

YÜKSEK OVER YANITLI HASTALARA KLINİK YAKLAŞIM

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Over yanıtı; over rezervine, hasta yaşına ve vücut kitle indeksine göre (BMI) öngörülebilir. Over rezerv testleri biyokimyasal veya ultrasonografik olarak yapılabilmektedir. Menstrüasyonun 2-3. günü bakılan follikül stimülan hormon (FSH), östradiol (E2), inhibin B ve menstrüel peryodun herhangi bir günü ölçülen Anti Mullerian Hormon (AMH) düzeyi biyokimyasal testler arasında yer alır. Ultrasonografik olarak ise, menstrüasyonun 2-4. günü antral folikül sayısı (AFC) over rezervi hakkında bilgi verir (1).

AMH glikopeptid yapıda, TGF-β ailesine ait bir hormondur. Over foliküllerindeki granüloza hücrelerinden salınır. Foliküler fazda primordial ve küçük antral foliküllerden AMH salınımı olur (2). AMH seviyesinin <0,7 ng/ml olması azalmış over rezervini gösterir. IVF (invitro fertilizasyon) sikluslarında ≤4 oosit elde edilmesinin muhtemel azalmış over rezervi olduğunu öngörür. AMH seviyesinin 1-3,5 ng/ml olan olgularda over rezervinin normal olduğu kabul edilir. AMH seviyesinin ≥3,5 ng/ml olduğu olgularda ise over rezervinin yüksek olduğu ve bu olguların yüksek over yanıtlı olgular olduğu kabul edilir (2-6). Bu olgular OHSS için yüksek riskli gruba girmektedir. Tedavi sırasında iatrojenik OHSS gelişmemesi için dikkat edilmelidir.

Yüksek over cevabı (hyper response), standart KOH protokolünün uygulandığı hastada > 15 oositin elde edilmesine denir. Yaşa bağlı olarak azalmakla birlikte, IVF sikluslarının yaklaşık % 7'sinde görülmektedir. Genç yaştaki olgular, polikistik over sendromu (PCOS), daha önceki IVF uygulamalarında fazla sayıda oosit elde edilen olgular ile over rezervi yüksek olan olgular yüksek over yanıtı için risk grubuna girmektedirler. AMH ve AFC over yanıtını ön görmede önemli predik-

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lışmada ise, düşük implantasyon oranları bildirilmiştir. Bunun anormal mayotik spindle ve kromozomal hizalanma, düşük oosit kalitesi nedeniyle olabileceğini ifade etmişlerdir (85).

Dopamin Agonistleri

OHSS patofiziolojisinde önemli rolü olan esas mediatör VEGF (vascular endothelial growth factor)'dır. Hiperstimüle overlerden salgılanan artmış VEGF, VEGF reseptör 2 (VEGFR-2) üzerinden etki göstererek, OHSS'deki klinik bulgulara neden olan vasküler permeabilite artışına neden olur. VEGFR-2'nin bloke edilmesi OHSS'nu önler. Dopamin agonistlerinin VEGFR-2 reseptörlerini bloke ederek OHSS riskini azalttığı gösterilmiştir (86). Dopamin agonistlerinin klinik gebelik veya gebelik kayıtları üzerine olumsuz etkilerinin olmadığı bildirilmiştir (87).

Anahtar kelimeler: Yüksek over cevabı, hiperresponder, over hiperstimülasyonu, polikistik over

REFERANSLAR

1. Seifer DB, MacLaughlin DT, Christian BP, Feng B, Shelden RM. Early follicular serum mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. *Fertil Steril* 2002; 77: 468-71.
2. La Marca A, Sighinolfi G, Radi D, et al. Antimullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). *Hum Reprod Update* 2010; 16: 113-30.
3. Almog B, Shehata F, Suissa S, et al. Agerelated normograms of serum antimüllerian hormone levels in a population of infertile women: a multicenter study. *Fertil Steril* 2011; 95: 2359-63.e1.
4. Barad DH, Weghofer A, Gleicher N. Utility of age-specific serum anti-mullerian hormone concentrations. *Reprod Biomed Online* 2011; 22: 284.
5. Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of antimullerian hormone measurement in a routine IVF program. *Hum Reprod* 2008; 23: 1359-65.
6. Huang X, Wang P, Tal R, Lv F, Li Y, Zhang X. A systematic review and meta-analysis of metformin among patients with polycystic ovary syndrome undergoing assisted reproductive technology procedures. *Int J Gynaecol Obstet* 2015; 131: 111-6.
7. Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Prediction of high ovarian response to controlled ovarian hyperstimulation: anti-Müllerian hormone versus small antral follicle count (2-6 mm) *J Assist Reprod Genet*. 2009; 26: 319-25.
8. Homburg R, Armar NA, Eshel A, Adams J and Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception and early pregnancy loss in polycystic ovary syndrome. *Br Med J* 1988; 297: 1024-1026.
9. Balen AH, Tan SL, MacDougall J and Jacobs HS. Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. *Hum Reprod* 1993; 8: 959-964.
10. La Marca A, Orvieto R, Giulini S, Jasonni VM, Volpe A, De Leo V. Mullerian-inhibiting substance in women with polycystic ovary syndrome: relationship with hormonal and metabolic characteristics. *Fertil Steril* 2004; 82: 970-2.
11. Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. *Am J Physiol Endocrinol Metab* 2009; 296: 238-43.
12. Nardo LG, Yates AP, Roberts SA, Pemberton P, Laing I. The relationships between AMH, androgens, insulin resistance and basal ovarian follicular status in non-obese subfertile women with and without polycystic ovary syndrome. *Hum Reprod* 2009; 24: 2917-23.

13. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; 19: 41-47.
14. Hamori M, Zwirner M, Clédon P and Tinneberg HR. Androgen response in polycystic ovarian syndrome to FSH treatment after LHRH agonist suppression. *Int J Fertil* 1992; 37: 171-175.
15. Tal R, Seifer DB, Khanimov M, Malter HE, Grazi RV, Leader B. Characterization of women with elevated antimüllerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes. *Am J Obstet Gynecol* 2014; 211: 59.e1-8.
16. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* 2009; 92(6): 1966-82.
17. Kataoka J, Tassone EC, Misso M, Joham AE, Stener-Victorin E, Teede H, Moran LJ. Weight Management Interventions in Women with and without PCOS: A Systematic Review. *Nutrient* 2017; 9(9):.
18. Thomson RL, Buckley JD, Moran LJ, et al. Comparison of aerobic exercise capacity and muscle strength in overweight women with and without polycystic ovary syndrome. *BJOG* 2009; 116: 1242-1250.
19. Greenwood EA. Association among depression, symptom experience, and quality of life in polycystic ovary syndrome. *Am J Obstet Gynecol* 2018; 219: 279.e1-279.e7.
20. Pfeifer S. Use of clomiphene citrate in infertile women: a committee opinion. Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril* 2013; 100(2):341-8.
21. Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. *Journal of Clinical Endocrinology and Metabolism* 2006; 91(3): 760-71.
22. Homburg R, Hendriks ML, König TE, et al. Clomifene citrate or low-dose FSH for the first line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. *Hum Reprod* 2012; 27: 468-473.
23. Gibreel A, Maheshwari A, Bhattacharya S. Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD008528.pub2].
24. Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017; 1: CD012103. doi: 10.1002/14651858.CD012103.pub2.
25. Cole PA, Robinson CH. Mechanism and inhibition of cytochrome P450 aromatase. *Journal of Medical Chemistry* 1990; 33(11): 2933-44.
26. Jirge PR, Patil RS. Comparison of endocrine and ultrasound profiles during ovulation induction with clomiphene citrate and letrozole in ovulatory volunteer women. *Fertility and Sterility* 2010; 93(1): 174-83.
27. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ, International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod*. 2018; 33(9): 1602-1618.
28. Roque M, Tostes AC, Valle M, Sampaio M, Geber S. Letrozole versus clomiphene citrate in polycystic ovary syndrome: systematic review and meta-analysis. *Gynecol Endocrinol*. 2015; 31(12): 917-21.
29. Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, Ng EH, Legro RS, Bhattacharya S, Norman RJ, Mol BW. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. *BMJ* 2017; 356(): j138.
30. Biljan MM, Hemmings R, Brassard N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. *Fertility and Sterility* 2005; 84(Supplement 1): 95.
31. Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R. Fetal safety of letrozole and clomiphene citrate for ovulation induction. *Journal of Obstetrics and Gynaecology Canada* 2007; 29(8): 668.

32. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertility and Sterility* 2006; 85(6): 1761-
33. Mathur R, Alexander CJ, Yano J, Trivax B, Azziz R. Use of metformin in polycystic ovary syndrome. *Am J Obstet Gynecol.* 2008; 199: 596-607.
34. Barbieri RL. Clomiphene versus metformin for ovulation induction in polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2007; 92: 3399-3401.
35. Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Endocrinol Metab.* 2012; 97: 1492-1500.
36. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev.* 2017; 11: CD003053. doi:10.1002/14651858.CD003053.pub6.
37. Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD006105.pub3]
38. Rimington MR, Walker SM, Shaw RW. The use of laparoscopic ovarian electrocautery in preventin cancellation of in-vitro fertilization treatment cycles due to risk of ovarian hyperstimulation syndrome in women with polycystic ovaries. *Hum Reprod* 1997; 12: 1443-1447.
39. Balen A. Surgical management of PCOS. *Best Pract Res Clin Endocrinol Metab* 2006; 20: 271-280.
40. Malkawi HY, Qublan HS, Hamaideh AH. Medical vs. surgical treatment for clomiphene citrate-resistant women with polycystic ovary syndrome. *J Obstet Gynaecol* 2003; 23: 289-293.
41. Dor J, Shulman A, Levran D, Ben-Rafael Z, Rudak E, Mashiach S. The treatment of patients with polycystic ovarian syndrome by in-vitro fertilization and embryo transfer: a comparison of results with those of patients with tubal infertility. *Hum Reprod* 1990; 5: 816-818.
42. Urman B, Fluker MR, Yuen BH, Fleige-Zahradka BG, Zouves CG, Moon YS. The outcome of in vitro fertilization and embryo transfer in women with polycystic ovary syndrome failing to conceive after ovulation induction with exogenous gonadotropins. *Fertil Steril* 1992; 57: 1269-1273.
43. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. *Reprod Biomed Online* 2006; 13: 628-638.
44. Broer SL, Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, et al. on behalf of the IMPORT study group. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. *Human Reproduction Update* 2013;19(1):26-36.
45. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Human Reproduction* 2011;26(7):176.
46. Chong AP, Rafael RW, Forte CC. Influence of weight in the induction of ovulation with human menopausal gonadotropin and human chorionic gonadotropin. *Fertil Steril* 1986; 46: 599.
47. Olive DL. The role of gonadotropins in ovulation induction. *Am J Obstet Gynecol* 1995; 172: 759.
48. van Tilborg TC, Broekmans FJ, Dölleman M, Eijkemans MJ, Mol BW, Laven JS, Torrance HL. Individualised FSH dosing and IVF outcome in agonist downregulated cycles: a systematic review. *Acta Obstet Gynecol Scand* 2016; 95: 1333-1344.
49. Lunenfeld B, Insler V. Classification of amenorrhoeic states and their treatment by ovulation induction. *Clin Endocrinol (Oxf)* 1974; 3(2): 223-37.

50. Buvat J, Buvat- Herbaut M, Marcolin G, Dehaene JL, Verbecq P, Renouard O. Purified follicle-stimulating hormone in polycystic ovary syndrome: slow administration is safer and more effective. *Fertil Steril* 1989; 52: 553-59.
51. Brzyski RG, Grow DR, Sims JA, Seltman HJ. Increase in androgen: estrogen ratio specifically during low-dose follicle- stimulating hormone therapy for polycystic ovary syndrome. *Fertil Steril* 1995; 64: 693-97.
52. Hamilton-Fairley D, Kiddy D, Watson H, Sagle M, Franks S. Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome. *Hum Reprod* 1991; 6(8): 1095-9.
53. van Santbrink EJ, Donderwinkel PF, van Dessel TJ, Fauser BC. Gonadotrophin induction of ovulation using a step-down dose regimen: single-centre clinical experience in 82 patients. *Hum Reprod* 1995; 10(5) :1048-53.
54. Lensen SF, Wilkinson J, Leijdekkers JA, La Marca A, Mol BWJ, Marjoribanks J, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). *Cochrane Database Syst Rev*. 2018; 2: CD012693. doi: 10.1002/14651858.CD012693.pub2.
55. Mathur R, Kailasam C, Jenkins J. Review of the evidence base strategies to prevent ovarian hyperstimulation syndrome. *Human Fertility* 2007;10:75-85.
56. Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertility and Sterility* 2016;106:1634-47.
57. Kupka MS, Ferraretti AP, Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al. European IVF-Monitoring Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. *Human Reproduction* 2014; 29(10): 2099-113.
58. Figen Turkcapar A, Seckin B, Onalan G, Ozdener T, Batioglu S. Human menopausal gonadotropin versus recombinant FSH in polycystic ovary syndrome patients undergoing in vitro fertilization. *Int J Fertil Steril* 2013;4:238–243.
59. Balen AH, Tan SL, Jacobs HS. Hypersecretion of luteinising hormone: a significant cause of infertility and miscarriage. *Br J Obstet Gynaecol*. 1993; 100: 1082–1089.
60. Dor J, Shulman A, Pariente C, Levran D, Bider D, Menashe Y and Mashiach S. The effect of gonadotropin-releasing hormone agonist on the ovarian response and in vitro fertilization results in polycystic ovarian syndrome: a prospective study. *Fertil Steril* 1992; 57: 366–371.
61. Macnamee MC and Brinsden PR. Superovulation strategies in assisted conception. In Brinsden PR (ed.) *A Textbook of In Vitro Fertilization and Assisted Reproduction*. Parthenon Publishing, London,1999; pp. 91–102.
62. Hamori M, Zwirner M, Clédon P and Tinneberg HR. Androgen response in polycystic ovarian syndrome to FSH treatment after LHRH agonist suppression. *Int J Fertil* 1992; 37: 171–175.
62. Porter RN, Smith W, Craft IL, Abdulwahid NA, Jacobs H. Induction of ovulation for in-vitro fertilisation using buserelin and gonadotropins. *Lancet* 1984;2(8414):1284-5.
63. Macnamee MC, Howles CM, Edwards RG, Taylor PJ, Elder KT. Short-term luteinizing hormone-releasing hormone agonist treatment: prospective trial of a novel ovarian stimulation regimen for in vitro fertilization. *Fertility and Sterility* 1989;52(2):264-9.
64. Hughes EG, Fedorkow DM, Daya S, Sagle MA, Van de Koppel P, Collins JA. The routine use of gonadotropin-releasing hormoneagonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta-analysis of randomized trials. *Fertility and Sterility* 1992;58:888-96.
65. Duijkers IJM, Klipping C, Willemse WNP, Krone D, Schneider E, Niebch G, et al. Single and multiple dose pharmacokinetics and pharmacodynamics of the gonadotrophin-releasing hormone antagonist cetrorelix in healthy female volunteers. *Human Reproduction* 1998;13(9):2392-8.
66. Huirne JA, Homburg R, Lambalk CB. Are GnRH antagonists comparable to agonists for use in IVF?. *Human Reproduction* 2007;11:2805-13.

67. Fleming R, Adam AH, Barlow DH, Black WP, MacNaughton MC, Coutts JR: A new systematic treatment for infertile women with abnormal hormone profiles. *British journal of obstetrics and gynaecology* 1982; 89(1):80-83.
68. Coccia ME, Comparetti C, Bracco GL, Scarselli G: GnRH antagonists. *European journal of obstetrics, gynecology, and reproductive biology* 2004; 115 Suppl 1:S44-56.
69. Al-Inany HG, Abou-Setta AM, Aboulghar M: Gonadotrophin-releasing hormone antagonists for assisted conception. *The Cochrane database of systematic reviews* 2006(3):Cd001750 10.1002/14651858.CD001750.pub2.
70. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J et al.: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *The Cochrane database of systematic reviews* 2011(5):Cd001750 10.1002/14651858.CD001750.pub3.
71. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *The Cochrane database of systematic reviews* 2016; 4:Cd001750 10.1002/14651858.CD001750.pub4
72. Abuzeid MI, Mitwally M, Abuzeid YM, Bokhari HA, Ashraf M, Diamond MP. Early initiation of gonadotropin-releasing hormone antagonist in polycystic ovarian syndrome patients undergoing assisted reproduction: randomized controlled trial ISRCTN69937179. *J Assist Reprod Genet.* 2012 Nov;29(11):1193-202. doi: 10.1007/s10815-012-9850-7.
73. Stanger JD and Yovich JL. Reduced in-vitro fertilization of human oocyte from patients with raised basal luteinising hormone levels during the follicular phase. *Br J Obstet Gynecol* 1985; 92: 385-393.
74. Elkind-Hirsch KE, Webster BW, Brown CP, Vernon MW. Concurrent ganirelix and follitropin beta therapy is an effective and safe regimen for ovulation induction in women with polycystic ovary syndrome. *Fertil Steril* 2003; 79: 603-607.
75. Albano C, Felberbaum RE, Smitz J, Riethmüller-Winzen H, Engel J, Diedrich K and Devroey P. Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. *Hum Reprod* 2000; 15: 526-531.
76. Hwang JL, Huang LW, Hsieh BC, Tsai YL, Huang SC, Chen CY, Hsieh ML, Chen PH and Lin YH. Ovarian stimulation by clomiphene citrate and hMG in combination with cetrorelix acetate for ICSI cycles. *Hum Reprod* 2003; 18: 45-49.
77. Prelevic GM, Puzigaca Z and Balint-Peric LA. Effects of an oral contraceptive containing cyproterone acetate (Diane 35) on the symptoms, hormone profile and ovarian volume of hirsute women with polycystic ovarian syndrome. *Ann NY Acad Sci* 1993; 687: 255-262.
78. Apparao KBC, Lovely LP, Gui Y, Lininger RA and Lessey BA. Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome. *Biol Reprod* 2002; 66: 297-304.
79. Hwang JL, Seow KM, Lin YH, Huang LW, Hsieh BC, Tsai YL, Wu GJ, Huang SC, Chen CY, Chen PH, Tzeng CR. Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35. Pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study. *Hum Reprod.* 2004;19(9):1993-2000. doi: 10.1093/humrep/deh375.
80. Pundir J, Sunkara SK, El-Toukhy T, Khalaf Y. Meta-analysis of GnRH antagonist protocols: do they reduce the risk of OHSS in PCOS? *Reprod Biomed Online.* 2012 Jan; 24(1):6-22.
81. Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database Syst Rev.* 2014 Oct 31; (10):CD008046.
82. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. *Fertil Steril.* 2014 Jul; 102(1):19-26.
83. Chen H, Wang Y, Lyu Q, Ai A, Fu Y, Tian H, Cai R, Hong Q, Chen Q, Shoham Z, Kuang Y. Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovar-

- an stimulation for in vitro fertilization and vitrified embryo transfer cycles. *Fertil Steril.* 2015 May; 103(5):1194-1201.e2.
84. Child TJ, Phillips SJ, Abdul-Jalil AK, Gulekli B, Tan SL. A comparison of in vitro maturation and in vitro fertilization for women with polycystic ovaries. *Obstet Gynecol.* 2002 Oct; 100(4):665-70.
85. Basatemer E, Sutcliffe A. Health of IVM children. *J Assist Reprod Genet.* 2011; 28(6):489-93.
86. Gómez R, González-Izquierdo M, Zimmermann RC, Novella-Maestre E, Alonso-Muriel I, Sanchez-Criado J, et al. Low-dose dopamine agonist administration blocks vascular endothelial growth factor (VEGF)-mediated vascular hyperpermeability without altering VEGF receptor 2-dependent luteal angiogenesis in a rat ovarian hyperstimulation model. *Endocrinology* 2006;147:5400-11.
87. Tang H, Mourad S, Zhai SD, Hart RJ. Dopamine agonists for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 11. [DOI: 10.1002/14651858.CD008605.pub3]