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INSULIN RESISTANCE SYNDROM IN PREECLAMPSIA – THE INFLUENCE ON THE OFFSPRING

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Preeclampsia is a multisystem disorder of unknown cause that is unique to human pregnancy. It is a major cause of perinatal and maternal morbidity and mortality, affecting 5% to 8% of all pregnancies. The clinical findings can manifest as either a maternal syndrome or fetal syndrome. There is increasing data supporting the role of the insulin resistance in preeclampsia, although this evidence has not been seen in all studies.

The aim of this research was to determine the influence of the insulin resistance on the offspring in preeclampsia. Sixty preeclamptic pregnancies underwent the research taking the serum insulin of 20uU/ml as the state of insulin resistance's cut off. Insulin sensitivity was examined by using HOMA and QUICKY indexes. Thirty preeclamptic pregnancies had the insulin resistance syndrome and thirty were the control group. Linear regression analysis and logistic linear analysis were used to examine the influence of the insulin resistance.

In the insulin resistance preeclamptic pregnancies, the duration of pregnancy was shorter (2.59; $p<0.01$) and the placental weight was lower (2.72; $p<0.01$). This group also had a statistically lower percentage of vaginal birth (9.64; $p<0.01$) and higher of caesarian sections (4,44; $p<0,05$). Newborns in the insulin resistance group were shorter (0.108; $p<0.001$) weighed less (2.81; $p<0.01$), had a lower Apgar score (3.11; $p<0.01$) and stayed in the hospital for a longer time (2,48; $p<0,05$).

The insulin resistance syndrome is not present in every preeclamptic pregnancy, but if it is present it affects the offspring in a negative way. *Acta Medica Medianae 2016;55(2):19-24.*

Key words: preeclampsia, insulin resistance, newborn

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Introduction

Insulin resistance and inflammation have been reported to contribute to the onset of hypertension and coronary artery disease, as a part of metabolic syndrome, and they may be present in hypertensive disorders of pregnancy (1, 2). Normal pregnancy can be considered as a state of insulin resistance. Fasting insulin concentration rising during the pregnancy with a peak in the third trimester, rapidly returns to pre-pregnancy levels after delivery (3). In preeclamptic pregnancies, metabolic changes similar to metabolic syndromeare also present (4). Insulin resistance, present in milder form in late pregnancy, has long been ascribed to rises in cortisol and placental hormones, including human placental lactogen, progesterone, and estrogen. Causes of further enhancement in hypertensive pregnancies remain unknown (5). One explanation could be inflammation, and indeed the rises in some inflammatory markers predict the onset of insulin resistance in pregnant subjects (6, 7). Among these candidates, tumor necrosis factor-alfa (TNF-alfa and leptin are known to be produced besides adipose tissue, also in the placenta, and could therefore play a central role in insulin resistance in pregnancy (8). Several studies have suggested that women who develop preeclampsia are at an increased risk of cardiovascular complications later in life (9). Indeed, many risk factors and pathophysiological abnormalities of preeclampsia are

similar to those of coronary artery disease. Insulin resistance has been implicated as a common factor. Microvascular dysfunction which is associated with insulin resistance could predispose to both coronary heart disease and preeclampsia (10).

Methods

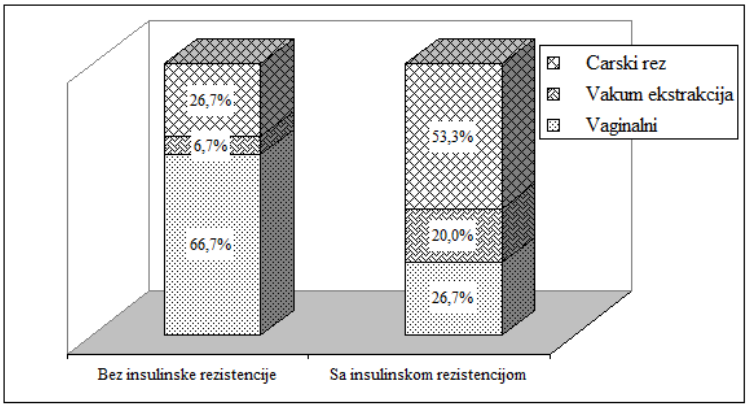
Sixty pregnant women were eligible to join the study at the University Clinic for Gynecology and Obstetrics, Niš and were admitted to the Department of High Risk Pregnancy Unit with the symptoms of preeclampsia. Preeclampsia was defined as blood pressure >160/110 mmHg and proteinuria occurring after 20 weeks of gestation with no prior history of hypertension or renal disease. Proteinuria was defined as >0.3 g/L per 24h urine collection, with no evidence of urinary tract infection. Thirty preeclamptic pregnancies had the insulin resistance syndrome and thirty were the control group. Serum insulin level of 20 uU/ml was taking as the state of insulin resistance's cut off. Insulin sensitivity was examined by using HOMA and QUICKY indexes. Linear regression analysis and logistic linear analysis were used to examine the influence of the insulin resistance. All subject provided written informed consent.

Results

In patients with insulin resistance, weight gain during pregnancy was significantly higher (20:17±4.37: 23.97±9.25 kg; z=2.94, p<0.01), clinical gestation at delivery was shorter (38.87 ±1.76:37.10±3.28 weeks; t=2:59 p<0.05), and the weight of the placenta was significantly lower (540.33±76.63: 475.67±105.49 g; t=2.72, p< 0.01). That group had a significantly smaller percentage of pregnancies ending with vaginal delivery (66.7:26.7%; χ^2=9.64, p<0.01), while a significantly higher percentage of cesarean section (26.7:53.3%; χ^2=4.44, p<0.05) (Graph 1) was found. In the representation of certain level of maturity of the placenta, amniotic fluid volume, as well as the frequency of application of vacuum extraction during labor, were not confirmed significant differences between the groups (Table 1). Normal CTG was significantly more present

Table 1. The course of pregnancy and birth characteristics of women compared to fasting level of serum insulin

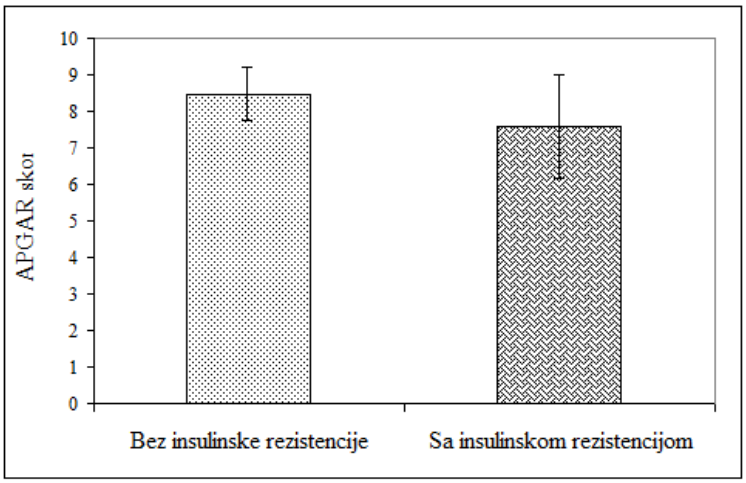
Parameters	Insulin level in serum		Comparison between the groups
	To 20 mU/L	Over 20 mU/L	
Increase in body mass (kg)	20.17±4.37	23.97±9.25	z=2.94 i p=0.003
Clinical gestation at delivery (weeks)	38.87±1.76	37.10±3.28	t=2.59 i p=0.012
Mode of delivery			
Vaginal	20 (66.7%)	8 (26.7%)	χ^2=9.64 i p=0.002
Vacuum extraction	2 (6.7%)	6 (20.0%)	n.s.
Caesarean section	8 (26.7%)	16 (53.3%)	χ^2=4.44 i p=0.035
Placental weight (g)	540.33±76.63	475.67±105.49	t=2.72 i p=0.009
Maturity of placenta			
I level	2 (6.7%)	6 (20.0%)	n.s.
II level	14 (46.7%)	12 (40.0%)	n.s.
III level	14 (46.7%)	12 (40.0%)	n.s.
The amount of amniotic fluid - AFI (mm)	88.33±22.30	91.53±27.03	n.s.



Graph 1. Mode of delivery by group

Table 2. Perinatal characteristics of newborns in comparison to the fasting level of serum insulin

Parameter	Levels of insulin in serum		Comparison among the groups
	Up to 20 mU/L	Over 20 mU/L	
CTG- record			
Normal	22 (73.3%)	13 (43.3%)	χ^2=5.46 i p=0.019
Warning	7 (23.3%)	11 (36.7%)	n.s.
Threatening	1 (3.3%)	6 (20.0%)	n.s.
Body weight (g)	3333.50±461.88	2816.67±896.58	z=2.81 i p=0.007
Body height (cm)	52.43±2.34	49.17±4.72	t=3.39 i p=0.001
APGAR score	8.47±0.73	7.57±1.41	t=3.11 i p=0.003
Duration of hospitalization(days)	8.53±4.30	17.87±10.14	z=2.48 i p=0.016



Graph 2. Average values of APGAR scores by group

in infants whose mothers did not have insulin resistance (73.3:43.3%; χ^2=5:46 p<0.05). Newborns whose mothers had insulin resistance had a significantly lower birth weight (3333±461 2816± 896 g; z=2.81, p<0.01) and body height (52.43± 2:34:49.17±4.72 cm; t=3.39 and p<0.01) (Table 2). Their APGAR score was significantly lower (8:47±0.73 7.57±1:41; t=3.11, p<0.01), and the length of hospitalization doubled (8:53±4.30: 17.87±14.10 days; z=2.48 The p<0.05) (Graph 2).

Discussion

Obesity and insulin resistance may predispose women to preeclampsia, perhaps on the basis of an increased systemic inflammation. It is known that chronic inflammatory activation of the immune system can induce insulin resistance, although its mechanism is not fully elucidated (11). The inflammatory system responds to danger signals which activate a cascade of events that ends with clinically evident preeclampsia. P-IPG is the first molecule that links all major aspects of this syndrome (12) (Figure 1).

The stimulus and its source are still unknown. An excess of circulating anti-angiogenic growth factors (Soluble FMS-like tyrosine kinase 1 and endoglin) have been found in preeclampsia. They induce a preeclampsia-like syndrome in pregnant rats, but it is still debated whether they are causative of preeclampsia (13).

Dr. David Barker first popularized the concept of fetal origins of adult disease (FOAD). The FOAD hypothesis holds that events during early development have a profound impact on one's risk for development of future adult disease (14). Fetal

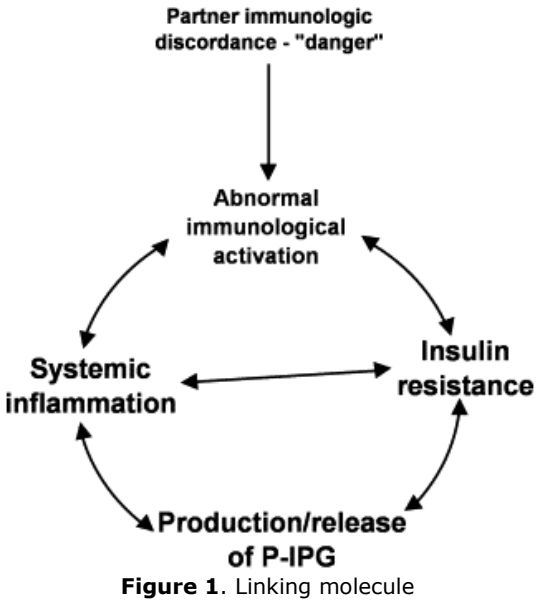


Figure 1. Linking molecule

programming implies that during critical periods of prenatal growth, permanent changes in metabolism or structures result from adverse intrauterine conditions. Low birth weight, a surrogate marker of poor placentation present in preeclampsia, is linked to coronary artery disease, hypertension, obesity, and insulin resistance. Clues originally arose from large 20th century, European birth registries. Implications of the FOAD extend beyond the low birth weight population and include babies exposed to stress, both nutritional and non-nutritional, during different critical periods of development, which ultimately result in a disease (15). Studies of the Preston records have shown that thinness at birth, measured by a low ponderal index (birth weight/length3), is associated with the "insulin resistance syndrome"- the occurrence of impaired glucose tolerance, raised blood pressure, and disturbed lipid metabolism in adult life (16). Biochemically, the syndrome is characterized by raised serum insulin concentrations, and it leads to coronary heart disease (17). There is evidence that infants who fail to put on weight have become resistant to growth hormone, which takes over control of growth from insulin in late fetal life. Altered settings of hormonal secretion or tissue sensitivity could prove to be one of the important mechanisms, whereby programming leads to pathology (18). Other studies have shown that placental enlargement is also followed by impaired glucose tolerance, disordered blood coagulation, and death from coronary heart disease (19). Insulin resistance and type-2 diabetes have also been found to be independently related to small size at birth in several studies around the world (20). Dietary manipulations in animal models provide further support and mechanistic explanations, in particular protein deficiency in pregnant rats, which elevates blood pressure, impairs glucose tolerance, and increases the likelihood of obesity in the progeny (21). Although there are still controversial areas, there is at present sufficient scientific evidence for fetal programming to be regarded as an additional risk factor for chronic disease, in interaction with genetic and lifestyle risk factors.

Conclusion

Many challenges remain regarding the prediction, prevention, and management of preeclampsia as a potential risk condition with deep impact on offspring health. The FOAD hypothesis has expanded greatly during the past decades, and is influential in medicine and epidemiology. Recently, the World Health Organization included low birth weight as a risk factor for cardiovascular disease. The heart of the hypothesis – that environmental influences during gestation have an effect on later development – is a major insight and constitutes a complement to genetic and more proximal factors (such as adult lifestyle) as causes of adult disease. Future research should expand our knowledge of biomarkers for early prediction and management of preeclampsia and aim to reduce the prevalence of disorder that is associated with adverse pregnancy outcome and FOAD. By understanding FOAD, health care professionals and policy makers will make this issue a high healthcare priority and implement preventive measures and treatment for those at higher risk for chronic diseases. The outline of a strategy for developing the fetal origins hypothesis is now in place; it seems reasonable to expect that it will bring rapid advance.

References

1. Festa A, D'Agostino RJr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102(1): 42-7. [CrossRef][PubMed]
2. Kaaja R, Laivuori H, Laakso M, Tikkanen MJ, Ylikorkala O. Evidence of the increased insulin resistance in preeclampsia. Metabolism 1999; 48(7): 892-6. [CrossRef][PubMed]
3. Yen SS. Endocrine regulation of metabolic homeostasis during pregnancy. Clin Obstet Gynecol 1973; 16(3): 130-47. [CrossRef][PubMed]
4. Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O. Serum lipoproteins, insulin and urinary prostanoid metabolites in normal and hypertensive pregnant women. Obstet Gynecol 1995; 85(3): 353-6. [CrossRef][PubMed]
5. Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. J Clin Endocrinol Metab 2008; 88(6): 2393-8. [CrossRef][PubMed]
6. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: Leptin, acylation

stimulating protein, and adiponectin. Curr Opin Lipidol 2002; 13(1): 51-9. [CrossRef][PubMed]
7. Kirwan JP, Haugel-De Mouzon S, Lepercq J, Challier JC, Huston-Presley L, Friedman JE, Kalhan SC, et al. TNF-alpha is a predictor of insulin resistancy in human pregnancy. Diabetes 2002; 51(7): 2207-13. [CrossRef][PubMed]
8. Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between preeclampsia and maternal coronary heart disease. BJOG 2003; 110(11): 1029-31. [CrossRef][PubMed]
9. Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 2004; 93(6): 805-8. [CrossRef][PubMed]
10. Arcaro G, Cretti A, Balzano S, Lechi A, Muggeo M, Bonora E, et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 2002; 105(5): 576-82. [CrossRef] [PubMed]
11. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006; 116(7): 1793-801. [CrossRef][PubMed]
12. Matzinger P. Friendly and dangerous signals: is the tissue in control? Nat Immunol 2007; 8(1): 11-3. [CrossRef][PubMed]
13. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 2006; 355(10): 992-1005. [CrossRef][PubMed]
14. Barker DJ. Fetal and infant origins of adult disease. BMJ 1990; 301(6761): 1111. [CrossRef][PubMed]
15. Barker DJ. Fetal origins of coronary heart-disease. BMJ 1995; 311:171–4. [CrossRef][PubMed]
16. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986; 1(8489):1077–81. [CrossRef] [PubMed]
17. Zimmet P, Alberti G, Kaufman F, et al. The metabolic syndrome in children and adolescents. Lancet. 2007 Jun 23; 369(9579): 2059-61. [CrossRef][PubMed]
18. Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: A historical perspective. J Am Soc Nephrol 2005; 16(9):2537–44. [CrossRef] [PubMed]
19. Huxley R, Owen CG, Whincup PH, Cook DG, Rich-Edwards J, Smith GD, et al. Is birth weight a risk factor for ischemic heart disease in later life? Am J Clin Nutr 2007; 85(5):1244–50. [PubMed]
20. Whincup PH, Kaye SJ, Owen GC, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: A systematic review. JAMA 2008; 300(24):2886–97. [CrossRef][PubMed]
21. Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? J Physiol 2004; 561(Pt 2):355–77. [CrossRef][PubMed]

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SINDROM INSULINSKE REZISTENCIJE U PREEKLAMPSIJI – UTICAJ NA NOVOROĐENČE

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Preeklampsija je multisistemski poremećaj nepoznatog uzroka, tipičan za ljudsku trudnoću. Glavni je uzrok perinatalnog i maternalnog morbiditeta i mortaliteta i pogađa od 5% do 8% svih trudnoća. Klinički nalaz se može manifesovati bilo kao maternalni ili fetalni sindrom. Sve više podataka podržava ulogu insulinske rezistencije u preeklampsiji, iako to nije potvrđeno u svim studijama.

Cilj ovog istraživanja bio je utvrditi uticaj inzulinske rezistencije na potomstvo u trudnoćama komplikovanim preeklampsijom. Istraživanju je podvrgnuto šezdeset preeklampsijom komplikovanih trudnoća, uzimajući vrednost nivoa isulina u serumu od 20 uU/ml kao graničnu vrednost insulinske rezistencije. Osetljivost na insulin je ispitana pomoću Homa i Quicky indeksa. Sindrom insulinske rezistencije imalo je trideset preeklampsijom komplikovanih trudnoća, a trideset je činilo kontrolnu grupu. Linearna regresiona analiza i logistička linearna analiza korišćene su kako bi se ispitao uticaj insulinske rezistencije.

U preeklamptičnim trudnoćama sa insulinskom rezistencijom trajanje trudnoće blio je kraće (2,59; p< 0,01), a težina posteljice manja (2,72; p<0,01). Ova grupa, takođe, imala je statistički niži procenat vaginalnih porođaja (9,64, p<0,01), odnosno veći procenat carskih rezova (4,44, p<0,05). Novorođenčad u grupi sa insulinskom rezistencijom imala su manju telesnu dužinu (0,108; p<0,001) težila manje (2,81, p<0,01), imala niži Apgar skor (3,11, p<0,01) i duži period hospitalizacije (2,48; p<0,05).

Sindrom insulinske rezistencije nije prisutan u svakoj trudnoći komplikovanoj preeklampsijom, ali ako je prisutan, utiče na potomstvo u negativnom smislu. *Acta Medica Medianae 2016;55(2):19-24.*

Ključne reči: *preeklampsija, insulinska rezistencija, novorođenče*