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SPECIFIČNOSTI TRUDNOĆE I POROĐAJA KOD GOJAZNOSTI*

GOJAZNOST, OBESITAS, BMI

Podaci porasta trendana ekstrema telesne mase, fokusiraju praksu i nauku na prevazilaženje poseledica.Neadekvatna ishrana i anoreksija, psiholoska i metabolička patnja, često je indukovana medijskim glorifikovanjem lica koja fasciniraju mladu populaciju. Isto tako, drugi ekstrem patološke krajnosti, patološki povećana telesna masa, posledice kulturoloških navika, brzine života, neadekvante kulture fizičke aktivnosti i ishrane, primene lekova, odražavaju se na zdravlje svake osobe.

Delikatnost organizma žene, u svim fazama rasta i razvoja, u oba navedena ekstrema telesne mase, ostavlja posledice u svakoj životnoj dobi. Sekvele su posebno opterećujuće u fazi postizanja graviditeta, prevazilaženju infertiliteta i steriliteta, ali i u održavanju zdravlja žene tokom trudnoće, i obezbeđivanju rađanja zdravog potomstva. Dalekosežne posledice na kasniji razvoj deteta koje se prenose kroz celokupan psiholoski i fizički razvoj jedinke, ostaju zaboravljene. Činjenica je da savremena medicina insitirana na prevenciji. Društveni i zdravstvni sistemi koji ekonomski imaju zavidne nivoe, ne dozvoljavaju retardaciju u smislu samo uspešnog saniranja posledica neadekvatnog odnosa prema sopstvenom zdravlju. Prioritet takvih savremenih sistema, kao što i mi činimo, odnosi se na prevenciju, i sprečavanje oboljenja kod deteta ne samo na rođenju već i svih onih oboljenja koja nastaju kao posledica loše „atmosfere“ koju plod ima dok se nalazi u svojoj „kućici“ . Poznato je da plod ima intereraktivnu ulogu sa organizmom majke. Efekti uticaja majke na plod, deo su koji možemo obezbediti ako probudimo sopstvenu medicinsku etiku, uvedemo mere lične odgovornosti individue koja ugrožava sopstveno zdravalje, a time dovodi u rizik i svoju buduću bebu kao člana društva u kome se rađa.

Fundrujantan porast patološke telesne mase od epidemijskih poprima endemijske razmere. Znajući da je smanjenje gojaznosti, jedan od prioritetih ciljeva, svih Svetskih zdravstvenih organizacija, dati su ciljevi za postizanjem smanjenja broja obolelih. U

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* Rad je stigao u Redakciju neposredno pred štampu Medicinskog glasnika. Lektura i korektura nisu urađene. Izvinjavamo se zbog mogućih grešaka.

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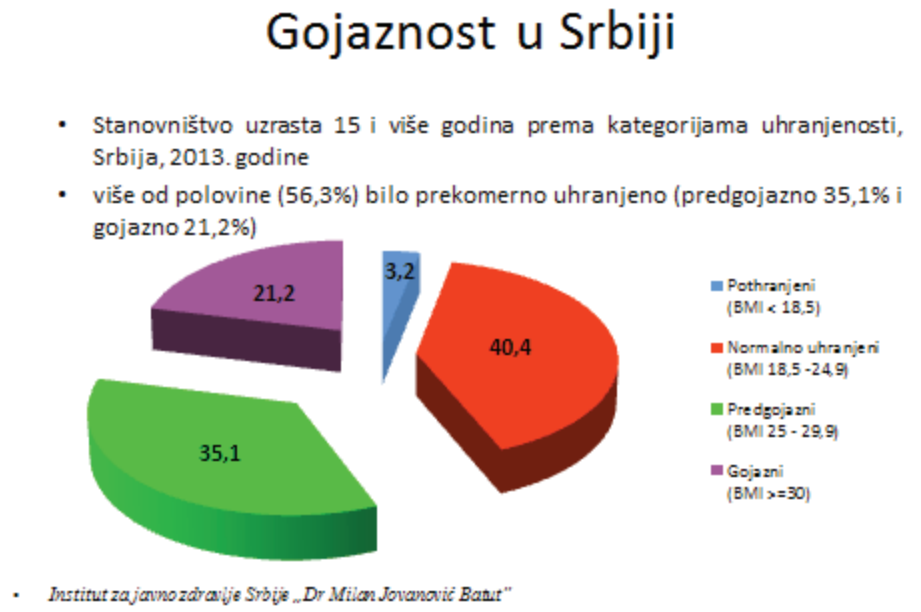
periodu nastupanja novog milenijuma, postavljen je cilj smanjenja tendence porasta „gojaznosti“. Ali rezultati su pokazali još veći porast gojaznosti u populaciji. Dobijamo zapanjujući i poražavajući rezultat. Iako je 2000. postavljen cilj smanjenja gojaznih za 20% do kraja 20. veka, broj patološki gojaznih je porastao na skoro pola populacije sveta. U populaciji odraslih, skoro trećina je gojazna. Razoružavajući je podatak da je i preko 15% dece gojazno u životnoj dobi od 6-11 godina.

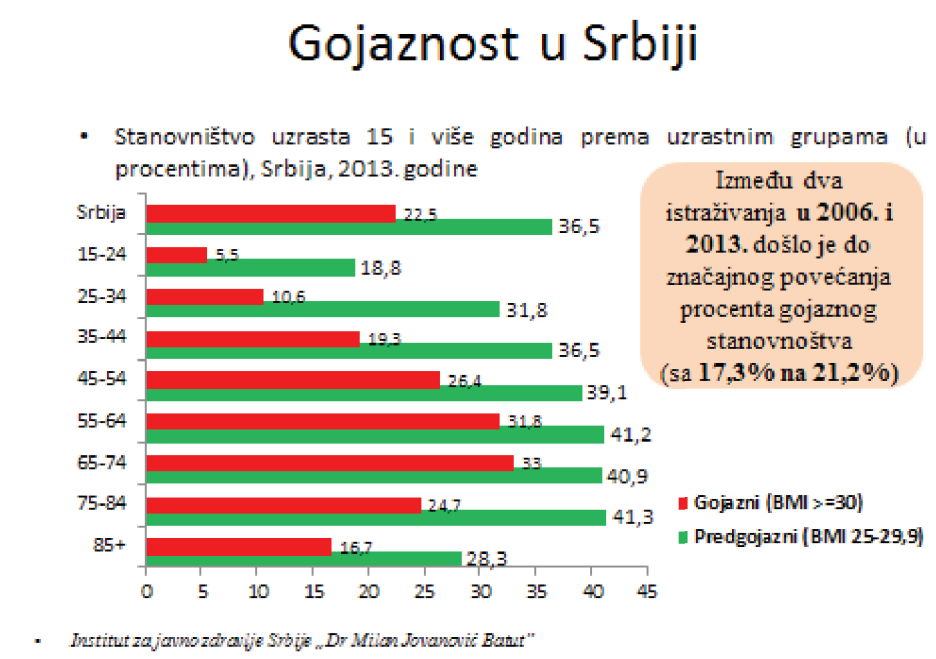
Allison and co workers , 1999; Ogden and associates 2002;Public Health servie, 1990; Elegal and coleagues 2002; hedley and associates, 2004.

Kako mi definišemo gojaznost?

Procena BMI je poznata kao Quetelet indeks.Matematički predstavlja podelu kilograma telesne mase sa visinom u odnosu na metar kvadratni. Veći broj svetskih organizacija uobičajenu skalu telesne mase, fiziološkim intervalom od 18,5-24,9. Preterana telesna masa je od 25-29,9. Dok je patološka gojaznost BMI preko 30. U intervalu patološke gojaznosti, podgrupe od 10 jedinica, predstavlju klase, po kojima se orjentišemo u daljim dijagnostikama, pristupima, očekivanju komplikacija i njihovom prevazilaženju. Prva klasa, klasa I BMI 30-34,9. Porast BMI 35-39,9 kao II klasa, i vrednosti BMI iznad 40 kao treća klasa.

Prevalenca gojaznosti ima trend stalnog porasta. U 2000. godini, u USA više od polovine odraslih bilo je „overweight“ili „Obesse“.





Analize ekonomskog utroška sredstava zdravstvene zaštite, predstavalja neizostavni signal neophodnosti smanjenja trenda ovakvih patologija. U studiji Nacional Health and Nutrition Survey, Ford otkriva da se preko 9,4% godišnjeg ekonomskog zdravstvenog utroška odnosi na ljude koji imaju patološku telesnu masu i koji su fizički neaktivni.

Koje su komplikacije gojaznosti? Efekti na trudnoću?

Bazirano na jednostavnom fiziološkom sledu endokrinološke i metaboličke kaskade nastale povećanim BMI, očekujemo manifestaciju Metaboličkog sindroma kao posledice i insulinske rezistencije. U „saradnji" sa gojaznošću, imamo i tip 2 dijabetesa, dislipidemiju, kao i hipertenziju. Započeta kaskada, algoritamski proširuje spektar klinički patoloških stanja. U povećanoj osnovi BMI, na insulinskoj rezistenciji, povećanju nepoželjnih lipida (triglicerida i Low Dissenty Lipoproteina), baziraju se kardiovaskularni poremećaji. Posledično nastajanje dijabetesa, kao i podupiranje začaranog kruga nove serije metaboličkih poremećaja, koji dodatno povećava mogućnost porasta BMI. Isto tako, opterećenjem krvnih sudova, i remećenjem kvaliteta histološke građe zida krvnog suda, predispozicije ka hipertenezizi kroz opterećeniji srčani volumem za potkrepljivanje potreba organizma povećane mase, ogleda se i u

oštećenju krvnih sudova koji dovode do cerebro-vaskularnih insulta, ili tranzitornih ishemičnih ataka.

U ginekologiji,klinička slika habitusa osobe koja je gojazna, može dati nekoliko prvih odgovora i smernica. Još je davne 2003. potvrđeno da se dramatičniji efekti gojaznosti na pojavu hipertenzije, dislipidemije, insulinske rezistencije i dijabetesa tipa 2, očekuju čak nešto češće kod „jabukolike“ u odnosnu na „kruškoliku“ građu tela. Procena obima struka, i utvrđeni dijametri iznad 88cm u fazi započinjanja trudnoće, objektivni su pokazatelji očekivanja komplikacija Metaboličkog sindroma, Sindroma X.

Tok trudnoće opterećen patološkom gojaznošću

- Očekuje se klinička manifestacija insulinske rezistencije. Od pojave gestacionog dijabetesa (GDM) do manifestacije potrebe za primenom terapija u toku trudnoće (DIP). Praksa ukazuje na sve veći trend pojave gestacionog dijabetesa.....

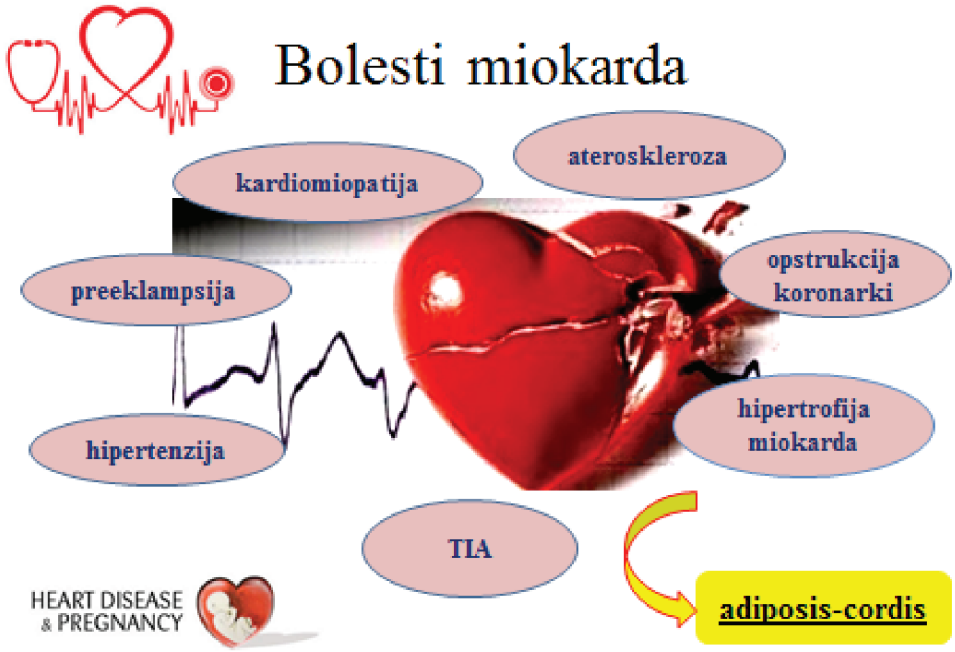
Nastanak Dijabetesa tipa 2, ili kako novoformulišemo GDM, u velikoj je meri posledica neadekvatne ishrane i nedovoljne fizičke aktivnosti. Skladno preporukama Svetske organizacije ginekologa i obstetričara FIGO (Federal International Gynecology Organisation), poželjno je svaku trudnicu testirati na potencijalni dijabet, ali i na mogući poremećaj funkcije štitne žlezde.

U literaturnim podacima, najveći broj ispitivanja, patološku gojaznost stavljaju kao jedan od primarnih uzročnika porasta frekvencije dijabetesa. Mada još u 2003. povezuju obesitas i dijabettipa 2, u 2007. Hossain zaključuje da se čak 90% dijabetesa tipa 2 formira od patološke gojaznosti.

Iako nastanak dijabetesa dominira u primarnoj kliničkoj slici, nisu zanemarive i mnogobrojne komplikacije koje bi izbegi da trudnica nema patološki BMI.

Duž vremenskih i geografskih koordinata, potvrđuju se podaci porasta bolesti miokarda, hipertenezije, pojava preeklamspije, kariomiopatija, opstrukcije koronarki, hipertrofije miokarda, kao i nastanak ateroskleroze, tranzitornih ishemičnih ataka (*Alpert 2001,Calle 2003, Chunali 2004, Flegal 2007, kenchaiah 2002, mokdad 2003, Must 1999, Ninomiya 2004, national Task Force of the Prevention and treatment of Obesity2000).*

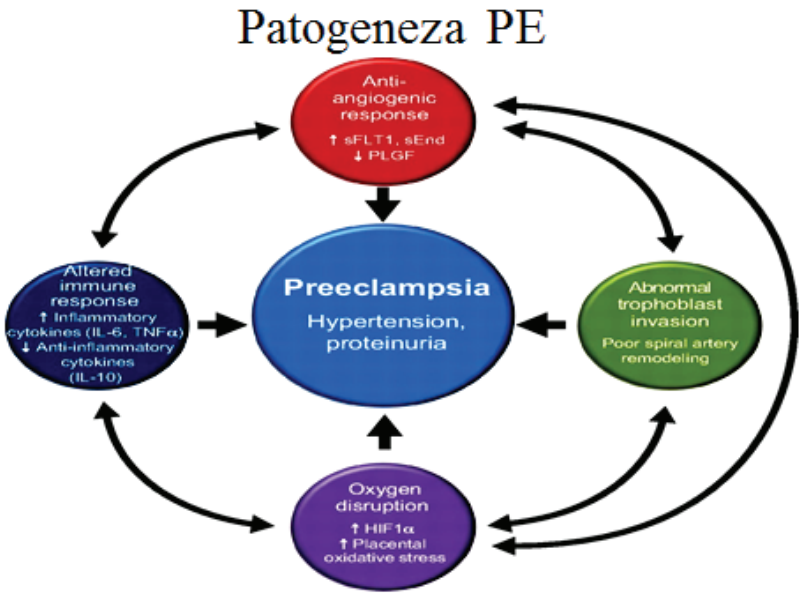
Rastuća frekvencija oboljenja miokarda, nastanak adiposis-cordis**,** posledično su manifestacije hipertenzije, hipervolemije, dislipidemnije*(Chinali 2004, Kenchaiah 2002,Ninomiya 2004...).*



- *(Alpert 2001,Calle 2003, Chunali 2004, Flegal 2007, kenchaiah 2002, mokdad 2003, Must 1999, Ninomiya 2004, national Task Force of the Prevention and treatment of Obesity2000)*

Hipertenzija, koronarna bolest srca, kardiomiopatija, posledice su postojanja povećanog volumena krvi. Usled takvog dodatnog opterećenja, uz očekivano uobičajeno fiziološko opterećenje organizma, očekuje se drastičnije opterećenje i rada srčanog mišića. Porast volumena krvi, srčanog udarnog volumena, dovode do hipertenzije i dislipidemije, kao i opstrukcije koronarnih krvnih sudova.

Objašnjenja su znatno jasnija napredovanjem imunologije i otkrivanjem mogućih uzročnika nastnaka hipertenzije.....



preeklamsija i to Rizik za nastankom preeklamsije se udvostručuje sa porastom BMI. I to na svakih 5-7 kg po metru kvadratnom, rizik se duplira.

Pojava kardiomiopatije, znatno je češća u stanjima patološke gojaznosti. Uobičajene iako retke slučajeve, otkivamo kod postojanja urođenih oboljenja, i prvi put otkrivenih patologija miokarda u stanju trudnoće. Ali u stanjima gojaznosti, kardiomiopatija je deo opšteg opterećenja organizma i kroz povećan srčani minutni volumen i kroz oštećen kvalitet krvnih sudova i dislipidemiju krvi koja ima niži procenat kiseonika.

U trunoći žena sa izrazito patološkim BMI, čak i u povećanoj gojaznosti srednjeg stepena, možemo očekivati nastanak moždanih ishemičnih ataka. U okviru manifestacije hipertenzije, ali i bez pojave hipertenzije. Ovakvi slučajevi predstavalju dogotrajnu,ili akutnu ekzalcerbaciju ateroskleroze, aktiviranje prostaglandina, i vaskulranih endotelnih faktora. Nastanak tranzitornog ishemičnog ataka, kao klinička slika smanjenog protoka i dotoka krvi u centralni nervni sistam. Ali i pojava moždanih izliva, kao posledica hipertenzije, i slabosti zida krvnog suda.

Kvalitet života, i žene van trudnoće i trudnice znatno je umanjen.Mogućnosti fizičke aktivnosti, ograničene su na postupnost i samo određene vežbe, zahtevaju veću upornost i motivaciju.

Dekonfor i socijalno epidemiološki aspekt, psihološki profil same individue i prihvatljivost u društvenoj zajednici, samopogleda na sopstveno telo, nemogućnost i neadaptiranost u okvire uobičajene kulture oblačenja i ponašanja. U oblasti seksologije, problemi nastaju kod oba partnera.

Standarni dnevno noćni ritam, često je praćen apneama, kako zbog faringealne masti, tako i zbog podizanja dijafragmeu horizontalnom položaju, podupreto gravidnim uterusom.

Poremećaji lokomotornog sistema,veća sklonost ka otocima i manja limfna drenaža, deo su habitusa osobe koje imapovećanu telesnu masu,a izraženije se manifestuje u graviditetu.

Češće stomatološka problematika,kao posledica metaboličkih disbalansa, sklonosti ka većem afinitetu mikrobiološke flore gljivičnog porekla, kao i mnogo intenzivnija problematika u održavanju kvaliteta vaginalne sluznice i izbegavanju gljivičnih infekcija. Povećana incidenca urinarnih infekcija, kao i u stanjima dijabetsa.

Kod parova sa povećanim BMI, kao i onih kojima drugi uzročnici dovode do steriliteta, nekada je dovoljno samo organizam vratiti u fiziološke optimume BMI, i prevazilazi se sterilitet. Započinjanje procedure vantelesne oplodnje, nije poželjno u stanju izrazite gojaznosti, jer niti efikasnost medikamenata niti pasaža cirkulatorna neće biti adekvatne da bi se postigao očekivani rezultat kakav bi bio u populaciji fizioloških BMI.

U trudnoći je znatno veća pojava patoloških stanja vezanih za gastrointestinalni trakt. Klinička manifestacija bolnosti ili pak pojavom zapušenosti žučnih kanala, frekventija je u ovoj grupaciji. Mehanički pritisak visceralne masti,otežana pasaža creva,i stalno aktivan centar za glad,podržavaju začarani krug problema. Bolesti jetre, kao nealkoholna masna jetra,posledica visokih vrednosti slobodnih masnih kiselina i hiperinsulinemije.

U vaskularnoj i limfnoj drenaži,pored otoka, drastičniji je porast pacijenata koji imaju životno ugrožavajuće stanje tromboze krvnih sudova.Pritisak gravidne materice dodatno uz visceralnu gojaznost, pritisak na venski sistem krvnih sudova abdomena i ekstremiteta, doprinosi pojavi tromboza. Iako je trudnoća fiziološki gledano hiperkoagulabilno stanje, ovi faktor fizičkog efekta kompresije gravidnog uterusa-visceralne masti- crevnih struktura, doprinose formiranju trombptičkih procesa i ugrožavaju život žene.

Iako u graviditetu primarnu koncentraciju dajemo majci i plodu, nikada ne zaboravljamo i klasičan ginekološki osvrt na problematiku. Potencijlano veći rizik ka nastanku promena grlića koje vode ka prekanceroznim i kanceroznim lezijama, imaju osobe koje kontinuirano pokazju sklonost ka infekcijama. Ne sme se zaboraviti da hronicitet infekcije, iako gljivičnog porekla, dovodi do oštećenja jedara ćelija. U populaciji koja nije grvidna,povećan BMI je deo predispozicije za nastanakom karcinoma endometrijuma.

U periodu porođaja, komplikacije variraju zavisno od nadovezanih komorbiditeta i nastalih patoloških stanja trudnoće.

Znatno je povećan broj operativno završenih porođaja, i to hitnih carskih rezova. Uzročnici su često neadekvatan Bishop skor za započinjanjem indukcije ili pak mehanička opstukcija aktivnosti uterusa i spuštanja ploda pod silom zemljine teže, što nastaje zbog obimne količine *visceralne masti abdomena* i male karlice. Ispitivanja koja su koristila i efekte magnetne rezonancije u kvalitativnom dokazivanju količine visceralnemasti, dala su objašnjenja povećanog broja carskog reza.

Drugi razlog povećanog broja operativnog porođaja, počiva u *stanju samog fetusa*. Kod gojaznih pacijenta, uz razvoj Gestacionog dijabetesa možemo očekivati makrozomiju, gde plod svojim dijametrima ne zadovoljava anatomski opseg karlice majke. Isto tako ako se na gojaznost nadoveže teža forma hipertenzije, i kod ploda uoči restrikcija fetalnog rasta (IUGR) i smanjen kapacitet ploda, dodatna opterećenja ploda koji već ima smanjen kapacitet, dodatno ugrožavaju život ploda.

U samom porođaju, teža primena epiduralne anestezije, otežana aplikacija, kao i neadekvatna pasaža medikamenata, nije vezana samo za regionalnu već i za povećane uobičajenih i pojavu retkih komplikacija opšte anestezije. Od tehnički otežane intubacije, preko češće pojave regurgitacije, i nemogućnosti respiratorne adaptacije nakon opšte anestezije (Dark 2002).

Nakon porođaja, bilo vaginalnog ili operativnog, očekujemo veća postpartalna krvarenja. Neretko dolazi do atonija mišića materice. Prerastegnutost uterusa, već više puta naglašavan smanjen kvalitet krvnih sudova, povećava mogućnost atoničnog krvarenja, kao i *postpartalnih histerektomija* ili abdominalnih rešavanja atonija podvezivanjem arterija *hipogastrika*.

U periodu puerperijuma, kompikacije vezane za abdominalnu patologiju, još se teže diferencijalno dijagnostikuju od standardno atipične slike izostajanja „defansa“ trbušnog zida.

Iako pacijenti uglavnom očekuju povećanu i olakšanu laktaciju, masno tkivo dominira i u dojkama, tako da inače onemogućena adekvatna pazaža hormonalne sprege, nema ni dovoljnu količinu receptora ni anatomski potkrepljenosti za produkcijom i sekrecijom mleka(Li 2003; Amrstron 2002; Ruowellu;)

Održavanje povećane telesne mase u perioperijumu i nakon njega, često su deo uobičajene kliničke slike, (Cotalano 2007, National research council 2007, Rode 2005...). Testovima za kvalitativno praćenje stepena zadovoljstva u životu, dobijamo značajan porat depresivnih stanja. Zavisno od klase povećanog BMI, raste i stepen depresije. Tako da se kroz tri gradacije patoloških BMI, depresija krece od 22,6 na 32,4 na 40 procenata.

Pojava**, (**iznenadne smrti ploda fetus mortus in utero, FMU) ukoliko nema ni jedan mogući etiopatogenetski faktor, dokazano se predominanto vezuje za samu gojaznost i njene „kvalitete“. Porast mrtvorođenosti je 1,6 puta, ako BMI raste od 25 na 29,8. Ako je BMI iznad 30 porast je i 2,6 puta veći, (Cnattingius 1998). Pojava FMU

je tri puta veća ako je BMI preko 25 (Stephansson 2001). Čak i u okvriu povećanog BMI, postoje kategorije. Chu 2007. porast incidence FMU kod „over- weight" nalazi 1,5 puta, dok je kod „Obesiti" 2,1 puta veći FMU. U isptivanoj grupi od 186 hiljada prvorotki, Skoti dokazuje 4x veću pojavu Fmu ako je BMI preko 35, u odnosu na grupu gde je BMI 20-25. Pojava inrauterine smrti ploda, i to iznenadnog stradanja ploda, objašnjava se poremećajem acidobazne i metaboličnе osnove, i najčešća je u periodu krajnje faze trećeg trimestra. Jos 2005. godine utvrđen je takozvani „Hazardni ratio". Od 28-36 nedelje gestacije iznosti 2,1 dok od 37-39 ng je 3,5 da bi u periodu od 40 ng skočio na čak 4,6 Hasard ratio.

Procenat anomalija raste. Veća je frekvencija defekta neuralne tube, kao i pojava omfalokele. Studije rađene 2008. Rasmussennalaze i 3,1 puta veći rizik za nastanak anomalija centralnog nervnog sistema. Slučaj kontrola studije Watkinsa pokazuje 3,5 puta veći rizik za natanakom omfalokela. Interakcija komorbiditeta, spektar patologije, dovodi do kompletnog opsega krajnjih variranja telesne mase, od intreautrine restrikcije rasta do makrozomije (jos od Bianco 2008, Cedergren 2004, Isaacs1994). Isto tako metabolički disbalans i fluktuencije kiseonika, remete stabilnost i kapacitet funkcionisanja organa ploda.Kliničari uočavaju poremećaje rasta i razvoja, postavljaju sekundarne zaključke na osnovu analize antropometrije ploda, relacija uterus-placenta-plod-sistem organa ploda, korišćenje dopler protoka, biofizičkih profila ploda, kardiotokografije (Grupa Metro Health Medical Centre u Clivlendu...Caralano 2005, Ehrenberg 2004, Sewell 2006...).

Postojanje Obesitasa, povećava rizike komplikacija prvog i drugog trimestr**a**. Studija Faster dokazuje povećanu frekvenciju svih komplikacija kao i nastanak učestalijih APO adverce pregnancy outcome.

Komplikacije u odnosu na rast i razvoj fetusa, postaju višestruko intenzivnije.

Gradacija problematike raste sa tepenom povećanja gojaznosti. Sa porastom BMI raste i frekvencauočenih patologija:

-gestacionog dijabetesa
- preeklamspije (Cunningham 1986)
- postterminske trudnoće(hall i Neubert 2005)
- hitnog carskog reza(Haeri 2009)
- primarno određenog carskog reza(Lynch 2008, Poobalan 2009,Bujorld 2005,Goodall 2005, Hibbard 2006,Robinson 2005, ..)
- postpartalnih krvarenja
- postpartalne depresije
- pelvičnih inflamatornih stanja
- urinarnih infekcija
- infekcija rana

-makrozomija
- iznenadnih stradanjaploda intrauterino, ili rađanja mrvog ploda
-anomalija ploda
- povećanje frekvence svih patoloških stanja,svakog od trimestara trudnoće
- komplikacije puerperijuma
- psihološke i socijano epidemiološke problematike
- fetalno programiranje, raste broj potencijlano obolelih u adultnom periodu

primeri

(1. Neill i Nelson Piercy, 2001, obesiti je povezan sa subferitilnoscu zbog povecane insulinske rezistnece; 2. Bellver 2009, nalazi veci fmu kod obesitasa; 3.Lashen 2004, povecan irzik pobacaja u prvom trimestru4. Chu 2008 povecano iskoristcavanje zdrasvtenog sistema;).

Fetalno programiranje, opasnost prenošenja impulsa promenjenog metabolizma, kao i impulsa koji se odnose na sam molekul DNK, raste. Zapravo raste naša spoznaja činjenice da čak i genetsku mapu možemo pogoršati neadekvatnim poštovanjem kvaliteta zdravalja. U stanjima patološke gojaznosti, poremećaji koji se odražavaju na intrauterino stanje ploda, ostavaljaju trajne posledice na dalji rast i razvoj ploda. Kod dece koje imaju već uočene ekstreme telesne mase, oštećenje metabolizma, kao i poremećaj količine kisonika, imamo poremećenu razvojnu plastičnost.

Baker je 1989. skrenuo pažnju naučne javnosti da bolesti odraslih počivaju u postignutom načinu života jedinske u detinjstvu. Tek je kasnije Forsdalh dao pravu sliku, i od 1977. smatra se da je sve ono što kao odrasli imamo u velikoj meri deo predispozicije koje smo dobili našim intrauterinim zrazvojem. Forsdalh je našavši veći broj smrti od metaboličkih bolesti i kardiovaskularnih bolesti u Norveškoj u periodu od 1964-67, analizirao da su svi rođeni od *1896-1925*. i da su bili izloženi *nutritivnom deficitu*, vulnerabilnoti tokom života, *permanentom oštećenju tkiva i organa.* Razvojna plastičnost je fenomen u kome se genotip menja na različite stimuluse tokom razvoja. Rast je kvantitativna karatkeristika opisana porastom broja ćelija., Razvoj je kvalitativna karatkeristika nastala funkcionalnom i fiziološkom maturacijom ćelija. Programiranje je odgovor organa koji se razvijaju na specifične izazove koji dovode do nastanka različitih fenotipova. Plastičnost je opet sposobnost organizma da stvara različite puteve svog razvoja, zavisno od specifičnosti okruženja. Plastičnost se jednostavnije objašnjava pojavom da od jednog gentoipa ima mogućnbosti astanka više fenotipova. Kontrolni mehanizmi razvojne plastičnosti su metaboički kao i insulinska sekrecija, vaskurani i vaskularna rezistencija, kao i endotelna disfuckija koja pokreće kaskadu inflamtornih i oksidativnih procesa.

Efekti na rast i raszvoj ploda odražavaju se direktrno glukokortikoidima kao i indirektno *inhibicijom placentnog 11 beta hidroksi sterodid HSD2 smanjene ekspre-*

sije Novorođena deca imaju sve predispozicije za pojavom stanja svojih roditelja. Povećanje HDl lipoproteina, centralna gojaznost, sklonost hieprtenziji kao i nastankau diajbetesatipa 2,uz dominantu pojavu sklonosti ka gojaznosti (Boney 2005, Catlano 2005).

Kako pristupamo dijagnostici, prevenciji i terapiji trudnice koja ima povećan BMI ili krajnju gojaznost?

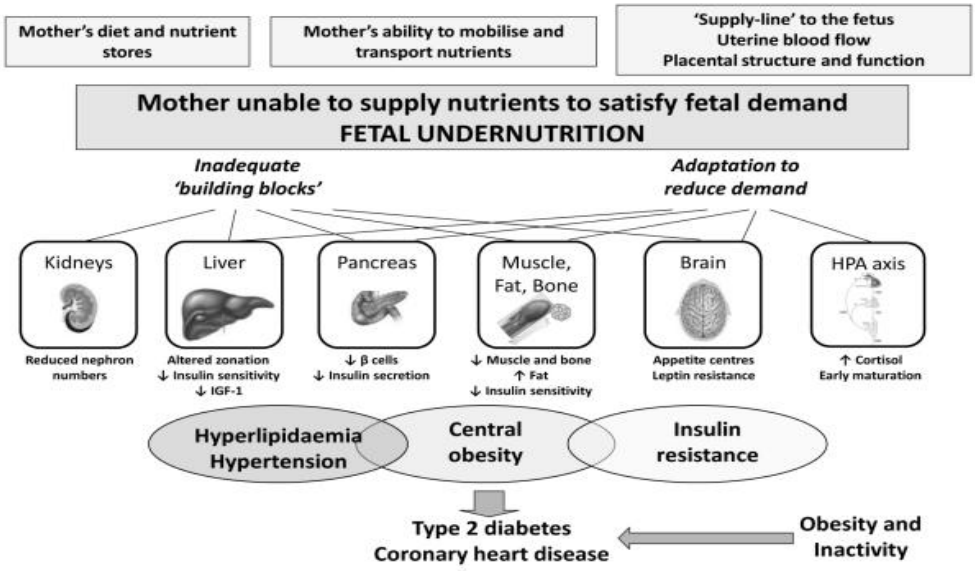
Identičan način savremenog vođenja trudnoće uz podizanje frekvencije i opreza pregleda. Od učestalijih merenja prirasta telesne mase, proveri sklonosti i lečenju infekcija cerviklanog i urinarnog trakta, kontroli prirasta telesne mase, kao i praćenju arterijskog pritiska, određivanju koncentracija glukoza i praćenju metabolizma uz obavezsno izbegavanje katabolizma. Dokazano je da katabolički procesi značajnijje remete razvoj poda, u odnosu na već izražene drastične hazarde povećane telesne mase. U vođenje trudnoeća aktivno se ukjučuje i specijalista higijene, i uz određivanje kvantiteta apostrofira se i kvalitet unetih namirnica kako bi se zadovoljile potrebe fiziološkog metabolizma i adaptiranost na poećanim osnovama BMI:

Preporučeno je da žene BMI ispod 18,5	dobiju 12,5-18kg, dok ukoliko je BMI od 18,5-24,9	dobiju 11,5-16kg
BMI od 25-29,9	dobiju 7-11,5kg overweight, a preko 30	dobiju 5 -9,1kg.

Aristotelova konstatacija „Fiozofsko pitanje, od kokoške do jaja“ odražava se u svim segmentima života. Moć praktične primene znanja perinatologije,obezbeđuje, ne samo održavanje zdravlja žene i sprečavanje komplikacija, obezbeđivanje zdravog potomstva, i smanjenje potencijala nastanka oboljenja u životu. U 20. veku, menja se obrazac pojave bolesti, stopa mortaliteta u svetu opada od infektivnih ali raste od horničnih kardiovaskularnog sistema, metabolizma. Raste stopa oboljenja koje možemo sprečiti našim učinkom u perinatologiji.

U takvim stanjima nutritivnog deficita, fetus se prilagođava, *centralizacijom krvotokta* (ka mozgu,jteri, srcu, pankreasu). Posledica toga je u neonatusu manji broj ćelija bubrega (sklonost hipertenziji), manji broj ćelija mišića (sklonost nagomilavanju masnog tkiva ukoliko nakon rođenja dobijaju veću telesnu masu). Prilagođavanje fetusa, ide ne samo centralizacijom krvotoka, već i *aktiviranjem hipotalamo-hipofizne osovine fetusa*, koja povećava sekreciju i osetljivost na hormone rasta (insulin,i insulini slični faktori rasta). Prilagođavanje i programiranje fetusa , je razvojna plastičnost. Razvojna pasttičnost je fenomen, gde genotip odgovara različitim fiziološkim i morfološkim promenama, narazličite nadražaje tokom razvića. Ali, i u ranom *neonatalnom životu, restrukturiranje tkiva*, kao i reprogramiranje endokrinih i metaboličkih osovina, dovodi do pojave oboljenja. Interesanto je da se efekti fetalnog programiranja, mogu uočiti, i *ako ne dođe do promene u telesnoj masi na rođenju ,* već proces na prvi mah,

deluje manje upadljivo. Koegzistencija efekata hipertenzije i neprepoznatog gestacog dijabetesa,daće adekvatnu telesnu masu, ali neće značiti da se aktivnosti navedenih patoloških kaskada neće potencijalno odražavati na život kasnije.



BOLESTI KOJE SE POTENCIJALO MOGU SPREČITI U NAJVEĆEM BROJU SLUČAJEVA

U stanjima nasuprot, Intrauterinoj restrikciji fetalnog rasta IUGR, apostrofira se MAKROZOMIJA, koja se smatra predispozicijom za nastankom :

- Dijabetesa; *Pankreas fetusa*, pod uticajem povećanih glikemija u gestacionom dijabetesu, ostaje oštećen usled *degranulacije beta ćelija* (mitohondije su edematozne, iendoplazmatični retikulum izdužen, malo mranula je u ćelijama).Dokaz hiperaktivnosti pankreasa je povećena telesna masa ploda (od 19.nedelje gesatcije pankreas ploda luči *insulin i insulinu slične faktore rasta*, što potvrđuje veća konentracija u krvi pupčanika dece sa markozomijom). Činjenica da se ceo proces odvija preko hipotalamo – hipofizne osovine potvrđen je podatkom da se te promene ne dešavaju kod one grupe *anencefalusa* gde je oštećena ta osovina, dok se kod anencefalusa sa sačuvanom osovinom jednako ispoljavaju.

- Karcinom dojke žene koja je rođena kao makrozomičan plod, oblašnjen je u segmentu etiopatogeneze, *mitotskom aktivnošću fetusa*, povećanim insulinom i insulinom sličnog faktora rasta IG.

- Metabolički sindrom, sindrom X kod dece: pod dejstvom porasta (glikemije, insulina, IGF, lipida, inflamatornih faktora)zapravo stvara *nutritijentima posredovanu teratogenezu*.

- Nealkoholna bolest,masne jatre dece: nastaje kao posledica *metaboličkih promena i hipoksije*. Zapravo promene na nivou pojave prekomerne količine *masnih kiselina*, dovode do *oksidativnog stresa i inflamacije* (prekomerne količine masne kiseline koriste, dovode do oksidacije mk, formiranje slobodnih radikala u mitohondrijama koje oštećuju balans oksidativnih i antioksidativnih enzima). Tako se remeti oksidativni kapacitet mitohondrija i smanjuje količina antioksidativnih enzima peroksidaza i superoksid dimsutaza. *Hepatociti Kuperove ćelije i stelatne ćelije,stradaju* tako, zbog oštećenih mitohondrija,preko oksidativnog stresa, inflmacije,i nastaje smrt ćelija.

Nealkoholna masna jetra i neadkevatni imunološki odgovor organizma: po Harmonu, nastaje kod patološke gojaznosti majke, Obesiti. Oni su posledica nastanka „mirkobioma novorođenčeta“,odnosno „prvog otiska“. Kod *gojaznih žena*, u crevima se luči *dva puta veća količina endotoksina crevnih bakterija*, u odnosu na creva trudnica adekvatne telesne mase. Takvi *endotoksini, krvlju, preko vene porte* dolaze pravo u jetru i *hepatocite* koji su „*prva Linija Odbrane od Antigena poteklih iz Creva“* .

- Gojaznost, Obestiti kod dece: nastaju kao posledica citotoksičnih lipida, maladaptivnih promena, proinflamatornih proteina.

Oksidaciju masnih kiselina kontroliše SIRT , sirtuinska inflamacija (NAD zavisna deacitlizaza), koja je senzor nutrijenata, koji modifikuje gene i proteine, tako što utiče na *postranskipcionu aktivnost gena*. Poznato je postojanje *SIRT 1(odgovornog za glukoznu i lipidnu homeostazu,* jer je glavna deacitilaza u postranslacionoj regulaciji proteina i gena). Ukoliko je veća količina masti u krvi, smanjuje se aktivnost *SIRT1, i tako se prilagođava organizam na „oksidativni stres“*.

Ali, ako se „organizam prilagodi“ smanjuje se količina SIRT1 i *SIRT3 koji reguliše povećava produkciju slobodnih radikala iz lipidnog ekscesa*. Tako se posledično smanjuje mitohondrijalna funkcija i smanjuje se oksidativni kapacitet.

Vremenom dolazi *do još većeg pada i SIRT1 i SIRT3* kao posledice mitohondrijalne disfunkcije. Tako nastaje neaktivnost celokupnog hepatičnog oksidativnog kapaciteta.

Restrikcija fetalnog rasta IUGR , sa sobom nosi rizike koronarne bolesti, dijabetesa, metabolopatija, hormonalnih promena, psihomotornih promena.

Koronarne bolesti: manja telesna masa na rođenju, manji ponderalni indeks, ukoliko su kasnije izloženi većem dobijanju masnog tkiva, od IUGR fetusa dolazi do razvoja koronarne bolesti (Eriksson 2001)

Crte ličnosti, emocionalni odgovori, povišen odgovor na stres: deca manje telesne mase, teže podnose i venepunkcije. Studije ponašanja, socijalizacije,seksologije

u Švedskoj dokazuju smanjenu društvenu adaptabilnost (Hertfor Shire Švedska). Postoji veća sklonost ka depresiji, suicidu, hormonalnom obrascu za raspoloženje. Osnov promene baziran je na promenama a) hipotalamo adrenalne osovine, kao i b) hipotalamo tireoidne funkcije.

Hormonani disbalansi ženske dece: kod IUGRa često se javlja ranija menarha. Promenjena je produkcija gonadotropina.

Autizam: ima začajan prirast pojavljivanja.

Mehanizam prilagođavanja, i epigenetika koja je međugeneracijsko prenošenje**,** potvrđeni su epidemiološkim studijama. Efekti intrauterine sredine utiču na događaje posle začeća ali i na događaje u kasnijem životu.

Prilagođavanje fetusa, ostvaruje se *1. promenom broja ćelija, 2. klonalnom selekcijom određenih tipova ćelija, 3. metaboličkom diferencijacijom, 4. genskom ekspresijom*.

„Obrazac DNK metilacije" uspostavljen je u toku emriogeneze i fetalnog razvoja. Davanjem folana majci (odgovornog za metilaciju proteina i metaboličke procese) utičemo na formiranje „Metil Grupa". Tako se sprovodi prevencija gojaznosti, insulinske rezistencije i dijabetesa.

Epigenetska povezanost, se može dokazati u epidemiološkim studijama. Holandska glad, ukazala je na „*signalne puteve Leptina*". Promene usled gladi, osovine *hipotalamus- hipofiza -adrenalna* žlezda, uz *placentu* kao medijator između majke i fetusa. Histološki glad dovodi na placenti do nitracije placnetnih proteina, metilacije gena, smanjene aktivnosti transportera nutrijenata (promenom 11beta HSD2 hidroksisteroid dehidrognaze) . Helsinki studija, povrđuje sklonost koronarnoj bolesti. Obdukcijom i genskom analizom 476 starijih ljudi oba pola, rođenih kao deca *sa IUGR, nađeni su Geni*vazani za nastanak Gestacionog dijabetesa (pro 12 polimorfizam *PPAR-Y gena*, koji utiče na nastanak GDM).

Posteljica kao vekovna enigma?

- PRELAZAK GLUKOZE KA FETUSU, regulisan je i preko *Progesterona, Humanog placentog laktogena HPL*, kao i steroida, peptida, glikoproteina, eikozonaoida.

- FETALNA ENDOKRINA FUNKCIJA,
- MIOMETRIJALNA AKTIVNOST,
- REGIONALNI PROTOK KRVI, *regulisani su Prostaglandinima F2 alfa i E2*.
- TRANSPORT KISEONIKA, identično je regulisan, indirektnim efektima prostaglandina

  (KORTIZOL menja placentnu steroidogenezu i sekreciju HPL. Tako se menja i razvoj dojki).

NOVI POGLED NA PLACENTU

Veličina placente, dobar je parametar je koji je dobar pokazatelj i prediktor razvoja adultnih bolesti. Natanak dijabeta tipa II i hipertenzije. Nekada je skriveni razlog IUGR placenta i njen uteroplacentni protok .

GENI IGF2 ČINE DEO PLACENTNOG „PROGRAMIRANJA“. Manja ekspresija gena dovodi do *manje placente, dok pojačana ekspresija dovodi do placentomegalije.*

Prirodno MALA placenta,ima uvećanu razmenjsku zonu na račun endokrine zone. Dovodi do ubrzanog stvaranja E16. (u njima je povećan transport metabolišućih analoga amino kiselina, koji dovode do promene placente i do ekspresije gena koji kodiraju specifični sistem transportera. Takav sistem transportera dovodi do ushodnog regulisanja transportera kroz gensku manipulaciju IgF2-H19 osovine.

PREKOMERNI rast placente,opet rezultuje smanjenim transportom kiseonika (na miševima je dokazana delecija H19.

Placenta igra centralnu ulogu u fetalnom programiranju,direktnom regulacijom ishrane fetusa i fetalnog rasta. Placenta je SENZOR za hranjive materije. Odgovorna je za TRANSPORT PROTEINA, preko svojih NOSAČA (broja,lokalzacije,afiniteta); (dokazi na miševima, dokazano 3 transportera glukoze GLUT 1, 3 i 9 različitih transportera aminokiselina). Znamo li šta UTIČE NA AKTIVNOST transportera? Dokazi animalnih modela i naša klinička praksa upućuje na efekte: hipoksije, toplotnog stresa, pre uhranjenosti ili pothranjenosti, izloženosti hormonima rasta i leptinu.

Placenta se smatra i SENZOROM RASTA, koji menja MAJČIN KOMPLARTMAN,utiče na metilacioni status placentnih gena, povećava placentni OKSIDTIVNI i NUTRITIVNI STRES i dovodi do FUNKCIONALNIH PROMENA PLACENTE.

Ishrana fetusa, potiče i od same placente. Hranjive materije za fetus, zavise i od mere u kojoj se *proizvode i koriste u samoj placenti*. Šta se dešava u stanjimaNEUHRANJENOSTI TRUDNICE, ili DUŽIH EPIZODA HIPOGLIKEMIJE; Prolongirana hipoglikemija, (duže davanje većih doza insulina) u prvom trenutku navodi placentu da *čuva* glukozu. Potom se *smanjuje* upotreba glukoze, a sekundarno produkcija *laktata*. Šta se dešava u PREUHRANJENOSTI, DIJABETESU, OBESITASU,KONZUMIRANJU VISOKO ENERGETSKIH DIJETA? Nastaje insulinska rezistencija i dijabetes.

Rast i razvoj ploda, zavise i od vaskularizacije i razmenjske barijere placete. Fetalno programiranje zavisi i od VREMENA NASTANKA PLACENTNOG INSULTA. Posledica je i anemija i hipoksija ploda.Iako hipoksija postoji fiziološki u toku organogeneze, u stanjima vezanim za *„veći stepen trofoblasne hipoksije“* ,nastaje metabolička aktinost „placentih mitohondrija“, i očekuje se nastanak IUGR-a, Hipertenzije i PE, kao i dijabetesa DM. Kako i anemija utiče? U stanjima anemije,

dolazi do a)povećane fetalne angiiogeneze u prvom trimestru; b) dilatacije kapilarnih sinusa;c)do istanjenja razmnske barijere. U stanjima manjih placenti i kod IUGR-a, sa negativnim ili endijastolnim protocima u trudnoći, krvni sudovi su slabo razgranati ili je istanjena razmenjska barijera. Retko se kod takvih protoka nalazi normalan obrzac stem ćelija arterija,kao kompenzacija povećane kapilarne angiogeneze i razvoja terminalnih vila.

Poremećaji placente dovode do kardiovskularnih bolesti. Objašnjenje počiva u *kompenzaciji* miokarda fetusa povećanjem „load"-a, kratkoročnom adaptacijom, nakon koje se *smanjuje broj kardiomiocita* i ostaje veća osetljivost na hipoksične insulte.

Nama dostupna klinička praksa, bazična medicina, kao i studije na animalnim modelima daju potvrdu kliničke prakse i pružaju dalja rešenja:

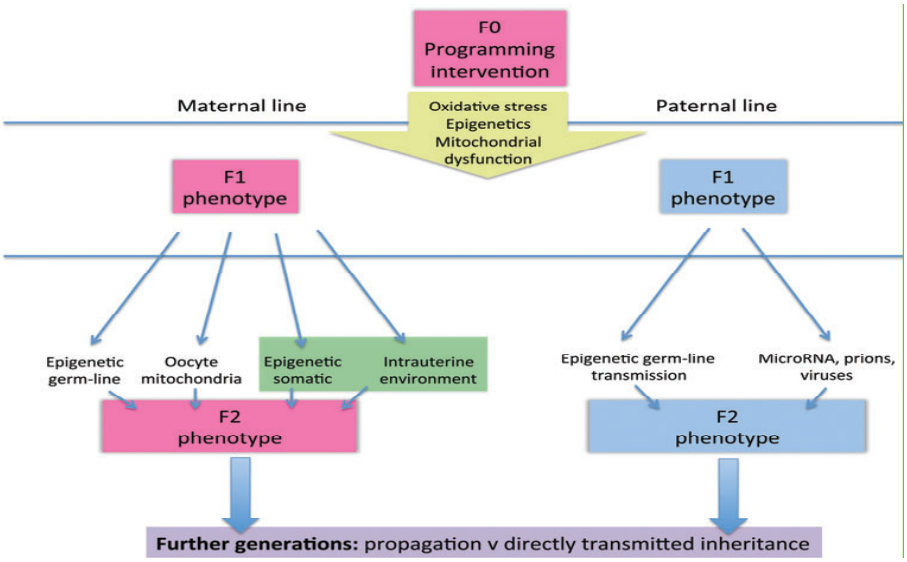
- davanjem FOLATA: povećava se placentna aktivnost „11betaHSD-2",preko maternalnih nivoa metil donora placentnih gena. Tako se smanjuje „placentni oksidativni stres" i „nutritski stres".
- pod efektima „stresa" fetusa, ili medikamentoznim davanjem glukokortikoida: aktivira se placentni enzim „11beta HSD2". Ukoliko je njegova enzimska snaga umanjena, povećava se izloženost fetusa glukokortikoidima, i to se odražava na rast i diferencijaciju fetalnih tkiva(10). znači „11beta HSD2" placente dokazan je kao faktor koji povećava „fetalnu izloženost majčinom kortizolu", i dovodi do razvoja KARDIOVASKKULRANIH BOLESTI I HIPERTENZIJE .
- činjenica da placenta ima MOĆ, da inaktivira HORMONE kao prostaglandine (PG), kateholamine, glukokortikoide, tiroksin,počiva u postojanju „PGDH PG dehidrogenaze prostaglandina". Taj enzim blokira aktivne prostaglandine (PG) i stvara ketoformu prostaglandina. U osnovi aktivnost tog elementa daje jedan od odgovora za nastanakom prevremenog porođaja. Ukoliko je trudnica izložena gladovanju,aktivira se „prostaglandin dehidrogenaza PGDH" pretvara *prostaglandine PG* u metabolite prostaglandina- *ketoformu prostagladnina*. Davanjem kortikosteroida u terapiji, smanjujemo aktivnost PGDH i time ostaju prirodni PG.
- Stimulisanje preuzimanja glukoze i aminokiseina na nivou trofoblasta potiče od IGF1 Insulin Growrth faktor 1. Ukoliko je on inhibiran nastaje Makrozomija fetusa i GDM gestacioni dijabetes.
- Regulisanje transporta L aminokiselina u placenti dokazano je mTPR signalnim putem enima i genetike.
- Fetalna pothranjenost dovodi kasnije do hipertenzije, dijabetes, kardiovaskularnih bolesti**.** Eksperimenti animalnih modela, davanja farmakoloterapije (streptozotocina), dijeta (glad), hipoksija (hirurške manipulacije ligatura a uterine), dokazuju da se konstatno odvijaju: a) kvantitativne promene tkiva

(masa beta ćelija pankreasaizmenjana); b) ćelijske promena (broja mitohondrija); c) molekularne promene (izmenjena ekspresija genakoji regulišu signalne puteve insulina) (6).

MEĐUGENERACIJSKI EFEKAT

Značaj transgenetarcijskog efekta ogleda se kao INTEGRALNI DEO RAZVOJA I PROGRAMIRANJA. Uslovljen je EVOLUTIVNIM mehanizmom adaptacije vrste na novu sredinu. Realno F3 generacija jer je Fo trudnoća bake, uticaj na F1 gamete majke, koja utiče na F2 fetus. Tako se prenose 2 impulsi".

FETALNO PROGRAMIRANJE nastaje: a) Transmisija alteracijom epigenoma (somatska i germinativna ćelija, odvija se mitohondrijama kao komponentama ooplazme, kao i u **b)**suboptimalnoj sredini uterusa.



Neuhranjena majke, daje fetus sa IUGR, nastaju KV i metaboličke bolesti i obesitas, kao i GDM.

TRANSFENERACIJSKO PRENOŠENJE, odgovor za narodnim „nasleđivanju" i „porodičnoj genezi", daje odgovor i za „poreklom i razvojem patologije trudnoće ali i razvojem obolenja"

MIKROHIMERIZAM I FETALNI I MATERNALNI je deo lanca od F beskonačno do gameta Fnovorođenčeta. ime samo po sebi, odražava kompleks, koji sadrži antička reč „lav, koza, zmaj".

FETALNI MIKROHIMERIZAM FCM, postojanje ćelija fetusa u krvi majke mogu dati POZITIVNE I NEGATIVNE EFEKTE i analizira ih TEORIJA KOOPERATIVNOSTI. Neko smtra da „indukuju“, dok mnogi misle da „štite“ od bolesti.

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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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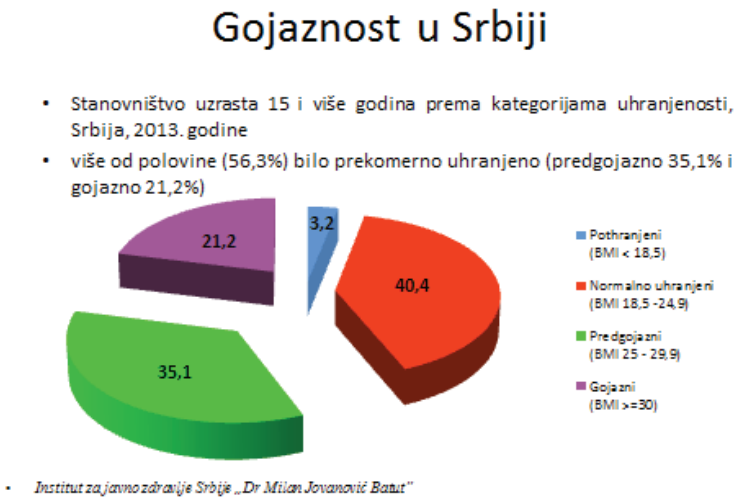
Extremely fast increase of pathological body mass is moving from epidemic to endemic size. Knowing the fact that the decrease of obesity is one of the priorities of all world health organizations, the aims for decreasing the number of affected are stated. With New millennium start, the aim to decrease 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 and11 are obese is disarming.

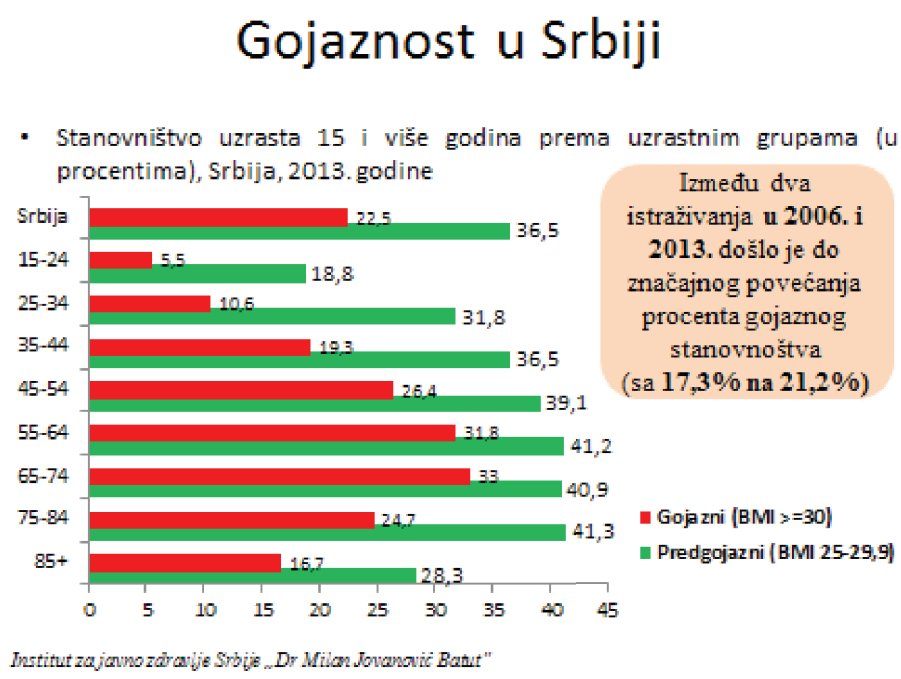
Allison and co workers, 1999; Ogden and associates 2002; Public Health service, 1990; Elegal and colleagues 2002; Hedley and associates, 2004

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.





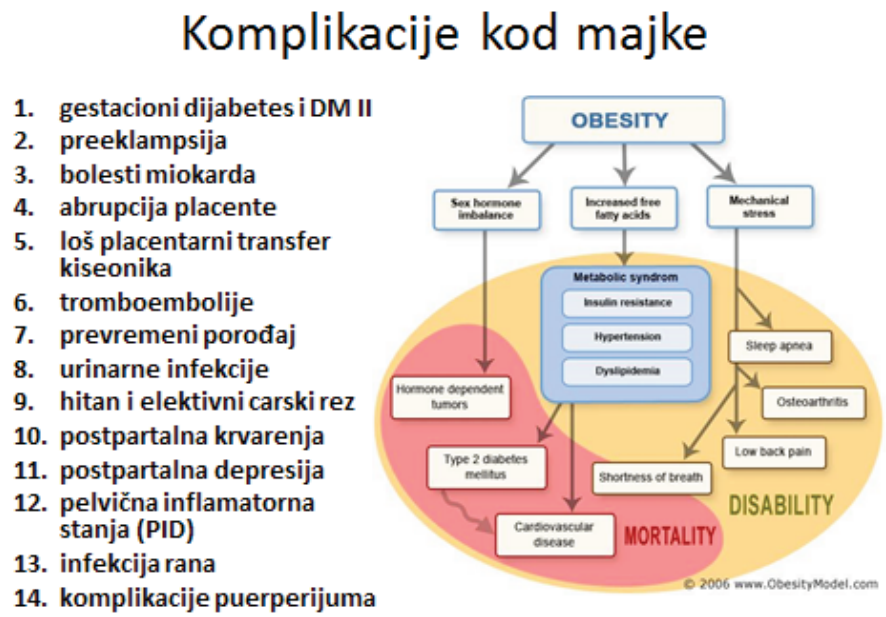
The analyses of **economic cost** of health care presents inevitable signal of necessity to decrease the trend of these pathologies. In the study of National Health and Nutrition Survey, Ford reveals that over 9.4% of yearly economic health cost is related to people with pathological body mass and physical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



- **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...

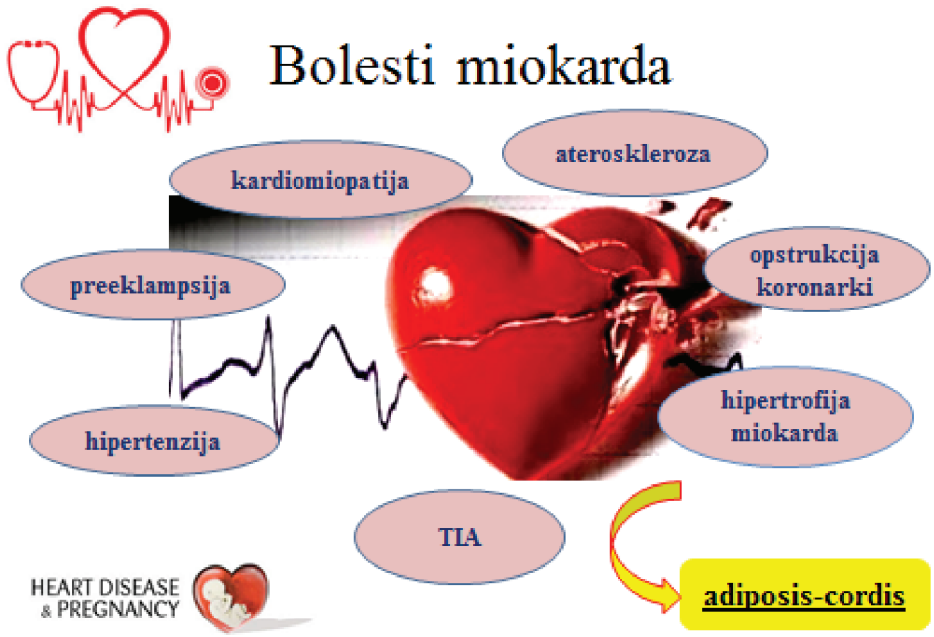
The incidence of type 2 diabetes, or as newly formulated GDM, is to a large degree the consequence of inadequate nutrition and insufficient physical activity. According to recommendations of FIGO (Federal International Gynecology Organization), it is desirable to test each and every pregnant patient 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, Chunali 2004, Flegal 2007, Kenchaiah 2002, Mokdad 2003, Must 1999, Ninomiya 2004, National Task Force of the Prevention and treatment of Obesity2000).*

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

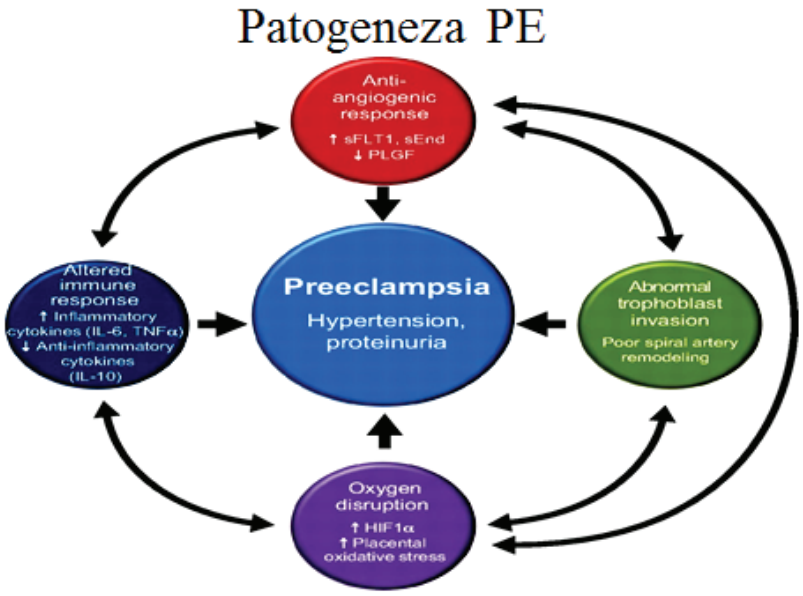


- *(Alpert 2001,Calle 2003, Chunali 2004, Flegal 2007, kenchaiah 2002, mokdad 2003, Must 1999, Ninomiya 2004, national Task Force of the Prevention and treatment of Obesity2000)*

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 id a part of general burden for the organism both via increased hearth 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 **gastrointestinal tract** is increased. Clinical manifestation of pain or incidence of bile duct obstruction is more frequent is 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 it 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 muscles 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 couincil 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,Bujorld 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?

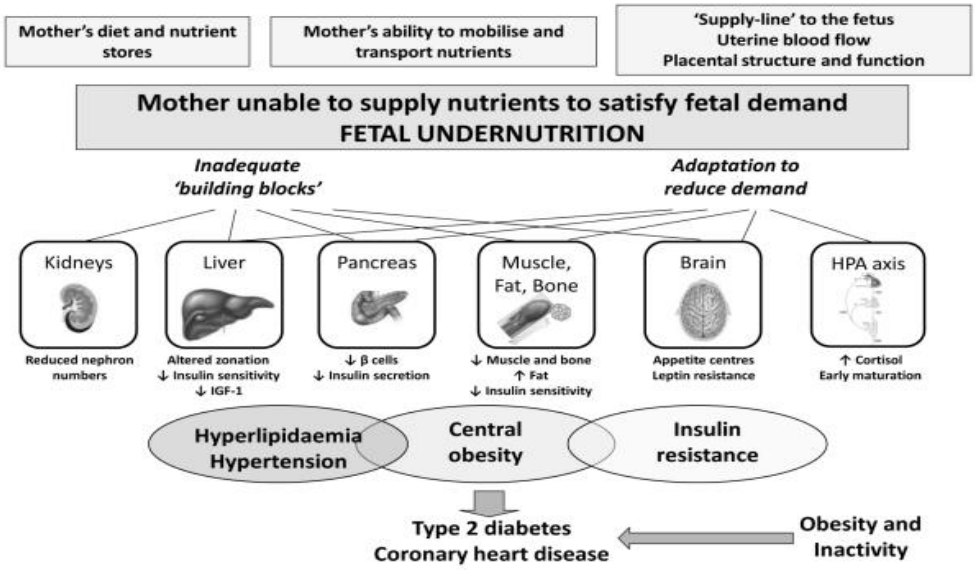
Identical modern way of pregnancy following together with increased frequency of examination and care during one. More frequent measurements of weight gain, checking the affinity and treatment of infections of the cervical and urinary tract, weight gain control, arterial blood pressure monitoring, glucose 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 seams 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 secrets insulin and insulin line 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 nutritient 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 hepatocites 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 deacitilisase) 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 adaptility (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, eicozonaoids.
- 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. Nutritients 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 angio genesis 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 myocard by increasing of load, short-term adaptation, after which the number of cardio myocites 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:

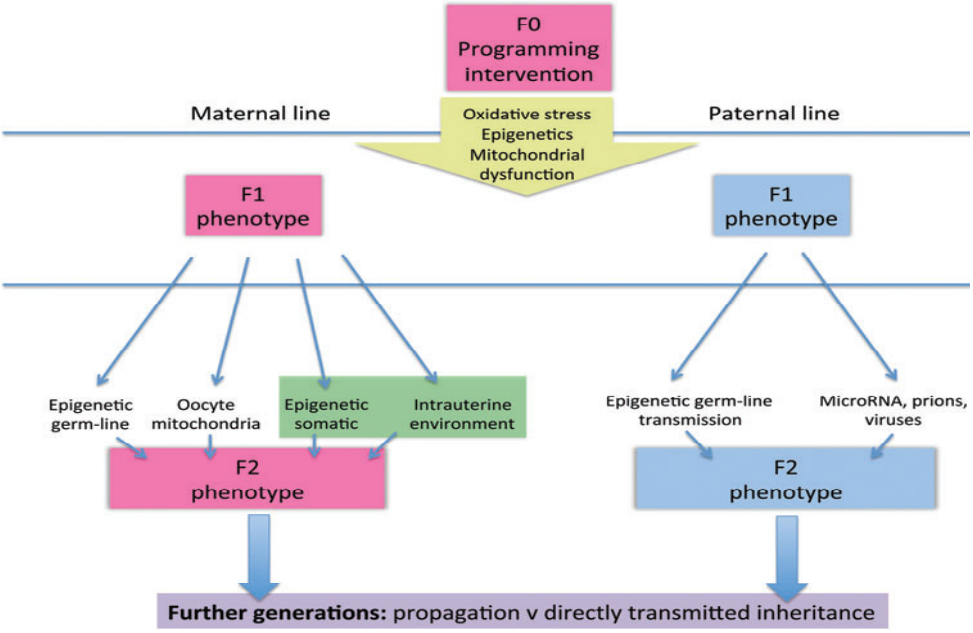
- By administration of folate the placental activity of 11 beta HSD-2 is increased, via maternal levels of methyl placental genes donors. Thus, placental ozydative stress and nutritive stress are decreased.
- Under the effects of fetal stress or medicament administration of glucocorticoids, placental 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, tyroxine, lies in the existence of PGDH PG.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 trasnsfers PG into prostaglandin metabolites – prostaglandin ketoform. By administration of corticosterioids 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 ligature), 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 mothernal gametes which influence F2 fetus. This is the way impulses are transferred.

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



Malnutritioned mother gives a fetus with IUGR, cardiovascular and metabolic diseases and obesitas, 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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