Bölüm
4

MATERNAL PLASENTAL FETAL ÜNİTE

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1. GİRİŞ

Fertilizasyonla başlayan doğuma kadar süre olan ortalama 280 günlük insan gebeliğinin başarıyla sonuçlanması için hemen tüm sistemlerin etkilendiği mükemmel bir değişim süreci ve adaptasyon gerektirir. Fertilizasyonla endometriumun hazırlanması, blastokistin implantasyonu, parturasyon süreci trofoblastlar ile endometrium-desidua arasındaki etkileşimle başlar. Birbirinden farklı immünolojik sisteme sahip olan anne ile fetüsün beraber yaşayabilmesi için eşsiz immünolojik modifikasyon, endokrin ve parakrin modifikasyonlar ile gerçekleşir. Plasenta anne ile fetüs arasında eşsiz bir iletişim, alışveriş ve aynı zamanda bariyer görevi görür. Bu bölümde anne ile fetüs arasında kurulan özelleşmiş endokrinolojik, immünolojik düzenlenmelerin yanında implantasyon, plasenta ve fetal membranlar açıklanmıştır.

2. FERTİLİZASYON VE İMPLANTASYON

Matür oosit (23 kromozomlu) tubada fertilize olduktan sonra zigota (46 kromozomlu diploid hücre) dönüşür. Zigot bölünürken oluşan her bir hücreye blastomer adı verilir. Bölünme sonucunda oluşan 16 blastomerli evreye morula adı verilir ve bu evrede (fertilizasyonydan yaklaşık 3-4 gün sonra) uterin boşluğa girer (1, 2).

Blastomerlerin arasına sıvı toplanması sonucu oluşan yapıya blastokist adı verilir. Fertilizasyondan yaklaşık 4 gün sonra 58 hücreli blastula'nın dışta yer alan 53 hücresi trofoblast gelişimini (trofoektoderm) içte yer alan 5 hücresi embriyo gelişimini sağlayacaktır. Beşinci günde yaklaşık 0.155 mm boyutuna ulaşan 107 hücreli blastokistin 8 hücresi embrio oluşumundan sorumluyken 99 hücresi trofobalstların oluşumundan sorumludur (2).

Zona pellusidadan kurtulan blastokist sitokinler ve hormonlar aracılığıyla direkt edometrium reseptivitesini etkiler. Blastokis erken dönemde IL1α, IL1B ve BHCG salgılayarak endometriumu uyarır (3, 4). Endometriumda bu uyaranlara cevap olarak koloni stimulan faktör (CSF-1) ve lösemi inhibitör faktör (LİF) salgılar (4). Bunlar trofoblastlardan proteaz üretimini uyarır. Bu proteazlar seçilimiş ektrasellüler matriks proteinleri yıkar ve trofoblast invazyonuna izin verir. Bu yüzden embryo hatching başarılı gebelik için kritik öneme sahiptir(5).

Blastokist İmplantasyonu

Fertilizasyondan 6-7 gün sonra embryo uterin duvara implante olur. Bu süreç birbirini takip eden üç olayla tamamlaır (5, 6); Bunlar 1) apozislyon, 2) adhesyon, 3) invazyon'dur.

Başarılı bir implantasyon için reseptif endometrium gereklidir, bunun içinde korpus luteumdan uygun bir şekilde salgılanan estrojen ve progesteron salınımı şarttır. Bu reseptivite siklusun 20 ile 24 günleriyle sınırlıdır (7). Blastokistin hücre implantasyon sahasında bulunan hücre yüzey reseptörleri ile blastokist yüzey reseptörleri arasında meydana gelen etkileşimle gerçekleşir.

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10. SONUÇ

Fertilizasyonla beraber endometriuma gelen sinyaller endometriumu başarılı bir gebelik için hazırlanmasını sağlar ve desidualizasyon başlar. İmplantasyonla beraber trofoblastlar maternal endometriumu invaze eder. Bu süreçte maternal immün yanıt modifikasyonu gerçekleşirken plasentasyon için temeller atılmış olur.

Plasenta semiallojenik fetüs'ün maternal toleransını artırırken ve besin, gaz ve antikorların seçici alışverişini yaparken aynı zamanda embriyoyu fizyolojik olarak oluşabilecek zararlı etkilerden korur. Plasentanın bu kritik fonksiyonlarında meydana gelen herhangi bir sıkıntı abortus, fetüsa karşı otoimmün yanıt ve sonrasında meydana gelen sıkıntılar, intrauterin gelişme gerilikleri, fetal hipoksi, fetal nörolojik sitem sıkıntıları, preeklampsi gibi sıkıntılar kaçınılmaz olur.

Oluşan gebeliğin devamı için fetüs ve plasentadan gelen bu sinyallere annenin uygun bir şekilde yanıtlar oluşturması şarttır. Bunlar başta immünolojik olmak üzere endokrin ve daha sonraki bölümlerde anlatılacak olan kardiyovasküler, solunum, gis vs gibi tüm sistemleri kapsamaktadır.

Anahtar Kelimeler: Amnion, , Desidua, Koryon, İmplantasyon, Plasenta gelişimi

Kaynakça

1. Primakoff, Paul, and Diana G. Myles. Penetration, adhesion, and fusion in mammalian sperm-egg interaction. Science. 2002;296:2183-85.
2. Cunningham, F. G., Leveno, K. J., Bloom, S. L., et al. Placentation, embryogenesis, and fetal development. Willimas obstetrics. 24th ed. New York: McGraw-Hill Education/Medical. 2014; 106-15.
3. Frank GR, Brar AK, Jikihara H, et al. Interleukin-1 beta and the endome-trium: an inhibitor of stromal cell differentiation and possible autoregulator of decidualization in humans. Biol Reprod. 1995;52:184-191.
4. O Guzeloglu-Kayisli, UA Kayisli, Taylor, H. S . et al. The role of growth factors and cytokines during implantation: endocrine and paracrine interactions." Seminars in reproductive medicine. © Thieme Medical Publishers. 2009; 27: 062-079.
5. Nikas, George. Cell-surface morphological events relevant to human implantation. Human Reproduction 14. suppl_2. 1999; 37-44.
6. Lessey B.A, Bruce A, Castelbaum AJ. Integrins and implantation in the human. Rev Endocr Metab Disord 2002; 3.2: 107-117.
7. Lessey BA, Ilesanmi AO, Lessey MA, et al. 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.
8. Navot D, Bergh P. Preparation of the human endometrium for implantation. Ann N Y Acad Sci. 1991; 622:212-219.
9. Licht P, Russu V, Wildt L. On the role of human chorionic gonadotropin (hCG) in the embryo-endometrial microenvironment: implications for dif-ferentiation and implantation. Semin Reprod Med. 2001;19:37-48.
10. Lindhard A, Bentin-Ley U, Ravn V, et al. Biochemical evaluation of endome-trial function at the time of implantation. Fertil Steril. 2002; 78:221-233.
11. Staun-Ram E, Shalev E: Human trophoblast function during the implantation process. Reprod Biol Endocrinol. 2005;3:56
12 . Kaneko Y, Murphy CR, Day ML et al. Extracellular matrix proteins secreted from both the endometrium and the embryo are required for attachment: a study using a co-culture model of rat blastocysts and Ishikawa cells. J Morphol. 2013;274.1: 63-72.
13. Pijnenborg R, Bland JM, Robertson WB, et al. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta. 1983; 4.4: 397-413.
14. Rogers PA, Donoghue JF, Walter LM, et al: Endometrial angiogenesis, vascular maturation, and lymphangiogenesis. Reproductive Sciences. 2009; 16.2: 147-151.
15. Lala PK, Lee BP, Xu G, et al. Human placental trophoblast as an in vitro model for tumor progression. Can J Physiol Pharmacol. 2002; 80.2: 142-149
16. McCombs H, Craig M. Decidual necrosis in normal pregnancy. Obstet-Gynecol. 1964; 24.3: 436-442.
17. Loke YM, King A. (1995) Human Implantation. Cell Biology and Immunology. Cambridge, Cambridge University Press.
18. Manaster I, Mizrahi S, Goldman-Wohl D, et al. Endometrial NK cells are special immature cells that await pregnancy. J Immunol. 2008; 181.3: 1869-1876.
19. Santoni S, Zingoni A, Cerboni C, et al. Natural killer (NK) cells from killers to regulators: distinct features between peripheral blood and decidual NK cells. Am J Reprod Immunol. 2007; 58.3: 280-288.
20. Hanna J, Goldman-Wohl D, Hamani Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006, 12.9: 1065.
21. Jiang Y, Hu Y, Zhao J, et al. The orphan nuclear receptor Nur77 regulates decidual prolactin expression in human endometrial stromal cells. Biochem Biophys Res Commun. 2011; 404.2: 628-633.
22. Lynch VJ, Brayer K, Gellersen B. HoxA-11 and FOXO1A cooperate to regu-late decidual prolactin expression: towards inferring the core transcriptional regulators of decidual genes. PLoS One. 2009; 4.9: e6845.
23. Riddick DH, Luciano AA, Kusmik WF, et al. Evidence for a nonpituitary source of amniotic fluid prolactin. Fertil Steril. 1979; 31.1: 35-39
24. Golander A, Hurley T, Barrett J, et al. Prolactin synthesis by human chorion-decidual tissue: a possible source of prolactin in the amniotic fluid. Science. 1978; 202.4365: 311-313.

25. Jabbour HN, Critchley HOD. Potential roles of decidual prolactin in early pregnancy. Reproduction. 2001; 121.2: 197-205.
26. Tyson JE, Hwang P, Guyda H, et al. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol. 1972; 113.1: 14-20.
27. Knöfler, M., Haider, S., & James, J. (2019). Human placenta and trophoblast development: key molecular mechanisms and model systems. Cellular and Molecular Life Sciences, 1-18.
28. Kaufmann P, Scheffen I. (1992) Placental development. In Polin R, Fox W (eds), p47: Fetal and Neonatal Physiology. Philadelphia: Saunders.
29. Arnholdt H, Meisel F, Fandrey K, et al. Proliferation of villous trophoblast of the human placenta in normal and abnormal pregnancies. Virchows Arch B Cell Pathol Incl Mol Pathol. 1991; 60.1: 365-372.
30. Hamilton W, Boyd J. Trophoblast in human utero-placental arteries. Nature. 1966; 212.5065: 906.
31. Benirschke, K., Burton, G. J., & Baergen, R. N. (2012). Placental shape aberrations. In Pathology of the human placenta (pp. 377-393). Springer, Berlin: Heidelberg.
32. Enders AC: A comparative study of the fine structure in several hemochorial placentas. Am J Anat. 1965; 116.1: 29-67.
33. King BF, Menton DN. Scanning electron microscopy of human placental villi from early and late in gestation. Am J Obstet Gynecol. 1975; 122.7: 824-828.
34. Tabata, T., Petitt, M., Puerta-Guardo et al. Zika virus replicates in proliferating cells in explants from first-trimester human placentas, potential sites for dissemination of infection. The Journal of infectious diseases. 2017; 217.8: 1202-1213
35. Gielen, M., et al. "Placental telomere length decreases with gestational age and is influenced by parity: a study of third trimester live-born twins." Placenta. 2014; 35.10: 791-796.
36. Fu B, Li X, Sun R, et al. Natural killer cells promote immune tolerance by regulating inflammatory TH17 cells at the human maternal-fetal interface. Proc Natl Acad Sci USA . 2013; 110.3: E231-E240.
37. Dunn CL, Critchley HO, Kelly RW. IL-15 regulation in human endometrial stromal cells. J Clin Endocrinol Metab. 2002; 87:1898.
38. Du, M. R., Guo, P. F., Piao, H. L. Et al. (2014). Embryonic trophoblasts induce decidual regulatory T cell differentiation and maternal–fetal tolerance through thymic stromal lymphopoietin instructing dendritic cells. The Journal of Immunology. 2014; 192.4: 1502-1511.
39. Co EC, Gormley M, Kapidzic M, et al. Maternal decidual macrophages inhibit NK cell killing invasive cytotrophoblasts during human pregnancy. Biol Reprod. 2013; 88.6: 155, 1-9.
40. Johnson PM, Christmas SE, Vince GS. Immunological aspects of implantation and implantation failure. Hum Reprod. 1999; 14.suppl_2: 26-36.
41. Vince GS, Johnson PM. Immunobiology of human uteroplacental macrophages—friend and foe? Placenta. 1996; 17.4: 191-199.
42. Thellin O, Coumans B, Zorzi W, et al. Tolerance to the foeto-placental "graft": ten ways to support a child for nine months. Curr Opin Immunol. 2000; 12.6: 731-737.
43. Qin X, Garibay-Tupas J, Chua PK, et al. An autocrine/paracrine role of human decidual relaxin. I. Interstitial collagenase (matrix metalloproteinase-1) and tissue plasminogen activator. Biol Reprod. 1997; 56.4: 800-811.
44. Elliott CL, Allport VC, Loudon JA, et al. Nuclear factor-kappa B is essential for up-regulation of interleukin-8 expression in human amnion and cervical epithelial cells. Mol Hum Reprod. 2001; 7.8: 787-790.
45. Bhaumick B, Dawson EP, Bala RM. The effects of insulin-like growth factor-I and insulin on placental lactogen production by human term placental explants. Biochem Biophys Res Commun. 1987; 144.2: 674-682.
46. Mijovic JE, Demianczuk N, Olson DM, et al. Prostaglandin endoperoxide H synthase mRNA expression in the fetal membranes correlates with fetal fibronectin concentration in the cervico-vaginal fluids at term: evidence of enzyme induction before the onset of labour. Br J Obstet Gynaecol. 2000; 107.2: 267-273.
47. Bonagura TW, Babischkin JS, Aberdeen GC, et al. Prematurely elevating estradiol in early baboon pregnancy suppresses uterine artery remodeling and expression of extravillous placental vascular endothelial growth factor and α1β1 integrins. Endocrinology. 2012; 153.6: 2897-2906.
48. Brosens I, Dixon H. The anatomy of the maternal side of the placenta. Eur J Endocrinol. 1966; 73.3: 357-363.
49. Crawford J. A study of human placental growth with observations on the placenta in erythroblastosis foetalis. Br J Obstet Gynaecol. 1959; 66: 885-896
50. Johnson EL, Chakraborty R: Placental Hofbauer cells limit HIV-1 replication and potentially offset mother to child transmission (MTCT) by induction of immunoregulatory cytokines. Retrovirology. 2012; 9.1: 101.
51. Cervar M, Blaschitz A, Dohr G, et al. Paracrine regulation of distinct trophoblast functions in vitro by placental macrophages. Cell Tissue Res. 1999; 295.2: 297-305.
52. Hertig AT. The placenta: some new knowledge about an old organ. Obstet Gynecol. 1962; 20.6: 859-866.
53. Bourne GL. (1962) The Human Amnion and Chorion. Chicago: Year Book.
54. Borell U, Fernstrom I, Westman A. An arteriographic study of the placental circulation. Geburtshilfe Frauenheilkd. 1958; 18.1: 1
55. Bleker O, Kloostermans G, Mieras D, et al. Intervillous space during uterine contractions in human subjects: an ultrasonic study. Am J Obstet Gynecol. 1975; 123.7: 697-699.
56. Nguyen H, Dubernard G, Aractingi S, et al. Feto-maternal cell trafficking: atransfer of pregnancy associated progenitor cells. Stem Cell Rev. 2006; 2.2: 111-116.
57. Gleicher N, Barad DH: Gender as risk factor for autoimmune diseases. J Autoimmun. 2007; 28.1: 1-6.
58. Greer LG, Casey BM, Halvorson LM, et al. Antithyroid antibodies and parity: further evidence for microchimerism in autoimmune thyroid disease. Am J Obstet Gynecol. 2011; 205.5: 471. e1-471. e4.
59. Stevens AM. Microchimeric cells in systemic lupus erythematosus. targets or innocent bystanders? Lupus. 2006; 15.11: 820-826.
60. Weetman AP. The immunology of pregnancy. Thyroid. 1999; 9.7: 643-646.

61. Hunt JS, Jadhav L, Chu W, et al. Soluble HLA-G circulates in maternal blood during pregnancy. Am J Obstet Gynecol. 2000; 183.3: 682-688.
62. McMaster M, Librach C, Zhou Y, et al. Human placental HLA-G expression is restricted to differentiated cytotrophoblasts. J Immunol. 1995; 154.8: 3771-3778.
63. Billingham RE, Head JR. Recipient treatment to overcome the allograft reaction, with special reference to nature's own solution. Prog Clin Biol Res. 1986; 224: 159-185.
64. Zhu, Bao Ting. Development of selective immune tolerance towards the allogeneic fetus during pregnancy: Role of tryptophan catabolites. International journal of molecular medicine. 2010; 25.6: 831-835.
65. Nemeth E, Tashima LS, Yu Z, et al. Fetal membrane distention: I. Differentially expressed genes regulated by acute distention in amniotic epithelial (WISH) cells. Am J Obstet Gynecol. 2000; 182.1: 50-59.
66. Jeffrey J: Collagen and collagenase. Pregnancy and parturition. Semin Perinatol. 1991; 15.2:118-126
67. Rowe T, King L, MacDonald PC, et al. Tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2 expression in human amnion mesenchymal and epithelial cells. Am J Obstet Gynecol. 1997; 176.4:915-921
68. Mogami H, Kishore AH, Shi H, et al. Fetal fibronectin signaling induces matrix metalloproteases and cyclooxygenase-2 (COX-2) in amnion cells and preterm birth in mice. J Biol Chem. 2013; 288.3: 1953-1966.
69. Economos K, MacDonald PC, Casey ML. Endothelin-1 gene expression and protein biosynthesis in human endometrium: potential modulator of endometrial blood flow. J Clin Endocrinol Metab. 1992; 74.1: 14-19.
70. Carvajal JA, Delpiano AM, Cuello MA, et al. Mechanical stretch increasesbrain natriuretic peptide production and secretion in the human fetal membranes. Reprod Sci. 2013; 20.5: 597-604.
71. Casey ML, MacDonald PC: The endothelin-parathyroid hormone related protein vasoactive peptide system in human endometrium: modulation by transforming growth factor-beta. Hum Reprod. 1996; 11.suppl_2: 62-82.
72. Whittle WL, Gibb W, Challis JR. The characterization of human amnion epithelial and mesenchymal cells: the cellular expression, activity and glucocorticoid regulation of prostaglandin output. Placenta. 2000; 21.4: 394-401.
73. McGregor WG, Kuhn RW, Jaffe RB. Biologically active chorionic gonadotropin: synthesis by the human fetus. Science. 1983; 220.4594: 306-308.
74. McGregor WG, Raymoure WJ, Kuhn RW, et al. Fetal tissue can synthesize a placental hormone. Evidence for chorionic gonadotropin beta-subunit synthesis by human fetal kidney. J Clin Invest. 1981; 68.1: 306-309.
75. Miller-Lindholm AK, LaBenz CJ, Ramey J, et al. Human chorionic gonadotropinbeta gene expression in first trimester placenta. Endocrinology. 1997; 138.12: 5459-5465
76. Morrish DW, Marusyk H, Siy O. Demonstration of specific secretory granules for human chorionic gonadotropin in placenta. J Histochem Cytochem. 1987; 35.1: 93-101.
77. Maruo T, Ladines-Llave CA, Matsuo H, et al. A novel change in cytologic localization of human chorionic gonadotropin and human placental lactogen in first-trimester placenta in the course of gestation. Am J Obstet Gynecol. 1992; 167.1: 217-222.
78. Iwashita M, Kudo Y, Shinozaki Y, et al. Gonadotropin-releasing hormone increases serum human chorionic gonadotropin in pregnant women. Endocr J. 1993; 40.5: 539-544.
79. Cole LA. Immunoassay of human chorionic gonadotropin, its free subunits, and metabolites. Clin Chem. 1997; 43.12: 2233-2243.
80. Bradbury J, Brown W, Guay L. Maintenance of the corpus luteum and physiologic action of progesterone. Recent Prog Horm Res. 1950; 5:151.
81. Hershman JM. Human chorionic gonadotropin and the thyroid: Hyperemesis gravidarum and trophoblastic tumors. Thyroid. 1999; 9.7: 653-657.
82. Duffy DM, Hutchison JS, Stewart DR, et al. Stimulation of primate luteal function by recombinant human chorionic gonadotropin and modulation of steroid, but not relaxin, production by an inhibitor of 3 beta-hydroxysteroid dehydrogenase during simulated early pregnancy. J Clin Endocrinol Metab. 1996; 81.6: 2307-2313.
83. Kane N, Kelly R, Saunders PTK, et al. Proliferation of uterine natural killer cells is induced by hCG and mediated via the mannose receptor. Endocrinology. 2009; 150.6: 2882-2888.
84. Goetzl L, Krantz D, Simpson J. L.et al. Pregnancy-associated plasma protein A, free β-hCG, nuchal translucency, and risk of pregnancy loss. Obstetrics & Gynecology. 2004; 104.1: 30-36.
85. Grumbach MM, Kaplan SL. On placental origin and purification of chorionic growth hormone prolactin and its immunoassay in pregnancy. Trans N Y Acad Sci. 1964; 27.2 Series 2:167-188
86. Walker WH, Fitzpatrick SL, Barrera-Saldana HA, et al. The human placental lactogen genes: structure, function, evolution and transcriptional regulation. Endocr Rev. 1991; 12.4: 316-328.
87. Ghoshal I, Suryakanth V. B, Belle V. S, et al. Role of Maternal Serum Human Placental Lactogen in First Trimester Screening. Indian Journal of Clinical Biochemistry. 2019; 34.3: 318-323.
88. Coya R, Martul P, Algorta J, et al. Progesterone and human placental lactogen inhibit leptin secretion on cultured trophoblast cells from human placentas at term. Gynecol Endocrinol. 2005; 21.1: 27-32.
89. Georgia S, Bhushan A. Pregnancy hormones boost beta cells via serotonin. NatMed. 2010; 16.7: 756.
90. Kim H, Toyofuku Y, Lynn FC; et al. Serotonin regulates pancreatic beta cell mass during pregnancy. Nat Med. 2010; 16.7: 804.
91. Corbacho AM, Martinez DLE, Clapp C et al. Roles of prolactin and related members of the prolactin/growth hormone/placental lactogen family in angiogenesis. J Endocrinol. 2002; 173.2: 219-238.
92. Diczfalusy E, Troen P. Endocrine functions of the human placenta. Vitam Horm.1961; 19:229-311.
93. Henson MC, Greene SJ, Reggio BC, et al. Effects of reduced maternal lipoprotein-cholesterol availability on

placental progesterone biosynthesis in the baboon. Endocrinology. 1997; 138.4: 1385-1391.
94. Simpson ER, Burkhart MF. Acyl CoA:cholesterol acyl transferase activity in human placental microsomes: inhibition by progesterone. Arch Biochem Biophys. 1980; 200:79-85.
95. Casey ML, MacDonald PC. Extraadrenal formation of a mineralocorticosteroid: deoxycorticosterone and deoxycorticosterone sulfate biosynthesis and metabolism. Endocr Rev.1982; 3.4: 396-403.
96. Conneely OM, Mulac-Jericevic B, DeMayo F, et al. Reproductive functions of progesterone receptors. Recent Prog Horm Res. 2002; 57: 339-356.
97. Cui, X., Sun, J., Liang, C., Zheng, Q, et al. "Progesterone promotes embryo adhesion by upregulating c-Fos/c-Jun transcription factor-mediate poFUT1 expression." Biology of reproduction (2019).
98. MacDonald PC. (1965). Placental steroidogenesis. In Wynn RM (ed): Fetal Homeostasis, Vol. I. P 265. New York: New York Academy of Sciences.
99. Siiteri PK, MacDonald PC. Placental estrogen biosynthesis during human pregnancy. J Clin Endocrinol Metab. 1966; 26:751-761.
100. Ryan KJ. Metabolism of C-16-oxygenated steroids by human placenta: the formation of estriol. J Biol Chem. 1959; 234.8: 2006-2008.
101. Baulieu EE, Bricaire H, Jayle MF et al. Lack of secretion of 17-hydroxycorticosteroids in a pregnant woman with Addison's disease. J Clin Endocrinol. 1956; 16.5: 690-693
102. Dombroski RA, Casey ML, MacDonald PC. 5-Alpha-dihydroprogesterone formation in human placenta from 5alpha-pregnan-3beta/alpha-ol-20-ones and 5-pregnan-3beta-yl-20-one sulfate. J Steroid Biochem Mol Biol. 1997; 63.1-3: 155-163.
103. Bonenfant M, Provost PR, Drolet R, et al. Localization of type 1 17beta hydroxysteroid dehydrogenase mRNA and protein in syncytiotrophoblasts and invasive cytotrophoblasts in the human term villi. J Endocrinol. 2000, 165.2: 217-222.
104. Gant NF, Hutchinson HT, Siiteri PK, et al. Study of the metabolic clearance rate of dehydroisoandrosterone sulfate in pregnancy. Am J Obstet Gynecol.1971; 111.4: 555-563.
105. Tulchinsky D , Frigoletto FD J.R , Ryan K.J et al. Plasma estetrol as an index of fetal well-being. The Journal of Clinical Endocrinology & Metabolism, 1975; 40.4: 560-567.
106. Mello, G., and P. Curiel. Urinary estriolin Rh isoimmunization. Annali di ostetricia, ginecologia, medicina perinatale. 1973; 94.1: 44-53.
107. Cassmer, O. Hormone production of the isolated human placenta. European Journal of Endocrinology. 1959; 32.3_Suppl: S9-S82.
108. McCabe ERB. Adrenal hypoplasias and aplasias. (2001). In Scriver CR, Beaudet AL, Sly WE, et al (eds) : The Metabolic and Molecular Bases of Inherited Disease 4263-4274. New York: McGraw-Hill.
109. MacDonald PC, Siiteri PK. Origin of estrogen in women pregnant with ananencephalic fetus. J Clin Invest. 1965; 44.3: 465-474.
110. France JT, Liggins GC: Placental sulfatase deficiency. J Clin Endocrinol Metab. 1969; 29.1: 138-141.
111. Grumbach MM: Aromatase deficiency and its consequences. Adv Exp Med Biol. 2011; 707:19-22.
112. Benn PA. Advances in prenatal screening for Down syndrome: I. General principles and second trimester testing. Clin Chim Acta. 2002; 323.1-2: 1-16.
113. Parker CR Jr, Illingworth DR, Bissonnette J, et al: Endocrinology of pregnancy in abetalipoproteinemia: studies in a patient with homozygous familial hypobetalipoproteinemia. N Engl J Med. 1986; 314:557-560.
114. Kauppila A , Tuimala R , Ylikorkala O et al. "Placental steroid synthesis from DHEAS during dexamethasone therapy." Obstetrics and gynecology. 1979; 54.1: 39-42.
115. MacDonald PC, Siiteri PK. Study of estrogen production in women with hydatidiform mole. J Clin Endocrinol Metab. 1964, 24.8: 685-690.
116. Khodr GS, Siler-Khodr TM. Placental luteinizing hormone-releasing factor and its synthesis. Science. 1980; 207.4428: 315-317.
117. Siler-Khodr TM, Khodr GS, Valenzuela G. Immunoreactive gonadotropin releasing hormone level in maternal circulation throughout pregnancy. Am J Obstet Gynecol. 1984, 150.4: 376-379.
118. Florio P, Mezzesimi A, Turchetti V, et al. High levels of human chromogranin A in umbilical cord plasma and amniotic fluid at parturition. J Soc Gynecol Investig. 2002; 9.1: 32-36.
119. Petraglia F, Florio P, Benedetto C, et al. Urocortin stimulates placental adrenocorticotropin and prostaglandin release and myometrial contractility in vitro. J Clin Endocrinol Metab. 1999:84.4: 1420-1423.
120. Florio P, Franchini A, Reis FM, et al. Human placenta, chorion, amnion and decidua express different variants of corticotropin-releasing factor receptor messenger RNA. Placenta. 2000; 21.1: 32-37.
121. Wadhwa PD, Porto M, Garite TJ, et al. Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. Am J Obstet Gynecol. 1998; 179.4: 1079-1085.
122. Jones SA, Brooks AN, Challis JR. Steroids modulate corticotropin-releasing hormone production in human fetal membranes and placenta. J Clin Endocrinol Metab. 1989; 68.4: 825-830.
123. Nicholson RC, King BR: Regulation of CRH gene expression in the placenta. Front Horm Res. 2001; 27: 246-257.
124. Genazzani AR, Fraioli F, Hurlimann J, et al. Immunoreactive ACTH and cortisol plasma levels during pregnancy. Detection and partial purification of corticotrophin-like placental hormone: the human chorionic corticotrophin (HCC). Clin Endocrinol (Oxf). 1975, 4.1: 1-14.
125. Pérez-Ibave DC, Rodríguez-Sánchez IP, Garza-Rodríguez ML et al. "Extrapituitary growth hormone synthesis in humans." Growth Hormone & IGF Research. 2014; 24.2-3: 47-53.
126. Patel N, Alsat E, Igout A, et al. Glucose inhibits human placental GH secretion, in vitro. J Clin Endocrinol Metab. 1995; 80.5: 1743-1746.
127. Bogic LV, Mandel M, Bryant-Greenwood GD. Relaxin gene expression in human reproductive tissues by in situ hybridization. J Clin Endocrinol Metab. 1995; 80.1: 130-137.

128. Wiest, E, Armbruster F.P, Loeser, E.L et al. Relaxin in amniotic fluid and serum of pregnant patients. Zeitschrift fur Geburtshilfe und Neonatologie. 1997; 201.1: 21-25.
129. Conrad K.P, Davison J.M .The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin?. American Journal of Physiology-Renal Physiology. 2014; 306.10: F1121-F1135.
130. Cock T.A, Auwerx J. Leptin: cutting the fat off the bone. The Lancet. 2003; 362.9395: 1572-1574.
131. Magarinos MP, Sanchez-Margalet V, Kotler M, et al. Leptin promotes cell proliferation and survival of trophoblastic cells. Biol Reprod. 2007, 76.2: 203-210.
132. Henson MC, Castracane VD. Leptin: roles and regulation in primate pregnancy. Semin Reprod Med.2002; 20:113-122,
133. Robidoux J, Simoneau L, St Pierre S, et al. Characterization of neuropeptide Y-mediated corticotropin-releasing factor synthesis and release from human placental trophoblasts. Endocrinology.2000; 141:2795-2804.
134. Bertelloni S, Baroncelli GI, Pelletti A, et al: Parathyroid hormone-related protein in healthy pregnant women. Calcif Tissue Int. 1994; 54.3: 195-197.
135. Simmonds CS, Karsenty G, Karaplis AD, et al: Parathyroid hormone regulates fetal-placental mineral homeostasis. J bone Miner Res 2010;25.3:594.
136. Petraglia F, Woodruff TK, Botticelli G, et al: Gonadotropin-releasing hormone, inhibin, and activin in human placenta: Evidence for a common cellular localization. J Clin Endocrinol Metab. 1992;74:1184
137. Petraglia F, Gallinelli A, De Vita D, et al: Activin at parturition: changes of maternal serum levels and evidence for binding sites in placenta and fetal membranes. Obstet Gynecol. 1994: 84:278-282.