

## POLİKİSTİK OVER SENDROMUNDА BESLENME VE DİYET YÖNETİMİ

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### GİRİŞ

Polikistik overlerin patofizyolojik özellikleri ve klinik önemini anlamak 18. yüzyılın ortalarından beri uğraşılan bir konudur. İlk tanımı, büyümüş, yumuşak kapsülle çevrili polikistik overler şeklinde 1844 yılında yapılmış olup zaman içinde disfonksiyonel uterus kanama ile büyük, polikistik overler arasında bir ilişki olduğu düşünülmüş ve bu teori de tedavi seçenekleri olarak overin wedge rezeksyonunu akillara getirmiştir. Gebe kadınların idrarlarından elde edilen gonadotropinlerin kemirgenlerde multiple ovarian kist oluşumunu indüklediği gözlendiğinde (Yıl 1926), anterior hipofiz hormonlarının overdeki morfolojik değişimlerden sorumlu olabileceği düşünüldü. Ardından 1935 yılında, Irving F. Stein ve Michael L. Leventhal tarafından anovulasyon ile ilişkili bir semptom kompleksi tanımlandı ve bu semptom kompleksi hiperandrojenizm, amenore ve infertilite olup yazarların adıyla tanımlanan bir sendrom olarak literatürde yer aldı. Bu iki hekim, amenore, hirsutizm ve büyük polikistik overleri olan 7 hasta sundular ki bu hastaların 4'ü obez idi. Üstelik bu hastaların hepsinin bilateral ovaryen wedge rezeksyon sonrası düzenli menstrüel siklus yaşadıklarını ve hatta iki hastanın gebe kaldığını rapor ettiler. Hipotezleri, kalınlaşmış olan ovaryen kapsüllerin

folliküllerin yüzeyden ayrılmasını engellediği yönündeydi (1).

Reproduktif dönemdeki kadınların % 4-12'inde görülen polikistik over sendromu (PKOS) bu prevalansı ile kadınlarda en yaygın görülen endokrinopati olmuştur (2,3,4). Tahminler, çalışma populasyonu, overin ultrasonografik görüntülenmesine dayanır ve bu şekilde bazı tanı kriterleri geliştirilmiştir.

Polikistik overlerin gelişiminden sorumlu olan patofizyolojik mekanizmalar, jinekologları uzun yıllar boyunca meşgul etmiş ve tanımlanması da oldukça zor olmuştur. Bununla birlikte basit ve kliniği oldukça iyi açıklayan bir cevap öne sürülebilir. Tipik polikistik over, yeterince uzun süren bir kronik anovulasyon olduğunda gerçekleşmektedir. Pelvik ultrasonografi ile ortaya konan polikistik overler anovulatuvar kadınların % 57'inde gözlenmiştir (5). Anovulasyonun pek çok sebebi olduğu için polikistik overin de pek çok sebebi vardır ve sonuç fonksiyonel bir bozulmadır.

Önceleri overlerde patolojik bozulmalar patofizyolojiden sorumlu tutulurken artık endokrin çevrenin bozukluklarının, overleri yansittığı düşünülmektedir.

PKOS patofizyolojisinden bahsetmek, beslenmenin bu endokrin çevre ile ilişkisini ve etkisini ortaya çıkarmakta faydalı olacaktır. Androjenler,

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na neden olabilmektedir. Tabii ki sigara kullanımı gibi kardiyometabolik riski artıran faktörlerle ilgili de çözüm sağlanmalıdır. Bu bağlamda hastalara psikolojik destek ve davranışsal terapiler de sağlanabilir.

Yüzde 5' lik bir kilo kaybı bile semptomlarda ve hormonal profilde önemli düzelmeler sağlamaktadır. Diyette kalori miktarı ve kaloriye hangi besin öğelerinin ne kadar katkıda bulunduğu önemli parametrelerdir. Diyete mutlaka düzenli egzersizin de eşlik etmesi gereklidir çünkü aynı beslenme programına rağmen PKOS'lu hastalarda kilo verme, kontrol hastalarına göre daha zor sağlanmaktadır.

Beslenme içerikleri arasında yağ, karbohidrat ve proteinin yanı sıra vitamin D, selenyum, magnezyum gibi vitamin ve mineraller de merak konusu olmuş ve bunlarla ilgili çeşitli çalışmalar yapılmıştır. Çoğunlukla kilit mekanizma insülin direnci olup insülin duyarlığını artırıcı düzenlemeler şu an için tedavi hedefleri arasında önde gelmektedir. Tabii ki semptomlara yol açan androjen fazlalığı ve ovulasyon bozuklukları da diğer tedavi hedefleri arasında yer almaktadır.

PKOS'lu kadınların ailelerinde de PKOS görülmesi, ailede genetik yatkınlığı akla getirirken ayrıca ailesel beslenme alışkanlıklarının da nesiller arasında aktarılabileceği göz önünde bulundurulmalıdır. Beslenme alışkanlıklarını ve yaşam tarzi değişikliklerinin ailenin daha sonraki nesillerinde de sağlıklı değişimlere öncülük edeceği akılda tutulmalıdır.

Koruyucu hekimliğin hastalık oluştuktan sonra tanı koyup tedavi edici hekimlikten çok önce hastalığın oluşumunu önleyebilmesi tedavi hedeflerinde değişikliklere yol açmaktadır, pek çok kronik hastalık için düşünülen bu hususun PKOS' da da ihmäl edilmemesi oldukça önemli bir strateji olacaktır.

## KAYNAKLAR

1. Clinical Gynecologic Endocrinology and Infertility 8 th Edition Ed: Marc A. Fritz and Leon Speroff Lippincott Williams & Wilkins 2011;Chapter 12: Chronic Anovulation and the Polycystic Ovary Syndrome p.495-532.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinology Metab* 83:3078-3082;1998.
3. Farah L, Lazenby AJ, Boots LR, Azziz R. Prevalence of polycystic ovary syndrome women seeking treatment from community electrologists. Alabama Professional Electrology Association Study Group *J Reprod Med*. 44:870-874;1999.
4. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandras FA, et al: A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 84:4006-4011;1999.
5. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J (Clin Res Ed)*. 1986;293:355-359
6. Judd HL. Endocrinology of polycystic ovarian disease. *Clin Obstet Gynecol* 1978;21:99-114.
7. Rebar R, Judd HL, Yen SS, Rakoff J, et al.: Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J Clin Invest*. 1976;57:1320-1329.
8. Barnes RB, Rosenfield RL. The polycystic ovary syndrome: pathogenesis and treatment. *Ann Intern Med*. 1989;110:386-399.
9. Cheung AP, Chang RJ. Pituitary responsiveness to gonadotrophin-releasing hormone agonist stimulation: a dose-response comparison of luteinizing hormone/follicle-stimulating hormone secretion in women with polycystic ovary syndrome and normal women. *Hum Reprod*. 1995;10:1054-1059.
10. Wild RA. Obesity, lipids, cardiovascular risk, and androgen excess. *Am J Med* 1995;98:27-32.
11. Anderson P, Seljeflot I, Abdelnoor M, et al. Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. *Metabolism* 1995;44:611-616.
12. Guzick DS, Talbott EO, Sutton-Tyrrell K, et al. Carotid atherosclerosis in women with polycystic ovary syndrome: initial results from a case-control study. *Am J Obstet Gynecol* 1996;174:1224-1229.
13. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. *Ann Intern Med* 1997;126:32-35.
14. Danigren E, Janson PO, Johansson S, et al. Polycystic ovary syndrome and risk for myocardial infarction. *Acta Obstet Gynecol Scand* 1992;71:559-604.
15. Dahlgren E, Johansson S, Lindstedt G, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a longterm follow up focusing on natural history and circulating hormones. *Fertil Steril* 1992;57:505-513.
16. Conway GS, Agrawal R, Betteridge DJ, et al. Risk factors for coronary artery disease in lean and obese women

- with the polycystic ovary syndrome. Clin Endocrinol (Oxf) 1992;37:119-125.
17. Dunaif A, Graf M. Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with the polycystic ovary syndrome. J Clin Invest. 1989;83:23-29.
  18. Barbieri RL, Ryan KJ. Hyperandrogenism, insülin resistance, and acanthosis nigricans syndromae: a common endocrinopathy with distinct pathophysiologic features. Am J Obstet Gynecol 1983;147:90-101.
  19. Ehrmann DA, Barnes RB, Rosenfield RL, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141-146.
  20. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18:774-800.
  21. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(3):347-363.
  22. Berek & Novak's Gynecology 15 th Edition Ed: Jonathan S. Berek Lippincott Williams & Wilkins 2012 Chapter 31 Endocrine Disorders Polycystic Ovary Syndrome p: 1075-1090.
  23. Jonard S & Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. Hum Reprod Update 2004;10, 107-117.
  24. Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:2031-2036.
  25. Norman RJ, Masters S, Hague W. Hyperinsulinemia is common in family members of women with polycystic ovary syndrome. Fertil Steril. 1996;66:942-947.
  26. Diamanti-Kandarakis, E. And Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33, 981-1030.
  27. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223-1236.
  28. Abbott DH, Padmanabhan V, Dumesic DA. Contributions of androgen and estrogen to fetal programming of ovarian dysfunction. Reprod Biol Endocrinol 2006;4:17.
  29. Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev Endocr Metab Disord 2007;8:127-141.
  30. Steckler T, Wang J, Bartol FF, et al. Fetal programming: prenatal testosterone treatment causes intrauterine growth retardation, reduces ovarian reserve and increases ovarian follicular recruitment. Endocrinology 2005;146:3185-3193.
  31. Eisner JR, Dumesic DA, Kemnitz JW, et al. Increased adiposity in female rhesus monkeys exposed to androgen excess during early gestation. Obes Res 2003;11:279-286.
  32. Legro RS, Driscoll D, Strauss JF III, et al. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci USA 1998;95:14956-14960.
  33. Kahsar-Miller MD, Nixon C, Boots LR, et al. Prevalance of polycystic ovary syndrome (PCOS) in first degree relatives of patients with PCOS. Fertil Steril 2001;75:53-58.
  34. Yildiz BO, Yarali H, Oguz H, et al. Glucose intolerance, insülin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:2031-2036.
  35. Escobar-Morreale HF& San Millian JL. Abdominal adiposity and the polycystic ovary syndrome. Trends Endocrinol Metab 2007;18:266-272.
  36. Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome. Fertil sterl 2004;81:19-25.
  37. Rosenfield RL. Clinical practice Hirsutism N Engl J Med 2005;353:2578-2588.
  38. Pierpoint T, McKeigue PM, Isaacs AJ, et al. Mortality of women with polycystic ovary syndrome at longterm follow-up. J Clin Epidemiol. 1998;51:581-586.
  39. Azziz R, Marin C, Hoq L, et al. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Epidemiol Metab 2005;90:4650-4658.
  40. Escobar-Morreale HF, et al. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. Fertil Steril 2011;95:1048-1058.
  41. Murri M, et al. Circulating markers of oxidative stress and polycystic ovary syndrome(PCOS): a systematic review and meta-analysis. Hu Reprod Update 2013;19:268-288.
  42. Moran LJ, et al. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010;16:347-363.
  43. De Groot PC, et al. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update 2011;17:495-500.
  44. Hoeger K. Obesity and weight loss in polycystic ovary syndrome. Obstet Gynecol Clin North Am 2001;28(1):85-97 vi-vii.
  45. Martinez-Bermejo E, Luque-Ramirez M, Escobar-Morreale HF. Obesity and the polycystic ovary syndrome. Minerva Endocrinol 2007;32(3):129-40.
  46. Panidis D, Farmakiotis D, Rousso D, Kourtis a, Katsikis I, Krassas G. Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insülin resistance and androgen levels. Fertil Steril 2008;89(4):899-906.
  47. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insülin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 2000;85(8):2767-74.
  48. Jakubowicz DJ, Nestler JE. 17 alpha-Hydroxyprogesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome offer dietary weight loss. J Clin Endocrinol Metab 1997;82(2):556-60.

49. Georgopoulos NA, Saltamavros AD, Vervita V, et al. Basal metabolic rate is decreased in women with polycystic ovary syndrome and biochemical hyperandrogenemia and is associated with insulin resistance. *Fertil Steril* 2009;92(1):250-255.
50. Hirschberg AL, Naessen S, Stridsberg M, Bystrom B, Holtet J. Impaired cholecystokinin secretion and disturbed appetite regulation in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2004;19(2):79-87.
51. Pagotto U, Gambineri A, Vicennati V, Heiman ML, Tschöp M, Pasquali R. Plasma ghrelin, obesity, and the polycystic ovary syndrome: correlation with insulin resistance and androgen levels. *J Clin Endocrinol Metab* 2002;87(12):5625-9.
52. Moran LJ, Noakes M, Clifton PM, Wittert GA, Tomlinson L, Galletly C, et al. Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. *J Clin Endocrinol Metab* 2004;89(7):3337-44.
53. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril* 2004;81(3):630-7.
54. 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(2):812-9.
55. Kasim-Karakas SE, Almario RU, Gregory L, Wong R, Todd H, Lasley BL. Metabolic and endocrine effects of a polyunsaturated fatty acid-rich diet in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004;89(2):615-20.
56. Krebs M, Krssak M, Bernroider E, Anderwald C, Brehm A, Meyerspeer M, et al. Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. *Diabetes* 2002;51(3):599-605.
57. Linn T, Santosa B, Gronemeyer D, Aygen S, Scholz N, Busch M, et al. Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia* 2000;43(10):1257-65.
58. Samaha FF, Iqbal N, et al. A low-carbohydrate as compared with a low fat diet in severe obesity. *N Engl J Med* 2003;348:2074-2081.
59. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. *Diab Care* 2004;27(9):2108-15.
60. Marmot M, Atinmo T, Byers T, Chen J, Hirohata T, Jackson A, Mann JN. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR;2007.
61. Moran LJ, Brinkworth GD, Norman RJ. Dietary therapy in polycystic ovary syndrome. *Semin Reprod Med* 2008;26(1):85-92.
62. Faghoori Z, Fazelian S, et al. Nutritional management in women with polycystic ovary syndrome: A review study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2017;11:429-432.
63. Krishnan S, Rosenberg L, Singer M, Hu FB, Djousse L, Cupples LA, et al. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med* 2007;167(21):2304-9.
64. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000;71(6):1455-61.
65. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diab Care* 2004;27(2):538-46.
66. Augustin LS, Gallus S, Bosetti C, Levi F, Negri E, Franceschi S, et al. Glycemic index and glycemic load in endometrial cancer. *Int J Cancer* 2003;105(3):404-7.
67. Augustin LS, Dal Maso L, La Vecchia C, Parpinel M, Negri E, Vaccarella S, et al. Dietary glycemic index and glycemic load, and breast cancer risk: a case-control study. *Ann Oncol* 2001;12(11):1533-8.
68. Augustin LS, Polesel J, Bosetti C, Kendall CW, La Vecchia C, Parpinel M, et al. Dietary Glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy. *Ann Oncol* 2003;14(1):78-84.
69. Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr* 2005;81(5):976-82.
70. Brynes AE, Mark Edwards C, Ghatei MA, Dornhorst A, Morgan LM, Bloom SR, et al. A randomised four intervention crossover study investigating the effect of carbohydrates on daytime profiles of insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men. *Br J Nutr* 2003;89(2):207-18.
71. Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, Landsberg L. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: the Normative Aging Study. *Am J Clin Nutr* 1993;58(2):129-36.
72. Stender S, Dyerberg J. Influence of trans fatty acids on health. *Ann Nutr Metab* 2004;48(2):61-6.
73. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. *Am J Clin Nutr* 2007;86(2):285-300.
74. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2012;77(3):343-350.
75. Homburg R, Amsterdam A. Polycystic ovary syndrome-loss of the apoptotic mechanism in the ovarian follicles? *Endocrinol Invest* 1998;21(9):552-557.
76. Bikle D. Nonclassic actions of vitamin D. *J Clin Endocrinol Metab* 2009;94(1):26-34.
77. Yıldızhan R, Kurdoğlu M, Adalı E, Kolusarı A, Yıldızhan B, Şahin HG, et al. Serum 25-hydroxyvitamin D concentrations in obese and nonobese women with polycystic ovary syndrome. *Arch Gynecol Obstet* 2009;280(4):559-63.
78. Hahn S, Haselhorst U, Ten S, Quadbeck B, Schmidt M, Roesler S, et al. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. *Exp Clin Endocrinol Diab* 2006;114(10):577-83.

79. Rahimi-Ardabili h, Pourghassem Gargari B, Farzadi L. Effects of vitamin D on cardiovascular disease risk factors in polycystic ovary syndrome women with vitamin D deficiency. *J Endocrinol Invest* 2013;36(1):28-32.
80. Rumawas ME, McKeown NM, Rogers G, Meigs JB, Wilson PW, Jacques PF. Magnesium intake is related to improved insulin homeostasis in the Framingham offspring cohort. *J Am Coll Nutr* 2006;25(6):486-92.
81. Morris BW, MacNeil S, Hardisty CA, et al. Chromium homeostasis in patients with type II (NIDDM) diabetes. *J Trace Elem Med Biol* 1999;13(1-2):57-61.
82. Lydic ML, McNurlan M, et al. Chromium picolinate improves insulin sensitivity in obese subjects with polycystic ovary syndrome. *Fertil steril* 2006;86(1):243-246.
83. Jamilian M, Bahmani F, et al. The effects of chromium supplementation on endocrine profiles, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome: a randomized, double blind, placebo-controlled trial. *Biol Trace Ele Res* 2015;28(Nov).
84. Amooee S, Parsanezhad ME, Ravanbod Shirazi M, Alborzi S, Samsami A. Metformin versus chromium picolinate in clomiphene citrate-resistant patients with PCOS: a double blind randomized clinical trial. *Iran J Reprod Med* 2013;11(8):611-8.
85. Coskun A, Arıkan T, Kilinc M, Arıkan DC, Ekerbicer HC. Plasma selenium levels in Turkish women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2013;168(2):183-6.
86. Luan de C, Li H, Li SJ, Zhao Z, Li X, Liu ZM. Body iron stores and dietary iron intake in relation to diabetes in adults in North China. *Diab Care* 2008;31(2):285-6.
87. Klonoff-Cohen H, Bleha J, Lam-Kruglick P. A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. *Hum Reprod* 2002;17(7):1746-54.
88. Stanton CK, Gray RH. Effects of caffeine consumption on delayed conception. *Am J Epidemiol* 1995;142(12):1322-9.
89. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. *Lancet* 1988;2(8626-8627):1453-6.
90. Cnattingius S, Signorello LB, anneren G, Claesson B, Ekbom A, Ljunger E, et al. Caffeine intake and the risk of first trimester spontaneous abortion. *N Engl J Med* 2000;343(25):1839-45.
91. Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and development risks of caffeine. *Teratology* 2001;64(1):51-78.
92. Escobar-Morreale HF, et al. Prevalence of 'obesity associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. *Hum Reprod Update* 2017;23:390-408.
93. Krebs-Smith SM, Pannucci TR, et al. Update of the Healthy Eating Index HE-2015. *J Acad Nutr Diet* 2018;118(9):1591-1602.
94. Hosseini MS, Dizavi A, et al. Healthy eating index in women with polycystic ovary syndrome: A case control study. *Int J Reprod BioMed* 2017;15(9):575-582.
95. Simon SL, McWhirter L, et al. Morning circadian Misalignment is associated with insulin resistance in girls with obesity and polycystic ovary syndrome. *Journal of Clinical endocrinology &Metabolism* 2019;104(8):3525-3534.
96. Moran LJ, March WA, Whitrow MJ, Giles LC, Davies MJ, Moore VM. Sleep disturbances in a community-based sample of women with polycystic ovary syndrome. *Hum Reprod*. 2015;30(2):466-72.
97. Shreeve N, Cagampang F, Sadek K, Tolhurst M, Houlden A, Hill CM, et al. Poor sleep in PCOS; is melatonin the culprit? *Hum Reprod*. 2013;28(5):1348-53.
98. Vgontzas AN, Legro RS, et al. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab* 2001;86(2):517-520.
99. Potter GDM, Cade JE, et al. Nutrition and the circadian system. *Br J Nutr* 2016;116(3):434-442.