

Bölüm 14

PREEKLAMPSİ GÜNCEL BİYOBELİRTEÇLERİ VE YENİ MEKANİZMALAR

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Preeklampsi, daha önce hipertansiyon tanısı almamış olanlarda, gebeliğin 20. haftasından sonra, hipertansiyon ve proteinüri veya proteinüri şartı olmaksızın hipertansiyon ve buna eşlik eden end-organ disfonksiyonu ile karakterize, multisistemik progresif bir hastalıktır. Hastalığa, plasental ve maternal vasküler disfonksiyon neden olur ve doğumdan sonra geriler. Vakaların % 80'inden fazlasında iyi maternal ve fetal sonuçlar olmasına rağmen, bu gebelikler maternal ve/veya fetal mortalite veya ciddi morbidite açısından hâlâ yüksek risk altındadır. Kalan olguların %20'si, preterm doğum riski altındadır. Preeklampsi kadınlar uzun vadede kardiyovasküler, böbrek ve kronik hipertansif hastalıklar açısından risk altındadır.(1)

2013'te, The American College of Obstetricians and Gynecologists (ACOG) , massif proteinüri ve intrauterin gelişme kısıtlılığını kriterlerden çıkartmıştır. ACOG'un güncel yayınında daha önce şiddetli preeklampsi olarak tanımlanan olgular, şiddetli özellikler içeren preeklampsi olarak değiştirilmiştir.(1)

Preeklampsi, dünyada maternal ve fetal/ neonatal mortalite ve morbiditenin önde gelen nedenlerindedir (1).Preeklampsi riski yüksek olan hastaların erken teşhisi bu nedenle obstetrinin önemli hedeflerden biridir(2).

Çok hassas ve spesifik fizyolojik ve biyokimyasal belirteçlerin mevcudiyeti, sadece risk altındaki hastaların tespitini sağlamaz aynı zamanda bu hastaların yakın izlemi, kesin tanısı ve zamanında müdahale ile oluşabilecek komplikasyonlarında en aza indirebilir.

Preeklampsi, gelişmiş ülkelerdeki gebeliklerin% 2-5'inde görülürken acil bakımın yetersiz olduğu gelişmekte olan ülkelerde bu oran gebeliklerin % 10'una ulaşabilmektedir (1).

Risk altındaki hastaları tespit etmek ve izlemek böylece en iyi antepartum bakımı sağlamak için preeklampsi klinik tablosu görülmeden önce tanıya izin verebilecek, yaygın olarak uygulanabilir ve uygun fiyatlı bir teste ihtiyacımız bulun-

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KAYNAKÇA

1. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol.* 2019;133(1)
2. Jim, B., and Karumanchi, S. A. (2017). Preeclampsia: pathogenesis, prevention, and long-term complications. *Semin. Nephrol.* 37, 386–397. doi: 10.1016/j.semnephrol.2017.05.011
3. Tjoa, M. L., Levine, R. J., and Karumanchi, S. A. (2007). Angiogenic factors and preeclampsia. *Front. Biosci.* 12, 2395–2402. doi: 10.2741/2241
4. Staff, A. C., Benton, S. J., von Dadelszen, P., Roberts, J. M., Taylor, R. N., Powers, R. W., et al. (2013). Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 61, 932–942. doi: 10.1161/HYPERTENSIONAHA.111.00250
5. March, M. I., Geahchan, C., Wenger, J., Raghuraman, N., Berg, A., Haddow, H., et al. (2015). Circulating angiogenic factors and the risk of adverse outcomes among haitian women with preeclampsia. *PLoS One* 10:e0126815. doi: 10.1371/journal.pone.0126815
6. Palomaki, G. E., Haddow, J. E., Haddow, H. R., Salahuddin, S., Geahchan, C., Cerdeira, A. S., et al. (2015). Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia. *Prenat. Diagn.* 35, 386–393.
7. Sircar, M., Thadhani, R., and Karumanchi, S. A. (2015). Pathogenesis of preeclampsia. *Curr. Opin. Nephrol. Hypertens.* 24, 131–138
8. Baltajian, K., Bajracharya, S., Salahuddin, S., Berg, A. H., Geahchan, C., Wenger, J. B., et al. (2016). Sequential plasma angiogenic factors levels in women with suspected preeclampsia. *Am. J. Obstet. Gynecol.* 215, 89–89
9. Roberts, J. M., Taylor, R. N., Musci, T. J., Rodgers, G. M., Hubel, C. A., and McLaughlin, M. K. (1989). Preeclampsia: an endothelial cell disorder. *Am. J. Obstet. Gynecol.* 161, 1200–1204.
10. Mostello, D., Catlin, T. K., Roman, L., Holcomb, W. L., and Leet, T. (2002). Preeclampsia in the parous woman: Who is at risk? *Am. J. Obstet. Gynecol.* 187, 425–429. doi: 10.1067/mob.2002.123608
11. Clowse, M. E. B., Jamison, M., Myers, E., and James A H. (2008). A national study of the complications of lupus in pregnancy. *Am. J. Obstet. Gynecol.* 199, 127.e1–127.e6.
12. Al-Jameil, N., Aziz Khan, F., Fareed Khan, M., and Tabassum, H. (2014). A brief overview of preeclampsia. *J. Clin. Med. Res.* 6, 1–7.
13. McFarlane, A., and Scott, J. S. (1976). Pre-eclampsia/eclampsia in twin pregnancies. *J. Med. Genet.* 13, 208–211. doi: 10.1136/jmg.13.3.208
14. Coonrod, D. V., Hickok, D. E., Zhu, K., Easterling, T. R., and Daling, J. R. (1995). Risk factors for preeclampsia in twin pregnancies: a population-based cohort study. *Obstet. Gynecol.* 85(5 Pt 1):645–650.
15. Robertson, A. K., Rudling, M., Zhou, X., Gorelik, L., and Flavell, R. A., Hansson, G. K. (2003). Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. *J. Clin. Invest.* 112, 1342–1350
16. Vikse, B. E., Irgens, L. M., Karumanchi, S. A., Thadhani, R., Reisaeter, A. V., and Skjaerven, R. (2012). Familial factors in the association between preeclampsia and later ESRD. *Clin. J. Am. Soc. Nephrol.* 7, 1819–1826.
17. Mongraw-Chaffin, M. L., Cirillo, P. M., and Cohn, B. A. (2010). Preeclampsia and cardiovascular disease death: prospective evidence from the child health
18. Mostello, D., Catlin, T. K., Roman, L., Holcomb, W. L., and Leet, T. (2002). Preeclampsia in the parous woman: Who is at risk? *Am. J. Obstet. Gynecol.* 187, 425–429.
19. Sohlberg, S., Mulic-Lutvica, A., Lindgren, P., Ortiz-Nieto, F., Wikstrom, A. K., and Wikstrom J. (2014). Placental perfusion in normal pregnancy and early and late preeclampsia: a magnetic resonance imaging study. *Placenta* 35, 202–206
20. Yung, H. W., Atkinson, D., Champion-Smith, T., Olovsson, M., Charnock-Jones, D. S., and Burton, G. J. (2005). Differential activation of placental unfolded protein response pathways implies heterogeneity in causation of early- and late-onset pre-eclampsia. *J. Pathol.* 234, 262–276

21. Lyall, F. Priming and remodelling of human placental bed spiral arteries during pregnancy—a review. *Placenta* 26(Suppl. A), S31–S36.
22. Kaufmann, P., Black, S., and Huppertz, B. (2003). Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol. Reprod.* 69, 1–7
23. Osol, G., and Mandala, M. (2009). Maternal uterine vascular remodeling during pregnancy. *Physiology* 24, 58–71.
24. Saleh, L., Verdonk, K., Visser, W., van den Meiracker, A. H., and Danser A H. (2016). The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. *Ther. Adv. Cardiovasc. Dis.* 10, 282–293.
25. Pijnenborg, R., Vercruyse, L., and Hanssens, M. (2006). The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta* 27, 939–958
26. Takimoto, E., Ishida, J., Sugiyama, F., Horiguchi, H., Murakami, K., and Fukamizu, A. (1996). Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. *Science* 274, 995–998.
27. Maynard, S. E., Min, J. Y., Merchan, J., Lim, K. H., Li, J., Mondal, S., et al. (2003). Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J. Clin. Invest.* 111, 649–658.
28. Levine, R. J., Maynard, S. E., Qian, C., Lim, K. H., England, L. J., Yu, K. F., et al. (2004). Circulating angiogenic factors and the risk of preeclampsia. *N. Engl. J. Med.* 350, 672–683.
29. Li, H., Gu, B., Zhang, Y., Lewis, D. F., and Wang, Y. (2005). Hypoxia-induced increase in soluble Flt-1 production correlates with enhanced oxidative stress in trophoblast cells from the human placenta. *Placenta* 26, 210–217.
30. Venkatesha, S., Toporsian, M., Lam, C., Hanai, J., Mammoto, T., Kim, Y. M., et al. (2006). Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat. Med.* 12, 642–649.
31. Kanasaki, K., Palmsten, K., Sugimoto, H., Ahmad, S., Hamano, Y., Xie, L., et al. (2008). Deficiency in catechol-O-methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia. *Nature* 453, 1117–1121.
32. Zhou, C. C., Irani, R. A., Zhang, Y., Blackwell, S. C., Mi, T., Wen, J., et al. (2010). Angiotensin receptor agonistic autoantibody-mediated tumor necrosis factor- α induction contributes to increased soluble endoglin production in preeclampsia. *Circulation* 121, 436–444.
33. Moffett, A., Hiby, S. E., and Sharkey, A. M. (2015). The role of the maternal immune system in the regulation of human birthweight. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370:20140071
34. Kelder, T. P., Penning, M. E., Uh, H. W., Cohen, D., Bloemenkamp, K. W. M., Bruijn, J. A., et al. (2012). Quantitative polymerase chain reaction-based analysis of podocyturia is a feasible diagnostic tool in preeclampsia. *Hypertension* 60, 1538–1544.
35. Pijnenborg, R., Vercruyse, L., and Hanssens, M. (2006). The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta* 27, 939–958.
36. Cindrova-Davies, T. (2009). Gabor than award lecture 2008: pre-eclampsia - from placental oxidative stress to maternal endothelial dysfunction. *Placenta* 30(Suppl. A), S55–S65.
37. Cindrova-Davies, T., Sanders, D. A., Burton, G. J., and Charnock-Jones D S. (2011). Soluble FLT1 sensitizes endothelial cells to inflammatory cytokines by antagonizing VEGF receptor-mediated signalling. *Cardiovasc. Res.*
38. Verdonk, K., Saleh, L., Lankhorst, S., Smilde, J. E., van Ingen, M. M., Garrelds, I. M., et al. (2015). Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. *Hypertension* 65, 1316–1323.
39. Staff, A. C., Benton, S. J., von Dadelszen, P., Roberts, J. M., Taylor, R. N., Powers, R. W., et al. (2013). Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 61, 932–942.
40. De Falco, S. (2012). The discovery of placenta growth factor and its biological activity. *Exp. Mol. Med.* 44, 1–9.

41. Taylor, R. N., Varma, M., Teng, N. N. H., and Roberts, J. M. (1990). Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. *J. Clin. Endocrinol. Metab.* 71, 1675–1677
42. Kar, M. (2014). Role of biomarkers in early detection of preeclampsia. *J. Clin. Diagn. Res.* 8, BE01–BE04.
43. Spradley, F. T., Tan, A. Y., Joo, W. S., Daniels, G., Kussie, P., Karumanchi, S. A., et al. (2016). Placental growth factor administration abolishes placental ischemia-induced hypertension. *Hypertension* 67, 740–747.
44. Levine, R. J., Maynard, S. E., Qian, C., Lim, K. H., England, L. J., Yu, K. F., et al. (2004). Circulating angiogenic factors and the risk of preeclampsia. *N. Engl. J. Med.* 350, 672–683.
45. Burke, S. D., Zsengeller, Z. K., Khankin, E. V., Lo, A. S., Rajakumar, A., DuPont, J. J., et al. (2016). Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia. *J. Clin. Invest.* 126, 2561–2574.
46. Granger, J. P., Abram, S., Stec, D., Chandler, D., Speed, J., and LaMarca, B. (2006). Endothelin, the kidney, and hypertension. *Curr. Hypertens. Rep.* 8, 298–303.
47. Thadhani, R., Hagmann, H., Schaarschmidt, W., Roth, B., Cingoz, T., Karunnanchi, S. A., et al. (2016). Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J. Am. Soc. Nephrol.* 27, 903–913.
48. Gregory, A. L., Xu, G., Sotov, V., and Letarte, M. (2014). Review: the enigmatic role of endoglin in the placenta. *Placenta* 35, S93–S99.
49. Ahmed, A. (2011). New insights into the etiology of preeclampsia: identification of key elusive factors for the vascular complications. *Thromb. Res.* 127(Suppl. 3), 72–75.
50. Santner-Nanan, B., Peek, M. J., Khanam, R., Richarts, L., Zhu, E., Fazekas de St Groth, B., and Nanan R. (2009). Systemic increase in the ratio between Foxp3C and IL-17-producing CD4C T cells in healthy pregnancy but not in preeclampsia. *J. Immunol.* 183, 7023–7030.
51. Venkatesha, S., Toporsian, M., Lam, C., Hanai, J., Mammoto, T., Kim, Y. M., et al. (2006). Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat. Med.* 12, 642–649.
52. George, E. M., and Granger, J. P. (2010). Recent insights into the pathophysiology of preeclampsia. *Expert Rev. Obstet. Gynecol.* 5, 557–566.
53. Saleh, L., Samantar, R., Garrelds, I. M., van den Meiracker, A. H., Visser, W., and Danser, A. H. J. (2017). Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. *Hypertension* 70, 594–600.
54. Bakrania, B., Duncan, J., Warrington, J. P., and Granger, J. P. (2017). The endothelin type a receptor as a potential therapeutic target in preeclampsia. *Int. J. Mol. Sci.* 18:E522.
55. Baltajian, K., Bajracharya, S., Salahuddin, S., Berg, A. H., Geahchan, C., Wenger, J. B., et al. (2016). Sequential plasma angiogenic factors levels in women with suspected preeclampsia. *Am. J. Obstet. Gynecol.* 215, 89.e1–89.e10
56. Rolnik, D. L., Wright, D., Poon, L. C., O’Gorman, N., Syngelaki, A., Matallana, C. D., et al. (2017). Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N. Engl. J. Med.* 377, 613–62
57. Bergmann, A., Ahmad, S., Cudmore, M., Gruber, A. D., Wittschen, P., Lindenmaier, W., et al. (2010). Reduction of circulating soluble Flt-1 alleviates preeclampsia-like symptoms in a mouse model. *J. Cell Mol. Med.* 14, 1857–1867.
58. Thadhani, R., Hagmann, H., Schaarschmidt, W., Roth, B., Cingoz, T., Karunnanchi, S. A., et al. (2016). Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J. Am. Soc. Nephrol.* 27, 903–913.
59. Onda, K., Tong, S., Beard, S., Binder, N., Muto, M., Senadheera, S. N., et al. (2017). Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. *Hypertension*, 69, 457–468.

60. Spradley, F. T., Tan, A. Y., Joo, W. S., Daniels, G., Kussie, P., Karumanchi A., et al. (2016). Placental growth factor administration abolishes placental ischemia-induced hypertension. *Hypertension* 67, 740–747.
61. Kumasawa, K., Ikawa, M., Kidoya, H., Hasuwa, H., Saito-Fujita, T., Morioka, Y., et al. (2011). Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. *Proc. Natl. Acad. Sci. U.S.A.* 108, 1451–1455.
62. Li, Z., Zhang, Y., Ying Ma, J., Kapoun, A. M., Shao, Q., Kerr, I., et al. (2007). Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves kidney damage in a rat model of preeclampsia