

Konu 28

Ovulasyon İndüksiyonunda Aşırı (High-responder) Yanıt Veren Hastaların Yönetimi

Dr. Engin ORAL
Dr. İlknur ÇİTİL

GİRİŞ

Polikistik over sendromu (PKOS) reproduktif çağıdaki kadınların %5-10'unu etkileyen ve en sık görülen endokrinopatilerden biridir. Etiyolojisi halen tam olarak bilinmemektedir, ancak birçok çalışma PKOS'un X kromozomuna bağlı, dominant geçişli bir hastalık olabileceğini düşündürmektedir (1). Sadece üreme endokrinolojisi penceresinden bakıldığında PKOS klinik bulguları itibari ile hafif menstruasyon düzensizliklerinden ciddi üreme disfonksiyonlarına kadar değişen geniş bir spektrumda yer alır. PKOS uzun vadede tip 2 diyabet, hipertansiyon, kardiyovasküler hastalıklar ve endometriyum kanseri gibi çok ciddi morbidite ve mortaliteye yol açabilecek önemli bir metabolik hastalıktır.

Tanımlama

Evrensel olarak kabul edilmiş tanı kriterlerini belirleme ihtiyacı ile 2003 yılında yapılan, Avrupa ile Kuzey Amerika'dan gelen PKOS uzmanlarının katıldığı Rotterdam toplantısında sendromun tanısına yönelik bir görüş birliğine varıldı. Bu toplantı ESHRE, ASRM tarafından desteklendi, "Fertility ve Sterility" ve "Human Reproduction" dergilerinde de yayınlandı (2,3).

Buna göre aşağıdaki 3 kriterden en az ikisinin olduğu kadınlar polikistik over sendromu olarak tanımlanmaktadır;

- Oligoovulasyon veya anovulasyon
- Klinik ve/veya biyokimyasal hiperandrojenizm bulguları
- Ultrasonografi ile PKO bulgusu (her overde 2-9 mm boyutlarında ≥ 12 mm folikül ve/veya over volümünün 10 ml'den daha büyük olması)

Polikistik overin sonografik özelliği, her overde 2-9 mm boyutunda 12 veya daha fazla folikül ve/veya over volümünün artmış olmasıdır (>10 ml). Bu tanımlamada foliküllerin over içindeki dağılımının (perifere dizilmiş veya over içine dağılmış), over stromasının ekojenitesinin nasıl olduğunun önemi yoktur. Ultrasonografide bu bulguların olması o overi PKO olarak değerlendirmek için yeterlidir (4,5). Unutulmamalıdır ki bazı kadınlarda düzenli adet görmelerine ve klinik ve biyokimyasal hiperandrojenizm bulgusu olmamasına rağmen ultrasonografide overler polikistik veya multikistik olarak değerlendirilmektedir.

Her ne kadar PKOS tanısı konusunda evrensel kabul edilmiş tanı kriterlerinin benimsenmesi için anlamlı adımlar atılmış olsa da polikistik over sendromlu infertil kadının yönetimi konusunda optimal tedavi tanımlanmamıştır. Bu konudaki açığı gidermek için 2008 yılında Selanik'te PKOS konusunda çalışan uzmanların katıldığı bir çalıştay düzenlendi. Bu çalıştayda PKOS'un yönetiminde; hayat tarzı değişiklikleri, farmakolojik ajanlarla ovulasyon indüksiyonu, insülin sensitize eden ajanlar, cerrahi ve Yardımla Üreme Yöntemleri (ART)'ne kadar geniş bir yelpazede yer alan birçok tedavi seçeneğine dair konsensus kararları alınmıştır (6). **Bu bölümde polikistik over sendromu ve infertilite sorunu ile başvuran bir kadının yönetiminden bahsedilecektir.**

Hayat Stili Değişiklikleri

Obezite

PKOS hastalarının %35- 60'ında obezite sorunu mevcuttur. PKOS ilişkili hiperandrojenizm, vücut kitle indeksinden bağımsız artmış

KAYNAKLAR

1. Speroff I, Fritz M. Anovulation and polycystic ovary. In: *Clinical Gynecologic Endocrinology and Infertility*, 7th edn. Lippincott Williams and Wilkins; Baltimore, MA, 2005; pp. 470-83.
2. 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. *Fertil Steril* 2004;81:19-25.
3. 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. *Hum Reprod* 2004;19:41-7.
4. Azziz R. Diagnostic criteria for polycystic ovary syndrome: a reappraisal. *Fertil Steril* 2005;83:1343-6.
5. Bucket WM, Bouzayen R, Watkin KL, Tulandi T, Tan SL. Ovarian stromal echogenicity in women with normal and polycystic ovaries. *Hum Reprod* 2003; 18:598-603.
6. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil Steril* 2008;89: 505-522.
7. Patel SM, Nestler JE. Fertility in polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 2006;35:137-55.
8. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrhic infertility. *J Clin Endocrinol Metab* 1998;83:2361-5.
9. Balen AH, Platteau P, Andersen AN, Devroey P, Sorenson P, Helmgard L, et al. The influence of body weight on response to ovulation induction with gonadotropins in 335 women with World Health Organization group II anovulatory infertility. *BJOG* 2006;113:1195-202.
10. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod Update* 2003;9:359-72.
11. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol* 2001;184:694-702.
12. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12:673-83.
13. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:812-9.
14. Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol* 1992;36:105-11.
15. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trials of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 2005; 353:2111-20.
16. Sjöström L, Lindroos AK, Peltonen M, Torgerson, Bouchard C, Carlsson B, et al. Life style, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-93.
17. Ducluzeau PH, Cousin P, Malyoison E, Bornet H, Vidal H, Laville M, Pugeat M. Glucose to insulin ratio rather than sex hormone binding globulin and adiponectin levels is the best predictor of insulin resistance in nonobese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:3626-31.
18. Ciampelli M, Leoni F, Cucinelli F, Mancuso S, Panunzi S, De Gaetano A, Lanzone A. Assessment of insulin sensitivity from measurements in the fasting state and during an oral glucose tolerance test in polycystic ovary syndrome and menopausal patients. *J Clin Endocrinol Metab* 2005;90:1398-406.
19. Cheang KI, Nestker JE. Should insulin-sensitizing drugs be used in the treatment of polycystic ovary syndrome. *Reprod Biomed Online* 2004;8:440-7.
20. Harborne LR, Sattar N, Norman JE, Fleming R. Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. *J Am Assoc Gynecol Laparosc* 2005;90:4593-8.
21. Lord JM, Flight IHK, Norman RJ. Insulin-sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 2003;(2), Art. No: CD003053. DOI:10.1002/14651858.CD003053.
22. Yılmaz M, Karakoç A, Toruner FB, Cakir N, Tiras B, Ayvaz G, Arslan M. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecol Endocrinol* 2005; 21:154-60.
23. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles and insulin sensitivity in polycystic ovary syndrome: a randomized, double blinded, placebo controlled 6 month trial, followed by open, long term clinical evaluation. *J Clin Endocrinol metab* 2000; 85:139-46.
24. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined life style modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double blind multicentre study. *Hum Reprod* 2006;21:80-9.
25. Glueck CJ, Goldenberg N, Wang P, Loftsring M, Sherman A. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone, and the development of gestational diabetes. A Prospective longitudinal assessment of women with polycystic ovary syndrome from pre-conception throughout pregnancy. *Hum Reprod* 2004;19:51-21.
26. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin or both for infertility in the polycystic ovary syndrome. *N Eng J Med* 2007;356:551-66.
27. Alivannis P, Giannikouris I, Paliouras C, Arvanitis A, Volanaki M, Zervos A. Metformin associated lactic acidosis treated with continuous renal replacement therapy. *Clin Ther* 2006;28:396-400.
28. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Rep*

- rod 2002;17:2858-64.
29. Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Hum Reprod* 2004;19:1734-40.
 30. Vanky E, Hjorth-Hansen H, Carlsen SM. Metformin and early pregnancy? *Fertil Steril* 2006;86:1551-2.
 31. Homburg R. Clomiphene citrate-end of an era? A mini-review. *Hum Reprod* 2005;20:2043-51.
 32. Messinis IE. Ovulation induction: a mini review. *Hum Reprod* 2005;20:2688-97.
 33. Eijkemans MJ, Imani B, Mulders AG, Habbema JD, Fauser BC. High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2). *Hum Reprod* 2003;18:2357-62.
 34. Parsanezhad ME, Alborzi S, Motazedian S, Omrani G. Use of dexamethasone and clomiphene citrate in the treatment of clomiphene resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospective double-blind, placebo controlled trial. *Fertil Steril* 2002;51001-4.
 35. Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R. Gonadotropin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome (Cochrane review). *The Cochrane Library*,(4):CD000410. 2000. Oxford: update Software.
 36. Kosmas IP, Tatsioni A, Fatemi HM, Kolibianakis EM, Tournaye H, Devroey P. Human chorionic gonadotropin administration vs luteinizing monitoring for intrauterine insemination timing, after administration of clomiphene citrate: a meta analysis. *Fertil Steril* 2007;87:607-12.
 37. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction of ovulation. *Hum Reprod Update* 1997;3:359-65.
 38. Daly DC, Walters CA, Soto-Albors CE, Tohan N, Riddick DH. A randomized study of dexamethasone in ovulation induction with clomiphene citrate. *Fertil Steril* 1984;41:844-8.
 39. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle stimulating hormone in poor responders. *Fertil Steril* 2002;77:776-80.
 40. Al-Omari WR, Suliman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. *Int J Gynaecol Obstet* 2004;85:289-91.
 41. Healy S, Tan SL, Tulandi T, Biljan M. Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril* 2004;82:1561-1563.
 42. Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T. A randomized trial of superovulation with two different doses of letrozole. *Fertil Steril* 2006;85:161-4.
 43. Balasch J, Fabregues F, Creus M, Casamitjana R, Puerto B, Vanrell JA. Recombinant human follicle-stimulating hormone for ovulation induction in polycystic ovary syndrome: a prospective, randomized trial of two starting doses in a chronic low-dose step up protocol. *J Asist Reprod Genet* 2000;17:561-5.
 44. White DM, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, et al. Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. *J Clin Endocrinol Metab* 1996;81:3821-4.
 45. Christin-Maitre S, Hugues JN. A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome. *Hum Reprod* 2003;18:1626-31.
 46. Practice committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. *Fertil Steril* 2006;86(suppl):S178-83.
 47. Homburg R, Howles CM. Low dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, results, reflections and refinements. *Hum Reprod Update* 1999;5:493-9.
 48. Grana-Barcia M, Liz-Leston J, Lado-Abel J. Subcutaneous administration of pulsatile gonadotropin-releasing hormone decreases serum follicle-stimulating hormone and luteinizing hormone levels in women with polycystic ovary syndrome: a preliminary study. *Fertil Steril* 2005;83:1466-72.
 49. Homburg R, Eshel A, Kilborn J, Adams J, Jacobs HS. Combined luteinizing hormone releasing hormone analogue and exogenous gonadotrophins for the treatment of infertility associated with polycystic ovaries. *Hum Reprod* 1990;5:32-5.
 50. Scheele F, Hompes PG, van der MM, Schoute E, Schoemaker J. The effects of a gonadotropin-releasing hormone agonist on treatment with low-dose follicle stimulating hormone in polycystic ovary syndrome. *Hum Reprod* 1993;8:699-704.
 51. Tan SL, Kingsland C, Campbell S, et al. The long protocol of administration of gonadotropin releasing hormone agonist is superior to the short protocol for ovarian stimulation for in vitro fertilization. *Fertil Steril* 1992;57:810-4.
 52. Daya S, Gunly J. Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction cycles. *Cochrane Database Syst Rev* 2003.
 53. European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. *Hum Reprod* 2001;16:644-51.
 54. North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. *Fertil Steril* 2001;75:35-45.
 55. Olivennes F, Taieb J, Frydman R, Bouchard P. Triggering of ovulation by a gonadotrophin releasing hormone agonist in patients pretreated with a GnRH antagonist. *Fertil Steril* 1996;66:151-3.
 56. Itskovitz-Eldor J, Kol S, Mannaerts B. Use of a single bolus of agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of OHSS: preliminary report. *Hum Reprod* 2000;15:1965-8.
 57. Fauser B, Jong D, Olivennes F, et al. Endocrine profile after triggering of final oocytes maturation with GnRH agonist after co-treatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for IVF. *J Clin Endocrinol Metab* 2002;87:709-15.