



Indian FERTILITY Society

ENDOMETRIAL RECEPTIVITY ARRAY (ERA)

INTRODUCTION

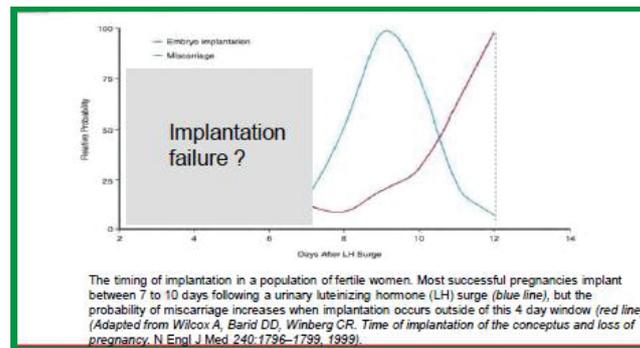
The human endometrium is a highly dynamic tissue which can undergo multiple changes during the menstrual cycle in response to steroid hormones, which helps in creating a receptive environment that is in synchronization with the arrival of an implanting blastocyst.

The endometrial cavity is lined by endometrium and is morphologically divided into functional and basal layers. The functional layer contains two main cellular compartments which together occupy two-thirds of endometrial thickness: an epithelial cell lining the surface and coating the epithelial glands, and the stroma which consists of an extracellular matrix, fibroblasts, blood vessels, and immune cells.¹⁻³ The functional layer develops throughout the menstrual cycle to receive the embryo, while the basal layer is responsible for regenerating the functional layer after the menses.²⁻⁴

The endometrial cycle can be divided into the three phases viz. proliferative phase, secretory phase and menstrual phase, which synchronize with the ovarian follicular and luteal phases. This synchronization between the ovarian cycle and the endometrial cycle is essential for embryo implantation, allowing blastocyst-stage embryos capable of implanting to be ready at the same time as the receptive mid-secretory phase endometrium, therefore, establishing a period commonly known as the window of implantation (WOI).

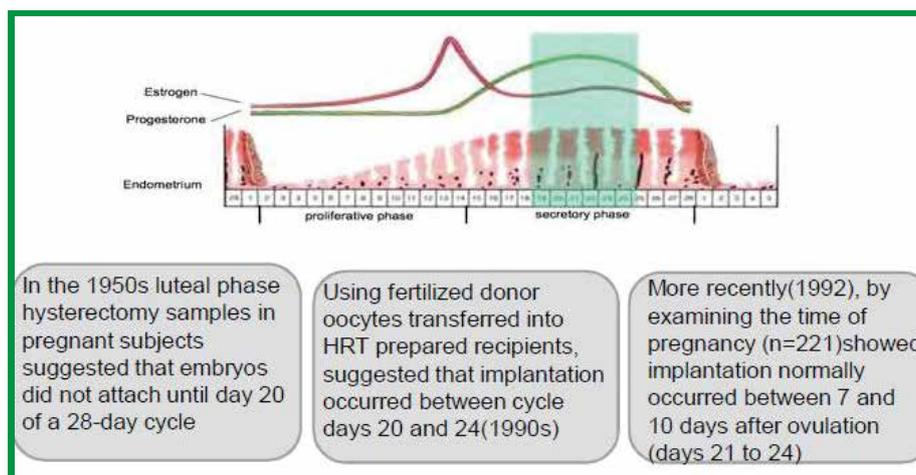
WINDOW OF IMPLANTATION (WOI)

It has always been assumed that the WOI opens on day 19th or 20th of the cycle, and lasts for 4 to 5 days,⁶ that is, 5 to 9 days postovulation during the mid-secretory or the midluteal phase.^{5,7} However, several studies suggest that the WOI might extend up to day 10 after ovulation.⁸



The timing of the WOI was stated by the early work of Hertig and Rock⁹, in a unique study of uterine samples in women attempting pregnancy before hysterectomy. This group defined for the first time the earliest events in embryo implantation in the human, by looking for and finding early embryos in the process of attachment and invasion, thus stating that early attachment and invasion occurred only after cycle day 19 of the menstrual cycle. The tissue collected during this early study provided critical histologic material that later became part of the Carnegie Series of implantation sites and formed the basis for a staging system of implantation in the human.¹⁰

Above studies were complemented by the work of Hodgen and coworkers in the primate endometrium¹¹ and Novot and colleagues using donor embryos in humans^{7,12-14} leading to the conclusion that the WOI occupies a 4- to 5-day interval in the human endometrial cycle, at the time when progesterone reaches peak serum concentrations. However, it is not known whether there is individual or intercycle variation in the duration of the WOI in each menstrual cycle.



Window of Implantation: Berg PA, Fertile Steril 1992;58:537-5.

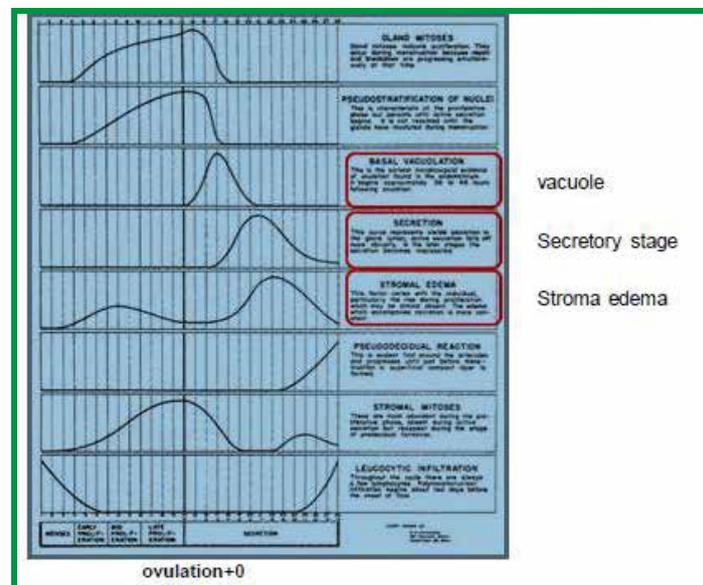
Wilcox AJ et al. The New England Journal of Medicine 340:1796-1799, 1999

Hertig AT et al, Am J Anat 98:435-493 1956

ASSESSMENT OF ENDOMETRIAL RECEPTIVITY: AN HISTORICAL PERSPECTIVE

The term “endometrial receptivity” refers to the ability of the uterine lining to accept and accommodate a nascent embryo, leading to successful pregnancy.¹⁵ It describes the phenomenon which allows embryo adhesion and placentation to occur. With the work of Rock and Bartlett,¹⁶ endometrial receptivity as an entity began to take shape. They later formalized a method of endometrial dating in the inaugural issue of this journal in 1950.¹⁷

Noyes et al¹⁷ took the first steps toward unraveling this biological mystery by setting up a series of morphological criteria which could be used to date the endometrium.^{17, 18} These criteria refer to gland mitosis, pseudostratification of nuclei, basal cell vacuolation, secretion, stromal edema, pseudodecidual reactions, stromal mitosis, and leukocytic infiltration. Taken together, they could be used to date the endometrium because the different levels of these parameters, as reported by trained pathologists from histological preparations, varied among the different stages of the endometrium.



Endometrial histological dating: Noyes R W, Hertih A T, Rock J. Obstetrical and Gynecological Survey, 1950,5(4):561-564

These criteria had been the gold standard during the past half century for analyzing the differentiation of the endometrium.

Recent studies have proven that due to considerable intersubject, intrasubject, and interobserver variability, histological endometrial dating is not accurate or precise enough to diagnose luteal phase deficiency with validity, or to guide the clinical management of women with reproductive failure. This is because histological dating provides poor intercycle association, and is prone to tissue-fixation artifacts which together limit the clinical usefulness of this method^{2,19,20}

THE SEARCH FOR NEW BIOMARKERS

With better understanding about the timeline of implantation, importance of synchrony between embryo and endometrium as a critical factor of successful pregnancy has increased.

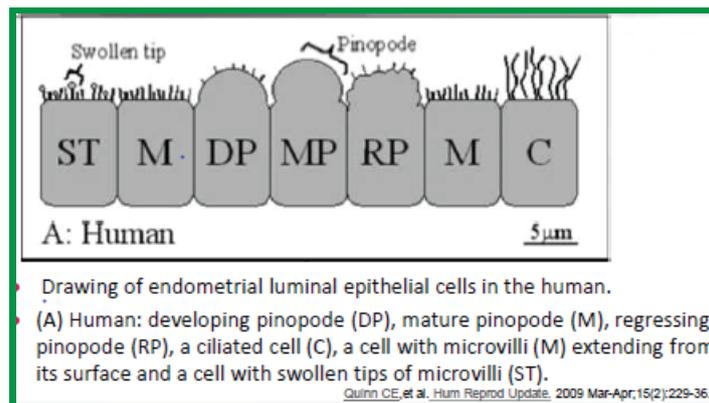
The endometrium can be viewed as a gatekeeper, allowing embryos to attach only under optimal conditions. The concept of a receptor-mediated mechanism of embryo attachment and invasion provided a strategy for choosing biologically relevant biomarkers of endometrial receptivity. Although the perfect protein marker would be functionally important to the process of implantation, consensus as to which biomarkers to use for endometrial receptivity has not been established.¹⁵

The luminal epithelium of the endometrium is composed of a sheet of specialized epithelial cells that are distinct from the glandular cells and underlying stroma²¹ and forms the primary to embryo attachment and invasion.^{22,23,24} Microscopic projections known as pinopodes (also called uterodomes) have been considered as potential markers of receptivity, with a vanishing expression pattern within the 4- to 5-day period of receptivity. Evidence suggests that embryos are attracted to and/or preferentially interact with these structures in vitro.²⁵

Pinopodes were first named by Enders and Nelson (“drinking foot”) as ultrastructural features in the rat uterus,²⁶ on the basis of their ability to take up ferritin from the uterine lumen.

In the human pinopodes were promoted as reliable biomarkers of the WOI by Psychyos and colleagues²⁷⁻³¹ and later by Nikas and colleagues.³²⁻³⁶

Morphology of Pinopodes



The quantitation of pinopodes proved highly subjective, and an absence of these structures lead to confusion, meaning whether they had already come and gone or conversely, or they were yet to appear. Most recent well designed studies have failed to show a reliable pattern for the expression of pinopodes,³⁷⁻³⁹ and thus their significance as markers of endometrial receptivity remains unproven.

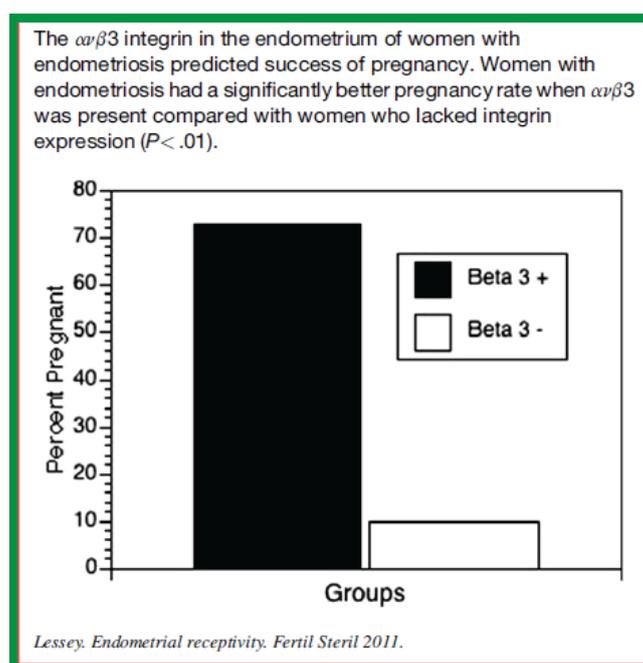
Other luminal moieties include MUC1, which is a carbohydrate glycoprotein that extends from the luminal surface and forms the glycocalyx layer. In the mouse (and most mammals) MUC1 is considered a barrier to implantation and disappears at the time of implantation.^{40,41} MUC1 is expressed throughout the WOI in humans, and unique glycosylation patterns have been suggested as the explanation as to how MUC1 might be involved in endometrial receptivity⁴²⁻⁴⁵ and are actively studied today. Other luminal endometrial biomarkers with a potential role in embryo attachment include trophinin, L-selectin ligand,⁴²⁻⁴⁶ and heparin-binding epidermal growth factor-like growth factor.⁴⁷⁻⁵¹ None of these biomarkers has been studied in sufficient detail to validate their usefulness for the assessment of endometrial receptivity.

One of the best-characterized endometrial biomarkers related to infertility is the $\alpha\beta 3$ integrin.⁵² Integrins are a class of cell adhesion molecules consisting of heterodimeric glycoproteins that are anchored to the plasma membrane and serve multiple functions within cells,⁵³ including functions within the endometrium.

The $\alpha\beta3$ integrin appears on the apex of luminal and glandular cell surfaces, coinciding with the opening of the WOI. The tight correlation between histology and $\alpha\beta3$ integrin expression has been demonstrated, and its expression persists into pregnancy with expansion to the decidua.⁵⁴

The appearance of $\alpha\beta3$ integrin on the apical surface is due to its presence in the subnuclear secretory granules that typically complete their transit by cycle day 19 to 2017. Expression of the intact heterodimer is rate-limited by production of the $\beta3$ subunit, which is regulated directly by the transcription factor HOXA1055. Both HOXA10 and $\alpha\beta3$ have been shown to be significantly reduced in the eutopic endometrium of women with mild but not moderate or severe endometriosis.^{56,57}

Similar to the integrin, endometrial HOXA10 is reportedly reduced in both adenomyosis and polycystic ovary syndrome⁵⁸, and its loss in hydrosalpinges is restored by salpingectomy in hydrosalpinges,⁵⁹ similar to the $\alpha\beta3$ integrin. Because HOXA10 is hypermethylated in women with endometriosis, the loss of $\alpha\beta3$ integrin as a downstream measure of endometrial receptivity may be epigenetically defined in certain women with endometriosis.⁶⁰ In early studies that were performed, this integrin seemed to address the issue of heterogeneity and endometriosis. In women with endometriosis that expressed this integrin, pregnancy rates were significantly better than in women with endometriosis who were lacking this integrin.



Both tubal disease with hydrosalpinges and endometriosis have been associated with decreased IVF success^{61,62} and surgical correction of both is associated with an improvement in subsequent pregnancy outcomes.^{63,64} The $\alpha\beta3$ integrin has been looked at as a predictor of IVF success, but only a limited number of studies have been published.⁶⁵⁻⁶⁷

Endometrial aromatase expression is an aberrant finding in women with endometriosis⁶⁸ and is associated with poor IVF pregnancy rates. Aromatase expression is associated with inflammation, as seen with red lesions (milder forms) of endometriosis,⁶⁹ the same stage in which a loss of integrin expression has been noted. Suppression of inflammation with prolonged GnRH analog has also been shown to improve IVF outcomes when used before IVF stimulation,⁷⁰ perhaps functioning to reduce endometriosis and improve endometrial receptivity.

Not all studies have found integrins to be useful biomarkers for infertile women. Concerns have arisen from several key reports.^{71,72}

A common thing that has emerged related to endometrial receptivity is based on the inflammatory changes that occur in response to infection, endometriosis, or tubal disease.⁷³⁻⁷⁴

Endometriosis is clearly an inflammatory condition.⁷⁵⁻⁷⁶ Superficial lesions seem to be more active than powder burn or scarred lesions at producing inflammatory cytokines.⁷⁷⁻⁷⁸ Immune mechanisms are the mediators of this inflammatory response and can be divided into “innate” immunity, including monocytes, macrophages, dendritic cells, neutrophils, basophils, and mast cells, and natural killer cells from the lymphoid lineage. The adaptive immune system includes the T and B cells, which require cells of innate immunity for establishment of an immunologic memory.⁷⁹

Bone marrow-derived cells traffic to endometrium via steroid-regulated chemokine production⁸⁰. Under normal circumstances, dendritic cells and treg cells increase at the implantation site, along with uterine natural killer cells that interact with the invading placental cells to both direct and limit trophoblast invasion.⁸¹ Bone marrow-derived decidual cells ultimately determine pregnancy outcomes. Because monocyte-derived leukocytes and uterine natural killer cells constitute 20%–40% of all endometrial cells, the types of cells trafficking to the endometrium is likely to be critical to the establishment of endometrial receptivity.⁸²⁻⁸³

A loss of function due to inflammatory leukocytes could account for unexplained infertility and recurrent pregnancy loss, especially in women with minimal and mild endometriosis.⁸⁴⁻⁸⁵ Given its central role in inflammation, the study of the immune system will likely provide many new biomarkers for research into endometrial receptivity.

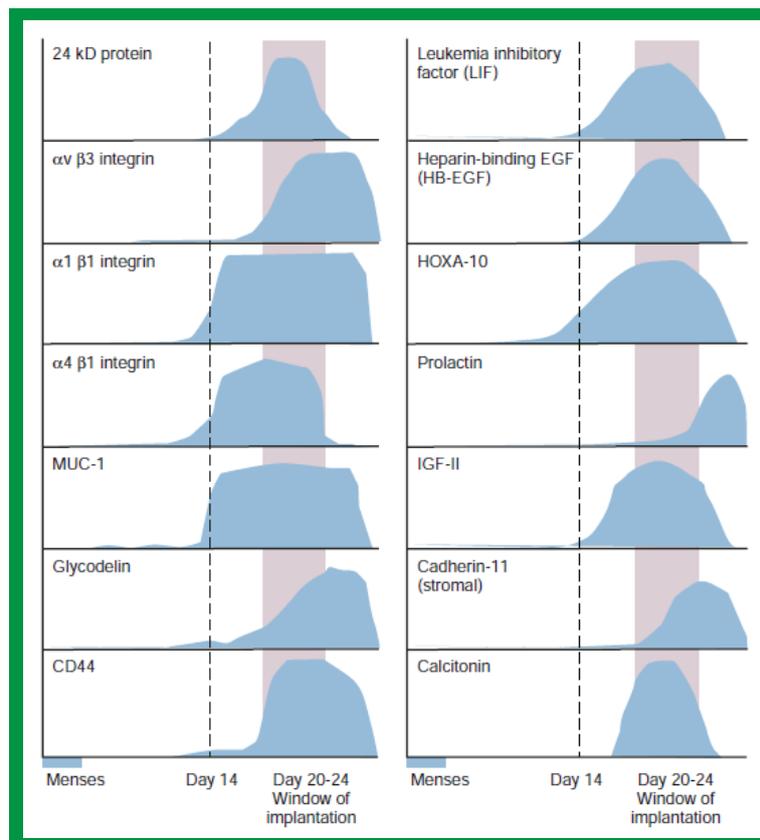


Fig: Candidate biomarkers of uterine receptivity showing their period of maximal expression relative to the presumptive window of implantation (gray bar). (Used with permission from Lessey BA. The use of biomarkers for the assessment of uterine receptivity. In Gardner DK, Weissman A, Howles CM, Shoham Z (eds). Textbook of Assisted Reproductive Technologies. London: Dunitz, 2001, p. 357.)

TRANSCRIPTOMICS OF THE HUMAN ENDOMETRIUM- ENDOMETRIAL RECEPTIVITY

Endometrial receptivity is the result of the synchronised and integrated interaction of ovarian hormones, growth factors, lipid mediators, transcription factors, and cytokines with paracrine signaling (reviewed by Cha et al., 2013).⁸⁶ Its objective identification using gene expression microarrays has been pursued since 2002.

Historically, it has always been accepted that the WOI is constant, always permitting embryo implantation, and so personalization was never considered, especially because the objective diagnosis of the endometrial factor and therefore the WOI did not previously exist. Based on these grounds, an important scientific and clinical objective had been to find a molecular signature which characterizes receptive endometrium in order to gain an objective insight into this crucial function (reviewed in Ruiz-Alonso et al., 2012).⁸⁷

Available data suggests that a 'transcriptional awakening process' takes place because most genes are upregulated compared to their expression in the pre-receptive phase (Riesewijk et al., 2003; Borthwick et al., 2003; Horcajadas et al., 2008; Haouzi et al., 2009 a, b; Díaz-Gimeno et al. 2011).⁸⁸⁻⁹² The early-secretory, or pre-receptive, phase is characterised by the predominance of products related to cell metabolism (fatty acids, lipids, eicosanoids, and amino alcohols), transport (with a large representation of transporters for the biological molecules involved in these metabolic processes), germ cell migration (which could facilitate sperm transportation and ensure an aseptic environment), and negative cell-proliferation regulation.

An increase in metabolism is consistent with the fact that this phase is biosynthetically highly active, which probably represents tissue preparation for embryo implantation; inhibition of mitosis during this phase is supported by the downregulation of numerous growth factors (Talbi et al., 2006).⁹³

The mid-secretory phase is characterised by its high level of metabolic and secretory activity, its non-proliferative phenotype, and increased sensitivity of the innate immune, stress, and wounding responses (Simmen and Simmen 2006; Giudice 2006; Talbi et al., 2006).^{94,95,93}

Genes whose expression changes during the transition between the early- and the mid-secretory phases, and the mid- and the late-secretory phases, are potential candidates for regulation by progesterone (Kao et al., 2002; Borthwick et al., 2003; Talbi et al., 2006).^{89,93} In fact, Ponnampalam et al., (2004)⁹⁶ detected a cluster of genes that follow a temporal regulation pattern during the endometrial cycle which is very similar to the increase in circulating progesterone during these phases. These genes have been identified amongst those participating in some of the major biological processes which take place during implantation, such as signaling, growth, differentiation, and cell adhesion. However, there are no significant gene changes associated with the estrogen peak (reviewed by Ruiz-alonso et al., 2012).⁸⁷

There are also genes that are overexpressed in the mid-secretory versus the early-secretory phases, and these are involved in processes related to cell adhesion, metabolism, response to external stimuli, signaling, immune responses, cell communication, and negative regulation of proliferation and development (Talbi et al., 2006; Díaz-Gimeno et al., 2011)^{92,93}.

The immune response plays an important role throughout the secretory phase. In the mid-secretory phase, the genes involved in the activation of the innate immune response are upregulated (including complements, antimicrobial peptides, and toll-like receptors), and there is also increased monocyte, T cell, and NK cell chemotaxis (CXCL14, granulysin, IL-15, carbohydrate sulfotransferase 2, and suppression of NK and T-cell activation)(Talbi et al., 2006).⁹³

Some overexpressed genes protect the endometrium and/or the embryo in this phase (Talbi et al., 2006)⁹³. GPX-3 is a selenium-dependent protein that has been associated with infertility in selenium-deficient women (Kingsley et al., 1998).⁹⁷ It protects the cell from oxidative damage by catalysing the reduction of hydrogen peroxide, lipid peroxides, and organic hydroxyperoxide by glutathione (Riesewijk et al., 2003).⁸⁸ DAF is a complement regulatory-protein with two postulated functions: protection of the embryo from maternal complement-mediated attack, and prevention of epithelial destruction by increased expression of complement at the time of implantation (Franchi et al., 2008).⁹⁸ This protein has been found in decreased levels in the endometrium of patients with recurrent abortion associated with antiphospholipid syndrome (Francis et al., 2006).⁹⁹

A study by Tseng et al., identified 126 upregulated genes in the mid- secretory phase compared to the late-secretory phase. Overexpressed processes included coagulation cascades and complex metabolism, including carbohydrates, glucose, lipids, cofactors, vitamins, xenobiotics, and amino acids, all of them suggesting that extracellular remodelling activity may occur in the mid-secretory phase (Tseng et al., 2010).¹⁰⁰

During the late secretory phase, estrogen and progesterone levels decrease and the main processes regulated are extracellular matrix degradation, inflammatory response, and apoptosis (Giudice 2006; Simmen and Simmen 2006).^{94,95} In the transition from the mid- to the late-secretory phase, changes in the extracellular matrix and cytoskeleton favour processes such as vasoconstriction, smooth muscle contraction, haemostasis, and the transition from an immune to an inflammatory response (Critchley et al., 2001; Tseng et al., 2010).^{100,101} The genes that are regulated in this transition mostly relate to innate or humoral and cellular immune responses (Talbi et al., 2006),⁹³ haemostasis, blood coagulation, steroid biosynthesis, and prostaglandin metabolism (Critchley et al., 2001).¹⁰¹ The processes represented in this late-secretory stage, such as matrix degradation, inflammatory response, and cell apoptosis, do not favour implantation.

Thus, the transition from the mid- to the late-secretory phase defines the closure of the WOI and a return to the non-receptive endometrial phenotype, and an intense immune system activation (Talbi et al., 2006),⁹³ which is consistent with the histological observation of leukocyte extravasation (Daly et al., 1982).¹⁰²

Regarding immune activation, the expression of Fc receptors, MHC molecules, and molecules secreted by T and NK cells are upregulated. This corresponds to the preparation of innate and adaptive immune responses: monocytes and granulocytes are primed to respond to antibodies because of Fc-receptor upregulation, and by expressing MHC-II molecules (Talbi et al., 2006).⁹³ TNF alpha and IL beta are secreted by white blood cells present in the stromal cell compartment at the end of the cycle, and stimulate the release of matrix-degrading enzymes which contribute to degradation of the vascular basal membrane and connective tissue (Salamonsen and Woolley 1999).¹⁰³ The above describes the predominant activities of the late-secretory phase and corresponds to decidualisation and preparation of the endometrium for the next menstrual phase, when the process starts again.

THE ENDOMETRIAL RECEPTIVITY ARRAY (ERA)- PERSONALIZATION OF EMBRYO TRANSFER

Given the need for reliable, objective, molecular dating methods for the endometrium, a specific tool was developed to identify the transcriptomic signature of the window of endometrial receptivity, called ERA (Díaz-Gimeno et al., 2011, 2013)^{92,104}.

The ERA is a customized array that has been designed to identify the endometrial receptivity status by comparing the transcriptomic profile of a test sample with those of control samples from 7 days after the luteinising hormone peak (LH+7) in a natural cycle, or five days after P administration (P+5) after E2 priming in a hormonal replacement therapy (HRT) cycle. It contains 238 genes that are differentially expressed between these profiles, which are coupled to a computational predictor that can diagnose the personalised endometrial WOI of a given patient regardless of their endometrial histology (Díaz-Gimeno et al., 2013).¹⁰⁴

The predictor was trained with gene expression profiles obtained from samples at different stages of the menstrual cycle (proliferative, pre-receptive, receptive, and post-receptive) in order to be able to classify a test sample according to the gene expression values obtained with the array. This classification has a specificity and sensitivity of 0.8857 and 0.99758 respectively (Díaz-Gimeno et al., 2011).⁹²

INDICATIONS OF ERA

Recurrent implantation failure patients - 2 or more implantation failures with own embryos or 1 with ovum donation. - Good quality embryos.

Patients with morphologically normal endometrium- ERA in the case of any corrected congenital uterine abnormalities.

Patients with normal, atrophic or hypertrophic endometrium - In case of atrophic or hypertrophic, it has to be consistent for all the cycles in the patient

BIOPSY

Hormone replacement therapy: Patient will start with estradiol from the 1st or 2nd day of the menstrual cycle. Ultrasound assessment will be performed between 7 to 10 days after start the estradiol administration. When a trilaminar endometrium > 6mm is reached with a serum progesterone <1ng/ml, the progesterone intake can start. Progesterone will be administered for five full days (120 hours)and biopsy taken after above.

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

Controlled Ovarian Stimulation: Biopsy can be taken on the next natural or HRT cycle.

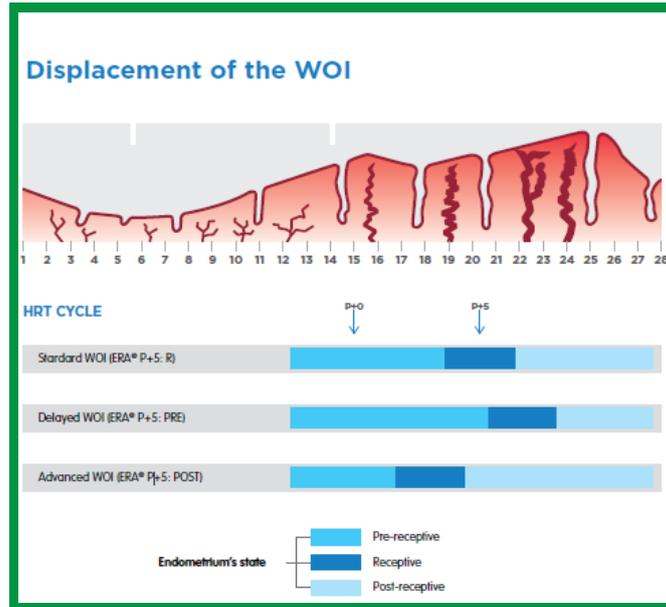
BIOPSY AND STORAGE

Biopsy: The cryotube is prepared and labelled either with the Patient's initials, DOB and date of biopsy or with the Patient's initials and MRN. Immediately after the biopsy is introduced into the cryotube, it is vigorously shaken for 10 seconds. The amount of tissue should reach the white line on the cryotube in order to preserve the genetic material.

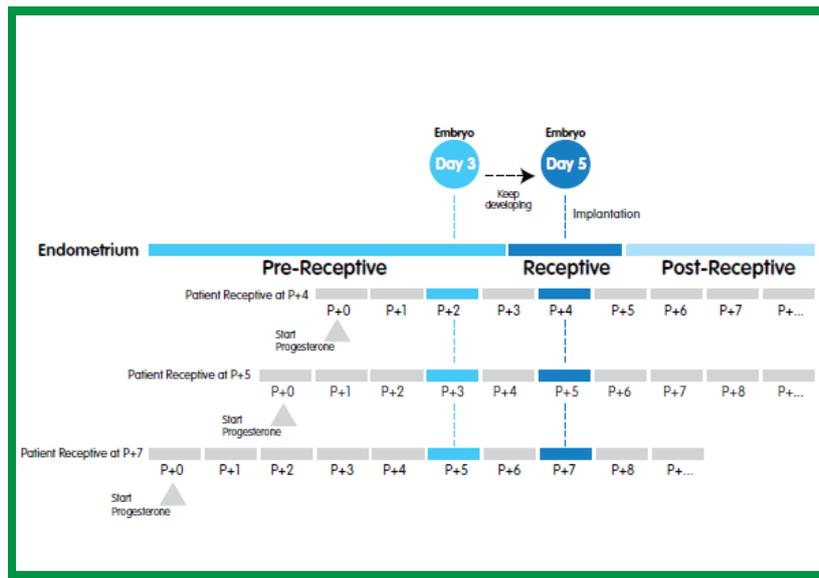
Storage: Immediately the biopsy sample is placed in a fridge (4-8°C/39-46°F) for at least 4 hours.

This preserved sample, in the original cryotube, can then be shipped at room temperature. Alternatively, the samples can be kept in the fridge for 3 weeks or frozen at -20°C/-4°F (recommended) until the moment of shipment. The sample can then be shipped at room temperature (<35°C/95°F).

Results



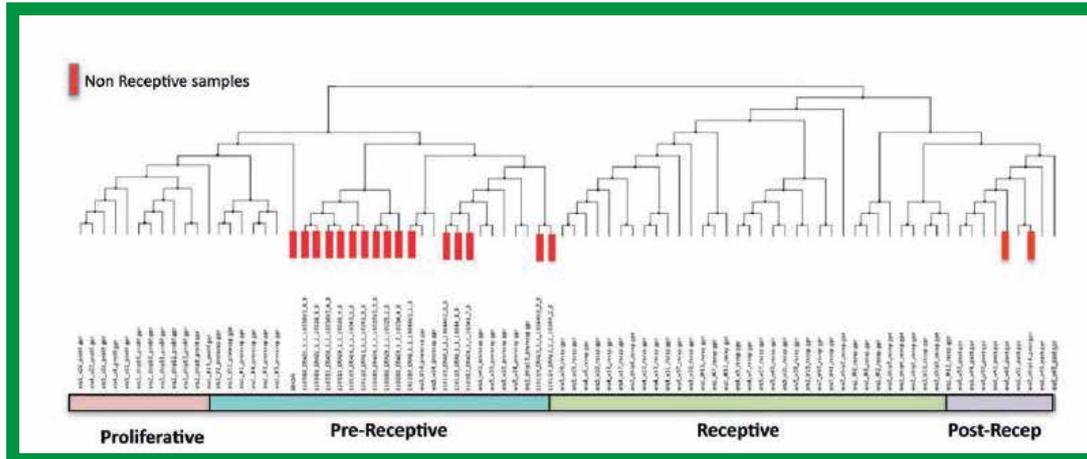
Personalization of the embryo transfer



CLINICAL OUTCOMES IN NON RECEPTIVE ERA

DATING THE WOI OF NON RECEPTIVE SAMPLES-

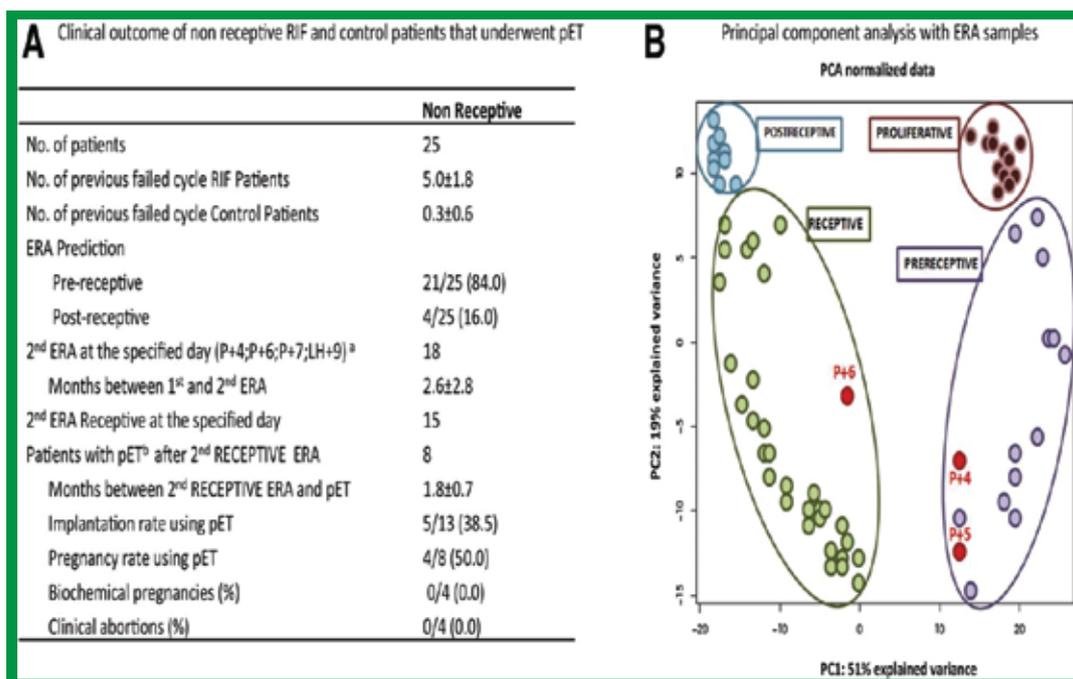
The predictor and clustering analysis indicate that 'Non Receptive' samples classify as Pre-Receptive or Post-Receptive and therefore personalization of the WOI is recommended in 90% of patients. Rarely a second biopsy may be needed.



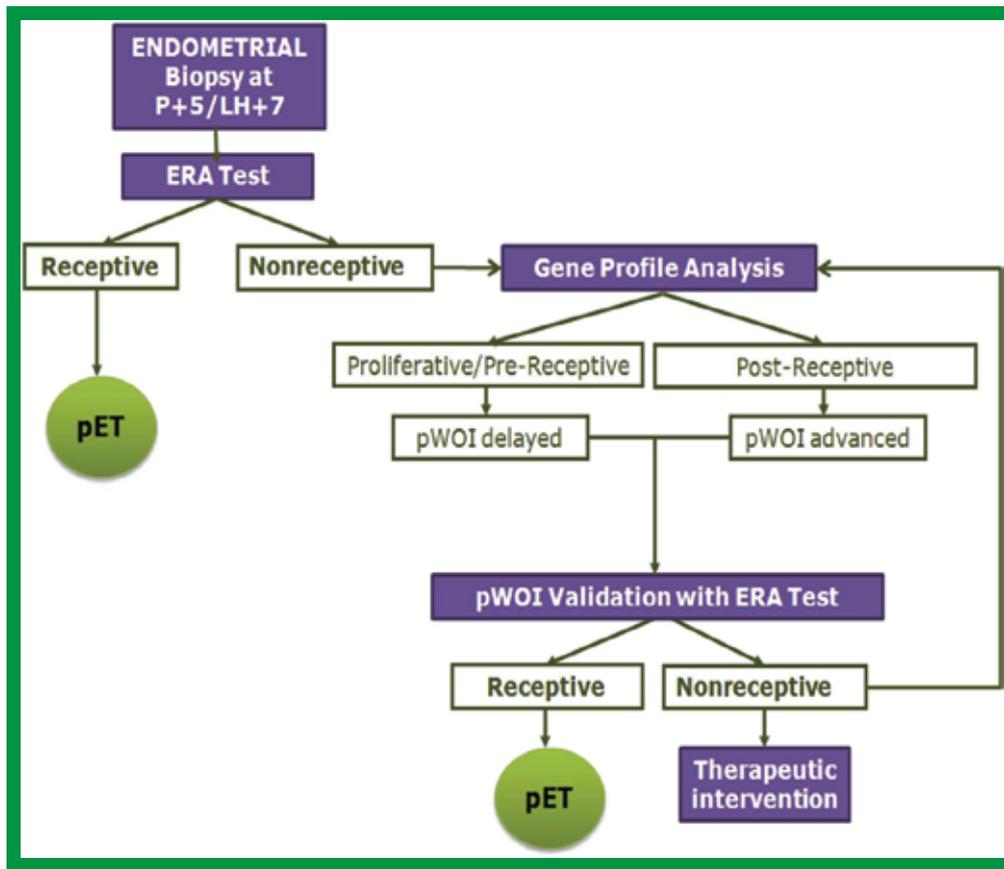
In a prospective interventional, multicentre, clinical trial the diagnostic and clinical value of the ERA test in patients with recurrent implantation failure (RIF) had been tested (Ruiz- Alonso et al., 2013).¹⁰⁵ Patients with at least three previous failed ovum donation cycles, and IVF patients less than 40 years old with at least three failed IVF cycles, composed the RIF group. Patients with no failed ART cycles composed the control group. In this trial, RIF and control patients underwent ERA-based endometrial receptivity diagnosis using an endometrial biopsy obtained either on day LH+7 in a natural cycle or on day P+5 in an HRT cycle (Ruiz-Alonso et al., 2013)¹⁰⁵.

One of the most significant results was that the ERA test identified 88% of the samples as receptive versus 12% as non-receptive in the control group, while in the RIF group 74.1% of the samples were receptive versus 25.9% which were non-receptive. In other words one in four patients with RIF had a displaced WOI and therefore their incapability to implant can be attributed to the endometrial factor.

The 'non-receptive' diagnosis, not only indicates that the endometrium is not ready for embryo adhesion, therefore making embryo transfer futile at this moment, but also gives us information about their profile of pre-receptivity or post-receptivity status.



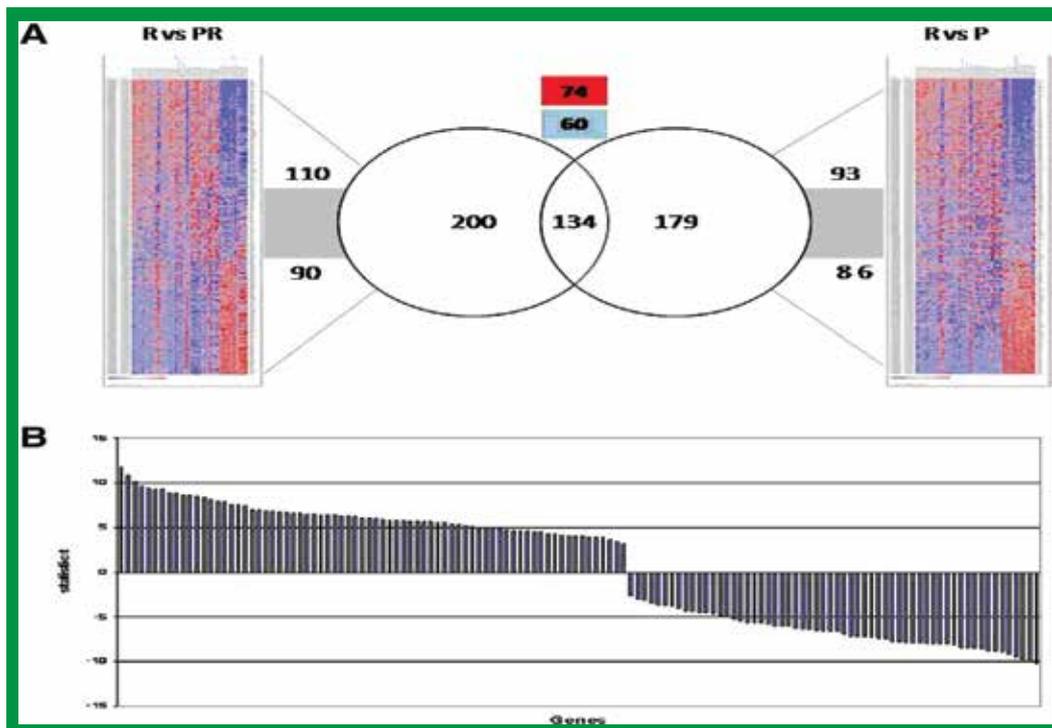
Clinical algorithm for pET.



Ruiz-Alonso. Personalized ET in patients with RIF. Fertil Steril 2013.

The ERA is more accurate than histological dating and is a highly reproducible method, even up to 40 months after first diagnosing the personalised WOI (Díaz-Gimeno et al., 2013).¹⁰⁴ In this comparative prospective study, the accuracy and reproducibility of the endometrial receptivity array (ERA) versus standard histologic methods were compared. 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 (0.446–0.791) and 0.685 (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.



The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity

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Since it was generally understood that timing and duration of WOI is constant in all women, phase of embryo development had been primary aspect guiding the timing of embryo transfer in ART till now.

However, with the information obtained from the ERA it is feasible to discover the status of the endometrium using the transcriptomic profile of a selected group of genes to identify a delayed or advanced WOI.

Therefore, we have now been able to diagnose displacement of the WOI and to perform embryo transfer according to the necessity in each patient (Ruiz-Alonso et al., 2013),¹⁰⁵ and thus helping to improve clinical success from the endometrial perspective using this novel approach. This highlights the need to synchronize embryonic and endometrial development, personalising the timing of embryo transfer.

Hence, this molecular tool based procedure has been clinically used in reproductive medicine to assess the endometrial factor with proven accuracy and consistency. This molecular signature can now be used to personalise the definition of patients' WOI and to investigate the effect of different treatments or conditions on the receptivity status of the human endometrium, or in the search for new, less invasive methods to evaluate receptiveness.

SUMMARY

ERA is a unique genomic tool for clinical endometrial evaluation designed to improve endometrium-related evaluations and diagnoses. It is also a new molecular research tool for endometrial research as it contains a finite number of genes involved in endometrial receptivity, thus avoiding the use of whole genome microarrays, which leads to reduction in associated costs and simplifies the data analysis. Furthermore, the methodology presented herein could serve to inspire new molecular approaches for diagnoses or evaluations, and to also switch from anatomical to molecular medicine.

Future directions in the transcriptomics of human Endometrium. In addition to gene expression microarrays, technology to measure gene expression called RNA sequencing (RNA-seq), based on next generation sequencing (NGS), is also emerging. This new technology is capable of true genome-wide analysis, sequencing all the mRNAs present in a sample. 25% of genes with low expression remain undetected with standard microarray technologies but are detected in RNA-seq reads (Wang et al., 2009; Mane et al., 2009).^{106,107}

The development and popularisation of the high-throughput technologies in the post-genomic era (microarrays, GWAS, NGS, etc.) have increased both the volume and the accuracy of data processing and have revolutionised medical diagnoses and treatments.

However, whether these technological improvements will translate into clinical diagnostic advances, remains to be seen. A randomized controlled trial analyzing the sensitivity and specificity of ERA based pET versus conventional ET is the need of the hour and possibly the final evidence to strengthen the confidence of the scientific community in ERA based pET.

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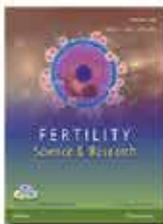
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