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ERA®

Endometrial Receptivity Analysis

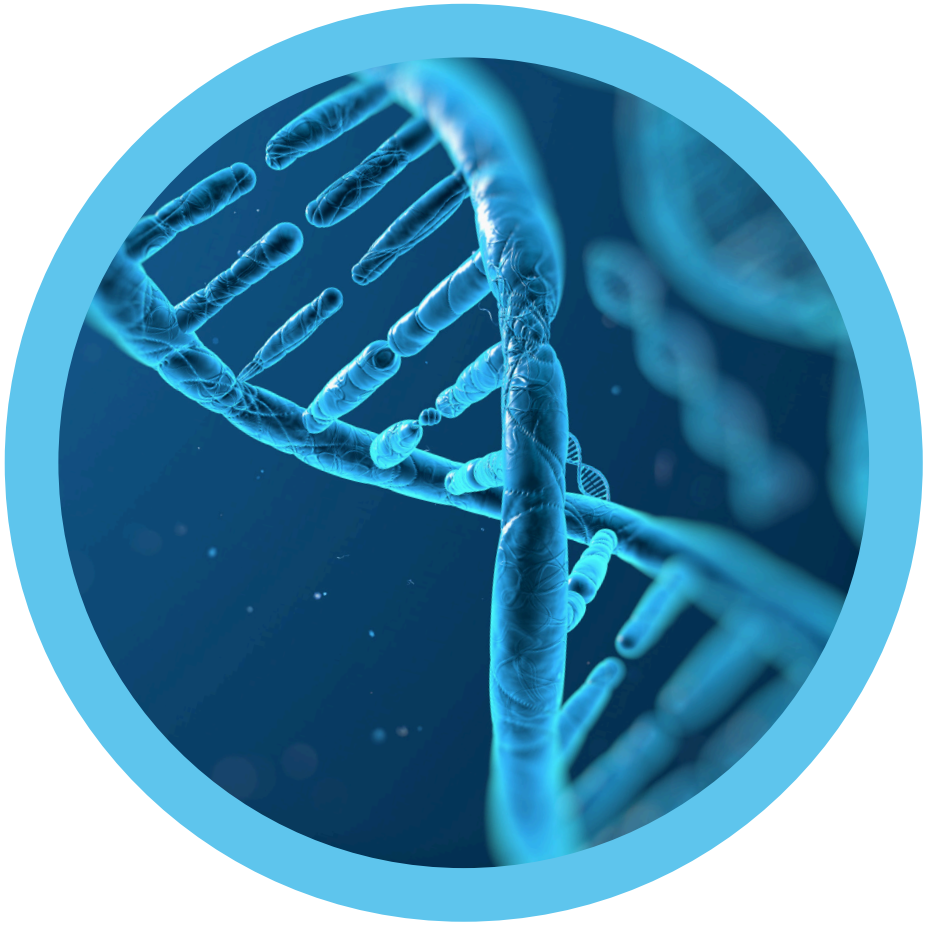
Patented in 2009

igenomix

PIONEERS IN **REPRODUCTIVE GENETICS**

igenomix
PIONEERS IN REPRODUCTIVE GENETICS

ERA® analyzes the expression of 248 genes using NGS to determine the personalized window of implantation for each patient



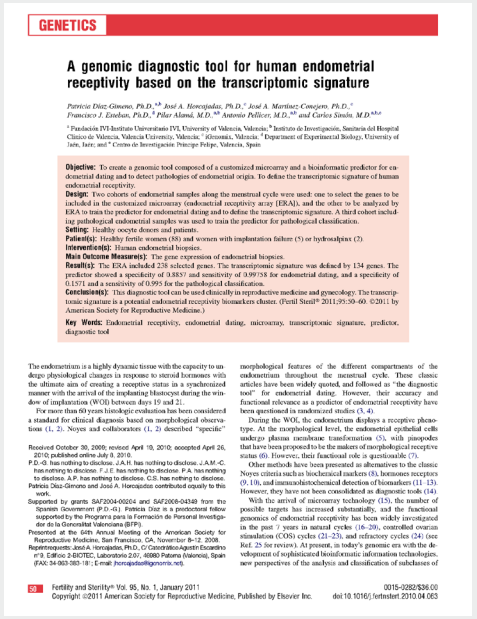
The ERA® test is a molecular tool based on gene expression used to determine when the endometrium is receptive

- The test consists of:
  - NGS analysis of the expression of 248 genes involved in endometrial receptivity.
  - An informatic predictor that analyzes the gene expression data and classifies the endometrium as “Receptive" or "Non Receptive” with a sensitivity of 90% and a specificity of 97%.

    Patented in 2009: PCT/ES 2009/000386

Scientific Support: IGENOMIX Publications

- The development of the ERA® diagnostic tool was published in the paper by Díaz-Gimeno et al, 2011 (Fertil Steril. 2011 Jan;95(1):50-60, 60.e1-15).
- ERA®'s effectiveness and consistency was demonstrated in the paper by Díaz-Gimeno et al, 2013 (Fertil Steril. 2013 Feb;99(2):508-17).



GENETICS

A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature

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Objective: To create a genomic tool composed of a customized microarray and a bioinformatic predictor for endometrial dating and to detect pathologies of endometrial origin. To define the transcriptomic signature of human endometrial receptivity.
Design: Two cohorts of endometrial samples along the menstrual cycle were used: one to select the genes to be included in the customized microarray (endometrial receptivity array [ERA]), and the other to be analyzed by ERA to train the predictor for endometrial dating and to define the transcriptomic signature. A third cohort including pathological endometrial samples was used to train the predictor for pathological classification.
Setting: Healthy oocyte donors and patients.
Patient(s): Healthy fertile women (88) and women with implantation failure (5) or hydrosalpinx (2).
Intervention(s): Human endometrial biopsies.
Main Outcome Measure(s): The gene expression of endometrial biopsies.
Result(s): The ERA included 238 selected genes. The transcriptomic signature was defined by 134 genes. The predictor showed a specificity of 0.8857 and sensitivity of 0.99758 for endometrial dating, and a specificity of 0.1371 and a sensitivity of 0.995 for the pathological classification.
Conclusion(s): This diagnostic tool can be used clinically in reproductive medicine and gynecology. The transcriptomic signature is a potential endometrial receptivity biomarkers cluster. (Fertil Steril® 2011;95:50–60. ©2011 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, endometrial dating, microarray, transcriptomic signature, predictor, diagnostic tool

The endometrium is a highly dynamic tissue with the capacity to undergo physiological changes in response to steroid hormones with the ultimate aim of creating a receptive status in a synchronized manner with the arrival of the implanting blastocyst during the window of implantation (WOI) between days 19 and 21.

For more than 60 years histologic evaluation has been considered a standard for clinical diagnosis based on morphological observations (1, 2). Noyes and collaborators (1, 2) described "specific" morphological features of the different compartments of the endometrium throughout the menstrual cycle. These classic articles have been widely quoted, and followed as "the diagnostic tool" for endometrial dating. However, their accuracy and functional relevance as a predictor of endometrial receptivity have been questioned in randomized studies (3, 4).

During the WOI, the endometrium displays a receptive phenotype. At the morphological level, the endometrial epithelial cells undergo plasma membrane transformation (5), with pinopodes that have been proposed to be the markers of morphological receptive status (6). However, their functional role is questionable (7).

Other methods have been presented as alternatives to the classic Noyes criteria such as biochemical markers (8), hormones receptors (9, 10), and immunohistochemical detection of biomarkers (11–13). However, they have not been consolidated as diagnostic tools (14).

With the arrival of microarray technology (15), the number of possible targets has increased substantially, and the functional genomics of endometrial receptivity has been widely investigated in the past 7 years in natural cycles (16–20), controlled ovarian stimulation (COS) cycles (21–23), and refractory cycles (24) (see Ref. 25 for review). At present, in today's genomic era with the development of sophisticated bioinformatic information technologies, new perspectives of the analysis and classification of subclasses of

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P.D.-G. has nothing to disclose. J.A.H. has nothing to disclose. J.A.M.-C. has nothing to disclose. F.J.E. has nothing to disclose. P.A. has nothing to disclose. A.P. has nothing to disclose. C.S. has nothing to disclose. Patricia Díaz-Gimeno and José A. Horcajadas contributed equally to this work.
Supported by grants SAF2004-00204 and SAF2008-04349 from the Spanish Government (P.D.-G.). Patricia Díaz is a predoctoral fellow supported by the Programa para la Formación de Personal Investigador de la Generalitat Valenciana (BFPI).
Presented at the 64th Annual Meeting of the American Society for Reproductive Medicine, San Francisco, CA, November 8–12, 2008.
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0015-0282/$36.00
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The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity

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Objective: To compare the accuracy and reproducibility of the endometrial receptivity array (ERA) versus standard histologic methods.
Design: A comparative prospective study (May 2008–May 2012).
Setting: University-affiliated infertility clinic.
Patient(s): Eighty-six healthy oocyte donors, regularly cycling, aged 20–34 years with a body mass index (BMI) of 19–25 kg/m².
Intervention(s): Endometrial biopsies were collected throughout the menstrual cycle. For the accuracy study, 79 samples were grouped into two cohorts: the training set (n = 59) for ERA machine-learning training and dating, and a dating subset (n = 49) for comparison between histologic and ERA dating. For the reproducibility study, seven women underwent ERA testing and it was repeated in the same patients on the same day of their cycle 29–40 months later.
Main Outcome Measure(s): Concordance of histologic and ERA dating related to LH as a reference, and interobserver variability between pathologists were statistically analyzed by the quadratic weighted Kappa index. The ERA reproducibility was tested and its gene expression visualized by principal component analysis.
Result(s): For each pathologist, concordance against LH peak yielded values of 0.618 (0.446–0.79) and 0.585 (0.545–0.824). Interobserver variability between pathologists yielded a Kappa index of 0.622 (0.435–0.839). Concordance for ERA dating against LH peak showed a value of 0.922 (0.815–1.000). Reproducibility of the ERA test was 100% consistent.
Conclusion(s): The ERA is more accurate than histologic dating and is a completely reproducible method for the diagnosis of endometrial dating and receptivity status. (Fertil Steril® 2013;99:508–17. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, diagnostic accuracy, consistency, machine-learning prediction, histologic dating

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertilityforum.com/diaz-gimenop-endometrial-receptivity-diagnostic-accuracy/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

The human endometrium is a highly dynamic tissue that has the capacity to undergo physiological changes in response to steroid hormones, with the ultimate purpose of creating a receptive status that is synchronized with the arrival of an implanting blastocyst. Since the 1950s, histologic evaluation has been widely used for endometrial dating (1, 2). However, its accuracy and functional relevance as a predictor of endometrial receptivity or fertility status have come to be questioned following the reports from randomized studies (3, 4). As a consequence, at present, the endometrial status is not investigated in the standard work-up performed in infertility clinics worldwide due to the absence of objective and reliable diagnostic tests that

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P.D.-G. is a co-inventor of the ERA patent. M.R.-A. has nothing to disclose. D.B. has nothing to disclose. N.B. has nothing to disclose. J.A.M.-C. has nothing to disclose. P.A. has nothing to disclose. N.G. has nothing to disclose. A.P. is a co-inventor of the ERA patent. C.S. is a co-inventor of the ERA patent.
Private funding provided by Fundación Instituto Valenciano de Infertilidad and IVIOMICS. Patricia Díaz-Gimeno has been a predoctoral fellow supported by the Programa para la Formación de Personal Investigador de la Generalitat Valenciana (BFPI/2007/106-AFPI/2007/106).
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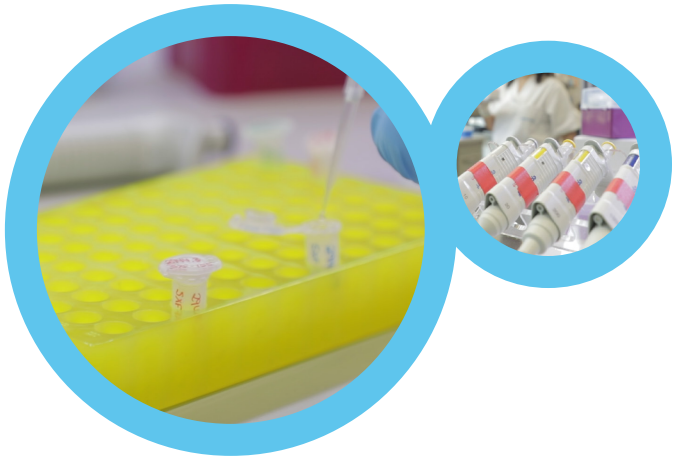
Fertility and Sterility® Vol. 99, No. 2, February 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.09.046

Igenomix Publication: Díaz-Gimeno P. et al. - Fertil Steril 2013; 99 (2): 508 - 17.
Díaz-Gimeno P. et al. - Fertil Steril 2011; 95 (1): 50-60.

The Diagnostic Value of Endometrial Evaluation:

- The ERA test diagnoses the state of the endometrium during the Window of Implantation and determines the optimal timeframe for embryo transfer.
- In a blinded study, the ERA test classified endometrial receptivity better than histology using the Noyes criteria.



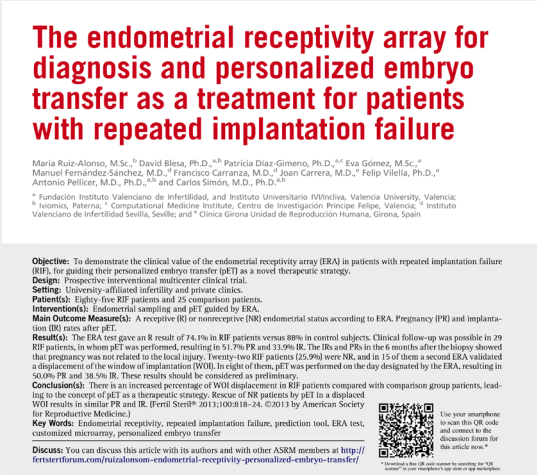
Pathologist 1 (P1)	Pathologist 2 (P2)	P1 vs P2	ERA®
0.618 (0.446-0.791)	0.685 (0.545-0.824)	0.622 (0.435-0.839)	0.922 (0.815-1.000)

0.61-0.80
Good Concordance
0.81-1.00
Very Good Concordance

Igenomix Publication: Díaz-Gimeno P. et al. - Fertil Steril 2013; 99 (2): 508 - 17.

Clinical Support: IGENOMIX Publications

- ERA clinical applicability to patients with implantation failure was demonstrated in publications by Ruiz-Alonso et al, 2013 and 2014.
- A randomised study is curently in progress to assess its applicability to patients without any prior assisted reproduction treatment (ClinicalTrials.gov Identifier:NCT01954758).



The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure

María Ruiz-Alonso, M.Sc.,[b] David Blesa, Ph.D.,[a,b] Patricia Díaz-Gimeno, Ph.D.,[b,c] Eva Gómez, M.Sc.,[a] Manuel Fernández-Sánchez, M.D.,[d] Francisco Carranza, M.D.,[d] Joan Carrera, M.D.,[e] Felip Vilella, Ph.D.,[a] Antonio Pellicer, M.D., Ph.D.,[a,b] and Carlos Simón, M.D., Ph.D.[a,b]

[a] Fundación Instituto Valenciano de Infertilidad, and Instituto Universitario IVI/Incliva, Valencia University, Valencia; [b] Iviomics, Paterna; [c] Computational Medicine Institute, Centro de Investigación Príncipe Felipe, Valencia; [d] Instituto Valenciano de Infertilidad Sevilla, Seville; and [e] Clínica Girona Unidad de Reproducción Humana, Girona, Spain

Objective: To demonstrate the clinical value of the endometrial receptivity array (ERA) in patients with repeated implantation failure (RIF), for guiding their personalized embryo transfer (pET) as a novel therapeutic strategy.
Design: Prospective interventional multicenter clinical trial.
Setting: University-affiliated infertility and private clinics.
Patient(s): Eighty-five RIF patients and 25 comparison patients.
Intervention(s): Endometrial sampling and pET guided by ERA.
Main Outcome Measure(s): A receptive (R) or nonreceptive (NR) endometrial status according to ERA. Pregnancy (PR) and implantation (IR) rates after pET.
Result(s): The ERA test gave an R result of 74.1% in RIF patients versus 88% in control subjects. Clinical follow-up was possible in 29 RIF patients, in whom pET was performed, resulting in 51.7% PR and 33.9% IR. The IRs and PRs in the 6 months after the biopsy showed that pregnancy was not related to the local injury. Twenty-two RIF patients (25.9%) were NR, and in 15 of them a second ERA validated a displacement of the window of implantation (WOI). In eight of them, pET was performed on the day designated by the ERA, resulting in 50.0% PR and 38.5% IR. These results should be considered as preliminary.
Conclusion(s): There is an increased percentage of WOI displacement in RIF patients compared with comparison group patients, leading to the concept of pET as a therapeutic strategy. Rescue of NR patients by pET in a displaced WOI results in similar PR and IR. (Fertil Steril® 2013;100:818–24. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, repeated implantation failure, prediction tool, ERA test, customized microarray, personalized embryo transfer

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/ruizalonsom-endometrial-receptivity-personalized-embryo-transfer/

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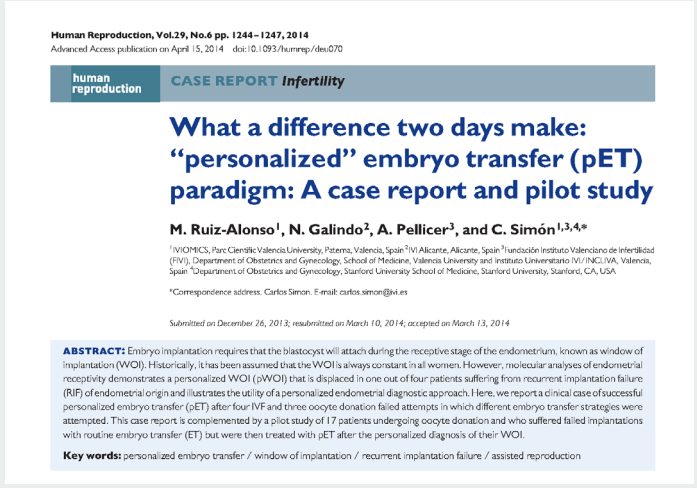

Human Reproduction, Vol.29, No.6 pp. 1244–1247, 2014
Advanced Access publication on April 15, 2014 doi:10.1093/humrep/deu070

human reproduction | CASE REPORT *Infertility*

What a difference two days make: "personalized" embryo transfer (pET) paradigm: A case report and pilot study

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Submitted on December 26, 2013; resubmitted on March 10, 2014; accepted on March 13, 2014

ABSTRACT: Embryo implantation requires that the blastocyst will attach during the receptive stage of the endometrium, known as window of implantation (WOI). Historically, it has been assumed that the WOI is always constant in all women. However, molecular analyses of endometrial receptivity demonstrates a personalized WOI (pWOI) that is displaced in one out of four patients suffering from recurrent implantation failure (RIF) of endometrial origin and illustrates the utility of a personalized endometrial diagnostic approach. Here, we report a clinical case of successful personalized embryo transfer (pET) after four IVF and three oocyte donation failed attempts in which different embryo transfer strategies were attempted. This case report is complemented by a pilot study of 17 patients undergoing oocyte donation and who suffered failed implantations with routine embryo transfer (ET) but were then treated with pET after the personalized diagnosis of their WOI.

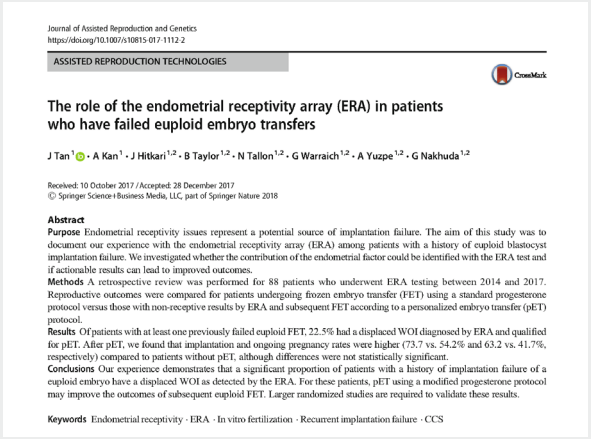
Key words: personalized embryo transfer / window of implantation / recurrent implantation failure / assisted reproduction

Ruiz-Alonso M. et al. - Fertil Steril 2013; 100 (3): 818-24.

Ruiz-Alonso M. et al. - Hum Reprod 2014; 29 (6): 1244-7.

Clinical Support: External Publications

- A number of IVF clinics around the world have published their clinical experience using the ERA test in their patients to assess endometrial receptivity and adjust the timing of transfer based on ERA test results.



Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-017-1112-2

ASSISTED REPRODUCTION TECHNOLOGIES

The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers

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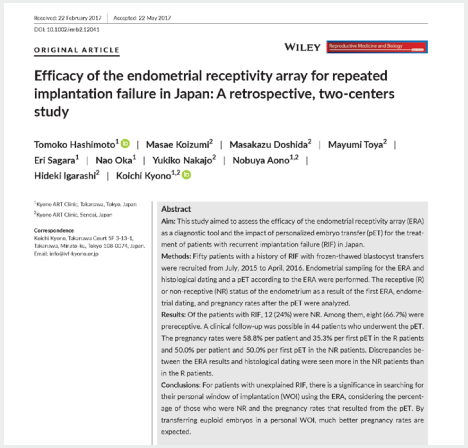
Abstract
Purpose Endometrial receptivity issues represent a potential source of implantation failure. The aim of this study was to document our experience with the endometrial receptivity array (ERA) among patients with a history of euploid blastocyst implantation failure. We investigated whether the contribution of the endometrial factor could be identified with the ERA test and if actionable results can lead to improved outcomes.
Methods A retrospective review was performed for 88 patients who underwent ERA testing between 2014 and 2017. Reproductive outcomes were compared for patients undergoing frozen embryo transfer (FET) using a standard progesterone protocol versus those with non-receptive results by ERA and subsequent FET according to a personalized embryo transfer (pET) protocol.
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.

Keywords Endometrial receptivity · ERA · In vitro fertilization · Recurrent implantation failure · CCS

Canada
Tan et al, 2018
J Assist Reprod Genet. 2018 Jan; doi: 10.1007/s10815-017-1112-2



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DOI: 10.1002/rmb2.12041

ORIGINAL ARTICLE

WILEY

Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study

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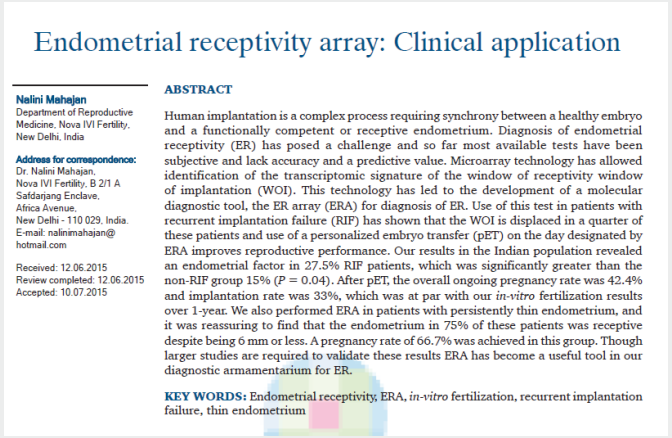
Abstract
Aim: This study aimed to assess the efficacy of the endometrial receptivity array (ERA) as a diagnostic tool and the impact of personalized embryo transfer (pET) for the treatment of patients with recurrent implantation failure (RIF) in Japan.
Methods: Fifty patients with a history of RIF with frozen-thawed blastocyst transfers were recruited from July, 2015 to April, 2016. Endometrial sampling for the ERA and histological dating and a pET according to the ERA were performed. The receptive (R) or non-receptive (NR) status of the endometrium as a result of the first ERA, endometrial dating, and pregnancy rates after the pET were analyzed.
Results: Of the patients with RIF, 12 (24%) were NR. Among them, eight (66.7%) were prereceptive. A clinical follow-up was possible in 44 patients who underwent the pET. The pregnancy rates were 58.8% per patient and 35.3% per first pET in the R patients and 50.0% per patient and 50.0% per first pET in the NR patients. Discrepancies between the ERA results and histological dating were seen more in the NR patients than in the R patients.
Conclusions: For patients with unexplained RIF, there is a significance in searching for their personal window of implantation (WOI) using the ERA, considering the percentage of those who were NR and the pregnancy rates that resulted from the pET. By transferring euploid embryos in a personal WOI, much better pregnancy rates are expected.

Japan
Hashimoto et al, 2017
Reprod Med Biol. 2017 Jun; 16(3):290-296. doi: 10.1002/rmb2.12041



Endometrial receptivity array: Clinical application

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ABSTRACT

Human implantation is a complex process requiring synchrony between a healthy embryo and a functionally competent or receptive endometrium. Diagnosis of endometrial receptivity (ER) has posed a challenge and so far most available tests have been subjective and lack accuracy and a predictive value. Microarray technology has allowed identification of the transcriptomic signature of the window of receptivity window of implantation (WOI). This technology has led to the development of a molecular diagnostic tool, the ER array (ERA) for diagnosis of ER. Use of this test in patients with recurrent implantation failure (RIF) has shown that the WOI is displaced in a quarter of these patients and use of a personalized embryo transfer (pET) on the day designated by ERA improves reproductive performance. Our results in the Indian population revealed an endometrial factor in 27.5% RIF patients, which was significantly greater than the non-RIF group 15% ($P = 0.04$). After pET, the overall ongoing pregnancy rate was 42.4% and implantation rate was 33%, which was at par with our *in-vitro* fertilization results over 1-year. We also performed ERA in patients with persistently thin endometrium, and it was reassuring to find that the endometrium in 75% of these patients was receptive despite being 6 mm or less. A pregnancy rate of 66.7% was achieved in this group. Though larger studies are required to validate these results ERA has become a useful tool in our diagnostic armamentarium for ER.

KEY WORDS: Endometrial receptivity, ERA, *in-vitro* fertilization, recurrent implantation failure, thin endometrium

India
Mahajan, 2015
J Hum Reprod Sci. 2015 Jul-Sep; 8(3):121-9. doi: 10.4103/0974-1208.165153

ERA indications – Which patients may benefit?

Recurrent implantation failure patients:

- Two or more implantation failures with good quality autologous embryos or one failed implantation with good quality donor eggs.

Patients with morphologically normal endometrium:

- ERA® after intervention in the case of a congenital uterine abnormality.

Patients with normal, atrophic or hipertrophic endometrium:

- ERA® can be used for patients with normal, atrophic or hypertrophic endometrium so long as the endometrial appearance is consistent for all cycles.

ERA biopsy cycle - When should the biopsy be taken?

Hormone replacement therapy

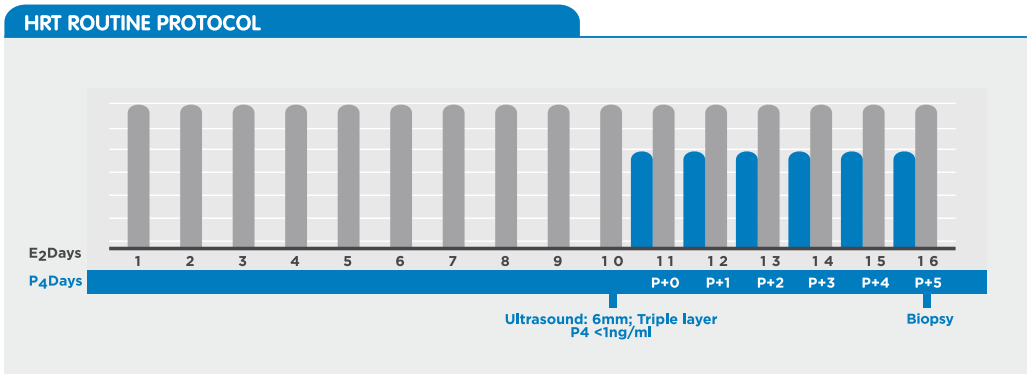
Patients start estradiol therapy from the 1st or 2nd day of the menstrual cycle. Ultrasound assessment is performed between 7-10 days after the start of estradiol administration. Start the progesterone (P4) intake when a trilaminar endometrium >6mm is reached with a serum progesterone <1ng/ml (within the 24 hours prior to starting exogenous progesterone). Progesterone is administered for five full days (120 hours).

Natural cycle

hCG (recombinant or urinary) is administered according to routine parameters in a natural cycle (follicle size >17mm). The biopsy will be taken 7 days (168 hours) after the hCG triggering.

Controlled ovarian stimulation

ERA® cannot be performed in a controlled ovarian stimulated cycle. Therefore it should be performed in a subsequent HRT or natural cycle as indicated above.



For more information about how to collect the endometrial biopsy, please read the EndomeTrio Manual at: endometrial.igenomix.com

ERA biopsy - How to take the endometrial biopsy?

- Prior to biopsy, the ERA Cryotube should be prepared and labeled with the patient's name and a second identifier (e.g. DOB or Medical Record Number/Unique Patient Identifier). The biopsied tissue should be introduced directly into the Cryotube and the Cryotube shaken vigorously for at least 10 seconds.

  The amount of tissue should not exceed the white line on the Cryotube in order to ensure proper preservation of the RNA within the biopsy sample.

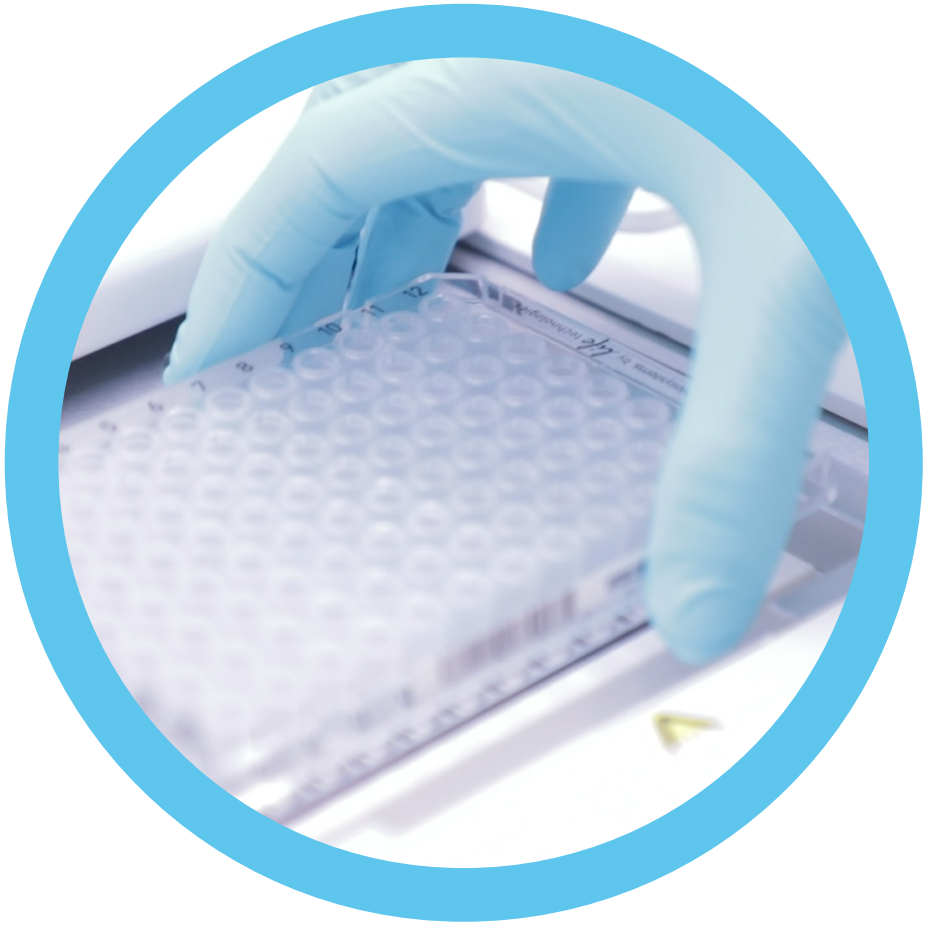
- **Storage**

  Immediately place the Cryotube in a refrigerator (4-8°C/39-46°F) and hold at this temperature for at least 4 hours. This preserved sample, in the original cryotube, can then be shipped at room temperature. If the sample is not going to be sent immediatly after the first 4 hours at 4-8°C, then it can be kept in the fridge for 3 weeks or frozen at -20°C/-4°F (recommended) until the time of shipment.

Shipment

- Samples are sent at room temperature (<35ºC/95ºF) accompanied with the patient's informed consent and a completed requisition form. Samples shipped at room temperature should reach us in a maximum of 4 to 5 days.
- We recommend including an ice pack for shipments made during the summer months.
- For more instructions regarding sample packaging, please contact us via **www.igenomix.com/era-form**

Confirm shipping by accessing the following link:
www.igenomix.com/era-form



ERA Report

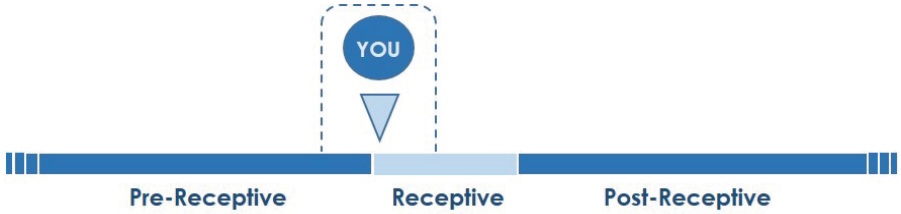
ERA (ENDOMETRIAL RECEPTIVITY ANALYSIS)

Patient information		Sample information		Clinic information	
Unique pat id.:	MUE-000	Date received:	20/12/2017	Clinic:	IVF Clinic
Sample type:	Endometrial biopsy	Report Date:	28/12/2017	Clinician:	Dr. Doe
Patient name:	Jane Doe	Progesterone:*	0.2 por < 1	No. biopsy:	1
Patient DOB:	23/09/84	Measure date:			
		First intake of P	14/12/2017 9:00 AM		
		Date of biopsy:	19/12/2017 9:00 AM		
		Cycle type:	HRT P+5 (120 hours)		

TEST RESULTS:

RECEPTIVE: EARLY RECEPTIVE

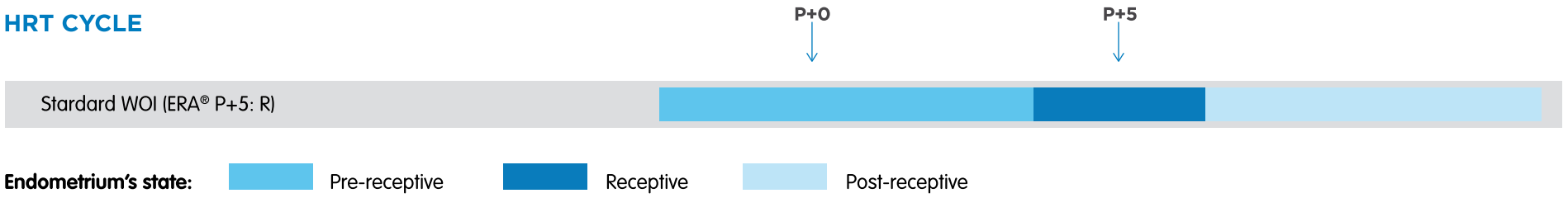
Recommendation: The personalized embryo transfer (pET) of a blastocyst/s should be performed with 132 ± 3 hours of progesterone administration (12 hours later than the time at which this endometrial biopsy was performed). A new endometrial biopsy is not required. **



ERA Results - Interpretation

Receptive:

This gene expression profile is concordant with a normal receptive endometrium. We recommend performing a blastocyst(s) transfer following the same protocol utilized during the Endometrial Receptivity Analysis biopsy cycle.



Early receptive:

The gene expression profile is concordant with an endometrium that is at the beginning of the receptive stage. We recommend progesterone administration (HRT cycle) or rest (natural cycle) for 12 hours more relative to when the biopsy was taken before performing a blastocyst(s) transfer.

Late receptive:

The gene expression profile is concordant with an endometrium that is at the end of the receptive stage. We recommend progesterone administration (HRT cycle) or rest (natural cycle) for 12 hours less relative to when the biopsy was taken before performing a blastocyst(s) transfer.

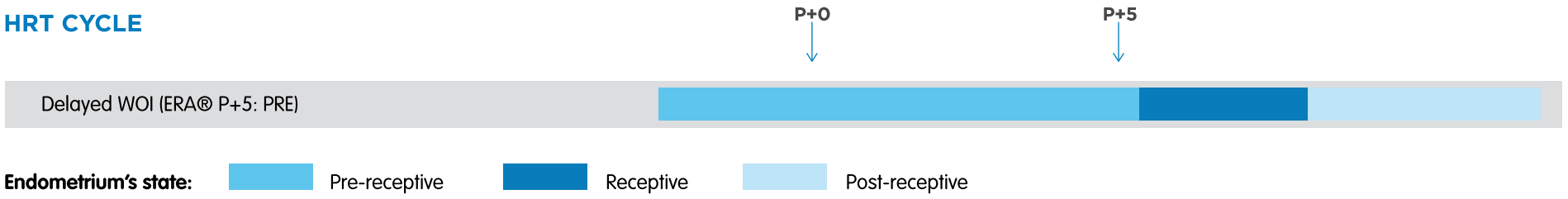
ERA Results - Interpretation

Pre-receptive:

This gene expression profile is concordant with an endometrium at a pre-receptive stage. According to the specific profile obtained it could be directly recommended to perform the blastocyst(s) transfer by adding 1 more day of progesterone exposure. In some cases (when 2 more days with progesterone exposure are needed) a new endometrial biopsy could be required.

Example 1:

A patient with a delayed WOI shows a pre-receptive result at P+5.



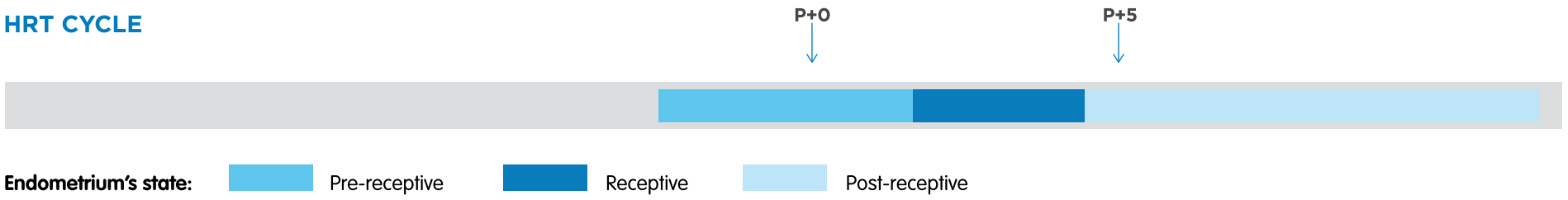
ERA Results - Interpretation

Post-receptive:

This gene expression profile is concordant with an endometrium at a post-receptive stage. To validate this result, the analysis of a second biopsy on the recommended day is needed.

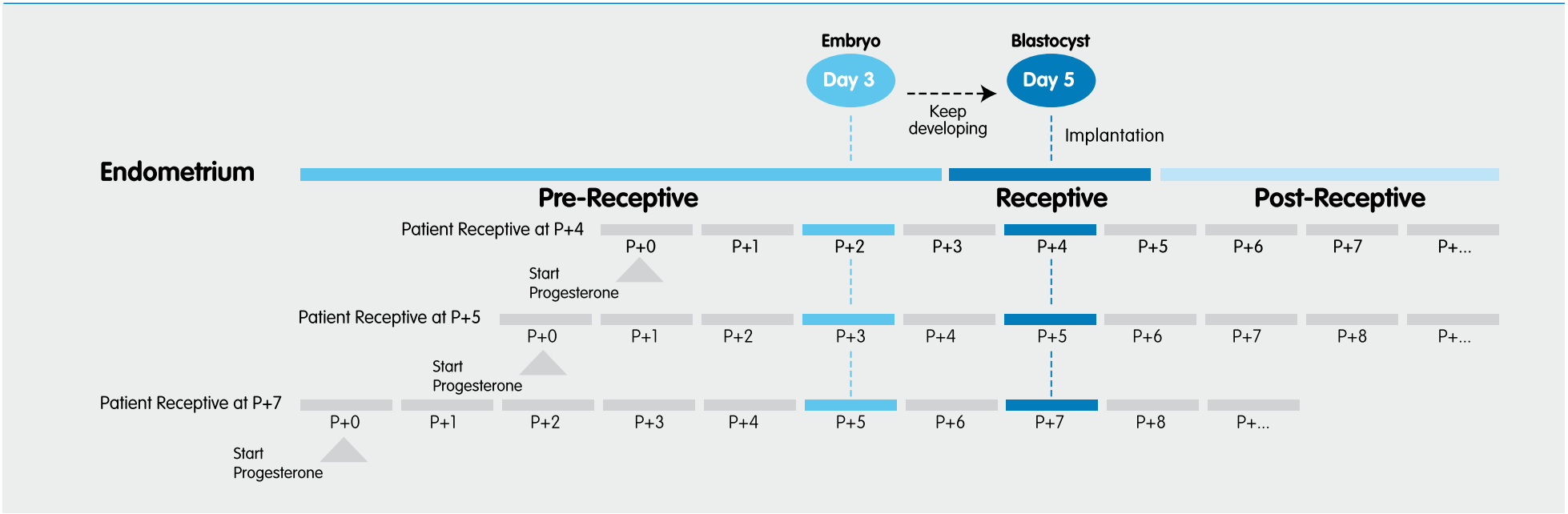
Example 2:

A patient with an advanced WOI shows a post-receptive result at P+5.



Personalized embryo transfer (pET)

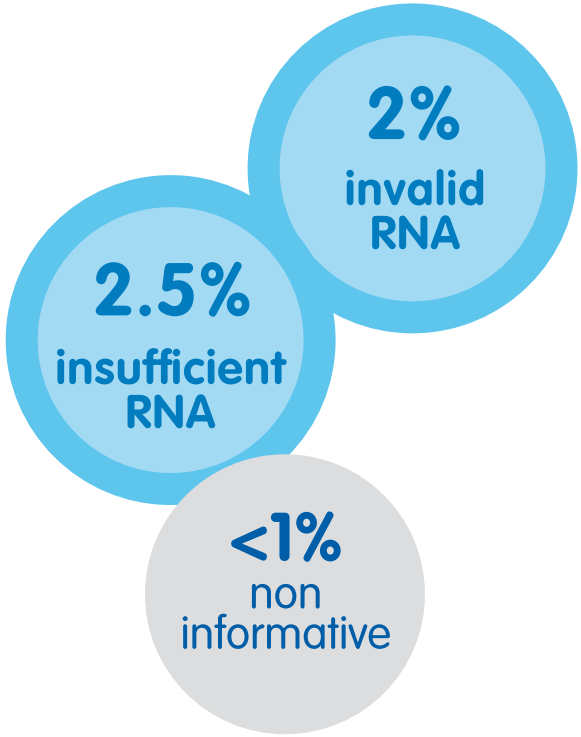
- A blastocyst (day 5-7) should be transferred on the day in which the endometrium was found to be receptive. A day-3 embryo should be transferred two days earlier than the day in which the endometrium resulted receptive.



Samples with No Result

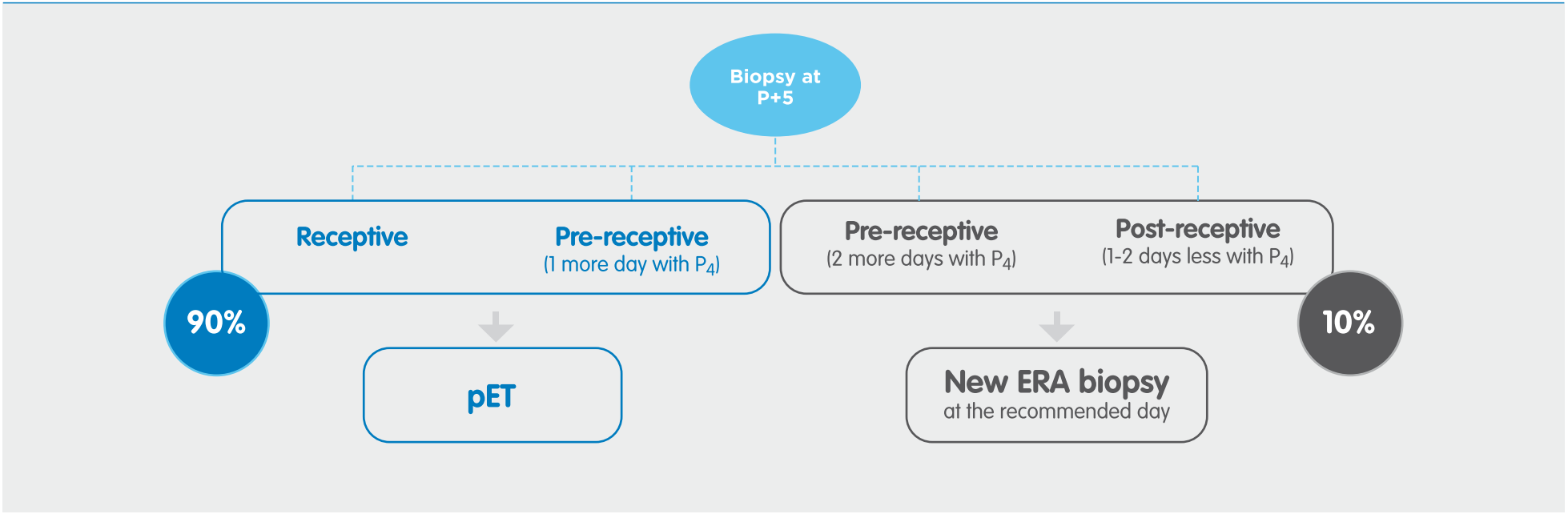
- **Invalid RNA (2%),** possible causes:
  - High temperatures (>35°C/95°F) during the shipment
  - Sample size too large
  - Too much blood or mucus
- **Insufficient RNA (2.5%),** possible causes:
  - Sample size too small
  - Too much blood or mucus
- **Non informative (<1%)**

NO CHARGE



ERA® Decision Tree

- If the patient results receptive or pre-receptive (needing just 1 more day with progesterone exposure) at P+5, then pET is directly recommended by following the specific indications given in the report. This happens in >90% of received samples.
- A 2nd endometrial biopsy is required if the ERA result is post-receptive (needing 1 day less of progesterone administration) or pre-receptive (but needing 2 additional days of progesterone administration).



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PIONEERS IN **REPRODUCTIVE GENETICS**

Clinical outcome

Updated results 30/11/2018

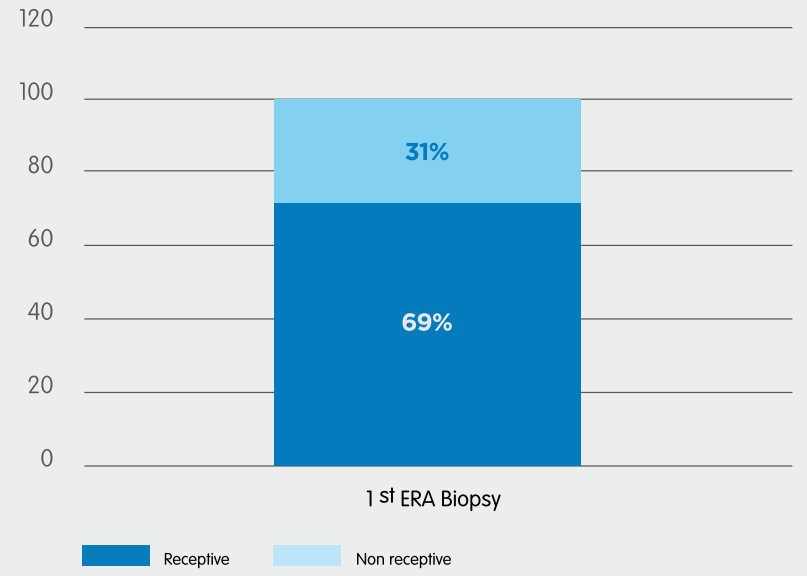
ERA® results

>55,000 patients

>70 countries

More than **>1,500** clinics

SAMPLES AT P+5 ANALYZED BY NGS

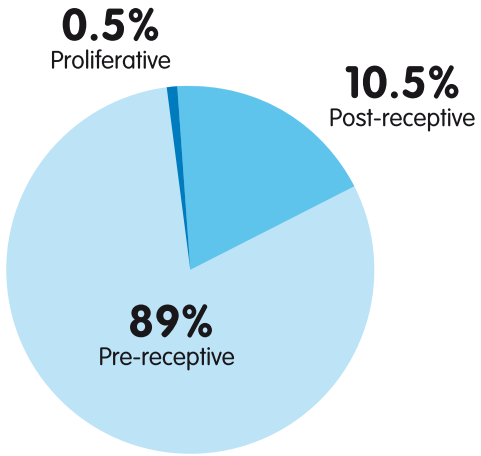


(<5% of samples cannot get a diagnosis)

ERA® results

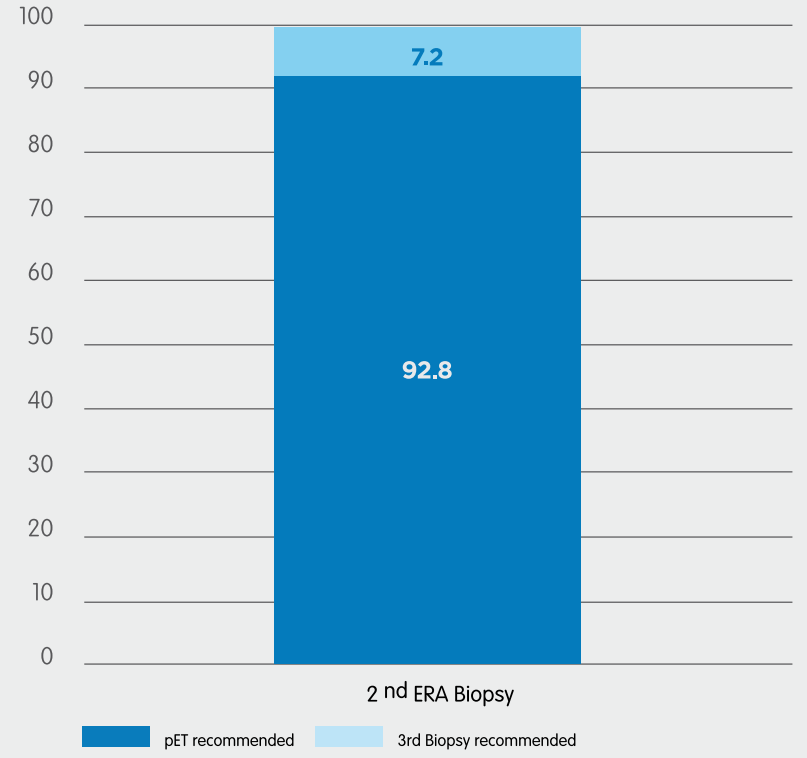
- In the case of post-receptive result or a pre-receptive result needing 2 more days of progesterone exposure, a 2nd endometrial biopsy is required.

NON RECEPTIVE CASES



- More than 95% of pre-receptive samples need just 1 more day of progesterone administration. In these cases pET can be confidently performed by following the report recommendations without a 2nd biopsy.

RESULTS OF 2ND ERA BIOPSIES



Receptivity and obesity

- Patients with body mass index (BMI) ≥ 30 show higher risk of having displaced WOI.

BMI Category	Normal (19-24.9) (n=163)	Overweight (25-29.9) (n=47)	Obese (≥30) (n=11)
Age (mean)	38.4	38.5	37.7
BMI (mean)	21.9	26.8	32.8
% non receptive patients by ERA®	25.2%	25.5%	36.4%

Igenomix Publication: Lathi R B et al, 2014. PCRS.

Receptivity and endometrial thickness

- Patients with atrophic endometrium (<6mm) show higher risk of having displaced WOI

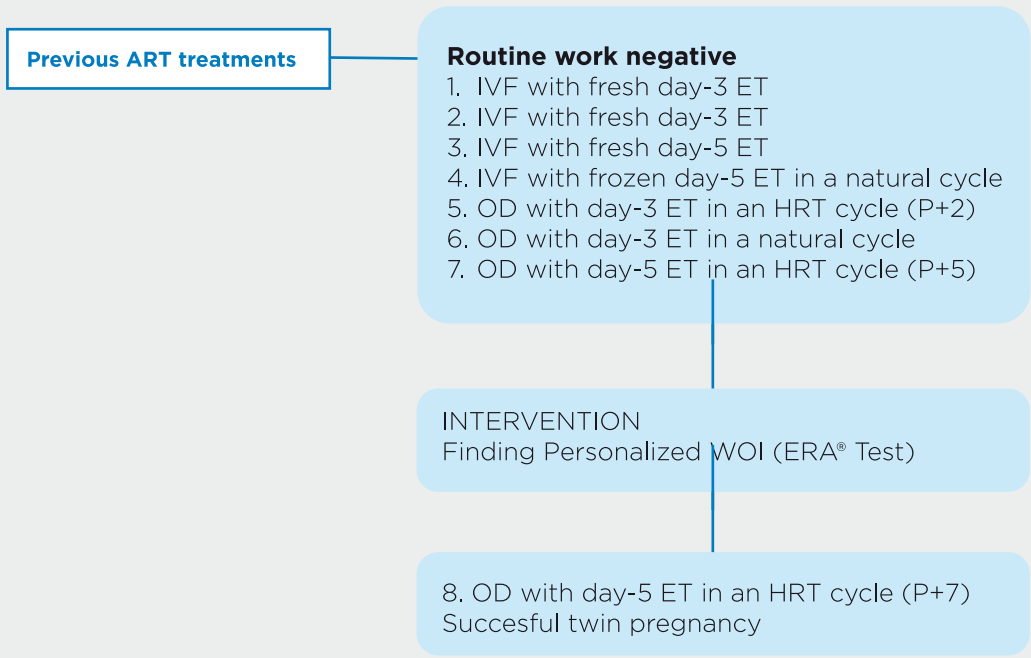
Endometrial thickness (mm)	Receptive	Non receptive
<6	6/4 (42.85%)*	8/14 (57.14%)*
6-12	333/431 (77.26%)*	98/431 (22.73%)*
>12	24/37 (64.86%)	13/37 (35.13%)

P: 0.0003 by Chi-square test

Igenomix Publication: Valbuena D et al, 2016 ESHRE.

Personalized Embryo Transfer (pET): Clinical Outcome

Published Case Report regarding clinical applicability of the ERA® test in a RIF patient



ET: Embryo Transfer
HRT: Hormonal Replacement Teraphy
IVF: In-Vitro Fertilization
OD: Ovum Donation
WOI: Window of Implantation

IGENOMIX Publication: Ruiz-Alonso, et al. Hum Reprod. 2014 Jun;29(6):1244-7.

Personalized Embryo Transfer (pET): Clinical Outcome

pET CLINICAL OUTCOME

	Receptive at P+5	Receptive at different day than P+5	TOTAL
Number of pET performed	175	86	261
Implantation rate	53,4% (126/236)	60,5% (66/109)	55,7% (192/345)
Pregnancy rate (bhCG +)	69,7% (122/175)	73,3% (63/86)	70,9% (185/261)
Biochemical pregnancy	9,8% (12/122)	4,8% (3/63)	8,1% (15/185)
Miscarriage	9% (11/122)	3,2% (2/63)	7% (13/185)
Ectopic	0,8% (1/122)	1,6% (1/63)	1,1% (2/185)
Ongoing / Pregnancy	80,3% (98/122)	90,5% (57/63)	83,8% (155/185)
Ongoing / pET	56% (98/175)	66,3% (57/86)	59,4% (155/261)

Igenomix Publication: Clemente-Ciscar M et al. 2018 ESHRE.

ERA® Randomized Controlled Study

- Interim results from a prospective randomized controlled study presented at ASRM show the improvement on Pregnancy Rate and Ongoing Pregnancy Rate.

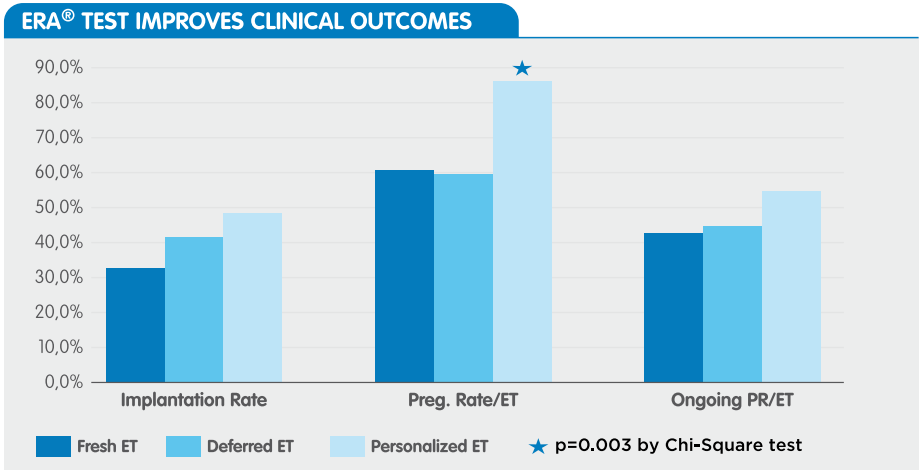
Award Winner

Society for Reproductive Endocrinology and Infertility (SREI)

Our paper **PROSPECTIVE, RANDOMIZED STUDY OF THE ENDOMETRIAL RECEPTIVITY ANALYSIS (ERA®) TEST IN THE INFERTILITY WORKUP TO GUIDE PERSONALIZED EMBRYO TRANSFER VERSUS FRESH TRANSFER OR DEFERRED EMBRYO TRANSFER*** has been awarded as Prize Paper by the Society for Reproductive Endocrinology and Infertility, in this year's ASRM Annual Meeting

	Fresh ET	Deferred ET	Personalized ET
Patients (n)	117	122	117
Transfers (n)	60	74	49
Preg. Rate/ET (%)	61.7%	60.8%	85.7 %*
Implantation Rate (%)	35.3%	41.4%	47.8%
Ongoing PR/ET (%)	43.3%	44.6%	55.1%

* p=0.003 by Chi-Square test



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