Konu 31

Prematür Over Yetmezliği

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1.GİRİŞ

Prematür over yetmezliği (POY), referans popülasyon için hesaplanmış tahmini ortalama menopoz yaşına göre, iki standart deviasyondan daha küçük yaştaki, amenore, seks steroid eksikliği ve yükselmiş/menopozal gonadotropin düzeylerine sahip kadınları tanımlayan (1), ovaryan disfonksiyon, foliküler kayıp ve intermitan over fonksiyonu ile karakterize bir sendromdur (2-5). Klinik pratikte, beklenen menopoz yaşından önce over fonksiyonlarının kesilmesi ya da 40 yaş altında gelişen hipergonadotropik hipogonadizm/amenore olgularını tarif etmek için kullanılmaktadır.

Prevalansına ilişkin yeterli veri yoktur. Farklı yayınlarda değişen yaş gruplarına göre %0.3-10 arasında değişen oranlar (6-8) bildirilmiş olmakla beraber, 40 yaş altındaki kadınların %1'ni, 30 yaş altındakilerin %0.1'ni, 20 yaş altındakilerin ise %0.01'ni etkilediği tahmin edilmektedir (9). Monozigot ve dizigot ikizlerde POY riski 3-5 kat artmıştır (10, 11).

Son yıllarda pediatrik onkolojik hastalıkların tedavilerinde elde edilen önemli başarılar sonucunda, kür oranlarının artması ve böylelikle kemoterapi ve/veya radyoterapi almış daha fazla sayıda kız çocuğunun olgun yaşlara ulaşması ile POY insidansının hızlı bir şekilde yükseleceği tahmin edilmektedir (7, 12).

POY mutlak bir erken menopoz durumu değildir. Menopozun aksine POY'da over fonksiyonları her zaman kalıcı olarak bitmemektedir (8). Radyasyon veya kemoterapinin indüklediği ovaryan yetmezlik olgularında dahi, yüksek bazal folikül stimülan hormon (FSH) ve düşük estradiol düzeylerinin geçici olabileceği gösterilmiştir (13). Over biyopsisi ile folikül yokluğunun teyit edildiği vakalar arasından, daha sonra gebelik izlenenler bildirilmiştir (8, 14, 15). Genç yaşlardaki spontan POY olgularının %50'sinde beklenmedik intermitan ovaryan fonksiyon ve mensturasyon izlenebilmektedir (2-5, 16). POY başlangıcından 16 yıl sonrasına kadar ovaryan aktivitenin yeniden başlayabildiği bildirilmiştir (17). Sağlıklı normal kadınlarla karşılaştırıldıklarında, 4 aylık gözlemde %20'sinde spontan ovulasyon saptanmakta ve folikül çapı ile serum estradiol düzeyleri arasında zayıf bir korelasyon bulunmaktadır (2). Tanı konulmasını takiben olguların %5-10'unda spontan gebelikler gözlenebilmektedir (18, 19).

Ovaryan yetmezlik ifadesi, tam olarak doğru olmayan, geri dönüşümsüz bir durum algısına neden olmaktadır. Literatürde bu konuda kullanılan alternatif terimler prematür menopoz, hipergonadotropik hipogonadizm, hipergonadotropik amenore ve primer hipogonadizmdir (20-22). Son yıllarda, klinik tablonun geri dönüşümlü olabileceğini yansıtması ve yetmezlik kelimesinin hastalarda oluşturduğu olumsuzluk hissine neden olmaması nedeniyle prematür ovaryan disfonksiyon teriminin kullanımı önerilmektedir (23). Ancak bu konuda henüz ortak bir konsensus oluşmamıştır.

2.Etyolojik faktörler

POY ortaya çıkış şekline göre primer (spontan POY) ya da sekonder (cerrahi, kemoterapi veya radyasyon ile indüklenmiş POY) olabilir. Olguların çoğunluğu idiyopatik olup, sıklıkla herhangi bir etyolojik faktör bulunamamaktadır (24). Etyolojik araştırmalar, vakaların daha çok küçük bir kısmını oluşturan genetik, otoimmün, enfeksiyöz ve iatrojenik faktörlerin ortaya çıkarılmasına veya ekarte edilmesine yöneliktir. Son yıllarda kemoterapötik ajanlar-

olup, kriyoprezervasyon için adaydırlar (61). Meme kanseri hastalarında kriyoprezervasyon için oosit toplanması, cerrahi tedavi zamanı ile kemoterapi başlama zamanı arasındaki ortalama süreyi, dolayısı ile kanser tedavisini geciktirmemektedir (128).

Son yıllarda oosit kriyoprezervasyonu başarı oranları giderek artmaktadır. 2005 yılından önce bildirilmiş yavaş soğutma tekniği ile oosit kriyoprezervasyonu çalışmaları sonuçlarında, transfer başına klinik gebelik oranı %20.6, implantasyon oranı %10.1 ve fertilizasyon oranı %64.9 iken, 2005 yılından sonra bildirilen çalışmaların meta-analizinde vitrifikasyon sonrası transfer başına klinik gebelik oranı %51, implantasyon oranı %20.5 ve fertilizasyon oranı %75.4'tür (129). Over kriyoprezervasyonu sonrası ise şu ana kadar bildirilmiş gebelik bulunmamaktadır.

Over transplantasyonu ortotopik (pelvik transplantasyon) ya da heterotopik (subkutan transplantasyon) olabilir. Heterotopik transplant daha az invazivdir, maliyeti daha ucuzdur ancak canlı doğum bildirilmemiştir (130). 2008 yılına kadar ovaryan transplantasyon sonrası 25 kadın gebelik istemiş, bunların %37'si ortotopik transplantasyon ile gebe kalabilmiştir (131).

Bugün için over kriyoprezervasyonu ve transplantasyonu konularında birçok etik ve teknik sorunlar bulunmaktadır.

Hodgkin hastalığı nedeni ile kemoterapi alan olgulardan GnRH agonisti ile hormonal supresyon yapılanların %96.9'unda kemoterapi sonrası menstruasyon yeniden başlarken, supresyon yapılmayanların ancak %63'ünde başlamıştır, bununla beraber elde edilen gebelik oranları arasında farklılık görülmemiştir (132). FSH'daki yükselmeyi önlemesi, utero-ovaryan perfüzyonu azaltması, over üzerine doğrudan etki ile intragonadal antiapopitotik molekülleri up-regüle etmesi ve undiferansiye germinal kök hücrelerini koruması fertilite koruyucu etkilerinin muhtemel mekanizmalarıdır (132). Hormonal supresyon fertilite koruyucu etki dışında kemoterapi sonrası ciddi trombositopeniye bağlı menorajinin önlenmesini de sağlar. Kemoterapi sonrası trombosit sayısı <25000 olan olgulardan GnRH agonisti ile supresyon yapılanların hiçbirisinde menoraji görülmezken, medroksiprogesteron asetat verilenlerin %21.4'ünde, herhangi bir tedavi verilmeyenlerin ise %40'ında orta-ağır menoraji izlenmiştir (133). Bir yıl süre ile adjuvan kemoterapi ile birlikte GnRH agonisti alan meme kanseri hastalarından 40 yaşından küçük olanların hepsinde menstruasyon geri dönmüştür, 40 yaşından büyüklerde ise bu oran %56'da kalmıştır (134). Estrojen reseptörü pozitif olanlarda ek klinik fayda sağlanması da muhtemeldir.

Apoptozis germ hücre kaybının bir mekanizmasıdır. Sfingomyozin 1 fosfat tedavisi, apoptozis için erken sinyal görevi gören bir sfingolipid olan ceramide'in etkisine karşı koyarak, radyasyonun indüklediği apoptozise karşı overleri korur (135).

Kriyoprezervasyon ile saklanmış oosit ya da embriyosu olmayan, ovaryan rezerv testleri ile teyit edilmiş menopozal gonadotropin düzeylerine sahip, fertilite arzusu olan ileri yaş olgulara oosit donasyonu önerilebilir.

KAYNAKLAR

1. Rees M & Purdie D. Premature menopause. In: Management of the menopause: the handbook. 4th edn. Royal Society of Medicine Press Ltd, 2006, pp. 142–149.
2. Nelson LM, Anasti JN, Kinzey JN et al. Development of luteinised Graffian folicles in patient with karyotypically normal spontaneous premature ovarian failure. J Clin Endocrinol Metab 1994; 79: 1470–75.
3. Rebar RW, Erickson GF & Yen SSC. Idiopathic premature ovarian failure: clinical and endocrine characteristics. Fertil Steril 1982; 37: 35–41.
4. Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: Evidence for accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab 1987; 65: 1231–1237.
5. Richardson SJ, Nelson JF. Follicular depletion during the menopausal transition. Ann NY Acad Sci 1990; 592: 13–20.
6. Aiman J, Smentek C. Premature ovarian failure. Obstet Gynecol 1985; 66: 9–14.
7. Panay N & Fenton A. Premature ovarian failure: a growing concern. Climacteric 2008 Feb; 11: 1–3.
8. Rebar RW & Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. Fertil Steril 1990; 53: 804–810.
9. Coulam CB, Adamson SC & Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol

1986; 67: 604.
10. Gosden RG.Survival of allografts in an experimental animal model. Pediatr Transplant. 2007 Sep; 11(6): 628-33
11. van Asselt et al. Heritability of menopausal age in mothers and daughters. Fertil Steril 2004 Nov; 82(5): 1348-51
12. Sklar CA, Mertens AC, Mitby P et al. Premature menopause in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006; 98: 890–896.
13. Damewood MD, Grochow LB. Prospects for fertility after chemotherapy or radiation for neoplastic disease. Fertil Steril 1986; 45: 443–59.
14. Szlachter BN, Nachtigall LE, Epstein J, et al. Premature ovarian failure: A reversible entity? Obstet Gynecol 1979; 54: 396–8.
15. Jequier AM, Davis SR. The premature menopause: An example of a difficult diagnostic problem. In Programs and Abstracts of the Ist Australasian Menopause Society Congress, Perth, Australia, 1997
16. van Karseren YM & Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999; 5: 483–492.
17. Cowchock FS, McCabe JL, Montgomery BB. Pregnancy after corticosteroid administration in premature ovarian failure (polyglandular endocrinopathy syndrome). Am J Obstet Gynecol 1988; 158: 118–9
18. Stenchever MA, Droegemueller W, Herbst AL et al. Primary and secondary amenorrhoea. In Stenchever MA, Droegemueller W, Herbst AL & Mishell DRJ (eds.). Comprehensive gynecology. St Louis: Mosby, 2001, pp. 1099–1123.
19. Horner E, Kay A & Panay N. Management of women with premature ovarian failure at a main teaching hospital. Maturitas 2006; 54: S50.
20. Rebar RW, Carter JM, Kim JG, Sites CK, Song DY, LaBarbera AR. Hypergonadotropic forms of amenorrhea. Randolf (MA): Serono Symposia; 1993. p. 275–93.
21. Rebar RW, Cedars MI. Hypergonadotropic amenorrhea. In: Filicori M, Flamigni C, editors. Ovulation induction: basic science and clinical advances. Amsterdam (Netherlands): Elsevier Science B.V.; 1994. p. 115–21.
22. Rebar RW. Primary hypogonadism in young women: socalled "premature ovarian failure." Menopause Manage 1995; 4: 25–8.
23. Panay N, Kalu E. Management of premature ovarian failure. Best Pract Res Clin Obstet Gynaecol 2009 Feb; 23(1): 129-40.
24. Rebar RW & Cedars MI. Hypergonadotropic forms of amenorrhoea in young women. Endocrinol Metab Clin North Am 1992; 21: 173–191.
25. Duncan M, Cummings L, Chada K. Germ cell deficient (gcd) mouse as a model of premature ovarian failure. Biol Reprod 1993; 49: 221–227.
26. Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Med Genet 2000; 97: 189–194.
27. Marozzi A, Vegetti W, Manfredini E et al. Association between idiopathic premature ovarian failure and fragile X permutation. Hum Reprod 2000; 15: 197–202.
28. Bussani C, Papi L, Sestini R et al. Premature ovarian failure and fragile X premutation: a study on 45 women. Eur J Obstet Gynecol Reprod Biol 2004; 112: 189–191.
29. LaBarbera AR, Miller MM, Ober C, Rebar RW. Autoimmune etiology in premature ovarian failure. Am J Reprod Immunol Microbiol 1988; 16: 115–22.
30. Rebar RW. Premature ovarian failure. Obstet Gynecol. 2009 Jun; 113(6): 1355-63
31. Tejada MI et al. Analysis of the molecular parameters that could predict the risk of manifesting premature ovarian failure in female premutation carriers of fragile X syndrome Menopause: The Journal of The North American Menopause Society 2008 (5); 15: 945-9
32. Davis SR. Premature ovarian failure. Maturitas 1996; 28:1–8.
33. Kim TJ, Anasti JN, Flack MR, et al. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol 1997; 89:777–779.
34. Ryan MM, Jones HR Jr. Myasthenia gravis and premature ovarian failure. Muscle Nerve 2004; 30: 231–233.
35. Balen A. Reproductive Endocrinology for the MRCOG and beyond. 1st ed. London: RCOG Press; 2003.
36. Monnier-Barbarino P, Forges T, Faure GC, Bene MC. Gonadal antibodies interfering with female reproduction. Best Pract Res Clin Endocrinol Metab 2005; 19: 135–148.
37. Drexhage HA, Bottazzo GF, Bitensky L, et al. Thyroid growth-blocking antibodies in primary myxoedema. Nature 1981; 289:594–596.
38. Lindstrom JM, Seybold ME, Lennon VA, et al. Antibody to acetylcholine receptor in myasthenia gravis: Prevalence, clinical correlates, and diagnostic value. Neurology 1976; 26: 1054–9.
39. Bakalov VK, Vanderhoof VH, Bondy CA et al. Adrenal antibodies detect asymptomatic autoimmune adrenal insufficiency in young women with spontaneous premature ovarian failure. Hum Reprod 2002; 17: 2096–2100.
40. Falorni A, Laureti S, Candeloro P et al. Steroid-cell auto-antibodies are preferentially expressed in women with premature ovarian failure who have adrenal auto-immunity. Fertil Steril 2002; 78: 270–279.
41. Nelson LM, Anasti JN, Flack MR. Premature ovarian ovarian failure. In: Adashi EY, Rock JA, Rosenwaks Z, editors. Reproductive Endocrinology, Surgery and Technology. Philadelphia: Lippincott-Raven; 1996. pp. 1394–1410.
42. Bannatyne P, Russell P, Sherman RP. Autoimmune oophoritis: A clinicopathologic assessment of 12 cases. Int J Gynecol Pathol 1990; 9:191–207.
43. Irvine WJ, Chan MMW, Scarth L, et al. Immunological aspects of premature ovarian failure associated with idiopathic Addison's disease. Lancet

1968; 2: 7574–90.
44. Sedmak DD, Hart WR, Tubbs RR. Autoimmune oophoritis: A histopathologic study of involved ovaries with immunologic characterization of the mononuclear cell infiltrate. Int J Gynecol Pathol 1987; 6: 73–89.
45. Coulam CB, Ryan RJ. Premature menopause etiology. Am J Obstet Gynecol 1979; 133: 639–643.
46. Forges T, Monnier-Barbarino P, Faure GC, Bene MC. Autoimmunity and antigenic targets in ovarian pathology. Hum Reprod Update 2004; 10: 163–175.
47. Nelson LM, Kimzey LM, MerriamGR, et al. Increased peripheral T lymphocyte activation in patients with karyotypically normal spontaneous premature ovarian failure. Fertil Steril 1991; 55: 1082–1087.
48. Wheatcroft NJ, Salt C, Milford-Ward A et al. Identification of ovarian antibodies by immunofluorescence, enzyme-linked immunosorbent assay or immunoblotting in premature ovarian failure. Hum Reprod 1997; 12: 2617–2622.
49. Nagamine K, Peterson P, Scott HS. Positional cloning of the APECED gene. Nat Genet 1997; 17:393–398.
50. The Finish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 1997; 17: 399–403.
51. Laml T, Preyer O, Umek W, et al. Genetic disorders in premature ovarian failure. Hum Reprod Update 2002; 8: 4834–4891.
52. Maclaren N, Chen QY, Kukreja A, et al. Autoimmune hypogonadism as part of an autoimmune polyglandular syndrome. J Soc Gynecol Investig 2001; 8:S52–S54.
53. Morrison JC, Givens JR, Wiser WL et al. Mumps oophritis: a cause for premature menopause. Fertil Steril 1975; 26: 655–659.
54. Vermeulen A. Environment, human reproduction, menopause, and andropause. Environ Health Perspec 1993; 101: 91–100.
55. Muller J. Disturbance of pubertal development after cancer treatment. Best Pract Res Clin Endocrinol Metab 2002; 16: 91–103.
56. Radford JA, Shalet SM, Lieberman BA. Fertility after treatment for cancer. BMJ 1999; 319: 935–936.
57. Meirow D. Ovarian injury and modern options to preserve fertility in female cancer patients treated with high dose radio-chemotherapy for hemato-oncological neoplasias and other cancers. Leuk Lymphoma 1999; 33: 65–76.
58. Larsen EC, Mu¨ ller J, Schmiegelow K, et al. Reduced ovarian function in longterm survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab 2003; 88: 5307–5314.
59. Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Am 1998; 27: 927–943.
60. Familiari GA, Caggiatti A, Nottola SA, et al. Ultrastructure of human ovarian primordial folicles after combination chemotherapy for Hodgkin's disease. Hum Reprod 1993; 8: 2080–2087.
61. Sonmezer M, Oktay K. Ferility preservation for female patients. Hum Reprod Update; 2004; 19: 477-80.
62. Shalet SM. Effect of cancer chemotherapy on gonadal function of patients. Cancer Treat Rev 1980; 7: 141-52
63. Koyama H, Wada T, Nishizawa Y, et al. Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. Cancer 1977; 39: 1403–1409.
64. Beerendock CCM, Braat DDM. Present and future options for the preservation of fertility in female adolescents with cancer. Endocr Dev 2005; 8: 166–175.
65. Bath LE, Tydeman G, Critchley HOD, et al. Spontaneous conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis: case report. Hum Reprod 2004; 19:2569–2572.
66. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001; 7:535–543.
67. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol. 1999 ; 17: 2365-70.
68. Meirow D. Reproduction post chemotherapy in young cancer patients. Mol Cell Endocrinol 2000; 27: 123–131.
69. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 1996; 14: 1718–1729.
70. Marmor D. [Fertility in women after cancer therapy]. Contracept Fertil Sex 1999; 27:417–422.
71. Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005; 62: 738–744.
72. Sklar C. Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monogr 2005; 34: 25–27.
73. Schuck A et al. Ovarian function following pelvic irradiation in prepubertal and pubertal girls and young adult women. Strahlenther Onkol 2005; 181:534–539.
74. Wallace WHB, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod 2003; 18: 117–121.
75. Sanders JE. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996; 87: 3045-3052.
76. Letur-Konirsch H, Guis F, Delanian S. Uterin restoration by radiation sequel regression with combined pentoxifylline-tocopherol: a phase II study, Fertil Steril 2002; 77: 1219-26
77. Green DM. Pregnancy outcome of female survivors of childhood cancer: A report from the childhood cancer survivor study. Am J Obstet Gynecol 2002; 187: 1070-80

78. Conway GS, Kaltsas G, Patel A et al. Characterisation of idiopathic premature ovarian failure. Fertil Steril 1996; 65: 337–341.
79. Chakravati S, Collins WP, Forecart JD et al. Hormone profile after the menopause. BMJ 1976; 2: 784–786.
80. Alzubaidi NH, Chapin HL, Vanderhoof VH et al. Meeting the needs of young women with secondary amenorrhoea and spontaneous premature ovarian failure. Obstet Gynecol 2002; 99: 720–725.
81. Tibiletti MG, Testa G, Vegetti Wet al. The idiopathic forms of premature menopause and early menopause show the same genetic pattern. Hum Reprod 1999; 14: 2731–2734.
82. Barnhart K, Osheroff J. We are overinterpreting the predictive value of serum folicle-stimulating hormone levels. Fertil Steril. 1999; 72 (1): 8-9.
83. Creus M et al. Day 3 serum inhibin B and FSH and age as predictors of assisted reproduction treatment outcome. Hum Reprod. 2000; 15 (11): 2341-6.
84. Thum MY, Abdalla HI, Taylor D. Relationship between women's age and basal folicle-stimulating hormone levels with aneuploidy risk in in vitro fertilization treatment. Fertil Steril 2008; 90 (2): 315-21
85. de Koning CH et al. The distribution of FSH receptor isoforms is related to basal FSH levels in subferile women with noemal menstrüel cycles. Human Reprod 2006; 21 (2): 443-6.
86. Frazier LM, Grainger DA, Schieve LA, Toner JP. Folicle-stimulating hormone and estradiol levels independently predict the success of assisted reproductive technology treatment. Fertil Steril 2004 Oct; 82 (4): 834-40.
87. Muttukrishna et al. Antral folicle count, anti müllerian hormone and inhibin B predictors of ovarian response in assisted reproductive rechnology? BJOG 2005; 112 (10): 1384-90.
88. Hansen KR, Morris JL, Thyer AC, Soules MR. Reproductive aging and variability in the ovarian antral folicle count: application in the clinical setting Fertil Steril 2003; 80 (3): 577-583
89. Nelson LM, Shawker TH, Merriam GR. Occult folicular development in patients with karyotypically normal spontaneous premature ovarian failure [abstract 693]. In Programs and Abstracts of the 72nd Annual Meeting of the Endocrine Society, Atlanta, Georgia, 1990.
90. Broekmans FJ, Kwee J, Hendriks DJ et al. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006; 12: 685–718.
91. Urbancsek J, Hauzman E, Klinga K, Rabe T, Papp Z, Strowitzki T. Use of serum inhibin B levels at the start of ovarian stimulation and at oocyte pickup in the prediction of assisted reproduction treatment outcome Fertil Steril 2005; 85 (2): 341-8
92. van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, Themmen AP. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. Hum Reprod. 2002 Dec; 17(12): 3065-71.
93. van der Stege JG et al. Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. Menopause. 2008 Jan-Feb;15(1):23-31.
94. Manuel M, Katayama PK, Jones HW Jr. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol 1976; 124: 293–300
95. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88:2404-2411.
96. Simon T. Why is cardiovascular health important in menopausal women? Climateric 2006; 9: 13-18.
97. Benetti-Pinto CL, Castro N, Grassiotto OD, Garmes HM. Leptin and adiponectin blood levels in women with premature ovarian failure and age- and weight-matched women with normal menstrüel cycles. Menopause. 2009 Jul 15.
98. Ettinger B, Pressman A, Sklarin P, Bauer DC, Cauley JA, Cummings SR. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. J Clin Endocrinol Metab 1998; 83: 2239–43
99. Singer D & Hunter M (eds.). Premature menopause: a multi-disciplinary approach. Whurr Publishers Ltd, 2000.
100. Liao KL, Wood N & Conway GS. Premature menopause and psychological well-being. J Psychosom Obstet Gynaecol 2000; 21: 167–174.
101. Kalantaridou SN, Vanderhoof VH, Calis KA, Corrigan EC, Troendle JF, Nelson LM. Sexual function in young women with spontaneous 46,XX primary ovarian insufficiency. Fertil Steril 2008; 90: 1805–11.
102. Kalantaridou SN, Naka KK, Papanikolaoua E et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J Clin Endocrinol Metab 2004; 89: 3907–3913.
103. Grodstein F, Manson JE & Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Women's Health (Larchmt) 2006; 15: 35–44.
104. Lokkegaard E, Jovanovic Z, Heitmann BL et al. The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. Maturitas 2006; 53: 226–233.
105. van Der Voort DJ, van Der Weijer PH & Barentsen R. Early menopause: increased fracture risk at older age. Osteoporos Int 2003; 14: 525–530.
106. Pouilles JM, Tremollieres F, Bonneu M et al. Influence of early age at menopause on vertebral bone mass. J Bone Miner Res 1994; 9: 311–315.
107. Sherwin BB. Estrogen and cognitive aging in women. Neuroscience 2006; 138: 1021–1026.
108. Rapp PR, Morrison JH & Roberts JA. Cyclic estrogen replacement improves cognitive function in aged ovariectomized rhesus monkeys. J Neurosci 2003; 23: 5708–5714.
109. Ng C, Sacks G, Turner C et al. Impact of alarmist media on HRT use for premature menopause

[Abstracts of the 20th Meeting of the ESHRE, Berlin Germany]. Hum Reprod 2004: i42.
110. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestogin in healthy postmenopausalwomen. Principal result from the Women's Health Initiative randomised controlled trial. JAMA 2002; 288: 321.
111. Mishell Jr. DR, Nakamural RM, Crosignani PG et al. Serum gonadotropins and steroid patterns during the normal menstrüel cycle. Am J Obstet Gynecol 1971; 111: 60–65.
112. Chetkowski RJ, Meldrum DR, Steingold KA et al. Biologic effects of transdermal estradiol. N Engl J Med 1986; 314: 1615–1620.
113. Rees M & Panay N. The use of alternatives to HRT for the management of menopause symptoms. RCOG, London Scientific Advisory Committee, 2006. Opinion Paper 6.
114. Davis SR. Testosterone influences libido and well being in women. Trends Endocrinol Metab 2001; 12: 33–37.
115. Braunstein GD, Sundwall DA, Katz M et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005; 165: 1582–1589.
116. Mascarenhas C, Lambe M, Bellocco R et al. Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival. Int J Cancer 2006; 119: 2907–2915.
117. Tangjitgamol S, Manusirivithaya S, Hanprasertpong J et al. Hormone replacement therapy after treatment of endometrial cancer. Gynecol Obstet Invest 2008; 65: 35–38.
118. Kanders BS & Lindsay R. The effect of physical activity and calcium intake on the bone density of young women age 24–35. Med Sci Sports Exerc 1985; 17: 284.
119. Loprinzi CL, Barton DL, Sloan JA et al. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause 2008 Apr 18
120. Guttmann H, Weiner Z, Nikolski E et al. Choosing an oestrogen replacement therapy in young adult women with Turner syndrome. Clin Endocrinol 2001; 54: 159–164.
121. Hampton NR, Rees MC, Lowe DG et al. Levonorgestrel intrauterine system (LNG-IUS) with conjugated oral equine estrogen: a successful regimen for HRT in perimenopausal women. Hum Reprod 2005; 20: 2653–2660.
122. Van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999; 5: 483–492.
123. Letur H, Martin-Pont B, Fe´ nichel P, GEDO. Spontaneous pregnancies and premature menopause. Gynecol Obstet Fertil 2004; 32: 748–755.
124. Donnez J, Squifflet J, Van Eyck AS et al. Restoration of ovarian function in orthotopically transplanted cryopreserved ovarian tissue: a pilot experience. Reprod Biomed Online 2008; 16: 694–704.
125. Huang JY, Tulandi T, Holzer H et al. Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy of fertility preservation. Fertil Steril 2008; 89: 567–572.
126. Son WY, Chung JT, Herrero B, Dean N, Demirtas E, Holzer H, Elizur S, Chian RC, Tan SL.Selection of the optimal day for oocyte retrieval based on the diameter of the dominant folicle in hCG-primed in vitro maturation cycles. Hum Reprod. 2008 Dec; 23(12): 2680-5.
127. Hefler LA, Grimm C, Bentz EK et al. A model for predicting age at menopause in white women. Fertil Steril 2006; 85: 451–454.
128. Madrigrano A, Westphal L, Wapnir I. Egg retrieval with cryopreservation does not delay breast cancer treatment. Am J Surg. 2007 Oct; 194(4): 477-81.
129. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006 Jul; 86(1): 70-80.
130. Oktay K, Buyuk E. Fertility preservation in women undergoing cancer treatment. Lancet. 2004 May 29; 363(9423): 1830.
131. Bedaiwy MA, El-Nashar SA, El Saman AM, Evers JL, Sandadi S, Desai N, Falcone T. Reproductive outcome after transplantation of ovarian tissue: a systematic review. Hum Reprod. 2008 Dec; 23(12): 2709-17.
132. Blumenfeld Z, Avivi I, Eckman A, Epelbaum R, Rowe JM, Dann EJ. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. Fertil Steril. 2008 Jan; 89(1): 166-73.
133. Meirow D, Rabinovici J, Katz D, Or R, Shufaro Y, Ben-Yehuda D. Prevention of severe menorrhagia in oncology patients with treatment-induced thrombocytopenia by luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate.Cancer 2006 Oct 1; 107(7): 1634-41. Erratum in: Cancer. 2007 Aug 15; 110(4): 936.
134. Recchia F, Saggio G, Amiconi G, Di Blasio A, Cesta A, Candeloro G, Rea S. Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. Cancer. 2006 Feb 1; 106(3): 514-23.
135. Morita Y, Perez GI, Paris F, Miranda SR, Ehleiter D, Haimovitz-Friedman A, Fuks Z, Xie Z, Reed JC, Schuchman EH, Kolesnick RN, Tilly JL.Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy.Nat Med. 2000 Oct; 6(10): 1109-14.