Pre-conceptual and Prenatal Health: Prevention of miscarriage and pregnancy complications

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London, UK 2017
Pre-conception

Do you have to plan to get pregnant?
Optimise Your Health

Full nutritional testing, individualised health report and personalised hair mineral analysis programme.
“Written and telephone follow-ups carried out in 1993 revealed that 327 (89%) of women had become pregnant and 327 children had been born since enrollment. There were no multiple pregnancies. In remarkable contrast to the couples’ previous experience, all their babies (137 males and 190 females) were born healthy and were well developed at birth which occurred from 36 to 41 weeks (mean 38.5 weeks). Average birth weight was 3265g (2368 – 4145). None were malformed and none were transferred to special baby care units. Among 204 couples with infertility problems, 175 (86%) had achieved healthy pregnancies.” (The Journal of Nutritional & Environmental Medicine (1995) 5, pages 205-208)
Outcomes

• 367 Couples enrolled (maternal age 22-45, paternal age 25-59)

• Viable births 89% of couples delivered at average gestational age 38.5 weeks average weight 7#3

• There were no miscarriages, perinatal deaths or malformations. No babies admitted to special care nurseries
Interventions

- Avoid conception for 6 months of intervention and for 6 months following miscarriage or pregnancy for both partners
- Supplementation with folic acid (400mg) and B-complex vitamins, vitamin E, C
- Avoid alcohol, tobacco and street drugs and certain medications
- Treatment of copper/zinc imbalance and iron, magnesium and manganese deficiency
- Evaluate and treat heavy metals (lead, cadmium)
- Test drinking water or filter
- Evaluate and treat genitourinary infections (found in 69% of study group) and “infestations” of parasites
- Other concerns: Electromagnetic radiation
- Diet: avoid refined carbs, tea, coffee and saturated fats preservatives, food colorings and flavouring, organic with emphasis on vegetables and organically grown meats and eggs
- Regular meals avoiding “unsupervised slimming regimes”
- Address food allergy/malabsorption e.g. wheat and dairy
- Work exposures in both partners
A Simple List To Keep In Mind

- Stressors
- Toxins
- Antigens, Allergens, Adverse food reactions
- Inflammation
- Nutrition
- Sleep, Sedentarism
Chemical Intolerance in Primary Care Settings: Prevalence, Comorbidity, and Outcomes

Chemical intolerance occurs in 1 of 5 primary care patients yet is rarely diagnosed by busy practitioners. Symptoms may resolve or improve with the avoidance of salient chemical, dietary (including caffeine and alcohol), and drug triggers.
Doctors unprepared for Toxins

- 2500 MD’s surveyed
- 78% agreed they could reduce toxic exposure
- 50% rarely take a history of exposure
- Less than 20% ask routinely about toxic exposures
- 1/15 have any training in the topic

- They explained that they lack knowledge, didn’t think patient’s could reduce harmful exposure and didn’t want to cause anxiety by bringing it up.

PLoS One June 25, 2014
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0098771
Patient decision making

• Participants struggled to help patients balance concerns about occupational risk with concerns about job loss and economic hardship. In contrast, providers with patients of higher socioeconomic status asked patients to do their own research and take ownership of their own choices.
How big is the problem?
Chemical exposure

- Certain PCB’s, organochlorine pesticides, PFCs, phenols, PBDE’s phthalates, polycyclic aromatic hydrocarbons and perchlorate were detected in 99-10% of pregnant women.
- Median number of detected chemicals by class ranged from 4/12 PFCs to 9/13 phthalates.
- Levels in pregnant women were at or (adjusting for co-variants) increased over general population.

http://dx.doi.org/10.1289/ehp.1002727 [online 14 January 2011]
Laboratory tests uncovered 167 chemical pollutants in blood & urine from nine volunteers, including an average of 53 carcinogens in each person. The people tested do not work with chemicals and do not live near an industrial facility.
Why is weed killer in our bodies?

Friends of the Earth Europe tested urine samples from volunteers in 18 countries across Europe for the weed killer glyphosate. The figures show the % of samples which were found to be positive.

- MALTA 90%
- GERMANY 70%
- POLAND 70%
- NETHERLANDS 63%
- CZECH REPUBLIC 60%
- BELGIUM 55%
- LATVIA 55%
- CYPRUS 50%
- CROATIA 40%
- SPAIN 40%
- FRANCE 30%
- HUNGARY 30%
- AUSTRIA 20%
- GEORGIA 20%
- SWITZERLAND 17%
- BULGARIA 10%
- MACEDONIA 10%

for more info: foeeurope.org
Clearly, we have fouled the pond
“What typically will happen is smart chemists will develop a new product, see that it has useful properties, put it into consumer goods and the chemical then gets disseminated very widely in the marketplace, and typically 10 or 15 or 20 years or more later, scientists begin to realize that this chemical is really quite toxic.”

Philip Landrigan, MD, M.Sc.
Mt Sinai School of Medicine
Prenatal exposure and adult disease

• The research revealed that women exposed to the most DDT before birth were 2.5 to 3.6 times more likely to develop high blood pressure before the age of 50 than those with the lowest prenatal exposure.

https://ehp.niehs.nih.gov/1205921/
What do these chemicals DO to us?
TOXINS

Most are Xenoestrogens
Endocrine Disruptor: “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”

BPA exposure disrupts human egg maturation

Boston - As many as 20 percent of infertile couples in the United States have unexplained reasons for their infertility. Now, new research led by Catherine Racowsky, PhD, director of the Assisted Reproductive Technologies Laboratory at Brigham and Women's Hospital (BWH), shows that exposure to BPA (Bisphenol-A) could be a contributing factor as to why some infertile couples are having difficulty conceiving. The study will be published online on July 31, 2013 in the journal Human Reproduction.

"To our knowledge, this is the first study that has shown that BPA has a direct effect on egg maturation in humans," said Dr. Racowsky. "Because exposure to BPA is so ubiquitous, patients and medical professionals should be aware that BPA may cause a significant disruption to the fundamentals of the human reproductive process and may play a role in unexplained infertility."

The randomized trial examined 352 eggs from 121 consenting patients at a fertility clinic. The eggs, which would have otherwise been discarded, were exposed to varying levels (20 ng/ml, 200 ng/ml and 20 μg/ml) of BPA in a laboratory setting. An egg from each patient was not exposed to BPA and served as the control. Researchers then examined the eggs and found that exposure to BPA caused:

- A decrease in the percentage of eggs that matured.
- An increase in the percentage of eggs that degenerated.
- An increase in the percentage of eggs that underwent spontaneous activation, the abnormal process when an egg acts as though it has been fertilized, even though...
Women have additional risks
Pregnancy effects

- Dilution by weight gain and increased plasma volume
- Transfer to the foetus
- Transfer into the milk
Foetuses and children are more vulnerable

- Children also have lower levels of some chemical-binding proteins, according to the Environmental Working Group (EWG), which allows more of a chemical to reach their organs, while systems that detoxify and excrete chemicals in adults are not fully developed

http://www.ewg.org/research/body-burden-pollution-newborns
Figure 3. Number of chemicals detected by chemical class in U.S. pregnant women, NHANES subsample B [metals, cotinine, organochlorine (OC) pesticides, phthalates, brominated flame retardants (PBDEs), and PAHs], 2003–2004 (n = 54; each vertical bar is one study participant).
BODY BURDEN: THE POLLUTION IN NEWBORNS

The Pollution in Newborns

A BENCHMARK INVESTIGATION OF INDUSTRIAL CHEMICALS, POLLUTANTS AND PESTICIDES IN UMBILICAL CORD BLOOD

Environmental Working Group, July 14, 2005
“Mixing cocktails”

• Studies show that exposure to multiple chemicals that act on the same adverse outcome can have a greater effect than exposure to an individual chemical. This has been recognised by the National Academy of Sciences (NAS), which recommends that future efforts accounting for risks from multiple chemical exposures combine effects from chemicals acting on the same adverse health outcome.

Birth defects and Autism

Chronic Low-level Toxicity

• Biologic effects of many toxicants are not linear—very low doses can have profound physiologic effects

• Chemical sensitivity varies considerably, depending on species, life stages, biochemical individuality and synergistic effects from multiple toxicants
...and this is just the beginning!

- Birth defects
- Childhood asthma
- Gastrointestinal disorders
- Neurodevelopmental disorders
  - ADD
  - ADHD
  - Autism spectrum
  - Learning disorders
  - Anxiety/depression
Assessing Chronic Toxicity: History

- Exposome history
  - Home & work environment
  - Diet & Lifestyle
- Medical Symptoms questionnaire (MSQ)
- Toxicity Exposure Questionnaires (TEQ)
- History of reactions to drugs, chemicals, odors, etc.
Treating toxic environment pre-conceptually

Step 1 Minimise exposure
Nutrition Can Modulate The Toxicity of Environmental Pollutants

- A convincing body of research indicates that nutrition is a modulator of vulnerability to environmental insults; thus, it is timely to consider nutrition as a vital component of human risk assessment.
- Nutrition may serve as either an agonist or an antagonist (e.g., high-fat foods or foods rich in antioxidants, respectively) of the health impacts associated with exposure to environmental pollutants.
Minimizing Toxic Exposure

- Avoid smoke from cigarettes or wood fires
- Minimize exposure to automotive exhaust
- Eat fresh foods (not canned or wrapped in plastic)
- Emphasize organically grown foods, especially meat & dairy
- Drink purified or spring water
Based on urine samples over an 8 day period, “BPA & DEHP exposures were substantially reduced when participants’ diets were restricted to food with limited packaging.”

(Silent Spring Institute)
Based on urine samples, “The median total dimethyl [phosphate] metabolite concentration was approximately 6X higher for children with conventional diets than for children with organic diets. The dose estimates suggest that consumption of organic fruits, vegetables and juice can reduce children’s exposure levels from above to below the US EPA’s current guidelines.”
In a group of 23 elementary school-age children, “We found that the median urinary concentrations of the specific metabolites for malathion & chlorpyrifos decreased to non-detect levels immediately after the introduction of organic diets & remained non-detectable until the conventional diets were re-introduced.

Dietary Exposure to Organophosphorus Pesticides

Chensheng Lu, Kathryn Toepel, Rene Irish, Richard A. Fenske, Dana B. Barr, and Roberto Bravo

doi:10.1289/ehp.8418 (available at http://dx.doi.org/)
Online 1 September 2005

In conclusion, we were able to demonstrate than an organic diet provides a dramatic & immediate effect against exposures to organophosphorus pesticides that are commonly used in agricultural production. We also concluded that these children were most likely exposed to these OP pesticides exclusively through their diet.”
Minimizing Toxic Exposure

• Eat generous amounts of sea vegetables, green algae, &/or spirulina
• Judicious fish & shellfish consumption
  – Highest mercury concentration in large predatory fish: tuna (steaks), swordfish, shark, king mackerel, tilefish
  – Oysters “downstream” from wastewater
• Avoid mercury amalgam fillings
• Don’t take acetaminophen (paracetamol) for a hangover
Minimizing Toxic Exposure

- Avoid synthetic pesticides/ herbicides and toxic cleaning agents
- Use nontoxic building materials & carpets
- Clean indoor air with plants and ionizers
- Use “natural” cosmetics, shampoos, nail polish & fragrances
Treating toxic environment pre-conceptually

Step 2: Improve Liver Detoxification
DETOXIFICATION/BIOTRANSFORMATION

• A constantly active process
• ATP (energy) dependent
• Highly nutrient dependent
• Polymorphic: marked inter-individual variability
Imbalanced Detoxification

Non-Polar Xenobiotic → Phase I CYP P450 → Reactive Intermediate → Damage to DNA, RNA, Proteins → Phase II Conjugation → Inert Water-Soluble Metabolite
CYP450 Induction

- Phase I induction can decrease blood levels of a drug or hormone
- Commonly induced enzymes: CYP 1A; CYP1B1; CYP2E1
- Occurs by upregulation of transcription
- Imbalanced induction (phase 1 > phase 2), may result in pathological detoxification
- Result is increased risk of cancer and inflammatory disease
CYP450 Inhibitors

- Cimetidine: multiple enzymes
- Antifungal medications
- SSRIs (fluoxetine, paroxetine, fluvoxamine)
- Grapefruit juice (furanocoumarins): CYP3A4
- Berberine: CYP2D6, CYP3A4, CYP2C9
- Green tea catechins: CYP1A1, 1A2, 1B1
- Garlic: CYP2E1
- Star fruit juice: CYP2A6, CYP1A2, CYP3A4
Phase II Enzymes: Conjugating Reagents

- Glucuronic acid (uridine-diphosphate-glucuronosyltransferases: UGT)
- Sulfate (sulfonyltransferases: SULT)
- Glutathione (gluthathione-S-transferases: GST)
- Acetate (N-acetylmethyltransferases: NAT)
- Amino acids (taurine, glycine, glutamine)
- Methyl group (methyltransferases; e.g. COMT)
N-acetylcysteine

- Rate limiting precursor for endogenous production of glutathione
- Used in high doses for treatment of acetaminophen hepatotoxicity
- Potent antioxidant
- Essential nutrient in detoxification regimens
- Typical dose: 500-3000 mg daily
Optimizing Bowel Health

- For allergic or vulnerable individuals:
  - Oligoantigenic diets
  - Gluten-free if applicable
  - Low lectin diets (paleolithic)
  - Nutrient dense functional foods
  - Bowel rehabilitation program (5R)
Treating toxic environment pre-conceptually

Step 3: Improve Gut function
Enhancing Excretion of Toxins

- Activated Charcoal
- Bile acid sequestrants (cholestyramine)
- Olestra (sucrose polyesters)
- D-glucaric acid
Beta-glucuronidase & Elimination of Toxins

- Toxins
  - Carcinogens
  - Tumor Promoters
  - Steroid Hormones
  - Sterols

Conjugation (Glucuronosyl Transferase)

Made Harmless

Deconjugation

Deconjugation by (β-Glucuronidase)

D-Glucarate

Excretion from Body
D-glucaric acid (Calcium or Potassium D-glucarate)

- Found in cruciferous vegetables, citrus, apples, apricots, bean sprouts & cherries
- Inhibits beta-glucuronidase
- Regulates blood levels of bile acids & steroid hormones
- Protects against cancer of breast, prostate, lung, colon, bladder, & skin (animal studies)
- Dosage: 500-1000 mg tid
Utilizing the 5R Bowel Program for Detoxification

- Remove pathogens
- Replace enzymes & hydrochloric acid
- Repair damaged intestinal mucosa
- Re-inoculate with
  - Prebiotics (arabinogalactan, inulin)
  - Probiotics
- Rebalance
Agents That Repair Intestinal Mucosa

- Probiotics
- Plant fibers
- L-glutamine
  - 5-15 grams daily
- Arabinogalactan (Western Larch bark)
  - 2-10 grams daily
Agents That Repair Intestinal Mucosa

- Aloe vera mucopolysaccharides
  - 100-500 mg daily
- Licorice root (deglycyrrhizinated)
  - 500-2000 mg daily
- Bovine colostrum
  - 5-15 grams daily
Intestinal bacteria play a major role in biotransformation and detoxification and may explain some of the differences in xenobiotic metabolism between individuals.

Mol Nutr Food Res. 2013 Jan;57(1):84-99
Effect of increasing Caesarean delivery on offspring microbiome

Treating toxic environment pre-conceptually

Step 4: Utilise other detox systems (skin)
Enhancing Excretion: Removal of Toxins

- Exercise = sweat
- Saunas = sweat
- Polysaccharides from algae & seaweeds
  - Chlorella pyrenoidosa
  - Fucus (bladderwrack)
  - Laminaria (kelp)
- NAC & alpha lipoic acid
- Systemic chelating agents
  - DMSA: oral
  - DMPS: IV or oral
Clearly, the first prenatal visit is not the time to address this issue!
Pre-conception Program

- Must remove toxic exposures to the extent possible
- Flush the system with clean water and regular bowel habits
- Oxygenate with exercise (sweating helps too)
- Encourage detoxification pathways (Phase 1 and Phase 2)
- Address nutritional deficiencies
- (Mobilise heavy metals)
Low Libido

- Complex issue
- 75% supratentorial, 25% hormonal
- What turns women on?
- How’s her relationship?
- How stressed is she? i.e., adrenals
- Self-care? Passion in life?
- How does she feel about her body?
- What issues around abuse are there?
- What cultural messages are you dealing with?
Miscarriage
Miscarriage

• Stress-Is this why giving progesterone works?
• Toxins-a growing problem that is treatable
• Allergens/Antegens-why treating food sensitivity and gluten sensitivity make sense, autoimmunity and miscarriage
• Infections-Genitourinary, Stealth infections, chronic sinus and gum disease
• Nutrition-Improving pre-conceptual nutrition
• Sleep, Sedentarism
Stress and Miscarriage

Luteal phase defect
Cortisol Steal
Gluten sensitivity
Eating disorders
Psychosocial characteristics
Caffeine
Pre-pregnancy coffee consumption at levels ≥4 servings/day is associated with increased risk of SAB, particularly at weeks 8-19.
Autoimmune and inflammatory causes of miscarriage

Celiac disease
Anti-phospholipid antibodies
AITD
Inflammatory-Infection, Endometriosis, other
Infectious causes of miscarriage

Genitourinary-Chlamydia, Mycoplasma, GC, Listeria, Zika?

Other viral and bacterial infections
Yeast (Oral Fluconazole)
Nutritional causes of miscarriage

- Methylation support
- Imbalance in Omega-3/Omega 6
- Zinc deficiency?
- Antioxidants-mixed results
- Adequate cholesterol
Trace elements is closely associated with fetal growth and development during pregnancy. Deficiency can lead to adverse pregnancy outcomes. Therefore, we should have a reasonable diet, replenish trace elements, therefore reducing the occurrence of adverse pregnancy outcomes.
There are significant differences between the two groups regarding consumed servings/day of vegetables, bread and cereal, meat, poultry, fish, eggs, beans, fats, oils and dairy products (P=0.012, P<0.001, P=0.004, P<0.001, P=0.019, respectively). There are significant differences between the two groups in all micronutrient including folic acid, iron, vitamin C, vitamin B6, vitamin B12 and zinc (P<0.001).
Treatment

• Improved outcomes when infertility treatments were preceded by weight loss and lifestyle changes\textsuperscript{1}

• Nutrients: Dependent on food sources, focus on B-vitamins, minerals, omega-3 FA’s (Watch Vitamin A levels)

• Treat infections prior to conception, consider probiotics

• 5R program for the gut
  – Remove
  – Replace
  – Re-populate
  – Repair
  – Rebalance

Clock genes (PER2) turn off during implantation to “synchronize the maternal and fetal circadian cycles and are involved in the endometrium’s “selection” of the embryo.
The risks to the pregnancy do not end in the first trimester....
“The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed programming.” - Godfrey and Barker
Having Faith
by Sandra Steingraber
Placement and Loss of methyl groups allows genes to be read: Epigenetics
Epigenetics
Development as an ‘epigenetic’ process...

“Development is an epigenetic process by which, each developing organism plays an active role in its own construction. This dynamic process is affected by systems that are present during embryonic and foetal life to acquire information about the nature of the environment and to use this information to guide development.” E.P. Davis
What is Prenatal Programming?

“The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed programming.” - Godfrey and Barker


Epigenetics: Changes in gene function or expression that continue beyond the life of a single cell or individual to its progeny without altering the genetic material
Development Origins of Health and Disease
Examples of Prenatal Programming

- IUGR increases risk of later diabetes, hypertension
- Prematurity increases risk of later obesity diabetes, hypertension and cardiovascular disease
- Overweight at birth increases the risk of obesity, diabetes, infertility and cancer
Methylation

5, methyl THF

Methionine

ATP

P_i+PP_i

S-adenosylmethionine (SAM)

Methionine synthetase

S-adenosyl homocysteine (SAH)

H_2O

Adenosine

THF

Methyl Cobalamin

S-adenosylmethionine (SAM)

Methionine synthetase

S-adenosyl homocysteine (SAH)

H_2O

Adenosine

THF

Methyl Cobalamin

S-adenosylmethionine (SAM)

Methionine synthetase

S-adenosyl homocysteine (SAH)

H_2O

Adenosine

THF

Methyl Cobalamin

S-adenosylmethionine (SAM)

Methionine synthetase

S-adenosyl homocysteine (SAH)

H_2O

Adenosine

THF
Cysteine + Glycine + Glutamate

Glutathione

- reduced

GSSG (spent glutathione)

Extracellular
it is essential that plasma folate be kept above a critical level (7.0 nmol/L; 1) because plasma folate is the main determinant of transplacental folate delivery to the fetus.
Folate related pregnancy complications:
Placental abruption
Pre-eclampsia
Spontaneous abortion and stillbirth
Threatened abortion/vaginal bleeding
Premature rupture of membranes
IUGR/prematurity
Foetal anomalies
Cysteine + Glycine + Glutamate

\[ \text{Glutathione} \]

- \( \text{GSSG (spent glutathione)} \)

Extracellular

Protein CH₃

Phospholipid CH₃

DNA CH₃
Male Infertility

• Incidence of C677T 19% in infertile males vs 10% in control
• Sperm counts increased in men supplemented with folic acid and zinc (response only in wild type C677T)

Am J Clin Nutr May 2006 vol. 83 no. 5 993-1016
What do you get from your mother?
Embryonic demethylation and remethylation
DNA Methylation

- Methylation of the DNA is critical for genome stability
- Evidence suggests that methylation is also essential for controlling the replication of massive amounts of viral DNA (45%) within the human genome
- Methylation-induced processes also play a pivotal role in repairing DNA damaged by oxidative stress or toxin exposure

Key steps in fertilization, early embryogenesis and implantation

Fertilization
- Penetration through zona
- Acrosome reaction
- Fusion of plasma membranes
- Sperm nucleus entering egg cytoplasm
- Zona pellucida

Prezygote
- Polar bodies
- Female pronucleus
- Male pronucleus

2 cell zygote
- Blastomere

8 cell zygote
- Zona pellucida

Implanted blastocyst
- Decidual tissue
- Enlarged maternal blood vessels
- Differentiating syncytiotrophoblast
- Differentiating inner cell mass
- Fibrin coagulum
- Healing uterine epithelium

Preimplantation blastocyst
- Blastocyst cavity
- Inner cell mass
- Trophectoderm

Morula
Paternal de-methylation

Active demethylation within hours of fertilization
Maternal de-methylation

Passive replication dependent demethylation after 2-cell stage
Demethylation and Remethylation
Paternal Imprinting=placenta
Maternal imprinting=embryo

- Androgenetic
  - 46XX from father
  - All alleles paternally imprinted
  - Molar pregnancy

- Gynogentic
  - 46XX from mother
  - All alleles maternally imprinted
  - Dermoid/cystic teratoma
Parental Investment Theory

Maternally imprinted
• Are involved in growth restriction (Igf-2, PEG-3)
• When demethylated produce larger litters of smaller offspring

Paternally imprinted
• Are involved in growth stimulation (Igf-2R, Gnas)
• When demethylated produce fewer larger/stronger offspring

Evolvability Model

• Organisms that can imprint (methylate DNA) have more flexibility in response to changing environment
• The individual can carry genes, such as those promoting growth without any phenotypic expression of them

Cysteine + Glycine + Glutamate

Glutathione - reduced GSSG (spent glutathione)

Extracellular Cystathionine βSynthase

Methionine synthetase

S-adenosylmethionine (SAM)

Methionine

CH₃

DNA methylation

CH₃-acceptor (Methylation)

S-adenosyl homocysteine (SAH)

H₂O

Adenosine

Homocysteine

Cystathionine βSynthase

GSTM1

5, methyl THE

Cobalamin

Hg detox

DNA methylation
A 19% reduction in NTD birth prevalence occurred following folic acid fortification of the US food supply.

Down Syndrome
Fate of fertilised ovum

Figure 3.1 The fate of a fertilized human ovum
Homocysteine and Folate Levels as Risk Factors for Recurrent Early Pregnancy Loss

WILLIANNE L. D. M. NELEN, MD, HENK J. BLOM, PhD, ERIC A. P. STEEGERS, PhD, MARTIN DEN HEIJER, PhD, CHRIS M. G. THOMAS, PhD, AND TOM K. A. B. ESRES, PhD

Objective: To estimate the relative risk of recurrent early pregnancy loss for different total plasma homocysteine and serum folate concentrations.

Methods: In a case-control study, we measured homocysteine (fasting and afterload), folate (serum and red cells), pyridoxal 5'-phosphate, and cobalamin concentrations in 133 women who had at least two consecutive spontaneous early pregnancy losses each and compared concentrations with those of 104 healthy controls.

Results: Women with recurrent early pregnancy losses had significantly lower serum folate concentrations than controls, whereas the other measurements were similar to those of controls. Elevated homocysteine, fasting greater than 18.3 \( \mu \text{mol/L} \) and afterload greater than 61.5 \( \mu \text{mol/L} \), was a risk factor for recurrent early pregnancy loss, with odds ratios (ORs) and 95% confidence intervals (95% CIs) of 3.6 (1.2, 12.7) and 2.7 (0.9, 8.8) in the group with recurrent miscarriages: 6.4 (1.9, 24.3) and 4.3 (1.2, 7.7) in primary aborters, and 4.2 (1.3, 13.6) and 3.4 (1.1, 12.3) in those with three or more miscarriages. The ORs (95% CIs) in the same study group were 2.3 (0.9, 6.2) and 1.9 (0.9, 4.6), respectively.

After observing the induction of fetal death by the folic acid antagonist 4-aminoazopyridoxal in 1982, Thierens et al. suggested that spontaneous abortions might be caused by folic acid deficiency. The first studies that investigated the relationship between folic acid deficiency and early pregnancy loss were published in the following decades. The consistent conclusion was that disturbed formine glutamic acid excretion tests or low folate concentrations might identify women predisposed to spontaneous abortion. More recent reports did not find lower folate concentrations, but they investigated folate concentrations in those women after, not during, their pregnancies. In several reports, other sensitive markers of dysfunctional folate metabolism appeared to be related to recurrent early pregnancy loss, one of which was elevated plasma total homocysteine concentration.

Homocysteine is a demethylated derivative of methionine, and B vitamins are needed for its efficient me-

“Elevated homocysteine and reduced serum folate concentrations were risk factors for recurrent spontaneous early pregnancy losses.”

Hyperhomocysteinemia is a risk factor in obstetrical complications such as pre-eclampsia, 'hemolysis, elevated liver enzymes, low platelet' (HELLP)-syndrome and placental insufficiency. The aim of our study was to investigate the alterations of homocysteine catabolism in these patients in relation to serum B-vitamins and renal function. Maternal fasting serum from pre-eclampsia (n=24), HELLP (n=20) and placental insufficiency (n=25) patients at the time of diagnosis and pregnant controls (n=34) was analyzed for homocysteine and its metabolites cystathionine and methylmalonic acid, the vitamins B6, B12 and folate, renal and additional parameters. Cystathionine, a parameter of homocysteine catabolism, was significantly increased in pre-eclampsia and HELLP compared with controls (mean concentrations: 343, 324, 248, 227 nmol/l; p=0.001). Homocysteine, folic acid, vitamin B6 and methylmalonic acid, however, did not differ significantly between groups. The main determinants of cystathionine are cystatin C and vitamin B6, whereas the main determinants of homocysteine are folate and uric acid. The strongest dependency of cystathionine on vitamin B6 was observed in pre-eclampsia and HELLP syndrome, probably by oxidative stress. Therefore, the demand for vitamin B6 is increased in these patients.
Folate recommendations

- Pre-conceptually: multivitamin with folate rich diet (fortified grains, spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges)

- Pre-conceptual 1mg in high risk groups (prior anomalies, Sikhs, epileptics, DM2, obesity: at least 3 months to 10-12 weeks 5mg folic acid then reduce to 1mg until end of lactation

Multiple Conditions

Methylation/transulfuration pathways

Vitamin deficiency

Genetics
SAD
Maternal Stress as a Programmer
The “Foetal Origins” Hypothesis

“...proposes that alterations in foetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life.” --Barker, DJP

How is the placenta involved in this developmental adaptation?
Feed forward transmission of programming

- Stressed mother
  - Reprogrammed fetus
    - Anxiety/Depression, Obese mother
      - Postpartum depression, PIH, premature delivery
        - Depression, Obesity, chronic disease
          - Shortened lifespan
Maternal Stress as a Programmer

• Maternal depression during pregnancy is associated with childhood and later adult depression
• Maternal pre-eclampsia associated with adult obesity, diabetes and hypertension
• Nutritional stress is associated with HPA programming
“...hormones are environment-dependent organizers of the neuroendocrine system.”

What do you get from your father?
What does the placenta do?

- Acts as an oxygen transfer device keeping the maternal and foetal circulations largely separate
- Acts as a transfer device for foetal nutrients
- Detoxifying and excretory organ
- Acts as an endocrine organ
Physiology: placental 11β-HSD-2 converts glucocorticoids to inert forms thus excluding active maternal steroids from the fetal compartment.
Maternal/Placental/Foetal Endocrinology of Stress

- Placental CRF
- Placental $11\beta$HSD-2
- Foetal control of labor
- Placental and Maternal control of labor
Cortisol response in infants exposed to prenatal Betamethasone.
Effect of Stress on PTL

Stress during the first trimester of pregnancy significantly predicts shorter gestational length. Adapted from Glynn et al. (2001)
Cortisol Effects

- Preterm labor
- Foetal brain development
- Depression in mother and infant
“... these [hormones] may alter the development of specific foetal tissues during sensitive periods of development or may lead to long-lasting changes in hormone secretion or tissue hormone sensitivity.”

On a scale of 1-10, How stressed are you right now?
Maternal-foetal Interaction

Repeated loud noise

Mediated by the placenta

CRF, 11\beta HSD-2

Increased maternal cortisol

IUGR, delayed motor, social, verbal skills

...and is there any thing we can do to change it?
Maternal-foetal Interaction

Increased neonatal handling

| sensitivity of HPA
| stress reactivity
| hippocampal GR,MR |
Cortisol Level in Plasma

Plasma cortisol measured every 20 minutes in normal subject

Pre-eclampsia

Disordered placentation

Decreased placental blood flow

Methylation defects

Genetic defects in methylation

Maternal stress

Upregulation of placental CRF

Increased foetal cortisol

Hypertension Diabetes, Obesity, ASCVD, ADD, etc.

Maternal Malnutrition

Methylation defects

Decreased foetal nutrition

Pre-eclampsia

IUGR

Altered maturation and brain development

Premature labor
A Lost Opportunity

“The prenatal and neonatal time periods however may be windows of special susceptibility for programming later disease. If this is true, this short period of time in a person’s life offers profound opportunities for prevention of later disease.” -Godfrey
What can we do to change the programming

- Prevent methylation defects with adequate methylation support
- Provide nutrient dense food
- Avoid low and high protein diets during pregnancy
- Address diabetes/insulin control
What can we do to change the programming

• Avoid maternal anxiety
• Avoid maternal depression with B-vitamin, EPA and Vitamin D supplementation
• Avoid unnecessary prenatal steroids
What can we do to change the programming

• Encourage maternal care of infant
• Avoid or screen surrogate mothering
• Adequate postpartum support for mothers
• Encourage paternal involvement and prevent paternal abuse of mother and baby
• Improve environment in Neo ICU’s
Nutritional approach for pregnancy: KISS

- Small frequent feedings
- 5-8 servings of colorful vegetables
- Good fat not bad fat
- Protein/carbohydrate balance
Post-partum Depression

- Remember that for 9 months nutrients go preferentially to the foetus
- Omega-3 FA
- B-vitamins
- Adequate protein
- Sleep
- Lower anxiety
- Progesterone
Traumatic Early Events and Elevated Cortisol


- Early-life adversity, such as physical or sexual abuse during childhood, results in long-lasting changes in the corticotropin-releasing factor-mediated stress response and a greatly increased risk of depression in genetically predisposed persons.
- Evidence from preclinical, epidemiologic, and clinical studies has convincingly demonstrated that stressful or traumatic events occurring in early life significantly increase the risk for depression and other psychiatric illnesses in adulthood.
Advice to new mothers (and fathers):

• Sleep when the baby sleeps
• Eat whenever you can (babies have radar for when you put a hot meal in front of yourself)
• You are her only mother/father so whatever you do, she will think it is right... (until she turns 13)
• Good enough...is good enough!
• If you love them enough they survive your worst parenting flaws.
Philosophical Pondering

• If the foetus is programmed for the environment it is coming into...
• If the reason for this is preservation of the species...
• ...why do we assume nature has made a mistake preparing children for a stressful environment and in cutting short our lives when the environment has become so damaged that it cannot support all the people who are here?
Now Breathe!