Ultrasonography of endometrium during natural and stimulated cycle.

Echographic assessment of subendometrial contraction

Dr. José Manuel Puente
IVI Madrid

Introduction

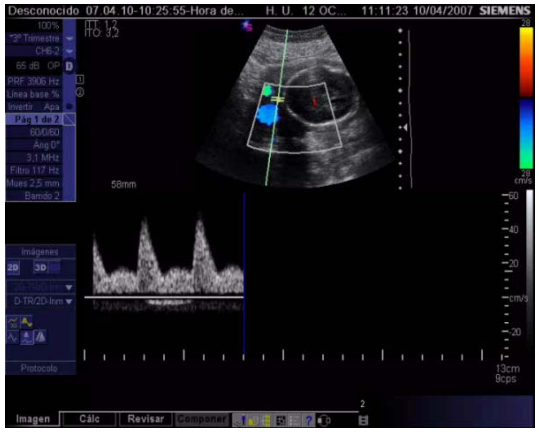
1.- Good embryo 2.- Optimal embryo transfer 3.-Endometrial receptivity 4.-Others

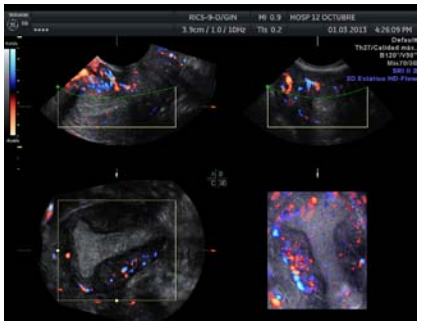
Introduction

Two thirds of the implantation failures are due to endometrial receptivity defects

Implantation failures (impaired placentation) could have consequences apart from infertility:

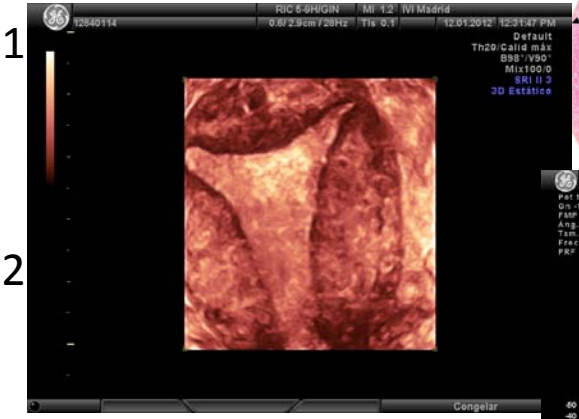
miscarriages
intrauterine growth restriction
preeclampsia
premature birth
fetal loss

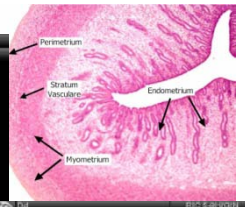




Endometrial receptivity

1





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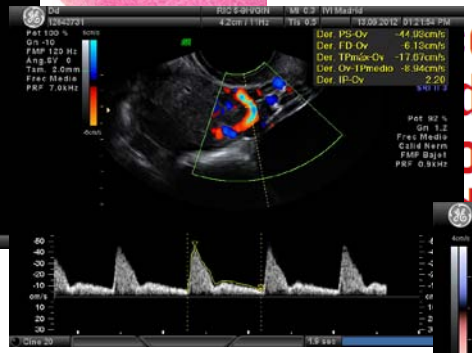
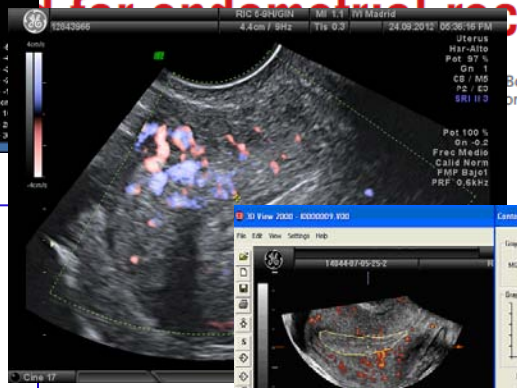
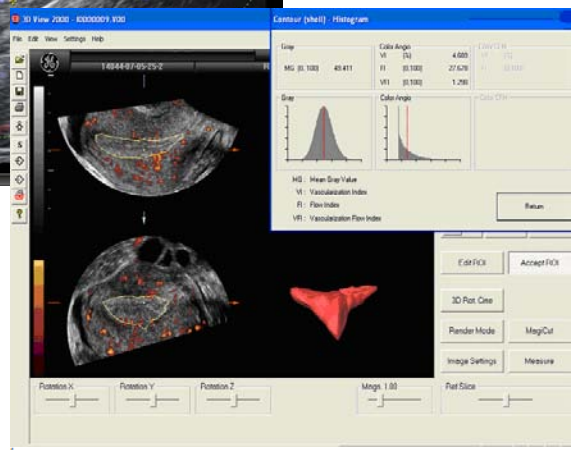


curacy and reproducibility of
dometrial receptivity array is
r to histology as a diagnostic
ceptivity

Bosch, M.D.,[d]
onio Pellicer, M.D.,[a,b,c,d]





3.- Ultrasonographic assessment

Endometrial size, pattern, volume

Pulsatility index in uterine arteries

3D three-dimensional power Doppler

Ultrasound Obstet Gynecol 2012; 39: 612–619
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.10098

Ultrasound assessment of the peri-implantation uterus: a review

Y. ABDALLAH*, O. NAJI*, S. SASO*, A. PEXSTERS†, C. STALDER*, S. SUR‡, N. RAINE-FENNING‡, D. TIMMERMAN†, J. J. BROSENS* and T. BOURNE*†

*Institute of Development and Reproductive Biology (IRDB), Imperial College London, London, UK; †Department of Obstetrics and Gynecology, University Hospitals, KU Leuven, Leuven, Belgium; ‡Academic Division of Reproductive Medicine, School of Human Development, University of Nottingham, Nottingham, UK

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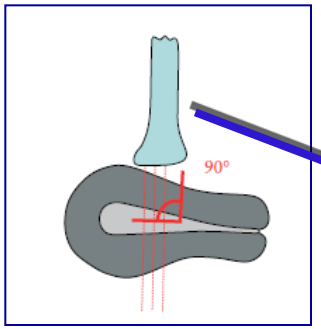
Ultrasonographic assessment

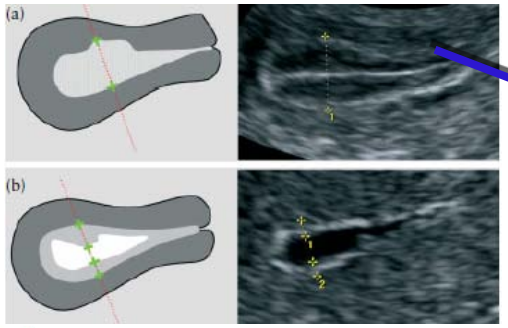
Ultrasound Obstet Gynecol 2010; 35: 103–112
Published online 15 December 2009 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.7487

Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group

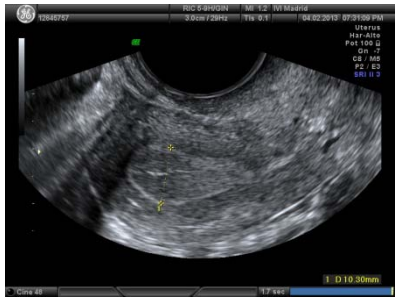
F. P. G. LEONE*, D. TIMMERMAN†, T. BOURNE‡, L. VALENTIN§, E. EPSTEIN¶, S. R. GOLDSTEIN**, H. MARRET††, A. K. PARSONS‡‡, B. GULL§§, O. ISTRE¶¶, W. SEPULVEDA***, E. FERRAZZI††† and T. VAN DEN BOSCH†



the angle between the endometrium and the ultrasound beam (the angle of insonation) should be 90◦ to optimize image quality.



the endometrium should be measured where it appears to be at its thickest



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Assessment of uterine contraction

1.- ULTRASONOGRAPHY

sagital view

subjetive assessment

M-mode

videotape stored

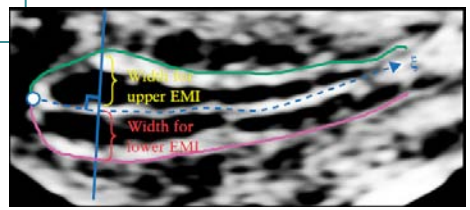
2.- INTRAUTERINE CATHETER

Ultrasound Obstet Gynecol 2011; 38: 217–224
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.8950

A new method for analysis of non-pregnant uteri
peristalsis using transvaginal ultrasound

D. MEIRZON*, A. J. JAFFA† ‡, Z. GORDON† and D. ELAD*

*Department of Biomedical Engineering, Tel-Aviv University, Tel Aviv, Israel; †Ultrasound Unit in Obstetrics and Gynecology, Lis Maternity Hospital, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; ‡Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel



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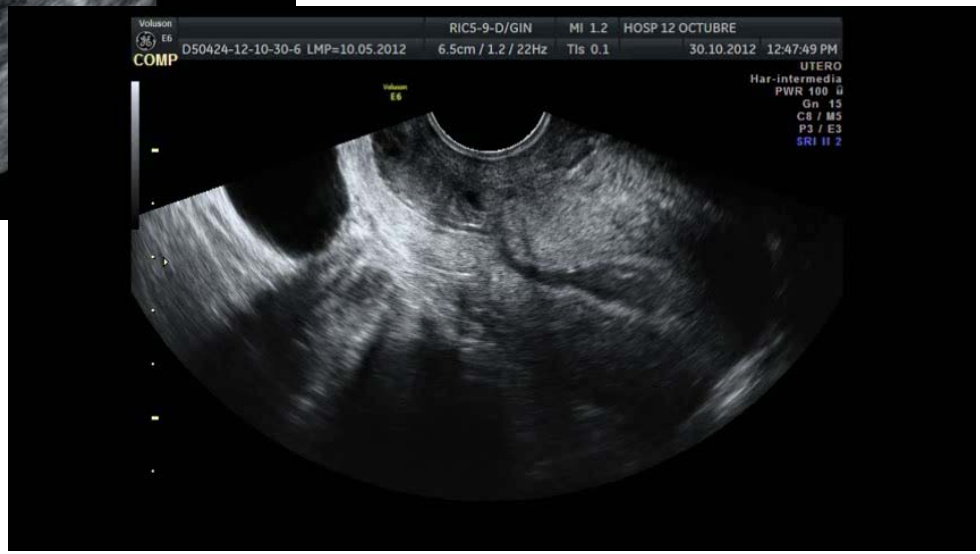
Ultrasonographic assessment

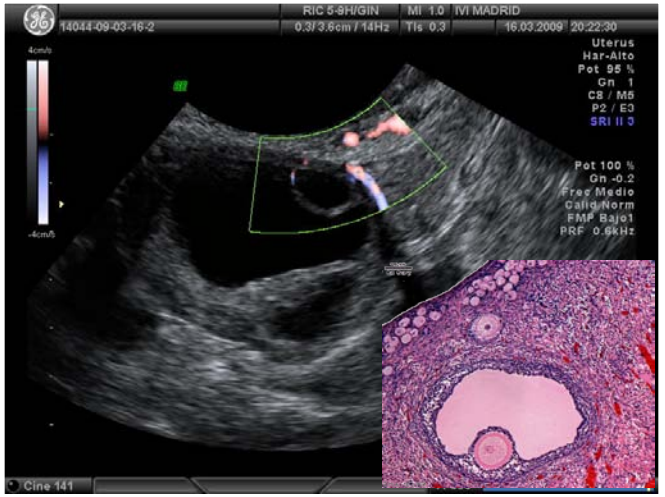
Natural cycle.

1.- Menstrual period (days 1-5)



Synechia
Stenosis

Ultrasonographic assessment



2.- Follicular phase (days 7-12) Periovulatory

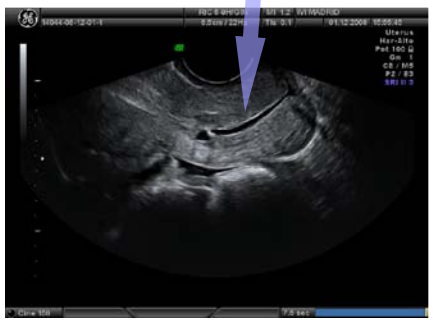
Increase in thickness 1mm per day
(2mm in late proliferative phase)

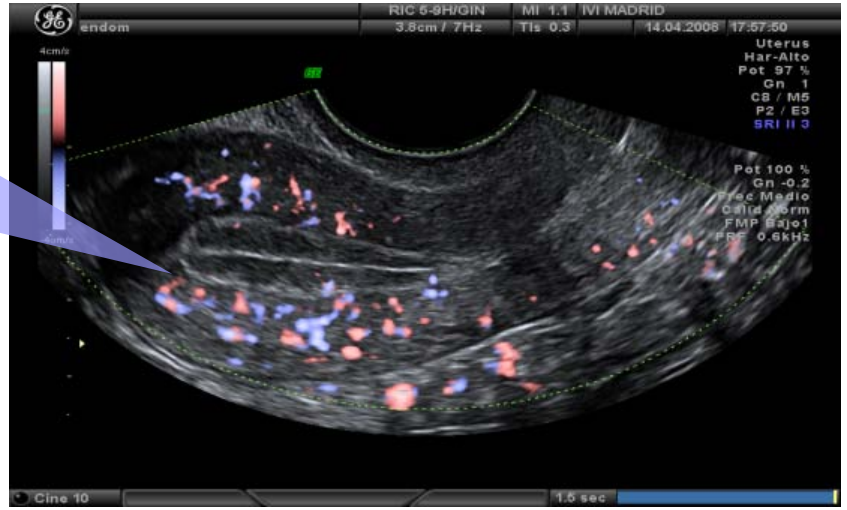
Decreases 0,5 mm on the day of LH surge

Increases 2 mm during luteal phase

Triple line apperareance

Mucus in endocervix





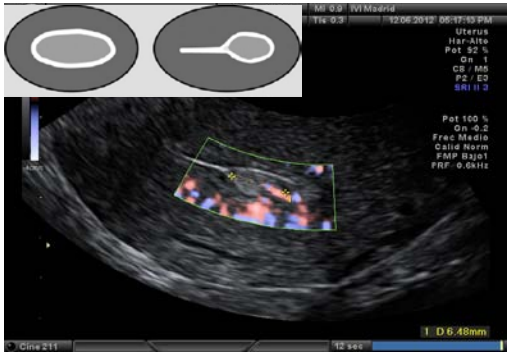
Ultrasonographic assessment

2.- Follicular phase (days 7-12) Periovulatory

Paid attention to:

- Polyps
- Synechia

Hysterosonography for evaluation of uterine cavity if required



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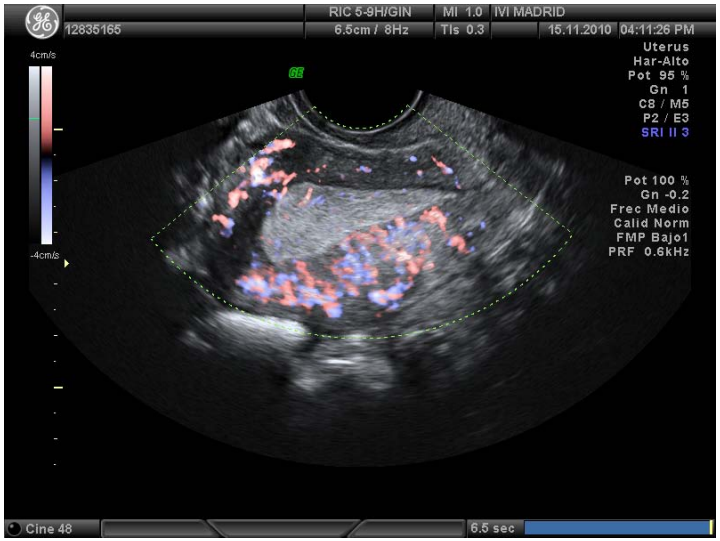
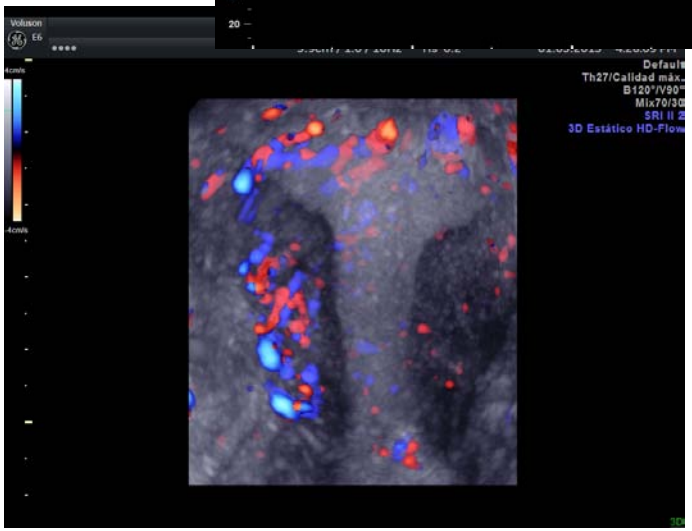
Ultrasonographic assessment

3.- Luteal phase-Implantation window

Dilatation of the vessels within the subepithelial capillary plexus
Oedema in the stroma
Hyperechogenic pattern beginning from depth layer to inner
Vascularization can be assessed





Ultrasonographic assessment

VASCULAR CHANGES IN THE ENDOMETRIUM

Human Reproduction Vol.19, No.2 pp.330–338, 2004 DOI: 10.1093/humrep/deh056

Quantifying the changes in endometrial vascularity throughout the normal menstrual cycle with three-dimensional power Doppler angiography

N.J.Raine-Fenning[1], B.K.Campbell, N.R.Kendall, J.S.Clewes and I.R.Johnson

Academic Division of Reproductive Medicine, School of Human Development, University of Nottingham, UK

[1]To whom correspondence should be addressed at: Academic Division of Reproductive Medicine, D Floor, East Block, Queens Medical Centre, Nottingham NG7 2UH, UK. E-mail: nick.fenning@nottingham.ac.uk

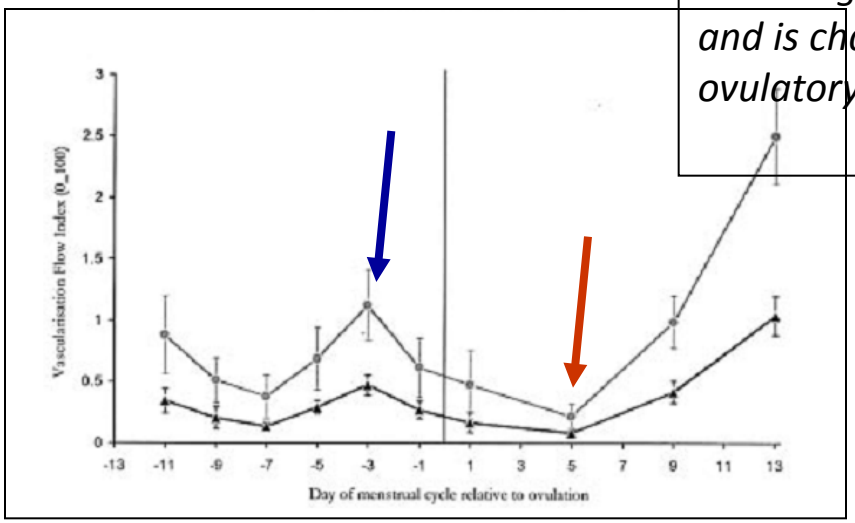
Editorial

The role of three-dimensional ultrasound in assisted reproduction treatment

N. RAINE-FENNING

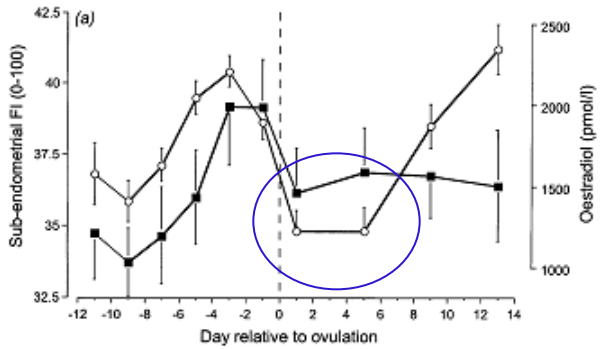
Academic Division of Reproductive Medicine, School of Human Development, D Floor, East Block, Queen's Medical Centre, Nottingham, NG7 2UH, UK
(e-mail: nick.fenning@nottingham.ac.uk)

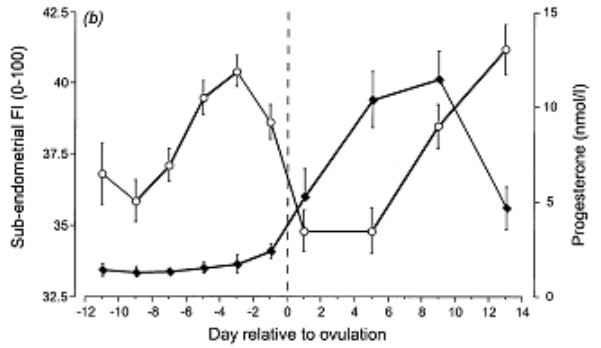
Endometrial vascularity, as assessed by 3D-PDA, varies significantly during the menstrual cycle and is characterized by a pre-ovulatory peak and post-ovulatory nadir during the peri-implantation window.

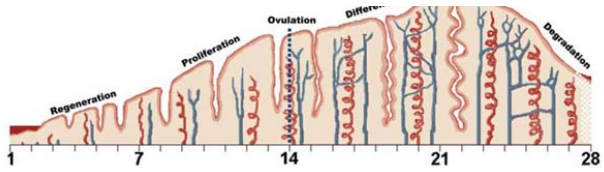


Ultrasonographic assessment

VASCULAR REMODELLING







Post-ovulatory phase

Dilatation of the vessels within the subepithelial capillary plexus

Oedema in the stroma at the time of the expected implantation

It is possible therefore that the power Doppler signal falls at this time as a result of an increase in the distance between individual vessels and a resultant decrease in microvessel spatial density

Late luteal phase

increase in the power Doppler signal due to an

increase in endometrial vascular density associated with the progressive coiling of the spiral arteries or endometrial compaction characteristic of the late luteal phase

Stimulated cycle.

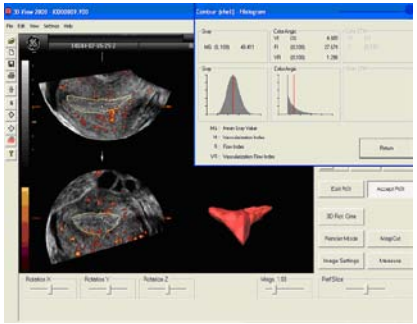
Human Reproduction Vol.21, No.1 pp. 164–170, 2006 doi:10.1093/humrep/dei277
Advance Access publication August 25, 2005.

The role of endometrial and subendometrial blood flows measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during IVF treatment

Ernest Hung Yu Ng[1], Carina Chi Wai Chan, Oi Shan Tang, William Shu Biu Yeung and Pak Chung Ho

Department of Obstetrics and Gynaecology, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

[1]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, The University of Hong Kong, 6/F, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong. E-mail: nghye@hkucc.hku.hk



3D power Doppler ultrasound examination performed on the day of oocyte retrieval

a) endometrial thickness, endometrial pattern, endometrial volume

b) pulsatility index (PI) and resistance index (RI) of uterine vessels

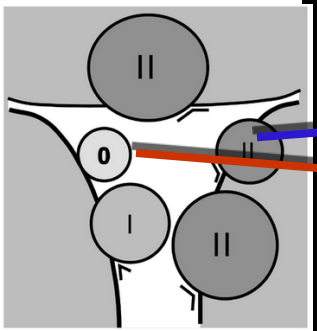
c)vascularization index (VI), flow index (FI) and vascularization flow index (VFI) endometrial and subendometrial regions

1.-non-significant trend of higher implantation and pregnancy rates in patients with absent endometrial or subendometrial blood flow

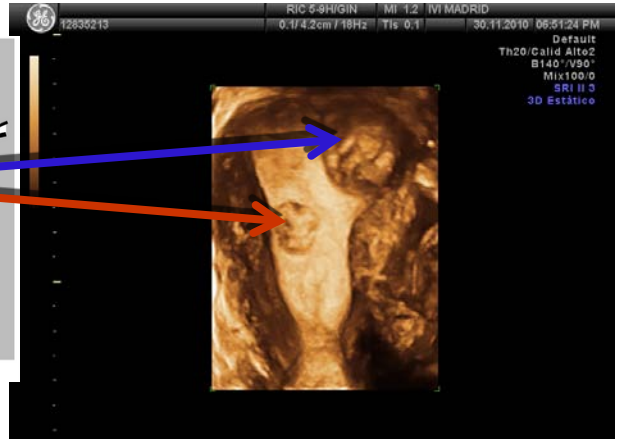
2.-Endometrial and subendometrial blood flows were not good predictors of pregnancy

Ultrasonographic assessment

Natural cycle.



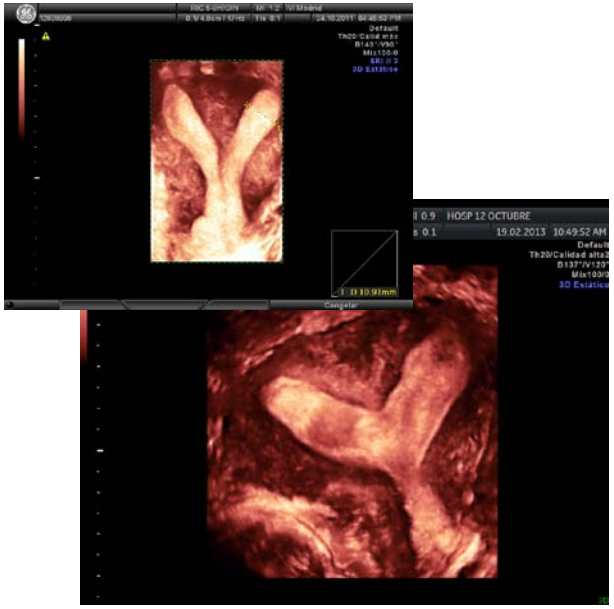
WAMSTEKER, 1990



3.- Luteal phase-Implantation window

Paid attention to:

- Uterine Leiomyoma
- Adenomyosis
- Congenital anomalies
- Consider evaluation of junctional zone



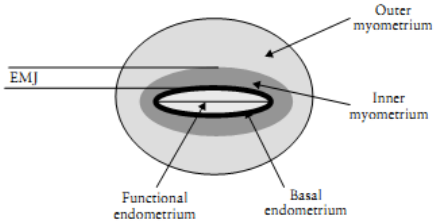
The role of "junction zone"

Editorial

The endometrial–myometrial junction: a fresh look at a busy crossing

J. NAFTALIN and D. JURKOVIC*

Gynaecology Diagnostic and Outpatient Treatment Unit, Elizabeth Garret Anderson Wing, University College Hospital, 235 Euston



Ultrasound Obstet Gynecol 2009; **34**: 1–11
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.6432

Human Reproduction, Vol.27, No.12 pp. 3365–3379, 2012
Advanced Access publication on October 23, 2012 doi:10.1093/humrep/des338

human reproduction ESHRE PAGES

Best practices of ASRM and ESHRE: a journey through reproductive medicine†‡

L. Gianaroli[1,*], C. Racowsky[2], J. Geraedts[3], M. Cedars[4], A. Makrigiannakis[5], and R. Lobo[6]

[1]Reproductive Medicine Unit, S.I.S.Me.R., Bologna, Italy [2]Brigham and Women's Hospital, Boston, USA [3]Maastricht University, Maastricht Netherlands [4]University of California San Francisco, San Francisco, CA, USA [5]University of Crete, Crete, Greece [6]Columbia University, New York, NY, USA

The myometrial junctional zone is structurally and functionally different from the outer endometrium and plays an important role in reproduction, especially in gamete transportation and implantation. During placentation, trophoblast invasion is preceded by decidual remodeling of endometrium and the junctional zone is essential for implantation. For this reason, evaluation of the uterus should include visualization of the myometrial junctional zone, considering that subtle lesions, such as adenomyosis, may be detected by magnetic resonance imaging. A novel approach for the investigation of the junctional zone could be performed with an ultrasound guided myometrial biopsy during diagnostic hysteroscopy using the spirotome, a device specifically designed for endometrial sampling.

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The role of "junction zone"

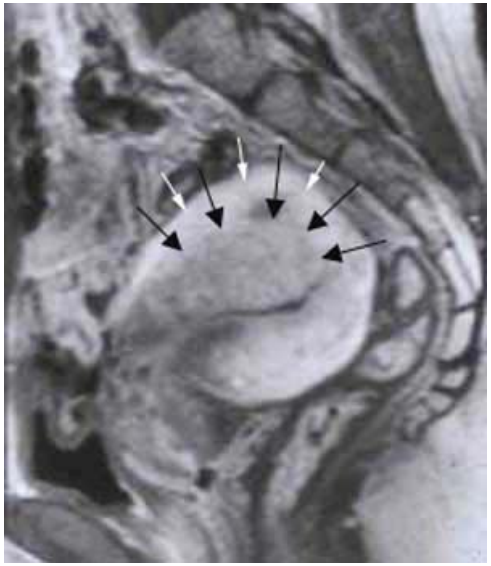
***RMN** Low-intensity signal T2*

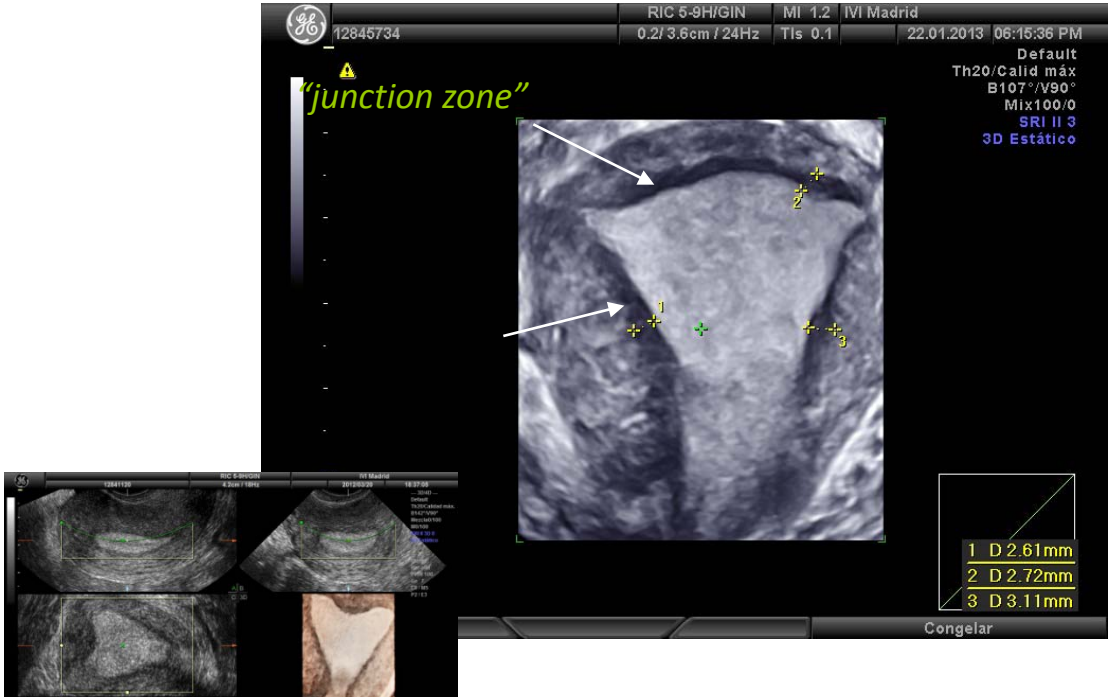
Transitional zone, placed between the endometrium and the outer myometrium

Composed by short muscle bundles arranged in a circular pattern

Estrogen and progesterone receptors that are regulated throughout the menstrual cycle

The circular arrangement of the muscle fibers may underlie the ability of the contractile activity to travel from fundus to cervix or in the opposite direction, depending on the local hormonal milieu and other factors.





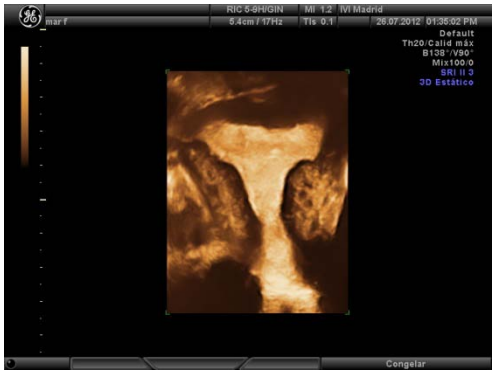
THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/j.1447-0756.2010.01189.x J. Obstet. Gynaecol. Res. Vol. 36, No. 3: 611–618, June 2010

Uterine junctional zone at magnetic resonance imaging: A predictor of *in vitro* fertilization implantation failure

Antoine Maubon, Alexandre Faury, Michel Kapella, Magalie Pouquet and Pascal Piver

Limoges University Hospital, Radiology and Medical Imaging department – MAP center, Limoges, Cedex, France



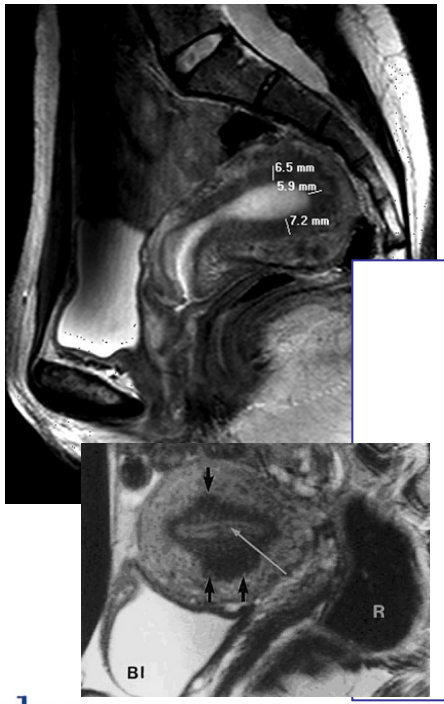


Table 2 Rates of pregnancy or failure in function of a threshold value of 7 mm for average junctional zone (AJZ)

	AJZ < 7 mm ($n = 113$)	AJZ > 7 mm ($n = 39$)
Pregnancy	62.8% (71)	25.6% (10)
No pregnancy	37.2% (42)	74.4% (29)
P	<0.01	

Table 4 Rates of pregnancy or failure in function of different combinations of average junctional zone (AJZ) and maximal junctional zone (MJZ) threshold values

	All other combinations ($n = 128$)	AJZ > 7 and MJZ > 10 ($n = 24$)
Pregnancy	63.5% (81)	4.2% (1)
No pregnancy	36.5% (47)	95.8% (23)
P	<0.01	

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Stimulated cycle.

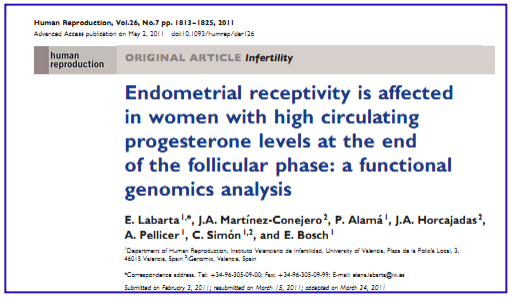
Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis

Matheus Roque, M.D.,[a,c] Karinna Lattes, M.D.,[a,d] Sandra Serra, M.Sc.,[a,d] Ivan Solà, B.Psych.,[e,f,g] Selmo Geber, Ph.D.,[c,h] Ramón Carreras, Ph.D.,[b] and Miguel Angel Checa, Ph.D.[b,d]

Roque et al . Fertil Steril. 2013 99(1):156-62.

1.- IVF outcomes may be improved by performing frozen ET compared with fresh embryo transfer.

2.- This could be explained by a better **embryo-endometrium synchrony** achieved with endometrium preparation cycles



Human Reproduction, Vol.26, No.7 pp. 1813–1825, 2011

human reproduction ORIGINAL ARTICLE *Infertility*

Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis

E. Labarta[1,*], J.A. Martínez-Conejero[2], P. Alamá[1], J.A. Horcajadas[2], A. Pellicer[1], C. Simón[1,2], and E. Bosch[1]

Elevated progesterone levels on the day of HCG administration can induce significant alterations in the gene expression profile of the endometrium

Human Reproduction, Vol.25, No.8 pp. 2092–2100, 2010

human reproduction ORIGINAL ARTICLE *Reproductive endocrinology*

Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for *in vitro* fertilization: analysis of over 4000 cycles

E. Bosch[1,*], E. Labarta[1], J. Crespo[1], C. Simón[1], J. Remohí[1], J. Jenkins[2], and A. Pellicer[1]

Serum progesterone levels of >1.5 ng/ml were associated with lower ongoing pregnancy rates following IVF/ICSI cycles

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Stimulated cycle.

Human Reproduction Update, Vol.9, No.6 pp. 515–522, 2003 DOI: 10.1093/humupd/dmg045

The endometrium in stimulated cycles for IVF

Claire Bourgain[1,3] and Paul Devroey[2]

[1]Department of Pathology and [2]Centre for Reproductive Medicine, University Hospital, Dutch-speaking Brussels Free University (Vrije Universiteit Brussel), Laarbeeklaan 101, 1090 Brussels, Belgium

1.- ovarian stimulation for IVF profoundly alters the luteal phase endometrial development

2.-only extremely deviant endometrial morphology seems to affect receptivity for implantation.

high E2 levels (>2,500 pg/mL) may impair the endometrium maturation and implantation. Simon C, et al Hum Rep 1997

high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy. Kolibianakis, E.M Fertil. Steril 2003

Human Reproduction, Vol. 15, (Suppl. 1), pp. 81–89, 2000

Uterine contractility during the menstrual cycle

Carlo Bulletti[1,4], Dominique de Ziegler[2,3], Valeria Polli[1], Lidia Diotallevi[1], Elena Del Ferro[1] and Carlo Flamigni[1]

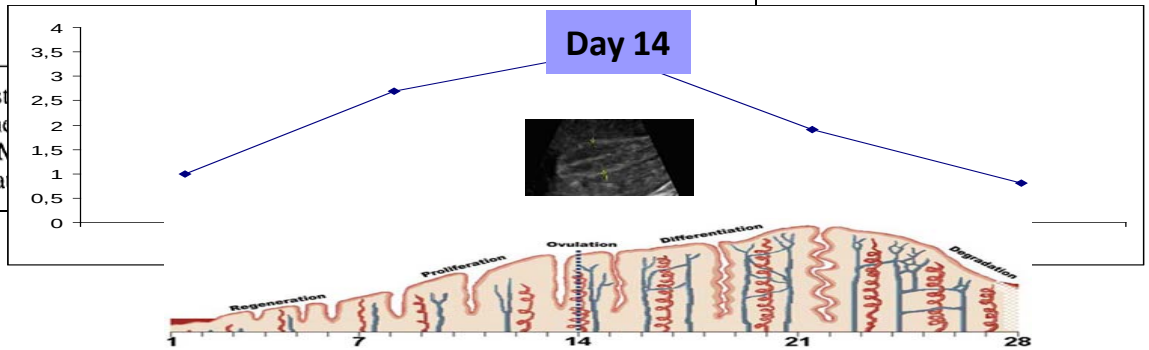
C.Bulletti *et al.*

Table I. Uterine contractility (UC) frequency

	Menstrual cycle stages					
	Mens	EF	LF	PO	EL	LL
Cycle days (day 0 = ovulation)	–14, –12	–11, –7	–6, –2	–1, +1	+2, +6	+7, +14
Frequency:						
US (UC/min) (n = 30)	1.2 ± 0.5	1 ± 0.3	2.7 ± 0.6	3.5 ± 0.6	1.9 ± 0.6	0.8 ± 0.3
IUP (UC/min) (n = 5)	1.1 ± 0.3	1.0 ± 0.3	2.9 ± 1.0	3.9 ± 0.5	2.2 ± 0.3	0.9 ± 0.3
P	NS					

UC frequency at the six menst
Data obtained with the two m
studied were during menses (M
(PO), early luteal (EL), and la
significant

frequency
direction of propagation



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frequency

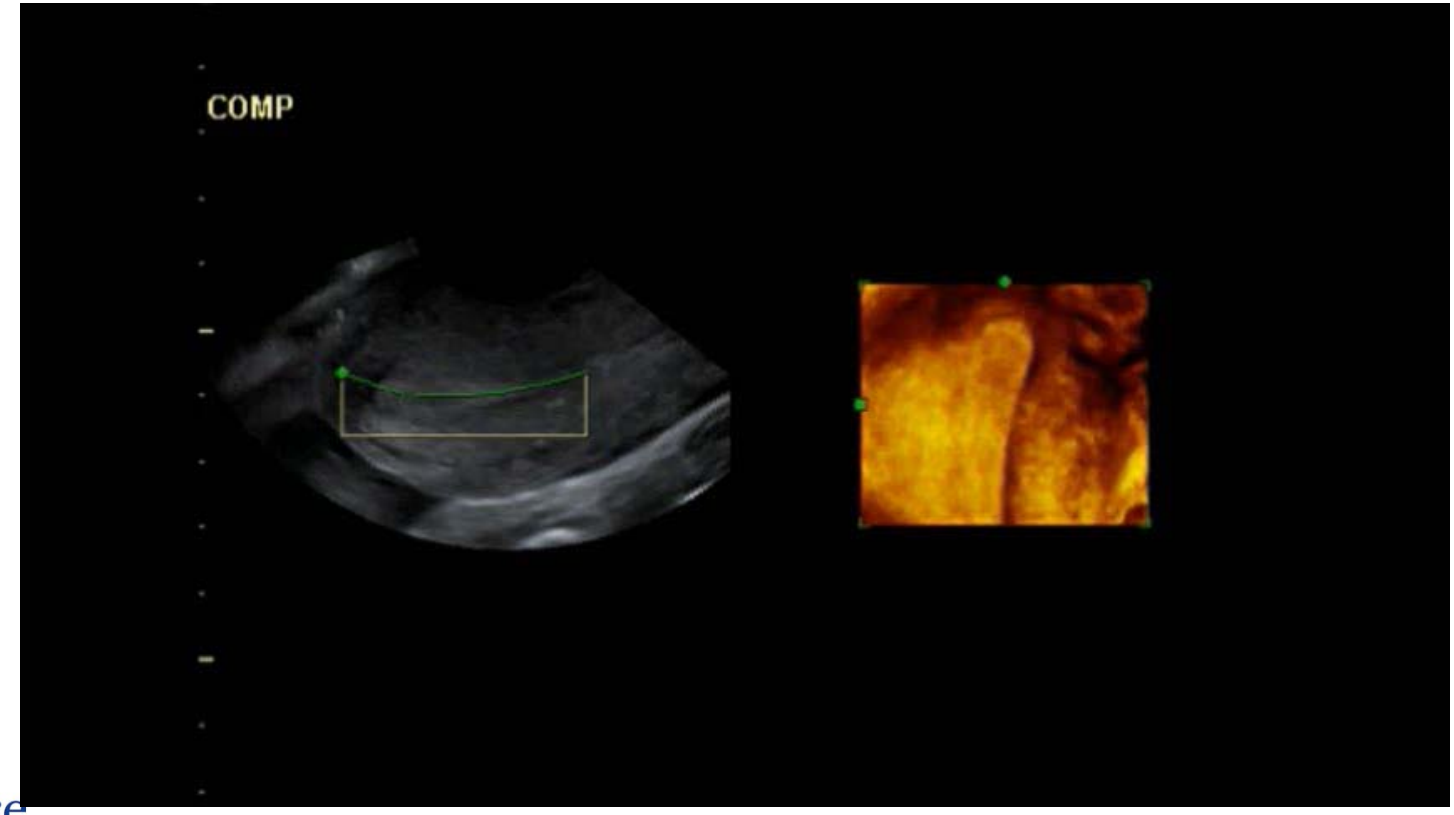
direction of propagation

Menstrual phase — Fundus to cervix

Follicular phase — Cervix-to-fundus

direction of propagation

During the 2nd phase of the cycle, the frequency and amplitude decrease perhaps to facilitate implantation
After ovulation, uterine contractility is characterized by a **relative quiescence**, with small, slow and superimposed uterine contractions, presumably as a response to the production of **progesterone** by the corpus luteum , and **facilitate the fundal implantation of the blastocyst**.



Stimulated cycle.

Human Reproduction, Vol. 15, (Suppl. 1), pp. 90–100, 2000

Hormonal influence on the uterine contractility during ovarian stimulation

Renato Fanchin[1], Jean-Marc Ayoubi, François Olivennes, Claudia Righini, Dominique de Ziegler and René Frydman

increased uterine contraction frequency during the early luteal phase in ovarian stimulation cycles (Fanchin *et al.*, 2000).

N= 59 IVF patients

uteri morphologically normal(hysteroscopy and ultrasound scans)

at least three good quality embryos

Stimulated cycle.

Human Reproduction, Vol. 15, (Suppl. 1), pp. 90–100, 2000

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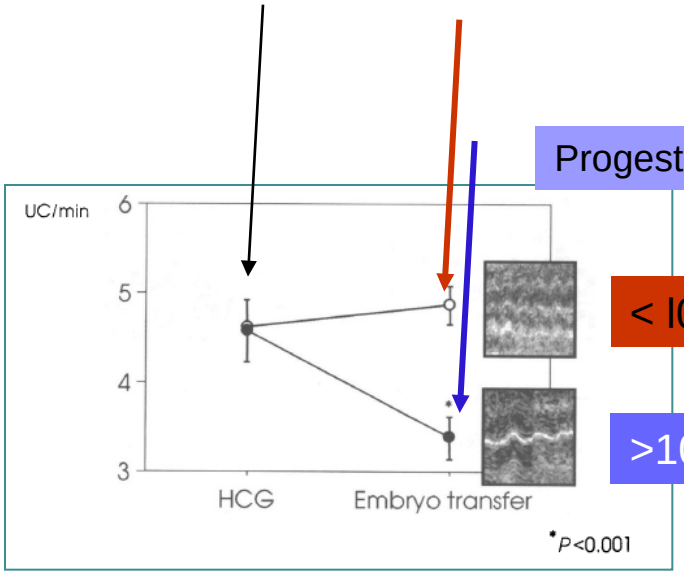

Progesterone (ng/ml)

< l00 (n = 34)

>100 (n = 25)

1.- utero-relaxing effects of progesterone in the non-pregnant uterus

2.- support the administration of progesterone before embryo transfer to increase tissue concentrations and improve the outcome of IVF.

PHARMACOLOGICAL TREATMENT TO REDUCE UTERINE ACTIVITY AND…IMPROVE IMPLANTATION??

Uterine Peristalsis in Women With Repeated IVF Failures: Possible Therapeutic Effect of Hyoscine Bromide

Aki Kido, MD, PhD,[1] Kaori Togashi, MD, PhD,[1] Hiroshi Hatayama, MD, PhD,[2] Takahiro Nakayama, MD, PhD,[2] Akira Yamamoto, MD, PhD,[1] Masako Kataoka, MD, PhD, MPhil,[1] Togas Tulandi, MD, MHCM[3]

[1]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto City, Kyoto, Japan
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[3]Department of Obstetrics and Gynecology, McGill University, Montreal QC

J Obstet Gynaecol Can 2009;31(8):732–735

Atosiban improves implantation and pregnancy rates in patients with repeated implantation failure

Vuong Thi Ngoc Lan [a,*], Vu Nhat Khang [b], Giang Huynh Nhu [b], Ho Manh Tuong [c]

Reproductive BioMedicine Online (2012) 25, 254–260

O-067 Oral **Effects of barusiban and atosiban on frequency of uterine contractions in the luteal phase after stimulation: a randomised placebo-controlled trial**

C. Blockeel[1], R. Pierson[2], B. Popovic-Todorovic[1], H. Visnova[3], J.A. García-Velasco[4], M. Mrázek[5], P.N. Barri[6], P. Pierzynski[7], W. Kuczynski[7], P. Devroey[1], V. Breinholt[8], L. Erichsen[9], B.M. Klein[10], J.C. Arce[8]

Hum . Rep 2009 ESHRE Amsterdam

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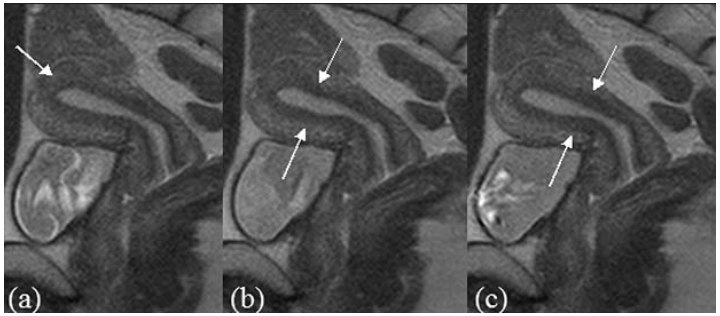

Study based on cine MRN

CONCLUSION

This preliminary report suggests that women with repeated IVF failures might have abnormal uterine peristalsis. It is possible that decreasing peristalsis by administration of hyoscine increases the chance of embryo retention, implantation, and successful pregnancy. Further study in a large number of patients is needed.

2009

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- ✓**Randomised, double-blind, parallel groups,placebo-controlled**
- ✓**multicentre trial**
- ✓**125 oocyte donors**

Objective : to evaluate the effects of the selective oxytocin antagonist, **barusiban** and the mixed **oxytocin / vasopressin V1a antagonist**, **atosiban** versus placebo on **luteal phase uterine contractions** after controlled ovarian stimulation and luteal phase supplementation with progesterone.

O-067 Oral **Effects of barusiban and atosiban on frequency of uterine contractions in the luteal phase after stimulation: a randomised placebo-controlled trial**

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Day 2 after oocyte retrieval

barusiban (n= 41)

(IV bolus 9 mg, IV infusion 2.16 mg/h),

atosiban (n= 42)

(IV bolus 6.75 mg, IV infusion 18 mg/h)

placebo (n= 41)

(IV bolus of saline, IV infusion of saline)

Transvaginal ultrasound recordings of a continuous cine-loop image of at least 5 minutes duration

Recordings were assessed for uterine contractility parameters by a central independent assessor, blinded to treatment allocation, using a computer-assisted time series motion analysis software.

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1.- Significant decrease from Day 2 to Day 5 after oocyte retrieval was observed irrespective of treatment group ($p<0,001$)

2.-**After 30 minutes of dosing** the frequence of uterine contractions was significantly reduced in the **barusiban and atosiban groups** compared with placebo ($p<0,001$ and $p<0,024$)

Conclusions: The data suggest that barusiban and atosiban could decrease uterine contractility in the luteal phase of controlled ovarian stimulation cycles supplemented with progesterone.

The largest effect is observed after reaching the highest exposure to drugs. **Further refinement is required** for identifying the optimal doses to maximise the effect observed and to maintain the reduction in uterine contractility beyond embryo transfer.

Inclusion Criteria:

Estimated Primary Completion Date: ***December 2013***

Women aged 18-37 years, who have undergone 2-4 previous (IVF) or (ICSI) cycles that all resulted in a negative βhCG test, despite transfer of at least one embryo/blastocyst of good quality

Women who have in the current controlled ovarian stimulation cycle for IVF/ICSI followed the long Gonadotrophin Releasing Hormone (GnRH) agonist or GnRH antagonist protocol, received hCG for triggering of final follicular maturation and have undergone oocyte retrieval for IVF/ICSI with the purpose of fresh transfer

Retrieval of at least 6 oocytes in the current controlled ovarian stimulation cycle

Subjects should have at least one embryo of good quality available for transfer on day 3, or at least one good quality blastocyst available for transfer on day 5

Exclusion Criteria:

A total of 6 or more controlled ovarian stimulation cycles for IVF/ICSI, abnormal karyotype, uterine pathology or hydrosalpinx. Diagnosed with acquired or congenital thrombophilia disease

Stimulated cycle.

Atosiban improves implantation and pregnancy rates in patients with repeated implantation failure

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71 women with repeated implantation failure
Pregnancy rate improved in all cases

Frequency of uterine contractions

≥ 16 contractions per 4 min 10/71 (14.1%)	<16 contractions per 4 min 61/71 (85.9%)

Cycles with **≥ 16** uterine contractions per 4 min

Before atosiban **18.8** ± 1.6 (16–20)	After atosiban **5.1** ± 2.6 (2–9)

Cycles with **<16** uterine contractions per 4 min

Before atosiban **3.9** ± 2.4 (0–8)	After atosiban **2.2** ± 1.7 (0–6

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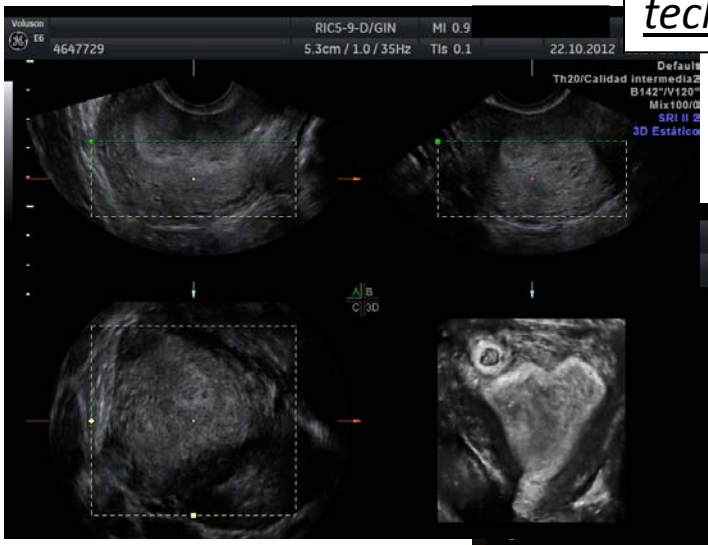
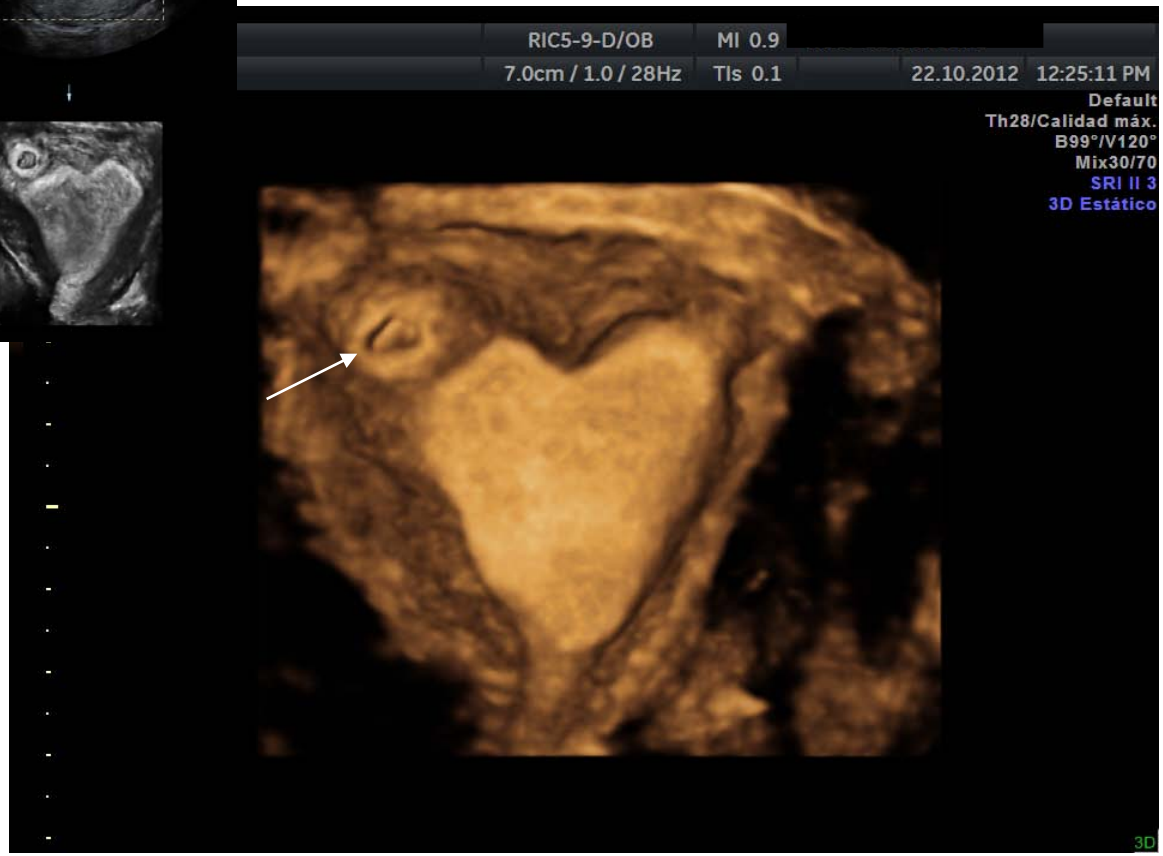
Ectopic pregnancy after assisted reproductive technology. A role for uterine contractility?





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To conclude…

Ultrasonography is a reliable tool in the assessment of endometrial receptivity in the setting of reproductive medicine

These concepts raise the possibility that early ultrasound markers predictive of implantation success or failure could be identified. Some of these are validated (endometrial size or volume, endometrial pattern and pulsatility index in uterine arteries)

Endometrial vascularity can be assessed also using 3D power Doppler

Endometrial and subendometrial vessels exhibits cyclic changes, increasing from the mid-follicular phase and peaks 3 days prior to ovulation before decreasing again over the next 5 days and then increasing until the next cycle

3D Power Dopler index (VI, FI, VFI) offers conflicting results among investigators between conception and non-conception cycles

To conclude…(2)

It´s possible to assess normal peristaltic activity studying uterus in 2D US sagital view

Uterus activity exhibits a cyclic pattern being the highest activity at the end of the follicular phase, closely related to estradiol levels.

In the luteal phase, the uterus remains relatively quiescent, probably enabling embryo implantation

Uterine contractility during the early luteal phase in controlled ovarian stimulation cycles is elevated compared to normal menstrual cycles

Supraphysiological levels of estradiol (i.e. in cases of IVF) are probably responsible of the higher frecuency of contractions in the follicular phase

In some cases , an excessive peristaltic activity is involved in implantation failure

Tocolytic agents, by reducing uterine activity, may improve the implantation rate in these cases

More investigation is needed to stablish the real role of uterine activity in the success or failure of implantacion and the use of tocolytics agents during the transfer

Thank you for your attention

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