

Endometrium in Improving IVF Outcomes: Assessing its Behavior and Making an Ally from an Enemy

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Specialized systems and protocols have been implemented in an effort to assist subfertile couples and this has led to the meticulous investigation of the factors affecting fertility at a macroscopical, microscopical and molecular level in order to establish the synergistic conditions that lead to successful reproduction. On this basis, the endometrium plays a crucial role in reproduction, as the tissue lining of the uterus is responsible for nurturing the developing embryo, but importantly and prior to implantation, it is the endometrial state, which is decisive of the fate of the early embryo. This state has been for a long time the subject of diagnostic and therapeutic interventions in the hope that through these, assisted reproduction specialists could improve the pregnancy rates. The current notion suggests that the inability of an embryo to implant is related to the asynchronous changes among itself and the endometrium.

The success of embryo implantation depends on the quality of the embryo, the endometrial receptivity and the synchronization between endometrial changes and embryonic development [1]. The endometrium is in a receptive state when it is capable to accept and support the embryo. Ovarian hormones control its preparation, and various protocols have been suggested [2]. Successful implantation occurs in a definite setting; a functional blastocyst "meets" a receptive endometrium and a synchronized "dialogue" between maternal and embryonic tissues begins [3,4]. The timing of this dialogue, referred as the "window of implantation", is characterized by significant changes at circulatory and tissue level, as well as in cellular and molecular level, with notable changes in steroid receptors and integrin expression [5-7].

During controlled ovarian hyperstimulation for IVF, the high E2 levels seem to cause differences in the development and receptivity of the endometrium, and they are considered to negatively affect the outcomes [8,9]. In contrast, other reports do not accept that receptivity is affected [10], whereas others have declined the endometrial receptivity to act as an ovarian stimulation biomarker: in this context, the study by Shapiro et al. [11] demonstrated equal probability of clinical pregnancy between fresh and frozen thawed embryos. Further confusion in the literature has been added when Richter et al. [12] reported reduced success rates in fresh transfers of later developing blastocyst, emphasizing that is the asynchrony of the developing embryo with endometrial receptivity and not the poor embryo quality that results in low IVF outcomes. Moreover, GnRH analogs have been considered as positively affecting the endometrial receptivity when compared to GnRH antagonists [13], but their comparison has yielded similar live birth rates in IVF cycles [14].

The current most simple way of monitoring a receptive endometrium is transvaginal ultrasonography and examination of the endometrial thickness, morphology and blood flow status (especially end-diastolic blood flow) [15,16]. The ideal range of all these parameters for implantation has been a matter of debate, when they were to be related to pregnancy outcomes on their own [3,17-21]. Their combination though has been reported to be the most effective mean for evaluation of uterine receptivity [22], but still, their value remains unclear when coming to prediction of IVF outcomes. Hysteroscopy performed

before an IVF cycle might be of essence, when surgically removing lesions altering the normal uterine cavity is the target. Intrauterine biopsy offers the opportunity to investigate the intrauterine micro-environment through the analysis of molecular factors that influence endometrial receptivity, but has the disadvantage of causing harm to a super-sensitive area, aiming to endorse a new organism that carries a foreign half-DNA.

To improve this, various pharmaceutical and interventional approaches have been implicated. The administration of peri-implantation glucocorticoids in IVF cycles did not manage to significantly improve the clinical outcome, while insufficient evidence exists for the subgroups of women with autoantibodies, unexplained infertility or recurrent implantation failure [23]. Similarly, when the use of heparin was studied analyzing data from randomized trials, no improvement in clinical pregnancy and live birth rates was found [24]. In contrast the use of "mild" protocols for ovarian stimulation in IVF [25], and the mechanical damage of the endometrium prior to the IVF cycle [26] seem to improve the outcome parameters, both suggesting promising alternatives to conventional protocols and attitudes in IVF.

The hypothesis that individual factors (intrinsic properties of the endometrium) significantly affect endometrial growth [27], came to probability, but phenomenally, it gives an alibi to our inability to understand the underlying mechanisms and pathophysiology and to treat them. Most probably, the complexity of the transition into a receptive uterus, including various biochemical and molecular changes in the endometrium together with the modulated expression of different cytokines, growth factors, transcription factors and prostaglandins and hormone receptors [2], is a key area that has not yet elucidated.

In this article, we would express the urgent need of a better understanding of the underlying mechanisms that drive endometrial receptivity during the luteal phase, proliferation and thickness of the epithelium, the cellular modifications with respect to receptor regulation and expression, as well as signaling and communication patterns that occur at molecular level. That would add to our knowledge of how this complex system responds in hormonal alternation and fluctuation, how receptivity is defined in this framework, and what

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are the intrinsic factors that we could be allowed to experiment with in order to restore receptivity in non-responsive cases and cases with repeated implantation failures, as well as on how to preserve implantation and physiological embryo development. The prospective candidates range from pinopodes as potential markers of receptivity, progesterone responsiveness and integrin function, adhesion molecules with particular interest to RIF-associated mRNAs inflammatory and immunologically mediated byproducts [3,28].

In conclusion, we still do not know fully the why and how, so we are not able to discover the way to improve it. Or isn't it so?

At the moment we could quote the suggestions of Revel [3], where endometrial biopsy samples, or samples obtained through secretions of the uterus, were proposed that could be used to identify molecules associated with uterine receptivity to obtain a better insight into human implantation. We would add that therapeutically, anatomical malformations should be treated by hysteroscopy, local injure prior to an IVF cycle [29] should be performed, while addition of various molecules to culture media, such as GC-CSF and gene therapy have the potential to constitute the future solutions. Finally, careful selection of patients to apply protocols and individualization of treatment strategies still constitute the cornerstone of success when improvement of IVF outcomes is the target.

References

1. Diedrich K, Fauser BC, Devroey P, Griesinger G; Evian Annual Reproduction (EVAR) Workshop Group (2007) The role of the endometrium and embryo in human implantation. *Hum Reprod Update* 13: 365-377.
2. Paulson RJ (2011) Hormonal induction of endometrial receptivity. *Fertil Steril* 96: 530-535.
3. Revel A (2012) Defective endometrial receptivity. *Fertil Steril* 97: 1028-1032.
4. Simon C, Martin JC, Pellicer A (2000) Paracrine regulators of implantation. *Baillieres Best Pract Res Clin Obstet Gynaecol* 14: 815-826.
5. Garcia E, Bouchard P, De Brux J, Berdah J, Frydman R, et al. (1988) Use of immunocytochemistry of progesterone and estrogen receptors for endometrial dating. *J Clin Endocrinol Metab* 67: 80-87.
6. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, et al. (1992) Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. *J Clin Invest* 90: 188-195.
7. Tabibzadeh S (1992) Patterns of expression of integrin molecules in human endometrium throughout the menstrual cycle. *Hum Reprod* 7: 876-882.
8. Simón C, Cano F, Valbuena D, Remohí J, Pellicer A (1995) Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol levels in high and normal responder patients. *Hum Reprod* 10: 2432-2437.
9. Paulson RJ, Sauer MV, Lobo RA (1990) Embryo implantation after human in vitro fertilization: importance of endometrial receptivity. *Fertil Steril* 53: 870-874.
10. Levi AJ, Drews MR, Bergh PA, Miller BT, Scott RT Jr (2001) Controlled ovarian hyperstimulation does not adversely affect endometrial receptivity in in vitro fertilization cycles. *Ferti Steril* 76: 670-674.
11. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, et al. (2011) Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. *Fertil Steril* 96: 516-518.
12. Richter KS, Shipley SK, Mc Veary I, Tucker MJ, Widra EA (2006) Cryopreserved embryo transfers suggest that endometrial receptivity may contribute to reduced success rates of later developing embryos. *Fertil Steril* 86: 862-866.
13. Orvieto R, Meltzer S, Rabinson J, Zohav E, Anteby EY, et al. (2008) GnRH agonist versus GnRH antagonist in ovarian stimulation: the role of endometrial receptivity. *Fertil Steril* 90: 1294-1296.
14. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, et al. (2011) Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev* 11: CD001750.
15. Friedler S, Schenker JG, Herman A, Lewin A (1996) The role of ultrasonography in the evaluation of endometrial receptivity following assisted reproductive treatments: a critical review. *Hum Reprod Update* 2: 323-335.
16. Schild RL, Knobloch C, Dorn C, Fimmers R, van der Ven H, et al. (2001) Endometrial receptivity in an in vitro fertilization program as assessed by spiral artery blood flow, endometrial thickness, endometrial volume and uterine artery blood flow. *Fertil Steril* 75: 361-366.
17. Engmann L, Sladkevicius P, Agrawal R, Bekir J, Campbell S, et al. (1999) The pattern of changes in ovarian stromal and uterine artery blood flow velocities during In Vitro Fertilization treatment and its relationship with outcome of the cycle. *Ultrasound Obstet Gynecol* 13: 26-33.
18. Ng EH, Chan CC, Tang OS, Yeung WS, Ho PC (2006) The role of endometrial and subendometrial blood flows measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during IVF treatment. *Human Reprod* 21: 164-170.
19. Jarvela IY, Sladkevicius P, Kelly S, Ojha K, Campbell S, et al. (2005) Evaluation of endometrial receptivity during in-vitro fertilization using three-dimensional power Doppler ultrasound. *Ultrasound Obstet Gynecol* 26: 765-769.
20. Lessey BA, Killam AP, Metzger DA, Haney AF, Greene GL, et al. (1988) Immunohistochemical analysis of human uterine estrogen and progesterone receptors throughout the menstrual cycle. *J Clin Endocrinol Metab* 67: 334-340.
21. Issacs JD, Wells CS, William DB, Odem RR, Gast MJ, et al. (1996) Endometrial thickness is a valid monitoring parameter in cycles of ovulation induction with menotropins alone. *Fertil Steril* 65: 262-266.
22. Dechaud H, Bessueille E, Bousquet PJ, Reyftmann L, Hamamah S, et al. (2008) Optimal timing of ultrasonographic and Doppler evaluation of uterine receptivity to implantation. *Reprod Biomed Online* 16: 368-375.
23. Boomsma CM, Keay SD, Macklon NS (2012) Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database Syst Rev* 6: CD005996.
24. Seshadri S, Sunkara SK, Khalaf Y, El-Toukhy T, Hamoda H (2012) Effect of heparin on the outcome of IVF treatment: a systematic review and meta-analysis. *Reprod Biomed Online* 25: 572-584.
25. Gibreel A, Maheshwari A, Bhattacharya S (2012) Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. *Cochrane Database Syst Rev* 11: CD008528.
26. Nastri CO, Gibreel A, Raine-Fenning N, Maheshwari A, Ferriani RA, et al. (2012) Endometrial injury in women undergoing assisted reproductive techniques. *Cochrane Database Syst Rev* 7: CD009517.
27. Scioscia M, Lamanna G, Lorusso F, Serrati G, Selvaggi LE, et al. (2009) Characterization of endometrial growth in proliferative and early luteal phase in IVF cycles. *Reprod Biomed Online* 18: 73-78.
28. Lessey BA (2011) Assessment of endometrial receptivity. *Fertil Steril* 96: 522-529.
29. Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, et al. (2003) Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. *Fertil Steril* 79: 1317-1322.