

## A felnőttkori betegségek praenatalis eredete

Sulyok Endre

Pécsi Tudományegyetem, Egészségtudományi Kar

### Összefoglalás

Barker ismerte fel elsőként, hogy a kedvezőtlen méhen belüli környezet (elégletes táplálás, krónikus hypoxia, stressz) és alacsony születési súly fontos kockázati tényező a felnőttkorban kialakuló metabolikus szindróma szempontjából. A környezeti hatások olyan adaptív reakciókat váltanak ki, melyek rövidtávon biztosítják a magzat túlélését, hosszú távon azonban olyan anyagszere-, endokrin- és vascularis folyamatokat indítanak el, melyek felnőttkorban obesitashoz, 2-es típusú diabeteshez és cardiovascularis megbetegedések kialakulásához vezetnek. Később igazolták, hogy a méhen belüli sorvadás mellett veszélyeztetettek a valódi koraszülöttek és azok a csecsemők, akik az első életévet követően un „pótló” súlygyarapodást mutatnak. Az alacsony születési súly és a felnőttkori betegségek közötti kapcsolat számos vonatkozása tisztázott. Kimutatták epigenetikus tényezők, a renin-angiotensin rendszer, a sympathoadrenalis rendszer, a hypothalamus-hypophysis-mellékvese kéreg rendszer, a nephronok számának csökkenése, az inzulin rezisztencia, zsírszöveti hormonok és az endothel dysfunction etiológiai szerepéit. Az etiológiai tényezők és a pathomechanismus megismerése lehetőséget kínál arra is, hogy az intrauterin sorvadás és koraszülöttség megelőzésén túl célzott kezelési eljárásokat is bevezessünk.

**Kulcsszavak:** felnőttkori betegségek, metabolikus szindróma, intrauterin környezet

### Praenatal origins of adult diseases

### Summary

Barker was the first to put forward the hypothesis that the adverse intrauterine environment (insufficient nutrient supply, chronic hypoxia, stress) and the subsequent fetal malnutrition is an important risk factor for development of metabolic syndrome in later life. The fetus responds to the unfavourable environment with adaptive reactions which ensure survival in the short-run, but at the expenses of metabolic-, endocrine- and vascular processes leading to adult diseases such as obesity, diabetes type 2 and cardiovascular pathologies. Later on, it was established that in addition to fetal malnutrition newborns born preterm and those with rapid catch-up growth after the first year are also at risk of adult diseases. Several aspects of the fetal/perinatal origin of adult diseases are clearly defined. It has been documented that epigenetic modifications, the renin-angiotensin system, the sympathoadrenal system, the hypothalamo-pituitary-adrenocortical axis, the reduced nephron number, insulin resistance, adipocytes-derived hormones and endothelial dysfunction play major pathogenetic roles. Our better understanding of the association of low birth weight and adult diseases allows us to introduce more targeted therapeutic measures in addition to the general approaches to prevent fetal malnutrition and preterm birth.

**Keywords:** adult diseases, metabolic syndrome, intrauterine environment

\* Az Egészség-Akadémia programsorozat 2009. december 7-én elhangzott előadása

### Irodalom

1. Barker DJP, Osmond C. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. Lancet **1986**; 1: 1077-1081.
2. Barker DJP, Osmond C. Death rates from stroke in England and Wales predicted from past maternal mortality. Brit Med J. **1986**; 295: 83-86.
3. Barker DJP, Osmond C, Law C. The intra-uterine and early postnatal origins of cardiovascular disease and chronic bronchitis. J Epidemiol Community Health **1989**; 43: 237-240.
4. Barker DJP, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. Brit Med J. **1990**; 301: 259-262.
5. Doyle LW, Faber B, Callanan C, Morley R. Blood pressure in late adolescence and very low birth weight. Pediatrics **2003**; 111: 252-257.
6. Hack M, Schluchter M, Cartar L, Rahman M. Blood pressure among very low birth weight (<1.5 kg) young adults. Pediatr Res. **2005**; 58: 677-684.
7. Lawlor DA, Hübner A, Tynelius P, Leon DA, Smith GD, Rasmussen F. Associations of gestational age and intrauterine growth with systolic blood pressure in a family-based study of 386 485 men in 331 089 families. Circulation **2007**; 115 :1-7.
8. Barker DJP. In utero programming of chronic disease. Clin Sci. **1998**; 95: 115-128.
9. Gluckman PD, Hanson MA, Pinal C. The developmental origins of adult disease. Maternal Child Nutr. **2005**; 1: 130-141.
10. Singhal A, Cole TJ, Fewtrell M, Kennedy K, Stephenson T, Elias-Jones A, Lucas A. Promotion of faster weight gain in infants born small for gestational age. Is there an adverse effect on later blood pressure? Circulation **2007**; 115: 213-220.

11. Simmons RA. Developmental origins of adult disease. *Pediatr Clin N Am* **2009**; 56: 449-466.
- 12.. Nuyt AM, Alexander BT. Developmental programming and hypertension. *Curr Opin Nephrol Hypertens* **2009**; 18: 1062-1071.
13. Woods LL, Rasch R. Perinatal Ang II programs adult blood pressure, glomerular number and renal function in rats. *Am J Physiol (Regulatory Integrative Comp Physiol)* **1998**; 275: R1593-R1599.
14. Pladys P, Lahaie I, Cambonic O, et al. Role of brain and peripheral angiotensin II in hypertension and altered baroreflex programmed during fetal life in rats. *Pediatr Res* **2004**; 55: 1042-1049.
15. Sherman RC, Langley-Evans SC. Early administration of angiotensin converting enzyme inhibitor captopril, prevents the development of hypertension programmed by intrauterine exposure to a maternal low-protein diet in the rat. *Clin Sci* **1998**; 94: 373-381.
16. McMullen S, Gardner DS, Langley-Evans SC. Prenatal programming of angiotensin II type 2 receptor expression in the rat. *Brit J Nutr* **2004**; 91: 133-140.
17. Sulyok E, Varga F, Csaba IF, Németh M, Tényi I, Györy E, Ertl T. Function of the renin-angiotensin-aldosterone system in relation to electrolyte balance in the small-for-date neonate. *Acta Paediatr Acad Sci Hung* **1980**; 21: 153-157.
18. Barker DJP, Bagby SP, Hanson MA. Mechanisms of disease: in utero programming in the pathogenesis of hypertension. *Nature Clin Pract Nephrology* **2006**; 2: 1-8.
19. Johansson S, Norman M, Legnevall L, Dalmaz Y, Lagercrantz H, Vanpee N. Increased catecholamines and heart rate in children with low birth weight: perinatal contributions to sympathoadrenal overactivity. *J Intern Med* **2007**; 261: 480-487.
20. Edwards LJ, McMillen IC. Impact of maternal undernutrition during the periconceptional period, fetal number, and fetal sex on the development of the hypothalamo-pituitary-adrenal axis in sheep during late gestation. *Biol Reprod* **2002**; 66: 1562-1569.
21. Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. *Reproduction* **2004**; 127: 515-526.
22. Seckl JR. Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol* **2004**; 151: U49-U62.
23. MacKenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? *Am J Kidney Dis* **1995**; 26: 91-98.
24. Brenner BN, Chertow GM. Congenital oligonephropathy: an inborn cause of adult hypertension and progressive renal injury? *Curr Opin Nephrol Hypertens* **1993**; 2: 691-695.
25. Merlet-Benichou C, Leroy B, Gilbert T, Lelievre-Pegorier M. Retard de croissance intra-utérine et déficit en néphrons. *Medicine* **1993**; 9: 777-780.
26. Ericsson JG, Lindi I, Uusitupa M, et al. The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* **2002**; 51: 2321-2324.
27. VanAssche FA, Aerts L. The fetal endocrine pancreas. *Contrib Gynecol Obstet* **1979**; 5: 44-57.
28. Philips DIW, Barker DJP, Hales CN, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. *Diabetologia* **1994**; 37: 150-154.
29. Wills J, Watson JM, Hales CN, Philips DIW. The relation of fetal growth to insulin secretion in young men. *Diabet Med* **1996**; 13: 773-774.
30. Wickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity and hypertension and its postnatal amplification by hypercaloric nutrition. *Am J Physiol* **2000**; 279: E83-E87.
31. Muhlhauser B, Smith SR. Early life origins of metabolic dysfunction: role of the adipocyte. *Trends Endocrinol Metab* **2008**; 20: 51-57.
32. Briana DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult disease: the role of adipocytokines. *Eur J Endocrinol* **2009**; 160: 337-347.
33. Brawley L, Poston L, Hanson MA. Mechanisms underlying the programming of small artery dysfunction: a review of model using low-protein diet in pregnancy in the rat. *Arch Physiol Biochem* **2003**; 111: 23-25.
34. Lamireau D, Nuyt AM, Hou K, Bernier S, Beauchamp M, Gobeil F, Lahaie I, Varma DR, Chemtob S. Altered vascular function in fetal programming of hypertension. *Stroke* **2002**; 33: 2992-2998.
35. Nuyt AM. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence of human studies and experimental animal models. *Clin Sci* **2008**; 114: 1-17.
36. Mohn A, Chiavaroli V, Cerruto M, et al. Increased oxidative stress in prepubertal children born small for gestational age. *J Clin Endocrinol Metab* **2007**; 92: 1372-1378.
37. Franco MC, Kawamoto EM, Gorjao R, et al. Biomarkers of oxidative stress and antioxidant status in children born small for gestational age: evidence of lipid peroxidation. *Pediatr Res* **2007**; 62: 204-208.
38. Liguori A, D'Armiento FP, Palagiano A, et al. Maternal C-reactive protein and developmental programming of atherosclerosis. *Am J Obstet Gynecol* **2008**; 198: 281-285.
39. Cambonie G, Comte B, Yzydorczyk C, Ntimbane T, Germain N, Le NLO, Pladys P, Gauthier C, Lahaie I, Abran D, Lavoie J-C, Nuyt AM. Antenatal antioxidants prevent adult hypertension, vascular dysfunction and microvascular rarefaction associated with in utero exposure to a low-protein diet. *Am J Physiol Regulatory Integrative Comp Physiol* **2007**; 292: 1236-1245.
40. Racasan S, Bream B, van der Giezen DM, et al. Prenatal l-arginine and antioxidant supplements reduce adult blood pressure in spontaneously hypertensive rats. *Hypertension* **2004**; 44: 83-88.
41. Vida G, Sulyok E, Lakatos O, Ertl T, Martens-Lobenhoffer J, Bode-Böger SM. Plasma levels of asymmetric dimethylarginine in premature neonates: its possible involvement in developmental programming of chronic diseases. *Acta Paediatrica* **2009**; 98: 437-441.
42. Martyn CN, Greenwald SE. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet* **1997**; 350: 953-955.
43. Khorram O, Momeni M, Desai M, Ross MG. Nutrient restriction in utero induces remodeling of the vascular extracellular matrix in rat offspring. *Reprod Sci* **2007**; 14: 73-80.