Early changes of endometrium after implantation

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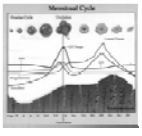
The author reports no relevant conflicts of interest

Possible use of knowledge

- Postpone ET for the next cycle if no chance for pregnancy in the current cycle?
- Predict the IVF/ET cycle success?
- Distinguish between normal and abnormal pregnancy at 4 wks of gestation?

What do we know so far?

- 80-85% of embryos transferred fail to implant
- Successfull implantation - synchrony between embryo and endometrium
- Asynchrony leads to failure to achieve pregnancy, fetal malformations and changes in fetal growth and metabolism



Barnes, Theriogenology 2000; Simon, Hum Reprod 1998

Transvaginal ultrasonography

- Non-invasive, practical
- Information on uterine receptivity
  - **Endometrial echogenicity**
  - **Uterine vascular network**
  - **Uterine contractility**

- Endometrial biopsy – “gold standard”

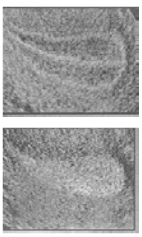
Endometrial biopsy

- Endometrial advancement = hiperechogenicity prior to ovulation
- Endometrial advancement >3 days = no pregnancy
  Lass, Hum Reprod 1998
- Endometrial biopsy before oocyte retrieval = no influence on IR
  van der Gaast, RBM 2003; Ubaldi, F&S 1997

Endometrial advancement Stimulation type	≤3 days	>3 days
Biochemical pregnancy		
hMG/agonist	13/32	0/7
Rec-FSH/antagonist	14/49	0/6
	27/81	0/13
Detection of gestational sac		
hMG/agonist	10/32	0/7
Rec-FSH/antagonist	11/49	0/6
	21/81	0/13
Ongoing pregnancy		
hMG/agonist	10/32	0/7
Rec-FSH/antagonist	8/49	0/6
	18/81	0/13

Changes before implantation - echogenicity

- *Sher, Hum Reprod 1991*
- Prospective, 330 women, late proliferative phase
- 33% CPR for hypoechogenic endometrium, 7% CPR for hyperechogenic endometrium



Changes before implantation - echogenicity

- *Fanchin, F&S 2000*
- Prospective, 228 women, late proliferative phase
- Computer analysis = 6 echogenicity groups; CPR fell from 59% to 3%

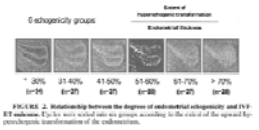
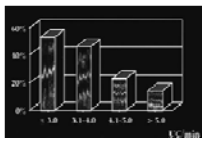


FIGURE 2. Relationship between the degrees of endometrial echogenicity and IVF-ET outcome. Cycles were sorted into six groups according to the extent of the upward hyperechogenic transformation of the endometrium.

Changes before implantation - uterine contractility



- 209 women, 220 cycles
- High frequency uterine contractions on the day of ET negatively affect IVF–ET outcome
- If frequency of contractions fall, CPR rises

Fanchin, Hum Reprod 1998

Changes before implantation - uterine contractility

- *Vlaisavljevic, UOG 2001*
- 122 women, day of HCG, ET, day +6, day +12
- No difference in PR

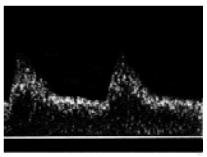
Table I. Echographic characteristics of the endometrium and serum estradiol and progesterone levels before embryo transfer

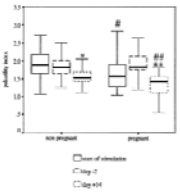
	Day of cycle -2		Day of cycle +2	
Characteristic	Pregnancy n = 29	No pregnancy n = 93	Pregnancy n = 29	No pregnancy n = 93
Thickness (mm)	10.2 ± 2.6	9.5 ± 2.6	12.2 ± 2.2	11.9 ± 2.7
Appropriate pattern %	100.0	97.7	72.4*	47.2
Movement percentage				
Amplitudes high	23.1	17.5	28.6	22.7
low	42.4	45.9	33.5	36.4
Direction antegrade	46.1	31.7	21.4	23.0
retrograde	11.5	18.25	25.0	21.8
both	7.9	16.2	15.7	14.3
Extent long	19.3	36.7	35.0	33.4
short	96.3	36.7	37.1	35.5
No movement	34.5	26.6	27.9	40.9
Progesterone (nmol/L)	2.3 ± 3.1	4.0 ± 13.3	115.4 ± 57.6	102.6 ± 55.1
Estradiol (nmol/L)	5.4 ± 3.0	4.4 ± 2.6	1.8 ± 1.4	2.5 ± 5.5

*Statistically different pregnant vs. non pregnant (χ^2, $P < 0.05$); day of cycle: -2, day of hCG administration; day of cycle +2, day of embryo transfer or day 2 after oocyte pick up.

Changes before implantation - uterine perfusion

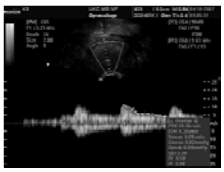
- *Bloechle, Hum Reprod 1997*
- 60 patients; beginning of stimulation, day of HCG, day 28
  - At beginning of stimulation, high resistance in non-pregnant; on day 28, low resistance in pregnant



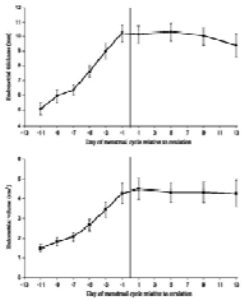


Changes before implantation - uterine perfusion

- *Ng, Reprod Biomed Online 2009*
- 293 patients, day of HCG and ET
- endometrial and subendometrial blood flow were not predictive of pregnancy in IVF treatment



Endometrial thickness and volume in normal menstrual cycle



Raine-Fenning, BJOG 2004

Changes before implantation - endometrial thickness

Endometrial thickness on day of HCG	Group A (n)	Group B (n)	Pregnancy rate
≤6 mm	5	12	29.40%
7 mm	31	34	24.40%
8 mm	95	96	24.70%
9 mm	70	171	29.00%
10 mm	162	321	33.50%
11 mm	140	240	36.80%
12 mm	174	273	28.80%
13 mm	120	202	27.20%
14 mm	82	122	40.20%
15 mm	38	63	38.00%
16 mm	19	27	41.30%
≥17 mm	16	20	44%
Total	882	1582	35.80%

Table 4. Pregnancy rates below and above 11 mm endometrial thickness

Endometrial thickness on day of HCG	Group A (n)	Group B (n)	Pregnancy rate
< 11 mm	283	634	30.90%
≥ 11 mm	599	948	38.70%
Total	882	1582	35.80%

P = 0.001
RR = 1.22, (95% CI 1.12–1.41)

- 2500 cycles, day of HCG; endometrial thickness cannot predict pregnancy

Al-Ghamdi, Reprod Biol Endocrinol 2008

Changes before implantation - endometrial volume

- Prediction of subsequent pregnancy
- No difference in PR
- Pregnancy is unlikely if endometrial volume is < 2 ml

Table 3: Summary of data published about the role of 3D-ultrasound for predicting outcome in IVF program

Author	N	Primary outcome	3D Method	Day 3D US	Sub endometrial area	Pregnancy rate (PR)	Findings
Raga (65)	72	Pregnancy rate	Multiplice	Embryo transfer		29.2%	No pregnancy if endometrial volume < 1 ml If endometrial volume ≥ 2 ml, no difference in PR
Schild (64)	47	Pregnancy rate	Multiplice	Oocyte retrieval		31.9%	No difference in endometrial volume between conception and non-conception cycles
Yaman (66)	65	Pregnancy rate	Multiplice	HCG		32.3%	No difference in endometrial volume between conception and non-conception cycles No pregnancy if endometrial volume < 2.5 ml
Zollner (67)	125	Pregnancy rate	Multiplice	Embryo transfer		22.2%	PR 9% if endometrial volume ≥ 2.5 ml PR 9% if endometrial volume < 2.5 ml

Alcazar, Reprod Biol Endocrinol 2006

Changes after implantation - endometrial thickness

	Pregnant			**Non-pregnant**	
	Day of cycle	N	Endometrial thickness	N	Endometrial thickness
Rabinowitz 1986	28	10	**15***	37	13
Vlaisavljevic 2001	26	29	**13.8**	93	10,9
Dmitrovic 2008	28	27	**17,5***	27	10

*Significant (biochemical pregnancies excluded)

Endometrial thickness in normal vs. abnormal pregnancy

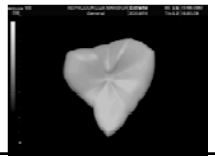
	Day of cycle	Normal pregnancy	Abnormal pregnancy	Ectopic
Spandorfer 1996	28	13,4*	9,3	5,9
Banerjee 2001	30	10,9*	8,9	6,5
Dmitrovic 2008	28	17,5*	12,6	

* Significant

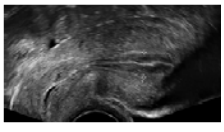
Changes after implantation - endometrial volume

	Pregnant		**Non-pregnant**	
	Day of cycle	Volume (ml)	Day of cycle	Volume (ml)
Martins 2007	24	6,49*	24	3,16
Zohav 2007	33	8*		
Dmitrovic 2008	28	10*	28	3,4

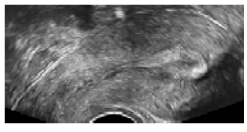
* - Significant



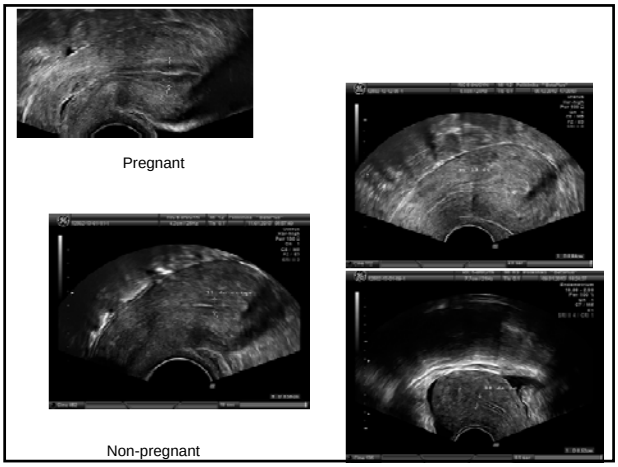
Antagonist protocol, 42 years old patient



Day of HCG, 10 mm

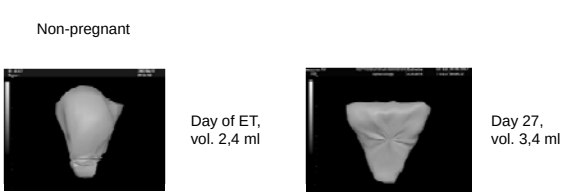


Day of ET, 12 mm



Pregnant

Non-pregnant



Non-pregnant

Day of ET, vol. 2,4 ml

Day 27, vol. 3,4 ml

Pregnant

Day of ET, vol. 4,2 ml

Day 27, vol. 8,9 ml

Dmitrovic 2008, J Assist Reprod Genet

Conclusions

- Endometrial changes and embryo quality seem to be equally important in terms of pregnancy in the current cycle
- However, no clinically applicable endometrial receptivity marker has been discovered yet

- Future research suggestion:
  - Correlation of *all* known endometrial changes visible on ultrasound to pregnancy prospects