

CHAPTER 31

EFFECTS OF SUPEROVULATION ON ENDOMETRIUM

Ismail BIYIK

What is the histological structure of the endometrium?

The endometrium is histologically composed of endometrial glands and stroma. The superficial 2/3 part is called as the functional layer and the lower 1/3 part is called the basal layer. The functional layer is divided into superficial stratum compactum and deep stratum spongiosum. Epithelial cells are histologically composed of two types: nonciliated cells with microvilli and ciliated cells.

What changes are happening in the menstrual cycle in the endometrium?

With the effect of the hypothalamohypophyseal ovarian axis, in the endometrium, proliferative phase, secretory phase, and menstruation, if pregnancy does not occur, are observed respectively. Before the proliferative phase, the endometrium is thin, and the endometrial glands are flat, narrow and short. At the end of the proliferative phase, endometrial glands become tortuous and long. Histologically, endometrial epithelium having a low columnar pattern in the early proliferative phase have a pseudostratified pattern before ovulation. During the proliferative phase, the stroma dense has a compact structure. In the proliferative phase, although estrogen predominance is present in the endometrium, progesterone effects are seen in addition to the oestrogen effect in the secretory phase. Progesterone acts as an estrogen antagonist in the endometrium. Progesterone reduces the concentration of estrogen receptor in endometrial cells (1). After the seventh day of ovulation, oedema increases in the stroma. When fertilization and implantation do not occur, due to the absence of hCG, the corpus luteum is disrupted and menstruation occurs.

How does ovulation occur?

In women whose menstruation cycle lasts 28 days, ovulation occurs on the 14th day of the cycle. In response to gonadotropins, estrogen is secreted from granulosa cells of ovarian follicles. When estrogen levels reach a critical level, LH surge occurs with positive feedback on the hypothalamus and pituitary. The LH peak activates proteolytic enzymes in the graft follicle and weakens the follicle wall.

adversely affect embryo implantation with supraphysiological E_2 levels and embryo implantation on the day of hCG trigger (90,91). Especially in high responder cases, the endometrium is negatively affected in patients with high progesterone level before hCG trigger. In IVF studies, it was emphasized that freezing and transferring the embryos to the next cycle did not decrease pregnancy rates in those with high P levels (usually $P > 1.5$), thus high P level had negative effects on the endometrium, not on the embryo (92,93).

Prior to oocyte retrieval, the adverse effects of elevated progesterone on endometrium are attributed to changes in endometrial gene levels (77,94) and reduced endometrial receptivity (94), leading to reduced implantation rates of adverse changes.

In GnRH-a/hMG cycles, high levels of E_2 and P on the day of hCG alter gene expression during the implantation period (90,95). In various studies, high progesterone levels in IVF cycles on the day of hCG trigger have been reported to have a negative effect on pregnancy outcomes (96,97). In the IVF cycle, prior to oocyte retrieval, high progesterone levels negatively affect NK mediated cytotoxicity in the endometrium (98).

What are the effects of luteal phase support on the endometrium?

In IVF cycles, ovarian stimulation protocols are often associated with luteal phase defect and poor implantation rates (99,100). In GnRH agonist/hMG cycles, decreased progesterone bioavailability has been shown in the absence of progesterone supplementation (22,101). Therefore, progesterone support is given in order to improve the endometrial structure and facilitate the implantation process in IVF cycles, especially in GnRH agonist cycles (102,103). In COH (controlled ovarioan hyperstimulation) cycles, progesterone supplementation with or without oestrogen does not alter ER alpha and PR expression in the endometrium (104). In GnRH agonist cycles, luteal phase support improves mid-luteal glandular delay (105).

References

1. Ferenczy A, Bertrand G, Gelfand MM. Proliferation kinetics of human endometrium during the normal menstrual cycle. *Am J Obstet Gynecol.* 1979;15;133(8):859-67.
2. Holesh JE, Hazhirkarzar B, Lord M. Physiology, Ovulation. 2019 Oct 19. StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2019 Jan-Available from <http://www.ncbi.nlm.nih.gov/books/NBK441996/>
3. Macklon NS, Stouffer RL, Giudice LC, Fauser BCJM. The science behind 25 years of ovarian stimulation for in vitro fertilization *Endocrine Reviews.* 2006; 27(2):170–207

4. Lessey BA. The role of the endometrium during embryo implantation. *Hum Reprod.* 2000;15 Suppl 6:39-50.
5. Kolb BA, Najmabadi S, Paulson RJ. Ultrastructural characteristics of the luteal phase endometrium in patients undergoing controlled ovarian hyperstimulation. *Fertil Steril.* 1997;67(4):625-30.
6. Psychoyos A, Mandon P. Scanning electron microscopy of the surface of the rat uterine epithelium during delayed implantation. *J Reprod Fertil.* 1971;26(1):137-8.
7. Enders AC, Nelson DM. Pinocytotic activity of the uterus of the rat. *Am J Anat.* 1973;138(3):277-99.
8. Nikas G, Drakakis P, Loutradis D, Mara-Skoufari C, Koumantakis E, Michalas S, Psychoyos A. Uterine pinopodes as markers of the 'nidation window' in cycling women receiving exogenous oestradiol and progesterone. *Hum Reprod.* 1995;10(5):1208-13.
9. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S. International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod.* 2009 Nov; 24(11):2683-7.
10. Joo BS, Park SH, An BM, Kim KS, Moon SE, Moon HS. Serum estradiol levels during controlled ovarian hyperstimulation influence the pregnancy outcome of in vitro fertilization in a concentration-dependent manner. *Fertil Steril.* 2010;93(2):442-6.
11. Bouchard P, Marraoui J, Massai MR, Medalie DA, De Ziegler D, Perrot-Applanat M, Frydman R, Bergeron C. Immunocytochemical localization of oestradiol and progesterone receptors in human endometrium: a tool to assess endometrial maturation. *Baillieres Clin Obstet Gynaecol.* 1991;5(1):107-15.
12. Fanchin R, de Ziegler D, Castracane VD, Taieb J, Olivennes F, Frydman R. Physiopathology of premature progesterone elevation. *Fertil Steril.* 1995;64(4):796-801.
13. Basir GS, O WS, Ng EH, Ho PC. Morphometric analysis of peri-implantation endometrium in patients having excessively high oestradiol concentrations after ovarian stimulation. *Hum Reprod.* 2001;16(3):435-40.
14. Toner JP. The significance of elevated FSH for reproductive function. *Baillieres Clin Obstet Gynaecol.* 1993;7(2):283-95.
15. Tang B, Gurpide E. Direct effect of gonadotropins on decidualization of human endometrial stroma cells. *J Steroid Biochem Mol Biol.* 1993;47(1-6):115-21.
16. Lass A, Gerrard A, Abusheikha N, Akagbosu F, Brinsden P. IVF performance of women who have fluctuating early follicular FSH levels. *J Assist Reprod Genet.* 2000;17(10):566-73.
17. Ubaldi F, Bourgain C, Tournaye H, Smitz J, Van Steirteghem A, Devroey P. Endometrial evaluation by aspiration biopsy on the day of oocyte retrieval in the embryo transfer cycles in patients with serum progesterone rise during the follicular phase. *Fertil Steril.* 1997;67(3):521-6.
18. Garcia JE, Acosta AA, Hsiu JG, Jones HW Jr. Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin/human chorionic gonadotropin for in vitro fertilization. *Fertil Steril.* 1984;41(1):31-5.
19. Sterzik K, Dallenbach C, Schneider V, Sasse V, Dallenbach-Hellweg G. In vitro fertilization: the degree of endometrial insufficiency varies with the type of ovarian stimulation. *Fertil Steril.* 1988 Sep;50(3):457-62.
20. Graf MJ, Reyniak JV, Battle-Mutter P, Laufer N. Histologic evaluation of the luteal phase in women following follicle aspiration for oocyte retrieval. *Fertil Steril.* 1988;49(4):616-9.
21. Develioglu OH, Hsiu JG, Nikas G, Toner JP, Oehninger S, Jones HW Jr. Endometrial estrogen and progesterone receptor and pinopode expression in stimulated cycles of oocyte donors. *Fertil Steril.* 1999;71(6):1040-7.

22. Bourgain C, Smitz J, Camus M, Erard P, Devroey P, Van Steirteghem AC, Kloppel G. Human endometrial maturation is markedly improved after luteal supplementation of gonadotrophin-releasing hormone analogue/human menopausal gonadotrophin stimulated cycles. *Hum Reprod.* 1994;9(1):32-40.
23. Salat-Baroux J, Romain S, Alvarez S, Antoine JM, Kopp K, Raulais D, de Brux J, Martin PM. Biochemical and immunohistochemical multiparametric analysis of steroid receptors and growth factor receptors in human normal endometrium in spontaneous cycles and after the induction of ovulation. *Hum Reprod.* 1994;9(2):200-8.
24. Bebington C, Doherty FJ, Ndukwe G, Fleming SD. The progesterone receptor and ubiquitin are differentially regulated within the endometrial glands of the natural and stimulated cycle. *Mol Hum Reprod.* 2000;6(3):264-8.
25. Norwitz ER. Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reprod Biomed Online.* 2006;13(4):591-9.
26. Burney RO, Talbi S, Hamilton AE, et al: Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology.* 2007;148:3814-3826.
27. Nikas G, Develioglou OH, Toner JP, Jones HW Jr. Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles. *Hum Reprod.* 1999;14(3):787-92.
28. Murphy CR. Understanding the apical surface markers of uterine receptivity—Pinopods—Or uterodomes? *Hum Reprod.* 2000;15(12):2451-4.
29. Damario MA, Lesnick TG, Lessey BA, Kowalik A, Mandelin E, Seppälä M, Rosenwaks Z. Endometrial markers of uterine receptivity utilizing the donor oocyte model. *Hum Reprod.* 2001;16(9):1893-9.
30. Stavreus-Evers A, Nikas G, Sahlin L, Eriksson H, Landgren BM. Formation of pinopodes in human endometrium is associated with the concentrations of progesterone and progesterone receptors. *Fertil Steril.* 2001;76(4):782-91.
31. Kolb BA, Paulson RJ. The luteal phase of cycles utilizing controlled ovarian hyperstimulation and the possible impact of this hyperstimulation on embryo implantation. *Am J Obstet Gynecol.* 1997;176(6):1262-7.
32. Paulson RJ, Sauer MV, Lobo RA. Embryo implantation after human in vitro fertilization: importance of endometrial receptivity. *Fertil Steril.* 1990;53(5):870-4.
33. Seppälä M, Suikkari AM, Julkunen M. Human endometrial proteins. *Reprod Nutr Dev.* 1988;28(6B):1649-54.
34. Cullinan EB, Abbondanzo SJ, Anderson PS, Pollard JW, Lessey BA, Stewart CL. Leukemia inhibitory factor (LIF) and LIF receptor expression in human endometrium suggests a potential autocrine/paracrine function in regulating embryo implantation. *Proc Natl Acad Sci U S A.* 1996;2;93(7):3115-20.
35. Bonagura TW, Pepe GJ, Enders AC, Albrecht ED. Suppression of extravillous trophoblast vascular endothelial growth factor expression and uterine spiral artery invasion by estrogen during early baboon pregnancy. *Endocrinology.* 2008;149(10):5078-87.
36. Arici A, Engin O, Attar E, Olive DL. Modulation of leukemia inhibitory factor gene expression and protein biosynthesis in human endometrium. *J Clin Endocrinol Metab.* 1995;80(6):1908-15.
37. Lessey BA, Yeh I, Castelbaum AJ, Fritz MA, Ilesanmi AO, Korzeniowski P, Sun J, Chwalisz K. Endometrial progesterone receptors and markers of uterine receptivity in the window of implantation. *Fertil Steril.* 1996;65(3):477-83.
38. Lessey BA, Castelbaum AJ, Sawin SW, Sun J. Integrins as markers of uterine receptivity in women with primary unexplained infertility. *Fertil Steril.* 1995;63(3):535-42.

39. Hii LL, Rogers PA. Endometrial vascular and glandular expression of integrin alpha(v)beta3 in women with and without endometriosis. *Hum Reprod.* 1998;13(4):1030-5.
40. Tavaniotou A, Bourgain C, Albano C, Platteau P, Smitz J, Devroey P. Endometrial integrin expression in the early luteal phase in natural and stimulated cycles for in vitro fertilization. *Eur J Obstet Gynecol Reprod Biol.* 2003; 1;108(1):67-71.
41. Wang JG, Douglas NC, Dicken C, Nakhuda GS, Guarnaccia MM, Sauer MV. Cryopreservation of supernumerary high quality embryos predicts favorable outcomes for patients undergoing repeated cycles of in vitro fertilization. *Fertil Steril.* 2008;89(2):368-74.
42. Lee JY, Lee M, Lee SK. Role of endometrial immune cells in implantation. *Clin Exp Reprod Med.* 2011;38(3):119-25.
43. Flynn L, Byrne B, Carton J, Kelehan P, O'Herlihy C, O'Farrelly C. Menstrual cycle dependent fluctuations in NK and T-lymphocyte subsets from non-pregnant human endometrium. *Am J Reprod Immunol.* 2000;43(4):209-17.
44. Junovich G, Mayer Y, Azpiroz A, Daher S, Iglesias A, Zylverstein C, Gentile T, Pasqualini S, Markert UR, Gutiérrez G. Ovarian stimulation affects the levels of regulatory endometrial NK cells and angiogenic cytokine VEGF. *Am J Reprod Immunol.* 2011;65(2):146-53.
45. Chaouat G. Inflammation, NK cells and implantation: friend and foe (the good, the bad and the ugly?): replacing placental viviparity in an evolutionary perspective. *J Reprod Immunol.* 2013;97(1):2-13.
46. Navot D, Scott RT, Droesch K, Veeck LL, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. *Fertil Steril.* 1991;55(1):114-8.
47. Kolibianakis EM, Devroey P. The luteal phase after ovarian stimulation. *Reprod Biomed Online.* 2002;5 Suppl 1:26-35.
48. Kolibianakis EM, Bourgain C, Platteau P, Albano C, Van Steirteghem AC, Devroey P. Abnormal endometrial development occurs during the luteal phase of nonsupplemented donor cycles treated with recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. *Fertil Steril.* 2003;80(2):464-6.
49. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. *Nat Med.* 2012;18(12):1754-67.
50. Horcajadas JA, Pellicer A, Simón C. Wide genomic analysis of human endometrial receptivity: new times, new opportunities. *Hum Reprod Update.* 2007;13(1):77-86.
51. Macklon, N.S. and Fauser, B.C. Impact of ovarian hyperstimulation on the luteal phase. *J. Reprod Fertil.* 2000, 55 (Suppl.),101±108.
52. Rogers PA, Polson D, Murphy CR, Hosie M, Susil B, Leoni M. Correlation of endometrial histology, morphometry, and ultrasound appearance after different stimulation protocols for in vitro fertilization. *Fertil Steril.* 1991;55(3):583-7.
53. Bourgain C, Ubaldi F, Tavaniotou A, Smitz J, Van Steirteghem AC, Devroey P. Endometrial hormone receptors and proliferation index in the periovulatory phase of stimulated embryo transfer cycles in comparison with natural cycles and relation to clinical pregnancy outcome. *Fertil Steril.* 2002;78(2):237-44.
54. Creus M, Ordi J, Fábregues F, Casamitjana R, Carmona F, Cardesa A, Vanrell JA, Balasch J. The effect of different hormone therapies on integrin expression and pinopode formation in the human endometrium: a controlled study. *Hum Reprod.* 2003;18(4):683-93.
55. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. *Fertil Steril.* 2002;78(2):280-5.
56. Yagel S, Ben-Chetrit A, Anteby E, Zacut D, Hochner-Celnikier D, Ron M. The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate. *Fertil Steril.* 1992;57(1):33-6.

57. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. *Fertil Steril.* 1993;59(4):756-60.
58. Massai MR, de Ziegler D, Lesobre V, Bergeron C, Frydman R, Bouchard P. Clomiphene citrate affects cervical mucus and endometrial morphology independently of the changes in plasma hormonal levels induced by multiple follicular recruitment. *Fertil Steril.* 1993;59(6):1179-86.
59. Martel D, Frydman R, Glissant M, Maggioni C, Roche D, Psychoyos A. Scanning electron microscopy of postovulatory human endometrium in spontaneous cycles and cycles stimulated by hormone treatment. *J Endocrinol.* 1987;114(2):319-24.
60. Birkenfeld A, Navot D, Levij IS, Laufer N, Beier-Hellwig K, Goecke C, Schenker JG, Beier HM. Advanced secretory changes in the proliferative human endometrial epithelium following clomiphene citrate treatment. *Fertil Steril.* 1986;45(4):462-8.
61. Bonhoff AJ, Naether OG, Johannisson E. Effects of clomiphene citrate stimulation on endometrial structure in infertile women. *Hum Reprod.* 1996;11(4):844-9.
62. Sharma V, Whitehead M, Mason B, Pryse-Davies J, Ryder T, Dowsett M, Campbell S, Collins W. Influence of superovulation on endometrial and embryonic development. *Fertil Steril.* 1990;53(5):822-9.
63. Lacin S, Vatansever S, Kuscü NK, Koyuncu F, Ozbilgin K, Ceylan E. Clomiphene citrate does not affect the secretion of alpha3, alphaV and beta1 integrin molecules during the implantation window in patients with unexplained infertility. *Hum Reprod.* 2001;16(11):2305-9.
64. Kuşçu NK, Koyuncu FM, Var A, Laçın S, Uyanık BS, Ceylan E. Clomiphene citrate does not adversely affect endometrial leukemia inhibitory factor levels. *Gynecol Endocrinol.* 2002;16(2):151-4.
65. Cortínez A, De Carvalho I, Vantman D, Gabler F, Iñiguez G, Vega M. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. *Fertil Steril.* 2005;83(1):110-5.
66. Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. *Arch Gynecol Obstet.* 2009;279(3):311-4.
67. Toner JP, Hassiakos DK, Muasher SJ, Hsiu JG, Jones HW Jr. Endometrial receptivities after leuprolide suppression and gonadotropin stimulation: histology, steroid receptor concentrations, and implantation rates. *Ann N Y Acad Sci.* 1991;622:220-9.
68. Abate V, De Corato R, Cali A, Stinchi A. Endometrial biopsy at the time of embryo transfer: correlation of histological diagnosis with therapy and pregnancy rate. *J In Vitro Fert Embryo Transf.* 1987;4(3):173-6.
69. Perrier d'Hauterive S, Berndt S, Tsampalas M, Charlet-Renard C, Dubois M, Bourgain C, Hazout A, Foidart JM, Geenen V. Dialogue between blastocyst hCG and endometrial LH/hCG receptor: which role in implantation? *Gynecol Obstet Invest.* 2007;64(3):156-60.
70. Fanchin R, Peltier E, Frydman R, de Ziegler D. Human chorionic gonadotropin: does it affect human endometrial morphology in vivo? *Semin Reprod Med.* 2001;19(1):31-5.
71. Papanikolaou EG, Bourgain C, Fatemi H, Verpoest W, Polyzos NP, De Brabanter A, Kolibianakis E, Tarlatzis B, Devroey P, Tournaye H. Endometrial advancement after triggering with recombinant or urinary HCG: a randomized controlled pilot study. *Reprod Biomed Online.* 2010 Jul;21(1):50-5.
72. Kim JW, Lee YS, Kim BK, Park DC, Lee JM, Kim IK, Namkoong SE. Cell cycle arrest in endometrial carcinoma cells exposed to gonadotropin-releasing hormone analog. *Gynecol Oncol.* 1999;73(3):368-71.
73. Meresman GF, Bilotas M, Buquet RA, Barañao RI, Sueldo C, Tesone M. Gonadotropin-releasing hormone agonist induces apoptosis and reduces cell proliferation in eutopic endometrial cultures from women with endometriosis. *Fertil Steril.* 2003;80 Suppl 2:702-7.

74. Van Steirteghem AC, Smits J, Camus M, Van Waesberghe L, Deschacht J, Khan I, Staessen C, Wisanto A, Bourgain C, Devroey P. The luteal phase after in-vitro fertilization and related procedures. *Hum Reprod.* 1988;3(2):161-4.
75. Novin MG, Bazy P, Rad JS, Sarani SA, Farzadi L, Ghasemzadeh A. Morphometric study of GnRH analog/HMG/HCG effects on ultrastructure of human endometrial epithelium in early and mid-luteal phase. *J Obstet Gynaecol Res.* 2007;33(5):681-7.
76. Novotný R, Malinský J, Oborná I, Dostál J. Nuclear channel system (NCS) in normal endometrium and after hormonal stimulation. *Acta Univ Palacki Olomuc Fac Med.* 1999;142:41-6.
77. Horcajadas JA, Riesewijk A, Polman J, van Os R, Pellicer A, Mosselman S, Simón C. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. *Mol Hum Reprod.* 2005;11(3):195-205.
78. Chen QJ, Sun XX, Li L, Gao XH, Gemzell-Danielsson K, Cheng LN. Effects of ovarian stimulation on endometrial integrin beta3 and leukemia inhibitory factor expression in the peri-implantation phase. *Fertil Steril.* 2008;89(5)Suppl:1357-63.
79. Macrow PJ, Li TC, Seif MW, Buckley CH, Elstein M. Endometrial structure after superovulation: a prospective controlled study. *Fertil Steril.* 1994;61(4):696-9.
80. Barash A, Czernobilsky B, Inslar V, Borenstein R, Rosenberg M, Fink A. Endometrial morphology and hormonal profiles in in vitro fertilization patients. *Eur J Obstet Gynecol Reprod Biol.* 1992; 21;44(2):117-21.
81. Macklon NS, van der Gaast MH, Hamilton A, Fauser BC, Giudice LC. The impact of ovarian stimulation with recombinant FSH in combination with GnRH antagonist on the endometrial transcriptome in the window of implantation. *Reprod Sci.* 2008;15(4):357-65.
82. Martínez-Conejero JA, Simón C, Pellicer A, Horcajadas JA. Is ovarian stimulation detrimental to the endometrium? *Reprod Biomed Online.* 2007;15(1):45-50.
83. Mirkin S, Nikas G, Hsiu JG, Díaz J, Oehninger S. Gene expression profiles and structural/functional features of the peri-implantation endometrium in natural and gonadotropin-stimulated cycles. *J Clin Endocrinol Metab.* 2004;89(11):5742-52
84. Simon C, Oberyé J, Bellver J, Vidal C, Bosch E, Horcajadas JA, Murphy C, Adams S, Riesewijk A, Mannaerts B, Pellicer A. 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(12):3318-27.
85. Orvieto R, Meltzer S, Rabinson J, Zohav E, Anteby EY, Nahum R. GnRH agonist versus GnRH antagonist in ovarian stimulation: the role of endometrial receptivity. *Fertil Steril.* 2008 Oct;90(4):1294-6.
86. Ruan HC, Zhu XM, Luo Q, Liu AX, Qian YL, Zhou CY, Jin F, Huang HF, Sheng JZ. Ovarian stimulation with GnRH agonist, but not GnRH antagonist, partially restores the expression of endometrial integrin beta3 and leukaemia-inhibitory factor and improves uterine receptivity in mice. *Hum Reprod.* 2006;21(10):2521-9.
87. Taylor HS, Daftary GS, Selam B. Endometrial HOXA10 expression after controlled ovarian hyperstimulation with recombinant follicle-stimulating hormone. *Fertil Steril.* 2003;80 Suppl 2:839-43.
88. Rackow BW, Kliman HJ, Taylor HS. GnRH antagonists may affect endometrial receptivity. *Fertil Steril.* 2008;89(5):1234-9.
89. Marchini M, Fedele L, Bianchi S, Losa GA, Ghisletta M, Candiani GB. Secretory changes in preovulatory endometrium during controlled ovarian hyperstimulation with busarelin acetate and human gonadotropins. *Fertil Steril.* 1991;55(4):717-21.
90. Simón C, Cano F, Valbuena D, Remohí J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. *Hum Reprod.* 1995;10(9):2432-7.

91. Pellicer A, Valbuena D, Cano F, Remohí J, Simón C. Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period. *Fertil Steril.* 1996;65(6):1190-5.
92. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Embryo cryopreservation rescues cycles with premature luteinization. *Fertil Steril.* 2010;93(2):636-41.
93. Polotsky AJ, Daif JL, Jindal S, Lieman HJ, Santoro N, Pal L. Serum progesterone on the day of human chorionic gonadotropin administration predicts clinical pregnancy of sibling frozen embryos. *Fertil Steril.* 2009;92(6):1880-5.
94. Labarta E, Martínez-Conejero JA, Alamá P, Horcajadas JA, Pellicer A, Simón C, Bosch E. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis. *Hum Reprod.* 2011;26(7):1813-25.
95. Pellicer A, Valbuena D, Cano F, Remohí J, Simón C. Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period. *Fertil Steril.* 1996;65(6):1190-5.
96. Al-Azemi M, Kyrou D, Kolibianakis EM, Humaidan P, Van Vaerenbergh I, Devroey P, Fatemi HM. Elevated progesterone during ovarian stimulation for IVF. *Reprod Biomed Online.* 2012;24(4):381-8.
97. Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins J, Pellicer A. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. *Hum Reprod.* 2010;25(8):2092-100.
98. Liu L, Huang J, Li TC, Hong XT, Laird S, Dai YD, Tong XM, Zhu HY, Zhang S. The effect of elevated progesterone levels before oocyte retrieval in women undergoing ovarian stimulation for IVF treatment on the genomic profile of peri-implantation endometrium. *J Reprod Immunol.* 2017;121:17-25.
99. Kovalevsky G, Patrizio P. High rates of embryo wastage with use of assisted reproductive technology: a look at the trends between 1995 and 2001 in the United States. *Fertil Steril.* 2005;84(2):325-30.
100. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Ovulation induction disrupts luteal phase function. *Ann N Y Acad Sci.* 2001;943:55-63.
101. Kolibianakis EM, Venetis CA, Papanikolaou EG, Diedrich K, Tarlatzis BC, Griesinger G. Estrogen addition to progesterone for luteal phase support in cycles stimulated with GnRH analogues and gonadotrophins for IVF: a systematic review and meta-analysis. *Hum Reprod.* 2008;23(6):1346-54.
102. Pabuccu R, Akar ME. Luteal phase support in assisted reproductive technology. *Curr Opin Obstet Gynecol.* 2005;17(3):277-81.
103. Posaci C, Smitz J, Camus M, Osmanagaoglu K, Devroey P. Progesterone for the luteal support of assisted reproductive technologies: clinical options. *Hum Reprod.* 2000;15 Suppl 1:129-48.
104. Brezina PR, Vlahos NF, Lai TH, Garcia JE, Wallach EE, Zhao Y. The impact of luteal phase support on endometrial estrogen and progesterone receptor expression: a randomized control trial. *Reprod Biol Endocrinol.* 2012; 24;10:16.
105. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. *Hum Reprod.* 2002;17(9):2287-99.