

HEALTHIER IVF – YES WE CAN

- READY
- S.E.T
- FREEZE ALL

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BACKGROUND

→ HYPOTHESIS

MATERIALS & METHODS

RESULTS: *Stimulated Vs Unstimulated ART*

CONCLUSIONS

HYPOTHESIS

IVF / ICSI / FET singleton pregnancies have a higher incidence of ante-partum haemorrhage, placenta praevia, low birth weight, pre-term delivery and Caesarean section than **GIFT** or non-ART pregnancies in sub fertile women or women from the general community.

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BIRTHS DATABASE

- ❖ Perinatal Data Collection Unit, Dept. Human Services, Victoria Australia
- ❖ Mandatory Reporting
- ❖ All births >20 weeks gestation
- ❖ 99.6% of all births: 1996 audit
- ❖ 1991 – 2004: 862,000 singleton births

IVF DATABASES

- ❖ Monash University – Monash IVF
- ❖ University of Melbourne – Melbourne IVF
– M.A.C.C
- ❖ Mandatory
- ❖ >99% of IVF patients coded

RETROSPECTIVE COHORT

– *record linkage study between births and
ART databases*

❖ 862,000 singleton births (1991-2004)



❖ 3 births randomly selected from
matched sub sample of all births,
matching done for each IVF or ICSI
birth on maternal year of birth and
baby year of birth

❖ GIFT and subfertiles are separate

RECORD LINKAGE

- ❖ Linkage WIZ
- ❖ Match data from ≥ 2 records
- ❖ Matches on common variables:
name, DOB, post code
- ❖ Sum of agreement/disagreement
weights

POWER CALCULATION

- ❖ PDCU Data
- ❖ Parity 1
- ❖ Singleton Births
- ❖ Epiinfo TM v6 - 80% power at 5% level

COMPARISON GROUPS

General Population	25,397
IVF stimulated cycle	2,184
IVF –unstimulated cycle	1,767
ICSI- stimulated cycle	2,688
ICSI – unstimulated cycle	1,519
GIFT	843
Subfertile	2,182

BACKGROUND

HYPOTHESIS

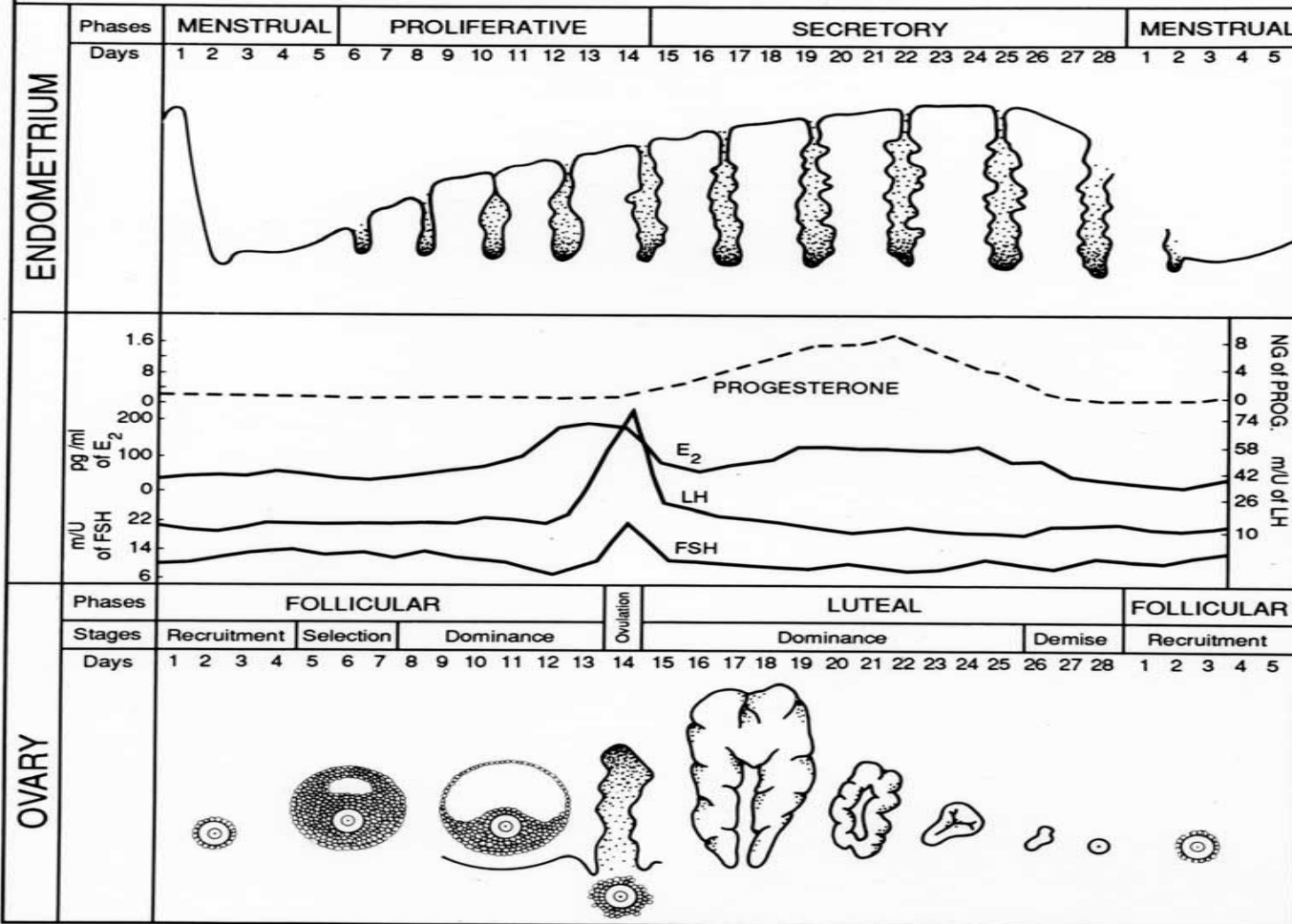
MATERIALS & METHODS



RESULTS: *Stimulated Vs Unstimulated ART*

CONCLUSIONS

NORMAL MENSTRUAL AND OVARIAN CYCLES



Chemokines strongly expressed

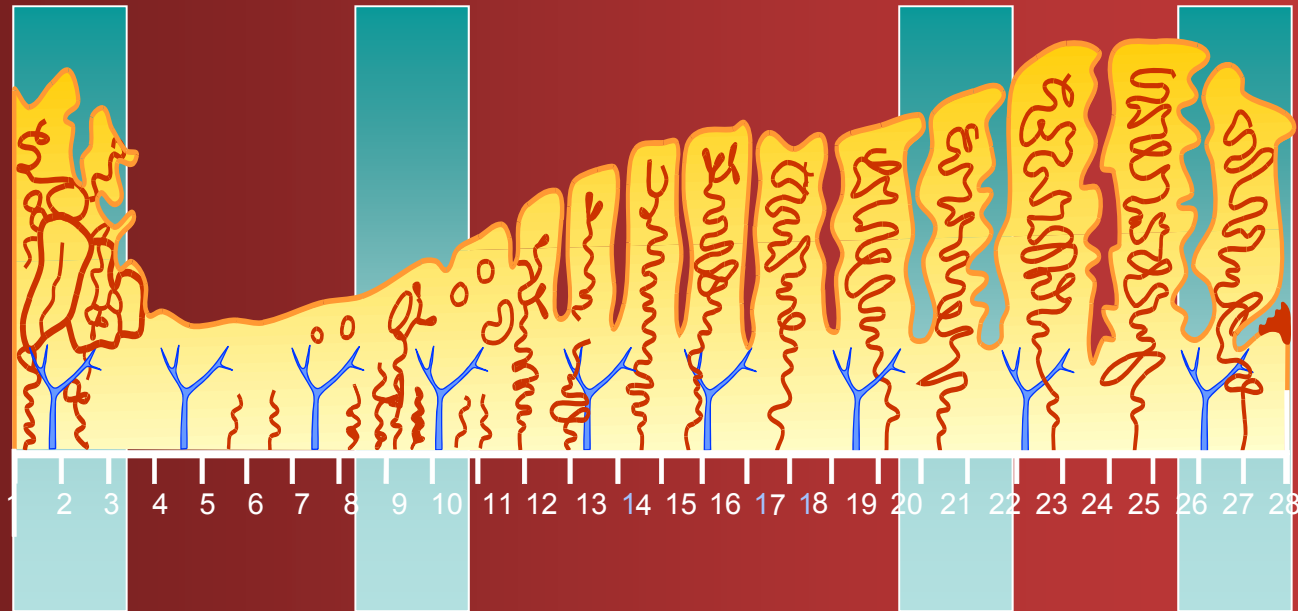
IL-8
HCC-4

MIP-1 β
HCC-4
Eotaxin

6Ckine
MIP-1 β
HCC-4
HCC-1

6Ckine
HCC-1
IL-8

MDC / MCP-3 / FKN



Leukocyte subtypes present

Menstrual

Ne
Eo
Mac

Proliferative

Mac

Mid Sec

uNK
Mac
T cells

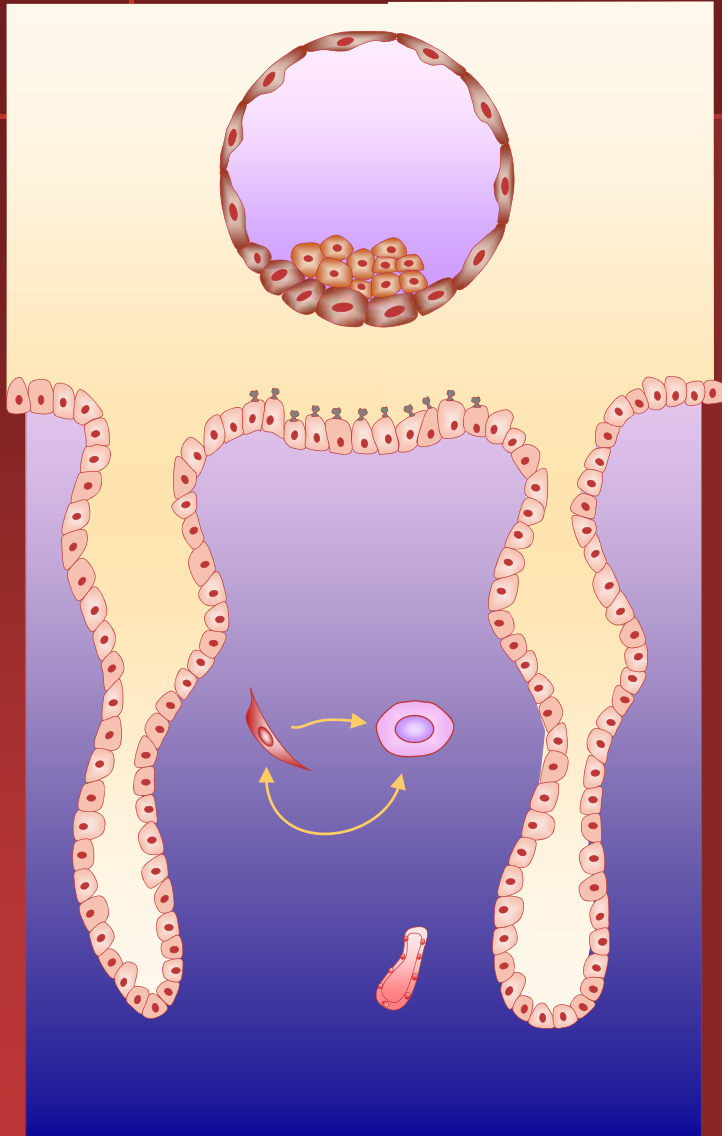
Late Sec

Ne
Eo
Mac



Jones et al, JCEM, 2006

Factors regulated during early implantation



Location

Factors

Trophoblast

Adhesion molecules
Cytokine & chemokine receptors
Proteases

Luminal epithelium

Glycocalyx components
Adhesion molecules
Cytokines / chemokines
Proteases
Calcium regulators

Glands

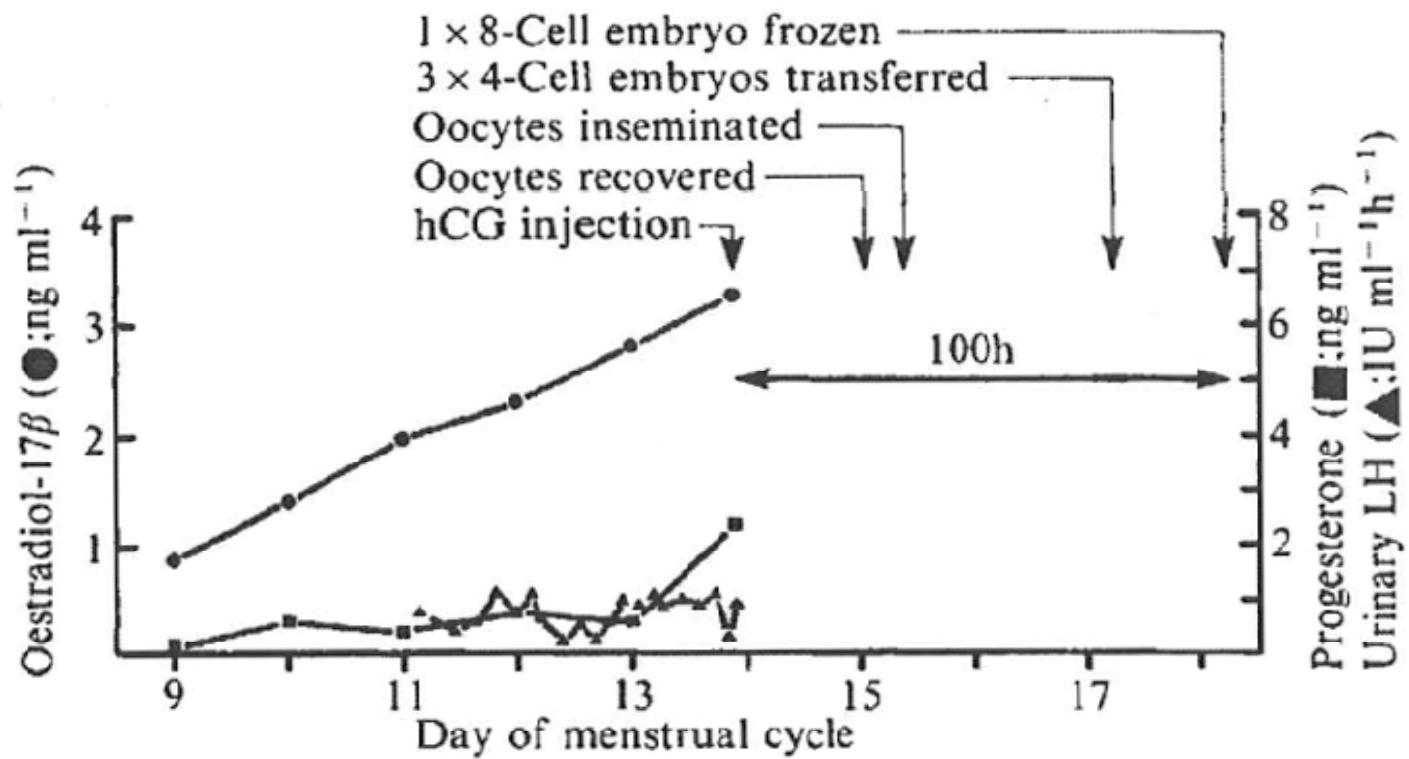
Cytokines / chemokines
Growth factors
Nutrients

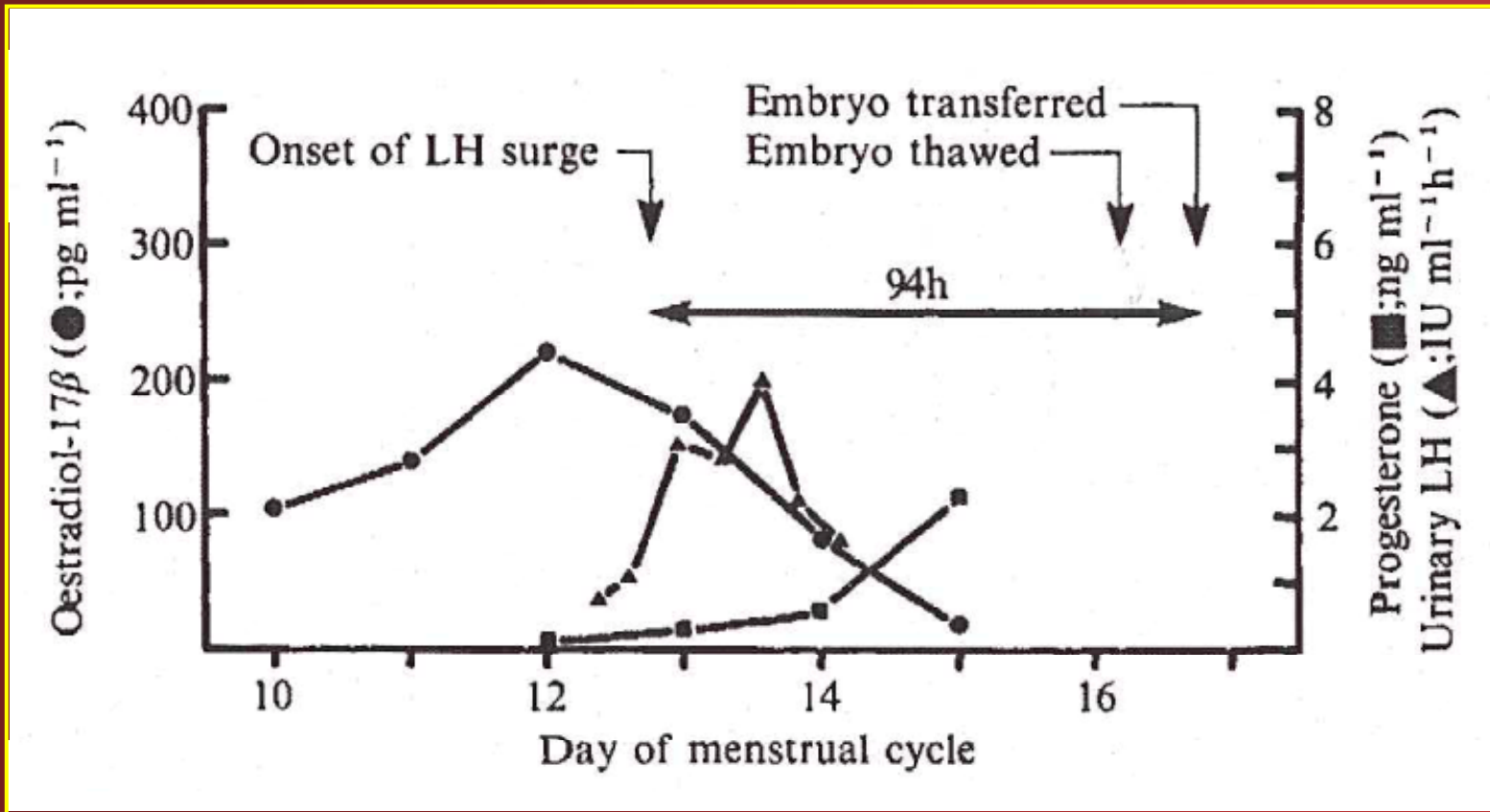
Extracellular matrix

Hyaluronan
Collagens
Degradative enzymes / inhibitors

Decidualizing stroma

Prostaglandins
Cytokines / chemokines
Growth factors
Proteases

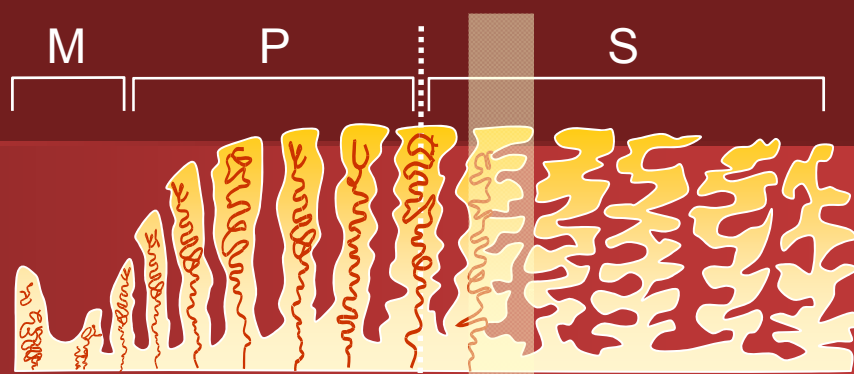
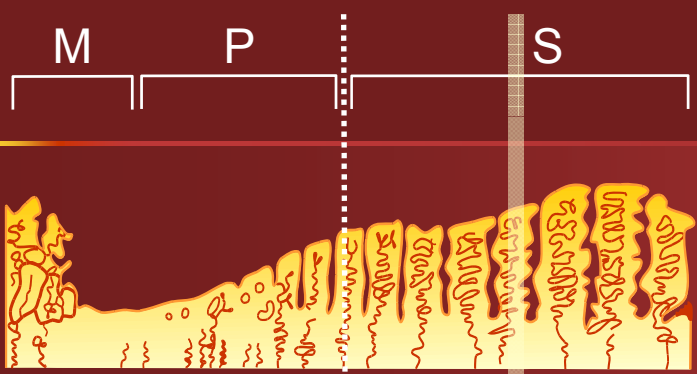




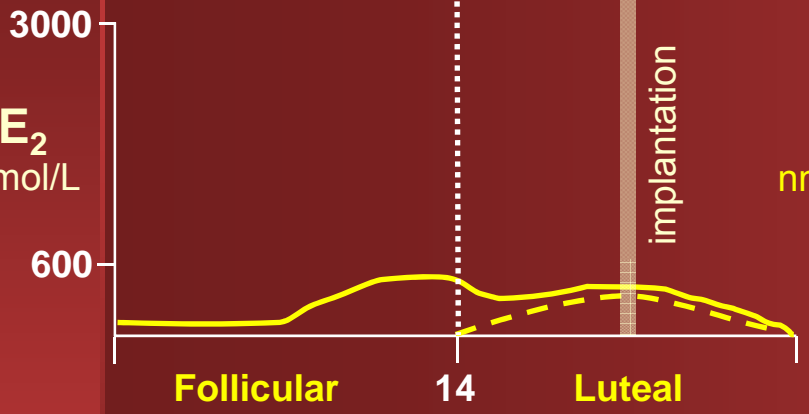
N cycle

ART Stimulated Cycle

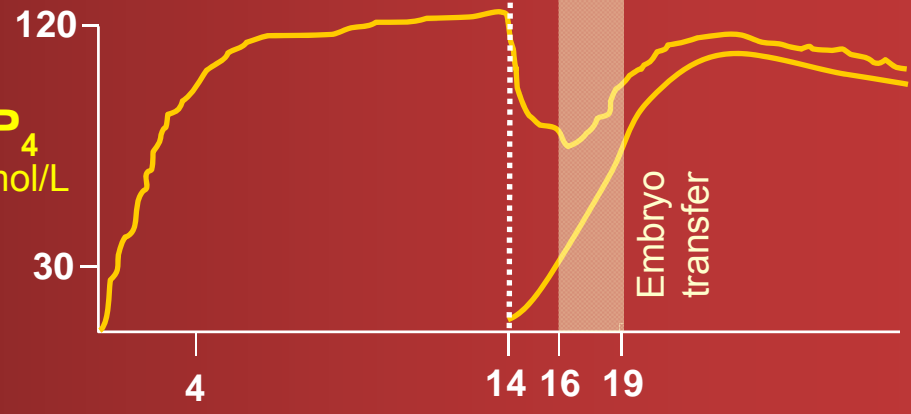
Endometrium



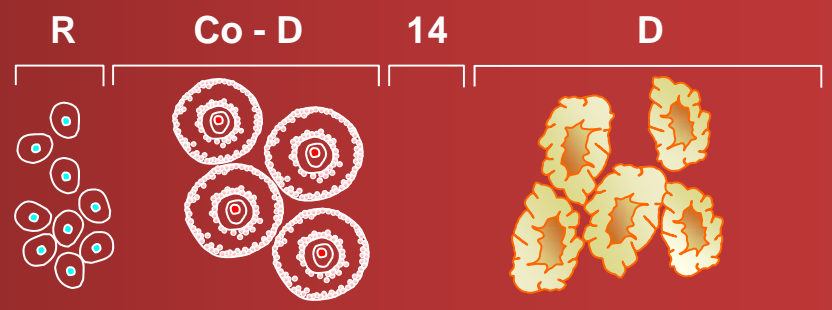
E₂ Pmol/L



P₄ nmol/L



Ovary



UTERINE RECEPTIVITY

- ❖ Human implantation occurs over a period of time.
- ❖ Implantation occurs only when the endometrium is receptive.
- ❖ High serum estradiol concentrations are detrimental to uterine receptivity.

Simon et al Human Reprod. 1995;10;2432
Wilcox et al NEJM 1999;340;1796

FREEZE ALL

→ Preterm birth & LBW

Low PAPP-A in ART pregnancies

Increased obstetric haemorrhages

Increased blastogenesis birth defects

FREEZE ALL

- ❖ Melbourne IVF 1978 – 2005
- ❖ ‘ART’ – IVF, ICSI, GIFT, AI, NonART
- ❖ 8179 singleton births
- ❖ 6570 first singleton births

FREEZE ALL

Preterm birth %

Non ART	8.6
IVF	12.5
ICSI	11.5
GIFT	10.0
FET	9.2

FREEZE ALL

Low birth weight %

Non ART	7.1
IVF	11.7
ICSI	11.5
GIFT	10.9
FET	6.5

FREEZE ALL

- ❖ Regression Modelling
- ❖ Covariates
 - Gestation, Parity
 - LUSCS, Birth defects
 - Male sex, Perinatal death
 - Socio-economic status

FREEZE ALL

CONCLUSIONS

- ❖ FET - Higher birthweight, Less LBW c/f fresh E.T.
- ❖ FET results similar to Non ART births
- ❖ Embryology for IVF/ICSI is not causal

FREEZE ALL

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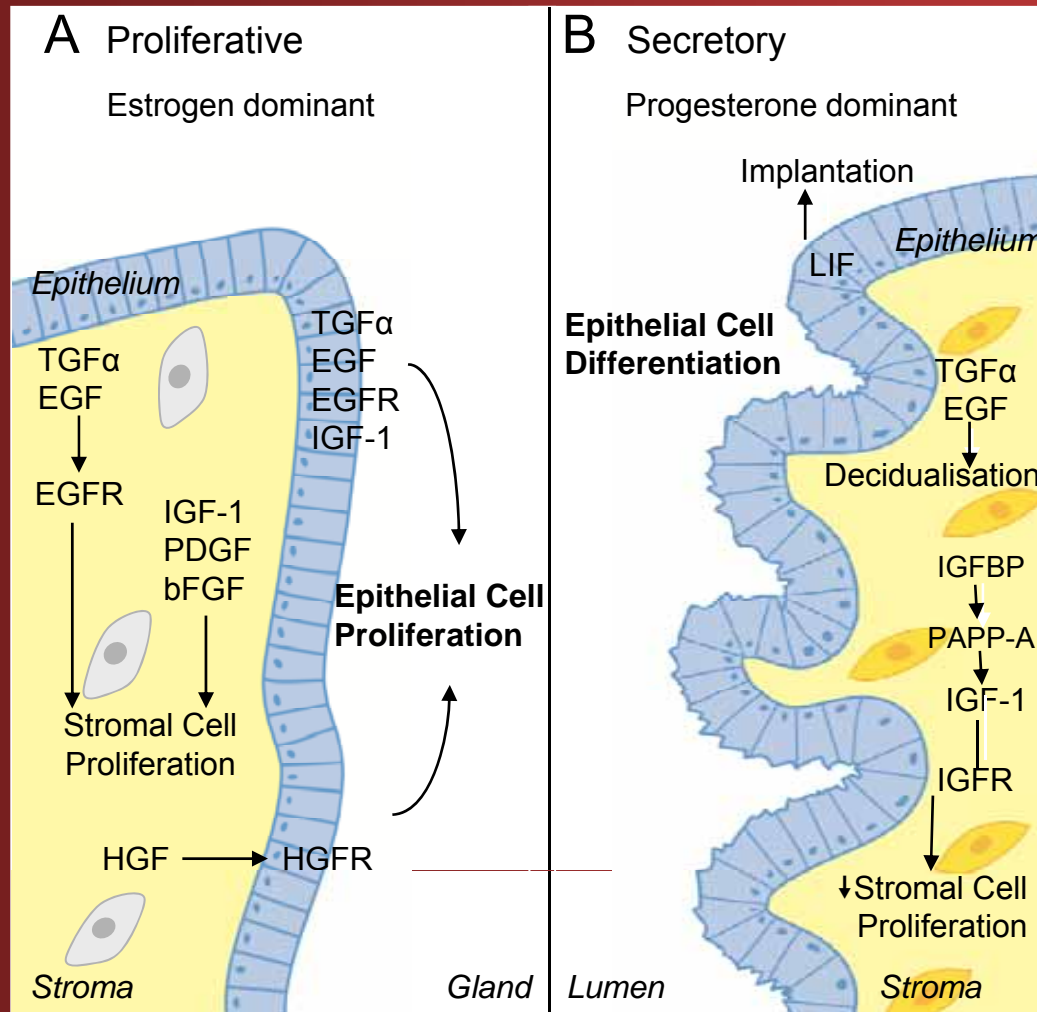
FREEZE ALL

- ❖ Record Linkage Study
- ❖ 1,739 singleton ART pregnancies
- ❖ 50,253 naturally conceived pregnancies
- ❖ VCGS – β hCG, PAPP-A, CRL, NT

FREEZE ALL PAPP-A

- ❖ A Matrix Metallo-Proteinase
- ❖ Produced by endometrium and trophoblast
- ❖ A growth factor
- ❖ Cleaves IGF-II from IGF-BP
- ❖ Low PAPP-A → LBW Art babies

PAPP-A ACTION



Gargett et al. Mol Cell Endocrinol 288:22-9, 2008.

FREEZE ALL

	$f\beta$ HCG		PAPP-A	
	Geometric	P	Geometric	P
	Mean MoM		Mean MoM	
<i>All pregnancies</i>				
Non ART (50,253)	0.98		1.00	
ART (1,739)	0.99	0.47	0.83	<0.001
<i>Complicated pregnancies *</i>				
Non ART (7,001)	0.94		0.90	
ART (366)	0.97	0.28	0.77	<0.001

* Adverse-NND, LBW, Prem, PIH

FREEZE ALL

<i>Comparison Group</i>	<i>f</i> βHCG Geometric Mean MoM	P	PAPP-A Geometric Mean MoM	P
(43,252)	0.99	1.02		
<i>Subtype of ART</i>				
IVF (513)	1.01		0.87	<0.001
ICSI (833)	1.00		0.84	<0.001
GIFT (27)	0.84		0.71	<0.001
<i>All ET's</i>				
Hormones (fresh)	0.98		0.78	<0.001
No hormones (FET)	1.05		0.99	0.277

FREEZE ALL

Preterm birth & LBW

Low PAPP-A in ART pregnancies

→ Increased obstetric haemorrhages

Increased blastogenesis birth defects

FREEZE ALL

- ❖ ↑Obstetric haemorrhages after ART
- ❖ APH, PP, PA, PPH
- ❖ Retrospective cohort study 1991-2004
- ❖ IVF/ICSI 6730 singleton births
- ❖ GIFT 779; Non ART 2167,
General population 24,619

FREEZE ALL

	IVF/ICSI (6,730)	General (24,619)	GIFT (779)	Non-ART (2,167)
APH	454 (6.7%)	881 (3.6) <i>P<0.001</i>	78 (10.0) <i>≤0.001</i>	98 (4.5) <i><0.001</i>
PP	174 (2.6)	273 (1.1) <i>P<0.001</i>		
PA	63 (0.9)	107 (0.4) <i>P<0.001</i>		
PPH	746 (11.1)	1,954 (7.9) <i>P<0.001</i>		

FREEZE ALL

	<u>APH</u>
Stimulated cycle fresh ET (4,058)	314 (7.7%)
Unstimulated cycle FET (2,045)	105 (5.1%)
Adjusted OR* (95% CI) P	153 (1.2-1.9) <0.001

*AOR: Parity, Age, YOB, Country of Birth, Marital status, Misc/TOP, Socio-economic status

FREEZE ALL

- ❖ ART damage increased with fresh ET *c/f* FET
- ❖ Even with singleton births
- ❖ Damage to mothers - obstetric
- ❖ Damage to babies - perinatal; for life.

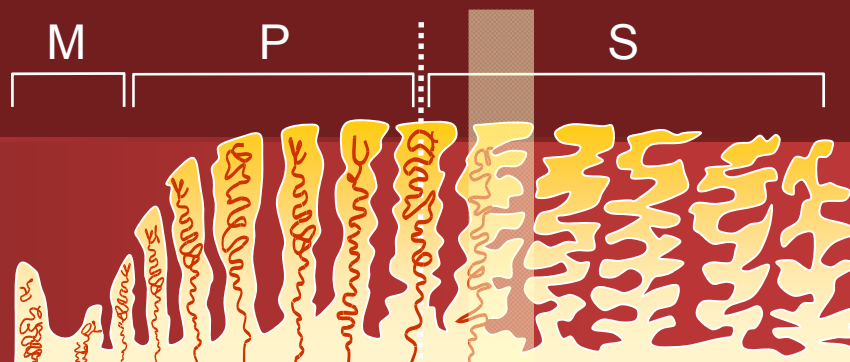
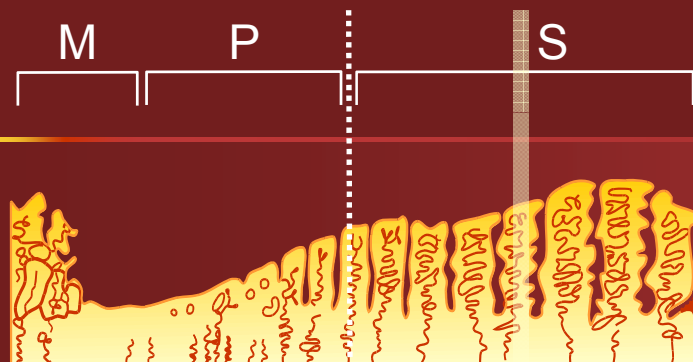
HEALTHIER IVF – YES WE CAN

- 1 Stimulated cycle - MII oocytes
- 2 Embryology - High quality
- 3 Freeze all high quality embryos
- 4 S.E.T. in natural menstrual cycle
- 5 Begin 3/12 after VEPU: consecutive N cycles

N cycle

ART Stimulated Cycle

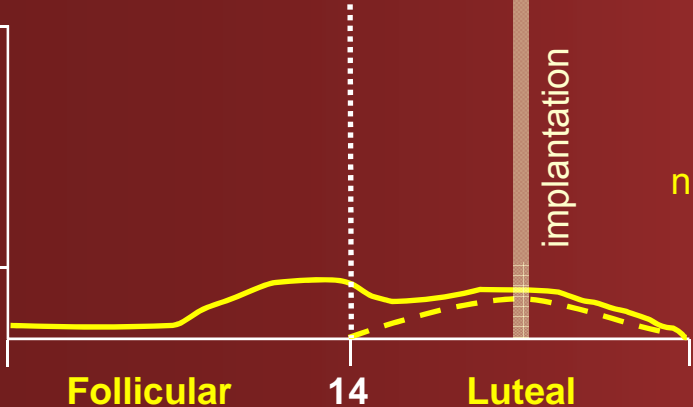
Endometrium



E₂
Pmol/L

3000

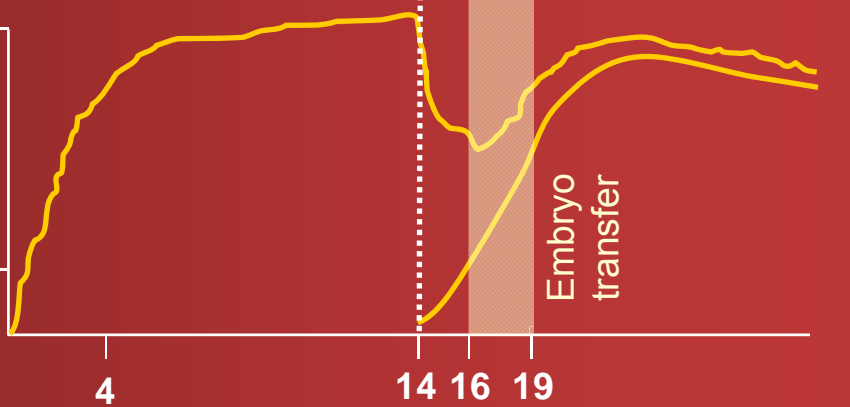
600



P₄
nmol/L

120

30



Ovary

