MicroRNAs as circulating biomarkers in the bloodstream to detect Implantation Window (IW)

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Medical Head: ART/PGD Division
Director: INSERM Unit

ART/PGD Department
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INSERM U 1203 ‘Early embryo development and pluripotency’

Montpellier-34295, France
cIVF/ICSI

- More than 8/10 transferred embryos fail to implant
- Birth live rate < 20%

>30% of implantation failures are thought to result from abnormal endometrial receptivity and/or to defects in the embryo-endometrium dialogue
huge biological wastage

. Inadequate COS

. Inadequate of Competent Embryo Selection

. Non optimum In vitro culture conditions

. Inadequate endometrial receptivity

. Fresh embryo replacement systematically should be reconsidered
Successful implantation requires:

- A competent embryo
- A receptive endometrium
- A synchronized dialogue between maternal and embryonic tissues

1/3 of implantation failures are thought to result from abnormal endometrial receptivity and/or to defects in the embryo-endometrium dialogue.
Why an Euploid Embryo does not IMPLANT?

Are we delivering the embryo at the wrong time?
Conventional approaches used in clinical practices for assessing endometrial receptivity

- Morphological examination
- Ultrasonography
- Cervicovaginal fluid
- Single biomarker
- Omics
Understanding the genome

Things we understand about the human genome <1 %

Things we need to better understand about the genome >99 %
Omics technologies

Physiology
→
Biomarkers
→
Diagnostic tools
Omics approaches to improve the understanding of the physiology of human endometrial receptivity

Transcriptomic analyses of the endometrial gene expression profile shift between the pre-receptive and receptive stages during natural cycles in the same patients

31 patients, 62 endometrial samples

Understand the molecular mechanisms governing the human endometrial receptivity

FROM PRE-SCREENING TO FUNCTIONAL ANALYSES

OMICS

miRNome
microRNAs

Transcriptome
mRNAs

Proteome
Proteins

BIOLOGY

qRT-PCR/western blot in fertile and RIF patients

Immunofluorescences of endometrium sections

Purification and primary culture of Human endometrial cells

Affymetrix® miRNA 4.1 Array Strips

GeneChip® Human Genome U133 Plus 2.0 Array
Haouzi et al., 2009a, b; 2010; 2011; 2012; 2014; 2015

Seldi-Tof + LC/MS/MS
(anion exchange, pH9)
Bissonnette et al., 2016

Complete overview to select/identify relevant biomarkers of endometrial receptivity
Assessing the human endometrial receptivity: the Win-Test®, Window Implantation Test

Biomarkers’s selection

Quantification by RT-qPCR

Non-receptive

Receptive

Diagnostic tool
Principle of the Win-Test

**Biopsy**

- Implantation window

**qRT-PCR**

- RNA extraction and quantification by qRT-PCR

**Results**

- Analysis and translation

- Receptive endometrium
- Non-receptive endometrium
Personalized embryo transfers according to Win-Test® results

To detect the implantation window under natural cycle or hormone replacement therapy (HRT)

And then, perform personalized embryo transfer in the respect of the synchronization of the fœto-maternal dialogue

Receptive endometrium ↔ Blastocysts

72h/48h before the endometrium become receptive ↔ Day 2/3 embryos
Detection of the implantation window

Patient:
33 years, male infertility (sperme donation)

1st evaluation: LH+7
2nd evaluation: LH+8
3rd evaluation: LH+9

Patient:
37 years, unexplained infertility
Patient history:
32 years
3 IVF attempts ↔ 6 fresh embryos transferred: failures
3 ovum donation (Spain, Czech republic) ↔ 7 fresh transferred embryos + 2 frozen embryos transferred: failures

1st evaluation: Win-Test at Pg+6
Partially receptive

2nd evaluation: Win-Test at Pg+8
Receptive

Suggestion: Day-5 embryo transfer at Pg+8 or a day-3 at Pg+6

2 day-3 frozen embryos transferred, subsequent cycle

Birth (2 boys)
The IW: a gradual opening-up and quick closing

- Implantation window (receptive endometrium)
- Periovulatory period (non-receptive endometrium)
- Patient

**HRT**

NR, Non-receptive
PR, Partially receptive
R, Receptive

Day after Pg administration

Day after LH surge
ER under Natural cycle or HRT

**When?**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Natural cycle (n=278)</th>
<th>HRT (n=959)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstruation</td>
<td>5.5%</td>
<td>9%</td>
</tr>
<tr>
<td>Proliferative phase</td>
<td>11.5%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Secretory phase</td>
<td>35%</td>
<td>41.5%</td>
</tr>
<tr>
<td>Distribution of receptive endometria (%)</td>
<td>38%</td>
<td>32.5%</td>
</tr>
</tbody>
</table>

Day after LH pick: 5, 6, 7, 8, 9

Day after Pg administration: 5, 6, 7, 8, 9
The Win-Test and personalized embryo transfer (pET): a means to optimize the pregnancy rates

Patients with RIF

Before Win-Test → IR: **8.1%**

After Win-Test → IR: **31.7%**
p<0.0001

<table>
<thead>
<tr>
<th>pET</th>
<th>No-pET</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=134 patients)</td>
<td>(n=52 patients)</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>36.9 ± 4.3</td>
</tr>
<tr>
<td><strong>Number of failed attempts</strong> (FET, FTET)</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td><strong>Number of non-implanted embryos</strong> (FET, FTET)</td>
<td>6.8 ± 4</td>
</tr>
</tbody>
</table>

Mean ± SD; FET, Fresh embryo transfer; FTET, frozen-thawed embryo transfer

<table>
<thead>
<tr>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ns</td>
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<tr>
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</table>

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<th>pET</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=134)</td>
<td>(n=52)</td>
<td></td>
</tr>
<tr>
<td><strong>Positive β-hCG (%)</strong></td>
<td>41.7</td>
<td>19.2</td>
</tr>
<tr>
<td><strong>Clinical pregnancy rate (%)</strong></td>
<td>35.1</td>
<td>17.3</td>
</tr>
<tr>
<td><strong>Live birth rate (%)</strong></td>
<td>27.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Per patient</td>
<td>Per cycle</td>
<td>Per patient</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>&lt;0.03</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

IR: 6.8%  IR: 5.3%, NS
The Win-Test and personalized embryo transfer (pET): a means to optimize the pregnancy rates

Before Win-Test → IR: 22.8%  Patients with NO RIF

After Win-Test → IR: 43.8%, p=0.03

<table>
<thead>
<tr>
<th>pET</th>
<th>Number of failed attempts (FET, FTET)</th>
<th>Number of non-implanted embryos (FET, FTET)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1.3 ± 1.1</td>
<td>1.3 ± 1.1</td>
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</tbody>
</table>

Mean ± SD; FET, Fresh embryo transfer; FTET, frozen-thawed embryo transfer

<table>
<thead>
<tr>
<th>pET</th>
<th>Per patient (n=37)</th>
<th>Per cycle (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive b-hCG (%) (%)</td>
<td>54.1</td>
<td>44.7</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>51.3</td>
<td>42.6</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>46.7</td>
<td>38.9</td>
</tr>
</tbody>
</table>
Personalized embryo transfers according to Win-Test® results

>1400 Endometrium biopsies received
44 Infeasible (4.7%)
60 Biopsies out protocols of IW (6.5%)
Age 37.42 ± 0.17 ans (21.7-50.8 ans)

Patients with >3 RIF

WIN TEST

Individualized IVF Tr

IR: 5.5 VS 29.7% (p<0000.1)
Without VS with Win Test respectively

39.4% Biochemical Preg/patient
35.5% ongoing Preg /patiente

Without taken into account (age, embryo quality...)
ERA vs Win-Test

ERA (Endometrial Receptivity Array)
Diaz-Gimeno et al. (2011)

Win Test
Haouzi et al. (2009)

Population
Fertile donors
Normo-ovulatory women referred for ICSI

Age des patientes
(âge, min-max)
22-39
22-36

Nombre d’Échantillons
20
62

Type de comparaison
LH+1/5 (n=15) vs. LH+7 (n=5)
LH+2 (n=31) vs. LH+7 (n=31)

Nombre de gènes différemment exprimés
238
1012

Tous les gènes
(seulement 134 sont spécifique de la réceptivité endométriale)

Sélection de 13 gènes
The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers.

Tan J1, Kan A1, Hitiyan J1,2, Taylor R1,2, Tallon N1,2, Warrach G1,2, Yuzpe A1,2, Nakhuda G3,4.

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3 Department of Obstetrics and Gynecology, University of British Columbia and the Children's and Women's Hospital and Health Centre of British Columbia, Vancouver, BC, Canada. gnakhuda@olivefertility.com.
4 Olive Fertility Centre, 555 West 12th Avenue #300, Vancouver, BC, V5Z 3X7, Canada. gnakhuda@olivefertility.com.

Abstract
PURPOSE: Endometrial receptivity issues represent a potential source of implantation failure. The aim of this study was to document our experience with the endometrial receptivity array (ERA) among patients with a history of euploid blastocyst implantation failure. We investigated whether the contribution of the endometrial factor could be identified with the ERA test and if actionable results can lead to improved outcomes.

RESULTS: Of patients with at least one previously failed euploid FET, 22.5% had a displaced WOI diagnosed by ERA and qualified for pET. After pET, we found that implantation and ongoing pregnancy rates were higher (73.7 vs. 54.2% and 63.2 vs. 41.7%, respectively) compared to patients without pET, although differences were not statistically significant.

CONCLUSIONS: Our experience demonstrates that a significant proportion of patients with a history of implantation failure of a euploid embryo have a displaced WOI as detected by the ERA. For these patients, pET using a modified progesterone protocol may improve the outcomes of subsequent euploid FET. Larger randomized studies are required to validate these results.

Does the endometrial receptivity array really provide personalized embryo transfer?

Bassil R1, Casper R1,2, Samara N1, Hsieh TB1, Barzilay E3, Orvieto R3,4, Haas J5,6.

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4 Tannenbaum Chair for Family Planning and Fertility Regulation, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
5 Trio Fertility Partners, 655 Bay St 11th floor, Toronto, Ontario, M5G 2K4, Canada. jgasah@hotmail.com.
6 Infertility and IVF Unit, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Tel Aviv University, Israel. jgasah@hotmail.com.

Abstract
PURPOSE: The aim of the present study was to determine the percentage of infertility patients who are diagnosed with a non-receptive endometrium according to the endometrial receptivity array (ERA) test and to examine whether adjusting the embryo transfer day according to the proposed shift in the window of implantation improves the pregnancy rate compared to non-ERA-tested patients.

RESULTS: During the study period, 503 patients (control group) underwent FET cycles without performing the ERA testing and 41 patients had FET following an ERA test. There were no between-group differences in patients’ age, number of previous transfers, endometrial thickness, number of transferred embryos, and ongoing pregnancy rates (35.2 vs. 39%, respectively, p = NS). Out of the 53 patients who performed the ERA test before their first or second FET, five endometrial samples (9.4%) were found to be post-receptive, 28 (51.9%) pre-receptive, and only 19 samples (35.8%) were receptive. Women in the study group with pre- or post-receptive endometrium on ERA testing, the appropriate adjustment in timing of FET according to the ERA test resulted in a 33.3% pregnancy rate, which is comparable to the 35.2% background ongoing pregnancy rate of the control group.

CONCLUSIONS: Performing the ERA test in a mock cycle prior to a FET does not seem to improve the ongoing pregnancy rate in good prognosis patients. Further large prospective studies are needed to elucidate the role of ERA testing in both good prognosis patients and in patients with recurrent implantation failure.
Toward a new generation of the Win-Test: non-invasive endometrial receptivity test

Objective: avoid to perform an endometrial biopsy

Tissue

Whole endometrial tissue

Bloodstream?

Whole blood

Plasma

Serum

Circulating microRNAs as biomarkers of human endometrial receptivity: myth or reality?
Cell-free nucleic acids as non-invasive biomarkers of gynecological cancers, ovarian, endometrial and obstetric disorders and fetal aneuploidy


MicroRNAs: new candidates for the regulation of the human cumulus–oocyte complex


Cell-free DNA in human follicular fluid as a biomarker of embryo quality

E. Scalici, S. Traver, N. Molinari, T. Mullet, M. Monforte, E. Vintejoux, and S. Hamamah

Circulating microRNAs in follicular fluid, powerful tools to explore in vitro fertilization process


Cell-free DNA in Human Follicular Microenvironment: New Prognostic Biomarker to Predict in vitro Fertilization Outcomes

Sabine Traver, Elodie Scalici, Tiffany Mullet, Nicolas Molinari, Claire Vincens, Samir Hamamah
Cell-free DNA

- Double-stranded molecules
- Short or long fragments
- Apoptotic or necrotic origine
- No identified physiological role

Circulating microRNAs

- Single-stranded molecules
- 19-25 nucleotides
- Two mechanisms of release
- Degradation of target mRNA and translation inhibition

Schwarzenbach et al., Nature Reviews Clinical Oncology, 2014
Circulating microRNAs: diagnostic, pronostic tools and therapeutic target in Oncology

- Circulating miRNAs:
- diagnostic and pronostic tools for certain cancers
- OncomiRs, over-expressed in tumour
  - Therapeutic targets
  - Anti-miR drug

Lindinger et al., Cancer Genetics, 2012

Circulating microRNAs: powerful tools in oncology and in other pathologies, including gynecological and obstetric disorders
## Overview of studies on miRNAs and Human endometrial receptivity

To date, there are very few studies on miRNAs profiles during the menstrual cycle

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Number of patients</th>
<th>Samples</th>
<th>Approach</th>
<th>Compared samples</th>
<th>Number of miRNAs up-regulated</th>
<th>Number of miRNAs down Regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuoakkanen et al., 2010</td>
<td>Fertile volunteer</td>
<td>8</td>
<td>Epithelial cells from endometrial tissue</td>
<td>miRNAs microarrays</td>
<td>Late proliferative (n=4) vs. mid-secretory phase (n=4)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sha et al., 2011</td>
<td>Infertile patients</td>
<td>5</td>
<td>Endometrial biopsies</td>
<td>Deep sequencing</td>
<td>Early proliferative (1 pool of 5) vs. mid-secretory phase (1 pool of 5)</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Altmäe et al., 2013</td>
<td>Fertile patients</td>
<td>7</td>
<td>Endometrial biopsies</td>
<td>miRNAs microarrays</td>
<td>Early proliferative (n=4) vs. mid-secretory phase (n=3)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Kresowik et al., 2014</td>
<td>Fertile patients</td>
<td>12</td>
<td>Endometrial biopsies Serum</td>
<td>RT-qPCR of 8 selected miRNAs</td>
<td>Proliferative (n=12) vs. secretory phase (n=12)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Vilella et al., 2015</td>
<td>Fertile patients</td>
<td>20</td>
<td>Endometrial Fluid</td>
<td>miRNAs microarrays</td>
<td>Early proliferative (n=4) vs. mid-secretory phase (n=4)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Revel et al., 2011</td>
<td>RIF and fertile patients</td>
<td>16</td>
<td>Endometrial biopsies</td>
<td>Taqman miRNAs array</td>
<td>Fertile (n=5) vs. RIF patients (n=11)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Choi et al., 2016</td>
<td>Healthy volunteer and RIF patients</td>
<td>22</td>
<td>Endometrial biopsies</td>
<td>miRNAs microarrays</td>
<td>Fertile (n=7) vs. RIF patients (n=15)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Shi et al., 2017</td>
<td>Infertile patients and RIF patients</td>
<td>12</td>
<td>Endometrial biopsies</td>
<td>miRNAs microarrays</td>
<td>Infertile (n=5) vs. RIF patients (n=7) (5-7 days post-ovulation)</td>
<td>93</td>
<td>12</td>
</tr>
</tbody>
</table>
miRNAs throughout the menstrual cycle

<table>
<thead>
<tr>
<th></th>
<th>Kuokkanen et al., 2010</th>
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<th>Altmäe et al., 2013</th>
<th>Kresowik et al., 2014</th>
<th>Vilella et al., 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIR30D</td>
<td>2.2</td>
<td>6.92</td>
<td>3.29</td>
<td>2.74</td>
<td>2.62 (/ES), 2.98 (/EP), 3.04 (/LP)</td>
</tr>
<tr>
<td>MIR30B</td>
<td>2.6</td>
<td>2.99</td>
<td>4.23</td>
<td>2.96</td>
<td>-</td>
</tr>
<tr>
<td>MIR31</td>
<td>2.1</td>
<td>3.32</td>
<td>-</td>
<td>1.49</td>
<td>-</td>
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<tr>
<td>MIR203</td>
<td>2.5</td>
<td>2.01</td>
<td>-</td>
<td>2.42</td>
<td>-</td>
</tr>
<tr>
<td>MIR503</td>
<td>-3.6</td>
<td>-4</td>
<td>-</td>
<td>-2.01</td>
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<tr>
<td>MIR193A-3P</td>
<td>5.2</td>
<td>2.27</td>
<td>-</td>
<td>-</td>
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<tr>
<td>MIR455-3P</td>
<td>-</td>
<td>-2.23</td>
<td>-</td>
<td>-</td>
<td>-3.14 (/ES)</td>
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<tr>
<td>MIR455-5P</td>
<td>-</td>
<td>-2.53</td>
<td>-</td>
<td>-</td>
<td>-1.95 (/ES)</td>
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<tr>
<td>MIR424</td>
<td>-</td>
<td>-3.18</td>
<td>-</td>
<td>-</td>
<td>-5.02 (/ES)</td>
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<tr>
<td>MIR29B</td>
<td>2.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (/EP), 3.67 (/LP)</td>
</tr>
<tr>
<td>MIR29C</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.22 (/LP)</td>
</tr>
<tr>
<td>MIR200C</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.51 (/EP), 2.46 (/LP)</td>
</tr>
<tr>
<td>MIR210</td>
<td>7.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.11 (/LP), 2.16 (/EP)</td>
</tr>
</tbody>
</table>

Fold changes during the implantation window are indicated

And few miRNAs are in common between these studies

ES, early secretory
EP, early proliferative
LP, late proliferative
Objectives

To perform the endometrial miRNome according to the endometrial receptivity status using the Win-test

To investigate the endometrial miRNome according to the pregnancy outcome after personalized embryo transfer using the Win-Test

To investigate in which measure the selected miRNAs can be quantified in the bloodstream
Patientes under HRT
Biopsies during the IW (Pg+6 to Pg+9)

**WIN TEST**

Endometrial receptivity status

Non-receptive vs. Receptive
(n=5)  (n=15)
Affymetrix miRNA 4.1 Array Strips

Endometrial receptivity-associated miRNAs?

Personalized embryo transfers in receptive patients

Negative β-hCG vs. Positive β-hCG
(n=6)  (n=5)
Affymetrix miRNA 4.1 Array Strips

Implantation failure-associated miRNAs?

Outcome

Miscarriage* vs. Live birth
(n=4)  (n=5)
Affymetrix miRNA 4.1 Array Strips

Miscarriage-associated miRNAs?

*8-12 weeks post-amenorrhoea

Study design
Endometrial receptivity-associated miRNAs

Supervised classification

Hierarchical clustering of 20 endometrium samples diagnosed as receptive or non-receptive during the theoretical IW

Validation by RT-qPCR in an independent cohort of endometrial tissues

TaqMan miRNA assay

Patent n°EB16391

The microarray signals of each candidate

Identification of 3 miRNAs over-expressed in non-receptive endometrium
Implantation failure-associated miRNAs

Positive β-hCG vs. Negative β-hCG

Number of miRNAs differentially expressed

<table>
<thead>
<tr>
<th>Expression console (Affymetrix)</th>
<th>Significant analysis of microarrays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative β-hCG vs. positive β-hCG</td>
<td>Anova</td>
</tr>
<tr>
<td>(n=6)</td>
<td>261</td>
</tr>
<tr>
<td>(n=5)</td>
<td></td>
</tr>
</tbody>
</table>

Fold change ≥ 2, FDR ≤ 5%

218 miRNAs in commun to the 3 statistical analyses

All over-expressed in the endometrium from the ‘negative β-hCG’ group

Identification of endometrial miRNAs associated with implantation failure
Implantation failure-associated circulating miRNAs can be quantified in serum samples and confirmed the microarray data

Positive b-hCG vs. Negative b-hCG

Selection of 5 miRNAs for quantification in serum samples

Patent n°EB16392
Endometrial miRNAs associated with miscarriage

**Miscarriage vs. Live birth**

**Number of miRNAs differentially expressed**

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<thead>
<tr>
<th>Expression console (Affymetrix)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage vs. Live birth</td>
<td>Anova</td>
</tr>
<tr>
<td>(n=4)</td>
<td>76</td>
</tr>
<tr>
<td>(n=5)</td>
<td></td>
</tr>
</tbody>
</table>

Fold change ≥2, FDR ≤ 5%

60 miRNAs in common to the 2 statistical analyses

All over-expressed in the endometrium from the ‘miscarriage’ group

**Selection of 5 miRNAs for quantification in serum samples**

**Patent n°EB16393**

miR-1

Identification of endometrial miRNAs associated with miscarriage that can be detected in serum samples
**Conclusion and perspectives**

MicroRNAs associated with:

**Endometrial receptivity, RIF & Miscarriages**

Develop a non-invasive diagnostic/pronostic tool to limit the use of invasive endometrial biopsies for the evaluation of ER and predict attempt outcomes.

This circulating miRNA-based test become a rapid, easy and cheaper clinical diagnostic tool to allow performing personalized embryo transfer.

It would be possible to select strategies by which microRNAs technologies can be used in novel, non-hormonal therapeutic approaches to avoid miscarriages and consequently, to increase the pregnancy rate.