Ultrasonography of endometrium during natural and stimulated cycle.

Echographic assessment of subendometrial contraction

Dr. José Manuel Puente
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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

3.- Ultrasonographic assessment
Endometrial size, pattern, volume
Pulsatility index in uterine arteries
3D three-dimensional power Doppler

Ultrasound assessment of the peri-implantation uterus: a review


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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.
Assessment of uterine contraction

1.- ULTRASONOGRAPHY
   sagittal view
   subjective assessment
   M-mode
   videotape stored

2.- INTRAUTERINE CATHETER
Ultrasonography of endometrium during natural and stimulated cycle. Echographic assessment of subendometrial contraction

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 appearance

- Mucus in endocervix
Ultrasonography of endometrium during natural and stimulated cycle. Echographic assessment of subendometrial contraction

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

Paid attention to:
- Polyps
- Synechia

Hysterosonography for evaluation of uterine cavity if required
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
Ultrasononographic assessment

VASCULAR CHANGES IN THE ENDOMETRIUM

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

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.
**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*
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, Carina Chi Wai Chan, Ol Shun Tang, William Shu Bin Yeung and Pak Chung Ho

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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

Stimulated cycle.

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
Natural cycle.

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

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

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 placentaion, 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.
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.
Uterine junctional zone at magnetic resonance imaging: A predictor of \textit{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, Creuse, France

<table>
<thead>
<tr>
<th>Table 2 Rates of pregnancy or failure in function of a threshold value of 7 mm for average junctional zone (AJZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AJZ &lt; 7 mm (n = 113)}$</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>No pregnancy</td>
</tr>
<tr>
<td>$P$</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 Rates of pregnancy or failure in function of different combinations of average junctional zone (AJZ) and maximal junctional zone (MJZ) threshold values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{All other combinations (n = 128)}$</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>No pregnancy</td>
</tr>
<tr>
<td>$P$</td>
</tr>
</tbody>
</table>
Stimulated cycle.

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.

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

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

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
Uterine contractility during the menstrual cycle

Carlo Bulletti¹,⁴, Dominique de Ziegler²,³, Valeria Polli¹, Lidia Diotallevi¹, Elena Del Ferro¹ and Carlo Flamigni¹

Table I. Uterine contractility (UC) frequency

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

UC frequency at the six menstrual cycle stages. Data obtained with the two methods (US and IUP) studied were during menses (Mens), pre-ovulation (PO), early luteal (EL), and late luteal (LL) phases. The differences were not significant.
Ultrasonography of endometrium during natural and stimulated cycle. Echographic assessment of subendometrial contraction frequency and direction of propagation.

Menstrual phase: Fundus to cervix
Follicular phase: Cervix-to-fundus
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.
Ultrasonography of endometrium during natural and stimulated cycle. Echographic assessment of subendometrial contraction.

Stimulated cycle.

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


Hormonal influence on the uterine contractility during ovarian stimulation

Renato Fanchin¹, Jean-Marc Ayoubi, François Olivennes, Claudia Righini, Dominique de Ziegler and René Frydman

N = 59 IVF patients

uteri morphologically normal (hysteroscopy and ultrasound scans)

at least three good quality embryos
Hormonal influence on the uterine contractility during ovarian stimulation

Renato Fanchin¹, Jean-Marc Ayoubi, François Olivennes, Claudia Righini, Dominique de Ziegler and René Frydman

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.
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

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2Rakush Hospital, Kyoto, Kyoto, Japan
3Department of Obstetrics and Gynecology, McGill University, Montreal QC


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


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. Blockeel1, R. Pierson2, B. Popovic-Todorovic1, H. Visnova3, J.A. Garcia-Velasco4, M. Mrázek5, P.N. Barri6, P. Pierzynski7, W. Kuczyński7, P. Devroey1, V. Breinholt8, L. Erichsen9, B.M. Klein10, J.C. Arce8

Hum. Rep 2009 ESHRE Amsterdam
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, MHCM3

1Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto City, Kyoto, Japan
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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.
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.

- Randomised, double-blind, parallel groups, placebo-controlled
- Multicentre trial
- 125 oocyte donors
Ultrasonography of endometrium during natural and stimulated cycle. Echographic assessment of subendometrial contraction.

**Day 2 after oocyte retrieval**

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>barusiban (n= 41)</td>
<td>(IV bolus 9 mg, IV infusion 2.16 mg/h)</td>
<td></td>
</tr>
<tr>
<td>atosiban (n= 42)</td>
<td>(IV bolus 6.75 mg, IV infusion 18 mg/h)</td>
<td></td>
</tr>
<tr>
<td>placebo (n= 41)</td>
<td>(IV bolus of saline, IV infusion of saline)</td>
<td></td>
</tr>
</tbody>
</table>

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.
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 frequency 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:

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

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


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)
Ectopic pregnancy after assisted reproductive technology. A role for uterine contractility?
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 exhibit 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 Doppler index (VI, FI, VFI) offers conflicting results among investigators between conception and non-conception cycles.
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 frequency 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 establish the real role of uterine activity in the success or failure of implantation and the use of tocolytics agents during the transfer.
Thank you for your attention

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