

CHAPTER 20

ENDOMETRIAL RECEPTIVITY ARRAY (ERA)

Semih DALKILIC, Nilufer CELIK, Suleyman AYDIN

Introduction

The number of couples who diagnosed with infertility improves nowadays. The cause of infertility can be pathological or physiological because human implantation and pregnancy is very complex process. In vitro fertilization (IVF) is one of the preferred medical techniques for getting pregnant. In this technique, fertilization takes place in vitro environment after that fertilized embryo transferred to uterus. Technology and achievement of IVF is improving in parallel with medical technology. However, there is still some restrictive criteria that effecting successful human implantation. For successful implantation;

- Healthy embryo
- Receptive endometrium
- Synchronized molecular communication between both endometrium and embryo.
- Prevention from host immune system is necessary.

What is the Endometrium?

Endometrium is a thin layer that lining down uterus and this layer composed of epithelial cells. It is highly complex and dynamic tissue and show different molecular, morphological, histological, biochemical and physiological alterations under the endocrine and paracrine signals during the menstrual cycle. Main determinant of the proliferative phase is estrogen and this sex steroid controls many alterations. Estrogen provides proliferation of stromal cells and glands as well as elongation of the spiral arteries. Receptive endometrium reflects allowing to implantation of blastocyst to endometrium. Embryo cannot implant to the endometrium in another phase. Endometrium acquires receptive phenotype at 19-20 day of menstrual cycle and this period called as window of implantation and proceeds 4-5 days. Serum progesterone level reaches to its peak during this short phase (1). In this receptive phase, endometrium undergoes some cytoskeletal, biochemical and morphological changes to become receptive for embryo implantation. It is very important to dating receptive endometrium during the IVF applications.

LRRC1	Leucine-rich repeat containing 1	-3.23
SORDbbcc	Sorbitol dehydrogenase	-3.21
EPHB3cc	EPH receptor B3	-3.20
TMSL8cc	Thymosin-like 8	-3.20
RASSF2cc	Ras association (RalGDS/AF-6) domain family 2, transcript variant 1	-3.19
TTC21B	mRNA for KIAA1992 protein (AB082523)	-3.17
OPRK1	Opioid receptor, kappa 1	-3.17
TMEM16Acc	Transmembrane protein 16A	-3.13
CRABP2cc	Cellular retinoic acid-binding protein 2	-3.10
FLJ10719cc	Hypothetical protein FLJ10719	-3.10
PRKCQcc	Protein kinase C, theta	-3.08
CDC2cc	Cell division cycle 2, G1 to S and G2 to M, transcript variant 1	-3.06
BUB1Bcc	BUB1 budding uninhibited by benzimidazoles 1 homologue beta (yeast)	-3.05
STEAP4	STEAP family member 4	-3.04
HEY1	Hairy/enhancer-of-split related with YRPW motif 1	-3.03

References

1. Lessey BA. Assessment of endometrial receptivity. *Fertil Steril* 2011;96:522-9).
2. PsychoyosA. Uterine receptivity for nidation. *Ann N Y Acad Sci* 1986;476: 36-42).
3. Murphy CR. Uterine receptivity and the plasma membrane transformation. *Cell Res* 2004;14:259-67.
4. Martin JC, Jasper MJ, Valbuena D, Meseguer M, Remohí J, Pellicer A, Sim_on C. Increased adhesiveness in cultured endometrial-derived cells is related to the absence of moesin expression. *Biol Reprod* 2000;63:1370-6.
5. Thie M, Harrach-Ruprecht B, Sauer H, Fuchs P, Albers A, Denker HW. Cell adhesion to the apical pole of epithelium: a function of cell polarity. *Eur J Cell Biol* 1995;66:180-91).
6. Ruiz-Alonso M, Blesa D, Diaz-Gimeno P et al. The endometrial receptivityarray for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril* 2013; 100:818-824).
7. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Fertil Steril* 1950;1:3-25.
8. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Am J Obstet Gynecol* 1975;122:262-3).
8. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. *Fertil Steril* 2004;82:1264-72.
9. Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. *Fertil Steril* 2004;81:1333-43
10. Balasch J, Vanrell JA, Creus M, Marquez M, Gonzalez-Merlo J. The endometrial biopsy for diagnosis of luteal phase deficiency. *Fertil Steril* 1985;44: 699-701, 17. Landis JR, Koch GC. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.
11. Nikas G. Cell-surface morphological events relevant to human implantation. *Hum Reprod* 1999;14:37-44.
12. Lessey BA. Assessment of endometrial receptivity. *Fertil Steril* 2011;96: 522-9
13. Quinn CE, Casper RF. Pinopodes: a questionable role in endometrial receptivity. *Hum Reprod Update* 2009;15:229-36).

14. 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
15. Meseguer M, Pellicer A, Simon C. MUC1 and endometrial receptivity. *Mol Hum Reprod* 1998;4:1089–98
16. Kumar S, Zhu LJ, Polihronis M, Cameron S, Baird DT, Schaltz F, et al. Progesterone induces calcitonin gene expression in human endometrium within the putative window of implantation. *J Clin Endocrinol Metab* 1998;83: 4443–50
17. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. *Nature* 1992; 359:76–9
18. Davis BJ, Lennard DE, Lee CA, Tiano HF, Morham SG, Wetsel WC, Langanbach R. Anovulation in cyclooxygenase-2-deficient mice is restored by prostaglandin E2 and interleukin-1beta. *Endocrinology* 1999;140:2685–95
19. Taylor H, Igarashi P, Olive D, Arici A. Sex steroids mediate Hoxa11 expression in the human peri-implantation endometrium. *J Clin Endocrinol Metab* 1999;84:1129–35
20. Schena M, Shalon D, Davis RW, Brown PO. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science* 1995; 270:467–70
21. Horcajadas JA, Pellicer A, Simón C. Wide genomic analysis of human endometrial receptivity: new times, new opportunities. *Hum Reprod Update* 2007;13:77–86. 30. Ruiz-Alonso M, Blesa D, Simón S. The genomics of the human endometrium. *Biochim Biophys Acta* 2012;1822:1931–42
22. Haouzi D, Mahmoud K, Fourar M, Bendhaou K, Dechaud H, De Vos J, et al. Identification of new biomarkers of human endometrial receptivity in the natural cycle. *Hum Reprod* 2009;24:198–205
23. Tapia A, Vilos C, Marín JC, Croxatto HB, Devoto L. Bioinformatic detection of E47, E2F1 and SREBP1 transcription factors as potential regulators of genes associated to acquisition of endometrial receptivity. *Reprod Biol Endocrinol* 2011;27:9–14
24. Schena m, Shalon d, Davis rw, Brown Po. quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science* 1995;270: 467-470.
25. Quackenbush J. Microarray analysis and tumor classification. *N Engl J Med* 2006; 354: 2463-2472
26. Patricia díaz-gimeno1, Maria ruíz-alonso, David blesa and Carlos simón. *int. j. dev. Biol.* 2014;58:127-137
27. Altmae S, Martínez-Conejero JA, Salumets A, Simon C, Horcajadas JA, Stavreus-Evers A. Endometrial gene expression analysis at the time of embryo implantation in women with unexplained infertility. *Mol Hum Reprod* 2010;16:178–87
28. Matsuzaki S. DNA microarray analysis in endometriosis for development of more effective targeted therapies. *Front Biosci* 2011;3:1139–53
29. Evans GE, Martínez-Conejero JA, Phillipson GT, Simón C, McNoe LA, Sykes PH, et al. Gene and protein expression signature of endometrial glandular and stromal compartments during the window of implantation. *Fertil Steril* 2012;97:1365–73.
30. Tapia A, Vilos C, Marín JC, Croxatto HB, Devoto L. Bioinformatic detection of E47, E2F1 and SREBP1 transcription factors as potential regulators of genes associated to acquisition of endometrial receptivity. *Reprod Biol Endocrinol* 2011;27:9–14
31. Simon C, Oberye J, Bellver J, Vidal C, Bosch E, Horcajadas JA, et al. Similar endometrial development in oocyte donors treated with either high- or standard-dose GnRH antagonist compared to treatment with a GnRH agonist or in natural cycles. *Hum Reprod* 2005;20:3318–27
32. Diaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA et al. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. *Fertil Steril* 2011; 95: 50–60
33. Ruiz-Alonso M, Blesa D, Simon C. The genomics of the human endometrium. *Biochim Biophys Acta* 2012; 1822: 1931–1942
34. Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero JA, Alam_a P, et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. *Fertil Steril* 2013;99:508–17.