## **Pregnancy & Birth as a Window to the World**

#### Long-term consequences for mothers and offspring



Pablo Picasso: Window to the World 1955,



George Saade SMFM Berwick et al. Health Aff 2008;27:759

- CARDIOVASCULAR DISEASES
- Pre-eclampsia
- Preterm delivery
- METABOLIC DISEASES
- Gestational diabetes
- Overweight and obesity
- MENTAL DISEASES
- Maternal anxiety
- Stress
- PELVIC FLOOR DISEASES
- Connective tissue change
- Trauma during birth

Pregnancy: An Underutilized Window of Opportunity to Improve Long-term Maternal and Infant Health—An Appeal for Continuous Family Care and Interdisciplinary Communication

Birgit Arabin<sup>1,2\*</sup> and Ahmet A. Baschat<sup>2,3</sup>

#### Arabin & Baschat. Frontiers 2017; 5:69-78.

## The Unfinished Agenda of Global Health Reinvigorated energy/ political will to improve

By 2030, 8.3 billion people are globally expected: 13% >65 y. Inaqualities of life expectancies: 45.6 y. Lesotho 86.4 y. Japan. *Murray, et al. Lancet 2013; 382: 9–11* 

Since 1990, non-communicable diseases (NCD) increased by 41.8%, injuries by 10%. This will affect generations to come. *Sepúlveda & Murray. Science 2014; 345; 6202:1275-9* 

The UN calls upon governments to reverse the NCD burden and identified the Sustainable Development Goals, to "end all forms of malnutrition" by 2030. GBD transition likely? *Commission on Ending Childhood Obesity. www.WHO.int/entity/end-childhood-obesity/final-report/enl* 



Ban Ki Moon "We strive for an international commitment that puts noncommunicable diseases high on the development agenda".

# The Global Burden of Diseases: Life ExpectancySepúlveda & Murray. Science 2014; 345; 6202:1275-9Cave Transition!

Since 1990 communicable diseases & neon./mat. death rates decreased by >25%



#### Age-standardized years of potential life lost/100,000 across life stages and regions



## Setting Priorities–globally, locally, individually

Mismatch between needs & development assistance for health (DAH), we need broader discussions and changes of attitude. The allocation of DAH improves health of the poor; but is influenced by underrecognition of the epidemiological transition. *Sepúlveda & Murray. Science 2014; 345 202:1275-9* 

	Low income		Lower inc	middle ome	Upper middle income		
	YLL	DAH	YLL	DAH	YLL	DAH	
HIV/AIDS	7.6%	41.6%	3.7%	32.0%	4.8%	41.1%	
Malaria	11.2%	14.3%	4.8%	9.6%	0.0%	2.2%	
Tuberculosis	3.1%	3.3%	3.5%	6.6%	1.0%	7.0%	
Maternal, newborn, and child health	37.8% 20.7%	17.1 % 0.2%	32.1%	23.7%	8,2% 66.3%	70% 2%	
Noncommunicable diseases Other	19.7%	23.5%	34.0% 21.9%	1.0%	20.8%	39.8%	

## Cardio-Vascular Diseases during Life Course A Model for Obstetric Syndromes

Not to see what nobody has seen, but to think what nobody has thought what everybody sees (Schopenhauer)

Obstetric syndromes unmask preceding risks, predict modifiable health risks of mother & offspring. (Barker /reverse Barker)

Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?



Seeming vs. genuine reality (Saul Bellow)



Gustav Klimt, 1902 Belvedere Vienna

## (Epi)genetic Impact on the Offspring

**Programming in vulnerable periods** 

Gender-specific transgenerational programming



Modified acc. to : Gluckman et al. NEJM 2008 ; 359:61; Gabory et al. Biol Sex Differences 2013; 4:5

Egyptian, ca. 1500 BC, Eg.Museum Berlin

## I Cardiovascular Diseases (Infarction, Stroke)



- 31% of all deaths in the US.
- Increasing rates for women between 35 and 44 years.
- Increasing rates hypertension/ mortality early adulthood.
- Ca.75% of patients with infarction/stroke have RR > 140/90.
- In 15 years mortality due to RR increased by 39%.
- If only 10% of hypertensive women (US) would get early treatment: 14.000 deaths/year in US would be prevented.

Mozaffarian D et al. Circulation 2016, 133(4):e38-e360. Ford ES. Circulation 2011, 123(16):1737-44

## **Cardiovascular Disease after Risk Pregnancies**

Forest Plots of studies: a) CVD (general) b) CVD (ischemic) c) Stroke Heida et al. Eur.J Prevent Cardiol 2016; 23:1863-79 Is this communicated?

#### **Pre-eclampsia**

#### Fetal growth restriction

#### **Preterm Birth**



## Different Conditions of Pre-eclampsia lead to Early Maternal CV Mortality Health risks depend on the reproductive experience



Norsk Epidemiologi 2015; 25 (1-2): 53-62

Registry based perinatal epidemiology: The importance of sibling and generation data

Rolv Skjærven

Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway E-mail: rolv.skjarven@uib.mo



Women with PE have a 6-fold increase of ESRD, but not their siblings or children





#### De Roo et al., 2018, in press, provided by R. Skjaerven

Vikse et al. Clin J Ann Soc Nephol 2012;7:1819-26

## **Maternal Preeclampsia**



Many patients with PE have features not consistent with the placental origin hypothesis. Uterine Doppler reflects general maternal CV status.



#### **Doppler a.ophthalmica predicts Pre-eclampsia**

Kane et al. Ophthalmic artery Doppler analysis: a window into the cerebrovasculature of women with PE. UOG 2017: 48; 15-21

## Link between Biomedical and Epidemiological Data?

AOGS ACTA Obstetricia et Gynecologica

Scandinavica

AOGS REVIEW ARTICLE

Acta Obstet Gynecol Scand. 2015;94(8):820-32.

Angiogenic biomarkers in pregnancy: defining maternal and fetal health

LENE G. RASMUSSEN<sup>1,2</sup>, JACOB A. LYKKE<sup>2,3,4</sup> & ANNE C. STAFF<sup>1,5</sup>

**Dysregulated angiogenic proteins** (PGF, sFlit-1) associated with PE/placental dysfunction, also dysregulated in CVD and DM targeting women who may benefit from prevention programs.





Deficient remodelling? Deficient cardiac performance?

Diastolic dysfunction LV concentric remodelling, Pericard perfusion Impaired contractility

Thilaganathan: Perspectives, UOG 2017

## Pre-eclampsia and Risk for Child / Later Adult Risk increase at 20 years for...

## Is this communicated?

#### & birth factors: & social risks: & health risks @20y:

#### Hypertension aOR: 6.25 (1.96 -19.96) aOR: 6.63 (1.17- 37.57) aOR: 6.74 (1.25 - 36.29)

When I Grow Up, I'm Going to Weigh 300 Lbs. Help!

Overweight/Obesity aOR 1.68 (1.18 - 2.39) aOR 1.62 (1.05 - 2.52) aOR 1.59 (1.02 - 2.48)

### These health risks persist or even increase with age. *Krantz et al. Pregnancy hypertension 2015;5(1):92*





## Preterm Birth and Risk for NCDs as Child/ Adult

### Prematurity is equally associated with epigenetic mechanisms

- Microalbuminuria at young adulthood.
- Altered glucose tolerance/ insulin résistance.
- Lung, behaviour, bone mineral density affected.
- Hypertension at the age of 20 years (arterial stiffness)



The early environment has long-lasting effects on gene expression when DNA imprinting is most active, and thus contributes to risk modifications for a wide range of NCDs. *Simeoni et al. Early Hum Dev* 2014;90:23-4

Fetuses exposed to cytokines: Re-programming of immune system, gest. age at birth is negatively correlated with infant's insulin resistance. *Wang et al. JAMA 2014, 311:587-596* 



Valerie A Luyclox\*, Norberto Perico\*, Marco Somaschini, Dario Manfelotto, Herbert Valensise, Irene Cetin, Umberto Simeoni, Karel Allegaert, Bjorn Egil Vikse, Eric A Steegers, Dwomoa Adu, Giovanni Montini, Giuseppe Remuzzi, Barry M Brenner, far the writing group of the Low Birth Weight and Nephron Number Working Group†

Luyckx et al. Lancet 2017; 22; 390:424-48



**I Metabolic Diseases** 

(Obesity, Diabetes, Hyperlipidemia)



Female(+18) Obesity

- (WHO, BMI>30), 2016 Ca. 65% of women (US) overweight or obese 41.5% obese.
- **Definition Metabolic Syndrome (WHO):**
- The Diabetes Prevention Program (DPP): Diabetes care 2002, 25(12):2165-2171
- BMI > 30 kg/m<sup>2</sup>, RR>140/90, proteinuria, high TG und HDL.
- Women with PE: High Insulin resistance/dyslipidemia p.p.
- Each criterion increases risk of PE

TRANSSITION Disease/DAI **Disability-Adjusted Life-Years** (in Millions, globally)

**Deaths (in Millions, globally)** The GBD 2015 Obesity Collaborators.







## **Epigenetics and Genetics in Families with Obesity**

#### Genetic / Epigenetic Variance (>12000 twins up to 19 years)







Margerita Sikorskaia 2001 Angela King Gallery New Orleans



2001 Angela King Gallery New Orleans

Obesogens: an emerging threat to public health Amanda S. Janesick, PhD; Bruce Blumberg, PhD

Janesick & Blumberg: AJOG 2016;214:559-65

## Programming fetal CVS (early ultrasound)

Ultrasound Obstet Gynecol 2016; 47: 433-442 Published online 14 March 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.14841

Maternal obesity affects fetal myocardial function as early as in the first trimester





Ingul et al. UOG 2016;47:433-42

### **Pregnancy Complications & Later Disease of the Child**

Gestational diabetes+LGA Metabolic syndrome at 11 years (increased insulin resistance and obesity) OR 10.4 (1.5-74.4)

Cumulative risk function for metabolic syndrome stratified for AGA and LGA: Only in children of mothers with GDM: 3.6-x fold risk of LGA children by 11y.

Boney et al. Pediatrics. 2005 ;115(3):e290-6.

### **Obesity and programming of early death**

Even after adjustment for age, gender, socioeconomic status, BW or BMI of child is the life expectancy significantly shorter. This implies:

Weight reduction before and reduced weight increase during pregnancy should help in reducing the detremental effects.

Reynolds et al. BMJ 2013;347: 34539





## What can we do? New Approach for Parenthood

**WHO Commission on Ending Childhood Obesity** 

**Problems higher in hard-to-access members of society.** (low socioeconomic status, educational attainment, migrants, displaced).



Jean Eugene Bunand 1890, Art Museum Basel

#### Commited societies/policy makers must give this priority (DAH).

www.who.int/entity/end-childhood-obesity/fi nal-report/en/acc. 14-02-2017 Ma et al. Lancet Diabetes Endocrinol 2016; 4: 1037–49 Godfrey et al. Lancet Diabetes Endocrinol 2017; 5: 53–64 Hanson & Gluckmann. Lancet Diab Endicrin 2016;4: 966-7

## Helping Doctors and Patients Make Sense of Health Statistics

Gerd Gigerenzer,<sup>1,2</sup> Wolfgang Gaissmaier,<sup>1,2</sup> Elke Kurz-Milcke,<sup>1,2</sup> Lisa M. Schwartz,<sup>3</sup> and Steven Woloshin<sup>3</sup>

#### UK Committee on Safety of Medicines (CSM) (1995):

"The third-generation oral contraceptive pills increased the risk of potentially life-threatening blood clots in the legs or lungs twofold - that is, by 100%".

= relative risk

= absolute risk

#### 100% = 1 vs. 2/7000

"The risk of thrombosis increases with the third generation pill from 1 to 2 out of 7,000 women."

Risk of thrombosis





### **How to explain Evidence to Lay Pregnant Women?**

#### (Cochrane bias tools 2012 & Prior tools BJOG 2017/ PRISMA tools & AMSTAR- tools) NO 18:Prevention by diet/exercise/both/psychology



#### Prevention by diet/exercise/both/psychology

GH	Event	ercise Total	C	ontrol	Odds Ratio	OR	95%-C	Weight	D Study Prior = no	Events Tot	e C al Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight
Prior = no Barakat 2016 Renaut2 2014 Random effects mode Heterogeneity: <i>I</i> <sup>2</sup> = 61%,	1 μ τ <sup>2</sup> = 0.276	0 382 9 125 <b>507</b> 12, p = 0	31 12	383 134 517		0.31 0.79 0.47	[0. 15; 0. 63 [0.32; 1.94 [0.19; 1.19]	30.0% 24.4% 54.4%	Bigaeffs2 2013 Bruno 2017 Petrella 2014 Renault1 2014 Thornton 2009 Zhang 2015 Random effects moo Heterogeneity J <sup>2</sup> = 74%	18 2 1 1 7 10 17 10 17 0 10 17 0 10 17 0	10 10 19 13 13 7 10 12 16 21 18 6 14 0.01	62 28 - 134 116 29 - <b>432</b>		2.38 0.11 0.09 0.58 0.43 0.10 <b>0.39</b>	[0.99, 5.72] [0.02, 0.52] [0.01, 0.82] [0.22, 1.52] [0.19, 0.95] [0.01, 1.85] [0.14; 1.08]	8.5% 5.3% 13.6% 15.5% 3.2% 60.6%
Gamaes 2016 Wang, Chen 2017 Random effects mode Heterogenety: <i>I</i> <sup>2</sup> = 56%.	1 τ <sup>2</sup> = 0.400	3 38 9 112 150 10, p = 0 657	9 22	36 - 114 150		0.26 0.85 0.55	[0.06; 1.04 [0.43; 1.68 [0.18; 1.71]	13.9% 31.7% 45.6%	Prior = yes Dodd 2014 Vinter 2014 Random effects mod Heterogeneity $r^2$ = 0%,	157  108  23  15  157  108  157  108  157  108  157  108  157  157  157  157  157  157  157  157	0 147 0 28 0	1073 154 1227	-	1.07 0.81 <b>1.03</b>	[0.84; 1.37] [0.45; 1.49] [ <b>0.82; 1.29]</b>	21.5% 17.9% <b>39.4%</b>
			Effect of	Fav Exercise	ours Exercise Favours C on Gestational Hypertensi	ontrol on and Pree	clampsia		Treasing generally 7 - 11 a	, t = 0.0140, p -		0.0 Favours	1 0.1 1 1 Intervention Favou	0 100 rs Control		
Study	Evente	Diet	Co	ntrol	Odde Patio	OP	65%	1 Weight	Be	E haviour Chang	flect of Die	ontrol	cise Gestational Hyp	ertension and P	reeclampsia	
Study Prior = no McCarthy 2016 Random effects model Heterogeneity: not applicab	Events 17	Diet Total I 187 187	Co Events 19	ntrol Total 184 184	Odds Ratio	0R 0.87 0.87	95%-4 [0.44; 1.7 [0.44; 1.7	CI Weight 3] 73.9% 3] 73.9%	Be Study Prior = no Bogaerts1 2013 Random effects mot Heterogeneix; not apple	haviour Chang Events Tot 10 i sel i cable	iffect of Dis le C al Events '6 10	ontrol Total 63 - 63 -	Odds Ratio	OR 0.80 0.80	95%-CI [0.31; 2.07] [0.31; 2.07]	Weight 15.2% 15.2%
Study Prior = no McCarthy 2016 Randore effects model Heterogeneity: not applicab Prior = yes Thompson 2016 Randore effects model Heterogeneity: not applicab Randore effects model	Events 17 Ne 3	Diet Total I 187 187 28 28 28 28	Co Events 19 0	ntrol Total 184 184 27 27 27	Odds Ratio	0R 0.87 0.87 - 7.55 ( 7.55 ( 1.53	95%-4 [0.44; 1.7 [0.44; 1.7; 0.37; 153.4; 1.37; 153.4;	Cl Weight 3] 73.9% 3] 73.9% 3] 73.9% 2] 26.1% 2] 26.1% 1] 100.0%	Be Study Prior = no Bogaensi 2013 Random effects moto Heterogenety, not apple Prior = yes Kernely 2018 Poston 2014 Random effects moto	haviour Chang Events Tot sel 10 cable 22 2i 27 77 5 5 5 5 5 5 5 5	e C al Events 6 10 6 10 76 15 3 27 6 6 9	ontrol Total 63 - 275 752 58 - 1095	Odds Ratio	OR - 0.80 - 0.80 - 0.80 - 0.80 - 1.54 1.00 0.85 1.14	95%-CI 0.31; 2.07] 0.31; 2.07	Weight 15.2% 15.2% 29.7% 46.3% 8.8% 84.8%

#### Nutritional counselling in pregnancy to OC HARDING CENTER FOR prevent gestational diabetes

Numbers for pregnant women who either did or did not receive nutritional counselling before their blood sugar level was tested (alucose tolerance test).

	Out of every 100 women without nutritional counselling	Out of every 100 women with nutritional counselling
Benefits		
How many women developed gestational diabetes?	13	13*
How many women developed high blood pressure due to pregnancy?	10	3
How many women had high blood pressure and protein in their urine (pre-eclampsia)?	8	8
Harms		
How many women had a caesarean section?	30	30
How many women had injuries to their genital area (perineal tears)?	1	1

The studies showed no difference, but there was a slight trend towards fewer cases of gestational diabetes through nutritional counselling.
Short summary: Nutritional counselling cannot prevent gestational diabetes and pre-eclampsia. About 3 out of every 100 women with nutritional counselling devolged high blood pressure due to pregnancy. This means that 7 out of every 100 women can be prevented from developing high blood pressure due to pregnancy. Nutritional counselling din to lead to an increase in cases:rean sections or injuries to the perimetil teas.
Source: Tieu et al. Cochrane Database Syst Rev 2017(1):CD006674.
Last update: January 208
Netronal State St

Nutritional counselling in pregnancy to prevent gestational diabetes

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How many women had a caesarean delivery?
How many women had injuries to their genital area (perineal tears)?

#### BISK LITERACY

.........

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0000000000

Numbers for pregnant women who either did or did not receive nutritional counselling before their blood sugar level was tested (glucose tolerance test).



Several icon arrays In progress... Based on Tieu et al, Cochrane Rev 2017

## **Statistics vs. Heuristics**

The weakness of complicated, the power of simple solutions





My Neighbours: Dog Uriel: Less can be more ! Calculations do not work in a World of Uncertainty. Benjamin Franklin: Weigh Pros and Cons.

**Complex situations require simple solutions. Remember Jeffrey Skiles / Canadian geeze hit engines.** 

Do doctors know the evidence, take the time, have no conflict of interest nor defensive decision making? Patients have to decide!

#### **Pregnancy Complications & Childhood Obesity: BMI-independent?** Individual participant data meta-analysis of 160 757 mother-offspring pairs Golab et al. Lancet Child Adolesc Health 2018; 2, 812-21

**GDM** 

GHD

PE



Childhood overweight acc.to complications and maternal pre-pregnancy BMI



Childhood overweight acc.to complications/ adjusted for different factors & BMI

### How to Translate Science to Patients? Show regional data to patients/ colleagues and polititians Make Science visible & understandable Use 1st Trimester to Induce Health Literacy!





Interventions to prevent adverse fetal programming due to maternal obesity during pregnancy

Peter W Nathanielsz, Stephen P Ford, Nathan M Long, Claudia C Vega, Luis A Reyes-Castro, and Elena Zambrano





C CEX MO MOEX

Nathanielsz et al. Nutrition reviews. 2013;71 Suppl 1:S78-87

## **Breastfeeding: Impact on Mothers/Offspring**

- Low activation HPA Axis
- Lower blood pressure
- Mobilization of fat tissue still recognizable after 7 years
- Lower rate of T-2 Diabetes also in case of GDM
- Prolactin increases pancreas mass
- Lower rates of infection and cancer (ovary, breast)

Ip et al. 2007(153):1-186. Bartick et al. : Obstetrics & Gynecology 2013, 122(1):111-19.

- Biologic signals for cell growth/differentiation
- Improved lung function (also in preterms)
- Lower rates of infection, asthma, dermatitis
- Lower rates of obesity and diabetes
- Lower rates of SID and leukemia

Johnston et al. Pediatrics 2012, 129 (3):e 827-841

Suboptimal Breastfeeding costs \$17.4 billions/year (US)

Margerita Sikorskaia 2002 Angela King Gallery New Orleans





## **Recommendations for postnatal follow up**



related to metabolic & cardiovascuar diseases



SBAR3: Situation, Background, Assessment, Recommendation Bridging the diabetes postpartum gap SBAR3 for obstetric-primary care transition Utilize reminder system.

Women with a history of PE benefit from CV assessment 1-2 years pp to identify need targ. intervention.

Noelke et al. AJOG 2017; 217: 314-21 DIAMIND RCT: Diabet Med 2015

Heida et al. Eur.J Prevent Cardiol 2016; 23:1863-79

Optimizing gestational	postpartum car diabetes mellit	e for the patient v us	Review Program formation and program count of the program formation and p			
Societies (US)	Time line / test	Interventions	Offspring	Pregnancy Disorder	Recommendation (NL)	
Am Diab. Ass	6-12 wk.pp. 75g OGTT, Retest 1-2 y	Methformin Int.lifestyle	Follow for obesity glucose tolerance Breast feeding!	1st wk pp. preeclampsia	Treatment hypertension (if necessary)	
Endocrine Society	24-72 h pp Fast. glucose	Couselling lifestyle Cave hypogylcemia	Child BW / GDM should become part permanent record, breast feeding !	6 wk pp to 49 years in women with PE, with SGA, sPB, rec. Miscarriage, POI	Optimizing lifestyle, inform about modifiable CV risks Treatment hypertension (if necessary)	
ACOG	6-12 wk pp. Fasting pl. glucose, 75g OGTT, retest	Refer to preventive therapy		At age of 50 years	Full CV risk profile Acc. to Dutch guidelines	

### **Maternal Obesity + Mental Health/Neurodevelopment**

ORIGINAL ARTICLE Wilden et al. Matern Child Nutr. 2018;14:e12481.

Prepregnancy overweight and obesity are associated with impaired child neurodevelopment

## Maternal obesity and excessive GWG are –modifiable- risk factors for adverse child cognitive development.

The effects are gender dependent and reflected by the brain transcriptome. Dietary change in pregnancy results in more dysregulated pathways in male than in female brains (p<0.001).

Hinkle et al. J epidemiol and community health. 2016;70(7):696-703. Edlow et al. AJOG 2016;Suppl.1:S 125; 206.

Maternal obesity is associated with lower verbal recognition (Peabody) scores in mid-childhood and with lower academic scores at 6, 10 and 14 years. *Wilden et al. Matern Child Nutr. 2018;14:e12481* 

Life-time trajectories are programmed and determine with genetics and life challenges the ultimate health. If maternal obesity is associated with psychosocial stress, brain function throughout life course is more affected. *Pugh et al. Journal of epidemiology and community health.* 2016;70(6):534-40. O'Donnell & Meaney. *Am J Psychiatr* 2017;174(4):319-28.

## **III Fetal Origins of Later Mental Health**

Pre-and postnatal nurturing care is essential to enable children to become citizens with adequate creative intellectual and emotional skills Main Outcome 5 to 18 months is at cognitive and temperamental levels 250 mil children (43%) <5 y at risk of not reaching their developmental potential



Modified acc. to Donnell & Meany, A.J Psychiatry 2017; 174:320-8

## **FGR and Mental Health**

Low BW associated with "hostility", e.g. a rival cynic personality with mistrust and negative affections in adult life.

Rikkonen et al. Psychosomatic medicine. 2008;70(3):306-13

Mothers with famine during conception/ 1st trimester have children at risk for schizophrenia, depression, inadequate stress responsiveness. *Roseboom et al. Maturitas.* 2011;70(2):141-5

Gest. age & BW explain only 1% of variance in child behavior when maternal mental health/ socioeconomic status were considered ! Still, the effects of maternal care or socioeconomic status are greater among children with LBW versus normal BW in the offspring. O'Donnell et al. Dev & Psychopath 2014;26:393-403, Buss et al. J Neuroscience 2007;27:2592-5

**Effect of breastfeeding on cognition greater in LBW / NBW children.** *Blair C et al. Development and psychopathology. 200E2;14(2):311-32* 

The "metaplasticity" extends: Effect of socioeconomic status on longterm memory greater among children exposed to antenatal glucocorticoid treatment.

Grant et al. Psychol Science. 2015;26(7):1054-62





## "Allostatic Load"

Allostatic = Physiologic consequences to increased neuroendocrine reaction to chronic stress (McEwen and Stellar, 1993).

## Transgenerational Transmission of stress



Cortisol, Epinephrine, Reactions to inflammatory processes HOMEOSTASIS (?)



Cytokins: block 11ß-HSD2 / Cortisol – Cortisone (not active) HSD11B2 prevents the fetus of the effect of Cortosol

"Two-hit hypothesis": Induced stress combined with injection of IL-18 causes preterm births up to the 3rd generation. *Olson et al. Int. J. Mol. Sci. 2015, 16, 29856–74* 

### "Environmental Enrichment" (EE)-a late Antagonist

**Transgenerational stress leads to reduced axon density and GCreceptors (CNS), disturbed motor coordination and anxious behavior** 



C= No transgenerational stress, TPS=Transgenerational stress, MPS=multigenerational stress

EE reduces neuro-morphologic consequences of transgenerational stress Stress markers are detectable:miR-182 expression + brain-derived neurotrophic factor (BDNF) neurotrophic-38(NT-3) regulation.

## **Early Origin of Adult Capabilities?**



Variations in maternal care alter transgenerational gene expression mediating CRF synthesis/release and thus stress reactivity, cognition in the offspring.

Cerebral oxytocin receptors regulate maternal behavior. Licking-grooming mothers have increased oxytocin receptors and altered sensitivity to estrogens and dopamine.

# Why do we not screen for maternal psychological disorders, stress, anxieties?



Nurturing parents spent regular time with their children from prenatal stage onwards up to 3 y. After talking: 58% positive, 26% negative attitudes, After music: 90-100% only positive attitudes. Manrique et al. 1992; in: Blum (ED) Human Bonding, Leonardo Publ

**ORIGINAL ARTICLE** 

"Need for interventional studies on the impact of music in the perinatal period: results of a pilot study on women's preferences and review of the literature"



Birgit Arabin<sup>1</sup> & Michael Jahn<sup>2</sup>

Maternal Emotional Well-being / Stress and Mental Health Maternal stress accounts for 17% of the variance cognitive abilities of children (PTB for1-2%) ! Bergman et al. J Am Acad Child and Adolescent Psychiatry. 2007;46(11):1454-63

Children of mothers with high anxiety scores have a 2-fold increase in behavioral problems equating to a doubling of prevalence of childhood psychiatric disorders. *O'Donnell & Meaney. Am J Psychiatry.* 2017;174(4):319-28.

Chronic stress predispose children for changes in brain connectivity leading to autism, ADHD, addiction, depression or schizophrenia. *Grant et al. Psychological science. 2015;26(7):1054-62* 

Mediators connecting stressed mothers with fetuses are cortisol, catecholamines, reactive oxygen species, cytokines, serotonin/tryptophan, maternal microbiota. *Rakers et al. Neuroscience and biobehavioral reviews. 2017. Epub 2017/02/27* 

The consequences may not be apparent until a critical age when exposed to other insults. Adequate preventive programs should not be too late.

## Lifestyle, Stress, IUGR

Multivariate analysis, 48 variables related to work load (n = 7892,1989-91)

East Germany<1990</th>West Germany<1990</th>1 child and ...Unfriendly environmentIrregular/night shiftsCompetition, no recognitionRisk for LBW< 5 centile</td>after correction with BMI, smoking, parity, ageaOR=2.3; 95% CI: 1.20 - 4.25aOR=2.2; 95% CI: 1.05 - 4.64



#### Berwick et al JAMA. 2012;307:1513-6

## **Therapeutic Options of Enrichment in Humans**



Prenatal influences fine-tune postnatal sound preference for the mother's voice/ lullabies suggesting prenatal sound discrimination. James et al. UOG 2002; 20:3431-38

Fetuses & newborns react to musical speech rhythms and orientate to the social world this relationship is musical (babies do not yet understand words).

De Caspar AJ, Fifer WP. Science 1980; 208: 1174-76



**From Destruction to Creation:** 

The intrauterine Sound A Symphony for the Baby (9)



## **IV Urogynecologic Diseases**



### Pelvic disease during pregnancy/ post partum & later disease

#### 2-3 days fter vaginal birth / 6 weeks and 12 months p.p.

- Vaginal examination for levator avulsion
- Perineal ultrasound: bladder neck, puborectalis position at rest, during PFMC supine position
- if possible before/ after vaginal birth 6 weeks post partum
- US & POPQ (pelvic organ prolapse quantification)
- Validated pelvic floor (PF) questionnaire
- Two days pp. 35% of women have a prolapse grade II, One year pp. 29% have symptoms of prolapse, 22% of incontinance. Impact of parity decreases with aging.

The Norwegian Epicont Study (N= 27900) Rortveit et al. 2001

#### **Prevalence of pelvic disease**









#### Dietz et al. UOG 2017; 49:252-6

## What can Obstetricians do During/After Pregnancy?

### **The Fourth Trimester & Inter-Pregnancy Care**

ACOG Committee Opinion No.736: Optimizing Postpartum Care. Obstet Gynecol 2018; 131:949-951

Postpartum care should become an ongoing process and tailored as well as communicated to each woman's individual needs...

- within 3 weeks p.p., followed with ongoing care as needed,
- at or < 12 weeks p.p. comprehensive visits including a full assessment of emotional well-being; infant care and feeding; contraception; chronic disease management; health maintenance.

Weight loss of 4.5 kg (>4000 mothers) causes decreased rates of GDM by 40% next pregnancy.

Jacobsen et al. J Thromb Haemost 2008; 6: 905-912

J Matern Fetal Neonatal Med 2018; 22:1-8 The JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2018 https://doi.org/10.001/1476/7058.2018.1450383



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REVIEW ARTICLE

How to improve health literacy to reduce short- and long-term consequences of maternal obesity?

Birgit Arabin<sup>a,b</sup>, Nina Timmesfeld<sup>c</sup>, Kathrin Noever<sup>a,b</sup>, Susann Behnam<sup>a,b</sup>, Christin Ellermann<sup>d</sup> and Mirjam A. Jenny<sup>d</sup>

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## **Vicious Circles: Undernutrition/Stress**

#### Hypertension, Diabetes, Metabolic Syndrome, Neurologic Disease



## **Vicious Circles: Overnutrition**

ıy A Cresswell , Oona M R Campbell, Mary J De Silva, Véronique Filippi

#### Hypertension, Obesity, Diabetes, Metabolic Syndrome, Cognitive Impairment



# Take-Home QuestionsEra 3 for Medicine and Health CareDo you dare to care?

D. Berwick JAMA 2016; 315:1329-30



- Would you shift to another strategy even by giving up prerogatives?
- Would you promote earlier/better information, apps, webprograms ?

Jan Vermeer, 1650, Art Gallery Dresden

- Would you share decisions with patients, colleagues, politicians?
- Do you support holistic approaches/ collective intelligence?
- Don' expext awards which usually go to those who want to maintain and not to improve a status quo.

### **Thanks for listening!**





For questions/ comments: Bine.clara.angela@gmail.com