Perinatal Management in the 21st Century

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Learning Objectives

Upon completion of this deck, you will be able to describe:

• The importance of hormones and hormone balance/metabolism in fertility, preconception and conception

• The need for Preconception, Prenatal and Postpartum care for the mother
  • Additionally: Describe the need for preconception care for the father

• The nutritional needs at each stage of pregnancy
  • Additionally: Understand normal weight gain and the implications for fetal health
Decreasing Life Expectancy & Neonatal/Maternal Outcomes

• Unprecedented reduction in life expectancy
  
• The new generation is predicted to live a shorter life than their parents

• Trend is strongly associated with obesity and diabetes

• Neonatal mortality (i.e., loss before 28 days of age): Per 1000 live births, US has 3.7 per 1,000 deaths (38th out of 202 nations)

• Miscarriage rates remain >19.7%

• WHO, 1989: Nutrient-associated chronic diseases are due to an incorrect balance or excess of nutrients—”Need to turn attention to the quality of diet”

## BIRTH PHENOTYPES & MATERNAL HEALTH

<table>
<thead>
<tr>
<th>BABY</th>
<th>MOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOO SMALL</td>
<td>High Blood Sugar</td>
</tr>
<tr>
<td><em>Small for Gestational Age (SGA)</em></td>
<td>Gestational Diabetes Mellitus (GDM)</td>
</tr>
<tr>
<td>TOO LARGE</td>
<td>High Blood Pressure</td>
</tr>
<tr>
<td><em>Large for Gestational Age (LGA)</em></td>
<td>Pregnancy Induced Hypertension (PIH)</td>
</tr>
<tr>
<td>TOO STRESSED</td>
<td></td>
</tr>
<tr>
<td><em>Stress Dysregulation (SDP)</em></td>
<td></td>
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<tr>
<td>TOO EARLY</td>
<td></td>
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<tr>
<td><em>Preterm Birth (PTB)</em></td>
<td></td>
</tr>
</tbody>
</table>
Healthy Parents=Healthy Kids
Preconception

• **Recognize:** Modifiable nutrition/lifestyle factors contributing to health

• **Empower:** Change

• **Goal:** Optimization of preventative care for all men & women of reproductive age...

  ✓ 49% of pregnancies are unintended¹

  ✓ 16.7% of pregnant women begin care in 2\(^{nd}\) trimester (after organogenesis)²

  ✓ NO traditional preconception care for men

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### Preconception RISK Assessment: Male & Female

#### Medical History
- Chronic Disease
- **Teratogens**
- Reproductive History
- **Genetic Conditions** *(variants, chromosomal abnormalities)*
- Social & Mental Health *(Stress response)*

#### Cont...
- Family History
- Substance Use
- Infectious Disease
- Environmental Exposure
- Lifestyle *(nutrients / movement)*
- Health Status
Preconception Male

• **Nutrition:** High intake of alcohol, caffeine, red meat and processed meat by males has a negative influence on the chance of pregnancy or fertilization rates in their partners\(^1\)

• **Health Status & BMI**
  
  o BMI: 86.3% of adults in the US will meet criteria for overweight (>25) or obese (>30) categories by the 2030\(^2\)
  
  o There is a significant, but mild influence of overweight/obese fathers and their child’s BMI after birth\(^3\)

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Advanced for Paternal Age (APA): >40 years¹

- Since 1980² trend in birth rates have changed:
  - Age 30-39 years: fertility rate increased by 21%
  - > age 40 years: fertility rate increased by 30%

In men <30 years of age fertility rate decreased by 15%

- Recognize: contraception, work/life intention, toxic exposure-ex: estrogenic compounds, industrialization of 3rd world nations, fertility services

Advanced Paternal Age & Risk of Adverse Birth Outcomes\textsuperscript{1-8}

- $\uparrow>35$ years increases risk of gestational hypertension & preeclampsia (PE) in pregnancy
- $\uparrow$ Preterm birth (PTB) by 14% $\geq45$ year old (US 2007-2016)
- $\uparrow$ PTB, very PTB, & small for gestational age (SGA) (Missouri 1989-2005)
- $\uparrow$ Stillbirth relative risk (RR) by 50% (Denmark-944,000 births)
- $\uparrow$ Risk of bipolar disease & schizophrenia
- $\uparrow$ Increased risk of death before 5 years of age (2% increase in congenital abnormality)
- $\uparrow$ Risk of autism by 21% for every 10 years of paternal age (meta analysis)
  - NO change in attention deficit disorder (ADD)

Preconception Female

**Health Status**
- BMI: 86.3% of adults in the US will meet criteria for overweight (>25) or obese (>30) categories by the 2030¹
- Overweight/Obesity: important risk factor for macrosomia (Large for Gestational Age, LGA)²

**Movement**
- Physical activity patterns across the life course may decrease risk of preterm birth with long-term physically active women at decreased risk of delivering preterm & with a low birth weight infant³

¹ Wang Y et al. *Obesity (Silver Spring).* 2008;16(10):2323-2330.
Advanced for Maternal Age (AMA): >35 Years

**Maternal**

- Increases risk of spontaneous abortion (SAb), gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), intrapartum complications (amniotic fluid embolism), twins, risk of developing chronic disease
- Decreased fertility with advancing age (>35 years)

**Neonatal**

- Increases risk of still birth congenital malformations, aneuploidy, & risk of autism

Children born to older mothers have positive physical and emotional health & the moms cope well with the physical/emotional demands of pregnancy & parenting.

Sutcliffe AG et al. BMJ. 2012;345:e5116.
• Human Teratogenic risk is undetermined for 90% of drugs approved for human use.

• In the Medicaid population 1 in 5 pregnant women fill an opioid prescription-a rate that increased 23% in 7 years. Medicaid covers the expenses of 40% of births in the US

• Endocrine disruptors: plastics & pesticides

• Infections: zika, CMV*, rubella, syphilis, CT*, GC*, HSV*, varicella

• EMF*: cell phones

• Pollution: air/H2O, polycyclic aromatic hydrocarbons (PAHs) (transport emissions)

• Use during pregnancy increased by 62% (2002-2014)

• Observed effect in the offspring depend on age & trimester during which they were exposed to the drug, and dose & route of administration of the drug

• Effects are not well understood, but adverse effect has been seen. Further research is needed

* CMV= Cytomegalovirus, CT= Chlamydia, GC= Gonorrhea, HSV= Herpes simplex virus, EMF= Electromagnetic frequency

6. Fine JD et al. JAMA Psychiatry. Published online March 27, 2019.
INFERTILITY

Recognize: Increased Use of Fertility Services

Defined

Prevalence

Incidence-Married\(^2\)

>12 months (< age 35) & >6 months (≥ age 35)\(^1\)

2006-2010: 11% (all women)\(^2\)

Age 15-34 years: 7.3-9.1%
Age 35-39 years: 25%
Age 40-44 years: 30%

\(^1\) Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril.* 2008;90(Suppl):560

Female Infertility Around the Globe

**Highest in:** South Asia, Central/Eastern Europe, North Africa/Middle East, Oceania, Sub-Saharan Africa, Central Asia

**2010: Age 20-44**

- 1.9% were unable to have 1\textsuperscript{st} live birth\(^1\)
- 10.5% were unable to have 2\textsuperscript{nd} live birth\(^1\)

**Recognize:** lack of obstetric services & increased maternal complications. For e.g. Postpartum hemorrhage, endometritis, pelvic inflammatory disease (PID)

# Causes of Infertility

**MALE:**¹  
- Pretesticular & Testicular deficiency- (Hormonal & Metabolic)  
- Posttesticular deficiency (Anatomical & Structural)

**FEMALE:**²⁻³  
- Ovulatory dysfunction: 27-32%  
- Tubal Damage: 12-14%  
- Endometriosis: 5-11%  
- Coital Problems: 6%  
- Unexplained: 10-29%  
- Other Causes: 5-14%

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Infertility: Sperm Quality & Probiotics

• 6-fold INCREASE with sperm motility & 2-fold DECREASE concentration of DNA fragmentation using *L. Rhamnoses & B. Longus*, 3 & 6 weeks$^1$

• Quality & quantity of sperm improved with *L. paracasei* & prebiotics$^2$

Sperm DNA Damage

Men whose partners had been affected by Recurrent Pregnancy Loss (RPL) had twice as much sperm DNA damage compared with the unaffected men. Men whose partners had suffered miscarriage also had a four-fold increase in the amount of reactive oxygen species compared with unaffected men.

Recognize

- ↑ Chronic disease
- DNA fragility
- Declining immune surveillance
- Toxic exposure
- ↓ Gut health
- Nutrient insufficiencies
- Stress response

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There is no doubt that diet is a modifiable factor that could impact male fertility.

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 (Spontaneous Abortion) and is modifiable

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Miscarriage—Definition & Disrupted Cycle

**Defined**

- Pregnancy loss before 20\textsuperscript{th} week gestation (WHO definition: weighing <500g\textsuperscript{1})
- 1990-2011\textsuperscript{2}
  - Risk of pregnancy loss: 19.7%
  - Risk of early pregnancy loss: 13.5% (<7 weeks)

**Causes**

- Reproductive factors/endocrine disruption\textsuperscript{3}
- Prolonged ovulation to implantation (disrupted luteal phase)\textsuperscript{4}
- Prolonged time to conception (follicular phase)\textsuperscript{5}

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Miscarriage—Meds & Substances

Maternal Heavy Smoking >10 cig/daily\(^1\) & Paternal smoking, too\(^2,3\)

EtOH\(^*\): 3 drinks/week, increases 1st trimester loss\(^4\)

Cocaine increases 1st trimester loss & PTB\(^5\)

NSAID use: around time of conception (1st 2 weeks)\(^6\)

Maternal Caffeine intake: 100-1000 mg\(^7,8\)

Empower: Change with improved well-being by recognizing root cause for addictive behaviors

*EtOH= Ethyl alcohol

Miscarriage: Endocrine System

1. Poorly controlled diabetes mellitus
2. Hyperprolactinemia
3. PCOS*: Miscarriage rate in women with PCOS may be as high as 20-40%

4. Thyroid
   • Increased thyroid peroxidase (TPO) or thyroglobulin antibodies (TgAb) (e.g., Hashimoto’s thyroiditis)
     - Common in 10% of females & 2% of males
     - ↑ in celiac (e.g., tissue transglutaminase antibodies (tTG))
     - Combined selenomethionine (83mcg) & myoinositol (600mg)
     - ↓ TPO-TgAb & thyroid stimulating hormone (TSH)

*PCOS= Polycystic ovary syndrome

Thyroid Function in Pregnancy

• An estimated 300,000 pregnancies impacted by thyroid disease in the United States annually.¹

• For the first 10-12 weeks of pregnancy, the baby is completely dependent on the mother for the production of thyroid hormone. By the end of the first trimester, the baby’s thyroid begins to produce thyroid hormone on its own. The baby, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones.¹

• Hypothyroidism is the most commonly encountered clinical disorder in pregnant women.²

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Thyroid Conditions Range From **Too Little** to **Too Much** Thyroid Hormone\(^1-5\)

- **Subclinical hypothyroid**
- **Overt hypothyroid**
- **Autoimmune thyroiditis, Hashimoto’s thyroiditis** (Hypothyroid)
- **Hyperthyroid** (autoimmune, Grave’s Disease)


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Thyroid disease is associated with disorders in maternal and fetal advancement

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preconception</th>
<th>Pregnancy</th>
<th>Postpartum</th>
</tr>
</thead>
</table>
| Hyperthyroidism, Overt 1,3-5   | Congenital malformations       | Maternal: heart failure, placental abruption, preeclampsia, preterm delivery  
Fetal: goiter, intrauterine growth restriction, small for gestational age, stillbirth, thyroid dysfunction |                                        |
| Hyperthyroidism, Subclinical 1,3-5 | —                              | None                                    |                                        |
| Hypothyroidism, overt 1-5      | Decreased fertility, increased miscarriage | Maternal: Anemia, gestational hypertension, miscarriage, placental abruption, preeclampsia, Myopathy  
Congestive heart failure  
Fetal: severe cognitive, neurological and developmental abnormalities, impaired brain development (if untreated in mother)  
preterm birth, low birth weight | Maternal thyroid dysfunction, hemorrhage |
| Hypothyroidism, subclinical 1-5 | Effects similar to overt hypothyroidism | Effects similar to overt hypothyroidism | Effects similar to overt hypothyroidism |

Nutrients Influencing Healthy Thyroid Function

**Proper production thyroxine (T4)**

- Iodine
- Iron
- Magnesium
- Selenium
- Zinc
- Vitamins C, D, E
- B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>
- Tyrosine

**Reduce TPOAb and TgAb**

- Myo-inositol
- Selenium

**Central and peripheral T4 to triiodothyronine (T3) via deiodinases**

- Selenium
  - Zinc

**Improve cellular sensitivity to thyroid hormones**

- Zinc
- Vitamin A

**Support mitochondria**

- Magnesium
- Vitamin C, E
- B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>
- CoQ<sub>10</sub>
- Selenium
### Polycystic Ovary Syndrome (PCOS)

#### Definition
- **Defined in 1935**
  - Androgen excess
  - Menstrual irregularity
  - Cardio metabolic dysfunction
  - Obesity
  - Insulin resistance
  - Anovulatory infertility

#### Criteria & Prevalence
- **NIH** (1990) – 6% (5-8%, n=18 trials)
- Rotterdam (2003) – 10% (8-13%, n=15 trials)
- Androgen excess & PCOS society – 10% (7-13%, n=10 trials)

#### Etiology
- **Heterogenous**
  - Interaction of multiple gene variants & environmental factors like diet & obesity
  - **Estimated 20% genetic influence**
    - 30+ gene variants so far, e.g. LH*/hCG receptor (LHCGR)
    - Thyroid adenoma associated protein (THADA) impaired beta cell function

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PCOS: Physiology

- **Impaired follicle development**
  - Increased LH to FSH ratio—hypersecretion of androgens in the theca cells\(^1\)

- **Insulin resistance & hyperinsulinemia**
  - 50-70% of women with PCOS\(^2\)
    - Hypersensitive to insulin-stimulating androgen secretion & GLUT 4 secretion\(^3\)

- **Obesity worsens ovulatory dysfunction & pregnancy outcome**
  - Common in PCOS—but occurs independent of PCOS—it’s 2 problems, not 1\(^4\)

- **Prevalence of obesity varies widely across populations & PCOS does not**
  - Prevalence of PCOS w/weight does not vary (8-2-9.9%)\(^4\)

- **Lifestyle factors**
  - High GI* diet, because of insulin resistance & association with obesity\(^5\)

- **Environmental factors**
  - Androgen mimicking environmental toxins\(^5\)-\(^7\)

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*\(\text{GI} = \text{Glycemic index}\)

PCOS: Interventions

• **Lifestyle intervention** is recommended as first-line management for women with PCOS and obesity\(^1\)

• Women with PCOS can significantly benefit from lifestyle changes, specifically, eating a low-glycemic diet, incorporating nutritional supplements, increasing their activity level, and managing stress\(^2-5\)

PCOS & Probiotics

• Co-administration of vitamin D₂: 50,000 IU + 8 BIL CFU probiotic VS. no probiotic for 12 weeks

  **Results**
  o Improved mood, markers of inflammation & androgen excess
  o Decreased total testosterone (T), hsCRP, malondialdehyde (MDA)*
  o Increased total antioxidant concentration (TAC), glutathione (GSH)
  o Improved Beck Depression scale

  *measures oxidative stress

• **Strains:** *L. acidophilus, B. bifidum, L reuteri* and *L. fermentum*

Testosterone, the hormone responsible for the secondary sexual characteristics of males, stimulates spermatogenesis.

Estrogen assists in endometrial regrowth, ovulation, and also responsible for the secondary sexual characteristics of females.

Gonadotropin-releasing hormone (GnRH) is responsible for the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Follicle stimulating hormone (FSH) stimulates the release of eggs from the ovaries. FSH is also critical for sperm production.

Luteinizing hormone (LH) stimulates the production of estradiol in the ovaries and the production of testosterone from Leydig cells in the testes.


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The Menstrual Cycle
Rhythmic, predictable, and turbulent as the ocean tides

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Hypothalamic-Pituitary-Gonadal (HPG) Axis Governs the Menstrual Cycle

**Day 1-14 Follicular phase:** Estrogen predominant—growth and development

**Day 14 GnRH surge generator:** Preovulatory surge of GnRH occurring several hours prior to LH surge

**Day 14 Luteal surge:** Mature follicle released for fertilization, marking the transition from estrogen dominance to progesterone dominance

**Day 15-28 Luteal phase:** Progesterone rises due to follicular luteinization, and the corpus luteum is formed continuing to secrete progesterone and estrogens, which further inhibits follicular development

**No fertilization:** Endometrial lining impacted by inflammatory prostaglandins resulting in menses; progesterone decline

**Day 28 Menstruation:** Discharge of unused endometrium; progesterone and estrogen low


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Fluctuating Estradiol and Progesterone Levels

Phases of the Ovarian Continuum

A. In childhood and menopause
B. In pubertal development
C. In PCOS, usually associated with the presence of increased adiposity
D. perimenopausal period
E. After breastfeeding during the period of returning fertility, the menopausal transition, and in women presenting hypothyroidism
F. Adequate hormonal balance between estradiol and progesterone
G-H. Exogenous hormone administration

Manage Aromatase (CYP19) and Control Estrogen Biosynthesis

Production and conversion of estrogen

Production:
Aromatase (CYP19) transforms androstenedione and testosterone to E1 and E2
Aromatase (CYP19) Is Critical to Ovarian Follicle Maturation, Estrogen Production, and the Luteal Surge

- Mature follicle **theca cells** provide **androstenedione**, an estrogen precursor, to the granulosa cells, where androstenedione is **aromatized** (CYP19) to **estrogen**

- **Granulosa cells** transform androstenedione to estrogen (the “**estrogen boost**”) that triggers the pituitary signal to transition to the luteal phase via **luteal surge**


The “Pregnenolone-” or “Cortisol Steal”

Increased demand for cortisol (i.e., chronic stress) reduces availability of estrogen precursors DHEA and androstenedione

This may result in reduced levels of pregnenolone and progesterone, whereby...

**E:P ratio increases**

Aromatase is upregulated by prostaglandins\(^1\)

- Responds to positive feedback cycle\(^2\)
- Increased levels of aromatase are found in higher fat-to-muscle ratio\(^2\)
- Increased aromatase levels are linked to:
  - Synovial fluid in rheumatoid arthritis
  - Uterine fibroids
  - Endometriosis
  - Breast cancer cells

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Cortisol Dysregulation

Relation Between Stress and Metabolic Disorders

HPA axis dysregulation is an important biological link between stress, depression, and diabetes.


Evidence Shows Reproductive Function Declines at Both Extremes of Human Energy Balance

- Hyperinsulinaemia in obese men has an inhibitory effect on normal spermatogenesis and can be linked to decreased male fertility.¹
- Women with PCOS demonstrate hyperinsulinaemia and/or insulin resistance.²
- Obesity also potentially adversely affects the endometrium, implantation and early fetal development³, thus increasing the risk of miscarriage.⁴


Nutritional Bio-actives Play Key Roles in Estrogen Metabolism

They share the same and different biochemical targets: production, storage/distribution, receptor binding/protection, Phase I and II detoxification.
Factors Associated with Risk for Endometriosis

<table>
<thead>
<tr>
<th>Factors Linked to Increased Risk</th>
<th>Factors Linked to Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of endometriosis</td>
<td>Current use of oral contraceptive pills</td>
</tr>
<tr>
<td>Earlier age at menarche</td>
<td>Increased parity</td>
</tr>
<tr>
<td>Short menstrual cycles (&lt;27 days) and long duration menses (&gt; 7 days)</td>
<td>Increased body mass index (BMI)</td>
</tr>
<tr>
<td>Reduced salivary cortisol levels</td>
<td>Regular exercise</td>
</tr>
<tr>
<td>Genetic influences</td>
<td>Later age at menarche</td>
</tr>
<tr>
<td>Infertility or nulliparity</td>
<td>Dietary intake of fish and omega-3 fatty acids</td>
</tr>
<tr>
<td>History of excessive caffeine or alcohol</td>
<td>History of breast feeding</td>
</tr>
<tr>
<td>History of chronic intestinal inflammatory conditions (Inflammatory Bowel Syndrome, Crohn’s, celiac disease, etc.)</td>
<td>Increased intake of omega-3 fatty acids and reduction of trans fats in diet</td>
</tr>
</tbody>
</table>


# Current Treatment and management strategies for Endometriosis ¹⁻⁶

<table>
<thead>
<tr>
<th>Conventional Medical Options</th>
<th>Lifestyle Modifications</th>
<th>Natural Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Pain Management</strong></td>
<td>- Aerobic exercise</td>
<td>- Nutritional/dietary changes</td>
</tr>
<tr>
<td>- Use of common analgesics or NSAIDs</td>
<td>- May reduce/moderate estrogen and increase endorphins</td>
<td>- Eliminate food allergies</td>
</tr>
<tr>
<td>- <strong>Hormonal therapy</strong></td>
<td>- Improve dietary intake</td>
<td>- Decrease fat intake</td>
</tr>
<tr>
<td>- Continuous oral contraceptives for shorter, lighter menses</td>
<td>- Increase intake of fruits and vegetables</td>
<td>- Avoid refined sugar and carbohydrates</td>
</tr>
<tr>
<td>- Keep S.estradiol &lt; 30</td>
<td>- Consider plant based diet</td>
<td>- Increase fiber to support regular elimination</td>
</tr>
<tr>
<td>- Gonadotropin-releasing hormone (Gn-RH) agonists and antagonists to lower estrogen levels, prevent menses and shrink endometrial tissues</td>
<td>- Increase amount of omega-3 fatty acids</td>
<td></td>
</tr>
<tr>
<td>- Progestin therapy including intrauterine devices, injections or pills can stop menses as well as endometrial implants</td>
<td>- Reduce alcohol and caffeine</td>
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<tr>
<td>- Aromatase inhibitors to reduce estrogen levels</td>
<td>- Alcohol shown to increase estrogen levels so reducing or stopping will help</td>
<td></td>
</tr>
<tr>
<td>- <strong>Surgical intervention</strong></td>
<td>- Stress reduction and emotional support</td>
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</tr>
<tr>
<td>- <strong>Conservative</strong> (laparoscopic) surgery to maintain fertility removes endometrial implants but preserves uterus and ovaries</td>
<td>- Avoid stressful situations and/or high stress people</td>
<td></td>
</tr>
<tr>
<td>- <strong>Semi-conservative</strong> surgery involves hysterectomy and implant removal</td>
<td>- Practice stress reduction techniques: yoga, meditation, journaling</td>
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<tr>
<td>- Radical surgery with hysterectomy and bilateral oophorectomy</td>
<td>- Meet with therapist or counselor if needed</td>
<td></td>
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<tr>
<td></td>
<td><strong>Acupuncture</strong></td>
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<tr>
<td></td>
<td>- Evidence based therapy that has been shown to reduce pain and stress associated with EMS</td>
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</tr>
</tbody>
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Human Chorionic Gonadotropin (hCG): The Pregnancy Hormone

- Major role of hCG during pregnancy includes ovulation induction, maintenance of the corpus luteum and stimulation of its progesterone production during the first 9 weeks of pregnancy.¹
- Abnormalities in the production and the circulating levels of hCG have been associated with a large array of pregnancy complications,² such as miscarriages, fetal chromosomal anomalies, preeclampsia³ and disturbances in fetal growth and development.⁴

Genetic Assessments

<table>
<thead>
<tr>
<th>Chromosomal</th>
<th>Gene Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rare (&lt;1%)</td>
<td>• Common (1-49%)</td>
</tr>
<tr>
<td>• Devastating</td>
<td>• Cumulative, with significant impact on global health</td>
</tr>
<tr>
<td>• Relatively little impact on global health</td>
<td>• Manipulatable</td>
</tr>
<tr>
<td>• Often non-manipulatable</td>
<td>o Other manipulatable gene processes¹</td>
</tr>
<tr>
<td></td>
<td>– Histone modification</td>
</tr>
<tr>
<td></td>
<td>– DNA methylation</td>
</tr>
<tr>
<td></td>
<td>– Imprintome</td>
</tr>
<tr>
<td></td>
<td>– Micro RNA</td>
</tr>
<tr>
<td></td>
<td>– mTORC*</td>
</tr>
</tbody>
</table>

¹other manipulatable gene processes include:


*mechanistic target of rapamycin complex (mTORC)*
We Know

MTHFR—
Methylenetetrahydrofolate reductase

• Common SNP
• Many MTHFR Polymorphisms > 40 identified
• C677>T and A1298>C most studied
• SNP’s associated with reduced MTHFR enzymatic activity in activating or methylating folate
  • 35% activity reduction heterozygous
  • 70%-90% activity reduction homozygous recessive

5-methyltetrahydrofolate (5-MTHF): An Alternative to Folic Acid

- **Methylenetetrahydrofolate reductase** (MTHFR) is less active in people with a genetic polymorphism of **MTHFR C677T**.

- This polymorphism results in less biologically available 5-MTHF which increases the risk of NTDs (Neural Tube Defects).²

- 5-MTHF supplementation can increase folate levels in early pregnancy that may prevent NTDs.¹³⁴

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Autism Spectrum Disorder (ASD)

• About 1 in 59 children has been identified with ASD according to estimates from CDC.¹
• ASD is 4 times more prevalent in males than in females. ¹
• Identified correlations:²-⁷
  ➢ genetic factors, environmental factors, short inter-pregnancy interval, environmental chemicals- alcohol, cocaine, and toxic metals taken by the mother during pregnancy
  ➢ folate deficiency, maternal stress
  ➢ sustained post-partum inflammation from previous pregnancy for short interval and infertility unintended pregnancy
  ➢ maternal infections during pregnancy
  ➢ maternal and fetal inflammation, maternal diseases (diabetes mellitus), including autoimmune diseases or allergic diseases such as asthma
  ➢ pregnancy and birth complications like extreme prematurity before 26 weeks, low birth weight, multiple pregnancies

Methylation Map

Address methylation issues 3 months prior through the 1st month after conception

720% increase risk ratio of Autism


Functional Roles of One-Carbon Metabolism

1. Gene regulation (activation/inactivation)
2. Biotransformation (phase 2)
3. Neurotransmitter formation: dopamine, epinephrine, and serotonin
4. Hormone biotransformation—estrogens
5. Immune cell differentiation (T cells, NK cells)
6. Energy metabolism (CoQ 10, carnitine, ATP)
7. Myelination of peripheral nerves
8. RNA and DNA synthesis (thymine-methyluracil)
9. Post transcriptional modulation (e.g. methylcytosine)

## Preconception Male: Assessment & Interventions

<table>
<thead>
<tr>
<th>Age &amp; BMI</th>
<th>Health Status</th>
<th>Lifestyle</th>
<th>Exposure</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Age</td>
<td>□ HTN</td>
<td>□ Alcohol / Tobacco / Drug / THC or CBD / Other</td>
<td>□ Medications that may interfere w/semen quality: antidepressants, calcium channel blockers, alpha-adrenergic blockers, antiepileptics, antiretroviral drugs</td>
<td>□ Intensity: ≥60% of VO$_2$ max &amp; ≤80% of VO$_2$ max</td>
</tr>
<tr>
<td>□ &lt;30 years</td>
<td>□ Hyperlipidemia</td>
<td>□ Smoking</td>
<td>□ Chemical exposure</td>
<td>□ Frequency: 5X weekly, &gt;30 minutes</td>
</tr>
<tr>
<td>□ &gt;40 years</td>
<td>□ DMII</td>
<td>□ Caffeine intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ BMI &amp; body composition</td>
<td>□ Testicular cancer</td>
<td>□ Vegan / Vegetarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ &gt;19</td>
<td>□ Stress-affective or psychotic disorders, ASD, ADD</td>
<td>□ Omega 6:Omega 3 ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ &lt;25</td>
<td>□ R/O sleep apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Protein (Amino Acids)

- □ Acetyl l-carnitine: 1000 mg

### Fats

- □ Omega 3 Fatty Acids: DHA & EPA

### Minerals

- □ Selenium: 80-300 mcg
- □ Zinc Picolinate: 10 mg

### Vitamins

- □ Vitamin A ≤5000 IUs
- □ Vitamin C: 1 gm
- □ Vitamin E: 100-200 mg
- □ Inositol: 2 gm
- □ Methylfolate: 1000 mcg-5 mg (higher dosing, 3-4 months)
- □ Methylcobalamin
- □ Vitamin D

### Antioxidants

- □ CoQ10: 200-300 mg
- □ NAC: 600 mg
- □ EGCG, green tea: 2-6 cups daily

### Probiotics

- □ *L. rhamnosus* & *B. Longus*
- □ *L. paracasei* & prebiotics

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<table>
<thead>
<tr>
<th>Age &amp; BMI</th>
<th>Health Status</th>
<th>Lifestyle</th>
<th>Exposure</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Teen</td>
<td>□ Thyroid Disruption (Hypo/Hyper)</td>
<td>□ Alcohol / Tobacco / Drug / THC or CBD / Other</td>
<td>□ Toxic exposures</td>
<td>□ Intensity: mild, moderate, high-habitual</td>
</tr>
<tr>
<td>□ &gt;20 years &amp; &lt;35 years</td>
<td>□ DMII</td>
<td>□ Smoking</td>
<td>□ Teratogens</td>
<td></td>
</tr>
<tr>
<td>□ AMA, &gt;35 years</td>
<td>□ HTN</td>
<td>□ Caffeine intake ≤ 500mg daily</td>
<td>□ NSAID use</td>
<td></td>
</tr>
<tr>
<td>□ V-AMA, &gt;45 years</td>
<td>□ PCOS</td>
<td>□ Vegan / Vegetarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ BMI &amp; body composition</td>
<td>□ Endometriosis</td>
<td>□ Omega 6:Omega 3 ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ &gt;19</td>
<td>□ Stress dysregulation (SDP)-affective or psychotic disorders, ASD, ADD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ &lt;25</td>
<td>□ Homocysteinemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Protein (Amino Acids)**

- Omega 3 Fatty Acids:
  - DHA 700-1000 mg
  - EPA 500 mg

**Fats**

- □ Omega 3 Fatty Acids:
  - DHA 700-1000 mg
  - EPA 500 mg

**Minerals**

- □ Iron (elemental iron) 25 mg
- □ Iodine 150 mcg
- □ Selenium 200 mcg
- □ Zinc 25 mg

**Vitamins**

- □ Vitamin A ≤ 5000 IUs
- □ Methylfolate 1000 mcg
- □ Methylcobalamin
- □ Vitamin D 2000 IUs
- □ B Vitamin, Complex

**Antioxidants**

- □ Carotenoids (R/O/Y)
- □ Vitamin C
- □ Vitamin E
- □ Lactobacilli species
Multiple Micronutrient Supplementation

“Randomized controlled trial supplementation has yielded mixed results and raised a hypothesis that it is unlikely to be one single micronutrient that will be beneficial in these complicated pregnancies and rather that more can be gained by comprehensively supporting maternal homeostasis through multiple-micronutrient supplementation (MMS).”

DHA & Preterm Birth: 600mg in Pregnancy

The Kansas University DHA Outcomes Study (KUDOS) found a significant reduction in early preterm births with a supplement of 600 mg DHA per day compared to placebo.

Breast Milk Has Higher Levels of Specialized Pro-resolving Lipid Mediators (SPMs)

- SPMs and their precursors are modulated in mothers and infants during pregnancy, thus may play an important role in maternal-fetal health.¹-⁴
- n-3 Fatty acid supplementation during pregnancy was associated with an increase in SPM precursors in the offspring at birth. ¹-⁴
- Increased DHA intake was associated with elevated maternal plasma Resolvin D1 (RvD1) and RvD2 in neonatal intensive care unit admission indicating that increased n-3 fatty acid intake may provide increased substrate for the production of SPM during high-risk pregnancy/delivery conditions.³
- Breast milk from inflamed mammary glands (mastitis) has lower SPM levels.⁵

³ Nordgren TM et al. Nutrients. 2019;11(11).
L-Carnitine

Energy production—association with insulin resistance (GDM)—miscarriage

• **Energy**: L-carnitine transports the chains of fatty acids into the mitochondrial matrix, thus allowing the cells to break down fat and get energy from the stored fat reserves

• **GDM**: Treatment with 2000 mg/day of Carnitine avoids a striking rise in free fatty acids, which is thought to be the main mediator of insulin resistance and gestational diabetes

• **Miscarriage**: Dietary carnitine supplementation may reduce the risk of spontaneous miscarriage

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Zinc

- Important cofactor for more than 300 identified zinc metalloenzymes
- Zinc insufficiency in late pregnancy disrupts neuronal replication and synaptogenesis
- Maternal deficiency is associated with decreased DNA, RNA, and protein content in the F1 brain
- Zinc deficiency affects one in five world inhabitants
- Zinc supplementation reduces the risk of preterm birth, though not SGA

### Perinatal Nutrient Deficiency Rates: Carnitine

<table>
<thead>
<tr>
<th>Carnitine Reference Range (nmol/ml)</th>
<th>1st Trimester</th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total: 34-78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free: 25-54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyl: 5-30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Range 500-3000mg (median dose, 1000mg)</th>
<th>Total</th>
<th>Free</th>
<th>Acyl</th>
<th>Total</th>
<th>Free</th>
<th>Acyl</th>
<th>Total</th>
<th>Free</th>
<th>Acyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester N=30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Trimester N=33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpartum N=9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Free</th>
<th>Acyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>56.7%</td>
<td>53.5%</td>
</tr>
<tr>
<td>12%</td>
<td>97%</td>
<td>84.8%</td>
</tr>
<tr>
<td>11.1%</td>
<td>11.1%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

### Perinatal Nutrient Deficiency Rates: Zinc

<table>
<thead>
<tr>
<th>Zinc Reference Range .66-1.0 mcg/ml</th>
<th>1st Trimester</th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=27</td>
<td>N=27</td>
<td>N=2</td>
</tr>
</tbody>
</table>

| Dose Range, 30-60 mg (Median Dose, 50mg) | 37% | 85% | 50% |

Vitamin D

- Approximately 2 out of 3 pregnant women in the United States have suboptimal vitamin D status, with even higher prevalence reported among Black and Mexican-American women\(^1\)

- 80% of vitamin D supply is derived from endogenous production in the skin whereas only about 20% of vitamin D supply is derived from oral intake-with individual and seasonal variations to take into account \(^2\)

Iron

Iron deficiency is estimated at 16.3% in pregnant women with a significantly higher prevalence among Non-Hispanic black, Mexican American and low-income pregnant women

### Perinatal Nutrient Deficiency Rates: Vitamin D

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester</th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OH, D3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient &lt;30ng/dl</td>
<td>25%</td>
<td>22.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Insufficient ≥30-&lt;50 ng/dl</td>
<td>55%</td>
<td>46.5%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Dose Range: 1000-10,000 IU/day, Median dose 2,000 IU

### Perinatal Nutrient Deficiency Rates: Iron

<table>
<thead>
<tr>
<th>Iron Dose Range 65-260 mg (Median Dose, 65 mg)</th>
<th>1st Trimester</th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=66</td>
<td>N=69</td>
<td>N=29</td>
</tr>
<tr>
<td>Hgb (gm/dL)</td>
<td>15.1%</td>
<td>49.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>28.8%</td>
<td>85.5%</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Choline & Placental Health

930 mg/day vs. 480 mg/day maternal choline

- Fetal brain development
- \( \uparrow \) pCRH* & GR* methylation & \( \downarrow \) pCRH transcription
- Extra choline decreased placental expression of cortisol regulating genes

*pCRH=placental corticotropin releasing hormone
*GR=glucocorticoid receptor

Other Common Deficiencies

• Magnesium¹
• Essential fatty acids²
• Probiotics³-⁴
• Iodine⁵-⁶

Risk factors influencing the maternal microbiota (Gestational Period)

- Weight gain
- Maternal BMI
- Diet
- Antibiotics

Maternal influence (Postnatal Period)

- Breast milk
  - Microbes
  - HMOs

Metabolic disease
  - Obesity
  - Diabetes

GI conditions
  - IBS
  - IBD
  - Crohn’s

Immune disease
  - Asthma
  - Allergy

At birth, Infant exposed to maternal microbiota

Successive colonization impacts host metabolism and immune education

First 1000 Days and Beyond—The Microbiome and Child Growth

The maternal nutrition and microbiota, delivery mode, gestation time, and type of feeding strongly influence the infant’s microbiota.

Maternal microbes are transmitted to offspring during childbirth, representing a key step in the colonization of the infant gut.

The mother’s microbiota may influence fetal growth and duration of pregnancy.

Interventions that target the microbiota during certain stages in the life cycle may help to improve child growth.
## Probiotic Usage During Pregnancy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A double-blind, placebo-controlled trial with women of a personal or partner history of atopic disease randomized at 14-16 weeks of gestation received either <em>Lactobacillus rhamnosus HN001</em> at a dose of $6 \times 10^9$ colony-forming units (cfu) or placebo to be taken daily from enrolment until 6 months postpartum if breastfeeding.</td>
<td>Mothers in the probiotic treatment group reported significantly lower depression and anxiety scores in the postpartum period.</td>
<td>Slykerman RF et al. <em>EBioMedicine</em>. 2017;24:159-165.</td>
</tr>
<tr>
<td>A double-blind, randomized, placebo-controlled parallel trial was conducted in New Zealand in which the pregnant women with a personal or partner history of atopic disease were randomized at 14–16 weeks’ gestation to receive <em>Lactobacillus rhamnosus HN001</em> ($6 \times 10^9$ colony-forming units) or placebo daily.</td>
<td>HN001 supplementation from 14 to 16 weeks’ gestation may reduce gestational diabetes mellitus (GDM) prevalence, particularly among older women and those with previous GDM.</td>
<td>Wickens KL et al. <em>Br J Nutr</em>. 2017;117(6):804-813.</td>
</tr>
<tr>
<td>In a randomized placebo-controlled trial pregnant women from 35-week gestation to 6 months' post-partum and from birth to age 2 years in infants received <em>Lactobacillus rhamnosus HN001</em> (HN001) ($6 \times 10^9$ cfu) or <em>Bifidobacterium lactis HN019</em> (HN019) ($9 \times 10^9$ cfu).</td>
<td>HN001 supplementation significantly reduced the prevalence of eczema at 11 years. HN019 has no effect on eczema.</td>
<td>Wickens KL et al. <em>Pediatr Allergy Immunol</em>. 2018;29(8):808-814.</td>
</tr>
<tr>
<td>In a double-blind, randomized placebo-controlled trial mothers from 14-16 weeks of gestation till 6 months post-partum if breastfeeding were taken <em>Lactobacillus rhamnosus HN001</em> (HN001) $6 \times 10^9$ cfu daily by but was not given directly to the child.</td>
<td>Maternal supplementation alone did not significantly reduce the prevalence of eczema without infant supplementation.</td>
<td>Wickens K et al. <em>Pediatr Allergy Immunol</em>. 2018;29(3):296-302.</td>
</tr>
<tr>
<td>Pregnant women beginning 2-5 weeks before delivery and continuing for 6 months during lactation received daily supplements of either $6 \times 10^9$CFU/day <em>Lactobacillus rhamnosus HN001</em>, $9 \times 10^9$ CFU/day <em>Bifidobacterium lactis HN019</em> (n=35) or a placebo.</td>
<td>HN001 supplementation showed protective cord blood immune parameters as well as immunomodulatory factors in breast milk.</td>
<td>Prescott SL et al. <em>Clin Exp Allergy</em>. 2008;38(10):1606-1614.</td>
</tr>
</tbody>
</table>
## Probiotic Usage During Pregnancy

<table>
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<tr>
<th>Study Design</th>
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</thead>
<tbody>
<tr>
<td>In a double blind randomized study, 62 pregnant women from atopic families received either Lactobacillus rhamnosus strain GG with a daily dose of $2 \times 10^{10}$ or placebo during the 4 weeks before giving birth and during breast-feeding.</td>
<td>Supplementation with probiotics during pregnancy and breast-feeding improved the immunoprotective potential of breast-feeding and protected against atopic eczema during the first 2 years of life.</td>
<td>Rautava S et al. J Allergy Clin Immunol. 2002;109(1):119-121.</td>
</tr>
<tr>
<td>415 pregnant women received probiotic milk containing Lactobacillus rhamnosus GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12 or placebo from 36 weeks of gestation to 3 months during breastfeeding.</td>
<td>The administration of probiotics to mothers reduced the cumulative incidence of atopic dermatitis in the offspring of nonselected women during the first 2 years of life.</td>
<td>Dotterud CK et al. Br J Dermatol. 2010; 163(3):616-623.</td>
</tr>
<tr>
<td>1223 pregnant women carrying children at increased risk for allergy were randomized to probiotic capsule containing $5 \times 10^9$ CFU LGG, $5 \times 10^9$ CFU Lactobacillus rhamnosus LC705, $2 \times 10^8$ CFU Bifidobacterium breve Bb99, $2 \times 10^8$ CFU Propionibacterium freudenreichii shermanii or placebo for 2 to 4 weeks before delivery. The infants received the same probiotics plus galacto-oligosaccharides or a placebo for 6 months.</td>
<td>The probiotic treatment reduced IgE-associated diseases- atopic eczema. Lactobacilli and bifidobacteria more frequently colonized the guts of supplemented infants.</td>
<td>Kukkonen K et al. J Allergy Clin Immunol. 2007;119(1):192-198.</td>
</tr>
<tr>
<td>159 mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, were randomized to receive 2 capsules of $1 \times 10^{10}$ CFU Lactobacillus rhamnosus GG for 2 to 4 weeks before delivery and 6 months postnatally to their infants.</td>
<td>The frequency of atopic eczema in the probiotic group was half that of the placebo group in children aged 2 years and extended up to 4 years in the follow up study.</td>
<td>Kalliomäki M et al. Lancet. 2001; 357(9262):1076-1079. Kalliomäki M et al. Lancet. 2003; 361(9372):1869-1871.</td>
</tr>
</tbody>
</table>
# Probiotic Usage During Pregnancy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>112 pregnant women with a family history of allergic diseases received starting at 4-8 wks before delivery and continuing until 6 months after delivery with either a mixture of <em>Bifidobacterium bifidum BGN4</em>, <em>B. lactis AD011</em>, and <em>Lactobacillus acidophilus AD031</em>, or placebo in a randomized, double-blind, placebo-controlled trial.</td>
<td>The prevalence of <strong>eczema</strong> during the first 12months of life in infants was significantly lower compared to the placebo group.</td>
<td>Kim JY et al. <em>Pediatr Allergy Immunol</em>. 2010;21(2 Pt 2):e386-393.</td>
</tr>
<tr>
<td>A mixture of <em>Bifidobacterium bifidum</em>, <em>Bifidobacterium lactis</em>, and <em>Lactococcus lactis</em> was administered to the mothers of high risk children and also to the offsprings for the first 12 months of life.</td>
<td>Parental-reported <strong>eczema</strong> during the first 3 months of life was significantly reduced in the probiotic treated group.</td>
<td>Niers L et al. <em>Allergy</em>. 2009; 64(9):1349-1358.</td>
</tr>
<tr>
<td>In a double-blind, randomized, placebo-controlled trial of families with allergic disease, mothers received <em>L reuteri ATCC 55730</em> (1 x 10^8 CFU) daily from gestational week 36 until delivery. The infants continued with the same probiotic for one more year.</td>
<td>The probiotic treated group has <strong>less IgE-associated eczema</strong> during the second year.</td>
<td>Abrahamsson TR et al. <em>J Allergy Clin Immunol</em>. 2007; 119(5):1174-1180.</td>
</tr>
</tbody>
</table>
# Probiotic Usage During Pregnancy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 Pregnant women at 35-37 weeks of gestation who were diagnosed by Group B Streptococcus (GBS) culture as being GBS positive for both vaginal and rectal GBS colonization were randomly assigned and treated two placebo capsules or two probiotic capsules containing <em>Lactobacillus rhamnosus</em> GR-1 and <em>Lactobacillus reuteri</em> RC-14 of 1X10⁹ cells of both strains before bedtime until delivery. The vaginal and rectal GBS colonization was again tested in all the women on admission for delivery.</td>
<td>Supplementation of <em>L. rhamnosus</em> GR-1 and <em>L. reuteri</em> RC-14 could reduce the vaginal and rectal GBS colonization in pregnant women which could reduce early-onset Group B Streptococcus (GBS) infection and the need for antibiotic treatment during labor.</td>
<td>Ho M et al. <em>Taiwan J Obstet Gynecol.</em> 2016;55(4):515-518.</td>
</tr>
<tr>
<td>A double-blind placebo-controlled randomized trial of pregnant women with a new diagnosis of gestational diabetes or impaired glucose tolerance test received a daily <em>Lactobacillus salivarius</em> UCC118 at a dose of 10⁹ colony-forming units or placebo capsule from diagnosis until delivery.</td>
<td>Although the probiotic did not appear to have any beneficial glycemic effect or to improve pregnancy outcomes but seems to be safe in pregnant women.</td>
<td>Lindsay K et al. <em>Am J Obstet Gynecol.</em> 2015;212:496.e1-11.</td>
</tr>
</tbody>
</table>
In vivo effectiveness of bacteriocin produced by *L. salivarius* UCC118

Animal studies have shown protective effect of *L. salivarius* UCC118 against *Listeria* infection\(^1\)

The effect was dependent upon the production of bacteriocin by UCC118\(^1\)

In addition, *L. salivarius* UCC118 has been shown to reduce certain *Firmicutes* genus members in mice and pig microbiota and *Spirochetes* levels in the mice and pig microbiota\(^2\)

This effect was also dependent upon the production of bacteriocin\(^2\)

Though these animal studies indicate potential benefit, it should be noted that no human studies exist at this time.


3 million births with increased access to care, increased use of prenatal care, with a modest reduction in preterm births. But—not associated with changes in C-section rate, low birth weight (LBW), or NICU admission¹.

Our conclusion:
Change what we do during that prenatal care!
Use What We Have: 9 Months

Control What We Can: Lifestyle

Assess the Individual: Always

Preconception—First 1000 Days and Beyond
How Quickly Can You Turn On or Off Certain Genes?

6 hrs

A pre-pregnancy BMI $\geq 30 \text{ kg/m}^2$ irrespective of the amount of weight gained during pregnancy, is the most important independent determinant of the risk of caesarean section, delivery of a LGA infant and postpartum weight retention.

Assess the Individual:
Why Weight & Gain Matters...

Maternal weight exceeding 200 pounds and gestational weight gain of over 40 pounds have each been found to be associated with increased risk of autism and other intellectual/developmental disabilities in the child.

### BMI + Basal Metabolic Rate + Activity + Singleton

<table>
<thead>
<tr>
<th>Low Weight Gain</th>
<th>High Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low gestational weight gain</strong></td>
<td><strong>High gestational weight gain</strong></td>
</tr>
<tr>
<td>is associated with:</td>
<td>is associated with:</td>
</tr>
<tr>
<td>• Higher risk of SGA</td>
<td>• Lower risk of SGA</td>
</tr>
<tr>
<td>• Higher risk of preterm birth</td>
<td>• Lower risk of preterm birth</td>
</tr>
<tr>
<td>• Lower risk of LGA</td>
<td>• Higher risk of LGA</td>
</tr>
<tr>
<td>• Lower risk of macrosomia</td>
<td>• Higher risk of macrosomia</td>
</tr>
<tr>
<td>• No difference in cesarean delivery</td>
<td>• Higher risk of cesarean delivery</td>
</tr>
</tbody>
</table>

The quality and quantity of the nutrition you eat, the pollutants and stress that you expose your body to while pregnant, all affect the generational health of your family.
Macronutrient Focus:
Low Glycemic Index
40% Carbohydrate-30% Protein-30% Fat

“Normal pregnancy can be associated with a decline in energy and micronutrient intake from diet. Low dietary GI and GL were the best predictors of a favorable micronutrient profile.”

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fats</th>
<th>Carbohydrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal &amp; Plant-based</td>
<td>High quality, cold-pressed, Omega 6:Omega 3 balance</td>
<td>Whole, complex &amp; unrefined, fiber-rich</td>
</tr>
<tr>
<td>Organic, grass-fed &amp; wild caught (cold-water, low-mercury)</td>
<td>PUFA*</td>
<td>Rainbow of Foods</td>
</tr>
<tr>
<td>Adjust for omnivore, vegetarian, vegan</td>
<td>MUFA*</td>
<td>Flavor diversity</td>
</tr>
<tr>
<td></td>
<td>SFA*</td>
<td>Pro/Prebiotic food</td>
</tr>
</tbody>
</table>

*PUFA= Polyunsaturated fatty acid, MUFA= Monounsaturated fatty acid, SFA= Saturated fatty acid

Quality>Quantity
Hydration

Quality:
Clear, no added salt / sugar

Electrolyte focus:
Ca++*, Cl-*, Mg+*, K+*, Na+*

Amount:
• Pregnant: ½ body weight (lbs) in fluid ounces
• Breastfeeding: Full body weight (lbs) in fluid ounces

Biomarker:
Urine is clear and odorless

*Ca= Calcium, Cl= Chloride, Mg= Magnesium, K= Potassium, Na= Sodium
<table>
<thead>
<tr>
<th>Common $S_x$ of Pregnancy-PP</th>
<th>Nutrition &amp; Lifestyle</th>
<th>Bioactives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Eating frequency + protein emphasis</td>
<td>Ginger root, $B_6$</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Protein emphasis + iron rich foods &amp; sleep hygiene</td>
<td>Carnitine, iron (vitamin C), vitamin A, B vitamins</td>
</tr>
<tr>
<td>Mood Imbalance</td>
<td>Essential fat emphasis-cold water fish + protein emphasis</td>
<td>EPA/DHA, inositol, B vitamins, lavender aromatherapy, turmeric</td>
</tr>
<tr>
<td>Hyperemesis</td>
<td></td>
<td>Ginger root</td>
</tr>
<tr>
<td>Restless Legs</td>
<td>Magnesium rich foods + electrolyte replenishment</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>Vitamin C rich foods</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Headaches</td>
<td>Hydrating foods + fluid</td>
<td>CoQ10, carnitine, riboflavin ($B_2$), magnesium</td>
</tr>
<tr>
<td>Constipation</td>
<td>Adequate fiber + hydrating foods/fluid/kiwi fruit + phytonutrient intake + pre/probiotic rich foods</td>
<td>Magnesium, fiber</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common Symptom of Pregnancy</th>
<th>Nutrition &amp; Lifestyle</th>
<th>Bioactives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Limit stimulants sugar/caffeine + support melatonin secretion during daytime</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Heartburn</td>
<td>Limit antagonists: spicy, processed, gluten, dairy, sugar &amp; focus on alkaline rich foods/fluid, positional sitting/laying/eating</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Protein emphasis + adequate iron rich foods + sleep hygiene</td>
<td>Carnitine, iron (vitamin C), vitamin A, B vitamins</td>
</tr>
<tr>
<td>Constipation</td>
<td>Adequate fiber + hydrating foods/fluid / kiwi fruit + phytonutrient intake + pre/probiotic rich foods</td>
<td>Magnesium citrate</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Protein emphasis + adequate iron rich foods + sleep hygiene + resting priority</td>
<td>Carnitine, iron (vitamin C), vitamin A, B vitamins</td>
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<tr>
<td>Mood Imbalance</td>
<td>Essential fat emphasis-cold water fish + protein emphasis</td>
<td>EPA/DHA, inositol, B vitamins, turmeric, lavender, vitamin D</td>
</tr>
<tr>
<td>Mastitis</td>
<td>Hydration, lymphatic support</td>
<td>SPMs, <em>L. Gasseri</em>, <em>L. Fermentum</em>, <em>L. Salivarius</em></td>
</tr>
<tr>
<td>Needs by Trimester</td>
<td>Fetal Development</td>
<td>Maternal Needs</td>
</tr>
<tr>
<td>--------------------</td>
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<td>----------------</td>
</tr>
</tbody>
</table>
| **1**              | **P:** Methionine, cysteine  
|                    | **F:** DHA         | **P:** Carnitine |
|                    | **M:** Iron, Mg    | **C:** Soluble & insoluble fiber |
|                    | **V:** A, D, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂  
|                    | **Phyto:** Carotenoids | **M:** Iodine, Iron, Mg, Se |
|                    | **C:** Soluble & insoluble fiber |
|                    | **V:** A, C, D, B₆ | **Phyto:** Ginger |
| **2**              | **P:** Carnitine  
|                    | **C:** Soluble & insoluble fiber |
|                    | **F:** DHA         | **M:** Iodine, Mg, Zn |
|                    | **M:** Boron, Ca, Iron, Mg, Molybdenum, Phosphorous, Zn  
|                    | **V:** A, D, E, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂,  
|                    | **Phyto:** Rainbow, carotenoids | **V:** A, C, D, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂ |
| **3**              | **P:** Carnitine  
|                    | **C:** Soluble & insoluble fiber |
|                    | **F:** EPA & DHA   | **M:** Copper, Iodine, Iron, Mg, Se, Zn |
|                    | **M:** Copper, Iodine, Iron, Mg, Se, Zn  
|                    | **V:** Choline, A, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂, D, E,  
|                    | **Phyto:** Rainbow, carotenoids | **V:** Choline, A, D, E, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂,  
|                    | **Phyto:** Rainbow | **Phyto:** Rainbow |
|                    | **Probiotics:** L. Gasseri, L. Fermentum, L. Reuteri, L. Salivarius, L. Helveticus, B. Longum |
| **4**              | **P:** Carnitine  
|                    | **C:** Soluble & insoluble fiber |
|                    | **F:** DHA         | **M:** Copper, Iodine, Iron, Mg, Se |
|                    | **M:** Calcium, Copper, Iron, Mg, Se, Zn  
|                    | **V:** Choline, A, D, E, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂,  
|                    | **Phyto:** Rainbow, lutein, zeaxanthin | **V:** Choline, Inositol, D, B₁, B₂, B₃, B₅, B₆, Folate, B₁₂,  
|                    | **Probiotics:** L. Reuteri, L. Rhamnoses | **Phyto:** Rainbow |
|                    | **Probiotics:** L. Gasseri, L. Fermentum, L. Reuteri, L. Salivarius, L. Helveticus, B. Longum |

Rydbom, Fetal & Maternal Needs In Pregnancy, GrowBaby, 2018