ARText
Vol : 9
June, 2019

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.

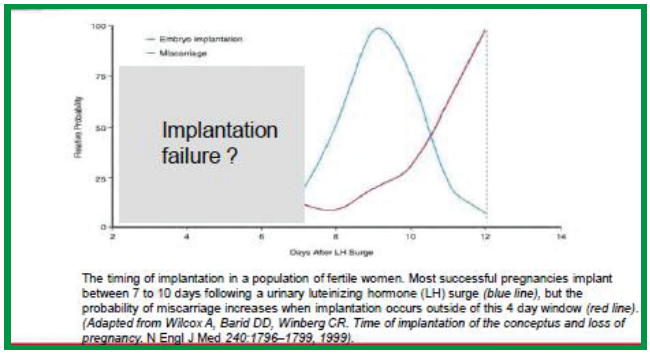
The endometrial cavity is lined by endometrium and is morphologically divided into functional and basal layers. The functional layer contains two main cellular compartments which together occupy two-thirds of endometrial thickness: an epithelial cell lining the surface and coating the epithelial glands, 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).

Guest Editors
Dr Richa Jagtap
Dr Anuja Choudhary

WINDOW OF IMPLANTATION (WOI)

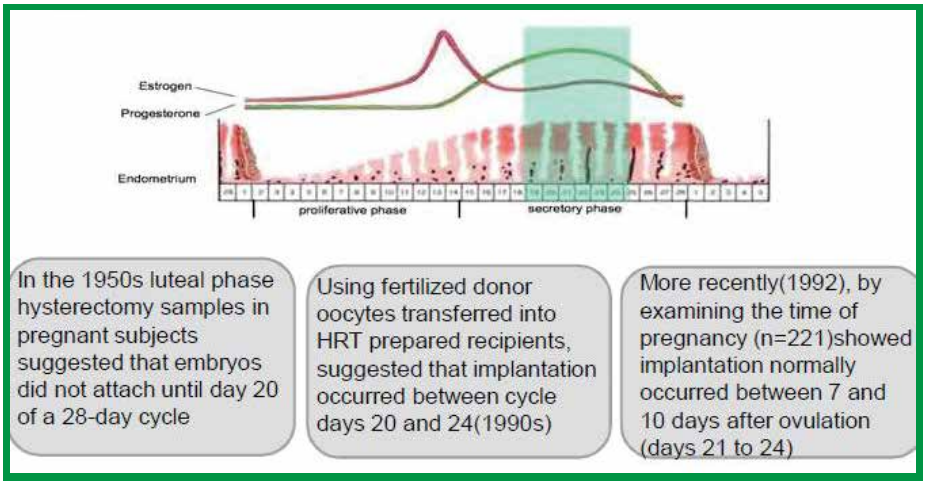
It has always been assumed that the WOI opens on day 19th or 20th of the cycle, and lasts for 4 to 5 days,[6] that is, 5 to 9 days postovulation during the mid-secretory or the midluteal phase.[5,7] However, several studies suggest that the WOI might extend up to day 10 after ovulation.[8]



The timing of implantation in a population of fertile women. Most successful pregnancies implant between 7 to 10 days following a urinary luteinizing hormone (LH) surge *(blue line)*, but the probability of miscarriage increases when implantation occurs outside of this 4 day window *(red line)*. *(Adapted from Wilcox A, Baird DD, Winberg CR. Time of implantation of the conceptus and loss of pregnancy.* N Engl J Med *240:1796–1799, 1999).*

The timing of the WOI was stated by the early work of Hertig and Rock [9], 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 endometrium[11] 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.

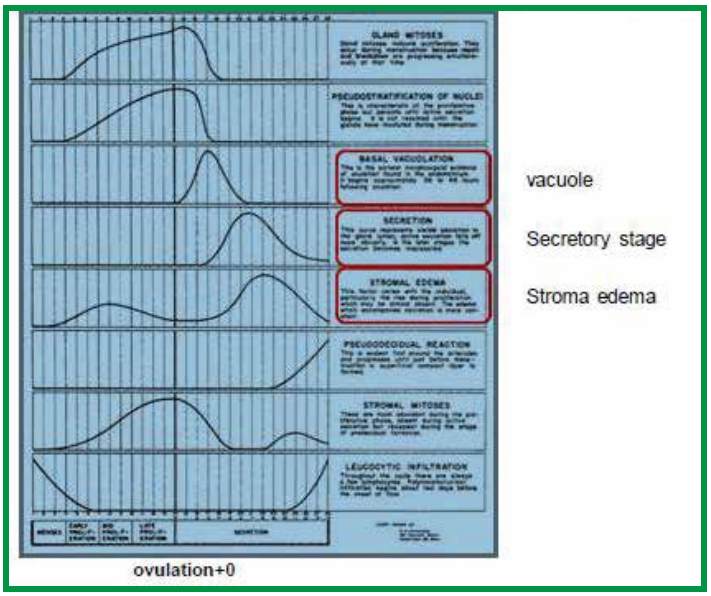


Window of Implantation: Berg PA, Fertile Steril 1992;58:537-5.
Wilcox AJ et al. The New England Journal of Medicine 340:1796-1799, 1999
Hertig AT et al, Am J Anat 98:435-493 1956

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 al[17] 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.



Endometral 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.

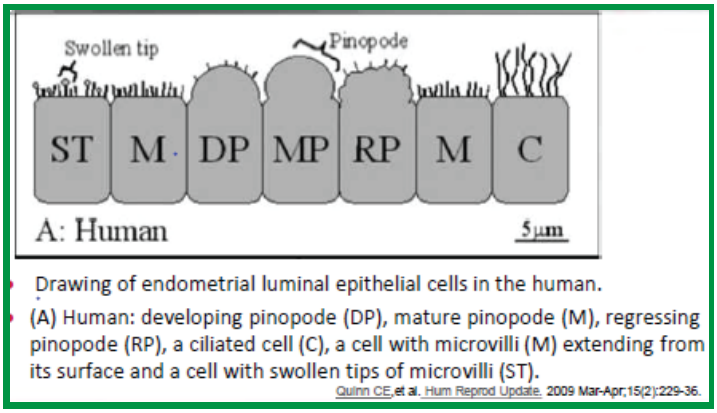
The endometrium can be viewed as a gatekeeper, allowing embryos to attach only under optimal conditions. The concept of a receptor- mediated mechanism of embryo attachment and invasion provided a strategy for choosing biologically relevant biomarkers of endometrial receptivity. Although the perfect protein 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 stroma [21] 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 colleagues [27-31] and later by Nikas and colleagues.[32-36]

Morphology of Pinopodes



Drawing of endometrial luminal epithelial cells in the human.
(A) Human: developing pinopode (DP), mature pinopode (M), regressing pinopode (RP), a ciliated cell (C), a cell with microvilli (M) extending from its surface and a cell with swollen tips of microvilli (ST).
Quinn CE,et al. Hum Reprod Update. 2009 Mar-Apr;15(2):229-36.

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.

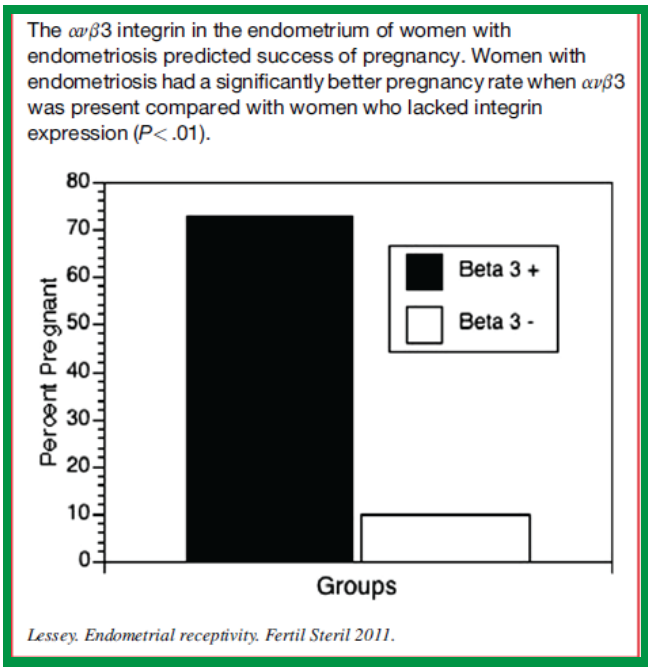
Other luminal moieties include MUC1, which is a carbohydrate glycoprotein that extends from the luminal surface and forms the glycocalyx layer. In the mouse (and most mammals) MUC1 is considered a barrier to implantation and disappears at the time of implantation.[40,41] MUC1 is expressed throughout the WOI in humans, and unique glycosylation patterns have been suggested as the explanation as to how MUC1 might be involved in endometrial receptivity [42-45] 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 αγβ3 integrin.[52] Integrins are a class of cell adhesion molecules consisting of heterodimeric glyoproteins that are anchored to the plasma membrane and serve multiple functions within cells,[53] including functions within the endometrium.

The αγβ3 integrin appears on the apex of luminal and glandular cell surfaces, coinciding with the opening of the WOI. The tight correlation between histology and αγβ3 integrin expression has been demonstrated, and its expression persists into pregnancy with expansion to the decidua.[54]

The appearance of αγβ3 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 b3 subunit, which is regulated directly by the transcription factor HOXA1055. Both HOXA10 and αγβ3 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 αγβ3 integrin . Because HOXA10 is hypermethylated in women with endometriosis, the loss of αγβ3 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.



The $\alpha v\beta 3$ integrin in the endometrium of women with endometriosis predicted success of pregnancy. Women with endometriosis had a significantly better pregnancy rate when $\alpha v\beta 3$ was present compared with women who lacked integrin expression ($P < .01$).

Lessey. Endometrial receptivity. Fertil Steril 2011.

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 αγβ3 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 endometriosis[68] 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.

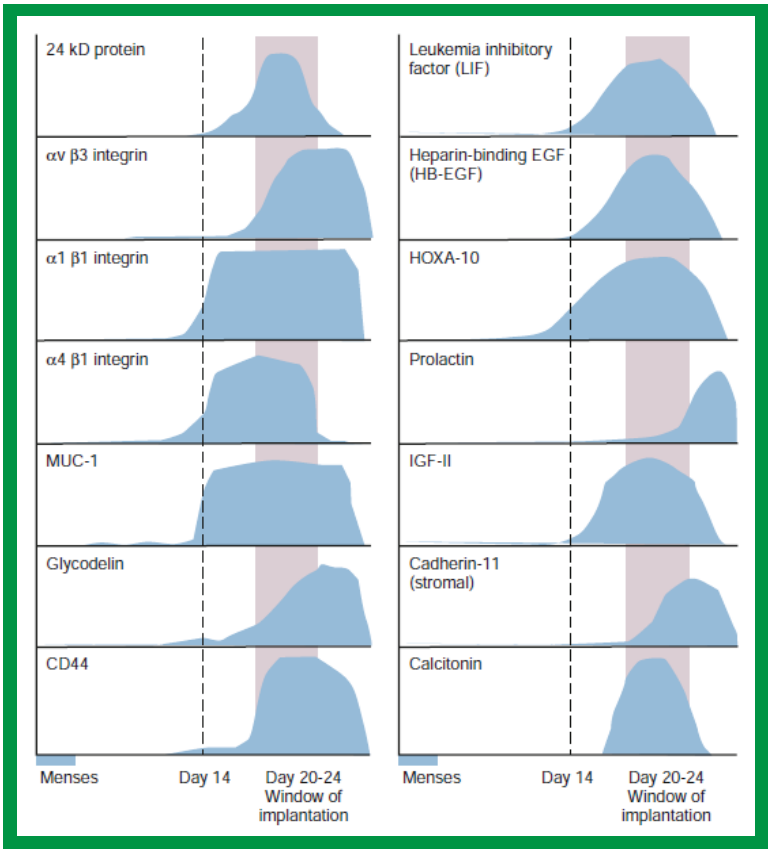


Fig: Candidate biomarkers of uterine receptivity showing their period of maximal expression relative to the presumptive window of implantation (gray bar). (Used with permission from Lessey BA. The use of biomarkers for the assessment of uterine receptivity. In Gardner DK, Weissman A, Howles CM, Shoham 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.

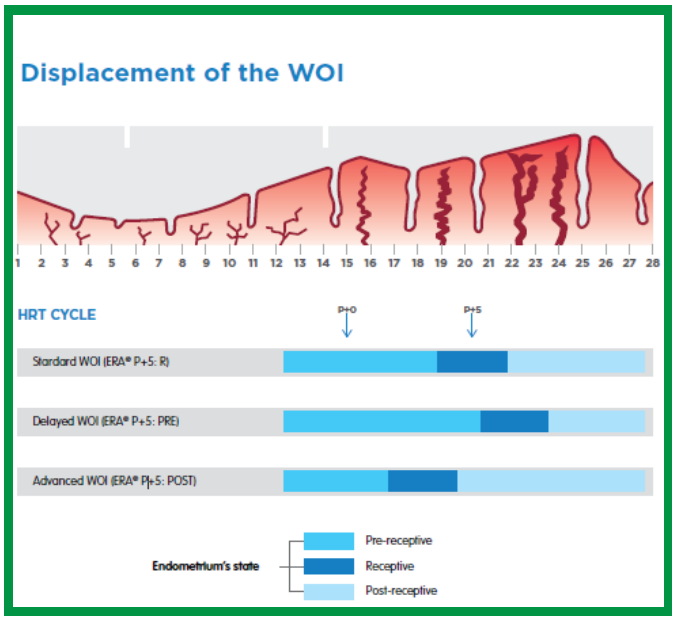
Controlled Ovarian Stimulation: Biopsy can be taken on the next natural or HRT cycle.

BIOPSY AND STORAGE

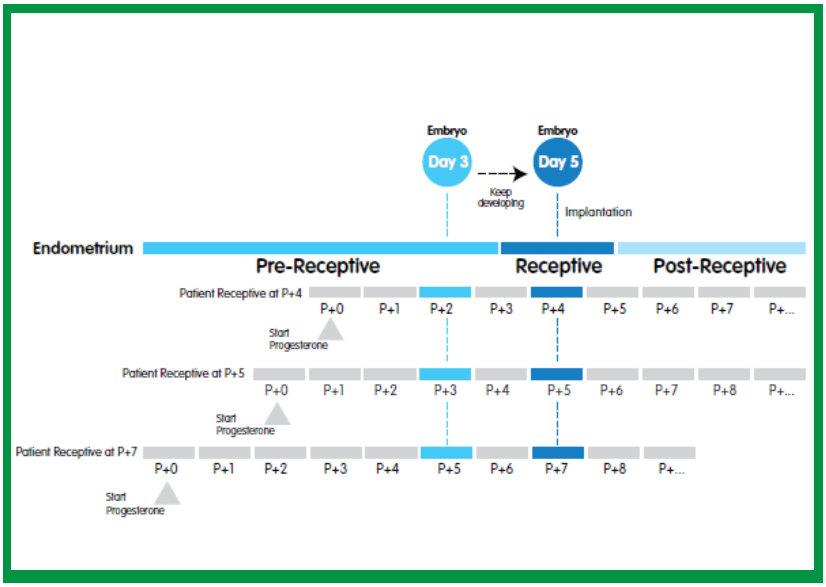
Biopsy: The cryotube is prepared and labelled either with the Patient's initials, DOB and date of biopsy or with the Patient's initials and MRN. Immediately after the biopsy is introduced into the cryotube, it is vigorously shaken for 10 seconds. The amount of tissue should reach the white line on the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



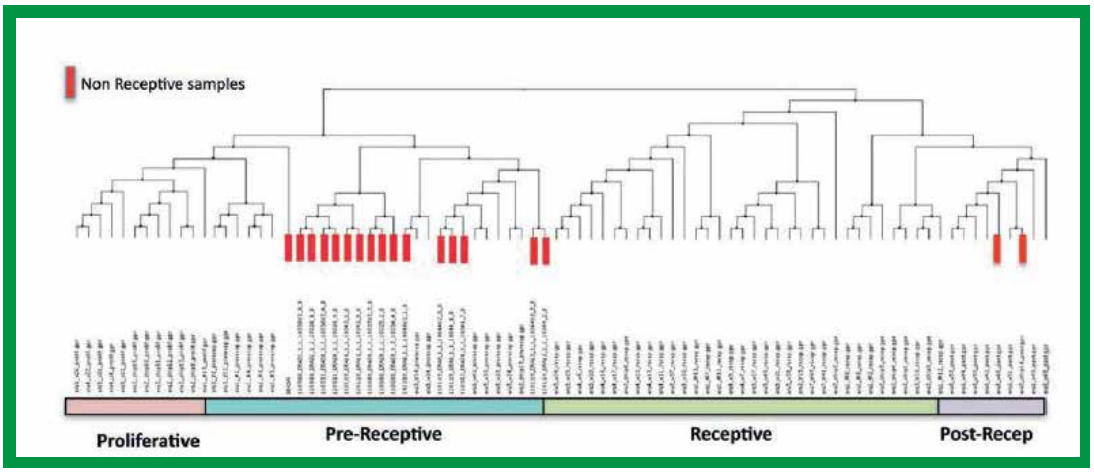
Personalization of the embryo transfer



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.

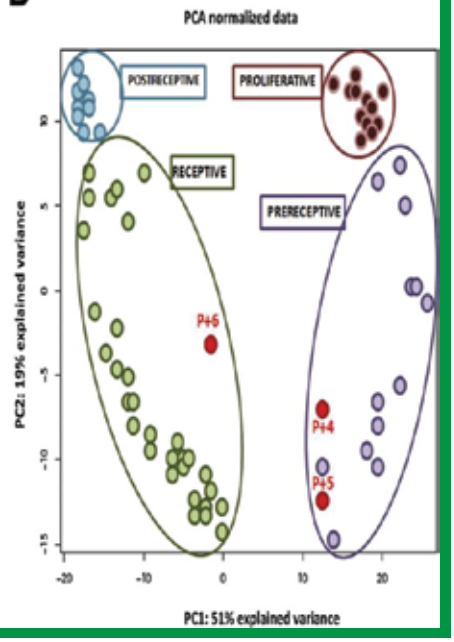
One of the most significant results was that the ERA test identified 88% of the samples as receptive versus 12% as non-receptive in the control group, while in the RIF group 74.1% of the samples were receptive versus 25.9% which were non-receptive. In other words one in four patients with RIF had a displaced 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.

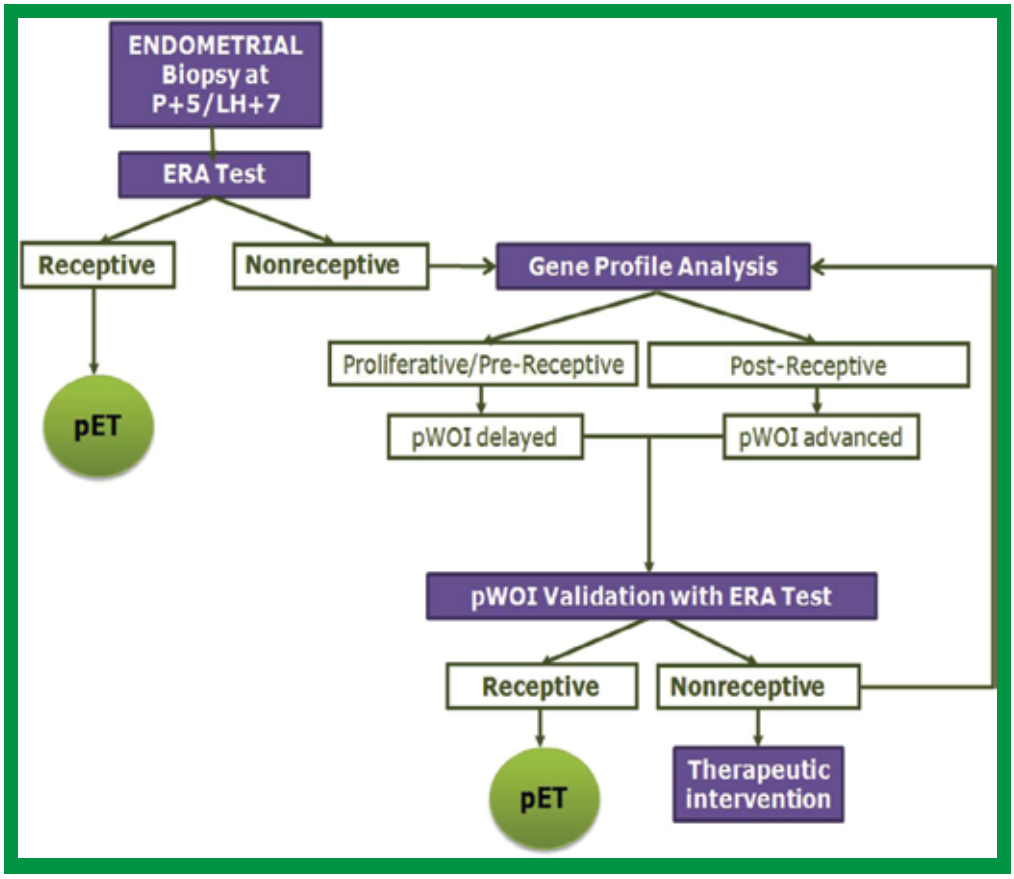
A Clinical outcome of non receptive RIF and control patients that underwent pET

	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



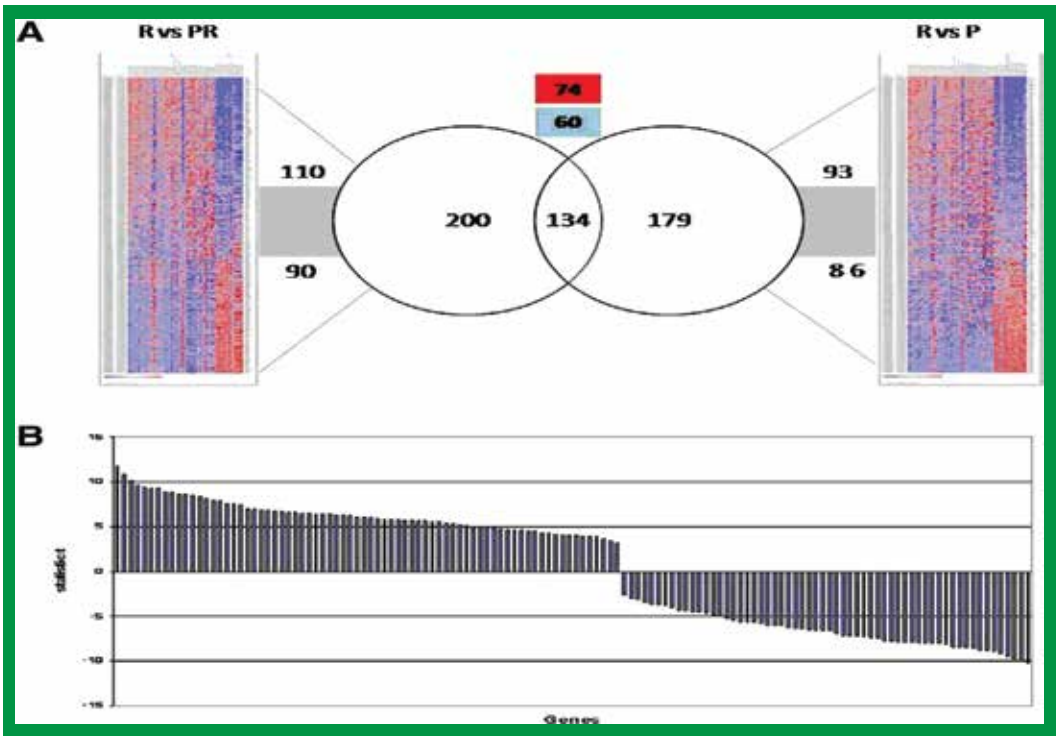
Clinical algorithm for pET.



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
Patricia Díaz-Gimeno, Ph.D.,a,b Maria Ruiz-Alonso, Ph.D.,c David Blesa, Ph.D.,c Nuria Bosch, M.D.,d

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 tecnologies 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.

REFERENCES:

1. Beier HM, Beier-Hellwig K. Molecular and cellular aspects of endometrial receptivity. Hum Reprod Update 1998;4(5):448–458
2. Diedrich K, Fauser BC, Devroey P, Griesinger G; Evian Annual Reproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. Hum Reprod Update 2007;13(4):365–377
3. Bulun SE, Adashi EY. The physiology and pathology of the female reproductive axis. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams Textbook of Endocrinology, 11th ed. Philadelphia, PA: Elsevier; 2009:549–622
4. Hawkins SM, MatzukMM. The menstrual cycle: basic biology. Ann N Y Acad Sci 2008;1135:10–18
5. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. N Engl J Med 1999;340(23):1796–1799
6. Lessey BA. Assessment of endometrial receptivity. Fertil Steril 2011;96(3):522–529
7. Navot D, Scott RT, Droesch K, Veeck LL, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. Fertil Steril 1991;55(1):114–118
8. Lenton EA, Neal LM, Sulaiman R. Plasma concentrations of human chorionic gonadotropin from the time of implantation until the second week of pregnancy. Fertil Steril 1982;37(6):773–778
9. Hertig AT, Rock J, Adams EC. A description of 34 human ova within the first 17 days of development. Am J Anat 1956;98:435–93.
10. Enders AC. Trophoblast differentiation during the transition from trophoblastic plate to lacunar stage of implantation in the rhesus monkey and human. Am J Anat 1989;186:85–98.
11. Hodgen GD. Surrogate embryo transfer combined with estrogen-progesterone therapy in monkeys: implantation, gestation, and delivery without ovaries. JAMA 1983;250:2167–71.
12. Laufer N, Navot D, Schenker JG. The pattern of luteal phase plasma progesterone and estradiol infertile cycles. Am J Obstet Gynecol 1982;143:808–13.
13. Navot D, Anderson TL, Droesch K, Scott RT, Kreiner RT, Kreiner D, et al. Hormonal manipulation of endometrial maturation. J Clin Endocrinol Metab 1989;68:801–7.

14. Navot D, Bergh PA, Williams M, Garrisi GJ, Guzman I, Sandler B, et al. An insight into early reproductive processes through the in vivo model of ovum donation. J Clin Endocrinol Metab 1991;72:408–14.

15. Bruce A. Lessey. Assessment of endometrial receptivity Fertility and Sterility_ Vol. 96, No. 3, September 2011 doi:10.1016/j.fertnstert.2011.07. 1095

16. Rock J, Bartlett MK. Biopsy studies of human endometrium, criterion of dating and information about amenorrhea, menorrhea, and tissue ovulation. JAMA 1937;108:2022.

17. Noyes RW, Hertig AI, Rock J. Dating the endometrial biopsy. Fertil Steril 1950;1:3–25.

18. Noyes RW, Haman JO. Accuracy of endometrial dating; correlation of endometrial dating with basal body temperature and menses. Fertil Steril 1953;4(6):504–517

19. Murray MJ, Meyer WR, Zaino RJ, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril 2004;81(5): 1333–1343

20. Coutifaris C, Myers ER, Guzick DS, et al; NICHD National Cooperative Reproductive Medicine Network. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004;82(5):1264–1272

21. Lessey BA, Ilesanmi AO, Sun J, Lessey MA, Harris J, Chwalisz K. Luminal and glandular endometrial epithelium express integrins differentially throughout the menstrual cycle: implications for implantation, contraception, and infertility. Am J Reprod Immunol 1996;35:195–204.

22. Cowell TP. Implantation and development of mouse eggs transferred to the uterus of non-progestational mice. J Reprod Fert 1969;19:239–45.

23. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, K^ıntgen F, et al. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature 1992;359:76–9.

24. Raab G, Kover K, Paria BC, Dey SK, Ezzell RM, Klagsbrun M. Mouse preimplantation blastocysts adhere to cells expressing the transmembrane form of heparin-binding EGF-like growth factor. Development 1996;122:637–45.

25. Bentin-Ley U, Sj^ıgren A, Nilsson L, Hamberger L, Larsen JF, Horn T. Presence of uterine pinopodes at the embryo-endometrial interface during human implantation in vitro. Hum Reprod 1999;14:515–20.

26. Enders AC, Nelson DM. Pinocytotic activity of the uterus of the rat. Am J Anat 1973;138:277–99.

27. Psychoyos A, Mandon P. Study of the surface of the uterine epithelium by scanning electron microscope. Observations in the rat at the 4th and 5th day of pregnancy [in French]. C R Acad Sci Hebd Seances Acad Sci D 1971;272:2723–5.

28. Psychoyos A. Hormonal control of ovo-implantation. Vitams Horm 1973;31:201–56.

29. Frydman MR, Glissant M, Maggioni C, Roche D, Psychoyos A. Scanning electron microscopy of postovulatory human endometrium in spontaneous cycles and cycles stimulated by hormone treatment. J Endocrinol 1987;114:319–24.

30. Martel D, Monier MN, Roche D, Psychoyos A. Hormonal dependence of pinopode formation at the uterine luminal surface.HumReprod 1991;6:597–603.

31. Martel D, Frydman R, Sarantis L, Roche D, Psychoyos A, Yoshinaga K. Scanning electron microscopy of the uterine luminal epithelium as a marker of the implantation window. In: Yoshinaga K, ed. Blastocyst implantation, Vol. 1. Boston: Adams Publishing Group; 1993:225.

32. Nikas G, Drakakis P, Loutradis D, Mara-Skoufari C, Koumantakis E, Michalas S, et al. Uterine pinopodes as markers of the 'nidation window' in cycling women receiving exogenous oestradiol and progesterone. Hum Reprod 1995;10:1208–13.

33. Nikas G, Psychoyos A. Uterine pinopodes in peri-implantation human endometrium—clinical relevance. Ann N YAcad Sci 1997;816:129–42.

34. Nikas G. Cell-surface morphological events relevant to human implantation. Hum Reprod 1999;14(Suppl. 2):37–44.

35. Nikas G. Pinopodes as markers of endometrial receptivity in clinical practice. Hum Reprod 1999;14(Suppl. 2):99–106.

36. Nikas G, Develioglu OH, Toner JP, Jones HW Jr. Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles. Hum Reprod 1999;14:787–92.

37. Acosta AA, Elberger L, Borghi M, Calamera JC, Chemes H, Doncel GF, et al. Endometrial dating and determination of the window of implantation in healthy fertile women. Fertil Steril 2000;73:788–98.

38. 3Quinn C, Ryan E, Claessens EA, Greenblatt E, Hawrylyshyn P, Cruickshank B, et al. The presence of pinopodes in the human endometrium does not delineate the implantation window. Fertil Steril 2007;87:1015–21.

39. Usadi RS, Murray MJ, Bagnell RC, Fritz MA, Kowalik AI, Meyer WR, et al. Temporal and morphologic characteristics of pinopod expression across the secretory phase of the endometrial cycle in normally cycling women with proven fertility. Fertil Steril 2003;79:9704.

40. Aplin JD. MUC-1 glycosylation in endometrium:possible roles of the apical glycocalyx at implantation. Hum Reprod 1999;14(Suppl 2):17–25.

41. DeSouza MM, Surveyor GA, Price RE, Julian J, Kardon R, Zhou XH, et al. MUC1/episialin: a critical barrier in the female reproductive tract. J Reprod Immunol 1999;45:127–58.

42. Surveyor GA, Gendler SJ, Pemberton L, Das SK, Chakraborty I, Julian J, et al. Expression and steroid hormonal control of Muc-1 in the mouse uterus. Endocrinology1995;136:3639–47.

43. Aplin JD, Hey NA, Graham RA. Human endometrial MUC1 carries keratan sulfate: Characteristic glycoforms in the luminal epithelium at receptivity. Glycobiology 1998;8:269–76.

44. Carson DD, DeSouza MM, Regisford EGC. Mucin and proteoglycan functions in embryo implantation. Bioessays 1998;20:577–83.

45. Carson DD, Julian J, Lessey BA, Prakobphol A, Fisher SJ. MUC1 is a scaffold for selectin ligands in the human uterus. Front Biosci 2006;11:2903–8.

46. Aplin JD. MUC-1 glycosylation in endometrium: possible roles of the apical glycocalyx at implantation. Hum Reprod 1999;14(Suppl 2):17–25.

47. DeSouza MM, Surveyor GA, Price RE, Julian J, Kardon R, Zhou XH, et al. MUC1/episialin: a critical barrier in the female reproductive tract. J Reprod Immunol 1999;45:127–58.

48. Surveyor GA, Gendler SJ, Pemberton L, Das SK, Chakraborty I, Julian J, et al. Expression and steroid hormonal control of Muc-1 in the mouse uterus. Endocrinology 1995;136:3639–47.

49. Aplin JD, Hey NA, Graham RA. Human endometrial MUC1 carries keratan sulfate: Characteristic glycoforms in the luminal epithelium at receptivity. Glycobiology 1998;8:269–76.

50. Carson DD, DeSouza MM, Regisford EGC. Mucin and proteoglycan functions in embryo implantation. Bioessays 1998;20:577–83.

51. Carson DD, Julian J, Lessey BA, Prakobphol A, Fisher SJ. MUC1 is a scaffold for selectin ligands in the human uterus. Front Biosci 2006;11:2903–8.

52. Lessey BA, Castelbaum AJ. Integrins and implantation in the human. Rev Endocr Metab Disord 2002;3:107–17.

53. Albelda SM, Buck CA. Integrins and other cell adhesion molecules. FASEB J 1990;4:2868–80

54. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA. Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. J Clin Invest 1992;90:188–95.

55. Daftary GS, Troy PJ, Bagot CN, Young SL, Taylor HS. Direct regulation of beta3-integrin subunitgene expression by HOXA10 in endometrial cells. Mol Endocrinol 2002;16:571–9.

56. Matsuzaki S, Canis M, Darcha C, Pouly JL, Mage G. HOXA-10 expression in the mid-secretory endometrium of infertile patients with either endometriosis, uterine fibromas or unexplained infertility. Hum Reprod 2009;24:3180–7.

57. Szczepanska M, Wirstlein P, Luczak M, Jagodzinski PP, Skrzypczak J. Reduced expression of HOXA10 in the midluteal endometrium from infertile women with minimal endometriosis. Biomed Pharmacother 2010;64:697–705.

58. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril 2010;95:1133–6.

59. Taylor HS, Bagot C, Kardana A, Olive D, Arici A. HOX gene expression is altered in the endometrium of women with endometriosis. Hum Reprod 1999;14:1328–31.

60. Cakmak H, Taylor HS. Molecular mechanisms of treatment resistance in endometriosis: the role of progesterone-hox gene interactions. Semin Reprod Med 2010;28:69–74.

61. Strandell A, Lindhard A. Hydrosalpinx and ART— salpingectomy prior to IVF can be recommended to a well-defined subgroup of patients. Hum Reprod 2000;15:2072–4.113.

62. Barnhart KT, Dunsmoor R, Coutifaris C. The effect of endometriosis on in vitro fertilization. Fertil Steril 2002;77:1148–55.

63. Strandell A, Lindhard A, Waldenstr^ım U,Thorburn J. Hydrosalpinx and IVF outcome: cumulative results after salpingectomy in a randomized controlled trial. Hum Reprod 2001;16:2403–10.

64. Littman E, Giudice L, Lathi R, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. Fertil Steril 2005;84:1574.

65. Thomas K, Thomson A, Wood S, Kingsland C, Vince G, Lewis-Jones I. Endometrial integrin expression in women undergoing in vitro fertilization and the association with subsequent treatment outcome. Fertil Steril 2003;80:502–7.

66. Casals G, Ordi J, Creus M, Fabregues F, Carmona F, Casamitjana R, et al. Osteopontin and alphavbeta3 integrin as markers of endometrial receptivity: the effect of different hormone therapies. Reprod Biomed Online 2010;21:349–59.

67. Revel A, Koler D, Prus A, Tsafrir A, Laufer N, Reich R. Implementation of integrin beta 3 level as predictor of implantation in IVF program. Fert Stert 2005;84(Suppl 1):S144–5.

68. Noble LS, Simpson ER, Johns A, Bulun SE. Aromatase expression in endometriosis. J Clin Endocrinol Metab 1996;81:174–9

69. Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. Endocrinology 2008;149:1190–204.

70. Lessey BA. Medical management of endometriosis and infertility. Fertil Steril 2000;73:1089–96.

71. Hii LL, Rogers PA. Endometrial vascular and glandular expression of integrin alpha(v)beta3 in women with and without endometriosis. Hum Reprod 1998;13:1030–5.

72. Surrey ES, Lietz AK, Gustofson RL, Minjarez DA, Schoolcraft WB. Does endometrial integrin expression in endometriosis patients predict enhanced in vitro fertilization cycle outcomes after prolonged GnRH agonist therapy? Fertil Steril 2010;93:646–51.

73. Laird SM, Tuckerman EM, Li TC. Cytokine expression in the endometrium of women with implantation failure and recurrent miscarriage. Reprod Biomed Online 2006;13:13–23.

74. Halis G, Arici A. Endometriosis and inflammation in infertility. Ann N YAcad Sci 2004;1034:300–15.

75. Halme J. Role of peritoneal inflammation in endometriosis-associated infertility. Ann N Y Acad Sci 1991;622:266–74.

76. Agic A, Xu H, Finas D, Banz C, Diedrich K, Hornung D. Is endometriosis associated with systemic subclinical inflammation? Gynecol Obstet Invest 2006;62:139–47.

77. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 1997;68:585–96.

78. Fujishita A, Hasuo A, Khan KN, Masuzaki H, Nakashima H, Ishimaru T. Immunohistochemical study of angiogenic factors in endometrium and endometriosis. Gynecol Obstet Invest 1999; 48(Suppl 1):36–44.

79. Kamei M, Carman CV. New observations on the trafficking and diapedesis of monocytes. Curr Opi Hematol 2010;17:43–52.

80. Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients JAMA 2004;292:81–5.

81. Du H, Taylor HS. Contribution of bone marrowderived stem cells to endometrium and endometriosis. Stem Cells 2007;25:2082–6.

82. Bulmer JN, Morrison L, Longfellow M, Ritson A, Pace D. Granulated lymphocytes in human endometrium: histochemical and immunohistochemical studies. Hum Reprod 1991;6:791–8.

83. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, et al. Innate or adaptive immunity? The example of natural killer cells. Science 2011;331:44–9.

84. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol 2004;5:266–71.

85. Jasper MJ, Tremellen KP, Robertson SA. Primary unexplained infertility is associated with reduced expression of the T-regulatory cell transcription factor Foxp3 in endometrial tissue. Mol Hum Reprod 2006;12:301–8.

86. CHA J, VILELLA F, DEY SK AND SIMÓN C. "Molecular Interplay in Successful Implantation" in Ten Critical Topics in Reproductive Medicine, S. Sanders, Ed. (Science/AAAS, Washington, DC, 2013), pp. [44-48].

87. RUIZ-ALONSO M, BLESA D, SIMÓN C (2012). The genomics of the human endometrium. Biochim Biophys Acta 1822: 1931-1942.

88. RIESEWIJK A, MARTIN J, HORCAJADAS JA, POLMAN J, PELLICER A, MOSSELMAN S, SIMÓN C (2003). Gene expression profiling of human endometrial receptivity on days LH2 versus LH7 by microarray technology. Mol Hum Reprod 9: 253-64.

89. BORTHWICK J, CHARNOCK-JONES S, TOM BD, HULL ML, TEIRNEY R, PHILLIPS SC, SMITH SK (2003). Determination of the transcript profile of human endometrium. Mol Hum Reprod 9: 19-33.

90. HORCAJADAS JA, RIESEWIJK A, MÍNGUEZ P, DOPAZO J, ESTEBAN FJ, DOMÍNGUEZ F, GIUDICE LC, PELLICER A, SIMÓN C (2008). Gene expression analysis of the endometrium reveals that controlled ovarian stimulation induces a genomic delay with potential clinical implications. J Clin Endocrinol Metab 93: 4500-4510

91. HAOUZI D, MAHMOUD K, FOURAR M, BENDHAOU K, DECHAUD H (2009a). Identification of new biomarkers of human endometrial receptivity in the natural cycle. Hum Reprod 24: 198-205.

92. DÍAZ-GIMENO P, HORCAJADAS JA, MARTÍNEZ-CONEJERO JA, ESTEBAN FJ, ALAMA P, PELLICER A, SIMÓN C (2011). A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. Fertil Steril 95: 50-60.

93. TALBI S, HAMILTON AE, VO KC, TULAC S, OVERGAARD MT, DOSIOU C, LE SHAY N, NEZHAT CN, KEMPSON R, LESSEY BA, NAYAK NR, GIUDICE LC (2006). Molecular phenotyping of human endometrium distinguishes menstrual cycle phases and underlying biological processes in normo-ovulatory women. Endocrinology 147: 1097-121.

94. SIMMEN FA, SIMMEN RC (2006). Orchestrating the menstrual cycle: discerning the music from the noise. Endocrinology 147: 1094-1096.

95. GIUDICE LC (2006). Application of functional genomics to primate endometrium: insights into biological processes. Reprod Biol Endocrinol 4(Suppl. 1):S4

96. PONNAMPALAM AP, WESTON GC, TRAJSTMAN AC, SUSIL B, ROGERS PA (2004). Molecular classification of human endometrial cycle stages by transcriptional profiling. Mol Hum Reprod 10: 879-893.

97. KINGSLEY PD, WHITIN JC, COHEN HJ, PALIS J (1998). Developmental expression of extracellular glutathione peroxidase suggests antioxidant roles in deciduum, visceral yolk sac, and skin. Mol Reprod Dev 49: 343-355.

98. FRANCHI A, ZARET J, ZHANG X, BOCCA S, OEHNINGER S (2008). Expression of immunomodulatory genes, their protein products and specific ligands/receptors during the window of implantation in the human endometrium. Mol Hum Reprod 14: 413-421.

99. FRANCIS J, RAI R, SEBIRE NJ, EL-GADDAL S, FERNANDES MS, JINDAL P, LOKUGAMAGE A, REGAN L, BROSENS JJ (2006). Impaired expression of endometrial differentiation markers and complement regulatory proteins in patients with recurrent pregnancy loss associated with antiphospholipid síndrome. Mol Hum Reprod 12: 435-442.

100. TSENG LH, CHEN I, CHEN MY, YAN H, WANG CN, LEE CL (2010). Genome-based ex- pression profiling as a single standardized microarray platform for the diagnosis of endometrial disorder: an array of 126-gene model. Fertil Steril 94: 114-119.

101. CRITCHLEY HO, KELLY RW, BRENNER RM, BAIRD DT (2001). The endocrinology of menstruation—a role for the immune system. Clin Endocrinol (Oxf) 55: 701-710

102. DALY DC, TOHAN N, DONEY TJ, MASLAR IA, RIDDICK DH (1982). The significance of lymphocytic–leukocytic infiltrates in interpreting late luteal phase endometrial biopsies. Fertil Steril 37: 786-791.

103. SALAMONSEN LA, WOOLLEY DE (1999). Menstruation: induction by matrix metal-loproteinases and inflammatory cells. J Reprod Immunol 44: 1-27.

104. DÍAZ-GIMENO P, RUIZ-ALONSO M, BLESA D, BOSCH N, MARTÍNEZ-CONEJERO JA, ALAMÁ P, GARRIDO N, PELLICER A, SIMÓN C (2013). The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 99: 508-517.

105. RUIZ-ALONSO M, BLESA D, DÍAZ-GIMENO P, GÓMEZ E, FERNÁNDEZ-SÁNCHEZ M, CARRANZA F, CARRERA J, VILELLA F, PELLICER A, SIMÓN C (2013). The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertil Steril 100: 818-824.

106. WANG Z, GERSTEIN M, AND SNYDER M (2009). RNA-Seq: a revolutionary tool for transcriptomics. Nat Rev Genet 10: 57-63.

107. MANE SP, EVANS C, COOPER KL, CRASTA OR, FOLKERTS O, HUTCHISON SK, HARKINS TT, THIERRY-MIEG D, THIERRY-MIEG J, JENSEN RV (2009).

Dr M Gouri Devi
President

Dr Pankaj Talwar
Secretary General

Contributors

Dr Richa Jagtap **Dr Anuja Choudhary**

WHY TO JOIN IFS

IFS is a Multi-disciplinary Society that values the input and participation of professionals in the scope of Reproductive Medicine.

INDIAN FERTILITY SOCIETY

IFS MEMBERSHIP
Benefits At A Glance

Dr. M Gouri Devi
President

Dr. Pankaj Talwar
Secretary General

- Pan India Society
- Collaboration with ESHRE & IFFS
- 2546 Members & 26 Chapters
- National Conference Fertivision every year with reduced registration fees
- Special Interest Group (13) for IFS Members to show cast their talent
- Research Wing of IFS has its own ethical committee for Research Project approval
- Publication Wing - Fertility Science & Research Journal
- IFS Fellowship Program in Clinical ART & Embryology in collaboration with Amity University
- ESHRE Certified Embryologist Examination in India, conducted by IFS every year
- IFS Outreach activities all over India
- IFS Master Courses
- Free access to IFS E-Pathshala contents and Official Journal
- IFS E-Pathshala - IFS Conversation, Nexus, ARText, Fertility News, CATALYST

indianfertilitysocietyifs ifsdelhi indianfertilitysociety/

IFS SECRETARIAT
302, 3rd Floor, Kailash Building,
26, Kasturba Gandhi Marg, CP,
New Delhi-110001

+91 9667742015
+91 9899308083
+91 11 40018184

indianfertilitysocietydelhi@gmail.com
www.indianfertilitysociety.org

INDIAN FERTILITY SOCIETY

IFS is a Multi-Disciplinary Society that values the input and participation of professionals in the scope of Reproductive Medicine.

2546+ Members

26 State Chapters

How To Join IFS

IFS Life Membership Fees

Clinicians:-
Rs. 5932/- + (18% GST -1068) = Rs.7000/-

Non Clinicians:-
Rs. 4237/- + (18% GST -763) = Rs. 5000/-

Online Procedure

It is the easiest way to Register yourself as the lifetime member of our family. while following the procedure, fill the online membership form and pay the membership fee.

Your registration number would be generated and you will get your membership certificate and also access to member portal on our website where you can manage your profile and get all important notification.

Offline Procedure

You can pay by cash or card at the registration counter provided.

or

you can easily download our offline membership form or use the offline form attached with this document, fill all required information attach the membership fee DD or Cheque and send on our secretariat address.

Account Details:
Account No: 50562010067180 | IFSC Code: ORBC0100179
Bank Name: Oriental Bank of Commerce
Branch: Connaught Place, New Delhi-110001

Dr. M. Gouri Devi
President

Dr. Pankaj Talwar
Secretary General

IFS Secretariat
Flat No. 302, 3rd Floor,
Kailash Building,
26, Kasturba Gandhi Marg,
C.P. New Delhi – 110001

+91 9667742015
+91-9899308083
91-1140018184

indianfertilitysocietydelhi@gmail.com
info@indianfertilitysociety.org
indianfertilitysocietyifs
ifsdelhi
indianfertilitysociety

INDIAN FERTILITY SOCIETY

Offline Registration Form

Download the form and send to the secretariat with recent pic and cheque/draft

Name		Qualification	
Date of Birth		Designation	
Workplace Phone No		Residence Phone No	
Mobile		E-mail	

Workplace Address

Residence Address

State		IFS Chapter	

Address to be used for correspondence

Workplace ○ **Residence** ○

Account Details:

Account No: 50562010067180 | IFSC Code: ORBC0100179
Bank Name: Oriental Bank of Commerce
Branch: Connaught Place, New Delhi-110001

Payment Details :

Amount : .....
Cash / Cheque / Demand Draft No. : ..... Dated : .....
Bank : : .....
Signature : : .....Name : ..... Date : .....

IFS Life Membership Fees

Clinicians:-
Rs. 5932/- + (18% GST -1068) = Rs.7000/-

Non Clinicians:-
Rs. 4237/- + (18% GST -763) = Rs. 5000/-

* Please make Cheque / Draft in favour of "INDIAN FERTILITY SOCIETY" payable at New Delhi.
*Please attaché two recent passport size photographs.

Who can apply for IFS Membership : All Professionals with postgraduate qualification such as Obstetricians & Gynaecologists, Clinical embryologists, andrologists, ultrasonologists, counsellors, geneticists and other involved in the care of infertility patients.

IFS Secretariat
Flat No. 302, 3rd Floor,
Kailash Building,
26, Kasturba Gandhi Marg,

+91 9667742015
+91-9899308083
91-1140018184

indianfertilitysocietydelhi@gmail.com
info@indianfertilitysociety.org
indianfertilitysocietyifs
ifsdelhi