

GİRİŞ

FERTİLİZASYON

Spermin Kapasitasyonu
Akrozom Reaksiyonu
Spermin Korona Radiataya Penetrasyonu
Spermin Zona Pellusidaya Penetrasyonu
Oosit Ve Sperm Hücre Membranlarının Füzyonu
Erkek Ve Dişi Pronükleusların Gelişimi
Zigotun Gelişimi
Erken Embriyoner Gelişim; Klivaj Evresi
Erken Embriyoner Gelişim; Blastosist Evresi

İmplantasyon

Endometriyal Reseptivite
İmplantasyonun Aşamaları Ve Moleküler Mekanizmalar
Apozisyon
Adezyon
İnvazyon
Maternal İmmün Sistem
Endometriyal Kabul Edilebilirlikte Mirna'lar
Endometriyal Reseptivitenin Değerlendirilmesinde Yeni Yaklaşımlar
KAYNAKLAR

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Oosit ve spermin çekirdek ve sitoplazmik komponentlerinin katılımıyla gerçekleşen, embriyonik hayatın başlangıç noktasını oluşturan bir olaylar dizisidir. Fertilizasyonun amacı haploid yapıda germ hücrelerinin birleşerek, anne ve babanın kromozomlarına sahip, diploid yapıda zigotun oluşumudur. Fertilizasyon biparental kalıtım ve insan türünün çeşitliliğinin temelini oluşturur.

Pubertenin başlamasıyla birlikte her bir ovaryan siklusta 15-20 primer folikül (preantral folikül) FSH etkisiyle büyümeye başlar. Normal şartlarda tek primer folikül matürasyonunu ta-

mamlar ve yalnız bir primer oosit I. mayozunu tamamlayarak sekonder oosit olarak ovaryumdan ovule olur. Tuba uterina ritmik olarak kasılmaya başlar ve fimbria ovarikaları ovaryum yüzeyinin üzerini süpürecek şekilde hareket eder. Granüloza hücreleri ile çevrili olarak ovule olan sekonder oosit fimbriaların hareketi ve tuba uterina epitelindeki siliar aktivitenin etkisiyle tuba uterina içinde ilerler. Tuba uterina içinde granüloza hücreleri (kumulus ooforus) sekonder oositi çevreleyen zona pellusida ile bağlantılarını kaybederler ve oositle temasları kaybolur. Sekonder oosit, fertilizasyon bölgesi olan tuba uterinanın ampullasına kadar ilerler. Bu süreçte sekonder oosit II. mayoz bölünmenin metafaz safhasında beklemeye devam eder (şekil 1).

¹ Bursa Uludağ ÜTF Histoloji-Embriyoloji AD ve Kadın Hastalıkları ve Doğum AD ÜYTE Merkezi

Endometriyum implantasyon penceresi periyodunda endometriyumun fonksiyonunu değerlendirmede yardımcı olan spesifik gen ekspresyonları gösterir. Endometriyal reseptivite testi (ERA testi) bir microarray teknolojidir ve endometriyumun implantasyon penceresinin transkriptomik imzasının tanımlanmasını sağlar. Tekrarlayan implantasyon başarısızlığı olan olgularda ERA kullanımı sonucunda, endometriyum implantasyon penceresi periyodunun yer değiştirdiği, ERA tarafından belirlenen periyodda yapılan embriyo transferlerinin reproduktif performansı arttırdığı gösterilmiştir (Hashimoto, Tan, Sebastian-Leon).

KAYNAKLAR

- Almeida EA, Huovila AP, Sutherland AE, Stephens LE, Calarco PG, Shaw LM, Mercurio AM, Sonnenberg A, Primakoff P, Myles DG and White JM: Mouse egg integrin $\alpha 6 \beta 1$ functions as a sperm receptor. *Cell* 81: 10951104, 1995.
- Bedford JM, Moore HDM and Franklin LE. Significance of the equatorial segment of the acrosome of the spermatozoon in eutherian mammals. *Exp Cell Res* 119: 119126, 1979.
- Bianchi E, Doe B, Goulding D and Wright GJ. Juno is the egg Izumo receptor and is essential for mammalian fertilization. *Nature* 508: 483487, 2014.
- Blobel CP, Myles DG, Primakoff P and White JM. Proteolytic processing of a protein involved in spermegg fusion correlates with acquisition of fertilization competence. *J Cell Biol* 111: 6978, 1990.
- Chang H and Suarez SS. Two distinct Ca(2+) signaling pathways modulate sperm flagellar beating patterns in mice. *Biol Reprod* 85: 296305, 2011.
- Chen H and Sampson NS: Mediation of spermegg fusion. Evidence that mouse egg $\alpha 6 \beta 1$ integrin is the receptor for sperm fertilinbeta. *Chem Biol* 6: 110, 1999b.
- Chen MS, Tung KS, Coonrod SA, Takahashi Y, Bigler D, Chang A, Yamashita Y, Kincade PW, Herr JC and White JM. Role of the integrin-associated protein CD9 in binding between sperm ADAM 2 and the egg integrin $\alpha 6 \beta 1$: Implications for murine fertilization. *Proc Natl Acad Sci USA* 96: 1183011835, 1999a.
- Clyman MJ. A new structure observed in the nucleolus of the human endometrial epithelial cell. *Am J Obstet Gynecol* 86:430-2, 1963.
- Contreras HR and Llanos MN. Detection of progesterone receptors in human spermatozoa and their correlation with morphological and functional properties. *Int J Androl* 24: 246252, 2001.
- Cornillie FJ, Lauweryns JM, Brosens IA. Normal human endometriyum. An ultrastructural survey. *Gynecol Obstet Invest* 20:113-29, 1985.
- Cox LJ, Larman MG, Saunders CM, Hashimoto K, Swann K, Lai FA. Sperm phospholipase C ζ from humans and cynomolgus monkeys triggers Ca²⁺ oscillations, activation and development of mouse oocytes. *Reproduction* 124: 611-623, 2002.
- de Lamirande E, Harakat A and Gagnon C: Human sperm capacitation induced by biological fluids and progesterone, but not by NADH or NADPH, is associated with the production of superoxide anion. *J Androl* 19: 215-225, 1998.
- Deguchi R, Shirakawa H, Oda S, Mohri T, Miyazaki S. Spatio-temporal analysis of Ca(2+) waves in relation to sperm entry site and animal-vegetal axis during Ca(2+) oscillations in fertilized mouse eggs. *Developmental Biology* 218:299-313, 2000.
- Dimitriadis E, White CA, Jones RL, Salamonsen LA. Cytokines, chemokines and growth factors in endometriyum related to implantation. *Hum Reprod. Update* 11(6): 613-630, 2005.
- Dockery P, Li TC, RogersAW, Cooke ID, Lenton EA, WarrenMA. An examination of the variation in timed endometrial biopsies. *Hum Reprod* 3:715-20, 1988.
- Dubrauszky V, Pohlmann G. Strukturveränderungen am Nucleolus von Korpusendometriyumzellen während der Sekretionsphase. *Naturwissenschaften* 47:523-524, 1960.
- Ebensperger C and Barros C. Changes at the hamster oocyte surface from the germinal vesicle stage to ovulation. *Gamete Res* 9: 387397, 1984.
- Ernesto JI, Weigel Muñoz M, Battistone MA, Vasen G, MartínezLópez P, Orta G, FigueirasFierro D, De la VegaBeltaran JL, Moreno IA, Guidobaldi HA, et al. CRISP1 as a novel CatSper regulator that modulates sperm motility and orientation during fertilization. *J Cell Biol* 210: 12131224, 2015.
- Eto K, Huet C, Tarui T, Kupriyanov S, Liu HZ, PuzonMcLaughlin W, Zhang XP, Sheppard D, Engvall E and Takada Y. Functional classification of ADAMs based on a conserved motif for binding to integrin $\alpha 9 \beta 1$: Implications for spermegg binding and other cell interactions. *J Biol Chem* 277: 1780417810, 2002.
- Evans J, Salamonsen AL, Winship A, Menkhorst E, Nie G, Gargett CE, Dimitriadis E. Fertile ground: human endometrial programming and lessons in health and disease. *Nature Reviews Endocrinology* 12: 654-667, 2016.
- Evans JP and Florman HM. The state of the union: the cell biology of fertilization. *Nat Cell Biol* 4: s57s63, 2002.
- Evans JP. The molecular basis of spermocyte membrane interactions during mammalian fertilization. *Hum Reprod Update* 8: 297311, 2002.
- Gardner D.K, Weissman A, Howles C.M, et al. *Textbook of Assisted Reproductive Techniques: Laboratory and Clinical Perspectives* 3th ed. 2009.
- Goodson SG, Qiu Y, Sutton KA, Xie G, Jia W and O'Brien DA. Metabolic substrates exhibit differential effects on functional parameters of mouse sperm capacitation. *Biol Reprod* 87: 75, 2012.
- Gordon M. Cyclic changes in the fine structure of the epithelial cells of human endometriyum. *Int Rev Cytol* 42:127-72, 1975.

- Guffanti E, Kittur N, Brodt ZN, Polotsky AJ, Kuokkanen SM, Heller DS, et al. Nuclear pore complex proteins mark the implantation window in human endometrium. *J Cell Sci* 121:2037-45, 2008.
- Hashimoto T, Koizumi M, Toya M, Sagara E, Oka N, Nakajo Y, Aono N, Igarashi H, Kyono K. Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study. *Reprod Med Biol* 16: 290-296, 2017.
- Huang TTF Jr and Yanagimachi R. Inner acrosomal membrane of mammalian spermatozoa: Its properties and possible functions in fertilization. *Am J Anat* 174: 249268, 1985.
- Ickowicz D, Finkelstein M and Breitbart H. Mechanism of sperm capacitation and the acrosome reaction: Role of protein kinases. *Asian J Androl* 14: 816821, 2012.
- Inoue N, Ikawa M, Isotani A and Okabe M: The immunoglobulin superfamily protein Izumo is required for sperm to fuse with eggs. *Nature* 434: 234238, 2005.
- Ito J, Kashiwazaki N. Molecular mechanism of fertilization in the pig. *Animal Science Journal* 83: 669–682, 2012.
- Jégou A, Ziyat A, BarraudLange V, Perez E, Wolf JP, Pincet F and Gourier C. CD9 tetraspanin generates fusion competent sites on the egg membrane for mammalian fertilization. *Proc Natl Acad Sci USA* 108: 1094610951, 2011.
- Johnson MH, Eager D, MuggletonHarris A and Grave HM. Mosaicism in organisation concanavalin A receptors on surface membrane of mouse egg. *Nature* 257: 321322, 1975.
- Kaji K, Oda S, Shikano T, Ohnuki T, Uematsu Y, Sakagami J, Tada N, Miyazaki S and Kudo A. The gamete fusion process is defective in eggs of Cd9deficient mice. *Nat Genet* 24: 279282, 2000.
- Kline D, Kline JT. Repetitive calcium transients and the role of calcium in exocytosis and cell activation in the mouse egg. *Developmental Biology* 149: 80-89, 1992.
- Kouchi Z, Fukami K, Shikano T, Oda S, Nakamura Y, Takehana T, Miyazaki S. Recombinant phospholipase Czeta has high Ca²⁺ sensitivity and induces Ca²⁺ oscillations in mouse eggs. *Journal of Biological Chemistry* 279: 10408–10412, 2004.
- Laird SM, Tuckerman EM, Li TC. Cytokine expression in the endometrium of women with implantation failure and recurrent miscarriage. *Reprod Biomed Online* 13(1): 13-13, 2006.
- Le Naour F, Rubinstein E, Jasmin C, Prenant M and Boucheix C. Severely reduced female fertility in CD9deficient mice. *Science* 287: 319321, 2000.
- Ledee-Bataille N, Lapree-Delage G, Taupin JL, Dubanchet S, Taieb J, Moreau JF, Chaouat G. Follicular fluid concentration of leukaemia inhibitory factor is decreased among woman with polycystic ovarian syndrome during assisted reproduction cycles. *Hum Reprod.* 16(10): 2073-2078, 2001.
- Liang J, Wang S, Wang Z. Role of microRNAs in embryo implantation. *Reprod. Biol.Endoc.* 15:90, 2017.
- Lishko PV, Kirichok Y, Ren D, Navarro B, Chung JJ and Clapham DE. The control of male fertility by spermatozoan ion channels. *Annu Rev Physiol* 74: 453475, 2012.
- LópezTorres AS and Chirinos M. Modulation of human sperm capacitation by progesterone, estradiol, and luteinizing hormone. *Reprod Sci* 12: 19, 2016.
- Meng FM, Zapantis G, Williams SZ, Lieman HJ, Buyuk E, Meier UT. Status of nucleolar channel systems in uterine secretions accurately reflects their prevalence-a marker for the window of implantation-in simultaneously obtained endometrial biopsies. *Fertil Steril* 109: 165-171, 2018.
- Miyado K, Yamada G, Yamada S, Hasuwa H, Nakamura Y, Ryu F, Suzuki K, Kosai K, Inoue K, Ogura A, et al. Requirement of CD9 on the egg plasma membrane for fertilization. *Science* 287: 321324, 2000.
- Moore, K.L., Persaud, T.V.N. & Torchia, M.G. *The developing human: clinically oriented embryology* (10th ed.). Philadelphia: Saunders 2015.
- More IA, McSeveney D. The three dimensional structure of the nucleolar channel system in the endometrial glandular cell: serial sectioning and high voltage electron microscopic studies. *J Anat* 130:673–82, 1980.
- Moricard R, Moricard F. Modifications cytoplasmiques et nucléaires ultrastructurales utérines au cours de l'état folliculo-lutéinique à glycogène massif. *Gynecol Obstet* 63:203–19, 1964.
- Morton H, Cavanagh AC, Athanasas-Plathis S, Quinn KA, Rolfe BE. Early pregnancy factor has immunosuppressive and growth factor properties. *Reprod Fertil Dev.* 4(4):411-422, 1992.
- Nomikos M, Yu Y, Elgmati K, Theodoridou M, Campbell K, Vassilakopoulou V, Zikos C, Livaniou E, Amso N, Nounesis G et al. Phospholipase Czeta rescues failed oocyte activation in a prototype of male factor infertility. *Fertility and Sterility* 99: 76–85, 2013.
- Obermair A, Obruca A, Pöhl M, Kaider A, Vales A, Leodolter S, Wojta J, Feichtinger W. Vascular endothelial growth factor and its receptors in male fertility. *Fertility and Sterility* 72(2):269-275, 1999.
- Okabe M. The cell biology of mammalian fertilization. *Development* 140: 44714479, 2013.
- Ozil JP, Markoulaki S, Toth S, Matson S, Banrezes B, Knott JG, Schultz RM, Huneau D, Ducibella T. Egg activation events are regulated by the duration of a sustained (Ca²⁺) cyt signal in the mouse. *Developmental Biology* 282: 39-54; 2005.
- Perez-Perez A, Toro A, Vilarino-Garcia T, Maymo J, Guadix P, Duenas JL, Fernandez-Sanchez M, Varone C, Sanchez-Margalet V. Leptin action in normal and pathological pregnancies. *J Cell Mol. Med.* 22(2): 716-727, 2018.
- Rogers NT, Hobson E, Pickering S, Lai FA, Braude P, Swann K. Phospholipase Czeta causes Ca²⁺ oscillations and parthenogenetic activation of human oocytes. *Reproduction* 128: 697–702, 2004.
- Roldan ER, Murase T and Shi QX. Exocytosis in spermatozoa in response to progesterone and zona pellucida. *Science* 266: 15781581, 1994.
- Rybak EA, Szymga MJ, Zapantis G, Rausch M, Beshay VE, Polotsky AJ, et al. The nucleolar channel system reliably marks the midluteal endometrium regardless of fertility status: a fresh look at an old organelle. *Fertil Steril* 95:1385–9, 2011.

- Sadler, T W (Thomas W); Langman, Jan. Medical embryology. 12th ed. / T.W. Sadler. Philadelphia : Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.
- Saunders CM, Larman MG, Parrington J, Cox LJ, Royse J, Blayney LM, Swann K, Lai FA. PLC ζ : a sperm-specific trigger of Ca $^{2+}$ oscillations in eggs and embryo development. *Development* 129: 3533–3544, 2002.
- Sebastian-Leon P, Garrido N, Remohi J, Pellicer A, Diaz-Gimeno P. Asynchronous and pathological windows of implantation: two causes of recurrent implantation failure. *Hum Reprod.* 33(4):626-635, 2018.
- Spornitz UM. The functional morphology of the human endometrium and decidua. *Adv Anat Embryol Cell Biol* 124:1–99, 1992.
- Stein KK, Primakoff P and Myles D: Spermegg fusion. Events at the plasma membrane. *J Cell Sci* 117: 62696274, 2004.
- Tan J, Kan A, Hitkari J, Taylor B, Tallon N, Warraich G, Yuzpe A, Nakhuda G. The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers. *J Assist Reprod Genet.* <http://orcid.org/0000-0003-3701-2382>, 2017.
- Terzakis JA. The nucleolar channel system of human endometrium. *J Cell Biol* 27:293–304, 1965.
- Tokuhiro K, Ikawa M, Benham AM and Okabe M. Protein disulfide isomerase homolog PDILT is required for quality control of sperm membrane protein ADAM3 and male fertility [corrected]. *Proc Natl Acad Sci USA* 109: 38503855, 2012.
- Tsai HD, Chang CC, Hsieh YY, Lo HY. Leukemia inhibitory factor expression in different endometrial locations between fertile and infertile women throughout different menstrual phases. *J Assist Reprod Genet.* 17(8): 415-418, 2000.
- Visconti PE, Ning X, Fornés MW, Alvarez JG, Stein P, Connors SA and Kopf GS. Cholesterol efflux mediated signal transduction in mammalian sperm: Cholesterol release signals an increase in protein tyrosine phosphorylation during mouse sperm capacitation. *Dev Biol* 214: 429443, 1999.
- Vishram S. Textbook of Clinical Embryology 1st Edition. Elsevier India 2013
- Wu JT, Chiang KC and Cheng FP. Expression of progesterone receptor(s) during capacitation and incidence of acrosome reaction induced by progesterone and zona proteins in boar spermatozoa. *Anim Reprod Sci* 93: 34-45, 2006.
- Wynn RM, Woolley RS. Ultrastructural cyclic changes in the human endometrium.II. Normal postovulatory phase. *Fertil Steril* 18:721–38, 1967.
- Yanagimachi R and Noda YD. Physiological changes in the postnuclear cap region of mammalian spermatozoa: A necessary preliminary to the membrane fusion between sperm and egg cells. *J Ultrastruct Res* 31: 486493, 1970.
- Yanagimachi R. The Physiology of Reproduction. Raven Press, New York, NY, pp189317, 1994.
- Yoneda A, Kashima M, Yoshida S, Terada K, Nakagawa S, Sakamoto A, Hayakawa K, Suzuki K, Ueda J, Watanabe T. Molecular cloning, testicular postnatal expression, and oocyte-activating potential of porcine phospholipase Czeta. *Reproduction* 132: 393–401, 2006.
- Zhu X and Evans JP. Analysis of the roles of RGD binding integrins, $\alpha(4)/\alpha(9)$ integrins, $\alpha(6)$ integrins, and CD9 in the interaction of the fertilin β (ADAM2) disintegrin domain with the mouse egg membrane. *Biol Reprod* 66: 11931202, 2002.