse
# cycles	91	87	151	149
# embryos	168	171	486	518
early PR	15.4	16.1	28.5	24.3

	Intercourse	No intercourse	P
#cycles	242	236	
# emb transferrred	654	689	
Clinical preg	57(23.6)	50(21.2)	NS
Ongoing pregt	47(19.4)	39(16.5)	NS
% viable embryo	11.01	7.69	0.036

Positive effects

Belline BS. *et al.* Fertil Steril 1986;46:252-6.

Marconi G, *et al.* Fertil Steril 1989;51:357-9.

No effects

Fishel S *et al.*. Ferrtil Steril 1989;51:135-8.

Quasim SM *et al.* Human Reprod 1996;11:1008-10.

Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The "too thin" endometrium
- Uterine contractility

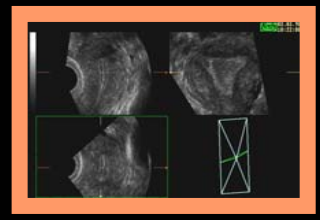
Ultrasound

To rule out endometrial polyps and/or sub mocosal fiibroids

Enhanced contrast (hystero-sonogram)

"3-D" reconstruction

Built-in or off-line systems



Hysteroscopy

Can be performed during OC pretreatment phase

Practical measures to optimize endometrial receptivity

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- Uterine contractility

- COH induces a >doubling of plasma testosterone levels. Possibly, more in some women (PCOD)?
- Okon MA *et al.* Fertil Steril 1998;69:682-90.

A are higher in women w/ recurrent miscarriages

- Tuckerman EM *et al.* Fertil Steril 2000;74:771-9.

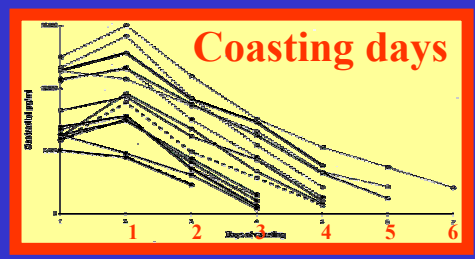
A inhibit endom cell growth

OC pill

Decreases plasma and ovarian androgens

Minimize FSH, possibly coasting

By reducing FSH stimulation, coasting may lower androgens with E2



dexamethasone

Decreases androgen (testosterone and A4) levels by blocking the adrenal contribution

- End-follicular phase androgens are lower
- Absolute value of FSH driven increase unchanged

Practical measures to optimize endometrial receptivity

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Aqueous fluid

Look for hydrosalpynx
Consider salpyngectomy or tubal ligation

	n cycle	Dx TF	Hydro (UTZ)	PR
n Pt	843	327	71	348(41.3%)
ECF +	57(6.8%)	40(12%)	5(7%)	15(26%)
ECF-	786(93.2%)	287(87.8%)	66(93%)	333(42.4%)
p	*Levi et al. ASRM 2000, # O-036*			0.02

Mucoid fluid

Sometimes (rarely) encountered throughout the menstrual cycle, unknown etiology.
Empirical approach:
D&C to R/o mucoid tumor and course of broad spectrum antibiotics

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Verify quality of measurements

- Measure "between" rather than "during" uterine contractions
- If < 5 mm, differ ET

Exclude

- Endometritis
- s/p RT
- Enzymatic induction

(donor-egg IVF and frozen embryo transfers)

Consider vaginal E2

- Estrace vaginal cream: 1g gel/0.1 mg E2
- Oral Estrace tablets 1-2 mg

(as safe as oral E2 despite E2 levels >1000 pg/ml)

Practical measures to optimize endometrial receptivity

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Low dose aspirin

Rubinstein et al.
Fertil Steril 1999;71:825-9.

	aspirin	*placebo*	*P*
age	35.9	35.4	NS
foll	19.8	10.2	,.05
oocytes	16.2	8.6	,.05
emb trans	3.3	3.3	NS
impl rate	17.8	9.2	,.05
clin PR	45	28	,.05
PI (ut art) d2	1.98	2.01	NS
PI (ut art) d hCG	1.22	1.96	<.05

Vasodilators

- NO donors
- phosphodiesterase inhibitors

Sher G. Human Reproduction, 2000;15:806-9.

Practical measures to optimize endometrial receptivity

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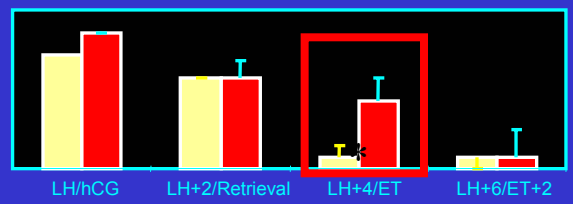
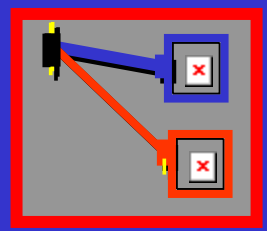
If UC frequency is excessive before ET:

Delay ET until blastocyst

Epiney et al.
ASRM 2000



Early onset of progesterone



Use utero relaxant

Candidates:

- betamimetics (terbutaline, ritordrine)
- NO donors *(terbutaline, nitroprussiate)*
- Ca channel blockers
- Xylocain

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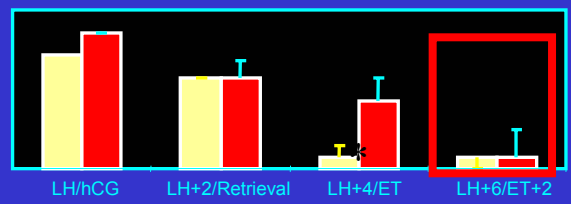

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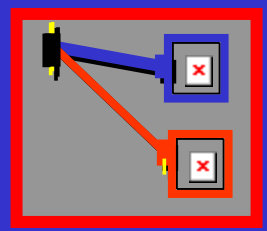

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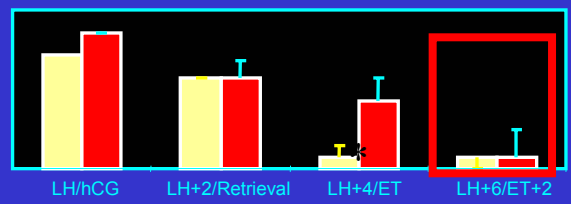
Epiney et al.
ASRM 2000



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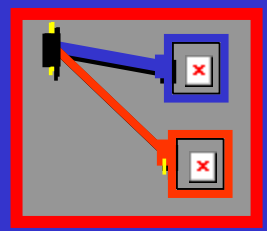

Day ET: 29%

Day retr.: 42%

Use utero relaxant

Candidates:
- betamimetics *(terbutaline, ritordrine)*
- NO donors *(nitroglycerin, nitroprussiate)*
- Ca channel blockers
- Xylocain

<ddeziegler@compuserve.com>

<ddeziegler@compuserve.com>