CHAPTER 15

ENDOMETRIAL CHANGES IN EARLY IMPLANTATION

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What are the main structural changes of the endometrium during implantation?

To better understand endometrial morphological changes in response to implantation, it would be helpful to classify endometrial changes. This classification can be made in two main groups: "general changes of endometrium" and "local changes of endometrium". General changes involves the entire endometrium. Prolongation or elevation of ovarian hormonal levels are important regulators of this process. Localized changes occur in the limited region that blastocyst implantation occurs. Localized changes can exaggerate or limit the general endometrial changes (1).

What is "decidua"?

The special zone in which blastocyst attaches and penetrates the epithelium of the endometrium is called "decidua". Decidua is divided into three basic groups ; (i) Decidua basalis is the area that blastocyst settled on, (ii) Decidua capsularis is an endometrial part that overlying the blastocyst, (iii) Decidua vera/decidua parietalis is the rest of the endometrium (2). The term "Decidualization" refers to the transformation of the stromal compartment of the endometrium undergoing pregnancy (3).

What does "predecidua" mean and what are the histological features of this stage of endometrium?

Edema observed in the superficial stromal cells on the 18th day of the cycle becomes generalized on the 21st day of the cycle. Starting from day 23, there is a significant increase in the cytoplasm of endometrial stromal cells adjacent to terminal spiral arteries. On day 25th edema coveres the vast majority of superficial layer of endometrium and the it was replaced by large cytoplasm of stromal cells and adjacent large endometrial stromal cells with large pale nuclei. At the 27th day of implantation, the superficial layer of endometrium appears almost solidified and endometrial stromal cells differentiate indistinguishably from the decidual cells of pregnant endometrium. This histological features seen at the endometrium is called "predecidua" (4-6).

plugs in the lumens of the spiral arterioles dissipate and significant flow starts within the intervillous space (49,50). Once this flow begins, the feeding task of uterine glands is also transferred to the placenta.

What is hemocorial placentation?

Hemochorial placentation is a type of placentation that forms the maternal-fetal interface in order to facilitate feeding of the formed embryo, to ensure waste exchange and to support the development of healthy offspring(51). In this form of placentation, it is aimed to transfer maternal nutrients first from mother to placenta and then from placenta to fetus.The main feature of this placentation is the vascular reconstruction of the maternal uterine spiral arteries (52,53). Deep endovasculer and interstisyel intrauterine invasion of trophoblasts is the most important step in the formation of hemocorial placentation. As a result of this invasion the smooth muscle of the spiral arteries disappears, basement membrane undergoes restructuring, pseudoendothelial phenotypic alteration occurs in trophoblasts (51).

References

1. Anders CA, Current Topic: Structural Responses of thePrimate Endometrium to Implantation Placenta (1991), 12,3 09-325
2. Anders CA, Current Topic: Structural Responses of the Primate Endometrium to Implantation Placenta (1991),12,3 09-325
3. Gellersen B, Brosens J, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure Endocrine Reviews 35: 851–905, 2014
4. Rock J, Bartlett MK.Biopsy studies of human endometrium: criteria of dating and information about amenorrhea, menorrhagia, and time of ovulation. JAMA. 1937;108:2022–2028.
5. Gellersen B, Brosens J, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure Endocrine Reviews 35: 851–905, 2014
6. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril. 1950;1:3–25.
7. Croy BA. Uterine natural killer cells: a specialized differentiation regulated by ovarian hormones. Immunol Rev. 2006;214:161–185.
8. Chazara O, Xiong S, Moffett A. Maternal KIR and fetal HLA-C: a fine balance. J Leukoc Biol. 2011;90:703–716.
9. van den Heuvel MJ, Chantakru S, Xuemei X, et al. Trafficking of circulating pro-NK cells to the decidualizing uterus: regulatory mechanisms in the mouse and human.Immunol Invest. 2005;34:273–293.
10. Xiong S, Sharkey AM, Kennedy PR, et al. Maternal uterine NK cell-activating receptor KIR2DS1 enhances placentation. J Clin Invest. 2013;123:4264–4272.
11. Gellersen B, Brosens J, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure Endocrine Reviews 35: 851–905, 2014
12. Price TM, Fertilization and Embryogenesis: Meiosis, Fertilization, Implantation, Embryonic Development, Sexual Differentiation, Comprehensive Gynecology, 1, 1-21
13. Maruyama and Yoshimura, 2008. Maruyama T., and Yoshimura Y.: Molecular and cellular mechanisms for differentiation and regeneration of the uterine endometrium. Endocr J 2008; 55: pp. 795-810

14. Cornillie FJ, Lauweryns JM, Brosens IA. Normal human endometrium. An ultrastructural survey. Gynecol ObstetInvest. 1985;20:113–129.
15. Lawn AM, Wilson EW, Finn CA. The ultrastructure of human decidual and predecidual cells. J Reprod Fertil. 1971;26:85–90.
16. Kajihara T, Tanaka K, Oguro T, et al. Androgens modulate the morphological characteristics of human endometrial stromal cells decidualized in vitro. Reprod Sci. 2014; 21:372–380.
17. Chen GT, Getsios S, MacCalman CD. Cadherin-11 is a hormonally regulated cellular marker of decidualization in human endometrial stromal cells. Mol Reprod Dev. 1999; 52:158–165.
18. MacCalman CD, Getsios S, Chen GT. Type 2 cadherins in the human endometrium and placenta: their putative roles in human implantation and placentation. Am J ReprodImmunol. 1998;39:96–107.
19. Iwahashi M, Muragaki Y, Ooshima A, et all. Alterations in distribution and composition of theextracellular matrix during decidualization of the human endometrium. J Reprod Fertil. 1996;108:147–155.
20. Gellersen B, Brosens J, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure Endocrine Reviews 35: 851–905, 2014
21. Price TM, Fertilization and Embryogenesis: Meiosis, Fertilization, Implantation, Embryonic Development, Sexual Differentiation, Comprehensive Gynecology, 1, 1-21
22. Beswick I.P., Gregory M.M. The aries stella Phenomenon and the diagnosis of pregnancy. BJOG:An İnternational Journal of Obstetrics and Gynecology,78(2),143-148.
23. Arias-Stella, 2002. Arias-Stella J.: The Arias-Stella reaction: facts and fancies four decades after. Adv Anat Pathol 2002; 9: pp. 12-23
24. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005.
25. Psychoyos, A. Endocrine Control of Egg Implantation (American Physiology Society, Washington, D.C., 1973).
26. Paria, B.C., Huet-Hudson, Y.M. & Dey, S.K. Blastocyst's state of activity determines the "window" of implantation in the receptive mouse uterus. Proc. Natl. Acad. Sci. USA 90, 10159–10162 (1993).
27. Vinketova K, Mourdjeva M, Oreshkova T. Human decidual stromal cells as a component of the implantation niche and a modulator of maternal immunity. J Pregnancy. 2016;2016:8689436.
28. Mori M, Bogdan A, Balassa T, Csabai T, Szekeres-Bartho J. The decidua-the maternal bed embracing the embryo-maintains the pregnancy. Semin Immunopathol. 2016;38:635-649.
29. Okada H, Tsuzuki T, Murata H, Decidualization of the human endometrium, Reprod Med Biol. 2018 Jul; 17(3): 220–227.
30. Maslar IA, Riddick DH. Prolaktin production by human endometrium during the normal menstruel cycle. Am J Obstet Gynecol. 1979;135:751-754
31. Garrido-Gomez T, Dominguez F, Quinonero A, et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology. Proc Natl Acad Sci USA. 2017;114:E8468-E8477
32. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev. 2014;35:851-905.
33. Sharma S, Godbole G, Modi D. Decidual control of trophoblast invasion. Am J Reprod Immunol. 2016;75:341-350.
34. Okada H, Tsuzuki T, Murata H, Decidualization of the human endometrium, Reprod Med Biol. 2018 Jul; 17(3): 220–227.
35. Virdis A, Dell'Agnello U, Taddei S. Impact of inflammation on vascular disease in hypertension. Maturitas. 2014;78:179-183.
36. Carmeliet P. Angiogenesis in health and disease. Nat Med. 2003;9:653-660

37. Nishigaki A, Okada H, Okamoto R, et al. The concentration of human follicular fluid stromal cell-derived factor-1 is correlated with luteinization in follicles. Gynecol Endocrinol. 2013;29:230-234.
38. Okada H, Tsuzuki T, Murata H, Decidualization of the human endometrium, Reprod Med Biol. 2018 Jul; 17(3): 220–227.
39. Tsuzuki T, Okada H, Shindoh H, et all. Effects of the hypoxia-inducible factor-1 inhibitor echinomycin on vascular endothelial growth factor production and apoptosis in human ectopic endometriotic stromal cells. Gynecol Endocrinol. 2016;32:323-328.
40. Hey-Cunningham AJ, Peters KM, Zevallos HB, et all. Angiogenesis, lymphangiogenesis and neurogenesis in endometriosis. Front Biosci (Elite Ed). 2013;5:1033-1056.
41. Hannan NJ, Stephens AN, Rainczuk A, et all. 2D–DiGE analysis of the human endometrial secretome reveals differences between receptive and nonreceptive states in fertile and infertile women. J Proteome Res. 2010; 9:6256–6264
42. Hempstock J, Cindrova-Davies T, Jauniaux E, et all. Endometrial glands as a source of nutrients, growth factors and cytokines during the first trimester of human pregnancy: A morphological and immunohistochemical study. Reproductive Biology and Endocrinology. 2004; 2:58,
43. Burton GJ, Scioscia M, Rademacher TW. Endometrial secretions: creating a stimulatory microenvironment within the human early placenta and implications for the aetiopathogenesis of preeclampsia. J Reprod Immunol. 2011; 89:118–125
44. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. Nat Med. 2012; 18:1754–1767
45. Dimitriadis E, Stoikos C, Stafford-Bell M,et all. Interleukin-11, IL-11 receptoralpha and leukemia inhibitory factor are dysregulated in endometrium of infertile women with endometriosis during the implantation window. Journal of reproductive immunology. 2006; 69:53–64
46. Filant J, Spencer TE, Uterine glands: biological roles in conceptus implantation, uterine receptivity, and decidualization, Int J Dev Biol. 2014 ; 58(0): 107–116
47. Burton GJ, Scioscia M, Rademacher TW. Endometrial secretions: creating a stimulatory microenvironment within the human early placenta and implications for the aetiopathogenesis of preeclampsia. J Reprod Immunol. 2011; 89:118–125
48. Wooding, FBP.; Burton, GJ. Comparative Placentation: Structures, Functions and Evolution. Berlin: Springer; 2008
49. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am J Pathol. 2000; 157:2111–2122
50. Filant J, Spencer TE, Uterine glands: biological roles in conceptus implantation, uterine receptivity, and decidualization, Int J Dev Biol. 2014 ; 58(0): 107–116
51. Soares MJ, Chakraborty D, Karim Rumi MA, et all. Rat placentation: An experimental model for investigating the hemochorial maternal-fetal interface. Placenta 33 (2012) 233-243
52. Red-Horse K, Zhou Y, Genbacev O, et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. J Clin Invest 2004;114:744e54.
53. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006;27:939e58.