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SPECIFICITIES OF PREGNANCY AND DELIVERY IN OBESITY

OBESITY, BMI

Data on increased trend of extreme body mass focuses the practice and science on overcoming the consequences. Inadequate nutrition and anorexia, psychological and metabolic issues, are often induced by media glorifying of persons who fascinate younger population. Also, the other pathological extreme, pathologically increased body mass, the consequence of cultural habits, fast way of living, inadequate physical activity and nutrition, and usage of medications, influence the health of every person.

Delicacy of female organism, in all phases of growth and development, in both stated body mass extremes, leaves consequences in each and every stage of life. The sequelae are especially observed in the phase of achieving pregnancy and overcoming infertility and sterility, but also in the stage of maintaining woman's health during pregnancy and providing healthy offspring. Long-term consequences to later child development, transmitted through whole psychological and physical development of an individual, remain forgotten. The fact is that modern medicine insists on prevention. Social and health systems having envious economic standards do not allow retardation in terms of successful overcoming of consequences of inadequate attitude towards one's own health. The priority of such modern systems, as well as ours, is the prevention and preventing disease in child not only at birth but also all the other diseases that are the consequence of bad atmosphere while fetus was in its 'house'. It is well known that fetus has interactive relation with maternal organism. The effects of maternal-fetal influence are part that we could provide if we wake up our own medical ethics, introduce measures of personal responsibility for an individual jeopardizing one's own health and putting at risk the future baby as a member of the society in which it is delivered.

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Extremely fast increase of pathological body mass is moving from epidemic to endemic size. Knowing the fact that the decrease of obesity is one of the priorities of all world health organizations, the aims for decreasing the number of affected are stated. With New millennium start, the aim to decrease the number of affected patients has been established. However, the results showed even higher increase of obesity in the population and we have even more stunning and defeating results. Even though in 2000 the aim was to decrease the number of obese by 20% by the end of 20th century, the number of obese persons has increased to almost half of world population. In the adult population, almost third is obese. The fact that over 15% of children aged between 6 and 11 are obese is disarming.

Allison and co workers, 1999; Ogden and associates 2002; Public Health service, 1990; Elegal and colleagues 2002; Hedley and associates, 2004

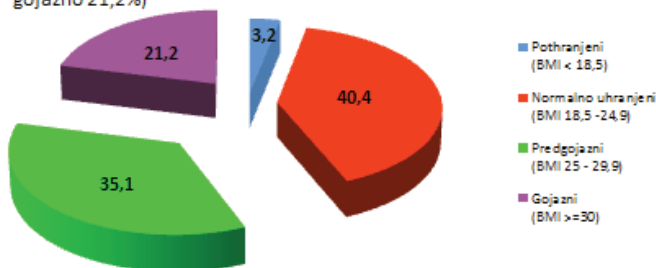
How do we define obesity?

The evaluation of BMI is known as the Quetelet index. Mathematically, it presents kilograms of body mass divided by height in relation to square meter. The larger number of world organizations uses the usual scale of body mass with physiological interval from 18.5 to 24.9. Excessive body mass is in the range between 25 and 29.9 while pathological obesity presents BMI over 30. In the range of pathological obesity, there are 10-unit subgroups which represent classes for us to use in further diagnosis, approaches, complications expectations and their overcoming. The first class being I BMI 30 to 34.9, second class II BMI 35 to 39.9 and values over 40 as third class.

The prevalence of obesity has a trend of constant increase. In 2000 in the USA, more than half of adults were overweight or obese.

Gojaznost u Srbiji

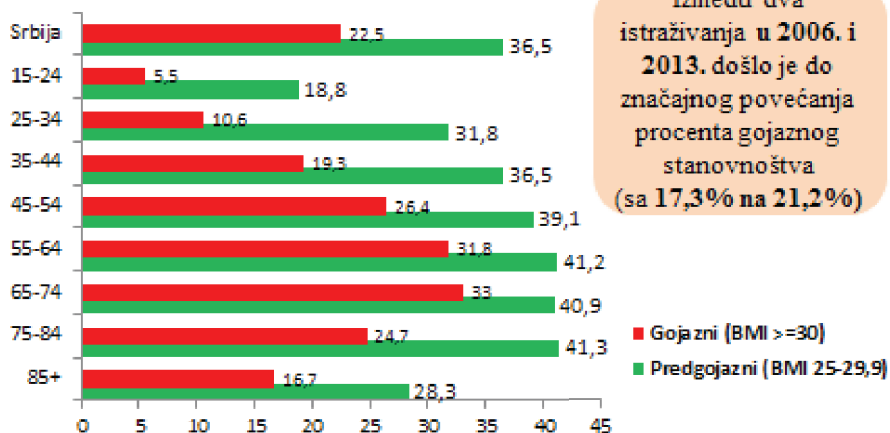
- Stanovništvo uzrasta 15 i više godina prema kategorijama uhranjenosti, Srbija, 2013. godine
- više od polovine (56,3%) bilo prekomerno uhranjeno (predgojzno 35,1% i gojazno 21,2%)



• Institut za javno zdravlje Srbije „Dr Milan Jovanović Banit“

Gojaznost u Srbiji

- Stanovništvo uzrasta 15 i više godina prema uzrastnim grupama (u procentima), Srbija, 2013. godine



- Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“

The analyses of **economic cost** of health care presents inevitable signal of necessity to decrease the trend of these pathologies. In the study of National Health and Nutrition Survey, Ford reveals that over 9.4% of yearly economic health cost is related to people with pathological body mass and physical inactivity.

What are the complications of obesity and effects to pregnancy?

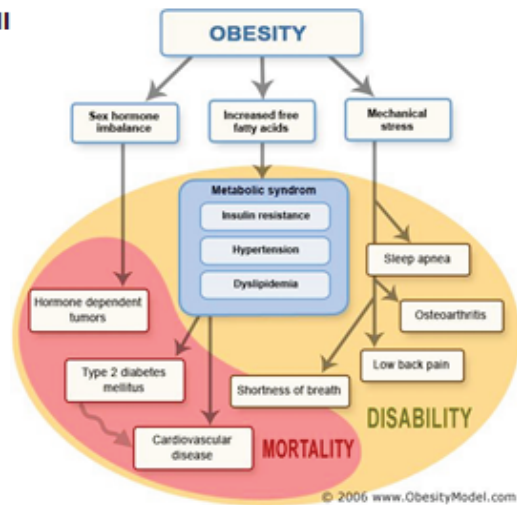
Based on simple physiological trace of endocrinological and metabolic cascade caused by increased BMI, we expect the manifestation of **metabolic syndrome** as a consequence and insulin resistance. In cooperation with obesity, we also have **type 2 diabetes, dyslipidemia, as well as hypertension**. Once triggered cascade widens by algorithm the spectrum of clinically pathological conditions. Cardiovascular disorders are based on increased BMI base, insulin resistance, increased unwanted lipids (triglycerides and Low Density Lipoproteins). The consequence is occurrence of diabetes, as well as supporting of vicious circle of new series of metabolic disturbances additionally increasing the possibility for increased BMI. Moreover, by burdening blood vessels and disturbing the quality of histological built of blood vessel wall, predisposition for hypertension because of more burdened hearth volume in order to satisfy needs of organism with increased mass is also reflected in the damage of blood vessels leading to cerebro-vascular insults or transitory ischemia attacks.

In gynecology, clinical picture of obese person habitus may give several starting answers and guide lines. Even in 2003, it is confirmed that more dramatic effects of obesity via incidence of hypertension, dyslipidemia, insulin resistance and type 2 diabetes, are expected more frequently in apple shaped than in pear shaped persons. The estimate of waist circumference and established measure over 88 cm in the phase of beginning of pregnancy are objective indicators that such complications as metabolic syndrome and syndrome X are expected.

The course of pregnancy burdened by pathological obesity

Komplikacije kod majke

1. gestacioni dijabetes i DM II
2. preeklampsija
3. bolesti miokarda
4. abrupcija placente
5. loš placentarni transfer kiseonika
6. tromboembolije
7. prevremeni porođaj
8. urinarne infekcije
9. hitan i elektivni carski rez
10. postpartalna krvarenja
11. postpartalna depresija
12. pelvična inflamatorna stanja (PID)
13. infekcija rana
14. komplikacije puerperijuma



- **Clinical manifestation of insulin resistance** is expected. From incidence of gestative diabetes (**GDM**) to manifestation of need to administer therapy during pregnancy (**DIP**). The practice shows increased trend of gestative diabetes...

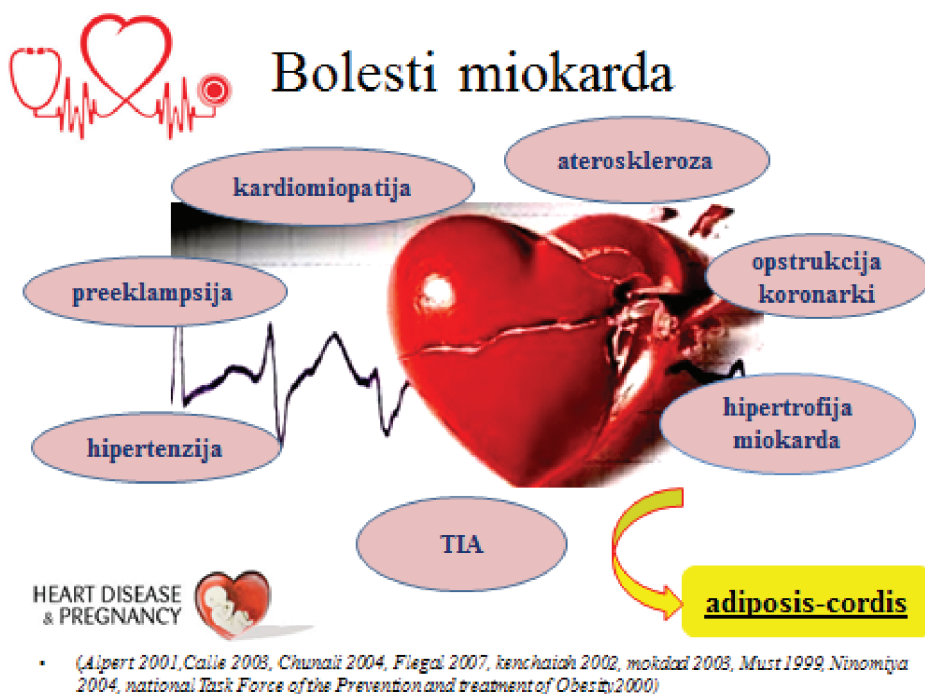
The incidence of type 2 diabetes, or as newly formulated GDM, is to a large degree the consequence of inadequate nutrition and insufficient physical activity. According to recommendations of FIGO (Federal International Gynecology Organization), it is desirable to test each and every pregnant patient to possible diabetes but also possible disturbance in thyroid gland function.

According to literature data, the large number of studies presents pathological obesity as one of the primary causes of increased frequency of diabetes. Even though in 2003 obesity in type 2 diabetes have been related, in 2007 Hossain concluded that even 90% of type 2 diabetes is formed from pathological obesity.

Even though the incidence of diabetes dominates in primary clinical picture, numerous other complications which could be avoided if the pregnant patient did not have pathological BMI are not negligible.

The increase in **myocardial diseases**, hypertension, incidence of preeclampsia, cardiomyopathies, coronary obstructions, myocard hypertrophy, as well as incidence of atherosclerosis and transitory ischemia attacks is confirmed along time and geographical coordinates (*Alpert 2001, Calle 2003, Chunalı 2004, Flegal 2007, Kenchaiah 2002, Mokdad 2003, Must 1999, Ninomiya 2004, National Task Force of the Prevention and treatment of Obesity 2000*).

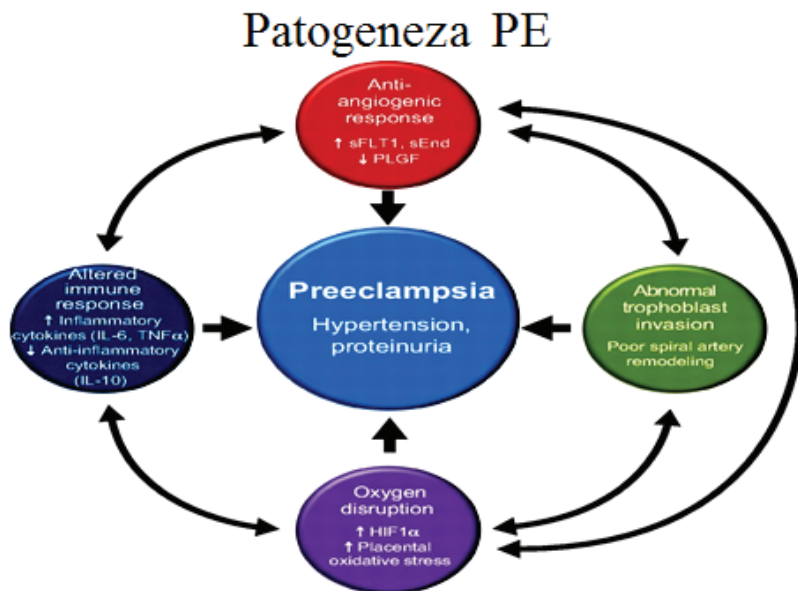
The increasing frequency of myocard diseases and incidence of **adipositas cordis**, are consequently the manifestations of hypertension, hypervolemia and dyslipidemia (*Chinalı 2004, Kenchaiah 2002, Ninomiya 2004*).



Hypertension, coronary disease, cardiomyopathy, are all consequence of increased blood volume. Due to such increased burden, together with expected usual physiological burdening of organism, more drastic load and work of coronary muscle is expected. The increase in blood volume and hearth strike volume lead to hypertension and dyslipidemia as well as coronary blood vessels obstruction.

The explanations are significantly clearer with the advance of immunology and discovery of possible causes of hypertension and preeclampsia where the risk for

preeclampsia is doubled with the increase of BMI. The risk is doubled in every 5 to 7 kg per square meter.



The incidence of **cardiomyopathy** is significantly more frequent in conditions of pathological obesity. Usual, even though rare cases, are found in congenital disorders and newly diagnosed myocard pathologies during pregnancy. However, in conditions of obesity, cardiomyopathy is a part of general burden for the organism both via increased heart minute volume and via damaged quality of blood vessels and blood dyslipidemia with lower percentage of oxygen.

During pregnancy of women with severe pathological BMI, even in the cases of increased obesity of medium degree, we may expect the incidence of **brain ischemia attacks** within hypertension manifestations but also without the incidence of hypertension. These cases present long-term or acute exacerbation of atherosclerosis, activation of prostaglandins and vascular endothelial factors, the incidence of transitory ischemic attack as a clinical picture of decreased flow and blood inlet into central nervous system, but also the incidence of **strokes** as a consequence of hypertension and weakness of blood vessel wall.

The quality of life, both in women outside of pregnancy and pregnant ones is significantly decreased. Possibility for physical activity is limited to graduality and specific exercises, demanding more persistence and motivation.

Discomfort and social-epidemiological aspect, psychological profile of the individual and acceptance within social community, body self-observation, inability

to adapt into usual cultural frame of dressing and behaving... In the area of **sexology**, the problems are present in both partners.

Standard day-night routine is often accompanied by **apneas**, due to pharyngeal fat but also as a consequence of diaphragm lifting in horizontal position, supported by gravid uterus.

Disturbances in **locomotor system**, increased tendency for **swelling and decreased lymph drainage**, are part of habitus of a person with increased body mass being more severely manifested during pregnancy.

More frequent **dentistry problems** as a consequence of metabolic disbalance, increased affinity for microbiological flora of fungal origin, as well as much more intense problems in maintaining the **quality of vaginal mucosa** and avoiding fungal infections. The increased incidence of **urinary infections**, as in conditions of diabetes.

In couples with increased BMI, as in those with other causes of sterility, sometimes it is sufficient to return the organisms to physiological BMI optimums to overcome sterility. The start of **in vitro fertilization** procedure is not indicated in the conditions of severe obesity because neither the efficiency of medications nor circulatory passage will be adequate to obtain expected results which would be obtained in the population with physiological BMI.

During pregnancy, the incidence of pathological conditions related to **gastro-intestinal tract** is increased. Clinical manifestation of pain or incidence of bile duct obstruction is more frequent in this population. The mechanical pressure of visceral fat, more difficult intestinal passage and constantly active hunger center support the vicious circle of problems. Liver diseases, such as non-alcoholic fatty liver, the consequence of high values of free fatty acids and hyperinsulinemia.

In the **vascular and lymph drainage**, besides swelling, more drastic is the increase of number of patients with life-threatening condition of blood vessels thrombosis. The pressure of gravid uterus, additionally to visceral obesity, the pressure to venous system of abdominal and extremity blood vessels, contributes to incidence of thrombosis. Even though pregnancy, physiologically observed, is a hypercoagulation state, these factors of physical compression of gravid uterus, visceral fat, intestinal structures, contribute to forming of thrombotic processes and endanger life of pregnant woman.

Although during pregnancy we primarily concentrate on mother and fetus, we never forget classical **gynecological approach** to the problem. Potentially, there is a higher risk for cervical changes leading to pre-cancerous and cancerous lesion in persons with continuous affinity to infections. It must not be forgotten that chronic infections, even though of fungal origin, lead to cell nucleus damage. In non-pregnant population, increased BMI is part of predisposition for incidence of endometrial carcinoma.

During the delivery period, the complications vary depending on accompanying morbidities and appeared pathological conditions of pregnancy.

The number of surgically ended deliveries, especially emergency cesarean sections, is significantly increased. The causes are often inadequate Bishop Score in order to start induction or mechanical obstruction of uterus activity and fetal descending due to gravity, because of abundant quantity of *abdominal visceral fat* and small pelvis. The studies using effects of magnetic resonance in determining quality of visceral fat explained the increased number of cesarean sections.

The other reason for increased number of surgical deliveries lies in the *condition of the fetus itself*. In obese patients, together with the development of gestative diabetes, we may expect fetal macrosomia where the fetus, with its diameter, does not comply with anatomical circumference of maternal pelvis. Moreover, if more severe form of hypertension is added to obesity and IUGR (intrauterine fetal growth retardation) is observed as well as decreased fetal capacity, additional burden to fetus with already decreased capacity, the fetal life is additionally in danger.

During the act of delivery, we find more difficult application of **epidural anesthesia**, difficult application as well as inadequate medications passage, not related only to regional anesthesia but also increase of usual and incidence of rare complications of **general anesthesia**. This ranges from technically more difficult intubation, via more frequent regurgitation to inability of respiratory adaptation after general anesthesia (Dark 2002).

After delivery, whether vaginal or surgical, we expect **increased postpartal bleeding**. The incidence of uterine muscle atony is not rare. Overstretching of the uterus, many times emphasized decreased quality of blood vessels, increase the possibility for atonic bleeding as well as postpartal hysterectomies or abdominal resolving of atonies by hypogastric artery ligation.

During **puerperium**, the complications related to abdominal pathology are even more difficult for differential diagnosis than standard atypical picture of absence of abdominal wall defans.

Even though the patients mainly expect increased and easy **lactation**, the fatty tissue also dominates in the breasts so already unable adequate passage of hormonal feedback does not have sufficient quality of receptors nor anatomic support for production and secretion of milk (Li 2003; Armstrong 2002; Ruowellu;)

Maintaining of increased body mass during perioperium and afterwards, is frequently part of usual clinical picture (Cotalano 2007, National research council 2007, Rode 2005). By using test for **qualitative observation of the degree of life satisfaction**, we obtain a significant increase in depression. Depending on the class of increased BMI, the degree of depression also increases. Thus, through three grades of pathological BMI, **depression** varies from 22.6 to 32.4 and 40 percents.

The incidence of **sudden fetal death (fetus mortus in utero, FMU)**, if there are no possible ethiopathogenetic factors, is evidently predominantly related to obesity and its qualities. The increase in still born is 1.6 times if BMI increases from 25 to 29.8. If BMI is over 30, the increase is 2.6 times higher (Cnattingius 1998). The incidence of FMU is three times higher if BMI is over (Stephansson 2001). There are categories even within increased BMI. Chu (2007) found the increase of FMU incidence in over- weight patients to be 1.5 times, while in obese patients it was 2.1 times higher. In the examined group of 186,000 of primipara patients, Scoti showed 4 times higher incidence of FMU if BMI was over 35 comparing to a group with 20-25 BMI. The incidence of intrauterine fetal death, the sudden fetal demise, is explained by the disturbance in acid-base and metabolic foundation, and is most frequent in the last stage of third trimester. Yet in 2005, the so-called hazard ratio is determined. It totals 2.1 from 28th to 36th week of gestation, 3.5 from 37th to 39th week of gestation, to be as high as 4.6 in the period from the 40th week of gestation.

The percentage of **anomalies grows**. The neural tube defect is more frequent as well as the incidence of omphalocele. The studies done in 2008 by Rasmussen found 3.1 higher risk for incidence of central nervous system anomalies. The case of control study of Watkins showed 3.5 times higher risk for incidence of omphalocele. Interaction of co-morbidities, spectrum of pathologies, leads to complete range of body mass variation, from intrauterine growth restriction to fetal macrosomia (since Bianco 2008, Cedergren 2004, Isaacs1994). Also, metabolic disbalance and oxygen fluctuation disturb the stability and capacity of fetal organs functioning. The clinicians observe disturbances in growth and development, give secondary conclusions based on analysis of fetal anthropometry, relations uterus-placenta-fetus-system of fetal organs, by using the Doppler flow, biophysical fetal profile and cardiotocography (Metro Health Medical Centre, Clivlendu, Caralano 2005, Ehrenberg 2004, Sewell 2006).

The existence of obesitas increases the risks for complications of first and second trimester. The study by Faster proves the increased frequency of all complications as well as the incidence of more frequent **APO (adverse pregnancy outcomes)**.

Complications in relation to growth and development of the fetus become many times more intense.

The gradation of the problems rises with the degree of obesity increase. With the increase of BMI, the frequency of observed pathologies also rises:

- **gestative diabetes**
- **preeclampsia** (Cunningham 1986)
- **post-term pregnancies** (Hall and Neubert 2005)
- **emergency cesarean section** (Haeri 2009)
- **primarily determined cesarean section** (Lynch 2008, Poobalan 2009, Bujorlrd 2005, Goodall 2005, Hibbard 2006, Robinson 2005)

- **postpartum hemorrhages**
- **postpartum depression**
- **pelvic inflammatory conditions**
- **urinary infections**
- **wound infections**
- **macrosomia**
- **sudden fetal intrauterine demise or still born**
- **fetal anomaly**
- **increased frequency of all pathological conditions in each trimester**
- **puerperium complications**
- **psychological and social-epidemiological problems**
- **fetal programming, increased number of potential diseases in adult life**

(1. Neill and Nelson Piercy, 2001, obesity is related to subfertility due to increased insulin resistance; 2. Bellver 2009 found higher FMU in obesitas; 3.Lashen 2004 found increased risk of first trimester miscarriage; 4. Chu 2008 found increased usage of health system).

Fetal programming, the danger to pass the impulse of changed metabolism, as well as the impulse related to the very DNA molecule, increased. Actually, our knowledge of the fact that we could even disturb the genetic map by our inadequate respect of the quality of health increases. In the condition of pathological obesity, the disturbances that reflect to intrauterine fetal condition leave permanent consequences to further growth and development of the fetus. In children with already observed extreme body mass, metabolism damage as well as disturbance of oxygen quantity, we have a disturbed developmental plasticity.

In 1989, Baker attracted the science attention by stating that the disease of adult lies in life style of an individual during childhood. Later, Forsdalh gave the real picture and since 1977 it is considered that what we have in adult life is largely predisposed by what we got in intrauterine development. Forsdalh found a larger number of deaths by metabolic diseases and cardiovascular diseases in Norway between 1964 and 1967, analyzed that they were all born between *1896 and 1925* and were exposed to nutritive deficiency, vulnerability during life, permanent tissue and organ damage. Developmental plasticity is a phenomenon where genotype is changed to different stimuli during development. Growth is a quantitative characteristic originating from functional and physiological cell maturation. Programming is a response of the developing organ to specific challenges leading to appearance of different phenotypes. Plasticity is again the ability of the organism to create different pathways for its de-

velopment, depending on the specificity of the surroundings. Plasticity is explained, more simply, by the appearance of more phenotypes from one genotype. Control mechanisms of developmental plasticity are metabolic as well as insulin secretion, vascular resistance and endothelial dysfunction triggering a cascade of inflammatory and oxidative processes.

Effects to the growth and development of the fetus are reflected directly by glucocorticoids as well as indirectly by inhibition of *placental 11 beta hydroxy steroid HSD2 of decreased expression*. Newborns have the predisposition for conditions of their parents. Increase in HDL lipoprotein, central obesity, affinity for hypertension as well as the incidence of type 2 diabetes, with dominant affinity to obesity (Boney 2005, Catlano 2005).

What is our approach to diagnosis, prevention and therapy of a pregnant patient with increased BMI or morbid obesity?

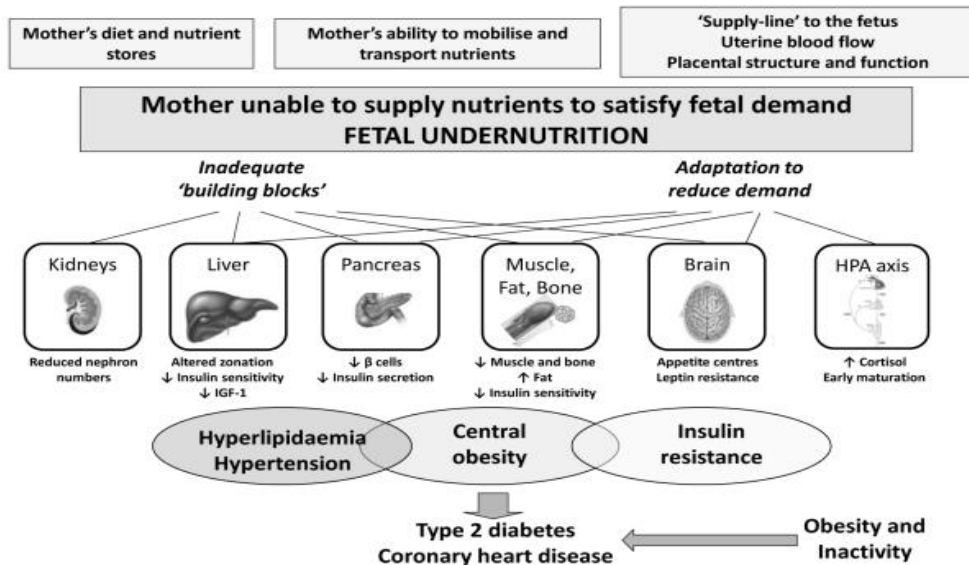
Identical modern way of pregnancy following together with increased frequency of examination and care during one. More frequent measurements of weight gain, checking the affinity and treatment of infections of the cervical and urinary tract, weight gain control, arterial blood pressure monitoring, glucose measurement, metabolism monitoring with necessary avoidance of catabolism. It is well-established that catabolic processes disturb the fetal development more significantly in relation to already stated drastic hazards of body mass increase. The hygiene specialist is included into pregnancy monitoring and, together with quantity determination, the quality of food is emphasized in order to satisfy the needs of physiological metabolism and adaptation to increased BMI bases: it is recommended that women with BMI under 18.5 gain 12.5 to 18 kg while BMI from 18.5 to 24.9 should gain 11.5 to 16 kg. those with BMI 25 to 29.9 should gain 7 to 11.5 kg, and if BMI is over 30, the pregnant women should gain 5 to 9.1 kg.

Philosophical question by Aristotle about the chicken and egg is reflected in all segments of life. The power of practical application of knowledge from perinatology provides not only the maintenance of female health and prevention of complications, but also provides healthy offspring and decrease of potential for incidence of disease later in life. In the 20th century, we have the changed pattern of disease incidence and the mortality rate from infectious diseases decreases in the world but increases with chronic cardiovascular and metabolic diseases. The rate of diseases we could prevent by our efforts in perinatology increases.

In these cases of nutritive deficiency, the fetus adapts by centralizing the blood flow towards brain, liver, hearth, and pancreas. The consequence of this is a smaller number of kidney cells in the neonate (affinity for hypertension), smaller number of muscle cells (affinity for deposition of fatty tissue if more weight is gained after birth).

The fetal adaptation goes not only by blood flow centralizing but also activation of hypothalamus-hipophysis axes of the fetus, increasing the secretion and sensitivity to growth hormones (insulin and insulin-like growth factors).

Adaptation and fetal programming is a developmental plasticity. Developmental plasticity is a phenomenon where genotype matches different physiological and morphological changes and different stimuli during development. However, even in early neonatal life, the tissue reconstruction, as well as endocrine and metabolic axes reprogramming, lead to disease incidence. It is interesting that the effects of fetal programming may be observed even with no change in body mass at birth, so the process seems less visible at first. The co-existence of effects of hypertension and undetected gestative diabetes will provide adequate body mass but will not mean that the activity of stated pathological cascades will not potentially influence life later.



Diseases which potentially may be prevented in the larger percentage of the cases

In conditions contrary to IUGR, fetal macrosomia is emphasized and considered to be a predisposition for the incidence of:

- Diabetes; fetal pancreas by the influence of increased glycemia in gestative diabetes remains damaged due to degranulation of beta cells (mitochondria are edematous, endoplasmatic reticulum is widened and few granules in the cells). The evidence of pancreas hyperactivity is fetal increased body mass (from the 19th week of gestation, fetal pancreas secretes insulin and insulin like growth factors which is confirmed by higher concentration in umbilical cord

blood in children with macrosomia). The fact that the whole process is done via hypothalamus-hipophysis axis is confirmed by the data that these changes are not observed in the group of anencephalus where the axis is damaged while is observed in anencephalus with preserved axis.

- Breast carcinoma in a woman born as macrosomic fetus is explained in the segment of etiopathogenesis, by mitotic fetal activity, increased insulin and insulin like growth factor IG.
- Metabolic syndrome, syndrome X in children: under the influence of increased glycemia, insulin, IGF, lipids, inflammatory factors, actually creates nutrient mediated teratogenesis.
- Non-alcoholic fatty liver disease in children: appears as a consequence of metabolic changes and hypoxia. Actually, the changes at the level of excessive quantity of fatty acids, lead to oxidative stress and inflammation (excessive quantities fatty acids use lead to oxidation of MK, forming of free radicals in mitochondria which damage the balance of oxidative and antioxydative enzymes). Thus the oxidative capacity of mitochondria is disturbed and the quantity if antioxydative enzymes peroxidase and superoxide dismutase is decreased. Cuper cell hepatocytes and stellate cells suffer due to damaged mitochondria via oxidative stress, inflammation, and cell death occurs.

Non-alcoholic fatty liver and inadequate immune response of the organism: according to Harmon is present with maternal pathological obesity. These are the consequence of incidence of ‘newborn microbioma’ i.e. ‘first imprint’. In obese women, the intestines secrete twice the quantity of intestinal bacteria endotoxines comparing to intestines of pregnant women with adequate body weight. Such endotoxines, via blood and vena porta, come to liver and hepatocytes which are the first line of defense from antigens originating from intestines.

- **Obesity in children:** a consequence of cytotoxic lipids, maladaptive changes and proinflammatory proteins.

The oxidation of fatty acids is controlled by SIRT, sirtuin inflammation (NAD dependent deacetylase) which is nutrient sensor modifying genes and proteins by influencing the posttranscriptive gene activity. If there is larger quantity of fat in blood, the activity of SIRT1 is decreased and thus adjusts the organism to oxidative stress, however, if the organism is adjusted, the quantity of SIRT1 and SIRT3 regulating production of free radicals from lipid success is decreased. This consequently decreases mitochondrial function and oxidative capacity. In time, SIRT1 and SIRT3 decrease even more as a consequence of mitochondrial disfunction. Thus, inactivity of the whole hepatic oxidative capacity appears.

IUGR carries the risks for coronary disease, diabetes, metabolopathies, hormonal changes, psychomotor changes.

Coronary disease: lower body mass at birth, lower ponderal index, if exposed later to larger fatty tissue gain IUGR fetus may develop coronary disease. (Eriksson 2001)

Character, emotional responses, and increased response to stress: children with lower body mass have difficulties to accept venous punctures. Behavioral studies, studies of socialization and sexology in Sweden prove decreased social adaptability (Hertfor Shire Sweden). The tendency to depression is increased, also suicide, hormonal mood pattern. The basis for the change is based on changes in hypothalamus adrenal axis and hypothalamus thyroid function.

Hormonal disbalance of female children: in IUGR children, early menorrhagia is frequent. The production of gonadotropin is changed.

Autism: significantly growing in incidence.

Mechanism of adaptation and epigenetic transferred through generations are confirmed by epidemiological studies. The effects of intrauterine environment influence the events after conception but also events later in life.

The fetal adjustment is accomplished by: 1. Change in number of cells; 2. Clonal selection of certain cell types; 3. Metabolic differentiation; 4. Gene expression.

The DNA mutilation pattern is established during embryogenesis and fetal development. By administering folan to mother (which is responsible for mutilation of proteins and metabolic processes) we influence the formation of methyl groups. Thus, the prevention of obesity, insulin resistance and diabetes is conducted.

Epigenetic relation may be proved in epidemiological studies. Starvation in Netherlands pointed to leptin signal pathways. Changes caused by hunger, axis hypothalamus-hipophysis-adrenal gland, together with placenta as a mediator between mother and fetus. Histologically, starvation at the level of placenta leads to nitration of placental proteins, gene mutilation, decreased activity of nutrient transporters (by changing 11 beta HSD2 hydroxisteroid dehydrogenase). Helsinki study confirmed affinity to coronary disease. By autopsy and gene analysis of 476 elder persons of both sexes, born with IUGR, genes related to incidence of gestative diabetes are found (pro 12 polymorphism *PPAR-Y gene* influencing the incidence of GDM).

Placenta as an enigma for centuries?

- The transfer of glucose to fetus is regulated also via progesterone, human placental lactogen HPL, as well as steroids, peptides, glycoprotein, eicozonooids.
- The fetal endocrine function,
- Myometrial activity,
- Regional blood flow regulated by prostaglandins *F2alfa and E2*.

- Oxygen transport is identically regulated by indirect effects of prostaglandin (Cortisole changes the placental steroid genesis and HPL secretion. Thus the development of breasts changes).

New view to placenta

The placenta size is a good parameter and an indicator of adult disease development, diabetes type 2 incidence and hypertension. Sometimes, IUGR hidden cause is in the placenta and its uteroplacental flow.

Genes IGF2 make a part of placental programming. Lower gene expression leads to smaller placenta while increased expression leads to placentomegalia.

Naturally smaller placenta has increased zone of change at the account of endocrine zone, leads to increased creation of E16 with increased transport of metabolizing amino acid analogues, changing the placenta and gene expression which code the specific transporting system. Such system leads to upregulation of transporters through gene manipulation of IgF2-H19 axis.

Placental overgrowth, on the other hand results in decreased oxygen transport (mice proven H19 depletion).

Placenta plays a central role in fetal programming by direct regulation of fetal nutrition and fetal growth. Placenta is a sensor for nutrients. It is responsible for protein transport via its carriers (number, localization, affinity); mice evidence, proven 3 glucose transporters GLUT 1,3 and 9 of different amino acid transporters. Do we actually know what influences transporter activity? The evidence from animal models and our clinical practice point to effects of hypoxia, heat stress, over nutrition or malnutrition, exposure to growth hormones and leptine.

Placenta is considered to be growth sensor which changes maternal compartment and influences methylative status placental genes, increases placental oxidative and nutritive stress and leads to placental functional changes.

Fetal nutrition comes from the very placenta. Nutrients for the fetus depend on the grade of production and usage in the placenta. What happens in conditions of pregnant woman malnutrition or longer episodes of hypoglycemia? Prolonged hypoglycemia (longer administration of higher doses of insulin) at first leads the placenta to preserve the glucoses. Then, the usage of glucose is decreased and secondary the production of lactates. What happens in conditions of over nutrition, diabetes, obesity, consuming of high energy diets? The insulin resistance or diabetes.

Fetal growth and development also depend on vascularization and placental change barrier. Fetal programming depends on the timing of placental insult. The consequence is also anemia and fetal hypoxia. Even though hypoxia exists physiologically during organ genesis, in conditions related to higher degree of trophoblast hypoxia, there is a metabolic activity of placental mitochondria and IUGR, hyperten-

sion, PE and DM are expected. What is the influence of anemia? In the conditions of anemia, there is a) an increased fetal angiogenesis in the first trimester; b) dilatation of capillary sinuses; c) thinning of transfer barrier. In conditions of smaller placenta and IUGR with negative or end diastolic flows during pregnancy, blood vessels have weak branching or thin transfer barrier. There is rarely a normal pattern of artery stem cells in these flows as a compensation to increased capillary angiogenesis and terminal villa development.

The placental disturbances lead to cardiovascular diseases. The explanation lies in compensation of fetal myocardium by increasing of load, short-term adaptation, after which the number of cardio myocytes is decreased and higher sensitivity to hypoxic insult remains.

Available clinical practice, basic medicine as well as animal models studies confirm clinical practice and give further solutions:

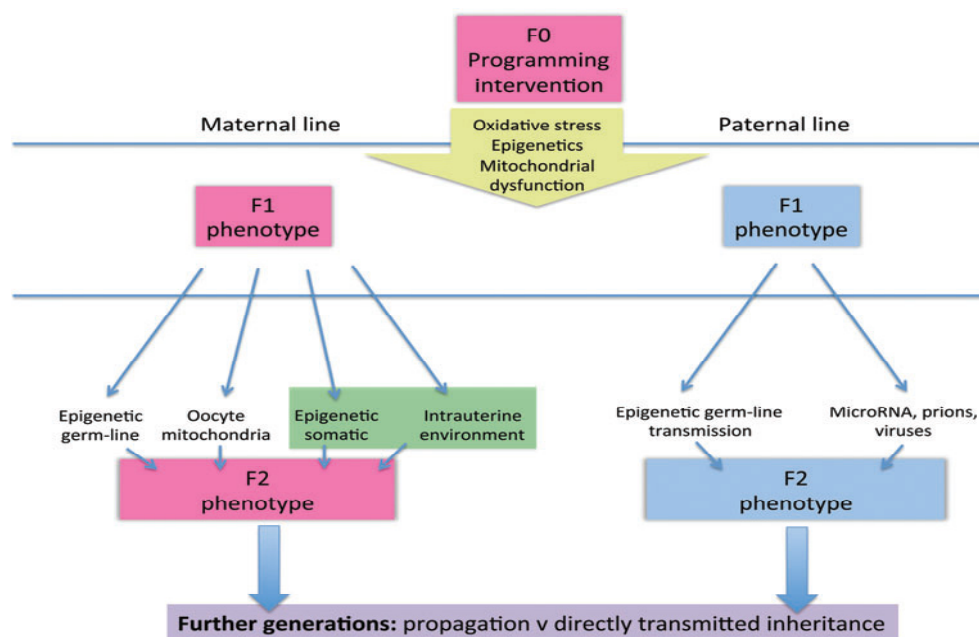
- By administration of folate the placental activity of 11 beta HSD-2 is increased, via maternal levels of methyl placental genes donors. Thus, placental oxydative stress and nutritive stress are decreased.
- Under the effects of fetal stress or medicament administration of glucocorticoids, placental enzyme 11beta HSD2 is activated. If its enzyme power is decreased, the exposure of fetus to glucocorticoids is increased which reflects growth and differentiation of fetal tissues. Thus, 11betaHSD2 of the placenta is a proven factor that increases fetal exposure to maternal cortisol and leads to development of cardiovascular diseases and hypertension.
- The fact that placenta has a power to inactivate hormones such as prostaglandins, catecholamines, glucocorticoids, thyroxine, lies in the existence of PGDH. This enzyme blocks active PG and creates prostaglandin ketoform. Basically, the activity of the element provides answer for preterm delivery. If a pregnant patient is exposed to starvation, PGDH is activated and transfers PG into prostaglandin metabolites – prostaglandin ketoform. By administration of corticosteroids in therapy, we decrease activity of PGDH and leave natural PG.
- The stimulation of glucose and amino acids intake at the level of trophoblast originates from IGF1. If it is inhibited, there is fetal macrosomia and GDM.
- The regulation of L amino acids transport in the placenta is proven by mTPR signal pathways of enzymes and genetics.
- Fetal malnutrition leads to later hypertension, diabetes and cardiovascular diseases. Experiments on animal models, administration of pharmacological therapy, diet, hypoxia (surgical manipulation of uterine artery ligation), prove that there is a constant process of: a) quantitative tissue change (the mass of

beta pancreatic cells changed); b) cell changes (number of mitochondria); c) molecular change (changed expression of genes which regulate insulin pathways) (6).

Intergeneration effect

The significance of transgeneration effect reflect as an integral part of development and programming. It is conditioned by evolution mechanism of species adaptation to new environment. In reality, F3 generation because it is Fo pregnancy of grandmother influencing F1 maternal gametes which influence F2 fetus. This is the way impulses are transferred.

FETAL PROGRAMMING appears as: **a)** Transmission of epigenome alteration (somatic and germinal cells), it is in mitochondria as ooplasm components as well as **b)** suboptimal uterine environment.



Malnourished mother gives a fetus with IUGR, cardiovascular and metabolic diseases and obesity, as well as GDM.

Transgeneration transfer, an answer for popular 'inheritance' and 'family genesis', provides an answer for origin and development of pregnancy pathologies but also disease development.

Microhymerism, both fetal and maternal, is a part of a chain from F infinity to F newborn. The name by itself reflects the complex containing anthic word for lion, goat, dragon.

Fetal microhymerism FCM, the xistance of fetal cells in maternal blood may give positive and negative effects and is analyzed by theory of cooperativity. There are opinions that it is induced while the others claim that it protects from disease.

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