ORIGINAL ARTICLE: INFERTILITY

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

Maria Ruiz-Alonso, M.Sc.,[b] David Blesa, Ph.D.,[a,b] Patricia Díaz-Gimeno, Ph.D.,[a,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 Principe 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;■:■–■. ©2013 by American Society for Reproductive Medicine.)
**Key Words:** Endometrial receptivity, repeated implantation failure, prediction tool, ERA test, customized microarray, personalized embryo transfer

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Repeated implantation failure (RIF) is an unaddressed major cause of infertility in otherwise healthy women and one that has remained poorly characterized (1, 2). Although various definitions of RIF exist (3), the clinical community agrees that after the failure of three in vitro fertilization (IVF) cycles in which one or two morphologically high-grade embryos are transferred, special protocols must be enforced. Unfortunately, there are no hard data from randomized controlled trials (RCTs) demonstrating that any of the current approaches to RIF are of any significant clinical value (1–3).

The causes of RIF can be grouped into several main clinical categories: pathologic alterations of

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Reprint requests: Carlos Simón, M.D., Ph.D., Fundación IVI Parc Cientific Universitat de València, c/Catedrático Agustín Escardino n°9, Edificio 3, 46980 Paterna, Valencia, Spain (E-mail: carlos.simon@ivi.es).

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the endometrial cavity, such as hyperplasia, submucous myomas/polyps, endometritis, and synechiae, which can be found in 18%–27% of cases (4); hydrosalpinx (5), either acting through a direct embryotoxic effect or adversely affecting endometrial receptivity (6); an increased incidence of embryonic chromosomal abnormalities (7); and lifestyle/other causes, such as hereditary and acquired thrombophilias (8).

All of the pathologic issues indicated above can be corrected, but the underlying problem remains, and the obvious fact that successful implantation requires synchrony between the embryo and the receptive endometrium (9) has not yet been addressed clinically. The clinical diagnosis of endometrial receptivity as the temporal window of opportunity in which the endometrial epithelium becomes adhesive to the blastocyst remains uncertain and subjective (10, 11). In fact, this is the main reason why the endometrial factor, in terms of its receptivity status, is not investigated during the infertility work-up: It is assumed that the window of implantation (WOI) is constant in time in all women, including RIF patients.

In the search for objective diagnostic criteria,pioneering work has demonstrated the feasibility of the molecular classification of human endometrial receptivity (12) and endometrial cycle stages (13, 14) with the use of transcriptomic profiling. Since then, accumulated evidence has demonst-
rated that it is possible to catalog and diagnose the human endometrium throughout the menstrual cycle, including its receptivity status in natural, controlled stimulated, and refractory cycles, as well as in pathologic conditions regardless of its morphologic appearance (15). There is some disagreement among transcriptomic studies of the endometrium, which may be attributed to differences in experimental designs, the type of array used, sampling conditions, sample selection criteria, sample size, day of the cycle when the sample is collected, the statistical analysis applied to the results, separation or not of tissue compartments, and other reasons. But in general, all studies conclude that it is possible to accurately catalog endometria at different stages based on their transcriptomic profiles (16).

Based on the large amount of information generated about the regulation and dysregulation of the genes implicated in the WOI, our group developed a molecular diagnostic tool that can identify a receptive endometrium with the use of a specific transcriptomic signature present in both natural and hormone replacement therapy (HRT) cycles. The endometrial receptivity array (ERA) consists of a customized array containing 238 genes expressed at the different stages of the endometrial cycle and is coupled to a computational predictor that is able to identify the receptivity status of an endometrial sample and diagnose the personalized WOI (pWOI) of a given patient regardless of the sample's histologic appearance (17). The accuracy of the ERA test is superior to endometrial histology, and results were reproducible in the same patients 29–40 months after the first test (18). In that paper, the authors showed that even though gene to gene there can be some differences, the transcriptomic profile of the ERA test, as a whole, did not differ significantly in samples from the same patient and that these samples were much closer between them than to most of the profiles of the control samples at the same menstrual stage.

Compelling evidence indicates that there is an endometrial receptivity alteration in patients with RIF. Classic morphometric analysis revealed that women with RIF undergoing insemination have retarded endometria in relation to their cyclical timing (19). More recently, genomic studies have demonstrated the dysregulation of 63 transcripts in the P+7 endometrium in women with RIF compared with fertile control subjects (20) and altered expression of 313 genes in endometrial samples collected on day 21 of the cycle in RIF versus fertile women (21). An in vitro study has also demonstrated differential hormonal regulation of endometrial genes in RIF versus patients who became pregnant after IVF treatment (22). Finally, aberrant endometrial prostaglandin synthesis has been reported in patients with RIF (23): further evidence suggesting they have an altered endometrium.

All these data strongly suggest the hypothesis that transcriptomic modification of the endometrium occurs in RIF patients during the WOI which could be due to a displacement of the WOI and/or pathologic alteration. The aim of the present study was to identify possible WOI displacements in RIF patients with the use of the ERA diagnostic tool, and to test the concept of personalization of the day of embryo transfer (pET) as a possible therapeutic option.

## MATERIALS AND METHODS

### Study Design

We designed a prospective interventional multicenter clinical trial in which, following embryo vitrification, patients with RIF and from a comparison group underwent an endometrial biopsy either on day LH+7 in a natural cycle or on day P+5 in an HRT cycle, following which an ERA diagnosis of receptive (R) or nonreceptive (NR) endometrium was given. In R cases, pET was performed in a subsequent cycle on the day designated as R by the ERA test. In the case of an NR ERA diagnosis, the test was repeated on the day indicated by the predictor until an R diagnosis was obtained, after which pET was performed in a subsequent cycle on the day that the ERA test indicated for receptivity. pET was performed in natural and HRT cycles on the day designated as R by the ERA test; vitrified embryos were transferred at day 3 or blastocyst stage, and an average of two embryos per ET were transferred.

### Patients

We designated RIF in IVF patients who were $\leq$40 years old or in ovum donation (OD) patients who were $\leq$51 years old, who underwent three or more previous failed cycles in which at least four morphologically high-grade embryos were transferred in total, and in which there was no other explanation for RIF after a through infertility work-up. The comparison group comprised IVF and OD patients with the same age inclusion criteria, undergoing treatment

within the same time period as the RIF patients included in this study but who had only one or no previous failed cycles. Patients were recruited for a period of 20 months during 2011–2012 and were followed for 2 months after this recruitment period.

The study group comprised 85 RIF patients with 4.8 ± 2.0 previous failed cycles, and the comparison group 25 patients with 0.4 ± 0.5 previous failed attempts. All 110 patients were recruited in six different centers: Instituto Valenciano de Infertilidad (IVI) Valencia (n = 46), IVI Sevilla (n = 25), IVI Barcelona (n = 18), IVI Madrid (n = 13), IVI Vigo (n = 4), and IVI Zaragoza (n = 4). We included RIF patients undergoing OD (n = 33) aged 42.0 ± 4.4 (range 33–50) years with body mass index (BMI) 23.7 ± 3.3 (range 19.7–30.9) kg/m$^2$; and IVF patients (n = 52) aged 36.0 ± 3.3 (range 23–40) years with BMI 23.0 ± 3.0 (19.0–31.2) kg/m$^2$; and non-RIF comparison group patients undergoing OD (n = 15), aged 42.5 ± 3.7 (range 35–51) years with BMI 22.9 ± 3.7 (range 19.0–31.6) kg/m$^2$ and IVF patients (n = 10) aged 36.0 ± 4.5 (range 27–40) years with BMI 22.5 ± 2.5 (range 19.8–28.0) kg/m$^2$.

Inclusion criteria for all IVF patients were normal ovarian reserve (FSH <8 mIU/mL) and at least six metaphase II oocytes obtained per oocyte retrieval. Inclusion criteria for OD recipients were minimum endometrial thickness of 6.0 mm and trilaminar pattern after proper estrogen priming. Exclusion criteria in all cases were nonoperated hydrosalpinx, submucous myomas or polyps, previous ET with high difficulty and/or bleeding without cervical hysteroscopy correction, and atrophic endometrium (<5.5 mm) after either controlled ovarian stimulation (COS) or HRT. All RIF patients recruited in this study underwent the following infertility work-up: vaginal ultrasound (hysterosonography or hysteroscopy when needed), karyotypes of both partners, lupus anticoagulant and anticardiolipin antibodies IgG or IgM, antithrombin III, protein C, protein S, serum homocystine, prothrombin G20210A mutation, MTHFR C677T mutation, and activated protein C resistance (when positive, screening for the factor V Leiden mutation was carried out).

This study was approved by Ethics Committee of IVI Valencia (no. 25/02/2006), which is an independent Institutional Review Board. Written informed consent was obtained from each of the patients enrolled.

## Endometrial Sampling and Processing

Endometrial biopsies were collected from the uterine fundus with the use of Pipelle catheters from Cornier Devices (CCD Laboratories) or similar, under sterile conditions either on day LH+7 in a natural cycle or on day P+5 in an HRT cycle.

The day of the endometrial biopsy in a natural cycle is determined according to the urine or serum detection of the LH peak, whereas in the HRT cycle it is calculated after proper $E_2$ priming leading to a trilaminar endometrium measuring ≥6.5 mm, after five full days of P impregnation (~120 h).

After the biopsy, the endometrial tissue was transferred to a cryotube containing 1.5 mL RNAlater (Qiagen), vigorously shaken for a few seconds, and kept at 4°C or in ice for ≥4 hours. The samples were then shipped at room temperature for ERA transcriptomic analysis.

## Sample Labeling and Microarray Hybridization

Total RNA was extracted with the use of the Trizol method according to the protocol recommended by the manufacturer (Life Technologies). Approximately 1–2 μg total RNA was obtained per milligram of endometrial tissue. RNA quality was assessed by loading 300 ng total RNA onto an RNA Labchip and was analyzed in an A2100 Bioanalyzer (Agilent Technologies). Good-quality RNA sample with RNA integrity number ≥7 was a prerequisite for ERA analysis.

Sample preparation and hybridization was adapted from the Agilent technical manual (one color). In short, first-strand cDNA was transcribed from 200 ng total RNA with the use of T7-Oligo(dT) Promoter Primers. Samples were transcribed in vitro and Cy-3 labeled, all with the Low Input Quick Amp Labeling kit (Agilent Technologies). The labeling reaction typically yielded 4–5 μg of complementary RNA (cRNA) with a specific activity >6. Fragmented cRNA samples were hybridized onto the customised ERA array (17), by incubation at 65°C for 17 hours with constant rotation. The microarray was then washed in two steps of 1 minute in two washing buffers (Agilent Technologies). Hybridized microarrays were scanned in an Axon 4100A scanner (Molecular Devices), and data were extracted with the use of the Genepix Pro 6.0 software (Molecular Devices).

## ERA Class Prediction and WOI Recommendation

ERA gene expression values were preprocessed and normalized and the endometrial receptivity status diagnosed by the ERA computational predictor (17). The ERA test diagnoses the endometrial samples as R or NR with an associated diagnostic probability. To analyze and visualize the gene expression profile of NR samples, a principal component analysis (PCA) with the use of Babelomics (24) was performed against the sample training sets (proliferative, prereceptive, receptive, and postreceptive samples) used in the development of the ERA prediction profile (17). This allows us to obtain a recommendation for a putative personalized WOI in a particular patient. To validate this personalized WOI, a second endometrial biopsy and ERA analysis was performed after the recommendation of the ERA classifier. The accuracy and consistency of the ERA diagnostic tool has been demonstrated to be superior to endometrial histology and was reproducible in the same patients 29–40 months after the first ERA test (18).

## Statistics and PCA

Fisher exact test was used to statistically analyze ($P<.05$) R and NR, and implantation (IR) and pregnancy (PR) rates between patient populations (OD vs. IVF and RIF vs. comparison group patients).

PCA is a mathematical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables (the expression values of the

238 genes of the ERA test) into a set of values of linearly uncorrelated variables called principal components. This transformation is defined in such a way that the first principal component accounts for as much of the variability in the data as possible (51% in our set of data), and each succeeding component in turn has the highest variance possible under the constraint that it be uncorrelated with the preceding components (PC2, in our study, which represents 19% of the remaining variability). PC1 and PC2 account for 70% of the variability in our data set.

## RESULTS

### Diagnostic and Clinical Outcome in RIF Patients with Receptive ERA Test Results

In comparison group patients, the ERA test gave an R result in 22 out of 25 patients investigated (88.0%) and an NR result in only 3 patients (12.0%; Table 1). Interestingly, in RIF patients the percentage of R results was 74.1% (63 out of 85 patients) and the percentage of NR results 25.9% (22 patients; Table 1), showing that RIF patients had more patients, although statistically nonsignificant ($P$=.182), with a displacement of their WOI. The proportion of RIF patients undergoing IVF versus OD was 61:39 versus 40:60 in comparison group patients. The proportions of R-NR results in OD and IVF patients seemed to be similar in the comparison group (87:13 and 90:10, respectively) but different in the RIF group, which had a high percentage of NR results in the OD group compared with the IVF group (67:33 and 79:21, respectively), although this was not statistically significant ($P$=.309).

Clinical follow-up was possible in 40 R patients (11 from the comparison group and 29 from the RIF group) in whom at least one ET was performed during the duration of the study. In IVF patients, embryos were vitrified on day 3 or at the blastocyst stage and ET performed in a subsequent natural or HRT cycle on the day designated as R by the ERA test. The clinical outcome of these patients in the comparison group was 81.8% PR and 55.0% IR versus 51.7% PR and 33.9% IR in the RIF R group with 4.8 ± 2.1 previous failed cycles (Table 1).

Although controversial, it has been suggested that the local injury induced by an endometrial biopsy might improve embryo implantation in the next ART cycle (25, 26). To determine whether the clinical results obtained after the R ERA test were related to local injury or the diagnostic efficiency of the ERA test, the clinical outcome of R patients (RIF and those of the comparison group) was followed for 6 months after the ERA test (Fig. 1). PRs and IRs were, respectively, 36.4% and 23.8% (n = 11) in the first month after the endometrial biopsy, 75.0% and 71.4% (n = 8) in the second, 50.0% and 37.5% (n = 4) in the third, 50.0% and 40.0% (n = 8) in the fourth, 50.0% and 42.8% (n = 4) in the 5th, and 50.0% and 33.3% (n = 2) in the 6th month. Three patients underwent ET >6 months after the endometrial biopsy. These data demonstrate that clinical results did not improve in the first month after the endometrial biopsy for the ERA test and therefore were not related to local injury.

**TABLE 1**

**Summary of the diagnostic and clinical outcomes of repeated implantation failure (RIF) and comparison group patients following the endometrial receptivity array (ERA) test.**

| | RIF | Control |
|---|---|---|
| No. of patients | 85 | 25 |
| Age (years) | 38.4 ± 4.7 | 39.9 ± 5.1 |
| No. of R ERA/total analyzed | 63/85 (74.1) | 22/25 (88.0) |
| No. of previous failed cycles | 4.8 ± 2.1 | 0.5 ± 0.5 |
| Total patients with pET after R ERA | 29 | 11 |
| Implantation rate after 1st pET | 19/56 (33.9) | 11/20 (55.0) |
| Pregnancy rate after 1st pET | 15/29 (51.7) | 9/11 (81.8) |
| Biochemical pregnancies | 3/15 (20.0) | 2/9 (22.2) |
| Clinical abortions | 0/15 (0.0) | 0/9 (0.0) |
| Ovum donation R patients/total | 22/63 (34.9) | 13/22 (59.1) |
| Patients with pET after R ERA | 16 | 8 |
| Implantation rate after 1st pET | 12/33 (36.4) | 7/15 (46.7) |
| Pregnancy rate after 1st pET | 9/16 (56.2) | 6/8 (75.0) |
| Biochemical pregnancies | 2/9 (22.2) | 1/6 (16.7) |
| Clinical abortions | 0/9 (0.0) | 0/6 (0.0) |
| IVF/ICSI receptive patients/total | 41/63 (65.1) | 9/22 (40.9) |
| Patients with pET after R ERA | 13 | 3 |
| Implantation rate after 1st pET | 7/23 (30.4) | 4/5 (80.0) |
| Pregnancy rate after 1st pET | 6/13 (46.2) | 3/3 (100.0) |
| Biochemical pregnancies | 1/6 (16.7) | 1/3 (33.3) |
| Clinical abortions | 0/6 (0.0) | 0/3 (0.0) |
| No. of NR ERA/total analyzed (%) | 22/85 (25.9) | 3/25 (12.0) |
| No. of previous failed cycles | 5.0 ± 1.8 | 0.3 ± 0.6 |
| Ovum donation patients/total | 11/22 (50.0) | 2/3 (66.6) |
| IVF/ICSI patients/total | 11/22 (50.0) | 1/3 (33.3) |

*Note*: Values are presented as mean ± SD or n (%). R = receptive; NR = nonreceptive.

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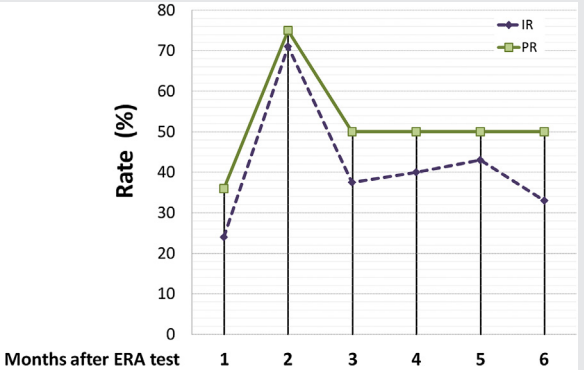
### Clinical Outcome in RIF Patients with Nonreceptive ERA Test Results with the Use of pET

NR endometrial samples were classified by the ERA predictor as prereceptive (n = 21; 84%) or postreceptive (n = 4; 16%). The referral doctor was informed of these results and a second

**FIGURE 1**




| Months after ERA test | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Number of patients | 11 | 8 | 4 | 8 | 4 | 2 |
| Implantation rate (%) | 23.8 | 71.4 | 37.5 | 40.0 | 42.8 | 33.3 |
| Pregnancy rate (%) | 36.4 | 75.0 | 50.0 | 50.0 | 50.0 | 50.0 |

Pregnancy and implantation rate per month in which the first pET was done after the ERA biopsy.

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ERA test suggested to confirm the suspected displacement of the WOI. In 18 cases a second ERA was performed, confirming the displacement of the WOI in those patients. In ERA prereceptive results, the second biopsy was recommended on LH+9 in natural cycles and P+6 or P+7 in HRT cycles, depending on the specific PCA profile of each sample. In ERA postreceptive results, the second test was recommended on P+4 or P+3. The results for these second biopsies were R in 15 of them (Fig. 2), whereas in 3 of them NR profile remained and further refinement was necessary.

Clinical follow-up was possible in eight patients in whom pET was performed, where it was considered that their pWOI was delayed to P+7 (n = 5) or P+6 (n = 2) or advanced to P+4 (n = 1). Day 3 embryos were transferred with this strategy in HRT cycles after 4 or 5 days of P administration, or day 5 blastocysts were transferred in HRT cycles after 4, 6, or 7 days of P administration, resulting in a 50.0% PR and a 38.5% IR (Fig. 2). Owing to the low number of patients, these results should be considered to be preliminary.

## DISCUSSION

In this study, we have for the first time objectively diagnosed the WOI and conducted pET from the endometrial perspective rather than embryo stage. Personalized medicine is a well accepted concept in reproductive medicine, from the adjustment of gonadotropin doses in COS according to ovarian reserve and BMI and fertilization technique selection (intracytoplasmic sperm injection [ICSI], IVF, or both) according to sperm features and clinical background, to consideration of embryo development criteria according to the number and quality of embryos available as well as clinical background of the patient. Interestingly, the endometrial status of all patients is treated equally at the time of ET, which is guided only by the embryo development stage and is supported by the administration of P/hCG in the luteal phase. Much effort has been dedicated to comparing clinical results with the use of different routes, dosages, or duration of P administration in IVF/ICSI cycles, but a recent updated Cochrane review indicates that there is no evidence favoring any of them (27).

The key point is that the objective diagnoses of the endometrial receptivity factor remain neglected and therefore so too do any clinical personalized approaches to improving clinical success from the endometrial perspective. Acknowledging the need for an objective endometrial diagnostic test that can guide and improve our clinical practice, and based on a decade of research in the transcriptomics of endometrial receptivity (16), our group developed the ERA test (17). In the work presented in the present paper, we demonstrate the diagnostic efficacy of the ERA test in the identification of WOI displacements, which are more frequent in RIF patients, that has led to the new clinical concept of pET. Interestingly, our initial finding was that 25.9% of our RIF patients were NR at the time when ET had previously failed, indicating a disrupted endometrial genomic pattern in that critical time window. Further evidence by other authors in HRT (20) and natural (21) cycles support our results.

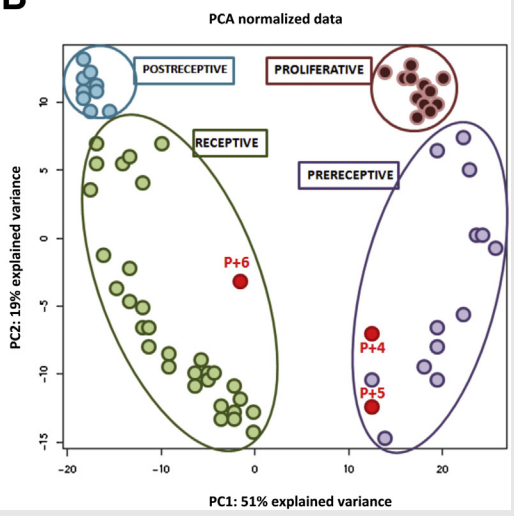
Taking this forward, we translated these genomic results to the clinic by transferring the embryos considering the pWOI of the patient. In patients with an R ERA-diagnosed

## FIGURE 2

**A** Clinical outcome of non receptive RIF and control patients that underwent pET

| | Non Receptive |
|---|---|
| No. of patients | 25 |
| No. of previous failed cycle RIF Patients | 5.0±1.8 |
| No. of previous failed cycle Control Patients | 0.3±0.6 |
| ERA Prediction | |
| Pre-receptive | 21/25 (84.0) |
| Post-receptive | 4/25 (16.0) |
| 2nd ERA at the specified day (P+4;P+6;P+7;LH+9) [a] | 18 |
| Months between 1st and 2nd ERA | 2.6±2.8 |
| 2nd ERA Receptive at the specified day | 15 |
| Patients with pET[b] after 2nd RECEPTIVE ERA | 8 |
| Months between 2nd RECEPTIVE ERA and pET | 1.8±0.7 |
| Implantation rate using pET | 5/13 (38.5) |
| Pregnancy rate using pET | 4/8 (50.0) |
| Biochemical pregnancies (%) | 0/4 (0.0) |
| Clinical abortions (%) | 0/4 (0.0) |

**B** Principal component analysis with ERA samples




(A) Clinical outcome of nonreceptive RIF and comparison group patients that underwent pET. Values are mean ± SD. (B) Principal component analysis (PCA) of three samples from the same patient at P+4, P+5, and P+6, the ERA gene expression training sets (proliferative, pre-receptive, receptive and post-receptive samples) used in the development of the ERA prediction tool (17). The points represent the samples in relation to 238 expressed genes. The three samples from the same patient (at P+4, P+5, and P+6) are represented in red. The samples from the training set are represented in different colors: proliferatives are *dark red*, pre-receptives are *purple*, receptives are *green*, and post-receptives are *blue*. The study samples P+4 and P+5 show a pre-receptive profile, while the P+6 sample shows a receptive profile. PC1, PC2 = first and second principal components that explain the highest variability that separates samples in the space.

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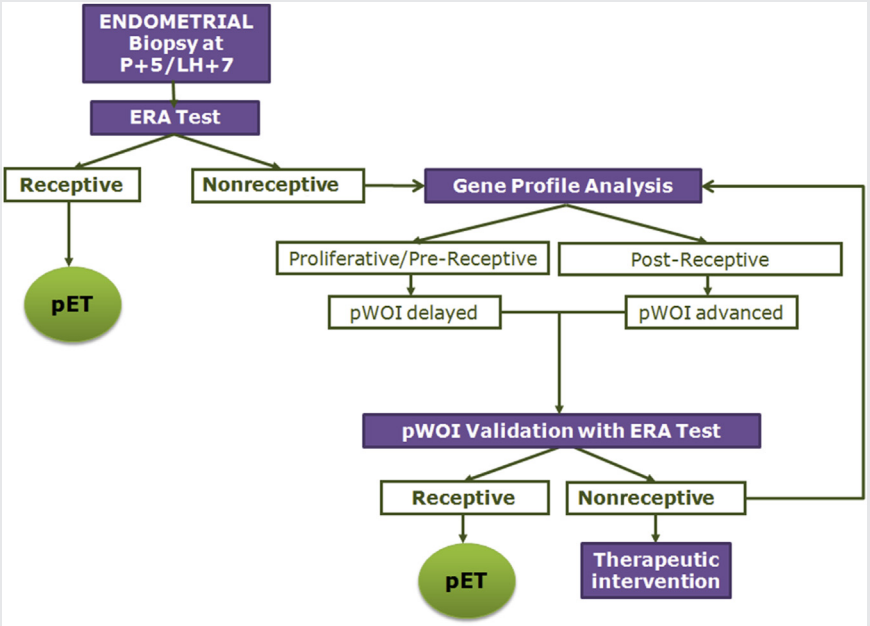
**FIGURE 3**




Clinical algorithm for pET.

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endometrium, embryos were transferred in a subsequent HRT or natural cycle and we observed that clinical results (PR) obtained in patients with RIF were similar to those in our general IVF population (53% vs. 48%, respectively). Additionally, the IR and PR were calculated on a monthly basis, demonstrating that embryo implantation and pregnancy was not related to the local injury induced by the endometrial biopsy (Fig. 1). The most striking finding was that in one in four RIF patients the WOI was displaced, and this NR endometrium was classified by our computational predictor as pre- or postreceptive, which was further verified by a second ERA test (Fig. 2A). The clinical proof that this displacement of the WOI might be clinically relevant is presented in this pilot study, demonstrating that when pET was employed in these RIF patients with NR endometrium, IR and PR increased to the level of receptive RIF patients. These results are promising, but because of the low number of patients analyzed in this study, conclusions should be taken with care. Figure 3 shows the decision tree suggested from this work.

The fact that the primary cause of RIF of unknown origin lies in the embryo, the maternal endometrium, or both should not be ignored. A recent prospective RCT from our group investigating the usefulness of preimplantation genetic screening (PGS) with the use of FISH for chromosomes 13, 15, 16, 17, 18, 21, 22, X, and Y in RIF patients with identical inclusion criteria has been published (28). In that study, we demonstrated a significant increase in ongoing PRs (47.9% vs. 27.9%; $P=.0402$) and ongoing IRs (36.6% vs. 22.1%; $P=.0112$) per oocyte retrieval in the PGS group versus the unscreened blastocyst group. Those results indicated that in IVF patients with RIF the embryonic factor due to chromosomal abnormality might account for $\geq$20% of failed PR and $\geq$14% of unsuccessful IR (28), a proportion that may well prove to be higher if more potent comparative genomic hybridization technologies are implemented. In the present paper, although the numbers are limited, our data indicated that displacement of the endometrial WOI clearly affects $\geq$25% of RIF patients, and we hypothesize that in some cases both displacement of the WOI and chromosomal abnormalities combined might contribute to RIF etiology.

Given our results, we therefore pose the question of whether RIF of endometrial origin is a "disease" or simply results from our incapacity to diagnose when the endometrium will be receptive in each patient. What we think is that some "implantation failure" patients should not be categorized as having a pathologic condition but as patients in whom ET timing should be personalized because their endometrial timing is different. In other words, we revisit the concept of implantation failure as a "timing failure to implant" in otherwise normal endometria. Transcriptomics studies have demonstrated a different endometrial expression profile in RIF versus fertile control subjects on specific days of the cycle (20, 21), although this could be explained by the fact that RIF patients have a displacement of the WOI. Furthermore, the fact that pET guided by the endometrial timing is able to obtain successful results further emphasizes the relevance of the personalization of the WOI with the use of an objective diagnostic tool.

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