MATERNALNO-FETALNA INTERAKCIJA I MODULIRANJE U STVARANJU NOVE POPULACIJE: PREGLED POSTOJEĆIH DOKAZA O POVEZANOSTI FETALNE ISHRANE I RAZVOJA HRONIČNIH BOLESTI U TOKU ŽIVOTA

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REVIEW ARTICLE

MATERNOFETAL INTERACTION AND MODULATION IN CREATING A NEW POPULATION: A REVIEW OF CURRENT EVIDENCE ON THE RELATIONSHIP BETWEEN FETAL NUTRITION AND THE DEVELOPMENT OF CHRONIC DISEASES LATER IN LIFE

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SAŽETAK

Koncept fetalnog programiranja pronašao je svoje mesto u nauci i nastavlja da kontinuirano osvetlljava put ka boljem razumevanju fetalnog života i njegovog uticaja na postnatalni i adultni život. Njegov obim je mnogo širi od uobičajenog prepoznavanja da stanja tokom trudnoće utiču na zdravlje novorođenčeta, što se potvrđuje kontinuiranim prikupljanjem dokaza iz opservacionih studija, kao i iz eksperimentalnih modela. Ono što hipotezu o fetalnom programiranju čini još težom za potvrdu ili prihvatanje jeste činjenica da je period od momenta dejstva stimulusa do posledica dosta dug, kao i brojni faktori koji mogu menjati ovu povezanost tokom života. Uprkos tome, hipoteze o doprinosu suboptimalnog fetalnog rasta i nutricije povećanom riziku od hroničnih bolesti se održavaju - "pothranjenost" in utero, kao i u ranom detinjstvu, trajno menja fiziologiju i metabolizam, što dovodi do povećane predispozicije za hronične bolesti tokom života (hipertenzija, bolest koronarnih arterija, moždani udar, dijabetes, i druge). Svrha ovog rada jeste pregled postojećih dokaza o povezanosti fetalne ishrane i rizika za hronične bolesti u kasnijem životu.

Temeljan pregled literature i analiza različitih vrsta studija fokusiranih na praćenje neonatusa do adultnog doba radi rasvetljavanja značaja fetalnog programiranja.

Veza između suboptimalnog fetalnog rasta i većeg rizika od metaboličkog sindroma, insulinske rezistencije, dijabetesa tipa 2, hipertenzije, sada je pokazana u nekoliko populacija i uzrasnih grupa.

Na osnovu dokaza koji su predstavljeni, može se zaključiti da fetalno programiranje pronalazi svoj značaj i na putu je da postane treći uzročni faktor nastanka hroničnih bolesti u toku života, zajedno sa genetskom predispozicijom i načinom života.

Ključne reči: fetalno programiranje, malnutricija, hronične bolesti

ABSTRACT

The concept of fetal programming has found its place in science and keeps lighting the way to better understanding of fetal life and its impact on postnatal and adult life. Its capacity is much wider than a common recognition of the fact that different disorders in pregnancy impact fetal health, and these capacities keep being confirmed by various observational studies and experimental models. Another fact that makes fetal programming even harder to confirm and accept is the long period between the stimulus and its consequences, as well as various factors that can change and influence this period of one's lifetime. Nevertheless, different hypotheses are present, concerning suboptimal fetal health and nutrition and their contribution to the development of chronic diseases during one's lifetime - inadequate nutrition during intrauterine period and early childhood can permanently change one's physiology and metabolism, which contributes to a possible development of chronic diseases (hypertension, coronary artery disease, stroke, diabetes, etc.). The aim of this paper is to review current evidence on the relationship between fetal nutrition and the risk of chronic diseases later in life.

A detailed review of current literature and the analysis of various studies aimed at following neonates to their adulthood in order to determine the significance of fetal programming.

An association between suboptimal fetal growth and a higher risk of metabolic syndrome, insulin resistance, diabetes type 2, and hypertension, has been proven by the studies conducted within different populations and age groups.

Based on the evidence presented in this paper, it can be concluded that fetal programming has been recognized as significant and is on the way to becoming the third contributing factor in the development of chronic diseases during one's lifetime, along with a genetic predisposition and lifestyle.

Keywords: fetal programing, malnutrition, chronic diseases

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UVOD

Prema hipotezi o fetalnom poreklu, promene u fetalnom rastu rezultiraju adaptacijama koje određuju vulnerabilnost prema kardiovaskularnim, metaboličkim i endokrinim bolestima tokom života. „Programiranje" je fenomen kod koga su dugoročne i ireverzibilne promene u strukturi i funkciji metabolizma indukovane kratkim stimulusima. Tokom fetalnog razvoja, promene u nutrijentima i hormonalnom miljeu konceptusa u kritičnom periodu mogu menjati ekspresiju fetalnog genoma, a to dovodi do trajnih efekata na grupu fizioloških funkcija i struktura. Važna tačka ove definicije jeste da se reprogramiranje može desiti samo tokom određenog perioda prozora kada je osoba senzitivna. Programiranje odražava opšti princip razvojne biologije, a veliki broj sistema i organa može biti određen intrauterinim razvojem [1].

Prema Barkerovoj hipotezi o ranom poreklu, suboptimalni fetalni rast i nutricija mogu da doprinesu povećanom riziku od hroničnih bolesti. Prema ovoj teoriji, „ pothranjenost" in utero, kao i u ranom detinjstvu, trajno menja fiziologiju i metabolizam, što dovodi do povećane predispozicije za hronične bolesti tokom života (hipertenzija, hiperlipidemija, gojaznost, dijabetes i druge), a smatra se i da je tajming nutritivnih promena tokom trudnoće od ključnog značaja. Mala količina nutrijenata u fetalnom životu tokom kritičnog perioda može smanjiti fetalni rast i trajno oštetiti razvoj i funkciju sistema, dovodeći do metaboličkih promena tokom života, kao što je npr. smanjena senzitivnost na insulin [2]. Termin „metabolički otisak "pre nego „programiranje" koristili su Vaterlant i Garza, kako bi obuhvatili adaptivne odgovore na specifična rana nutritivna stanja [3]. Lukas naglašava da fetalno programiranje prevazilazi okvire resetovanja metabolizma, pa smatra da je „programiranje" prikladniji termin nego „otisak" (imprinting). Ovaj tip otiska ima snažnu biološku osnovu, a uključuje privremene promene molekula DNK koje mogu da prošire svoj uticaj i na nekoliko generacija. Intergeneracijski efekti, kao što je zabeleženo kod potomstva pojedinaca koji su bili izloženi gladovanju in utero, podržavaju teoriju genomskog imprintinga [4]. Kao što je pretpostavio i Hejlz, fetalno stanje može uticati na rezidualnu funkciju organa, a efekti se mogu ispoljiti tek u srednjem životnom dobu [5]. Dokaza o povezanosti fetalnog rasta i hroničnih bolesti tokom života sve je više, a čak i da fetalno programiranje ne podržava teoriju o hroničnim bolestima, moglo bi predstavljati dodatni rizik spoljašnje sredine koji reaguje sa ostalim determinantama tokom života ili ih moduliše. Ovo bi mogla da bude važna politika i da ima značajne implikacije u prevenciji hroničnih bolesti koje su povezane sa ishranom, posebno u populaciji gde je inciden-

INTRODUCTION

According to the fetal origins hypothesis, changes in fetal growth result in adaptations that determine vulnerability to cardiovascular, metabolic, and endocrine diseases during one's lifetime. "Programming" is a phenomenon which implies long-term and irreversible alterations in metabolic structure and functions induced by short stimuli. During fetal development, changes in the milieu of nutrients and hormones of the conceptus during a critical period can alter fetal gene expression, which results in lasting effects on a group of physiological functions and structures. An important point of this definition is the fact that reprogramming can occur only during a certain window period when the person is sensitive. Programming reflects a general principle of developmental biology, and a large number of systems and organs can be determined by intrauterine development [1].

According to Barker's early-origin hypothesis, suboptimal fetal growth and nutrition may lead to an increased risk of chronic diseases. According to this theory, in utero and early childhood "undernutrition" permanently alter physiology and metabolism leading to an increased predisposition to chronic diseases during one's lifetime (hypertension, hyperlipidemia, obesity, diabetes, etc.), and it is also believed that the timing of dietary change during pregnancy is crucial. A small amount of nutrients during a critical period of fetal life may reduce fetal growth and permanently damage the development and functioning of the system leading to metabolic changes later in life such as reduced sensitivity to insulin [2] .The term "metabolic imprinting" rather than "programming" was used by Waterland and Garza to encompass adaptive responses to specific early nutrition [3]. Lucas emphasizes that fetal programming goes beyond resetting one's metabolism, so he believes that "programming" is a more appropriate term than "imprinting". This type of imprinting has a strong biological basis, and it involves temporary changes in DNA molecules that can expand their influence on several generations. Intergenerational effects, as observed in the offspring of individuals who had been exposed to starvation in utero, support the theory of genomic imprinting [4]. As Hales hypothesized, fetal condition may affect the residual functions of organs and the effects may occur not before midlife [5]. There is increasing evidence of a link between fetal growth and chronic diseases during one's lifetime, and even if fetal programming did not support the theory of chronic diseases, it could represent an additional environmental risk that interacts with other determinants during life or modulates them. This could be an important policy that may have significant implications for the prevention of nutri-

ca dece sa niskom telesnom težinom na rođenju visoka, što oslikava loš nutritivni status majke. Svrha ovog rada jeste pregled postojećih dokaza o povezanosti fetalne ishrane i rizika za nastanak hroničnih bolesti kasnije tokom života, mehanizama i puteva zasnovanih na epidemiološkim i eksperimentalnim podacima, kao i rasvetljavanje nekih implikacija za politiku i strategije zemalja u razvoju. Fokus je na fetalnom programiranju, a priznaje se da se proces može proširiti i na rani postnatalni život.

ULOGA FETALNIH GLUKOKORTIKOIDA

U sklopu fetalnog programiranja razmatra se uloga fetalnih glukokortikoida i potencijalne dugoročne posledice kod fetusa koji je duže vreme bio izložen njihovim visokim koncentracijama. Uloga fetalnih glukokortikoida je ne samo stimulacija diferencijacije tkiva i povećavanje stope maturacije organa, pre svega pluća, srca, bubrega i imunog sistema, već i koordinacija različitih adaptacionih mehanizama potrebnih za prelazak iz intrauterine u ekstrauterinu sredinu. Fiziološki, koncentracije glukokortikoida kod fetusa rastu pred porođaj, kao signal maturacije tkiva, dok se u patološkim uslovima njihove koncentracije povećavaju ranije u toku trudnoće, i to usled placentarne insuficijencije, tj. fetoplacentnog stresa, ili u slučaju nedostatka placentnog enzima koji štiti fetus od majčinih glukokortikoida [6]. Ovaj enzim (11- β -hidroksisteroid-dehidrogenaza) koji je zaslužan za održavanje nižeg nivoa kortizola kod fetusa nego kod majke (u fiziološkim uslovima) vrši ubrzanu konverziju kortizola do inertnih formi. Značaj uloge ovog enzima je zapažen u studijama na ljudima ali i na životinjama, jer se njegova disfunkcija javlja i kod osoba sa insulinskom rezistencijom i posledičnim potencijalnim metaboličkim sindromom, zbog visokog nivoa glukokortikoida [7]. Posledično, pokazana je i obrnuta veza koncentracije kortizola u plazmi i težine deteta na rođenju u tri različite populacije. Studija koja je ovo pokazala takođe povezuje ove visoke vrednosti kortizola i sa visokim vrednostima krvnog pritiska, mada je povezanost bila jača kod gojaznih osoba [8]. Uzimajući u obzir saznanje da se kod odraslih osoba koje su imale malu telesnu težinu na rođenju zapažaju više koncentracije kortizola, može se pretpostaviti da ulogu u posledičnim potencijalnim vrednostima visokog krvnog pritiska kod njih ima i fetalna nefrogeneza (s obzirom na to da bebe sa malom težinom na rođenju imaju manje nefrona) sa doživotnim efektom na renalnu funkciju i kardiovaskularnu kontrolu. Studija koja se ovim detaljinije bavila sprovedena je na pacovima i pokazala je da je moguće da deca čije su majke u toku trudnoće imale ishranu siromašnu proteinima imaju više vrednosti krvnog pritiska, usled poremećaja u fetalnoj nefro-

tion-related chronic diseases, especially in populations with high prevalence of low birth weight, which reflects poor maternal nutritional status. The aim of this paper is to review current evidence of the link between fetal nutrition and the risk of developing chronic diseases later in life, mechanisms and pathways based on epidemiological and experimental data, as well as to determine some of the implications for policies and strategies in developing countries. The focus is on fetal programming, but it is recognized that the process may extend into early postnatal life.

THE ROLE OF FETAL GLUCOCORTICOIDS

The role of fetal glucocorticoids and potential long-term consequences in a fetus that has been exposed to high concentrations for a long period of time are considered within fetal programming. Apart from stimulating cell differentiation and increasing the rate of organ maturation, primarily the lungs, the heart, kidneys and the immune system, fetal glucocorticoids coordinate various adaptation mechanisms required for the transition from intrauterine to extrauterine life. Physiologically, concentrations of glucocorticoids in a fetus increase before birth, as a sign of tissue maturation, whereas in pathological conditions the concentrations increase earlier during pregnancy due to placental insufficiency (fetoplacental stress) or due to a lack of a placental enzyme that protects the fetus from the mother's glucocorticoids [6]. This enzyme (11 β-Hydroxysteroid dehydrogenase), which is responsible for maintaining a lower level of cortisol in the fetus in comparison with the mother (in physiological conditions), rapidly converts cortisol into its inert form. The significance of this enzyme has been recognized in studies conducted on both humans and animals, as its dysfunction also occurs in individuals with insulin resistance and possibly resulting metabolic syndrome due to high levels of glucocorticoids [7]. Consequently, an inverse correlation between plasma cortisol concentrations and infant birth weight was demonstrated in three different populations. The study that proved this also linked high cortisol levels to high blood pressure, although the correlation was stronger in obese individuals [8]. Taking into account that higher cortisol concentrations are found in adults who had low birth weight, it can be assumed that fetal nephrogenesis also plays a role in potentially high blood pressure values (considering that babies with low birth weight have fewer nephrons at birth) with lifelong effects on renal function and cardiovascular control. A study that dealt with this in more detail was conducted on rats and showed that the offspring of mothers who had low-protein diet during pregnancy could have higher blood pressure due to impaired

genezi [9]. Još jedna studija koja ide u prilog tome jeste ona koju su sproveli Lengli-Evans i saradnici, a koja implicira da sled događaja od glukortikoidnog dejstva u fetusu do hipertenzije kod odraslih obuhvata razvoj preosetljivosti na glukokortikoide odraslih, sa aktivacijom sistema renin-angiotenzin i povećanom osetljivošću krvnih sudova na angiotenzin II, a sve sa osvrtom na pothranjenost majke [10]. S tim u vezi, zaključuje se da glukokortikoidi mogu da smanje razvoj vaskulature i programiraju bubrežni sistem renin-angiotenzin. Rani prelaz sa ćelijske proliferacije na ćelijsku diferencijaciju, za koji je zaslužan povišen kortizol, sa nepravilnom šemom rasta za dati stadijum razvoja, može dovesti do štetnih posledica kasnije u životu, od kojih se pominju sklonost ka visokom krvnom pritisku i hiperglikemiji. Još jedan značaj preterane izloženosti fetusa glikokortikoidima ogleda se u tome da u odraslom dobu može dovesti do insulinske rezistencije i intolerancije na glukozu različitim mehanizmima – menjanjem ekspresije glukoregulatornih gena u tkivima (npr. u skeletnim mišićima), regulacijom glukoneogeneze izazvane kortizolom u bubregu i jetri, a spominju se i evenutalne promene u beta ćelijama pankreasa [11,12].

ULOGA INSULINU SLIČNIH FAKTORA RASTA (IGFS)

Danas se zna da su insulinu slični faktori rasta (IGFs) glavni posrednici prenatalnog rasta kod ljudi, a čini se da je njihovo stvaranje in utero nezavisno od hormona rasta. Uloga hormona rasta koji dovodi do rasta uglavnom je vezana za postnatalni period, dok IGFs imaju primarnu ulogu u prenatalnom periodu. Prema Glukmanu, IGF-2 je dominantan rano u gestaciji (u toku embrionalnog razvoja) kad placenta ne ograničava dostupnost supstrata, dok je kasnije tokom gestacije (tokom fetalnog perioda), kao i u perinatalnom periodu, dominantan IGF-1, koji je pod strogom kontrolom ishrane [13]. Različite studije tvrde da bioraspoloživost i delovanje IGFs mogu biti izmenjeni kad god je fetalni rast ugrožen. Sposobnost da deca koja su rođena sa zastojem u rastu (IUGR) nadoknade rast postnatalno proučavana je, između ostalog, i od strane Sajanfaranija i saradnika (smatra se da 20% dece koja se rode kao IUGR ne nadoknade rast postnatalno). Pokazano je da intrauterino reprogramiranje hipotalamo-pituitarno-adrenalne osovine može dovesti do trajne modifikacije neuroendokrinog odgovora na stres, te da deca koja su imala povišen kortizol mogu biti manje sposobna da postnatalno nadoknade rast. Pretpostavlja se da tokom neonatalnog perioda kortizol ograničava proteolizu IGF vezujućeg proteina 3 (IGFBP3) i da samim tim smanjuje bioraspoloživost IGF-a [14]. Niski nivoi IGF-1 primećeni su i kod dece koja su rođena kao mala

fetal nephrogenesis [9]. Another study that supports this finding is the one conducted by Langley-Evans and colleagues which implies that the sequence of events from glucocorticoid action in the fetus to hypertension in adulthood includes the development of sensitivity to glucocorticoids in adults, with the activation of the renin-angiotensin system and increased sensitivity of blood vessels to angiotensin II, all with reference to maternal malnutrition [10]. Having this in mind, it has been concluded that glucocorticoids may diminish vascular development and program the renal renin-angiotensin system. An early transition from cell proliferation to cell differentiation due to elevated cortisol together with irregular growth pattern for a given developmental stage, may lead to consequences later in life, some of which are high blood pressure and hyperglycemia. Another reason why excessive fetal exposure to glucocorticoids is significant is the fact that in adulthood it may lead to insulin resistance and glucose intolerance through various mechanisms – by altering the expression of glucoregulatory genes in tissues (e.g., in skeletal muscles), by regulating cortisol-induced gluconeogenesis in the kidney and the liver, and possible changes in pancreatic beta cells are also mentioned [11,12].

THE ROLE OF INSULIN-LIKE GROWTH FACTORS (IGFS)

Insulin-like growth factors (IGFs) are now known to be the main mediators of prenatal growth in people, and their generation in utero appears to be independent from growth hormone. The role of growth hormone, which brings about growth, is mainly related to the postnatal period, whereas IGFs have a primary role in the prenatal period. According to Gluckman, IGF-2 is dominant early in gestation (during embryonic development) when the placenta does not limit substrate availability, while later during gestation (during the fetal period), as well as in the perinatal period, IGF-1 is dominant being strictly controlled by nutrition [13]. Various studies claim that the bioavailability and the activity of IGFs can be altered whenever fetal growth is compromised. Cianfarani and colleagues, among others, have studied the possibility of postnatal catch-up growth for children born with intrauterine growth restriction (IUGR) – it is estimated that 20% of children born with IUGR do not experience postnatal catch-up growth. It has been shown that intrauterine reprogramming of the hypothalamic-pituitary-adrenal axis can lead to a permanent modification of the neuroendocrine stress response and that children who had elevated cortisol level may be less likely to catch up postnatally. It is hypothesized that during the neonatal period cortisol limits proteolysis of IGF-binding protein-3 (IGFBP3) and

za gestacijsku starost (small for gestational age – SGA) ali koja nisu pokazala nadoknadu rasta i ostala su niska (u poređenju sa decom normalnog i niskog rasta koja su na rođenju imala adekvatnu veličinu za gestacijski uzrast). I kod ove dece su zapaženi niski nivoi proteina IGFBP3, a kao razlog tome takođe se spominje njegova proteoliza. Smanjena stopa i abnormalni obrazac sekrecije hormona rasta takođe su bili prisutni, nagoveštavajući da defekt osovine hormona rasta-IGF-1 koji se održava može nastati kod one dece sa SGA koja ne nadoknade rast postnatalno [15]. Prema hipotezi nadoknade rasta, koju su postavili Sajanfarani, Džermani i Branka, tkiva potroše insulin i IGF-1 tokom fetalnog života, kada postoji nedostatak hranljive podloge, jer je sistem IGF-1 tada isključen. Nakon rođenja, u prisustvu obilja oba hormona, a zbog adekvatnog snabdevanja hranljivim materijama, pretpostavlja se da insulinska rezistencija razvija odbrambeni mehanizam protiv hipoglikemije. Preterana aktivacija sistema IGF određuje ranu postnatalnu nadoknadu rasta, ali i dovodi do insulinske rezistencije kao metaboličke adaptacije sa potencijalno štetnim dugoročnim efektima [16].

UTICAJ ISHRANE

Koncept programiranja je mnogo širi od uobičajenog prepoznavanja da stanja tokom trudnoće utiču na zdravlje novorođenčeta. Ono što hipotezu o fetalnom programiranju čini još težom za potvrdu ili prihvatanje jeste činjenica da je period od momenta dejstva stimulusa do posledica dosta dug, zatim brojni faktori koji mogu menjati ovu povezanost tokom života, kao i mogućnost da smanjen fetalni rast i hronične bolesti nisu uzročno povezane, ali imaju zajedničko poreklo, kao što je loš socioekonomski status ili genetska predispozicija. Nezavisno od toga, hipoteza o fetalnom programiranju osvaja teren, kako se prikupljaju dokazi iz opservacionih studija, posebno iz eksperimentalnih modela.

Podaci o efektima majčine ishrane na veličinu i proporcije na rođenju prilično su ograničeni. Podaci o unosu mikronutrijenata iz hrane i suplemenata kod trudnica i dalje su oskudni, a treba razmotriti i tajming neodgovarajuće ishrane ili suplemenata, uz tip nutrijenata i status majke. Nekoliko mikronutrijenata čini se presudnim za fetalni rast i možda i za fetalno programiranje, iako su mehanizmi i dalje nejasni. Na osnovu postojećih dokaza, vitamini B2, B6, B12 kao i folna kiselina, putem metilacije DNK, utiču na fetalni genom i samim tim deo su fetalnog programiranja. Vitamin A, gvožđe, hrom, cink, i vitamin C verovatno takođe imaju važnu ulogu u fetalnom programiranju, ali ima prostora za dalje studije vezane za njihov značaj [17]. Još manji broj studija povezuje ishranu majke i rezultujuće mere

thereby reduces the bioavailability of IGF [14]. Low levels of IGF-1 were also observed in children who were small for gestational age (SGA) but who did not experience catch-up growth and remained short (in comparison with children of normal and short stature who had had an adequate size for gestational age at birth). Low levels of IGFBP3 were also observed in these children and its proteolysis was believed to be the reason. A reduced rate and an abnormal pattern of growth hormone secretion were also present, suggesting that an ever-present defect in the growth hormone-IGF-1 axis may occur in those SGA children who do not catch up postnatally [15]. According to the "catch-up" growth hypothesis proposed by Cianfarani, Germani and Branca, tissues use up insulin and IGF-1 during fetal life, when there is a lack of substrate as IGF-1 is turned off. After birth, when both hormones are abundantly present, and due to an adequate supply of nutrients, it is assumed that insulin resistance develops a defense mechanism against hypoglycemia. Excessive activation of the IGF system determines early postnatal compensatory growth, but it also leads to insulin resistance as a metabolic adaptation with potentially harmful long-term effects [16].

THE IMPACT OF NUTRITION

The concept of programming is much wider than a common recognition of the fact that conditions in pregnancy influence fetal health. What makes the hypothesis of fetal programming even more difficult to confirm or accept is the fact that the period between the stimulus and its consequences is rather long, then numerous factors that may alter this link during life, as well as the possibility that reduced fetal growth and chronic diseases are not linked but have a common origin, such as low socioeconomic status or a genetic predisposition. Nevertheless, fetal programming hypothesis is gaining ground as evidence from observational studies and especially experimental models accumulates.

Data on the effects of maternal nutrition on the size and proportions at birth are rather limited. Data on the intake of micronutrients from food and supplements in pregnancy are still scarce, and the timing of inadequate nutrition or supplementation should be considered, along with the type of nutrients and maternal condition. Several micronutrients appear to be crucial for fetal growth and possibly for fetal programming, although the mechanisms remain unclear. Based on existing evidence, vitamins B2, B6, B12 as well as folic acid, through DNA methylation, affect the fetal genome and are thus part of fetal programming. Vitamin A, iron, chromium, zinc, and vitamin C probably also play an important role in fetal programming,

kod deteta, osim težine i veličine na rođenju. U južnoj Engleskoj, prospektivna studija koja je obuhvatila 693 prvorotke koje su nosile po jedan plod, pokazala je da placentalne težine i težine na rođenju dece rođene na vreme nisu povezane sa unosom bilo kojih makronutrijenata. U drugom trimestru, vitamin C bio je jedini mikronutrijent nezavisno povezan sa težinom na rođenju, uzimajući u obzir majčinu visinu i eventualnu konzumaciju duvana. Vitamin C, vitamin E i folna kiselina svi su bili povezani sa težinom placente nakon prilagođavanja majčinim karakteristikama, ali samo je vitamin C ostao prediktivan u simultanoj regresiji, iako je veza bila slaba [18]. U današnje vreme neophodno je naglasiti i uticaj životne sredine i samog kvaliteta namirnica koje se konzumiraju, na kasniji život. S tim u vezi, pokazano je da unos hrane bogate pesticidima (pre ili postnatalno) može dovesti do poremećaja puberteta (utiču na vreme nastanka, progresiju i završetak puberteta), s obzirom da se ponašaju kao supstance koje mogu menjati funkcije endokrinog sistema (*endocrine disrupting chemicals - EDCs*) [19]. Studije su pokazale pozitivnu vezu između izlaganja *EDCs* i komplikacija trudnoće (vanmaterične trudnoće, gubici trudnoće, gestacioni dijabetes melitus, hipertenzija u trudnoći, prevremeni porođaj), kao i rađanja dece sa IUGR, dece male ili velike težine za gestacijsku starost [20]. Važno je spomenuti i prediktore prisutne kod majke. Na osnovu velikog korpusa dokaza, čini se da su glavni maternalni antropometrijski prediktori težine na rođenju njena težina (najviše povezana), visina, obim nadlaktice i BMI. Studija sprovedena od strane Mohantija i saradnika, grupiše ove parametre kod žena po bojama, te se smatra da žene čiji su parametri u „crvenoj zoni" imaju veće šanse da rode decu niske telesne težine [21].Takođe, antropometrijski parametri kod majke mogu se uzeti u obzir u ranoj trudnoći i prilikom predviđanja gestacionog dijabetes melitusa, što je takođe proučavano [22].

SKLONOST KA METABOLIČKIM POREMEĆAJIMA

Najjača povezanost težine dece na rođenju i hroničnih bolesti kasnije u toku života verovatno se vidi kroz razvijanje metaboličkog sindroma (sindrom X), a kroz njega i razvijanje visokog krvnog pritiska, hipertrigliceridemije, često gojaznosti, kao i insulinske rezistencije i dijabetesa. Naglašava se značaj potencijalnog razvoja dijabetesa u kasnijem životnom dobu jer je aktuelan trend povećavanja njegove prevalence kod odraslih osoba, samim tim i kod žena, zbog potencijalne trudnoće opterećene ovim komorbiditetom. Prevalenca pregestacionog dijabetesa kod trudnica povećala se u prethodnoj deceniji u Beogradu, i očekuje se njen dalji porast, kao i to da će se duplirati do 2050. godine [23].

but further research is needed concerning their significance [17]. Even fewer studies link maternal nutrition to the child's body measurements except for weight and size at birth. In Southern England, a prospective study which included 693 primiparous singleton women showed that placental weight and full-term birth weight were not associated with the intake of any micronutrient. In the second trimester, vitamin C was the only micronutrient that independently correlated with birth weight, considering maternal height and possible tobacco consumption. Vitamin C, Vitamin E and folic acid were all associated with placental weight after adjusting for maternal characteristics, but only vitamin C remained predictive in simultaneous regression, although the correlation was weak [18]. Nowadays it is necessary to emphasize the impact of the environment and the quality of food consumed on one's life. With respect to this, it has been shown that the intake of food rich in pesticides (prenatally or postnatally) can lead to puberty disorders (pesticides affect the onset, progression, and completion of puberty), considering that they act as substances than can alter the functions of the endocrine system (*endocrine disrupting chemicals - EDCs*) [19]. Studies have shown a positive correlation between EDC exposures and pregnancy complications (ectopic pregnancies, miscarriages, gestational diabetes mellitus, hypertension in pregnancy, premature birth), as well as children born with IUGR, small for gestational age or large for gestational age [20]. It is also important to mention maternal predictors. Based on a large body of evidence, the main maternal anthropometric predictors of birth weight appear to be their weight (the strongest correlation), height, mid-upper arm circumference, and BMI. A study conducted by Mohanty and colleagues grouped these parameters in women by color, and it is considered that women whose parameters are in "the red zone" are more likely to give birth to children with low body weight [21]. Besides, maternal anthropometric parameters can be taken into account in early pregnancy and when predicting gestational diabetes mellitus, which has also been researched [22].

TENDENCY TO METABOLIC SYNDROME

The strongest correlation between birth weight and chronic diseases later in life is probably observed through the development of metabolic syndrome (syndrome X), including the occurrence of high blood pressure, hypertriglyceridemia, often obesity, as well as insulin resistance and diabetes. The significance of the potential development of diabetes in later life is emphasized as there is an increasing trend in its prevalence in adults (including women) because of a poten-

Takođe, pokazano je da žene sa dijabetesom tipa 1, u trudnoći imaju veće šanse za komplikacije u trudnoći i lošije neonatalne ishode u poređenju sa onima koje imaju dijabetes tipa 2 ili gestacioni dijabetes melitus [24]. Kao što je pokazano u brojnim studijama, pothranjenost majke u kritičnim periodima fetalnog razvoja povezuje se sa fetalnim programiranjem u pravcu gojaznosti, insulinske rezistencije, metaboličkog sindroma i dijabetesa tipa 2, kasnije u životu, naročito ako je prisutna složenija i bogatija ishrana ove dece postnatalno. Adipogeneza koja započinje in utero i ubrzava se u neonatalom životu najzaslužnija je za ovaj rizik [25]. Prema već spomenutoj Hejlzovoj teoriji, pothranjenost majke tokom kritičnih perioda razvoja fetusa dovodi do kompenzatornih promena u fetusu uključujući i njegovu sposobnost da skladišti masno tkivo, što doprinosi razvoju centralne gojaznosti kasnije u životu, kada postoji diskrepanca između predviđene i sprovedene postnatalne ishrane [5]. Pokazano je da su veći rizik od abdominalne gojaznosti i veći procenat masti u telu udruženi sa malom težinom na rođenju, što su, između ostalih, pokazali i Žake i saradnici u studiji sprovedenoj kod 25-godišnjih muškaraca i žena. Zaključili su da je kod dece sa IUGR smanjeno preuzimanje glukoze stimulisano insulinom, sa manjim stepenom supresije slobodnih masnih kiselina u masnom tkivu. Ovo ukazuje na to da masno tkivo ima ulogu u insulinskoj rezistenciji dece sa IUGR, kao što smanjen fetalni rast verovatno dovodi do povećanja masti u jetri tokom života, bez značajnih promena količine masti u telu [26]. Oni takođe smatraju da deca sa IUGR, u sklopu svoje nadoknade rasta, u prvim godinama života, imaju veće koncentracije leptina, ali koji gubi efekat na BMI i pol (smatra se da je to rezultat adaptivne rezistencije na leptin, koji pogoduje njihovom pokušaju da nadoknade rast) [27]. Dalje, sprovedenim sistematskim prikazom i meta analizom koja se bavila proučavanjem dece koja su rođena sa malom telesnom težinom (LBW i SGA) i potencijalnim razvojem dijabetesa tipa 2 u odraslom dobu, pokazano je da ova deca imaju 2,3 puta veću šansu da obole od dijabetesa tipa 2, te da su pod većim rizikom i za insulinsku rezistenciju kao takvu [28]. Kod ove dece je takođe pokazano da u prvim danima života razvijaju rezistenciju na hormon rasta, kao i na IGF1, sve u sklopu rezistencije na insulin, te stoga autori smatraju da bi ovo moglo objasniti njihove poteškoće da nadoknade rast u detinjstvu kao i veću sklonost ka metaboličkom sindromu i kasnije u toku života [29]. U Australiji, Flenegen i saradnici uočili su da je mala dužina na rođenju, ali ne i mršavost, povezana sa insulinskom rezistencijom, i to samo kod muškaraca. Oni su ispitivali senzitivnost na insulin i sekreciju insulina u vezi sa veličinom tela na rođenju kod muškaraca i

tial pregnancy burdened by this comorbidity. The prevalence of pregestational diabetes in pregnant women has increased in the past decade in Belgrade and it is expected to continue rising, and even to double by 2050 [23]. Also, it has been shown that women with type 1 diabetes have an increased risk of pregnancy complications and unfavorable neonatal outcomes compared to those with type 2 diabetes or gestational diabetes mellitus [24]. As shown in numerous studies, maternal undernutrition in critical periods of fetal development is associated with fetal programming towards obesity, insulin resistance, metabolic syndrome, and type 2 diabetes in later life, especially if these children have a more complex diet postnatally. Adipogenesis, which begins in utero and is accelerated in neonatal period, is most responsible for this [25]. According to the previously mentioned Hales' theory, maternal undernutrition during the critical periods in fetal development leads to compensatory changes in the fetus including its ability to store adipose tissue, which contributes to the development of central obesity later in life when there is a mismatch between predicted and actual postnatal nutrition [5]. It has been shown that a higher risk of abdominal obesity and a higher percentage of body fat correlate with low birth weight, which was also confirmed by Jaquet and colleagues, among others, in a study that included 25-year-old men and women. They concluded that insulin-stimulated glucose uptake was reduced in children with IUGR with diminished suppression of free fatty acids in adipose tissue. This suggests that adipose tissue plays a role in insulin resistance of children with IUGR as well as that reduced fetal growth probably leads to an increased level of fat in the liver during life with no significant changes in body fat [26]. They also believe that children with IUGR in first years of life, as part of their growth compensation, have higher concentrations of leptin, but that it loses its effect on BMI and gender (this is considered to be the result of adaptive resistance to leptin which is in accordance with their attempt to catch up) [27]. Furthermore, a systematic review and meta-analysis of children with low birth weight (LBW and SGA) and potential development of type 2 diabetes in adulthood showed that these children were 2.3 times more likely to develop type 2 diabetes and that they had a higher risk of insulin resistance as such [28]. These children have also been shown to develop resistance to growth hormone and IGF-1 in first days of life as part of their insulin resistance, so the authors believe that this could account for their difficulties in catching up during their childhood and for a greater tendency to metabolic syndrome later in life [29]. In Australia, Flanagan and colleagues observed that short birth length

žena starosti 20 godina, rođenih u terminu, korišćenjem intravenskog testa na glukozu, uz minimalni gubitak glukoze. Pokazano je da je mala veličina na rođenju (ali samo kod muškaraca u ovoj studiji) udružena sa povećanom rezistencijom na insulin i hiperinsulinemijom, nezavisno od telesne mase ili procenta masti u telu, i pretpostavlja se da se starenjem smanjuje tolerancija na glukozu kod ljudi koji su rođeni kao mali za gestacijsko doba, i to kao posledica insuficijencije kompenzatornih mehanizama [30]. U hertfordširskoj meta analizi, pokazano je da je težina na rođenju povezana sa stopom dijabetesa tipa 2 i hroničnih bolesti u kasnijem toku života u vidu krive J oblika i da je više naznačena kod ženske dece [31]. Takođe, nešto ranije sprovedena hertfordširska kohortna studija proučavala je uzroke smrti kod odraslih osoba koje su rođene sa malom telesnom težinom i pokazano je da su muškarci skloniji da preminu od kardiovaskularnih bolesti i slučajnih padova, dok se kod žena izdvajaju kardiovaskularne bolesti, muskoloskeletne bolesti, pneumonija i dijabetes. Ono što oslikava sve veći značaj niske telesne težine na rođenju, a što je ova kohorta pokazala, jeste da povećanje telesne težine za jednu standardnu devijaciju redukuje smrtnost u populaciji (svih uzroka), do 75. godine, za 0,86% [32]. U Finskoj, sprovedena studija na 7086 osoba koje su rođene sa niskom telesnom težinom, pokazala je kumulativnu incidencu dijabetesa za muškarce 7,9% i za žene 5,4%, a incidenca se povećavala sa smanjenjem telesne težine, dužine, ponderalnog indeksa i težine posteljice. Takođe je primećeno da su deca majki koje su u trudnoći imale visok BMI, imala ubrzan rast tokom detinjstva i samim tim i veću učestalost dijabetesa tipa 2 [33]. Kohortna studija u Indiji je pokazala da su komponente insulinske rezistencije „programirane" in utero, kao i da mogu postati vidljive još u detinjstvu. U grupi od skoro 400 dece uzrasta od 4 godine, kod onih čija je težina na rođenju bila ≥ 2.5 kg, koncentracije insulina u plazmi bile su značajno veće nakon 30 minuta od unosa glukoze, nezavisno od aktuelne veličine tela. Glukoza u plazmi i insulin bili su nezavisno i obrnuto povezani sa težinom na rođenju, mada su aktuelna težina i debljina kožnog nabora bile u pozitivnoj korelaciji sa glukozom i insulinom. U uzrastu od 8 godina, niska težina na rođenju je kod ove dece povezana sa grupom poremećaja u okviru same insulinske rezistencije, iako je i aktuelna težina bila jak faktor [34]. Slično, u studiji koja je sprovedena u Južnoj Africi, kod dece uzrasta 7 godina, primećena je negativna korelacija između težine na rođenju i sekrecije insulina ili glukoze u krvi, nakon oralnog testa tolerancije na glukozu. Dužina na rođenju takođe je bila u negativnoj korelaciji sa insulinskom rezistencijom. Ona deca koja su rođena kao mala za gestacijsku starost, a

alone, not thinness, correlated with insulin resistance and that this was so only in men. They examined insulin sensitivity and insulin secretion in relation to body size at birth in 20-year-old men and women born at term, by using the intravenous glucose tolerance test wih minimal glucose loss. It was shown that small size at birth (only in men in this particular study) was associated with an increased risk of insulin resistance and hyperinsulinemia, regardless of their body mass or body fat percentage, so it is assumed that glucose tolerance decreases with age in people who were born small for gestational age owing to insufficiency of compensatory mechanisms [30]. In a Hertfordshire meta-analysis, it was shown that birth weight correlated with the rate of type 2 diabetes and chronic diseases in later life in a J curve and that it was more pronounced in female children [31]. Also, an earlier Hertfordshire cohort study examined mortality outcomes in adults who had had low birth weight and it was shown that men were more likely to die from cardiovascular disease and accidental falls, whereas women were more prone to cardiovascular disease, musculoskeletal disorders, pneumonia, and diabetes. What presents the ever-increasing significance of low birth weight and what this cohort study proved is the fact that a one-standard-deviation increase in birth weight reduced all-cause mortality rate by age 75 by 0.86% in the entire population [32]. In Finland, a study including 7086 individuals with low birth weight showed a cumulative incidence of 7.9% for men and 5.4% for women and the incidence increased as body weight, length, fetal ponderal index, and placental weight decreased. It was also noted that offspring of mothers who had had high BMI in pregnancy experienced accelerated growth during childhood and thus had a higher incidence of type 2 diabetes [33]. A cohort study conducted in India showed that the components of insulin resistance were "programmed" in utero, as well as that they may become visible as early as childhood. In the group of almost 400 children aged 4, those who weighed ≥ 2.5 kg at birth had significantly higher plasma insulin concentration 30 minutes after glucose intake regardless of the current body size. Plasma glucose and insulin were independently and reversely related to birth weight, although the current weight and skinfold thickness were positively related to glucose and insulin. At the age of 8, low birth weight in all children was associated with a group of disorders within insulin resistance, although the current weight was a strong predictor as well [34]. Similarly, in a study conducted in South Africa, in children aged 7 a negative correlation between birth weight and insulin secretion or blood glucose was noted upon the oral glucose tolerance test. There was a negative correlation between

intenzivno su rasla do 7. godine, češće su razvijala insulinsku rezistenciju u odnosu na decu koja su ostala mala [35]. Ova povezanost potvrđena je i u Švedskoj, gde su Karlson i saradnici pronašli da su muškarci čija je težina na rođenju bila manja od 3 kg i koji su imali istoriju dijabetesa u porodici, imali 10 puta veći rizik za oboljevanje od dijabetesa u odnosu na one čija je težina na rođenju bila veća (rizik za one sa pozitivnom anamnezom iznosio je 5,4, a za one bez anamneze 2,3). Efekti povećanja telesne mase bili su veći kod onih čija je dužina ili težina u toku prve godine bila niska [36]. Čak je i među Pima Indijancima koji imaju visoku stopu dijabetesa tipa 2, zabeležena povezanost između niske težine na rođenju i kasnije rezistencije na insulin. Pokazano je da su deca sa niskom težinom na rođenju, od 5. do 29. godine mršavija ali imaju veću rezistenciju na insulin (pokazanu putem koncentracija 2h glukoze), u poređenju sa decom normalne telesne težine. Deca sa velikom telesnom težinom na rođenju su u ovom periodu svojih života bila gojaznija, ali su ispoljavala manju rezistenciju na insulin od one koja bi se očekivala shodno njihovoj gojaznosti. Telesna težina na rođenju je pozitivno korelirala sa trenutnom težinom i visinom, uz korekciju za godine i pol, u svakoj ispitivanoj starosnoj grupi [37]. Takođe, na Pima Indijancima je proučavana i potencijalna povezanost telesne težine na rođenju i razvoja dijabetesa pre 40. godine. U ovoj visokorizičnoj populaciji, i niska i visoka telesna težina na rođenju su bile povezane sa razvojem dijabetesa u adolescenciji (od 10. do 19. godine), ali je samo niska telesna težina bila povezana sa razvojem ove bolesti u ranom životu (od 20. do 39. godine) [38].

SKLONOST KA KARDIOVASKULARNIM BOLESTIMA

Negativna korelacija telesne težine na rođenju i krvnog pritiska, posebno sistolnog, zapažena je u svim starosnim grupama, u kohortnim, retrospektivnim i longitudinalnim studijama, u industrijalizovanim zemljama i zemljama u razvoju. Lo i Šil su napravili pregled 34 studije (25 kohortnih, 4 studije slučajeva i kontrola ili komparativnih studija i 5 longitudinalnih studija) koje opisuju povezanost krvnog pritiska i težine na rođenju u kvantitativnom smislu i u nepatološkim grupama, a obuhvatile su 66 000 osoba. Skoro sve su zabeležile negativnu korelaciju, osim nekoliko izuzetaka sa novorođenčadi i adolescentima. Oko polovine svih studija koristile su multiplu regresionu analizu, a sve su se prilagodile aktuelnoj težini koja je smatrana najvažnijom pridruženom varijablom. Krvni pritisak je uobičajeno bio niži za 2-3 mmHg sa svakim kilogramom povećanja telesne mase. U samo jednoj studiji koja je obuhvatila adolescente u Izraelu, i to samo kod devojčica, posto-

length at birth and insulin resistance as well. Children who were small for gestational age and experienced intense growth by the age of 7 more often developed insulin resistance compared to children who remained small [35]. This correlation was confirmed in Sweden where Carlsson and colleagues discovered that men whose birth weight was below 3 kg and who had a family history of diabetes were ten times more likely to develop diabetes compared to those whose birth weight was higher (the risk for those with a positive family history was 5.4, whereas for those without a family history it was 2.3). The effects of weight gain were greater in those whose length or weight during the first year of life were low [36]. Even in the Pima Indians, who have a high prevalence of type 2 diabetes, a positive correlation between low birth weight and insulin resistance later in life has been noted. It has been shown that children with low birth weight are thinner in the period between ages 5 and 29 but have more pronounced insulin resistance (indicated by the 2-hour plasma glucose level) compared to children with normal body weight. Children who had high birth weight were more overweight in this period of their lives, but their insulin resistance was less pronounced than what would be expected according to their obesity. There was a positive correlation between birth weight and the current weight and height, adjusted for age and sex, in all examined age groups [37]. Also, a potential link between birth weight and the development of diabetes before the age of 40 was studied in the Pima Indians. In this high-risk population, both low and high birth weight were associated with the development of diabetes in the period of adolescence (between ages 10 and 19), but only low birth weight was associated with the development of this disease in early life (between ages 20 and 39) [38].

TENDENCY TO CARDIOVASCULAR DISEASE

A negative correlation between birth weight and blood pressure, especially systolic blood pressure, has been found in all age groups, within cohort, retrospective, and longitudinal studies, in industrial countries and developing countries. Law and Shiell reviewed 34 studies (25 cohort studies, 4 case-control or comparative studies, and 5 longitudinal studies) which described the relationship between blood pressure and birth weight quantitatively and in non-pathological subjects and which included 66.000 individuals. Almost all of them noted a negative correlation, except for a few exceptions with newborns and adolescents. Around half of all studies used multiple regression analysis, and all adjusted for current weight, which was considered the most important confounding variable. Blood pressure

jala je pozitivna korelacija između telesne težine na rođenju i krvnog pritiska [39]. Inverzna povezanost veličine na rođenju (težina, dužina ili ponderalni indeks) sa koronarnom bolešću, hipertenzijom, dijabetesom tipa 2, i sindromom insulinske rezistencije zabeležena je na svim kontinentima. Potencijalni pridruženi faktori obuhvataju pol, starost, aktuelne dimenzije tela, kao i socioekonomski status, ali se oni prilagođavaju u studijama. Inverzna povezanost između fetalnog rasta i markera kardiovaskularnog rizika i insulinske rezistencije zapažena je kod dece i adolescenata [40]. U još jednoj istorijskoj kohorti muškaraca, Šefild, Barker i saradnici potvrdili su da je povećan rizik od hroničnih bolesti udružen sa zaostajanjem u fetalnom rastu, kao i inverznu povezanost ponderalnog indeksa na rođenju i mortaliteta od hroničnih bolesti. U ovim kohortama je pokazano da je smrt usled moždanog udara povezana sa malom težinom na rođenju, kao i sa malom težinom muške dece [41]. Studija koja je obuhvatila muškarce rođene između 1924. i 1933. godine u Helsinkiju, otkrila je da je stopa smrtnosti od hroničnih bolesti (CHD) veća kod onih koji su na rođenju imali nizak ponderalni indeks (PI) i malu telesnu težinu, a koji su nadoknadili zaostatak u rastu do 7. godine. Ovo je pokazalo da slaba fetalna nutricija, praćena poboljšanjem u ishrani nakon rođenja, može dodatno povećati rizik od CHD. Kako su inicijalna merenja preduzeta u 7. godini, bilo je moguće proceniti rast u detinjstvu i ispitati vezu sa CHD, uz korekciju za telesnu težinu. Najveći rizik od smrti usled kardiovaskularnih bolesti (CVB) (5,3) imali su ljudi sa najmanjim PI na rođenju, u kombinaciji sa najvećim BMI u periodu od 7. do 11. godine. Ovo se poredi sa rizikom od svega 1,2 kod onih koji su u detinjstvu imali visok BMI, ali nisu bili mali za gestacijsko doba. Ovo pogoršanje rizika povezanog sa malom težinom na rođenju sastoji se u tome da ubrzano postnatalno povećanje težine deluje štetno, ili da je usled fetalnog programiranja građa tela u kasnijem životu promenjena. Još jedna mogućnost je da je ubrzani rast povezan sa CVB preko indukovanih promena IGF-1 insulinske osovine [42]. Glavna potencijalna pridružena varijabla negativne korelacije krvnog pritiska i težine na rođenju jeste aktuelna veličina tela i socioekonomski status, u većini hroničnih bolesti, kao i gestacijsko doba na rođenju i krvni pritisak majke, tokom i van trudnoće. Voker i saradnici zabeležili su negativnu korelaciju između težine na rođenju i krvnog pritiska kod mladih odraslih ljudi od 16 do 26 godina starosti. Nakon korekcije za krvni pritisak majke 9 do 19 godina nakon porođaja (pri čemu je pritisak majke u pozitivnoj korelaciji sa pritiskom deteta, a u negativnoj korelaciji sa njegovom težinom), negativna korelacija bila je slabija, što ukazuje na urođenu predispoziciju

typically declined in the range of 2 to 3 mm Hg per kilo of body weight gain. Only in one study involving adolescents in Israel, and only in girls, was there a positive correlation between birth weight and blood pressure [39]. An inverse correlation between size at birth (weight, length, or fetal ponderal index) and cardiovascular disease, hypertension, type 2 diabetes, and insulin resistance syndrome was observed in all continents. Potential confounding factors include sex, age, current body size, as well as socioeconomic status, but they are all adjusted in studies. A negative correlation between fetal growth and markers for cardiovascular risk and insulin resistance was observed in children and adolescents [40]. In another previous cohort study with male subjects, Sheffield, Barker and colleagues confirmed that an increased risk of chronic diseases was associated with fetal growth retardation, as well as an inverse correlation between fetal ponderal index at birth and chronic disease mortality. These cohorts showed that stroke deaths were associated with low birth weight, as well as with low birth weight in male babies [41]. A study that included men born between 1924 and 1933 in Helsinki, revealed that chronic disease (CHD) mortality rate was higher in those who had had low ponderal index (PI) and small birth weight but who had caught up by the age of 7. This showed that poor fetal nutrition followed by improved nutrition postnatally may further increase the risk of CHD. As the initial measurements were made at the age of 7, it was possible to assess childhood growth and examine the relationship with CHD, adjusted for body weight. The highest risk of death due to cardiovascular disease (5.3) was found in individuals who had the lowest PI at birth combined with the highest BMI in the period between ages 7 and 11. This is compared with the risk of 1.2 in those who had high BMI in childhood but were not small for gestational age. The fact that the risk is higher if birth weight was low is explained by the harmful action of rapid postnatal weight gain or by changed body structure later in life due to fetal programming. Another possibility is that rapid growth is associated with cardiovascular disease through induced changes in GH-IGF-1 axis [42]. The main potential confounding variables of negative correlation between blood pressure and birth weight are the current body size and socioeconomic status in most chronic diseases, as well as gestational age at birth and maternal blood pressure, during pregnancy and outside pregnancy. Walker and colleagues found a negative correlation between birth weight and blood pressure in young adults aged 16 to 26 years. After correction for maternal blood pressure 9 to 19 years postpartum (where maternal blood pressure correlated positively with blood pressure of

ka hipertenziji, što je pridružena varijabla LBW [43]. Druge brojne studije podržavaju ovaj trend. U studiji sprovedenoj u Japanu, kod dece starosti 3 godine, sistolni pritisak bio je u pozitivnoj korelaciji sa sistolnim pritiskom majke tokom trudnoće, dok je korelacija bila negativna u odnosu na težinu na rođenju [44]. U studiji sprovedenoj od strane Bonamija i saradnika, pokazano je da deca koja su rođena kao SGA imaju 54% veću šansu da razviju hipertenziju u kasnijem životu, od dece koja su imala adekvatnu težinu za gestacijsku starost [45]. U meta analizi sprovedenoj na 1571 odrasloj osobi koje su rođene sa veoma malom telesnom težinom (<1500g) u poređenju sa 777 kontrola, pokazano je da deca rođena sa veoma niskom telesnom težinom imaju više vrednosti krvnog pritiska, i to sistolnog, za 3,4 mmHg, a dijastolnog za 2,1 mmHg. Jedini perinatalni događaj povezan sa visokim vrednostima krvnog pritiska bila je preeklampsija majke [46]. Značaj povišenog krvnog pritiska i njegove adekvatne kontrole ogleda se u podacima koji pokazuju da smanjenje sistolnog krvnog pritiska za 2 mmHg redukuje mortalitet na populacionom nivou, i to od ishemijske bolesti srca za 7% do 14%, a od moždanog udara za 9% do 19% [45]. Takođe se naglašava da se kod dece koja su rođena sa malom telesnom težinom (bilo da su prevremeno rođena ili su bila mala za gestacijsko doba), dojenje pokazalo kao protektivan faktor za razvoj arterijske hipertenzije. Deca težine ispod 2500g koju su majke dojile imala su nižu prevalencu hipertenzije. Pokazalo se da i dojenje i izbegavanje naglog dobijanja na težini u detinjstvu mogu da smanje rizik od gojaznosti, dislipidemije i intolerancije na glukozu [46].

ZAKLJUČAK

1. Na osnovu dokaza koji su predstavljeni, može se zaključiti da fetalno programiranje pronalazi svoj značaj i na putu je da postane treći uzročni faktor nastanka hroničnih bolesti u toku života, zajedno sa genetskom predispozicijom i načinom života. Međutim, praznine u znanju su velike, posebno na polju samog programiranja, uloge maternalne nutricije u specifičnom periodu, fetalne (i placentalne) procene rasta i efektivnih mera da se smanji rizik kod dece koja su pretrpela zaostatak u rastu.
2. Činjenica da su deca koja su rođena sa malom telesnom masom u većem riziku od hroničnih bolesti u odraslom dobu, time što u detinjstvu ubrzano rastu, a naročito ako postanu gojazna, predstavlja posebnu implikaciju za programe. S tim u vezi, zaključuje se da deca koja su rođena sa malom težinom treba da budu ciljna populacija za promociju zdrave ishrane i prevenciju gojaznosti, posebno kroz školski sistem.

the offspring and negatively with their weight), a negative correlation was weaker, which implies the inherited predisposition to hypertension as a confounding variable to LBW [43]. Other numerous studies have supported this trend. In a study conducted in Japan in 3-year-old children, systolic blood pressure corelated positively with maternal systolic pressure during pregnancy, while there was a negative correlation to birth weight [44]. The study conducted by Bonamy and colleagues showed that children born with SGA were 54% more likely to develop hypertension later in life compared to children who had adequate weight for gestational age [45]. In a meta-analysis of 1571 adults born with very small birth weight (<1500g) compared to 777 controls it was shown that children who had been born with very low birth weight had 3.4 mm Hg higher systolic blood pressure and 2.1 mm Hg higher diastolic blood pressure. The only perinatal event associated with high blood pressure was maternal pre-eclampsia [46]. The significance of elevated blood pressure and its adequate control is reflected in the data showing that the reduction of systolic blood pressure by 2 mm Hg reduced population-level mortality from ischemic heart disease by 7% to 14% and from stroke by 9% to 19% [45]. It has also been emphasized that in children who had low birth weight (who were either born prematurely or were small for gestational age) breastfeeding has proved to be a protective factor for the development of arterial hypertension. There was lower prevalence of hypertension in children who weighed less than 2500g and were breastfed. It has been shown that both breastfeeding and avoiding rapid weight gain in childhood can reduce the risk of obesity, dyslipidemia, and glucose intolerance [46].

CONCLUSION

1. Based on the evidence presented, it can be concluded that fetal programming has been recognized as significant and is on its way to becoming the third contributing factor in the development of chronic diseases during life, together with a genetic predisposition and lifestyle. However, there are large gaps, especially in the field of programming, the role of maternal nutrition in the specific period, the assessment of fetal (and placental) growth, and effective measures for reducing the risk in children who have experienced growth retardation.
2. The fact that children who had low birth weight have a higher risk of chronic diseases in adulthood when growing rapidly in childhood and especially if they become obese, is a special implication for programs. In this regard, it has been concluded that children with low birth weight should be the target

3. Naglašavaju se i dalji podsticaji da se poboljša ishrana majke – za razliku od genetskih teorija, fetalno programiranje najčešćih hroničnih bolesti odraslog doba daje opravdanje, ukoliko je potrebno, da se stavi akcenat na optimalni fetalni rast i razvoj. Dugoročne posledice fetalne malnutricije predstavljaju dodatni argument da se veća koncentracija usmeri ka ishrani mladih devojaka i žena, poželjno pre trudnoće, ili tokom same trudnoće. Ističe se i značaj uticaja životne sredine, a samim tim i kvaliteta hrane koja se konzumira, zbog potencijalnog štetnog uticaja supstanci koje mogu menjati funkciju endokrinog sistema (*EDCs*) na tok trudnoće, sa daljim kratkoročnim i dugoročnim posledicama po neonatuse. Zaista, prevencija smanjenog fetalnog rasta mogla bi poboljšati preživljavanje i razvoj deteta, kao i doprineti smanjenju rizika od hroničnih bolesti, posebno od gojaznosti, dijabetesa i drugih hroničnih bolesti koje su postale epidemijske širom sveta. Svakako, prevencija hroničnih bolesti kroz način života i adekvatnu ishranu može predstavljati veliki izazov u zemljama u kojima je pothranjenost majki i dece velika.
4. Postoji ozbiljna potreba da se bolje proceni dalji uticaj smanjenog fetalnog rasta u zemljama u razvoju i populacijama u tranziciji. Dalja istraživanja različitih aspekata modela ranog porekla bolesti moraju da se uklope u odgovarajuću zdravstvenu politiku.

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population for the promotion of healthy diet and obesity prevention, especially through the education system.
3. Further incentives to improve maternal nutrition are emphasized – unlike genetic theories, fetal programming of most common chronic diseases of adulthood justifies, if necessary, focusing on optimal fetal growth and development. Long-term consequences of fetal malnutrition represent an additional argument towards focusing more attention on the nutrition of young girls and women, preferably before pregnancy, or during pregnancy. The importance of the environmental influence and the quality of food consumed are also emphasized due to the potentially harmful effect of the substances that may alter the functions of the endocrine system (EDCs) to the course of pregnancy, with further short-term and long-term consequences to neonates. Indeed, prevention of fetal growth restriction could improve child survival and development, as well as contribute to reducing the risk of chronic diseases, especially obesity, diabetes, and other chronic diseases which have reached epidemic proportions worldwide. Certainly, the prevention of chronic diseases through lifestyle and adequate nutrition can be a huge challenge in countries where malnutrition in mothers and children is high.
4. There is a serious need to better assess the further impact of fetal growth restriction in developing countries and populations in transition. Further research of various aspects of the early origin of disease must fit into appropriate healthcare policy.

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