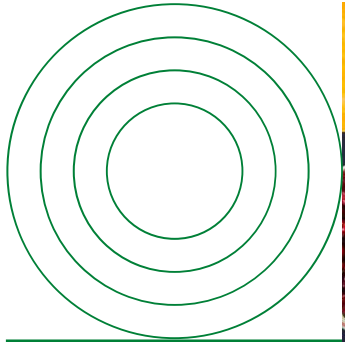




Creating Resilience: Toxins, Immunity & the Genetic Ecosystem Across the Lifespan

Leslie Stone MD, FP/OB Fellow, IFMCP

Emily Stone Rydbom, BCHN, CNP



“The immune system in early life is functionally distinct & responsive to programming that persists into adulthood.”

Seth Thomas Scanlon

**Tolerogenic-
Critical
Timing**

**Anti-
inflammatory**

T Regulatory Cells

T Helper Cells – *Balanced* TH1/TH2

Interleukin: IL6 & IL10

Epigenetic factors

Tolerogenic Microbiome: Less diverse & Bifidobacterium/Lactobacillus dominance

Nutrient mediators/co-factors

**Early
Activation-
Disruption**

**Pro-
Inflammatory**

Cytotoxic T Cells, CD8

Imbalanced TH1/TH2

↓ Interferon Gamma, IL6, IL10 response & ↑ IL4

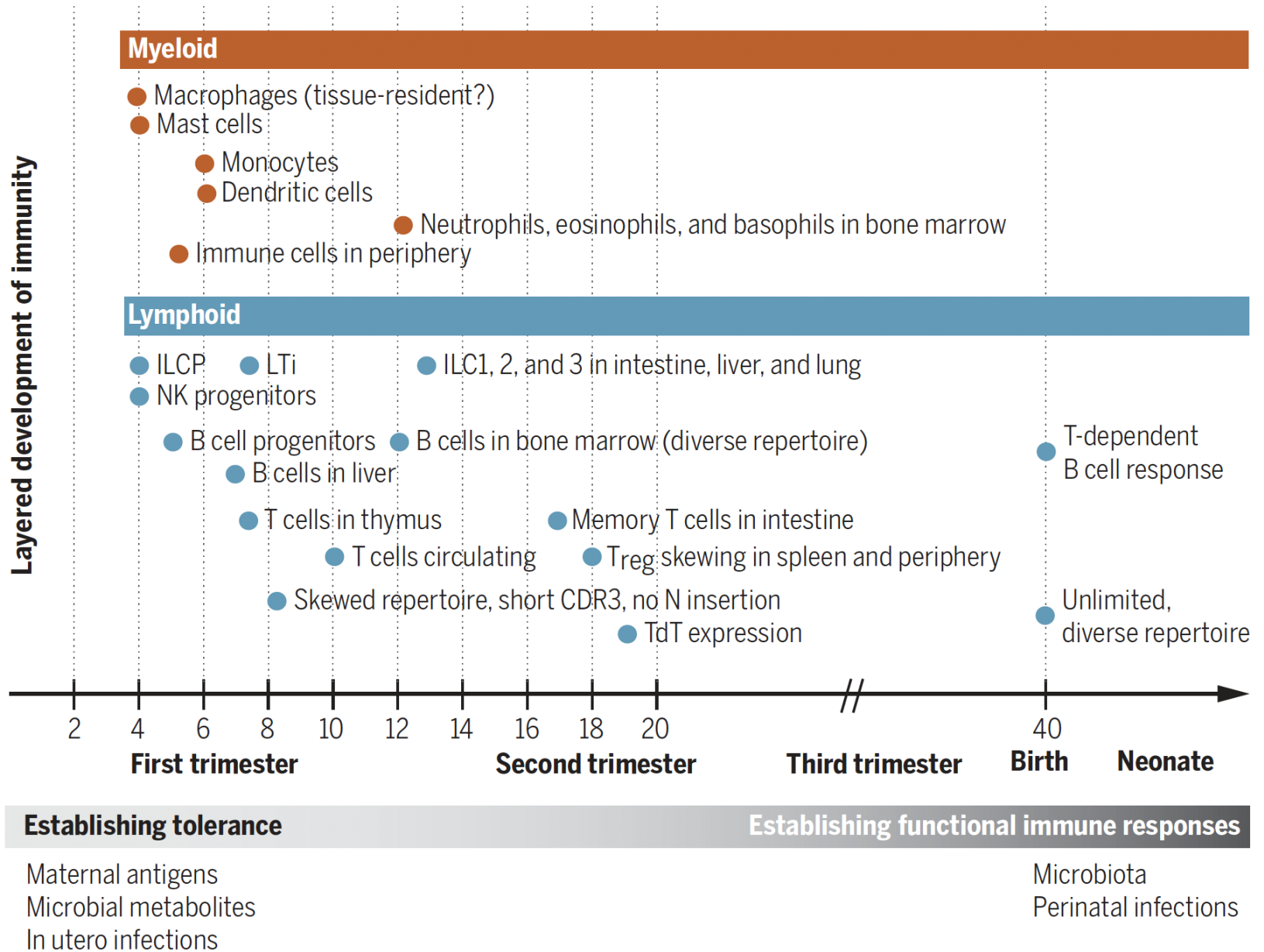
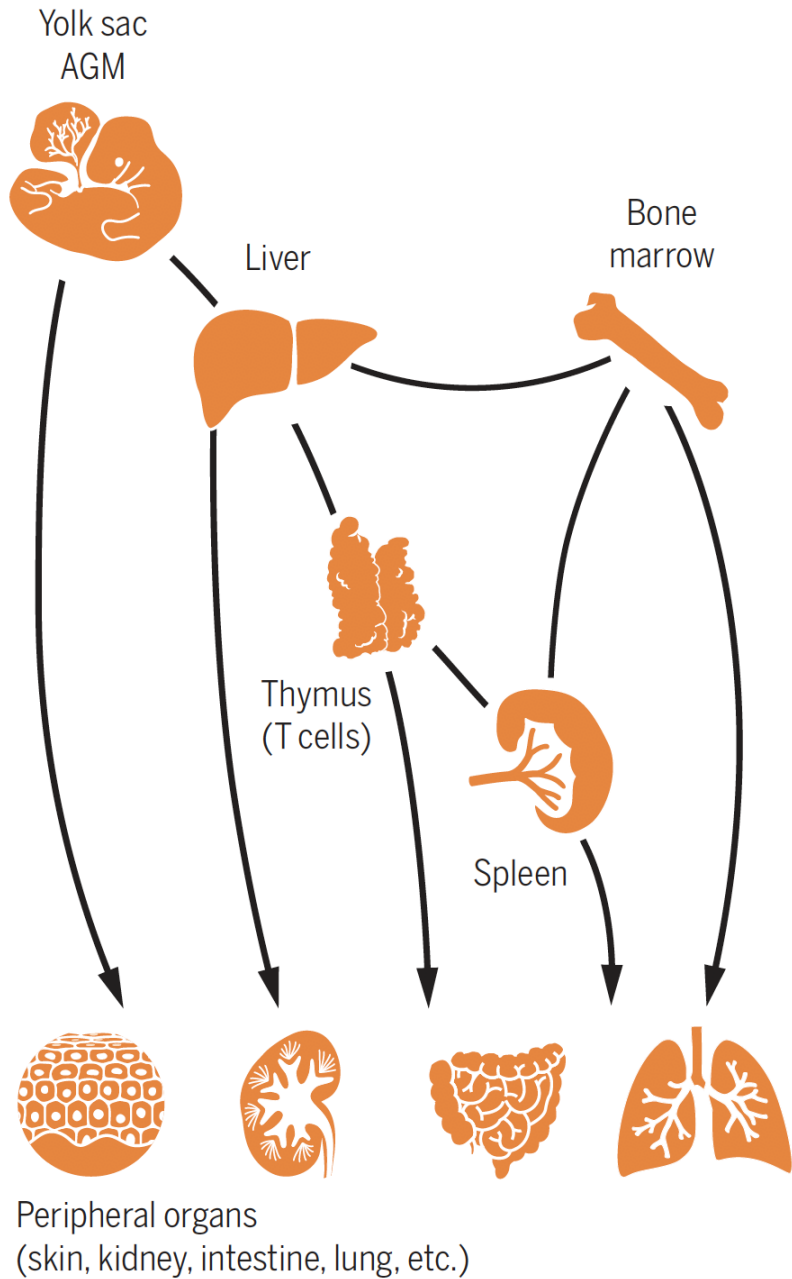
↓ Expression DNA Methylation-ACSL3

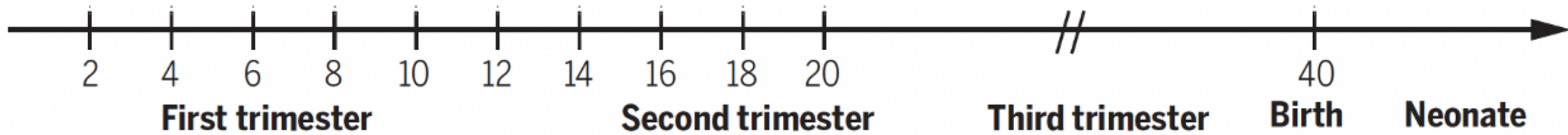
↑ Maternal IgE antibodies

↓ Thymic volume

Microbiome: More diverse & eneterobacteraceae, enterococcus and opportunistic pathogens

Developmental timeline of the human immune system



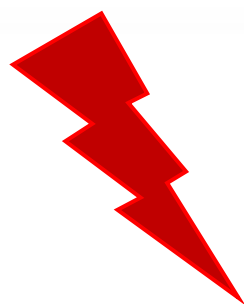
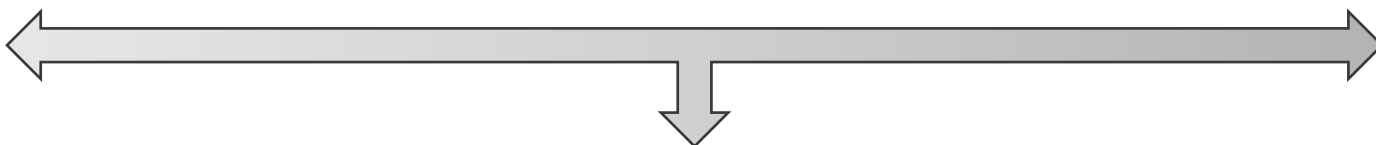


Establishing tolerance

Maternal antigens
Microbial metabolites
In utero infections

Establishing functional immune responses

Microbiota
Perinatal infections



Thymic Disruption mediated by PTB
(decreased Tregs in cord blood)

Betamethasone and Tobacco
(apoptosis of DP thymocytes)

Vit A Deficiency
(decreased dendritic cells)

Cadmium Exposure
(decreased macrophages and Th1-type cytokines),

Prenatal Stress
(clonal expansion of Th2)

Airborne Particulates
(decreased IFNG and increased IL4)

Shared Mediators of Immune Dysfunction & PTB/SGA

Psychosocial Stress

Increases pro-inflammatory cytokines associated with increased F1 allergy risk¹

Anxiety

Decreases Interferon gamma (IFNG) and increases IL4 responder frequencies in infants²

Maternal IgE

Increased maternal serum IgE associated with increased serum IgE in children at 1 year³

Maternal Allergy

Alters T cell subsets in cord blood and increases risk of atopy during first 2 years of life⁴

Xenobiotic Exposure

PAH & traffic particulates increases childhood asthma associated with DNA methylation 5''CpG island ACSL3⁵

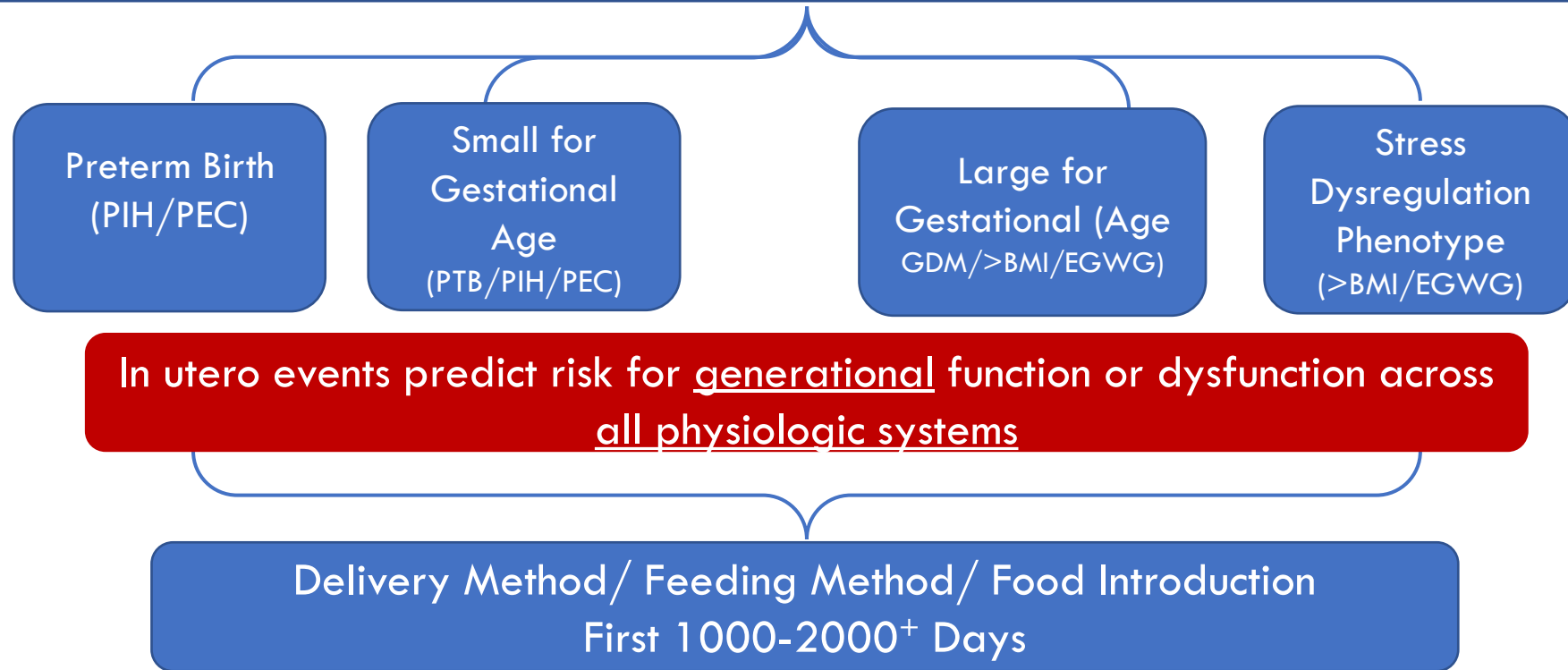
Maternal Infections

SARS CoV
MERS CoV
SARS CoV-2 (COVID-19)
Flu (H1NI)
Zika
BV

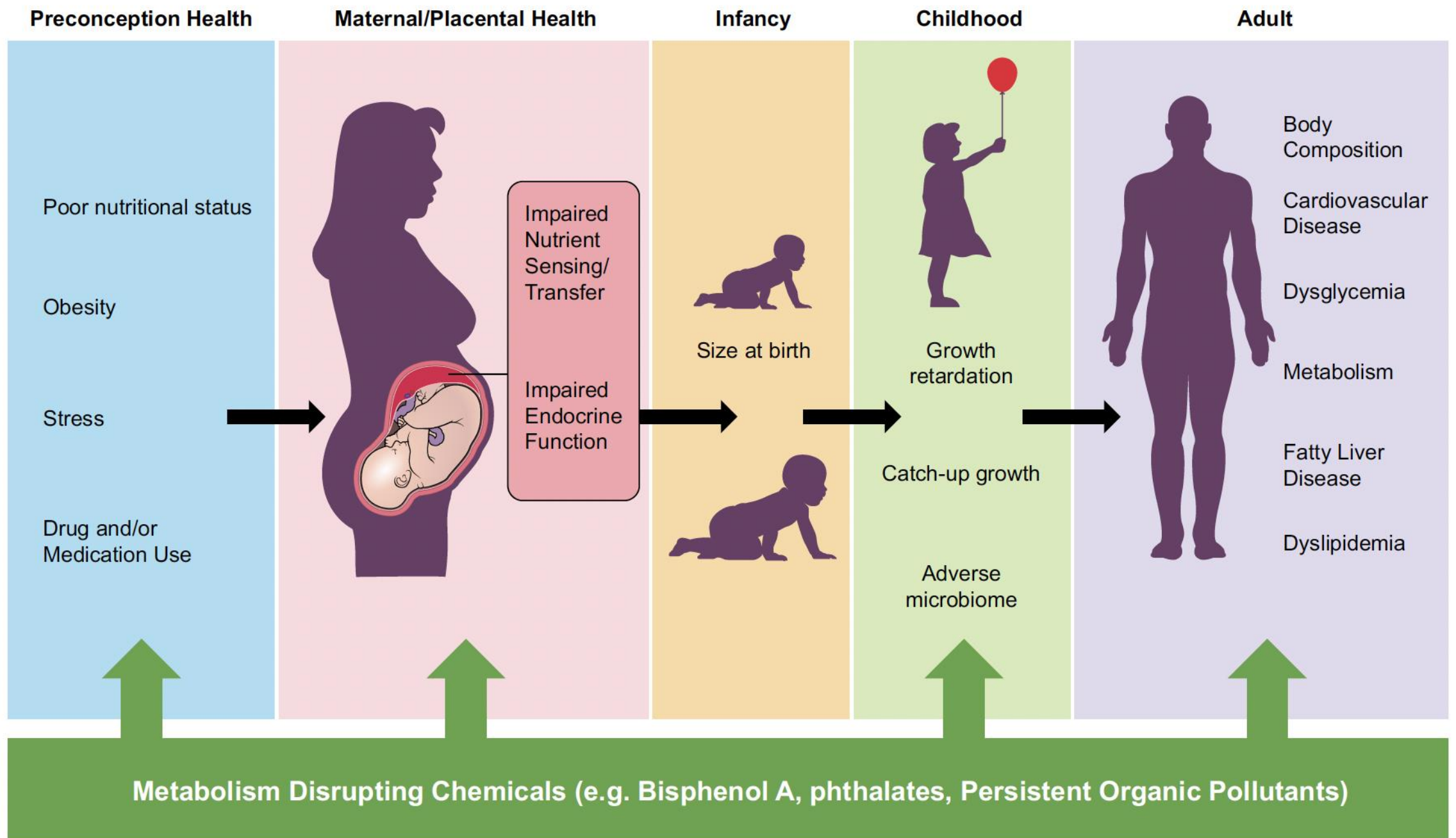
Preterm Birth

<32 weeks and SGA results in decreased thymic volume and decreased IL6 & IL10 response to LPS in cord blood⁶

Developmental Programming of Health & Disease (DOHaD)

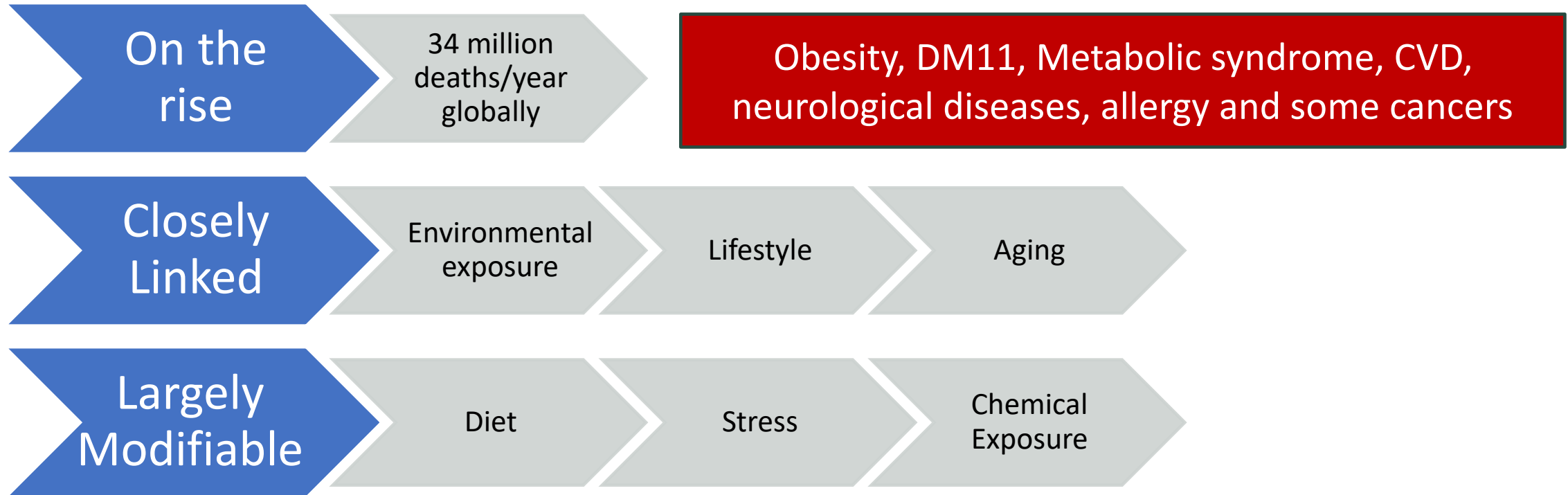


PIH: Pregnancy Induced Hypertension/PEC: Preeclampsia/PTB: Preterm Birth/GDM: Gestational Diabetes Mellitus/BMI: Body Mass Index/EGWG: Excessive Gestational Weight Gain




Image, Figure 1 from Hoffman, et al, *Physiol. Rev* 101: 739-795, 2021

Non-Communicable Diseases (NCDs)



Starting preimplantation (preconception) throughout a lifetime



Most Risk is not hard-wired, but epigenetically modifiable!





Human Genome

**6 billion nucleotides –
99.6% identical**

**“SNPs” –
27 million nucleotides**

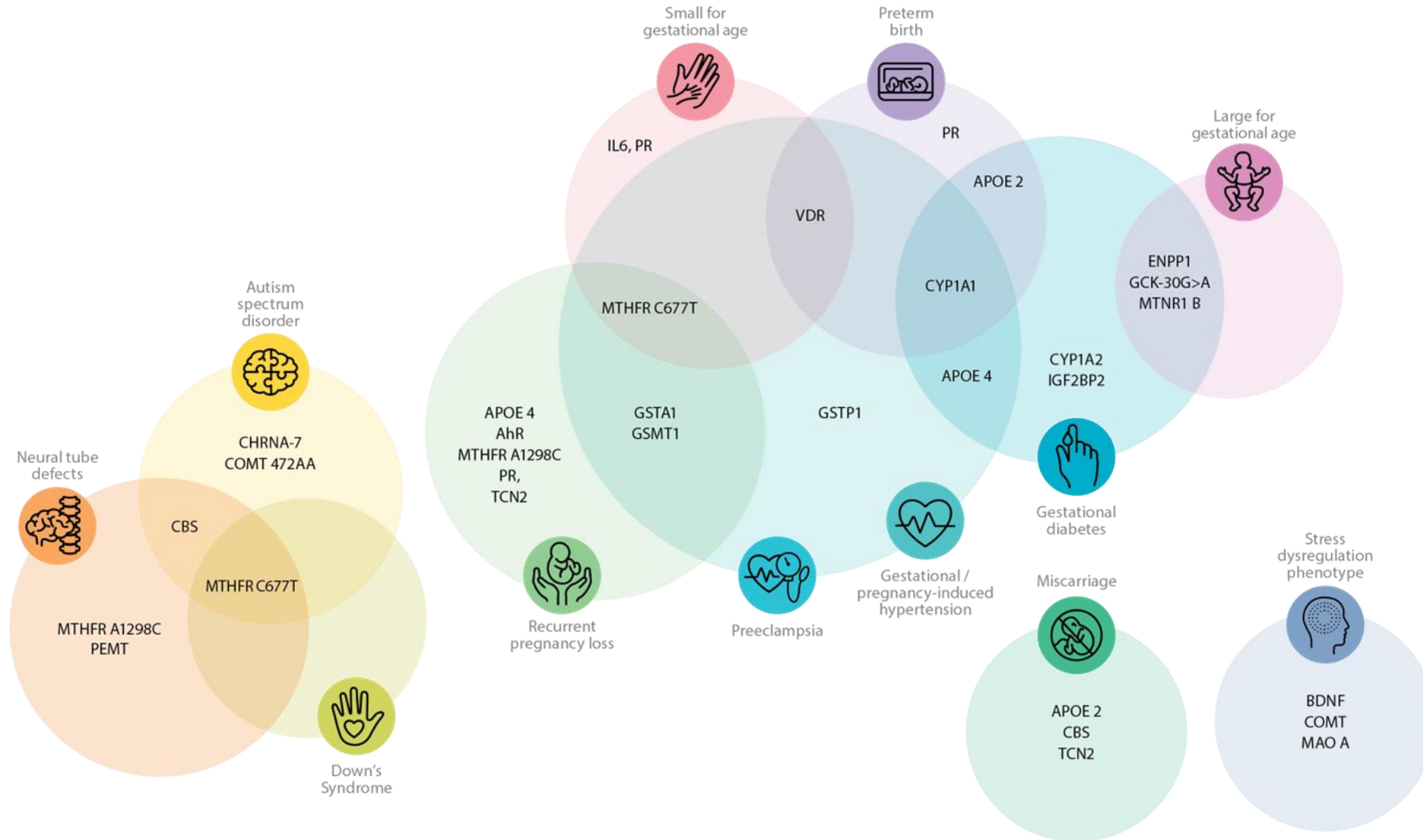
*Diversity and
Adaptability*

Phenotype Condition Outcome



- ✓ **Overlap**
- ✓ **Interplay**
- ✓ **Opportunity**

42 SNPs in 27 genes involved in 11 key biological processes associated with preconception outcomes, as well as maternal and fetal health outcomes.



Nutrients Commonly Depleted/Inadequate Intake

...with **Developmental Consequences**

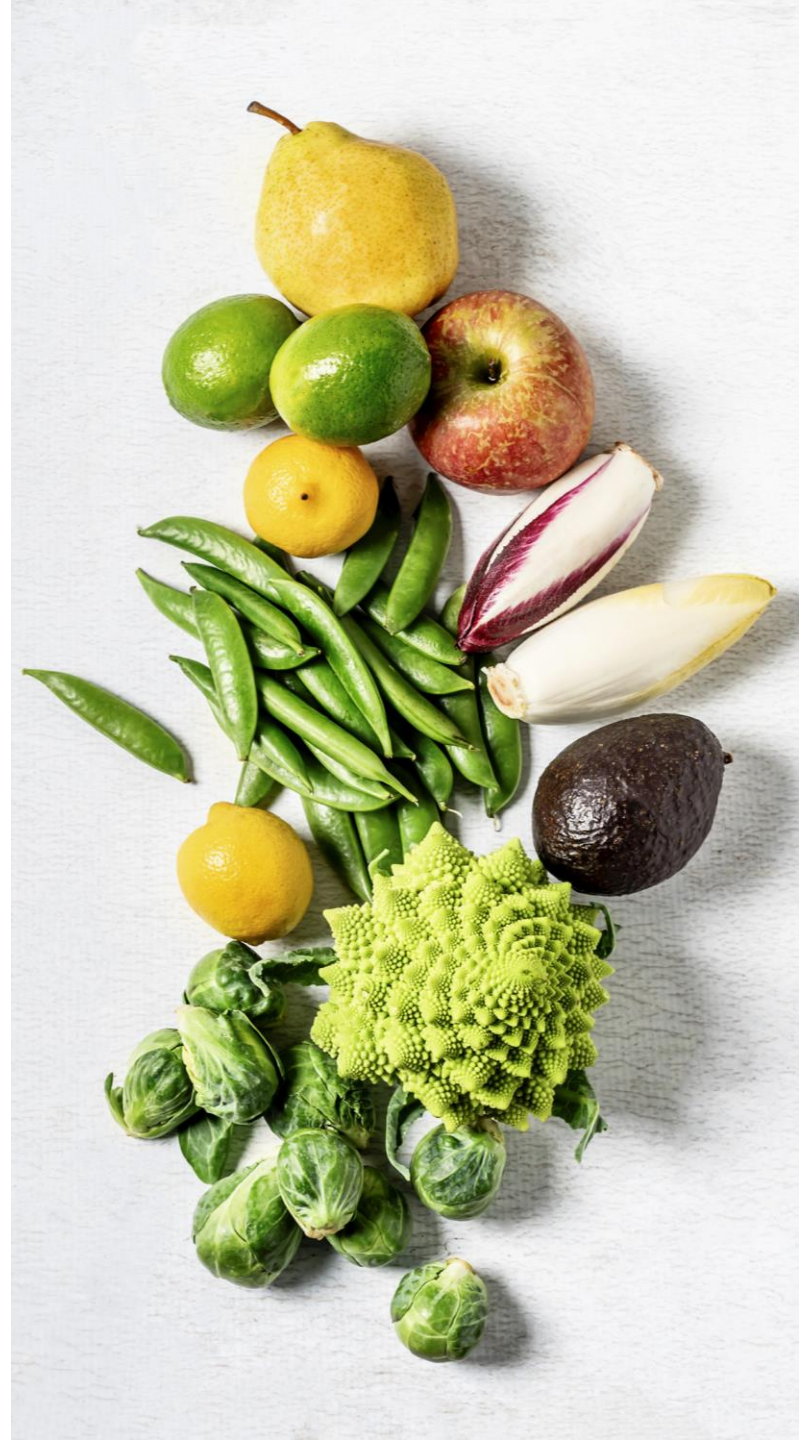
Vitamins: Riboflavin, Niacin, Pyridoxyl-5-phosphate, Folate, Cobalamin, Choline, Betaine

Minerals: Magnesium, Zinc, Calcium, Iron

Fats: Omega-3 fatty acids

Amino Acids: Methionine, cysteine

Phytochemicals: Genistein, sulforaphane, resveratrol





**DOHaD
&
Common
Nutrient
Deficiencies**

- **25-OH D deficiency:** ↑ risk of GDM, ↑ risk of LGA, ↑ risk of F1 DMII
- **Carnitine deficiency:** ↑ risk of GDM, ↑ risk of LGA
- **Zinc deficiency:** ↑ risk of PTB, ↑ risk of SGA, ↓ risk of F1 neural function
- **Iron deficiency:** ↑ risk of SGA
- **EFA deficiency:** ↑ risk of PTB, ↓ F1 brain weight
- **Lack of microbiome diversity:** ↑ F1 asthma, allergy, atopy
- **Maternal protein calorie deficiency:** ↑ risk of SGA

Genetic Ecosystem Across the Lifespan



MTHFR C677T
RPL
Preeclampsia
Small for Gestational Age

MTHFR A1298C
RPL
NTD

TCN2
RPL
Miscarriage

VDR
Preterm Birth
Small for Gestational Age
Gestational HTN

MTNR1B
GDM

APO e2
Miscarriage
Preterm Birth
GDM

Mother

Baby



MTHFR C677T
NTD
ASD
Down's syndrome
Vascular dementia
Stroke
Some CA
Schizophrenia*
T2DM
Male Infertility

MTHFR A1298C
Male infertility
Some CA
Protective for Hypothyroid

* African, Asian, Caucasian
** European descent

TCN2
Failure to thrive
Substance misuse
B12 cellular delivery
Infertility
Recurrent Implantation failure
Crohn's disease
Hyper-homocystinemia**

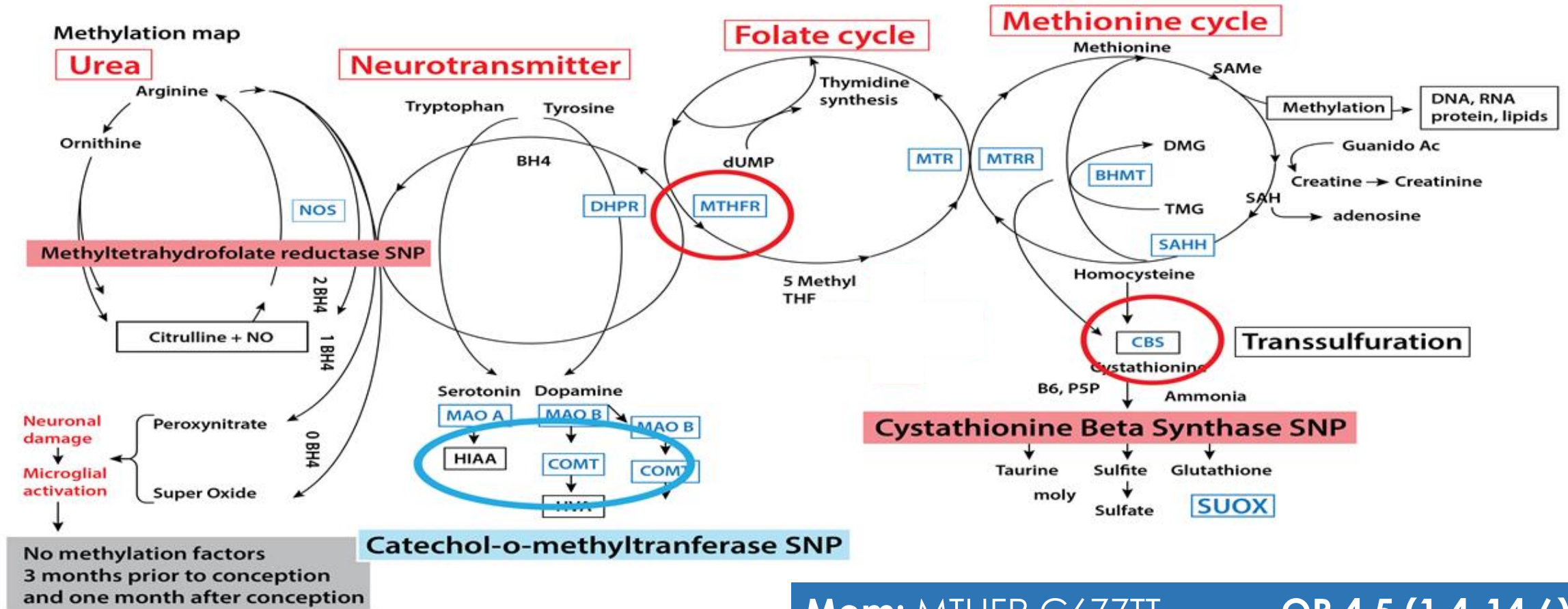
VDR
Asthma
HTN
>BFP
OA
Osteoporosis
Vitamin D deficiency
Squamous/Basal Cell cancer
Melanoma

MTNR1B
T2DM
Childhood-Obesity risk
Adulthood-Obesity traits
Chronotype-
Breast CA
Colorectal CA

APO e2
Protective for Alzheimer's
Hyper-Lipoproteinemia
T2DM

One Carbon Metabolism Map: Genetic Ecosystem Across the Lifespan

Address methylation issues 3 months prior through the 1st month after conception: Shift AUTISM Risk



Mom: MTHFR C677T & CBS rs234715 GT+TT
Child: COMT 472 AA

OR 4.5 (1.4-14.6)
OR 2.6 (1.2-5.4)
OR 7.2 (2.3-22.4)

Schmidt RJ et al. *Epidemiology*. 2011;22(4):476-485.



MTHFR C677T & A1298C

Homocysteine (tHcy) as embryotoxic

- **Mechanism:** elevation compromises DNA synthesis by increasing demand for 5-MTHF to methylate homocysteine.
- **Decreased first time and recurrent miscarriage rates and NTD** with periconceptual supplementation of folate and B12 in MTHFR C677T homozygous, compound heterozygous, and TC C776G



Methyl Support –

- C677T homozygotes are believed to have reduced levels of active folate (5-methyl-THF) and increased plasma levels of Hcy because it cannot be remethylated to Methionine: **support with B6, B9, B12 and adequate dietary protein**
- **Limit synthetic folic acid** - Consuming this synthetic form >200 mcg per meal may exceed the dihydrofolate reductase capacity (DHFR) to convert folic acid into THF - leading to the accumulation of unmetabolized folic acid (UMFA)

TCN2 C776G – transcobalamin 2 transport protein

Associated with Recurrent Miscarriage

Action: *encodes for the main
carrier protein that transports
B12 from blood into cells³*

- CC genotype associated with lower serum B12 ($p = 0.03$) compared to GG and CG genotypes ($p = 0.045$)²
- GG genotype and lower serum B12 associated with higher serum Hcy ($p = 0.06$) compared to others²

1: Preliminary GBH data – Molina PIP

2: Eur J Clin Nutr. 2010; 64(11), 1338-1343.

3: Eur J Clin Nutr. 2008 Aug;62(8):1010-21

TCN2 SNP
Prevalence
61%¹



Interventions

- **Support:** Address digestion
- **Include B12 rich foods:** Vitamin B12 is essential for DNA synthesis and fatty acid metabolism.
- **Consider:** B12 supplementation
- **Assess:** serum B12, MMA, homocysteine
- **Other Risks:** vegan diet, >BMI

Park HS, et al., J Assist Reprod Genet. 2019 Jul;36(7):1513-1522. PMID: 31123954;

Wiedemann A, et al., Cell Rep Med. 2022 Jul 19;3(7):100670. PMID: 35764087.

Temova Rakuša Ž, et al., Molecules. 2022 Dec 28;28(1):240.. PMID: 36615431

Baltaci D., et al., Turk. J. Med. Sci. 2012;42:802–809.

VDR – Vitamin D Receptor

VDR SNP
Prevalence
89%¹

When supplemented²:

- ✓ Higher pregnancy rates
- ✓ Improved ovarian reserve parameters in women with diminished ovarian reserve
- ✓ Curtailed fibroid growth in those with uterine myomas
- ✓ Lessened dysmenorrhea in endometriosis patients
- ✓ Improved menstrual regularity, lowered testosterone, AMH, and insulin levels in women with PCOS

Very common nutrient insufficiency: check it!

1: GBH-Molina PIP

2: Simpson S, Pal L. Vitamin D and infertility. Curr Opin Obstet Gynecol. 2023 Aug 1;35(4):300-305. PMID: 37266579.

Interventions

Consider:

- Vitamin D3 – 5,000 IUs
- Vitamin K2 – 50-90 mcg
- Magnesium rich foods
- Calcium rich foods
- Mushrooms in diet
- Address gut health

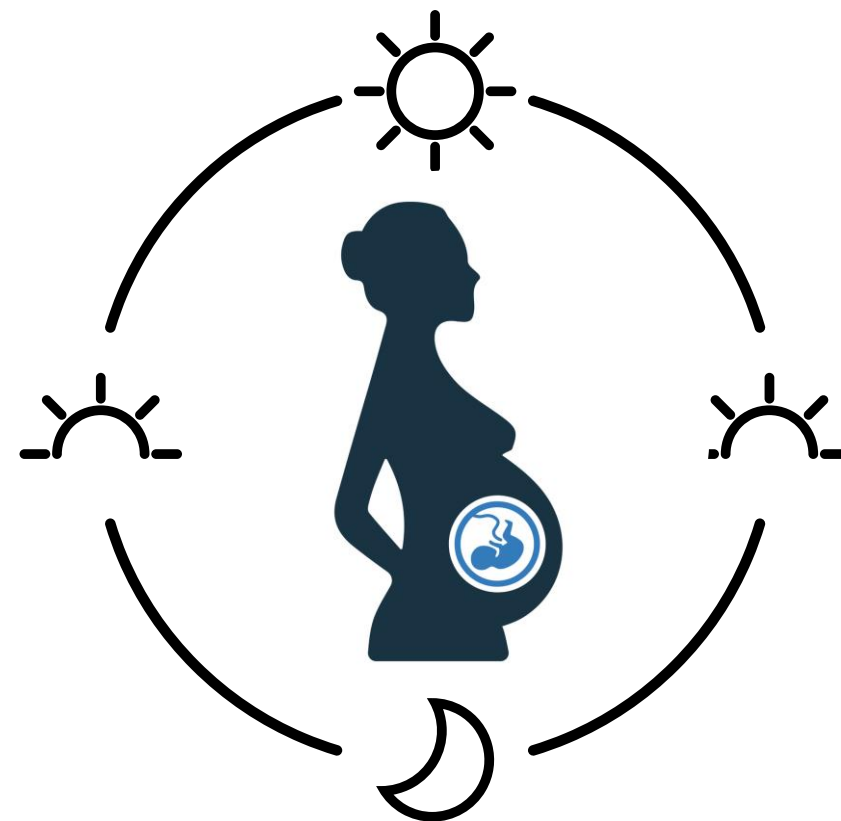
Environmental factors can influence VDR regulation like diet, exposure to sunlight (in northern hemisphere - sunlight exposure in AM from April-October), infections, and pollution.

MTNR1B – Melatonin Receptor 1 B

MTNR1B rs10830963 G allele (risk) associated with:

- ✓ Disturbed circadian phenotypes
- ✓ Altered melatonin secretion
- ✓ Overexpression of *MTNR1B* in human islet cells

... factors that can elevate the risk of diabetes.





SNP
Prevalence
39-50%²

MTNR1B & GDM

GDM and T2DM have shared pathophysiology:

- *Mothers with GDM may have 8.9-fold increased risk of T2DM*
- *15.6% GDM, AMA (>35 yo)*

MTNR1B rs10830963 presented a higher genetic effect size for GDM when compared to T2DM.

MTNR1B & GDM – Modulating Effects

Genetic effects of *MTNR1B* on maternal GDM via gene-environment or gene-gene interactions:

1. Pre-pregnancy BMI (≥ 25 kg/m²)
2. Maternal adiposity
3. Physical activity
4. Placenta hormones
5. Paternal or fetal genotypes

Zhu H, Zhao ZJ, Liu HY, Cai J, Lu QK, Ji LD, Xu J. The melatonin receptor 1B gene links circadian rhythms and type 2 diabetes mellitus: an evolutionary story. *Ann Med*. 2023 Dec;55(1):1262-1286. doi: 10.1080/07853890.2023.2191218. PMID: 36974476; PMCID: PMC10054309.



apoE –Apolipoprotein E

A protein that transports fats in the blood

Associated with: RPL because it might contribute to thrombogenesis, with cholesterol-triglyceride metabolism being involved promoting atherosclerosis

RPL and Apo E gene polymorphisms:

- Apo E4 polymorphism could be a risk factor
- Apo E3 polymorphism may be a protective factor
- Apo E2 polymorphism may be another potential risk factor





Interventions

Address: Gestational Cardiovascular Health score in preconception

Optimize: selenium, EPA/DHA, phytosterols, & choline

Decrease: oxidative stress

Perak AM, et al., Am J Obstet Gynecol. 2021 Feb;224(2):210.e1-210.e17. PMID: 32768430

Shared Opportunities for Health

Systems based assessment of health allows precise targeting of intervention

Micro/Macronutrients

Lifestyle/Behavior

Toxic exposure/mitigation

Microbiome

Targeted genomics

Unique biomarker assessment



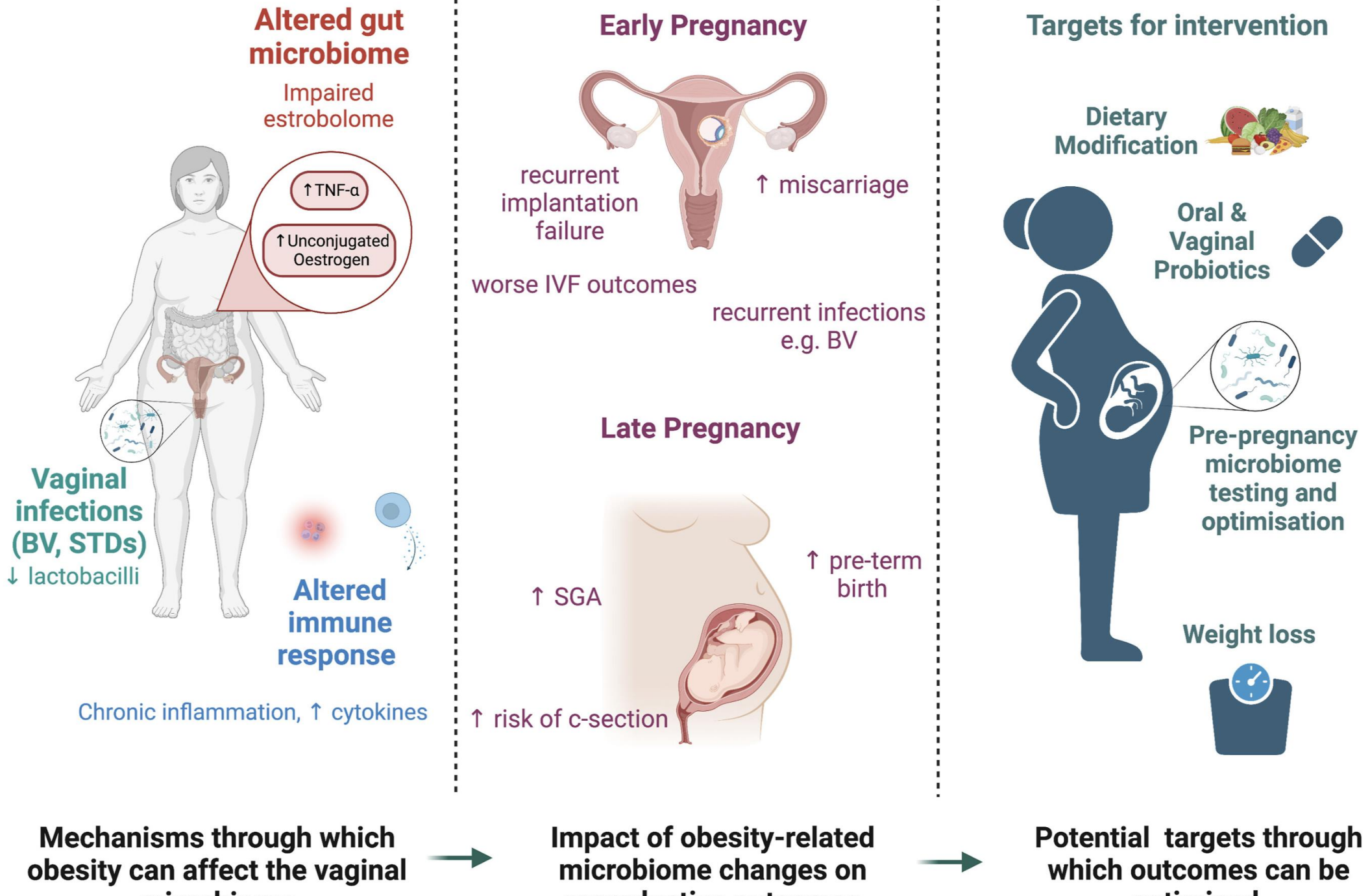


Figure 2: Garg A, Ellis LB, et al. 2023 Aug;90:102365. PMID: 37399714.

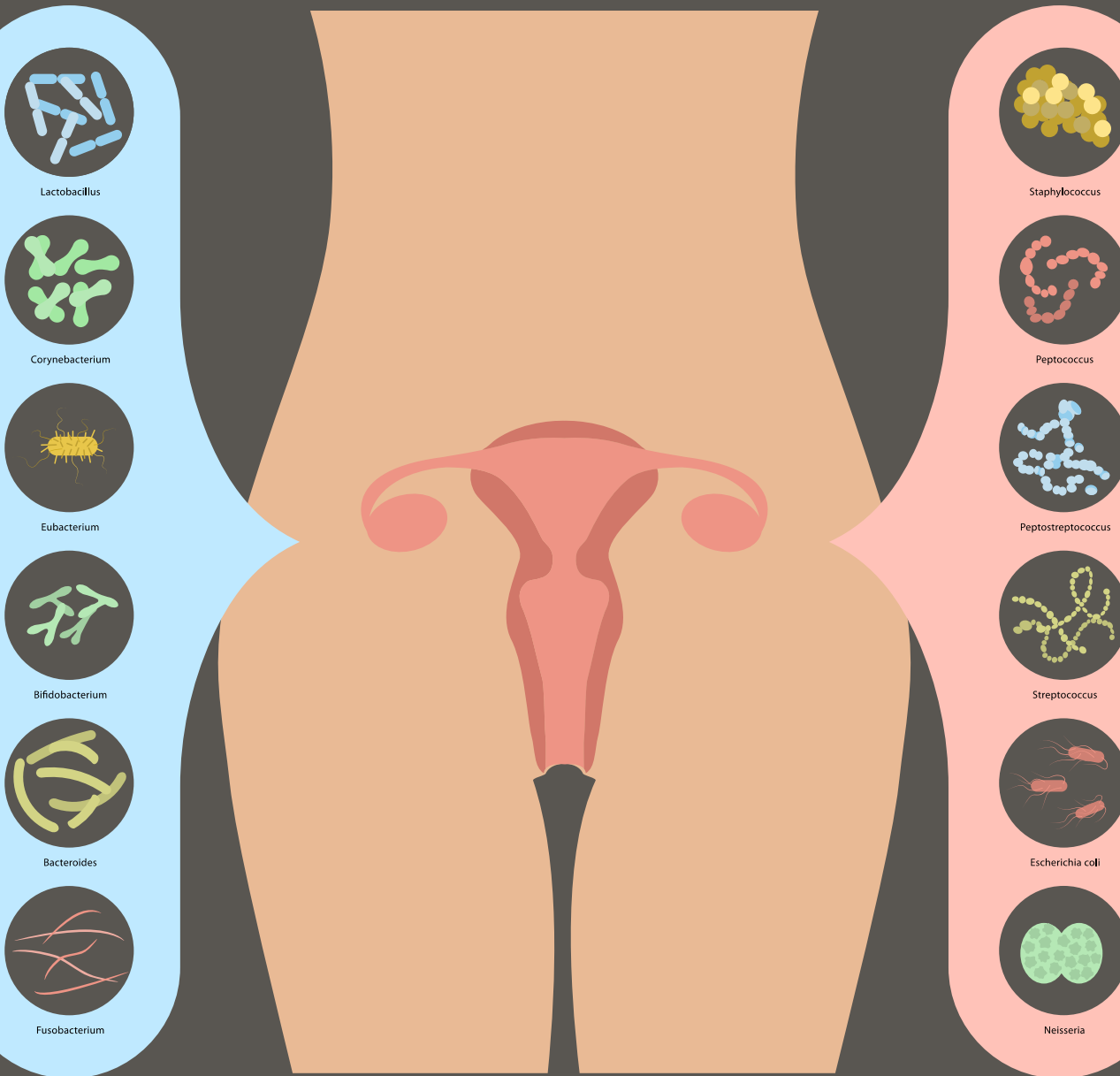
Female Infertility – Microbiome

The CDC estimates **30% of US women** suffer from bacterial vaginosis, with prevalence surpassing **60% for African American women**¹

Bacterial vaginosis (BV) is more prevalent in infertility...

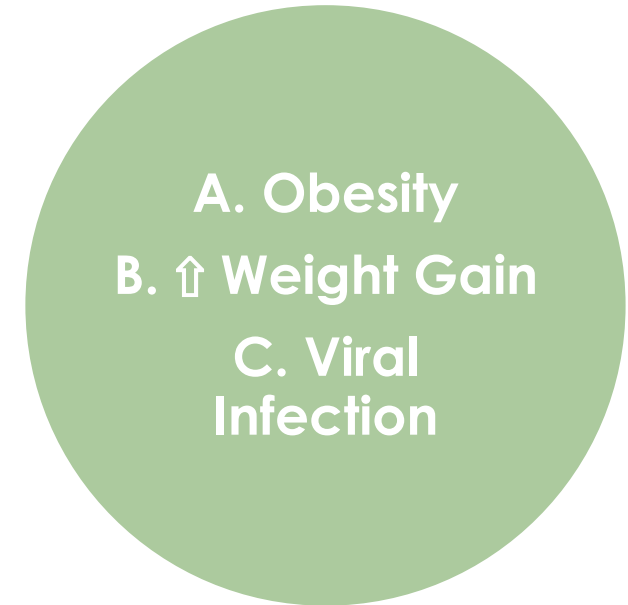
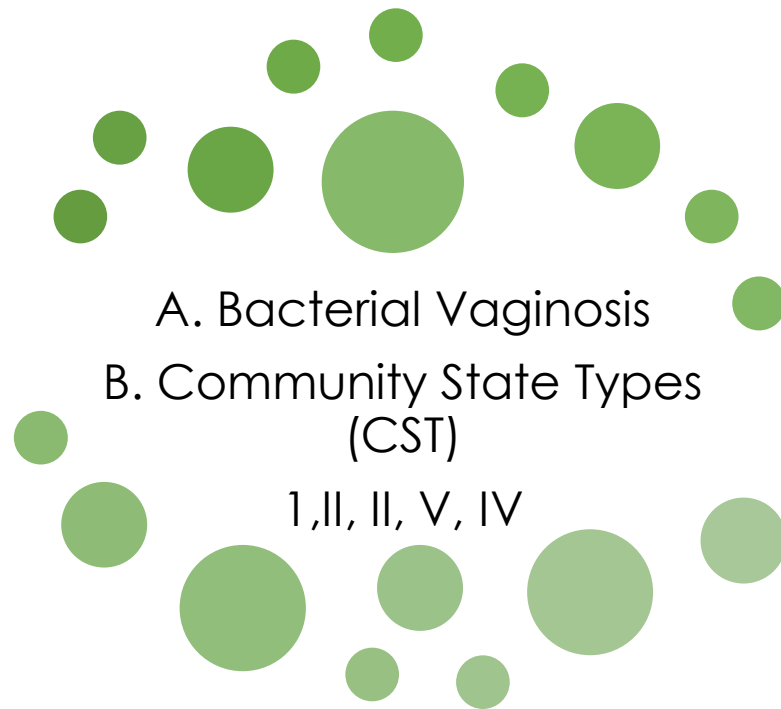
- Oral and vaginal treatment with *L. brevis*, *L. salivarius*, *L. plantarum*, *L. acidophilus*, and *L. thermophilus* reduced BV²
- BV is associated with tubal factor infertility³

Recognize: Vaginal microbiome is associated with early SAb and is modifiable



1. Dunlop AL et al. *Adv Neonatal Care*. 2015;15(6):377–385.
2. Mastromarino P et al. *Indian J Med Res*. 2014;140(Suppl)
3. Haahr T et al. *BJOG*. 2019;126(2):200-207.

Preconception & Placental Factors



A. Increased Intrauterine infections:
SAb-PTB³

B. CST I, II, III, V Lactobacillus dominant &
more common in Caucasians.

C. CST IV-strict and facultative anaerobic
dominant eg Gardnerella & more common
in African American & Hispanic Women^{1,2,3,8}

A. Macrophage accumulation-
Inflamed placenta-PTB⁴

B. Decreased Spp richness/diversity-
PTB⁵

C. Inhibits capacity of
macrophages to inhibit bacterial
growth disrupting symbiosis-PTB⁶⁻⁷



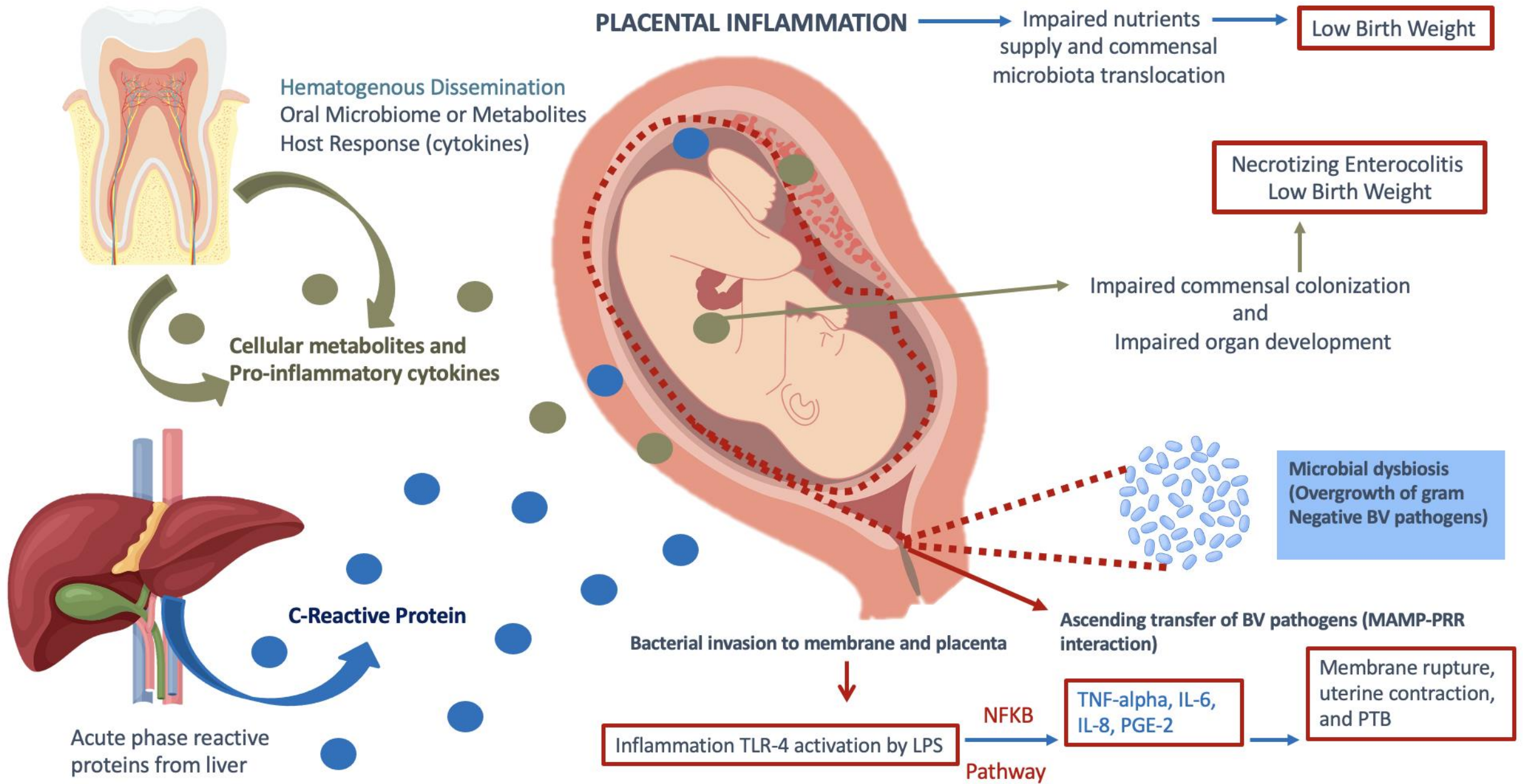
Oral Findings & Systemic Health – Preconception

Linking poor oral health to infertility and poor outcomes of IVF in women

Periodontitis is associated with:

1. Bacteremia in the uterus
2. Activation the immune system - overproduction of pro-inflammatory cytokines & prostaglandins
3. Spread of bacterial products and endotoxins like lipopolysaccharides in the blood circulation

Findings: Dx of periodontitis took approximately two months longer to achieve the desired gestation ...



Interventions

Best nitrate-rich food sources:

- Brassicaceae (arugula, radish, & mustard)
- *Chenopodiaceae* (beetroot, Swiss chard, & spinach)
- *Amaranthaceae* (amaranthus or amaranth)
- *Asteraceae* (lettuce)
- *Apiaceae* (celery and parsley)

Focus On: vitamins A, C, D, an array of B vitamins, calcium, polyphenols, and **dietary fiber**

Genomics – VDR & association with *chronic periodontitis* (inverse relationship between serum 25-OH D3 and periodontal disease inflammation)

Nielsen SJ, et al., J Nutr. 2016 Dec;146(12):2530-2536 PMID: 27798338
Chou S-S, et al., Journal of Food and Drug Analysis. 2003;11(3):233–8.
Luetic S, et al., 2023 Apr 15;12(8):1655. PMID: 37107450;
Cafiero C, et al., Biomolecules. 2022 Jun 15;12(6):833. PMID: 35740958.

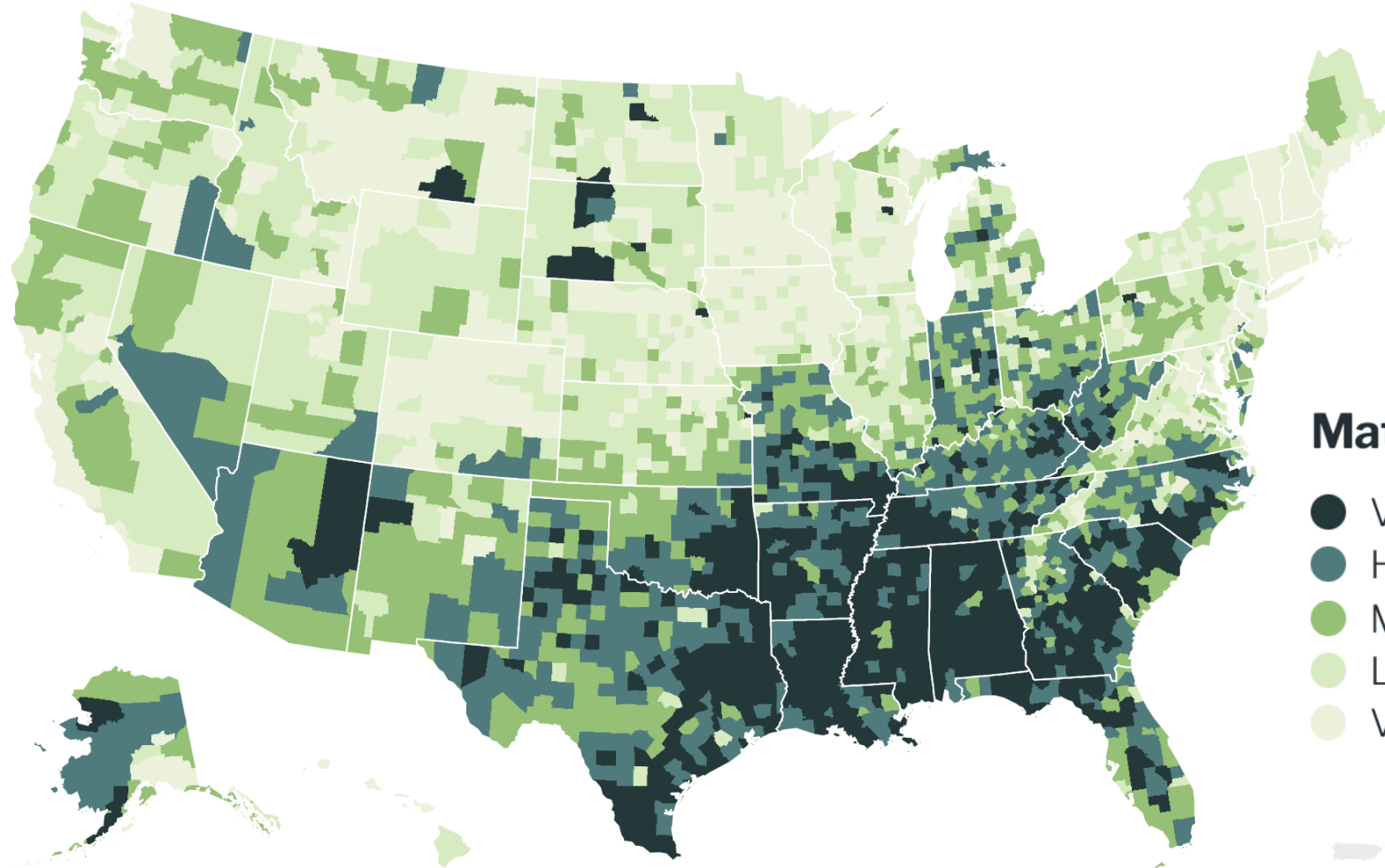


Toxic Exposures, Immunity, Preconception & DOHaD





XXXXXX – Five Important Numbers



Maternal Vulnerability

- Very High
- High ×
- Moderate
- Low
- Very Low

Maternal vulnerability in the US – A Shameful Problem for One of the World's Wealthiest Countries. Surgo Ventures. Accessed Apr 10, 2024. <https://mvi.surgoverventures.org>

Reproductive healthcare

Physical health

Mental health & substance abuse

General healthcare

Socioeconomic determinants

Physical environment

Lead

- **Preconception:** SAb,
- **Pregnancy:** PTB, SGA, PIH
- **F₁, Cognitive impairment** – Pb affects DNA methylation

Mercury

- **Preconception:** Male factor infertility/subfertility (reduced semen quality), increased menstrual & hormonal disorders (hair/blood/urine) – SAb
- **Pregnancy:** malformations & LBW
- **F₁ Neurodevelopmental Concerns:** Brain damage, hearing & vision problems

Arsenic

- **Preconception:** Altered sperm counts/motility, oxidative damage-spermatogenesis & oogenesis
- **Pregnancy:** PTB & SGA
- **F₁ Chronic Disease Concerns:** Later lung CA & CVD

Uptodate, Accessed February 1, 2020

Dack K, Fell M, Taylor CM, et al., *Int J Environ Res Public Health*. 2021 Jul 3;18(13):7140. .PMID: 34281082.

Kurzius-Spencer M, et al., *J Expo Sci Environ Epidemiol* 24(2):156–162, PMID: 23860400.

Henriques, Magda, et al., *Reproductive Toxicology*, Vol 85, 2019, Pgs 93-103, ISSN 0890-6238

Zargari F, Rahaman MS, et al., *J Xenobiot*. 2022 Jul 18;12(3):214-222. PMID: 35893266.

Lead Exposure: Interventions

Mineral Support: Zinc, Iron, Calcium, Selenium

Vitamin Support: *Vitamins C* (chelating agent of Pb, with a similar potency to that of EDTA), B₁ & B₆

Check: Iron studies, zinc, selenium, CMP

Dietary Recall: Phytochemicals - Quercetin, catechins, anthocyanins, curcumin, narigenin (garlic, onions, ginger, EGCG, grapes, curry, tomato)

Gut: *Lactobacillus rhamnosus*, *L. plantarum*, and *Bifidobacterium longum* are capable of binding heavy metals



Mercury Exposure: Interventions

Antioxidant: Selenoenzymes – Se (assess using Selenoprotein P)

Safety: Include fish in the diet and empower proper decisions for nutrition – *awareness is key!*

- Substantial evidence suggests that consuming 1-2 servings of fish per week, particularly oily fish (e.g., salmon, herring, sardines, 8-12 oz) is beneficial for cardiovascular health due to its high n-3 PUFAs content
- Check local advisories on water quality in oceans, lakes, and rivers where local fish are caught & Monterey Bay Seafood Watch

Katsonouri A, et al., *Int J Hyg Environ Health*. 2023 Jul;252:114213.. PMID: 37393843.
Downer MK, et al., *BMC Cardiovasc Disord*. 2017 Jan 5;17(1):9. PMID: 28056794
Segal TR, et al., *Fertil Steril*. 2019 Oct;112(4):613-621. PMID: 31561863.
Tinggi U, Perkins AV. *Nutrients*. 2022 Dec 14;14(24):5308. PMID: 36558469.



Arsenic Exposure: Interventions

Choose: Plants! Adequate protein. Micronutrient intake. Deficiencies = slow removal from the body

- Administration of modified citrus pectin showed a significant (130%) increase in the urinary excretion of arsenic

Preparation: Rice & Rice Bran - washing and soaking, increase the volume of cooking water that rice encounters, followed by draining off the excess water generated during cooking

Dietary Awareness: Rice, apple juice, carrots...updated Q10 years

Bjørklund G, et al., *Molecules*. 2022 Jul 29;27(15):4871. PMID: 35956821.

Signes A, et al., *Eur Food Res Technol* 226(3):561–567

Nachman KE, et al., *Environ Health Perspect*. 2018 Aug;126(8):84503. PMID: 30235424

United States Food and Drug Administration. [accessed 14 June 2016]; *Total Diet Study*. 2016d Available: <http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm>.

Eliaz I., et al., *Phytother. Res*. 2006;20:859–864. doi: 10.1002/ptr.1953.

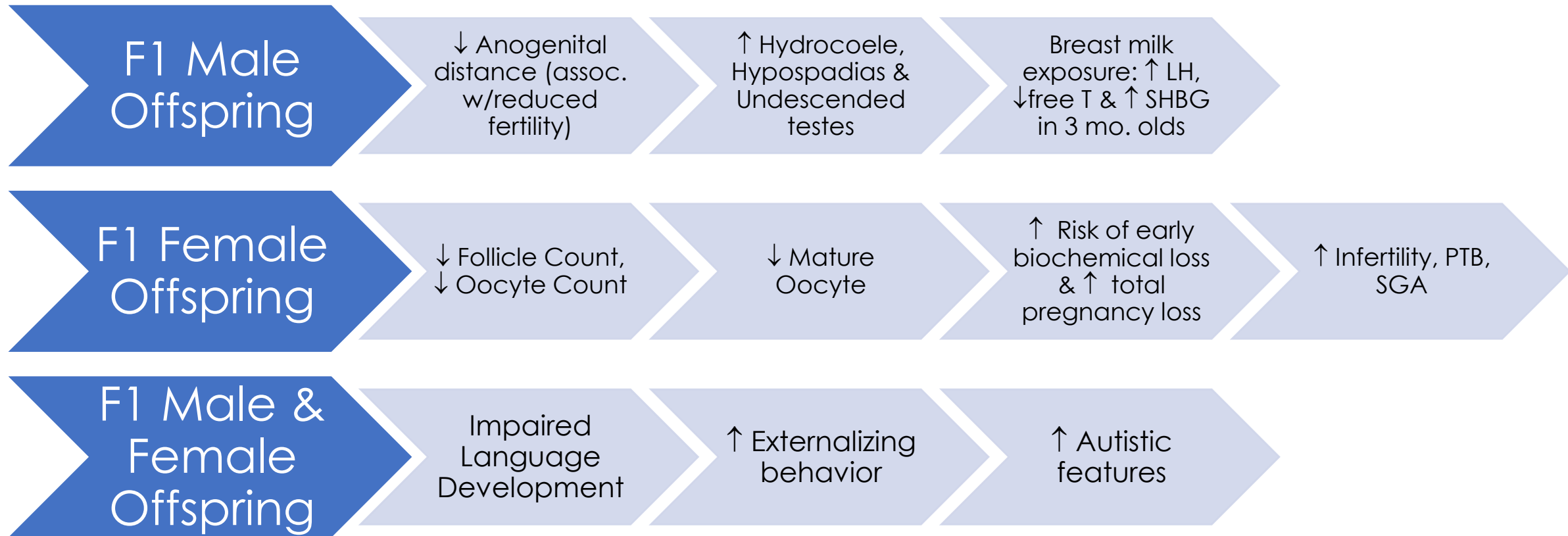




Maternal Plastic Exposure



Effect



Maternal Exposure – BPA

- Air
- Dust
- Water
- Food & Drinking packaging
- **EFFECT:** F1 ↑ hyperactivity in 2 y/o female

Uptodate, Accessed February 1, 2020

Postnatal BPA Exposure

- ↑ Obesity
- ↑ PCOS
- ↑ Asthma
- ↑ CVD
- ↑ LFTs
- ↑ T2DM

Uptodate, Accessed February 1, 2020

IVF: elevated levels of urinary BPA is associated with fewer oocytes retrieved and peak serum E_2 levels.

Sugiura-Ogasawara M. et al., *Hum Reprod.* 2005; 20: 2325-2329

Phthalates - Through a Lifetime

Adults

- ↑ Abnormal sperm morphology
- ↑ DNA damage

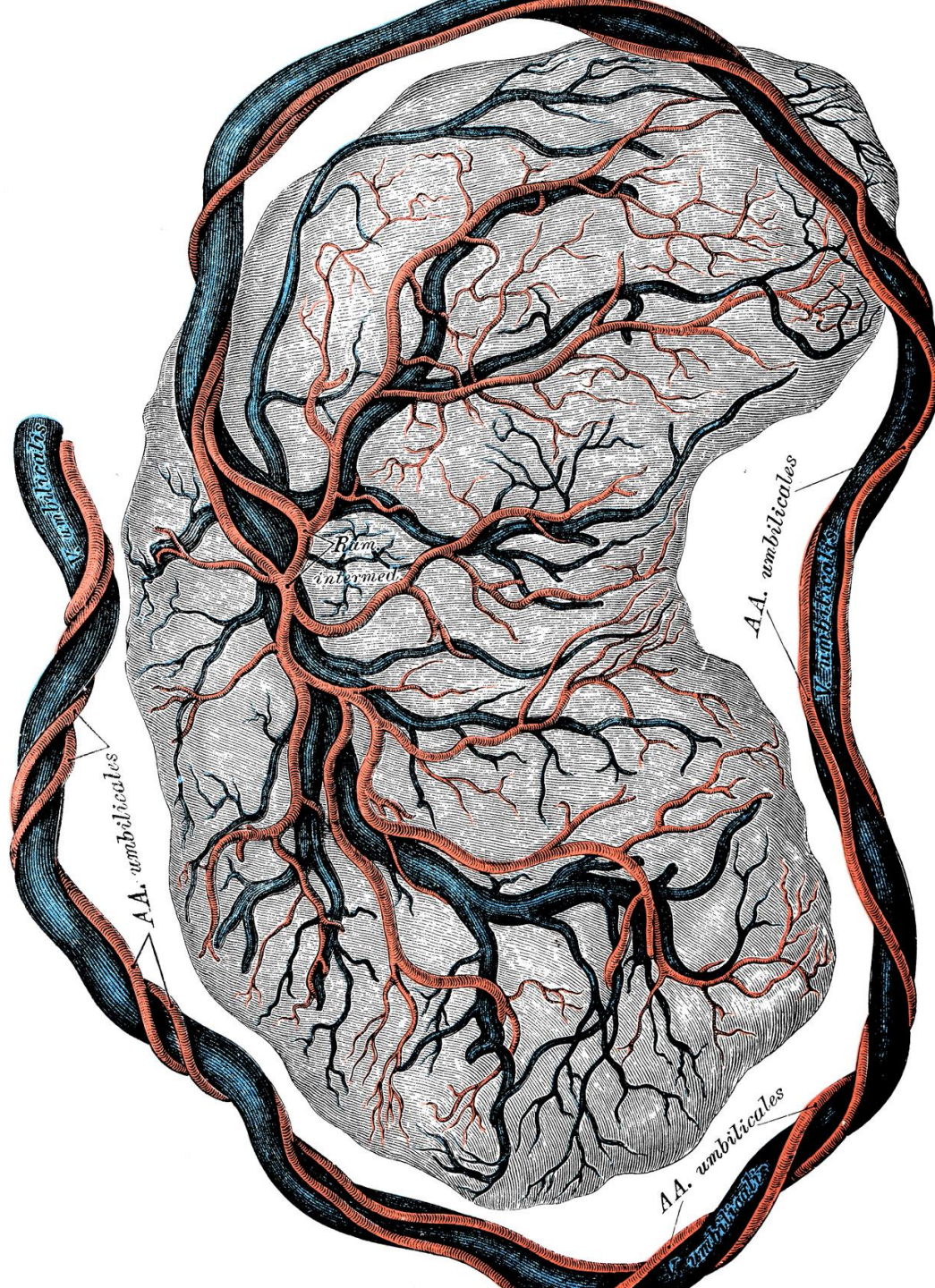
Women undergoing IVF with a higher concentration of phthalates had lower numbers of oocytes retrieved, lower pregnancy rates, and higher risk of early pregnancy loss before 20 weeks' gestation

Pediatrics

- ↑ Eczema
- ↑ Asthma



"Plasti-centa" & DOHaD



Developmental impact:

- ✓ Oxidative stress
- ✓ DNA damage
- ✓ Organ dysfunction
- ✓ Metabolic disorder
- ✓ Immune dysfunction
- ✓ Neurotoxicity
- ✓ Reproductive dysfunction

No human data: all in cell, organoid or animal models.

Interventions – Focus & Consistency



Daily Choices

- Move away from all plastic whenever possible.
- Bring your own glass/stainless to-go cups/containers.
- Take off the plastic lid on all hot beverages.
- Don't warm up plastic containers in the microwave or oven.
- Don't drink from plastic water bottles, especially if they were left in a hot car or hot room.
- Limit the purchase of food wrapped in plastic
- Handwash plastic containers rather than use the dishwasher.
- Read personal care product labels & find alternative products that don't have phthalates in them
- Use an air purifier.
- Dust/vacuum consistently.

Food, Nutrient, Lifestyle

- **Zinc rich foods** – particularly important for male preconception health (oysters, nuts/seeds, plain yogurt, animal protein)
- **Dark leafy greens/cruciferous veggies** (kale, cabbage, broccoli, Brussels sprouts, spinach)
- **Bitter foods & fluids** (dandelion greens, eggplant, grapefruit, coffee, ginger, mint, sesame, apple cider vinegar, endive, chicory)
- Include weekly **movement** or activity that induces **sweating**
- EWG VERIFIED™
- Fragrance Free





Exposure – Pesticides

1. Hormonal impairments
2. Molecular alterations
3. Oxidative stress
4. DNA methylation

...**Effect on fertility** (polycystic ovary syndrome, endometriosis, and uterine fibroids), **pregnancy** (PTB & miscarriage) and its **outcomes**.

Reshi MS, et al., Adv Exp Med Biol. 2022;1391:59-69. PMID: 36472816.
Kumar S, et al., Indian J Med Res. 2019 Dec;150(6):532-545. PMID: 32048617.
Chiang C, et al., Semin Reprod Med. 2017 May;35(3):241-249. PMID: 28658707.
Felisbino K, et al., Sci Total Environ. 2024 Feb 25;913:169317. PMID: 38104833.
Maritano S, et al., Environ Int. 2022 May;163:107229. PMID: 35405505.
Ali JH, et al., Ecotoxicol Environ Saf. 2023 May;256:114801. PMID: 36989559.
Simões M, et al., Environ Int. 2023 Aug;178:108085. PMID: 37421898.
Kubsad, D., et al. Sci Rep 9, 6372 (2019)

Seasonal Impact – *Spring/Summer*

Soil & H₂O Infertility



Organophosphates
Glyphosate/Chlorpyrifos/
Atrazine/Insecticides/Herbicides/
Fungicides:

2 million tons –

- **0.1% intended target**
- **\$81.74 billion global industry – 2028**

Yadav I.C., et al., *Sci. Total Environ.* 2015;511:123–137. doi: 10.1016/j.scitotenv.2014.12.041.

Syafudin M, et al., *Int J Environ Res Public Health.* 2021 Jan 8;18(2):468. PMID: 33430077.

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Pesticides - DOHaD

- NTDs, birth defects, shorter telomere length, LBW or SGA, & LGA

Prenatal exposure & First 1000+ days

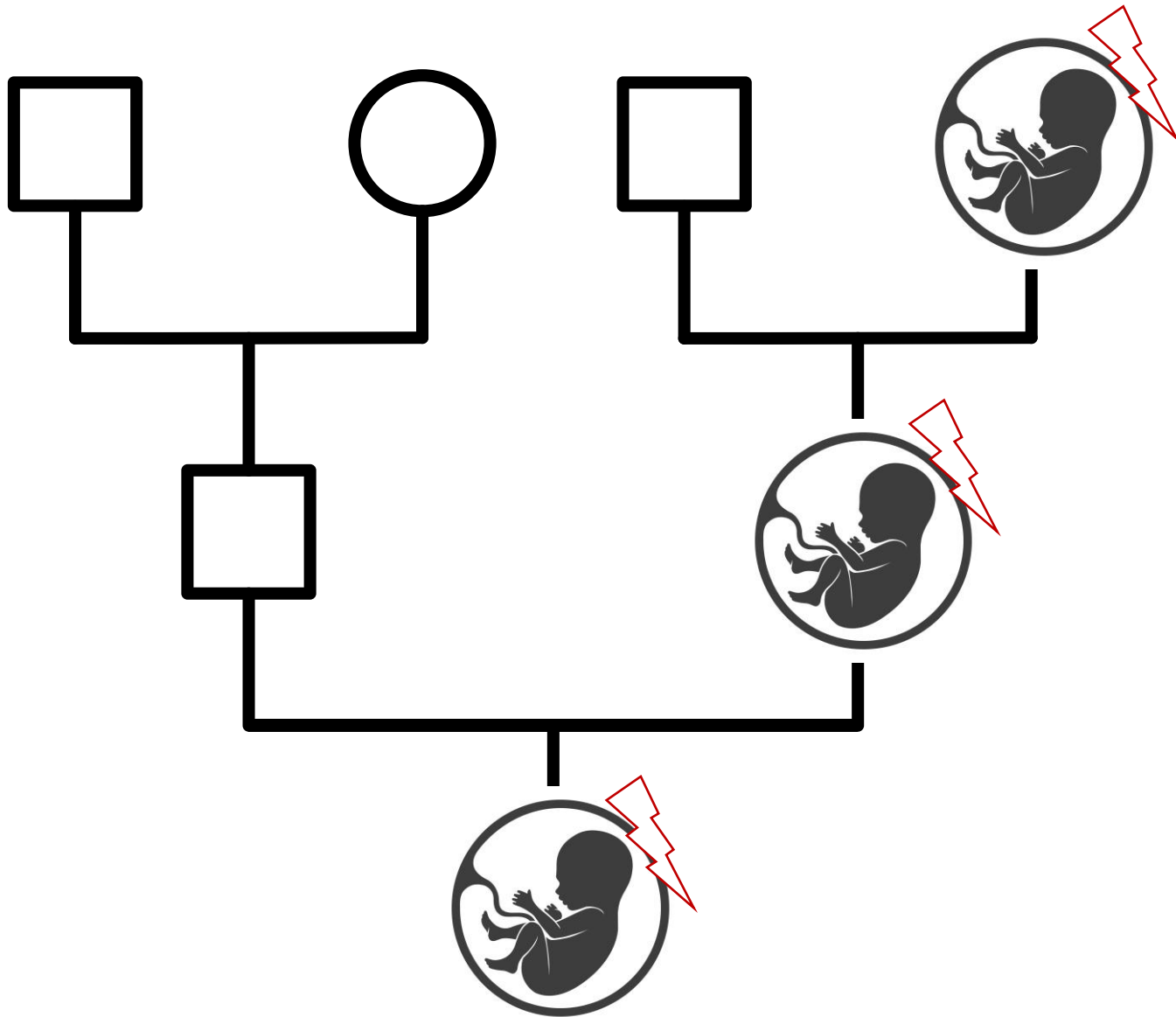
- Risk of ASD
- risk of ADHD
- Infant wheezing
- Neurocognitive deficits
- Developmental disorders
- Cancer
- Early puberty & urogenital abnormalities

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F3⁺ Generation

F0 - Direct Exposure

- F1 – No Exposure
- F2 – No Exposure
- F3 – No Exposure

...yet an increase in anomalies & diseases

Atrazine & Glyphosate induce the transgenerational inheritance of disease and germline (e.g., sperm) epimutations.

Nutrition/Nutrients:

- Vitamins C, D, E & Se, Zn, NAC, EGCG, EVOO, curcumin
- Body Composition Support
- Gut Support
- Organic Diet/Mediterranean/High-plant
- Lipophilic toxins – Ghee
- Brassinosteroids – peas, alliums, dill, ginger, cucumber, celery, cauliflower

Genetics: null genotype - GSTM1 and GSTT1

Methylation of pesticides was reported to be critical for detoxification in plants.

Lifestyle:

- EWG – C15/D12 – Produce/Product awareness
- Water, vinegar, baking soda, limonene
- Activated carbon/RO

Interventions



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Cord Blood – Forever Chemicals (PFAS)

Reproductive Toxicity

- >90% detection rate of Per- and polyfluoroalkyl substances (PFAS) in maternal plasma.
- 96%-100% placental detection (highest levels in nulliparous women) – may have sex specific affect on fetal weight
- 100% cord blood detection (30,000 samples)

Developmental: SGA & LGA accelerated puberty, increased obesity, increased cholesterol, bone variations, behavioral changes, impaired immune response including to vaccines, increased risk for cancer including prostate, kidney, and testicular.

As of 2024 - EPA is issuing a “**zero tolerance**” restriction on PFAS in municipal water supply.



Bach CC et al., *Crit Rev Toxicol*. 2015;45(1):53–67.

Hall SM, et al., *Chemosphere*. 2022 May;295:133873.

Perkins, T. (2022, September 23). 'Forever chemicals' detected in all umbilical cord blood in 40 studies. *The Guardian*. <https://www.theguardian.com/environment/2022/sep/23/forever-chemicals-found-umbilical-cord-blood-samples-studies>

Lauritzen HB, et al., *PLoS One*. 2016 Nov 8;11(11):e0166127. PMID: 27824939.



Interventions

Anti-inflammatory Diet : Emphasis on color diversity & folate sources (higher serum folate concentration & lower the PFAS levels)

Dietary patterns: vegetables, fruits and Omega-3 rich fish

Gut Health (PFAS & PFOAs are readily absorbed by the gut & not metabolized)

- ✓ **Fiber**
- ✓ **Probiotics** (*Lactobacillus plantarum* CCFM738 exhibited the highest binding capability)
- ✓ **Fermented Foods**

Lipid management (PFAS assoc. increase w/TC and LDL, yet lipid lowering diets can decrease PFAS & TC+LDL levels)

Cooking at Home


Skip: non-stick, microwave popcorn, water-repellant, stain-resistant

Choose: biodegradable, reverse osmosis

Product & Policy Awareness: EWG.org

Removed via: stool, urine, blood, breastmilk, not sweat

Zhou R, et al., *Food Funct.* 2023 Oct 2. PMID: 37779497.
Dzierlenga MW, et al., *Environ Int.* 2021 Jan;146:106292. PMID: 33395939
Lin PD, Cardet al., *Environ Int.* 2020 Apr;137:105217. PMID: 32086073
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Xing J, et al., (2016) *Appl Microbiol Biotechnol* 100(15):6755–6766.
Morgan S, et al., *Environ Toxicol Pharmacol.* 2023, 98:104062.
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Yu Zhang, BA., et al., *JAMA Netw Open.* 2023;6(5):e2314934.
Hampson HE, et al., *Environ Int.* 2024 Mar;185:108454. PMID: 38316574.



Most Risk is not hard-wired, but epigenetically modifiable!

Slide 14 References: Nutrient insufficiencies and Mat'l./Neo. Outcomes

Zinc

- Eur J Nutr. 2008;47 Suppl 3:38-50
- Mercer JG Neurologic Development, in Nutrition and Development: short and long-term consequences for health. Hoboken NJ. Wiley-Blackwell; 2013:97-115.
- Maternal deficiency associated with decreased DNA, RNA, and protein content in the F1 brain.
- ZN supplementation reduces the risk of preterm birth but not SGA.

Carnitine

- Lohninger A, Radler U, Jinniate S et al. Gynakol Geburtshifflche Rundsch. 2009;49(40): 230-5.
- Treatment with 2000mg carnitine avoids a striking rise in FFAs, which is thought to be the main cause of insulin resistance and GDM, despite not reaching serum levels of sufficiency.

EFA, folic acid, D and iodine

- Nutrients 2012; 4(7): 799-840. Benefits of DHA, folic acid, vitamin D and iodine on fetal and infant brain development and function following maternal supplementation during pregnancy and lactation.

DHA

- Am J Clin Nutr. 2019 May; 109(5): 1380-1392. PMID 31004139. KUDOS study, DHA, PTB and visual behavioral developmental consequences and economic impact.

Vit D

- Am J Obstet Gynecol. 2010 May ; 202(5):e1-429.e9. doi:10.1016/j.ajog.2009.09.002, PMC 3540805. Implications of Vit D deficiency in pregnancy and lactation. Risk for PEC/HDP, SGA, neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased autoimmune diseases.
- J Res Med Sci 2016;21:2. The effect of Vitamin D suppl on GDM in high-risk women. D supplementation in the first and second trimesters of reducing GDM and controlling GTT and GTC.

Magnesium

- Nutr Rev. 2012 Mar;70(3): 153-64. Suboptimal magnesium status in the US: are the health consequences underestimated?

Protein Calorie

- A J Clin Nutr 2007;85(suppl): 6145-205. Global brain cell proliferation, differentiation, synaptogenesis, growth factor synthesis, SGA.

Microbiome

- Nutrition development: short and long term consequences for health. Hoboken, NJ: Wiley-Blackwell; 2013: 116-29. Establishing gut microbiota Clin Exp Allergy. 2013;43(4)434-42. L reuteri decrease allergen responsiveness pre and post-natal.

Iron

- Scientific Reports (2021) 11:1347, doi.org/10.1038/s41598-020-7991-y, www.nature.com/scientific-reports/. Murine model, supplementation significantly improves IDA and it's adverse effects.
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- Lee HS, Kim S, et al. Iron Status and Pregnancy outcomes in Korean pregnant women. Eur J Clin Nutr. 60, 1130-1135, doi.org/10.1038/sj.ejcn.1602429(2006).Sim
- Srour MA, et al, Prevalence of anemia and iron-def. anemia among Palestinian pregnant women and association with fetal outcome. Anemia 2018, 9135625, doi.org/10.1155/2018/9135625(2018). Fetal consequences: increased spontaneous miscarriage, PTB, IUFD, IUGR and SGA, HTN, neurologic impairment.