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[1]
- The new generation is predicted to live a shorter life than their parents[2]
- Trend is strongly associated with obesity and diabetes[3]
- 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)[4]
- Miscarriage rates remain >19.7%[5]
- 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"[6]

1. Olshansky SJ et al. *N Engl J Med.* 2005;352(11):1138-1145.
2. Glei DA et al. National Research Council. *International Differences in Mortality at Older Ages: Dimensions and Sources*. 2010.
3. WHO. https://apps.who.int/iris/bitstream/handle/10665/272596/9789241565585-eng.pdf. Accessed May 5, 2019.
4. UN IGME. www.childmortality.org. Accessed October 22, 2014.
5. Rossen LM et al. *Paediatr Perinat Epidemiol*. 2018;32(1):19-29.
6. https://www.who.int/nutrition/publications/obesity/WHO_TRS_797/en/, WHO 1989 Tech Report, Series 797,34-42., Accessed May 14, 2014

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BIRTH PHENOTYPES & MATERNAL HEALTH

BABY

TOO SMALL

Small for Gestational Age (SGA)

TOO LARGE

Large for Gestational Age (LGA)

TOO STRESSED

Stress Dysregulation (SDP)

TOO EARLY

Preterm Birth (PTB)

MOM

High Blood Sugar

Gestational Diabetes Mellitus (GDM)

High Blood Pressure

Pregnancy Induced Hypertension (PIH)

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Healthy Parents=Healthy Kids

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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 unintended[1]
  - ✓ 16.7% of pregnant women begin care in 2nd trimester (after organogenesis)[2]
  - ✓ NO traditional preconception care for men

1. Finer LB et al. *Contraception*. 2011;84(5):478-485.
2. CDC. National Vital Statistics Reports. Timing and Adequacy of prenatal care in the United States, 2016.

Preconception RISK Assessment: **Male & Female**

Medical History	**Cont…**
• Chronic Disease	• Family History
• **Teratogens**	• Substance Use
• Reproductive History	• Infectious Disease
• **Genetic Conditions (variants, chromosomal abnormalities)**	• **Environmental Exposure**
• Social & Mental Health (Stress response)	• **Lifestyle (nutrients / movement)**
	• **Health Status**

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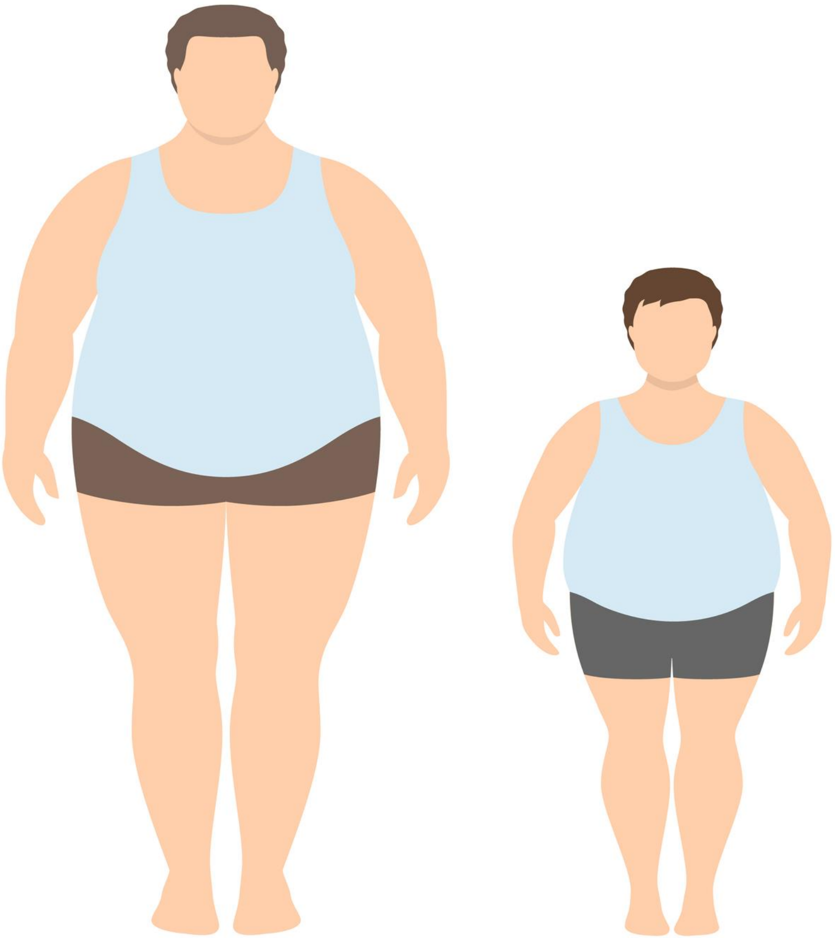
Preconception Male

- **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**
  - BMI: 86.3% of adults in the US will meet criteria for overweight (>25) or obese(>30) categories by the 2030[2]
  - There is a significant, but mild influence of overweight/obese fathers and their child's BMI after birth[3]



1. Salas-Huetos A et al. *Hum Reprod Update*. 2017;23(4):371-389.
2. Wang Y et al. *Obesity (Silver Spring).* 2008;16(10):2323-2330.
3. Mei H et al. *BMJ Open*. 2018;8(6):e018755.

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Advanced for Paternal Age (APA): $\geq$40 years[1]

- **Since 1980[2] 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

1. Ramasamy R et al. *Fertil Steril.* 2015;103(6):1402-1406.
2. Harris et al. *Rev Urol*. 2011; 3(4):e184-e190.

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Advanced Paternal Age & Risk of Adverse Birth Outcomes[1-8]

- ↑>35 years increases risk of gestational hypertension & preeclampsia (PE) in pregnancy
- ↑Preterm birth (PTB) by 14% ≥45 year old (US 2007-2016)
- ↑PTB, very PTB, & small for gestational age (SGA) (Missouri 1989-2005)
- ↑Stillbirth relative risk (RR) by 50% (Denmark-944,000 births)
- ↑Risk of bipolar disease & schizophrenia
- ↑Increased risk of death before 5 years of age (2% increase in congenital abnormality)
- ↑Risk of autism by 21% for every 10 years of paternal age (meta analysis)
    - NO change in attention deficit disorder (ADD)

1. Ramasamy R et al. *Fertil Steril.* 2015;103(6):1402-1406.
2. Crosnoe LE et al. *Curr Opin Obstet Gynecol.* 2013;25(3):181-185.
3. Hamilton BE et al. *Natl Vital Stat Rep.* 2015;64(12):1-64.
4. Ford WC et al. *Hum Reprod.* 2000;15(8):1703-1708.
5. Khandwala YS et al. *BMJ.* 2018;363:k4372.
6. Alio AP et al. *Am J Mens Health.* 2012;6(5):427-435.
7. Urhoj SK et al. *Eur J Epidemiol.* 2017;32(3):227-234.
8. Wu S et al. *Acta Psychiatr Scand.* 2017;135(1):29-41.

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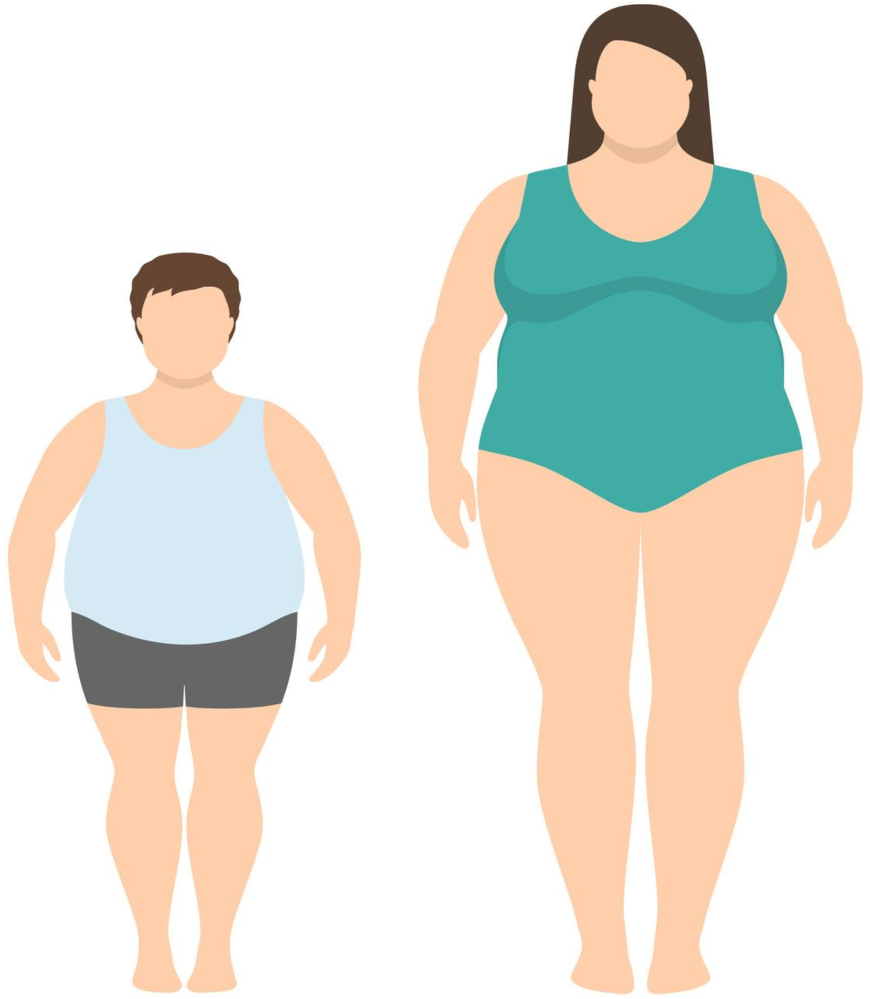
Preconception Female

- **Health Status**
  - BMI: 86.3% of adults in the US will meet criteria for overweight (>25) or obese(>30) categories by the 2030[1]
  - 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 infant[3]



1. Wang Y et al. *Obesity (Silver Spring).* 2008;16(10):2323-2330.
2. Dai RX et al. *Arch Gynecol Obstet*. 2018;297(1):139-145.
3. Vamos CA et al. *Matern Child Health J.* 2015;19(8):1775-1782.

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Advanced for Maternal Age (AMA): >35 Years

Maternal[1-9]

- 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[10]

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

1. Fitzpatrick KE et al. *BJOG*. 2016;123(1):100-109.
2. Waldenström U et al. *BJOG*. 2017;124:1235-1244.
3. Haslinger et al. *Swiss Med Wkly*. 2016;146:w14330.
4. Mathews TJ et al. *Natl Vital Stat Rep*. 2002;51(1):1-13.
5. Hamilton BE et al. *Natl Vital Stat Rep*. 2015;64(12):1-64.
6. Bacak SJ et al. *Am J Obstet Gynecol*. 2005;192(2):592-597.
7. Nybo Andersen et al. *BMJ*. 2000;320(7251):1708.
8. Khalil A et al. *Ultrasound Obstet Gynecol*. 2013;42(6):634-643.
9. Solomon CG et al. *JAMA*. 1997;278(13):1078-1083.
10. Khalil A et al. *Ultrasound Obstet Gynecol*. 2013;42:634-643.

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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.
Yarrow A. Latecomers: children of parents over 35, Free Press, MacMillan, New York 1991.
Morris M. Last-chance children: growing up with older parents, Columbia University Press, New York 1988.

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Teratogens

- Human Teratogenic risk is **undetermined** for 90% of drugs approved for human use.[1]
- 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[2]

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

1. Van Gelder MMHJ et al. *Human Reprod Update*. 2010;16(4):378-394.
2. Desai RJ et al. *Obstet Gynecol*. 2014;123(5):997–1002.

Environmental

- Endocrine disruptors: plastics & pesticides[3]
- Infections: zika, CMV*, rubella, syphilis, CT*, GC*, HSV*, varicella[3]
- EMF*: cell phones[3]
- Pollution: air/H_2O, polycyclic aromatic hydrocarbons (PAHs) (transport emissions)[4]

3. Up to Date. https://www.uptodate.com/contents/the-preconception-office-visit. Accessed May 1, 2019.
4. Zhu Y et al. *Am J Epidemiol*. 2017;186(3):334–343.

Emerging…

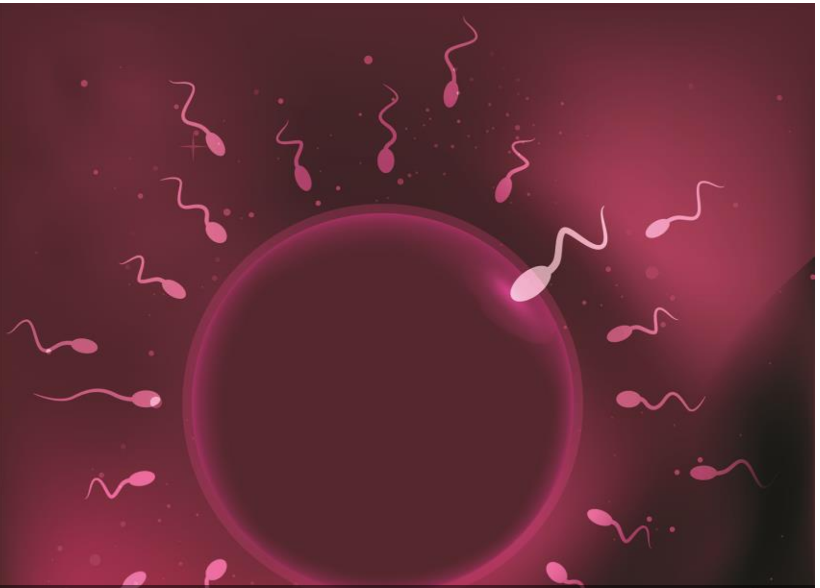
- Use during pregnancy increased by 62% (2002-2014)[5]
- Observed effect in the offspring depend on age & trimester during which they were exposed to the drug, and dose & route of administration of the drug[6]
- Effects are not well understood, but adverse effect has been seen. Further research is needed[7]

5. Science Daily. https://www.sciencedaily.com/releases/2019/04/190409135933.htm. Accessed May 5, 2019.
6. Fine JD et al. *JAMA Psychiatry.* Published online March 27, 2019.
7. Correa F et al, *Reproduction.* 2016 Dec;152(6):R191-R200.

INFERTILITY

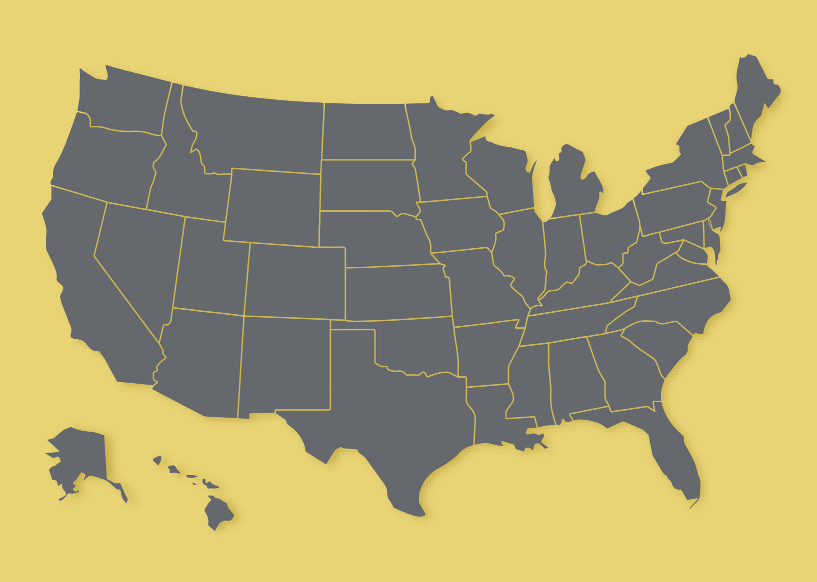
Recognize: Increased Use of Fertility Services

Defined



>12 months (< age 35) &
>6 months (≥ age 35)[1]

Prevalence



2006-2010: 11% (all women)[2]

Incidence-Married[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(5 Suppl):S60
2: Chandra A et al. *Natl Health Stat Report*. 2013;14(67):1-18.
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Female Infertility Around the Globe

Highest in: South Asia, Central/Eastern Europe, North Africa/Middle East, Oceania, Sub-Saharan Africa, Central Asia[1]

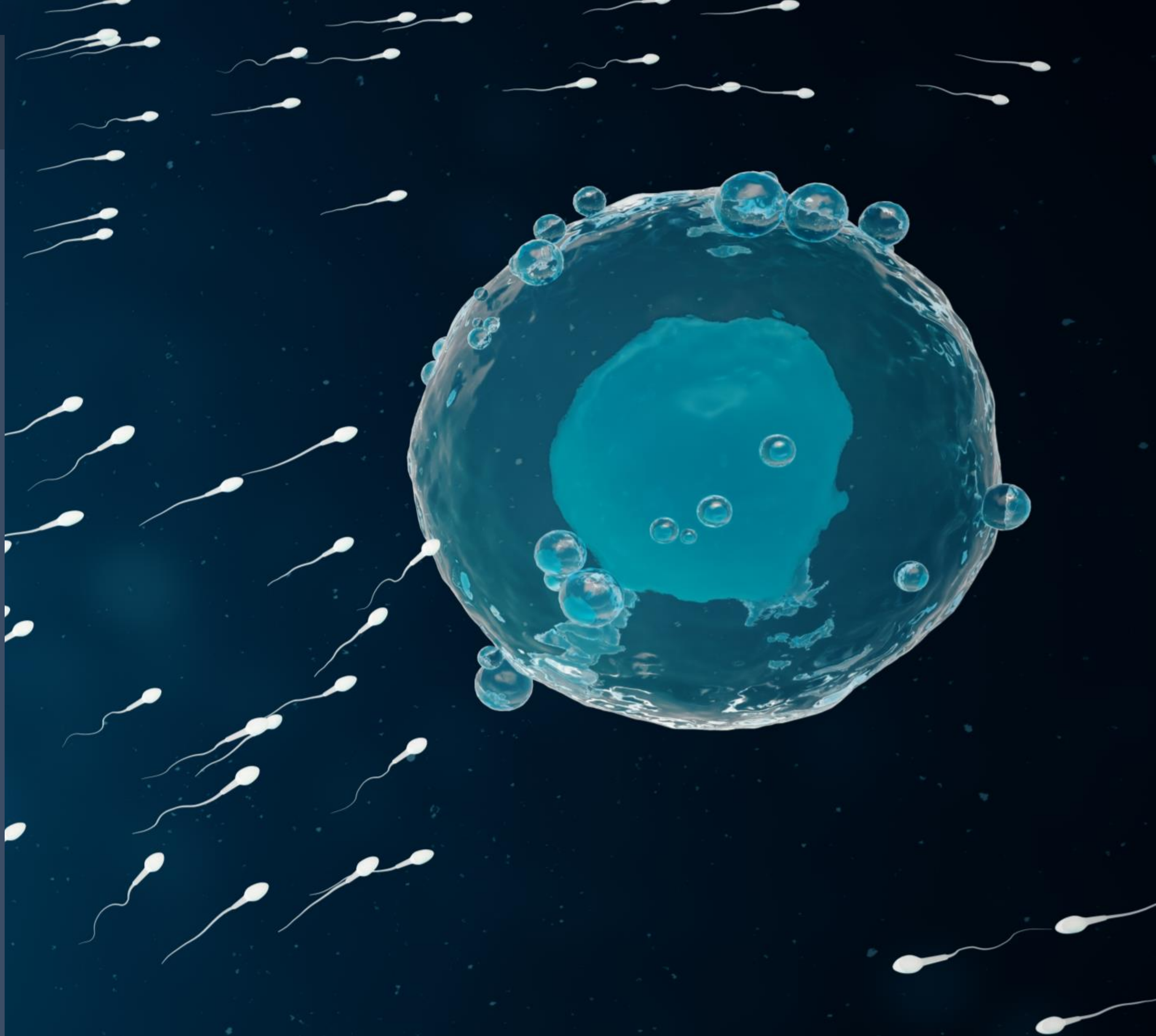
2010: Age 20-44

- 1.9% were unable to have 1st live birth[1]
- 10.5% were unable to have 2nd live birth[1]

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

1: Mascarenhas MN et al. *PLoS Med*. 2012;9(12):e1001356.

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%

1. Friedman SK et al. *US Pharm*. 2012;37(6):39-42.
2. Al-Inany H. *Clin Evid*. 2005;2005:0819.
3. Bhattacharya S et al. *Hum Reprod*. 2009;24(12):3096-3107.

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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]

1. Valcarce DG et al. *Benef Microbes.* 2017;8(2):193-206.
2. Maretti C. *Andrology.* 2017;5(3):439-444.

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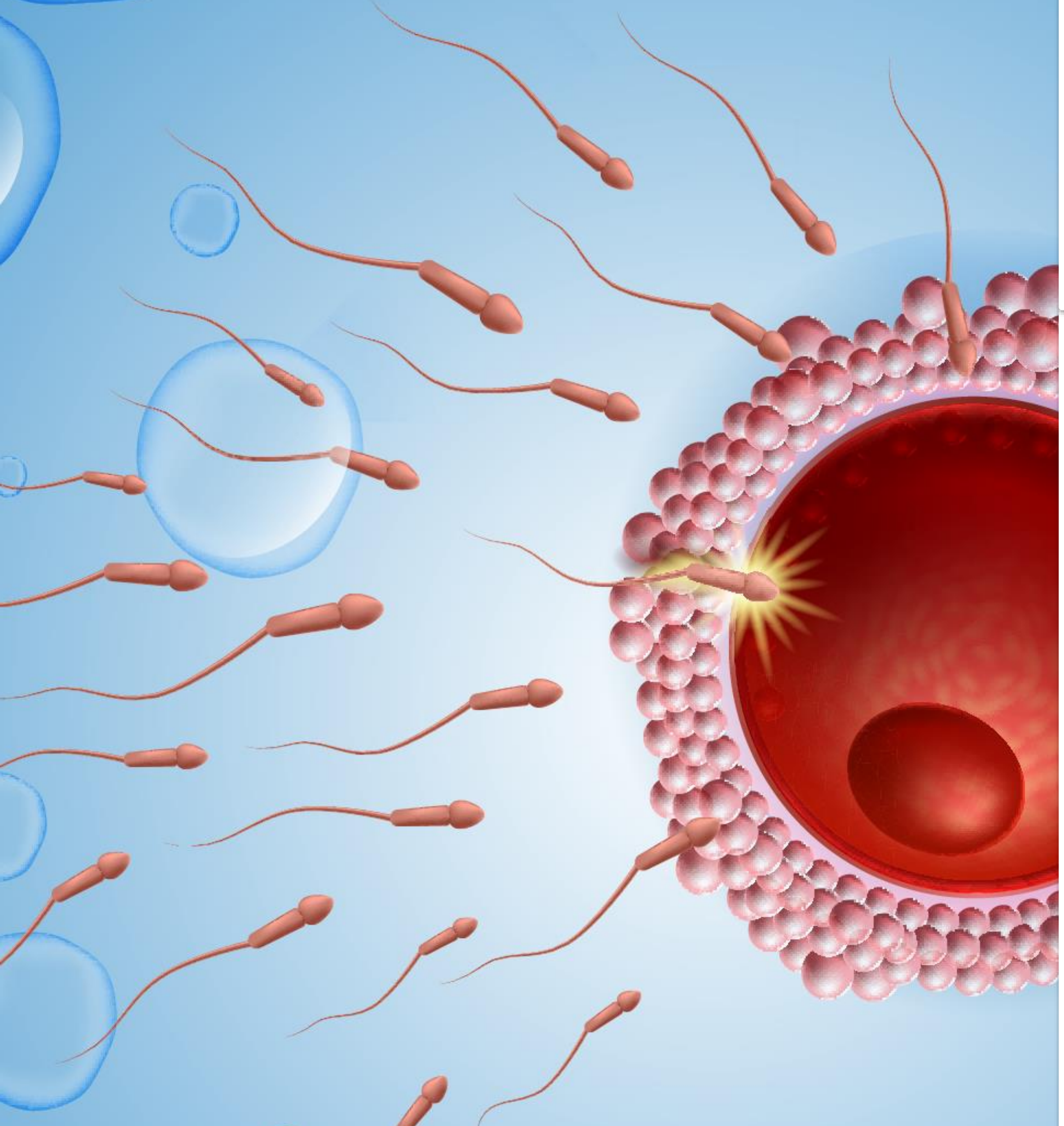
Sperm DNA Damage

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

https://www.sciencedaily.com/releases/2019/03/190323145146.htm. Accessed May 5, 2019.



Recognize

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

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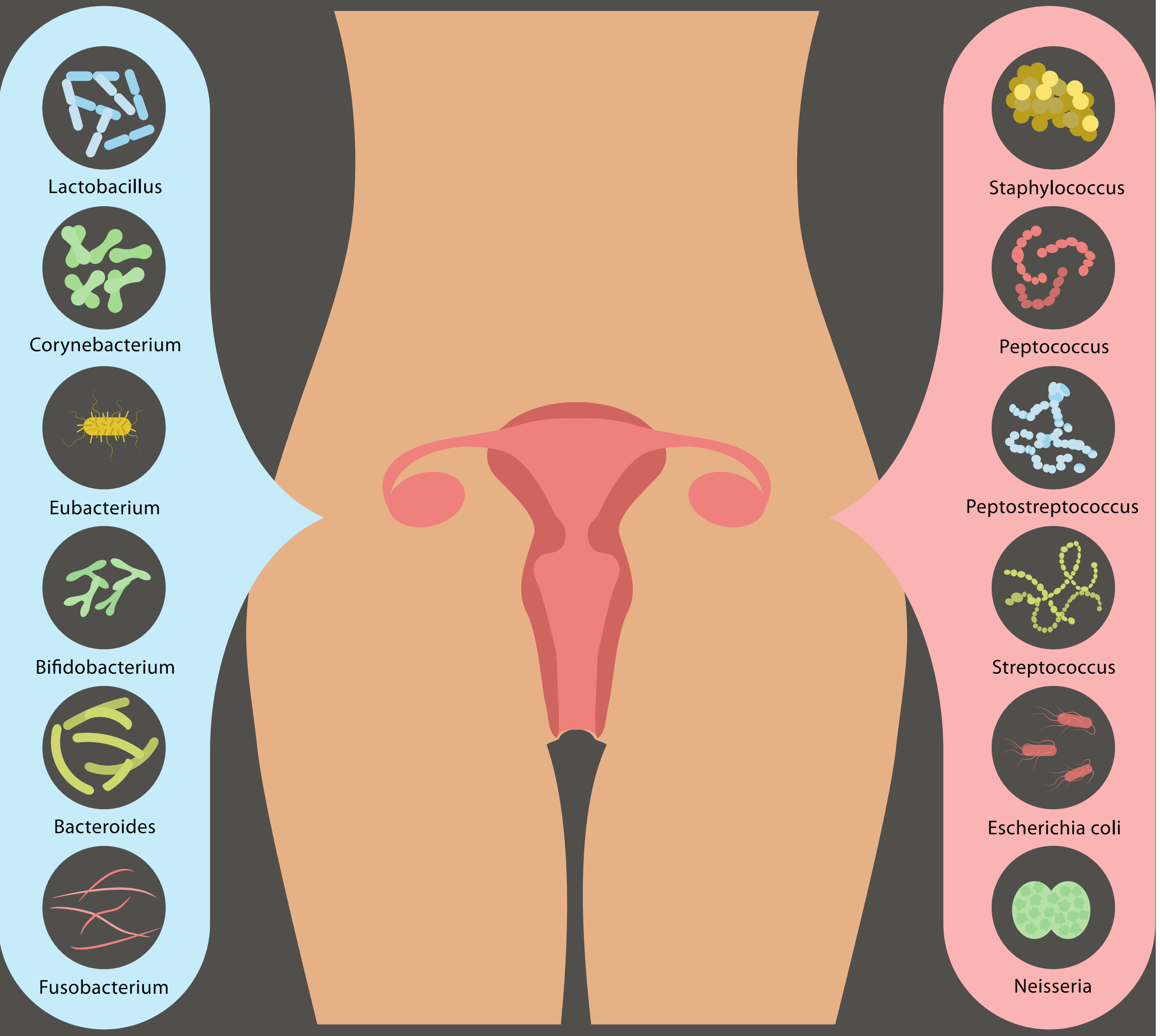
… & Empower

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

Chavarro JE et al. *Human Reprod*. 2014;29(3):429–440.



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 BV[2]
- BV is associated with tubal factor infertility[3]

Recognize: Vaginal microbiome is associated with early Sab (Spontaneous Abortion) 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 1):S91–S97.
3. Haahr T et al. *BJOG*. 2019;126(2):200-207.

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Recognize: Reproductive factors are modifiable

Miscarriage—Definition & Disrupted Cycle

Defined

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

Causes

- Reproductive factors/endocrine disruption[3]
- Prolonged ovulation to implantation (disrupted luteal phase)[4]
- Prolonged time to conception (follicular phase)[5]

1. Wilcox AJ et al. *N Engl J Med*. 1988;319(4):189-194.
2. Rossen LM et al. *Paediatr Perinat Epidemiol.* 2018;32(1):19-29.
3. Krieg SA et al. *Fertil Steril.* 2016;106(4):941-947.
4. Wilcox AJ et al. *N Engl J Med.* 1999;340(23):1796-1799.
5. Axmon A et al. *Fertil Steril.* 2005;84(4):966-974.

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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

1. Chatenoud L et al. *Ann Epidemiol.* 1998;8(8):520-526.
2. Venners SA et al. *Am J Epidemiol.* 2004;159(10):993-1001.
3. Wang L et al. *J Epidemiol Community Health.* 2018;72:783-789.
4. Windham GC et al. *Epidemiology.* 1997;8(5):509-514.
5. Ness RB et al. *N Engl J Med.* 1999;340(5):333-339.
6. Li DK et al. *Am J Obstet Gynecol.* 2018;219(3):275.e1-275.e8.
7. Brent RL et al. *Birth Defects Res B Dev Reprod Toxicol.* 2011;92(2):152-187.
8. Hahn KA et al. *Hum Reprod.* 2015;30(5):1246-1255.

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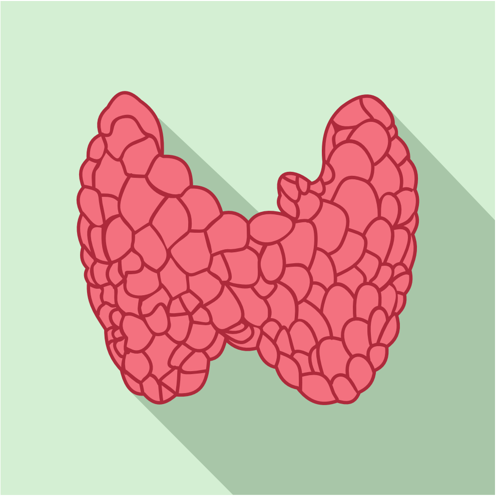
Miscarriage: Endocrine System

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



*PCOS= Polycystic ovary syndrome

4. Thyroid

- Increased thyroid peroxidase (TPO) or thyroglobulin antibodies (TgAb) (e.g., Hashimoto's thyroiditis) [1,3]
    - Common in 10% of females & 2% of males[2]
    - ↑ in celiac (e.g., tissue transglutaminase antibodies (tTG) [1]
    - Combined selenomethionine (83mcg) & myoinositol (600mg) [3]
        - ↓ TPO-TgAb & thyroid stimulating hormone (TSH)

1. Kaur R et al. *Int J Appl Basic Med Res.* 2016;6(2):79-83.
2. Vanderpump MJ et al. The epidemiology of thyroid disease. In: The Thyroid: A Fundamental and Clinical Text, 7th ed, Braverman LE, Utiger RD (Eds), Lippincott-Raven, Philadelphia 1996. p.474.
3. Nordio M et al. *J Thyroid Research*. 2013;2013:1-5.

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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]

1. American Thyroid Association. https://www.thyroid.org/wp-content/uploads/patients/brochures/Thyroid_Disesease_Pregnancy_brochure.pdf. Accessed March 27, 2019.
2. Dieguez M et al. *Clin Endocrinology*. 2016;8:121–126.

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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)

1. Alexander EK et al. *Thyroid*. 2017;27(3):315-389.
2. Taylor PN et al. *Front Endocrinol*. 2018;9:626.
3. Korevaar TIM et al. *Nat Rev Endocrinol*. 2017;13:610–622.
4. Krassas GE et al. *Endocr Rev*. 2010;31:702–755.
5. Cooper DS et al. *Lancet*. 2012;379:1142-1154.

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Thyroid disease is associated with disorders in maternal and fetal advancement

Condition	Preconception	Pregnancy	Postpartum
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

1. Carney LA et al. *Am Fam Physician*. 2014;89(4):273-278.
2. Reid SM et al. *Cochrane Database Syst Rev*. 2010;(7):CD007752.
3. De Groot L et al. *J Clin Endocrinol Metab*. 2012; 97(8):2543-2565.
4. Tagnaro-Green A et al. *Thyroid*. 2011;21(10):1081-1125.
5. Alexander EK et al. *Thyroid*. 2017;27(3):315-389.

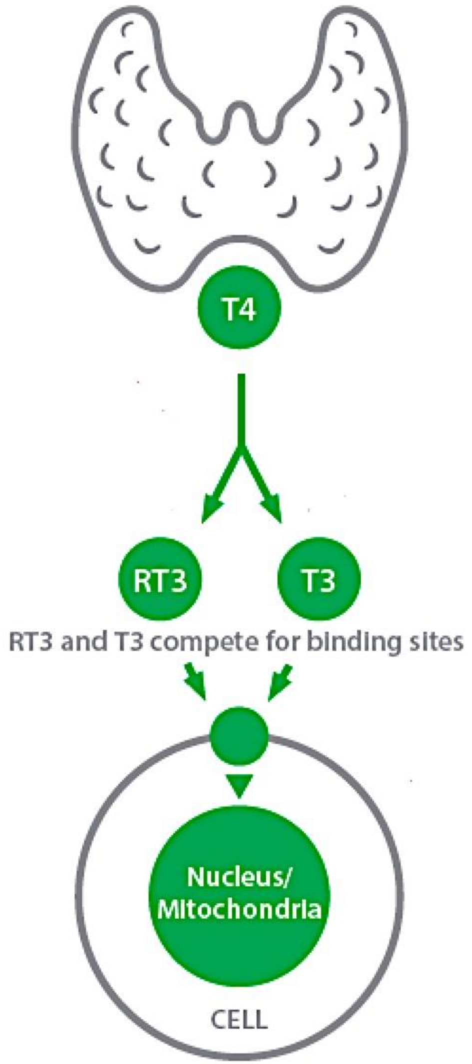
Nutrients Influencing Healthy Thyroid Function

Proper production thyroxine (T4)[1,3,8-12]

- Iodine
- Iron
- Magnesium
- Selenium
- Zinc
- Vitamins C, D, E
- B_2, B_3, B_6
- Tyrosine

Reduce TPOAb and TgAb[1,2]

- Myo-inositol
- Selenium



↑ Central and peripheral T4 to triiodothyronine (T3) via deiodinases[1,4]

Selenium
- Zinc

Improve cellular sensitivity to thyroid hormones[4]

- Zinc
- Vitamin A

Support mitochondria[1,9-12]

- Magnesium
- Vitamin C, E
- B_2, B_3, B_6
- CoQ_{10}
- Selenium

1. Köhrle J. *Curr Opin Endocrinol Diabetes Obes*. 2015;22(5):392-401.
2. Nordio M et al. *Int J Endocrinol.* 2017; 2017:2549491.
3. Velasco I et al. *Nutrients.* 2018;10(3):290.
4. Severo JS et al. *Int J Vitam Nutr Res*. 2019;1-9.
5. Kim D. *Int J Mol Sci*. 2017;18(9):1949.
6. Li S et al. *J Nutr Sci Vitaminol (Tokyo).* 2016;62(6):397-401.
7. Apeland T et al. Clin Biochem. 2006;39(3):282-6.
8. Citterio CE et al. Nat Rev Endocrinol. 2019;15(6):323-338
9. Henriques BJ et al. *Curr Drug Targets.* 2016;17(13):1527-34.
10. Fricker RA et al. *Int J Tryptophan Res*. 2018;11:1178646918776658.
11. Mantel D et al. *Antioxidants (Basel*). 2019;16;8(2).
12. Wesselink E et al. *Clin Nutr*. 2019;38(3):982-995.

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Polycystic Ovary Syndrome (PCOS)

Definition[1]	Etiology
Defined in 1935 • Androgen excess • Menstrual irregularity • Cardio metabolic dysfunction • Obesity • Insulin resistance • Anovulatory infertility **Criteria & Prevalence**[2] • 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)	• **Heterogenous** ○ Interaction of multiple gene variants & environmental factors like diet & obesity[3] ○ ***Estimated 20% genetic influence*** – 30+ gene variants so far, e.g. LH*/ hCG receptor (LHCGR)[2] – Thyroid adenoma associated protein (THADA) impaired beta cell function[4]

. *NIH=National Institutes of Health, LH= Luteinizing hormone

1. Stein IF et al. *Am J Obstet Gynecol.* 1935;29(2):181-191.
2. Bozdag G et al. *Hum Reprod*. 2016;31(12):2841-2855.
3. https://www.uptodate.com/contents/etiology-and-pathophysiology-of-polycystic-ovary-syndrome-in-adolescents, Accessed May 1, 2019
4.Legro RS et al. *Proc Natl Acad Sci U S A*. 1998;95(25):14956-14960.

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]

*GI= Glycemic index

1. Fauser BCJM et al. *Endocr Rev.* 1997;18(1):71-106.
2. Up to Date. www.uptodate.com/contents/epidemiology-and-genetics-of-the-polycystic-ovary-syndrome-in-adults. Accessed May 1, 2019.
3. Chen YH et al. *Diabetes*. 2013;62(7):2278-2286.
4. Yildiz BO et al. *J Clin Endocrinol Metab.* 2008;93(1):162-168.
5. Carmina E et al. *Hum Reprod.* 2003;18(11):2289-2293.
6. Kandaraki K et al. *J Clin* Endocrinol *Metab.* 2011;96(3):E480-E484.
7. Vagi SJ et al. *BMC Endocr Disord.* 2014;14:86.

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PCOS: Interventions

- **Lifestyle intervention** is recommended as <u>first-line</u> 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]

MYO-INOSITOL[6]

2 X 2000 mg

DAILY

FOLIC ACID[6]

2 × 200 μg folic acid

1: Cutler DA et al. *Trials*. 2018;19(1):632.
2: Bergh CM et al. *J Obstet Gynecol Neonatal Nurs*. 2016;45(1):111–122.
3: Marsh KA et al. *Am J Clin Nutr*. 2010;92(1):83–92.
4: Harrison CL et al. *Hum Reprod Update*. 2010;17(2):171–183.
5: Stefanaki C et al. *Stress*. 2015;18(1):57–66.
6: Regidor PA et al. *Int J Endocrinol*. 2016;2016:1–5.

PCOS & Probiotics

- Co-administration of vitamin D_2: 50,000 IU + 8 BIL CFU probiotic VS. no probiotic for 12 weeks

Results

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

*measures oxidative stress

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

Ostadmohammadi V et al. *J Ovarian Res*. 2019;12(1):5.

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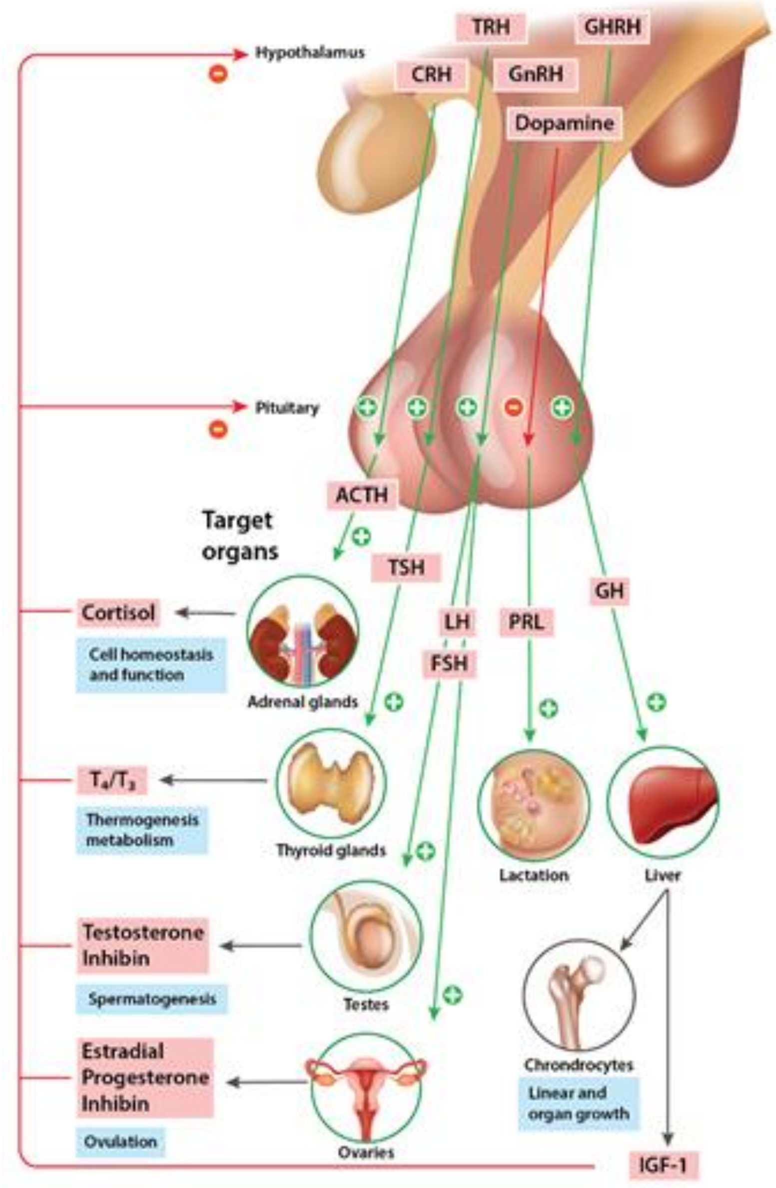
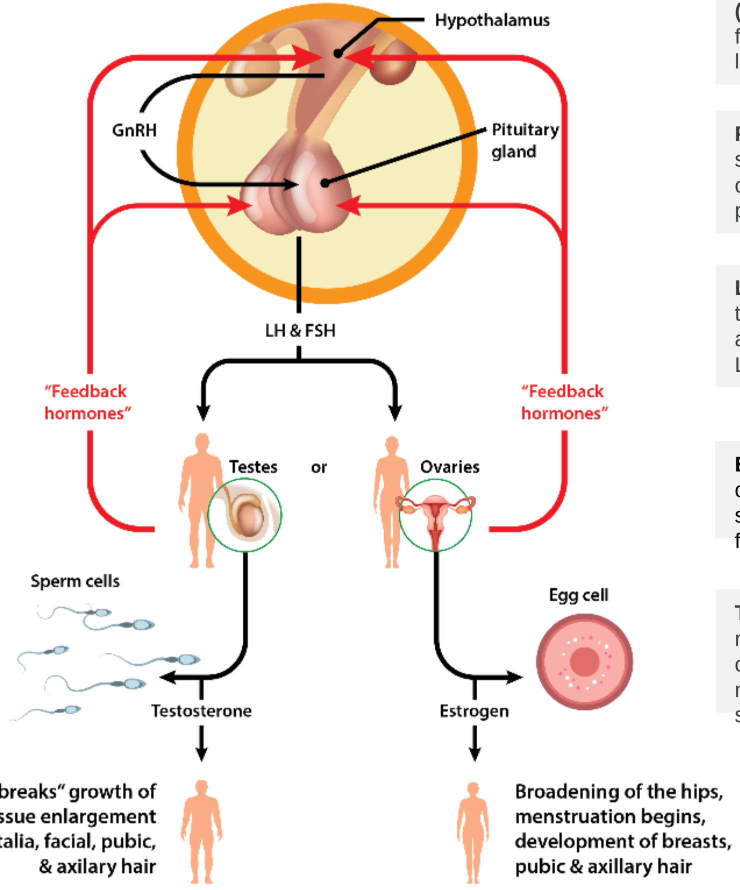
Hypothalamus—Where Healthy Hormonal Function Begins



Adapted from: 17th Edition of Harrison's Manual of Medicine. Fauci AS, Braunwald E. Et al.

Hormonal Control During Puberty



Modified chart from:
https://commons.wikimedia.org/wiki/File:Flow_diagram_showing_normal_hormonal_control_of_puberty.gif Accessed April 15, 2019.
https://creativecommons.org/licenses/by-sa/3.0/legalcode

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.

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

Testosterone, the hormone responsible for the secondary sexual characteristics that develop in the male during adolescence, stimulates spermatogenesis.

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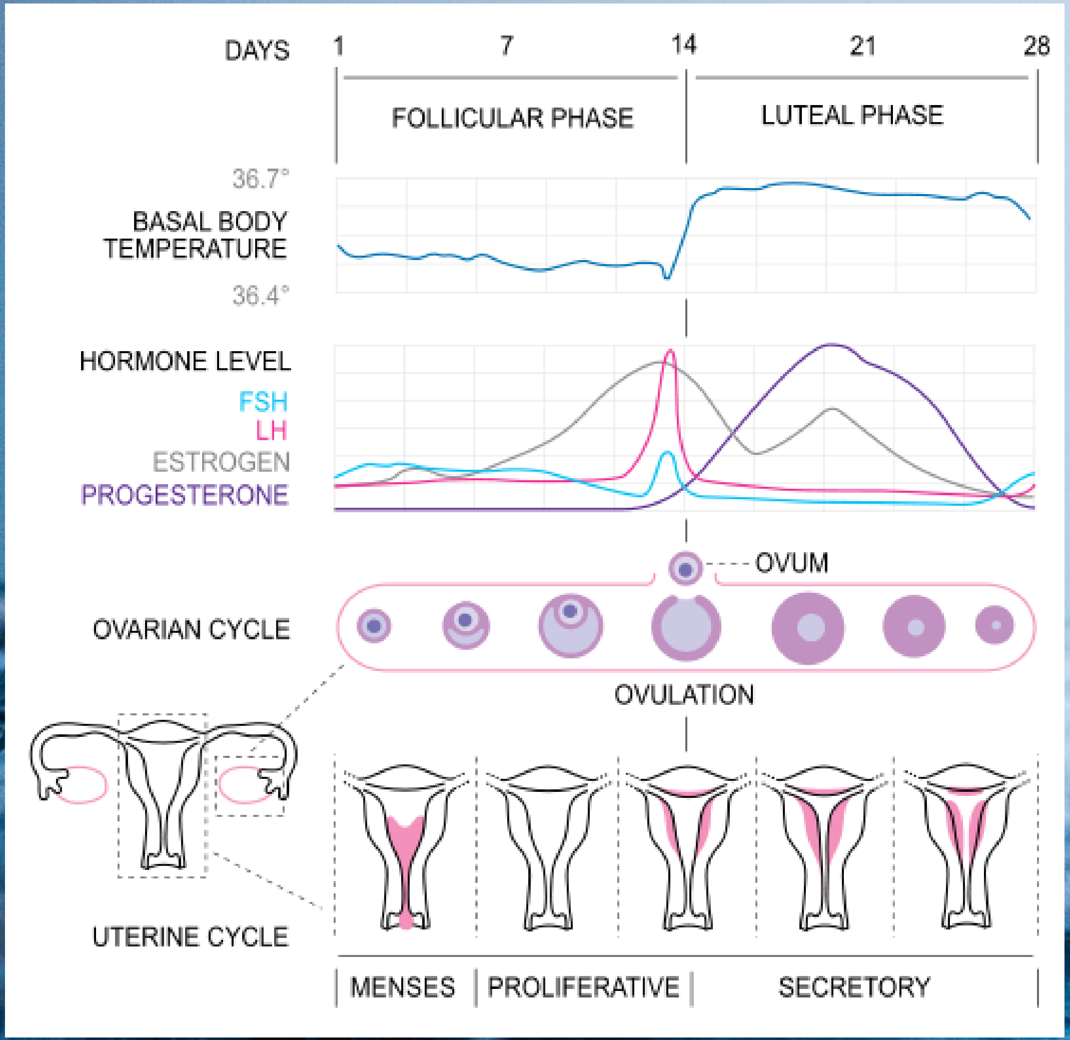
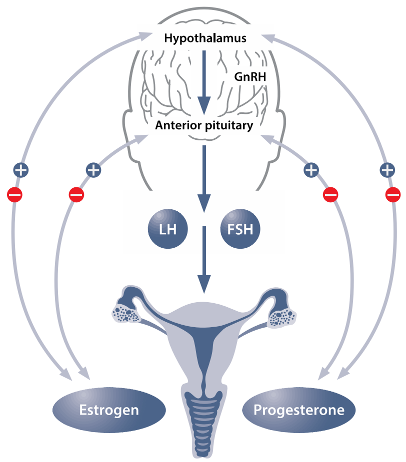
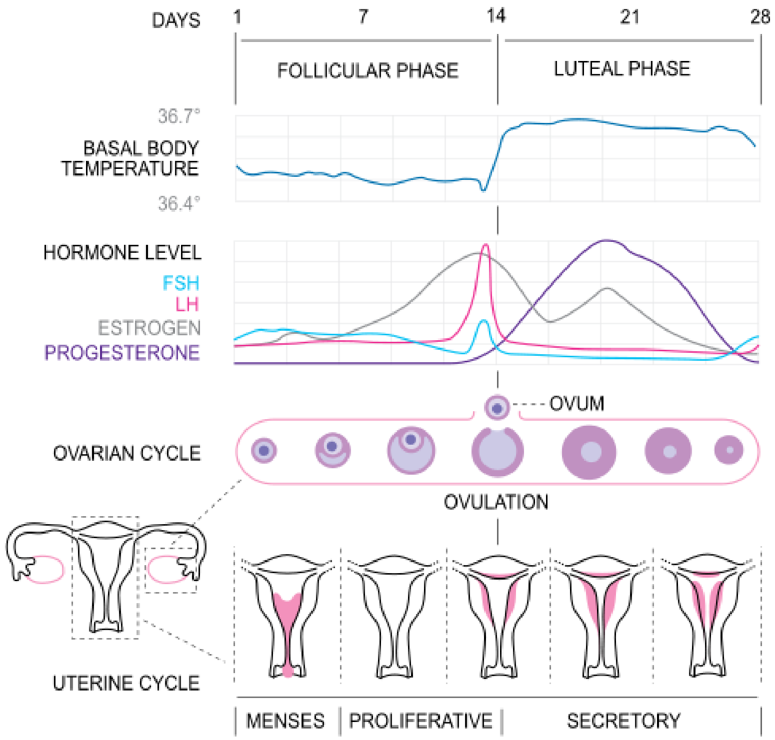
The Menstrual Cycle

Rhythmic, predictable, and turbulent as the ocean tides



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

https://commons.wikimedia.org/wiki/File:MenstrualCycle2_en.svg. Accessed April 14, 2019.
https://creativecommons.org/licenses/by-sa/3.0/legalcode

Hawkins SM. *Ann N Y Acad Sci*. 2008;1135:10-8.

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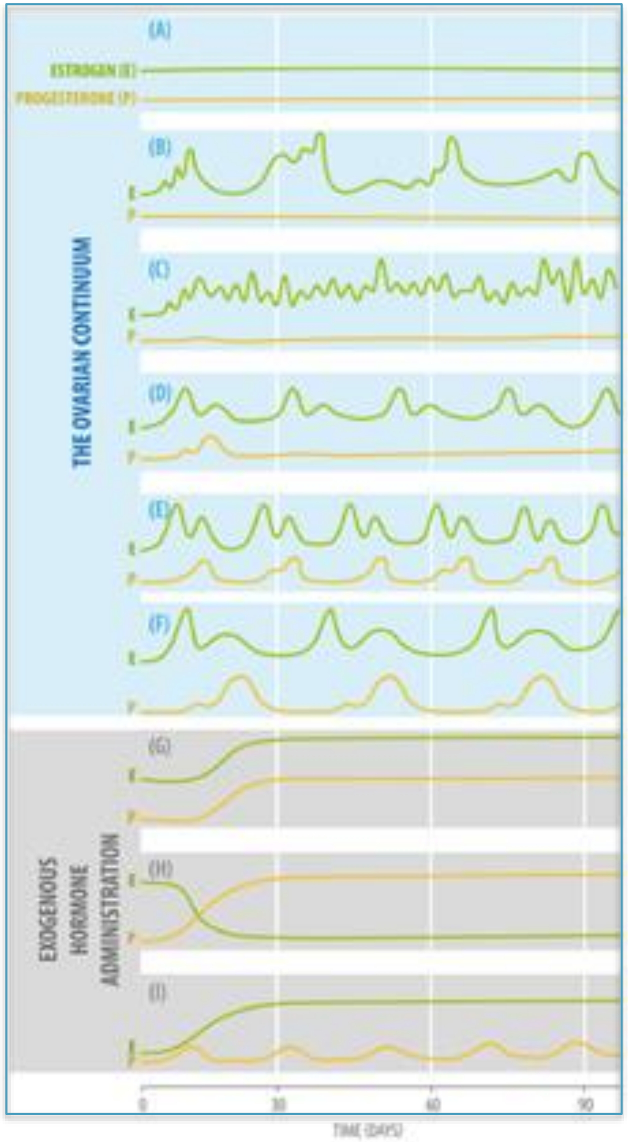
Fluctuating Estradiol and Progesterone Levels

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



Cycles with No Ovarian activity

Anovulatory cycles With fluctuating Estrogen levels

Cycles with Anovulatory Ovarian activity With constantly increased Estrogen levels

Cycles with a luteinized Unruptured follicle

Cycles with ovulation Followed by deficient Luteal phase

Ovulatory cycles With adequate Luteal phases

Combined contraception (ie. Oral, vaginal ring, Patches & IM)

Only progesterone (ig, oral, subdermal Implant & IM)

Hormone therapy (ie. Transdermal & oral)

Figure: Del Río JP et al. *Front Public Health.* 2018;6:141. http://creativecommons.org/licenses/by/4.0/. Accessed March 27, 2019.

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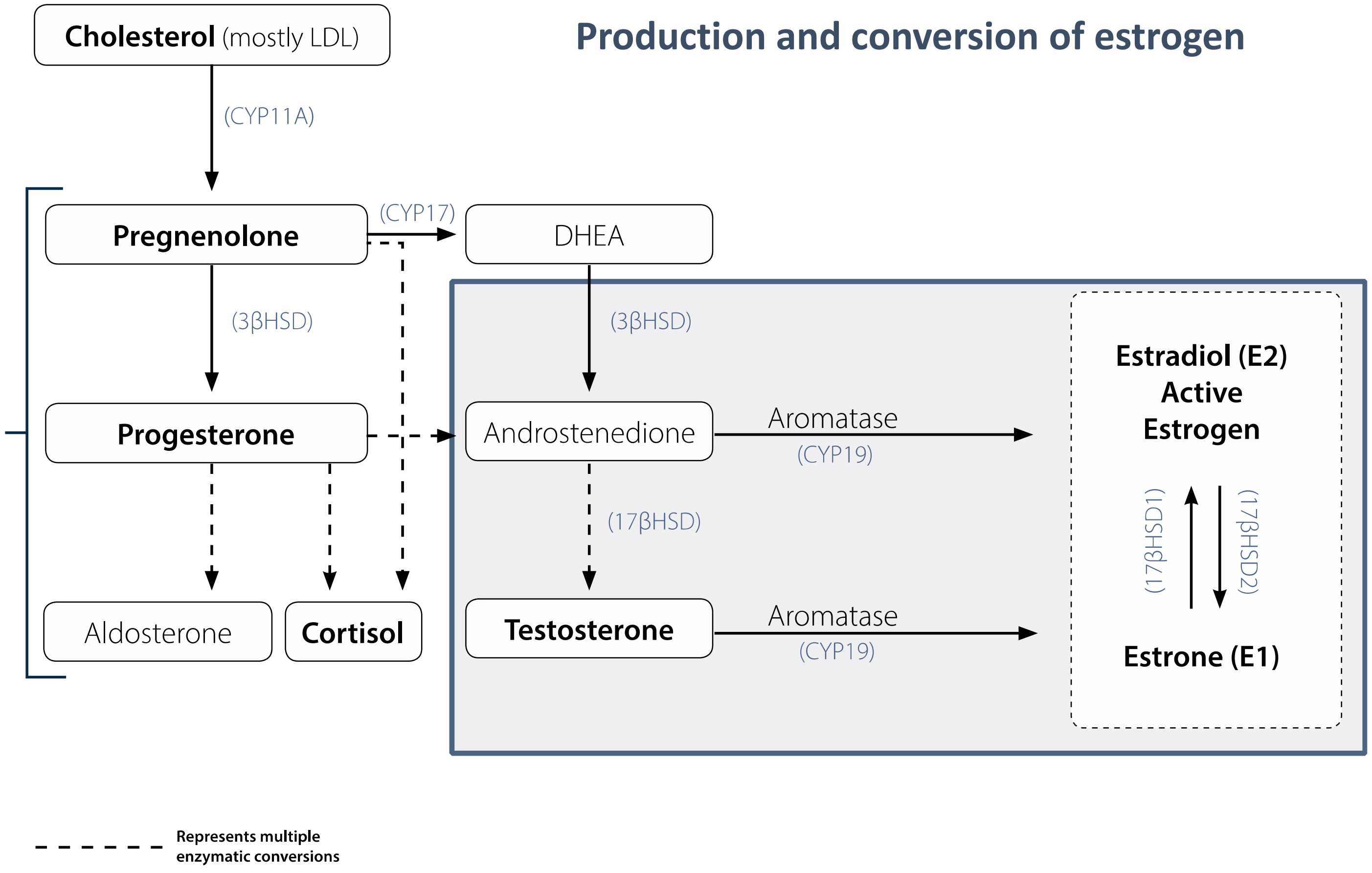
Manage Aromatase (CYP19) and Control Estrogen Biosynthesis



Production and conversion of estrogen

Production:

Aromatase (CYP19) transforms androstenedione and testosterone to E1 and E2

Tsuchiya Y et al. *Cancer Lett.* 2005;227(2):115–124.

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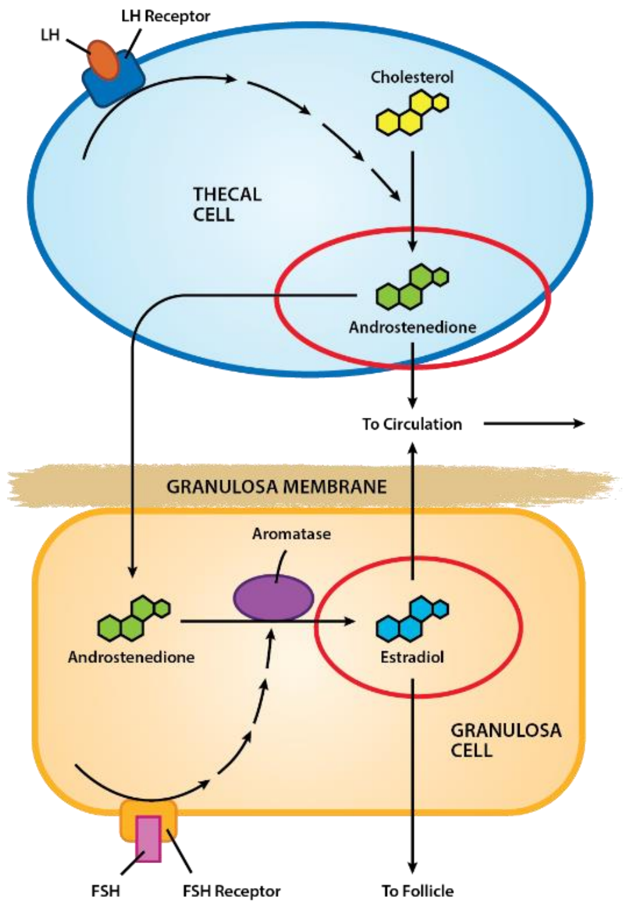
Aromatase (CYP19) Is Critical to Ovarian Follicle Maturation, Estrogen Production, and the Luteal Surge

- 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**



Adapted from: http://what-when-how.com/acp-medicine/amenorrhea-part-1/. Accessed April 25, 2019.

Del Río JP et al. *Front Public Health.* 2018;6:141.

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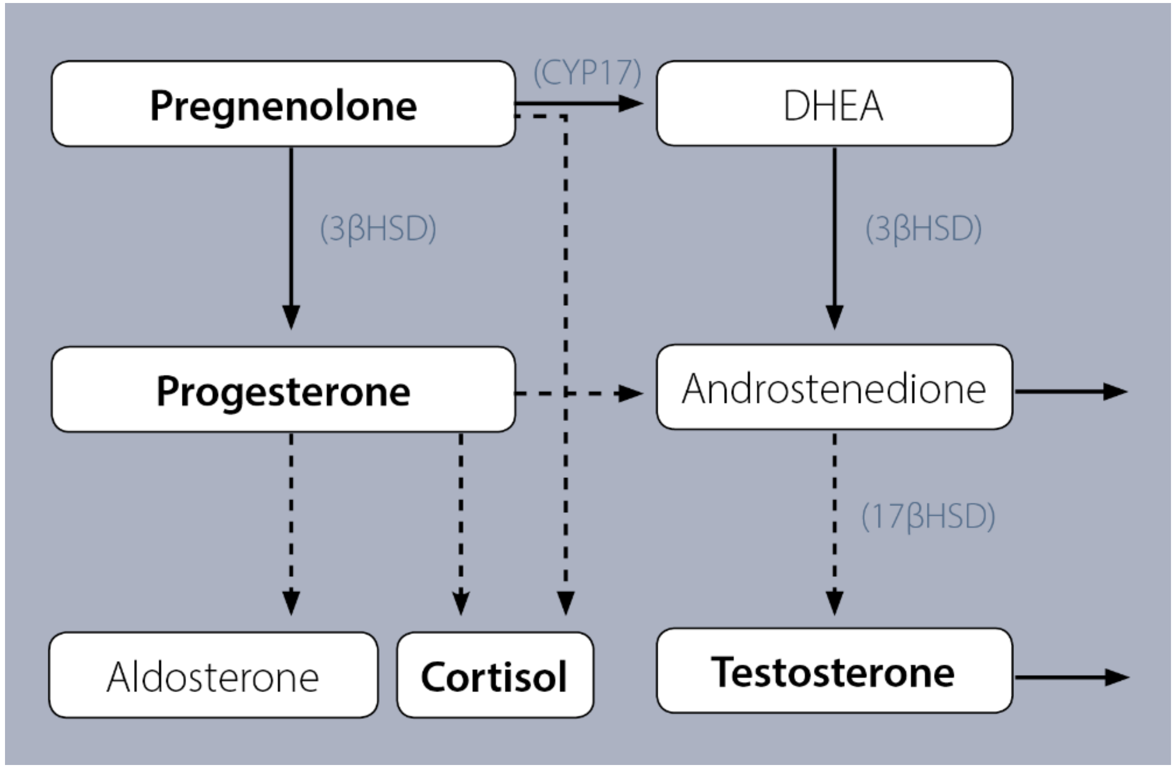
The "Pregnenolone-" or "Cortisol Steal"



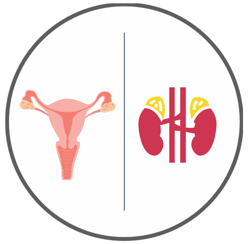
Increased demand for cortisol (i.e., chronic stress) reduces availability of estrogen precursors DHEA and androstenedione

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

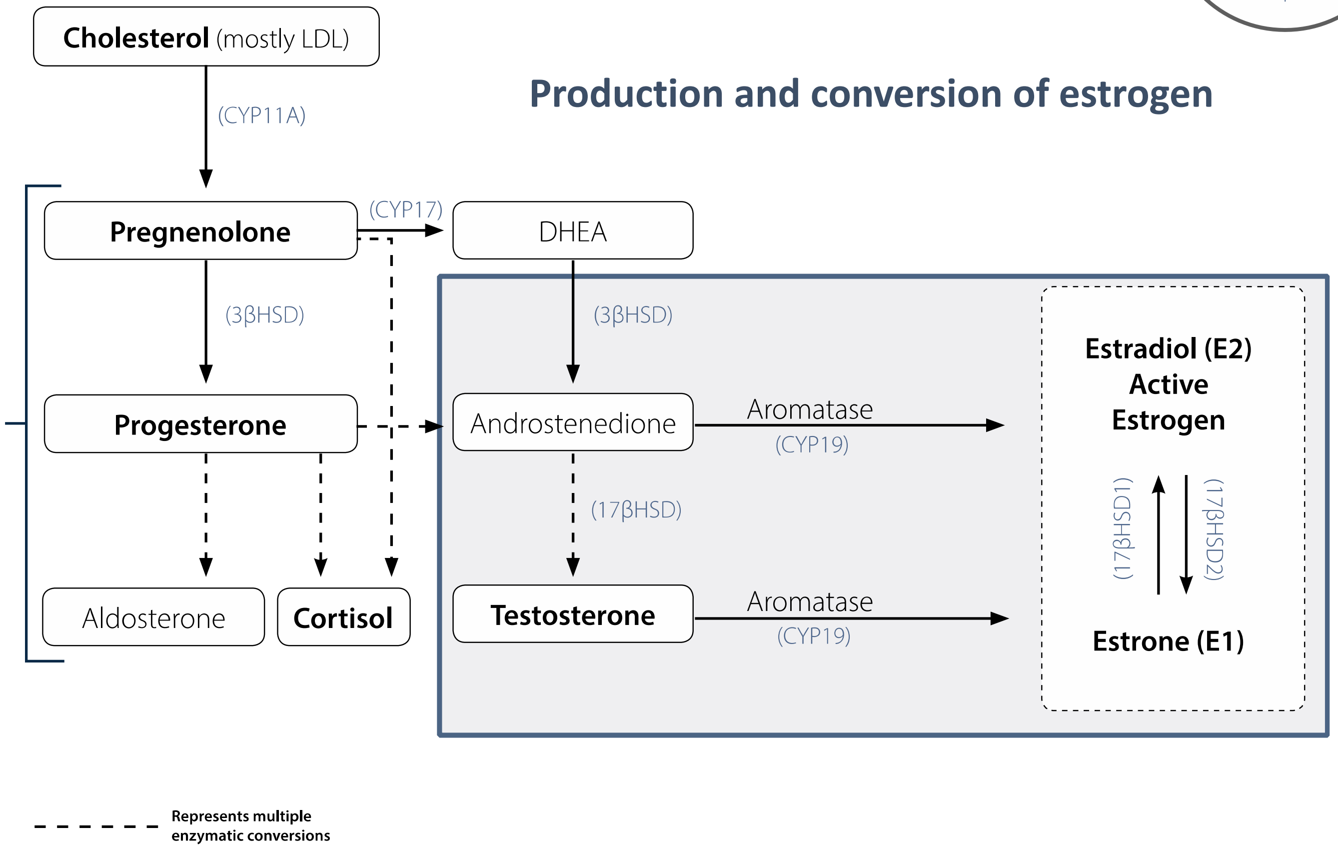
E:P ratio increases

Miller WL et al. *Endocr Rev.* 2011;32(1):81–151.

Aromatase Is Stimulated by Inflammation and Contributes to Excess Estrogen Body Burden



- 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:[2]
  - Synovial fluid in rheumatoid arthritis
  - Uterine fibroids
  - Endometriosis
  - Breast cancer cells



1. Richards JA et al. *J Clin Endocrinol Metab*. 2003;88(6):2810-2816.
2. Bulun SE et al. *Sem Repr Med.* 2004;22(1):45.

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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.

Morris P et al. *Cancer Prev Res.* 2011;4(7):1021–1029.
Steptoe A et al. *Proc Natl Acad Sci U S A.* 2014;111(44):15693-15698.
Carvalho LA et al. *Psychoneuroendocrinology*. 2015;51:209-218.

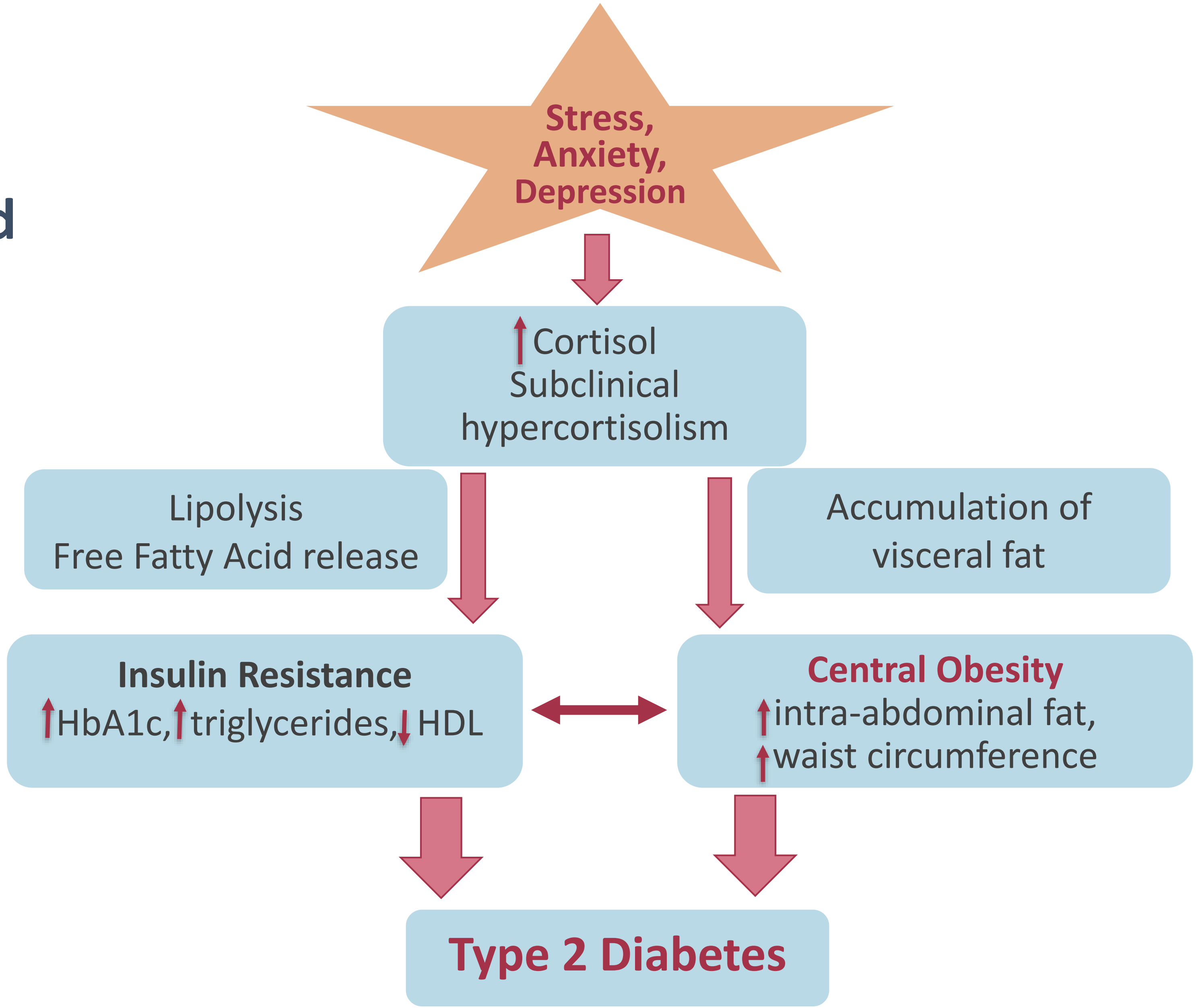

Image adapted from: Joseph JJ et al. *Ann N Y Acad Sci*. 2017; 1391(1): 20–34.

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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 development[3], thus increasing the risk of miscarriage.[4]

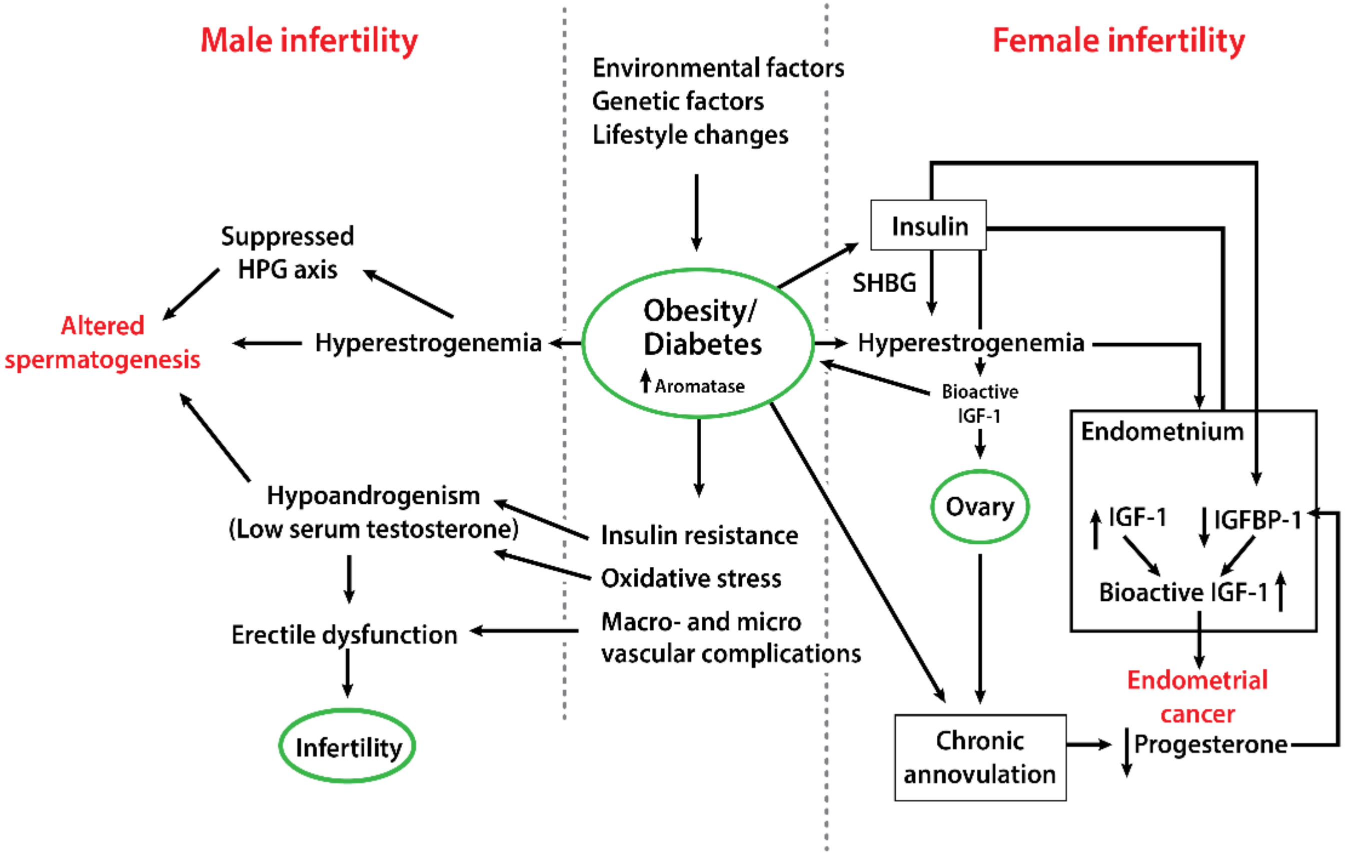

Image adapted from: Venkatesan V et al. *Indian J Med Res*. 2014;140(Suppl 1):S98–S105.

1. Agbaje IM et al. *Hum Reprod*. 2007;22:1871–1877.
2. De Lio V et al. *Endocr Rev*. 2003;24:633–667.
3. Hall LF et al. *Obstet Gynecol Surv*. 2005;60:253–260.
4. Lashen H et al. *Hum Reprod*. 2004;19:1644–6.

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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

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Factors Associated with Risk for Endometriosis[1-7]

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

Table adapted from: Parasar P et al. *Curr Obstet Gynecol Rep*. 2017;6(1):34-41.

1. Alghetaa HF et al. *J Immun*. 2018;200(1):108.
2. Pan Q et al. *Mol Hum Reprod.* 2007;13:797–806.
3. Kwa M et al. *J Natl Cancer Inst.* 2016;108(8).
4. Baker JM et al. *Maturitas.* 2017;103:45-53.
5. Bailey MT et al. *Hum Reprod.* 2002;17(7):1704-1708.
6. Ek M et al. *BMC Women's Health.* 2015;15:59.
7. Santoro L et al. *Biomed Res Int*. 2014;2014:236821.

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Current Treatment and management strategies for Endometriosis[1-6]

Conventional Medical Options	Lifestyle Modifications	Natural Therapies
• **Pain Management** - Use of common analgesics or NSAIDs • **Hormonal therapy** - **Continuous oral contraceptives** for shorter, lighter menses - Keep S.estradiol < 30 - **Gonadotropin-releasing hormone (Gn-RH)** agonists and antagonists to lower estrogen levels, prevent menses and shrink endometrial tissues - **Progestin therapy** including intrauterine devices, injections or pills can stop menses as well as endometrial implants - **Aromatase inhibitors** to reduce estrogen levels • **Surgical intervention** - **Conservative** (laparoscopic) surgery to maintain fertility removes endometrial implants but preserves uterus and ovaries - **Semi-conservative** surgery involves hysterectomy and implant reduction - **Radical** surgery with hysterectomy and bilateral oophorectomy	• **Aerobic exercise** - May reduce/moderate estrogen and increase endorphins • **Improve dietary intake** - Increase intake of fruits and vegetables - Consider plant based diet - Increase amount of omega-3 fatty acids • **Reduce alcohol and caffeine** - Alcohol shown to increase estrogen levels so reducing or stopping will help • **Stress reduction and emotional support** - Avoid stressful situations and/or high stress people - Practice stress reduction techniques: yoga, meditation, journaling - Meet with therapist or counselor if needed • **Acupuncture** - Evidence based therapy that has been shown to reduce pain and stress associated with EMS	• **Nutritional/dietary changes** - Eliminate food allergies - Decrease fat intake - Avoid refined sugar and carbohydrates - Increase fiber to support regular elimination • **Vitamins and minerals** - Vitamin A: 50,000 IU - Vitamin C: 3-5 g - Vitamin E: 400 IU - Vitamin D: 1000 IU - Vitamin K: 90 mcg - Vitamin B6: 50 mg - Vitamin B12: 300 mcg - Folate: 400 mcg - Niacin: 10 mg - Riboflavin 1 mg - Thiamin: 0.75 mg - Selenium: 250-400 mcg - Zinc: 30 mg - Magnesium: 200 mg - Manganese: 1 mg - Calcium D-glucarate: 1.5 g - Mixed Carotenoids: 1.5 mg • **Supplements & Botanicals** - Flaxseed (Lignans): 1.84 mg - Silymarin extract: 280 mg - Curcumin: 100 mg - NAC: 100 mg - Rosemary: 100 mg - Omega-3 fatty acids: 2-5 g - Quercetin: 500 mg - Digestive enzymes - Probiotics (*L.acidophilus* and *L.bifidus*)

1. Greene AD et al. *Reproduction*. 2016;152(3):R63-R78.
2. Alghetaa HF et al. *J Immun*. 2018;200(1):108.
3. Dai Y et al. *Reprod Health*. 2018;15(1):82.
4. Hansen KA et al. *Clin Obstet Gynecol.* 2010;53(2):403-412.
5. Soave I et al. *J Endometr Pelvic Pain Dis.* 2018;10(2) 59–71.
6. Endometriosis. https://www.metagenicsinstitute.com/blogs/endometriosis-symptoms/ Accessed on April 11, 2019.

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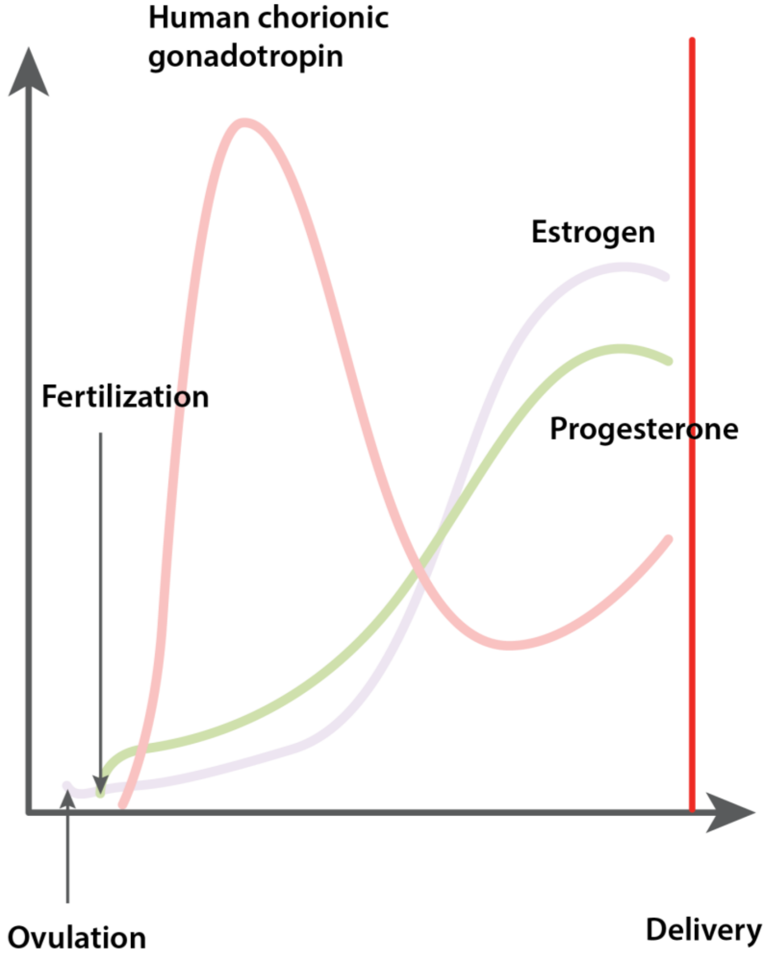
Human Chorionic Gonadotropin (hCG): The Pregnancy Hormone

- 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, preeclampsia[3] and disturbances in fetal growth and development.[4]



Adapted from: Lu J et al. *Reprod Biol Endocrinol.* 2018;16(1):80.

1. Lu J et al. *Reprod Biol Endocrinol.* 2018;16(1):80.
2. Paulesu L et al. *Int J Mol Sci.* 2018;19(3): 914.
3. Norris W et al. *Placenta.* 2011;32 Suppl 2:S182-S185.
4. Barjaktarovic M et al. *Eur. J. Epidemiol.* 2017;32:135–144.

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Genetic Assessments

Chromosomal	Gene Variant

• Rare (<1%)
• Devastating
• Relatively little impact on global health
• Often non-manipulatable
	• Common (1-49%)
	• Cumulative, with significant impact on global health
	• Manipulatable
	  ○ Other manipulatable gene processes[1]
	    – Histone modification
	    – DNA methylation
	    – Imprintome
	    – Micro RNA
	    – mTORC*

*mechanistic target of rapamycin complex (mTORC)

1. Jirtle RL ET AL. *Environmental Epigenomics in Health and Disease: Epigenetics and Complex Diseases*. Springer-Verlag Berlin Heidelberg. 2013.

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We Know

MTHFR—

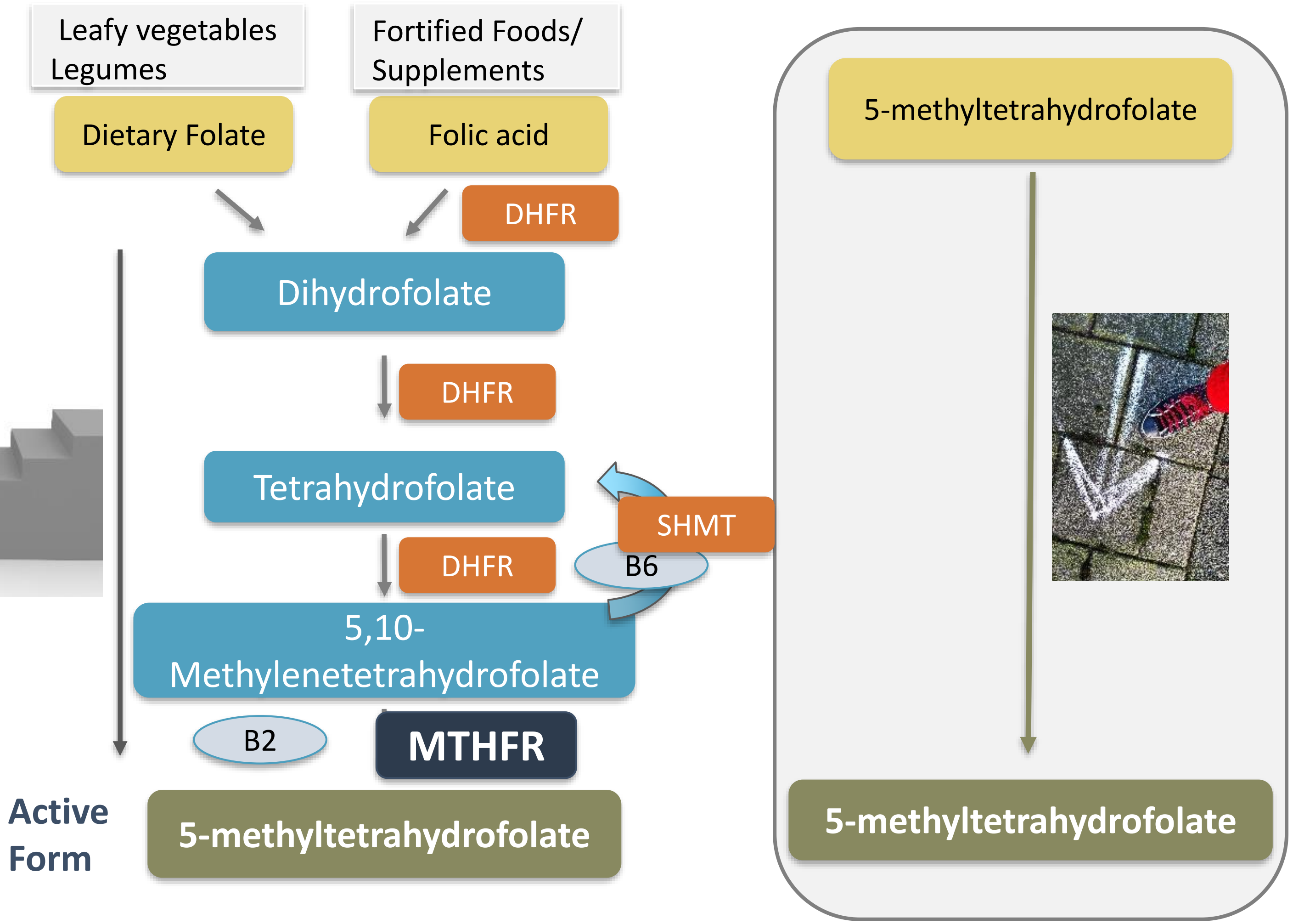
Methylenetetrahydrofolate reductase

- Common SNP[1]
- Many MTHFR Polymorphisms > 40 identified[2]
- C677>T and A1298>C most studied[3]
- SNP's associated with reduced MTHFR enzymatic activity in activating or methylating folate[4]
  - 35% activity reduction heterozygous[3]
  - 70%-90% activity reduction homozygous recessive[3]

1. Genetics Home Reference. http://ghr.nlm.nih.gov/gene/MTHFR. Accessed April 29, 2019.
2. McBride C. (2012, April 18). Applications of genomics to improve public health [Lecture 12]. National Human Genome Research Institute's Current Topics in Genome Analysis 2012. Retrieved from http://www.genome.gov/Course2012/
3. Shiao SPK et al. *Biol Res Nurs*. 2016;18(4):357–369.
4. Nazki FH et al. *Gene*. 2014;533(1):11-20.

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.[1,3-4]



1. Greenber JA et al. *Rev Obstet Gynecol.* 2011;4:52-59.
2. Molloy AM et al. *Annu Rev Nutr*. 2017;37:269-291.
3. Scaglione F et al. *Xenobiotica.* 2014;44:480-488.
4. Obeid R et al. *J Perinat Med.* 2013;41(5):469-483.

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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

1. https://www.cdc.gov/ncbddd/autism/data.html. Accessed on April 12, 2019.
2. Ornoy A et al. *Front Neurosci*. 2016;10:316.
3. Brown AS et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;57:86-92.
4. Gardener H et al. *Pediatrics. 2011;*128:344–355.
5. Xiang AH et al. *JAMA*. 2015;313(14):1425-1434.
6. Vohr MD et al. *Pediatrics.* 2017;139(Suppl 1):S38-S49.
7. Wang C et al. *Medicine.* 2017; 96:18.

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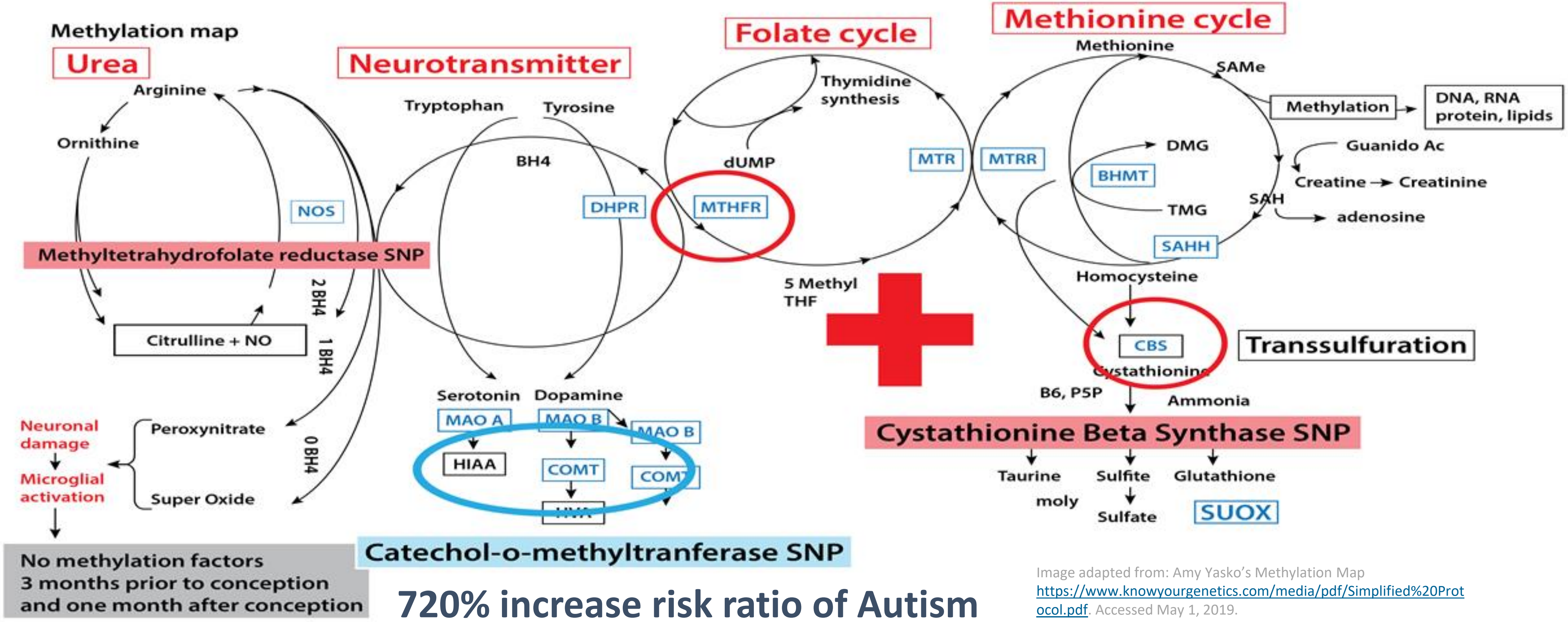
Methylation Map

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



720% increase risk ratio of Autism

Image adapted from: Amy Yasko's Methylation Map https://www.knowyourgenetics.com/media/pdf/Simplified%20Protocol.pdf. Accessed May 1, 2019.

Schmidt, RJ et al. *Epidemiol*, 2011;22(4):476-85.

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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)

Schmidt RJ et al. *Epidemiology*. 2011;22(4):476–485.
Phillips T. *Nature Education* . 2008;1(1):116.
Yasko Methylation Map. https://www.dramyyasko.com/diagrams-listing/. Accessed April 16, 2014.

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Preconception Male: Assessment & Interventions

Age & BMI	Health Status	Lifestyle	Exposure	Movement
☐ **Age** ☐ <30 years ☐ >40 years ☐ **BMI & body composition** ☐ >19 ☐ <25	☐ **HTN** ☐ **Hyperlipidemia** ☐ **DMII** ☐ **Testicular cancer** ☐ **Stress-affective or psychotic disorders, ASD, ADD** ☐ **R/O sleep apnea**	☐ **Alcohol / Tobacco / Drug / THC or CBD / Other** ☐ **Smoking** ☐ **Caffeine intake** ☐ **Vegan / Vegetarian** ☐ **Omega 6:Omega 3 ratio**	☐ **Medications that may interfere w/semen quality:** antidepressants, calcium channel blockers, alpha-adrenergic blockers, antiepileptics, antiretroviral drugs ☐ Chemical exposure	☐ **Intensity:** $\geq$60% of VO_2 max & $\leq$80% of VO_2 max ☐ **Frequency:** 5X weekly, >30 minutes
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 $\leq$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

Khandwala YS et al. *BMJ.* 2018;363:k4372.
Jayasena CN et al. *Clin Chem*. 2019;65(1):161-169.
Boeri L et al. *BJU Int.* 2019;123(5):891-898.
Jozkow P et al. *Endokrynologia Polska*. 2012;63:44-49.
Sermondade N et al. *Hum Reprod Update*. 2013;19(3):221-231.
Comhaire F. *Andrologia*. 2010;42(5):331–340.
Doba T et al. *Biochimica et Biophysica Acta*. 1985;835(2):298–303.
Comhaire F et al. *Prostaglandins Leukot Essent Fatty Acids*. 2000;63(3):159–165.

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Preconception Female: Assessment & Interventions

Age & BMI	Health Status	Lifestyle	Exposure	Movement
☐ **Age** ☐ Teen ☐ >20 years & <35 years ☐ AMA, >35 years ☐ V-AMA, >45 years ☐ **BMI & body composition** ☐ >19 ☐ <25	☐ Thyroid Disruption (Hypo/Hyper) ☐ DMII ☐ HTN ☐ PCOS ☐ Endometriosis ☐ Stress dysregulation (SDP)-affective or psychotic disorders, ASD, ADD ☐ Homocysteinemia	☐ Alcohol / Tobacco / Drug / THC or CBD / Other ☐ Smoking ☐ Caffeine intake ≤500mg daily ☐ Vegan / Vegetarian ☐ Omega 6:Omega 3 ratio	☐ Toxic exposures ☐ Teratogens ☐ NSAID use	☐ **Intensity:** mild, moderate, high-habitual ☐ **Frequency:** 5X weekly, >30 minutes
Protein (Amino Acids)	**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 **Probiotics** ☐ *Lactobacilli* species

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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)."

Perkins AV et al. Placenta. 2016;48 (Suppl 1):S61-S65.

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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.

Shireman TI et al. *Prostaglandins Leukot Essent Fatty Acids*. 2016;111:8–10.

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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]

1. Elliott E et al. *Prostaglandins Leukot Essent Fatty Acids.* 2017;126:98-104.
2. See VHL et al. *Br J Nutr*. 2017;118(11):971-980.
3. Nordgren TM et al. *Nutrients*. 2019;11(1)98.
4. Mozurkewich EL et al. *Front Pharmacol.* 2016;7:274.
5. Arnardottir H et al. *Mucosal Immunol*. 2016; 9(3): 757–766.

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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[1]
- **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[2]
- **Miscarriage**: Dietary carnitine supplementation may reduce the risk of spontaneous miscarriage[3]

1. Pekala J et al. *Curr Drug Metab*. 2011;12(7):667-678.
2. Lohninger A et al. *Gynakol Geburtshilfliche Rundsch*. 2009:49(40):230-235.
3. Ku CW et al. *BBA clinical*. 2017;*8*:48-55.

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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

King JC et al. *Modern Nutrition in Health and Disease*. 11th ed. Baltimore, MD: Lippincott Williams and Wilkins;2014:189-205.
Benton D et al. Eur J Nutr. 2008;47 Suppl 3:38-50.
Mercer JG. Neurologic development: *Nutrition and development: short and long term consequences for health*. Hoboken, NJ: Wiley-Blackwell;2013:97-115.

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Perinatal Nutrient Deficiency Rates: Carnitine

Carnitine Reference Range (nmol/ml)	**1st Trimester** N=30			**3rd Trimester** N=33			**Postpartum** N=9		
Total: 34-78 **Free:** 25-54 **Acyl:** 5-30									
Dose Range 500-3000mg (median dose, 1000mg)	**Total** 63%	**Free** 56.7%	**Acyl** 53.5%	**Total** 12%	**Free** 97%	**Acyl** 84.8%	**Total** 11.1%	**Free** 11.1%	**Acyl** 11.1%

Perinatal Nutrient Deficiency Rates: Zinc

Zinc Reference Range .66-1.0 mcg/ml	**1st Trimester** N=27	**3rd Trimester** N=27	**Postpartum** N=2
Dose Range, 30-60 mg (Median Dose, 50mg)	37%	85%	50%

Stone LP et al. *Glob Adv Health Med*. 2014;3(6):50–55.

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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]

1. Looker AC et al. *Am J Clin Nutr.* 2008;88(6):1519–1527.
2. Pilz S et al. *Int J Environ Res Public Health*. 2018;15(10):2241.

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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

Gupta PM et al. *J Clin Nutr.* 2017;106(Suppl 6):1640S-1646S.

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Perinatal Nutrient Deficiency Rates: Vitamin D

25-OH, D3	**1st Trimester** N=64	**3rd Trimester** N=58	**Postpartum** N=26
Deficient **<30ng/dl**	25%	22.4%	11.5%
Insufficient **≥30-<50 ng/dl**	55%	46.5%	69%
Dose Range: 1000-10,000 IU/day, Median dose 2,000 IU			

Perinatal Nutrient Deficiency Rates: Iron

Iron Dose Range **65-260 mg (Median Dose, 65 mg)**	**1st Trimester** N=66	**3rd Trimester** N=69	**Postpartum** N=29
HgB (gm/dL)	15.1%	49.2%	6.9%
Hct (%)	28.8%	85.5%	10.3%

Stone LP et al. *Glob Adv Health Med*. 2014;3(6):50–55.

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Choline & Placental Health

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

- ✓ Fetal brain development
- ✓ ⇧pCRH* & GR* methylation & ⬇ pCRH transcription
- ✓ Extra choline decreased placental expression of cortisol regulating genes

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

Jiang X et al. *FASEB J*. 2012;26:3563-3574.
Caudill MA et al. *J Am Diet Assoc*. 2010;110:1198–1206.

Other Common Deficiencies

- Magnesium[1]
- Essential fatty acids[2]
- Probiotics[3-4]
- Iodine[5-6]

1. Rosanoff A et al. *Nutr Rev.* 2012;70(3):153-164.
2. Morse NL. *Nutrients.* 2012;4(7):799-840.
3. McCartney A. Establishing of gut microbiota and bacterial colonization of the gut in early life. Nutrition and development: short and long term consequences for health. Hoboken, NJ: Wiley-Blackwell; 2013:116-129.
4. Forsberg A et al. *Clin Exp Allergy*. 2013;43(4)434-442.
5. Trofimiuk-Mudlner M et al. *Recent Pat Endocr Metab Immune Drug Discov*. 2017;10(2):85-95.
6. Pearce EN et al. *Am J Clin Nutr.* 2016;104 (Suppl 3):918S-923S.

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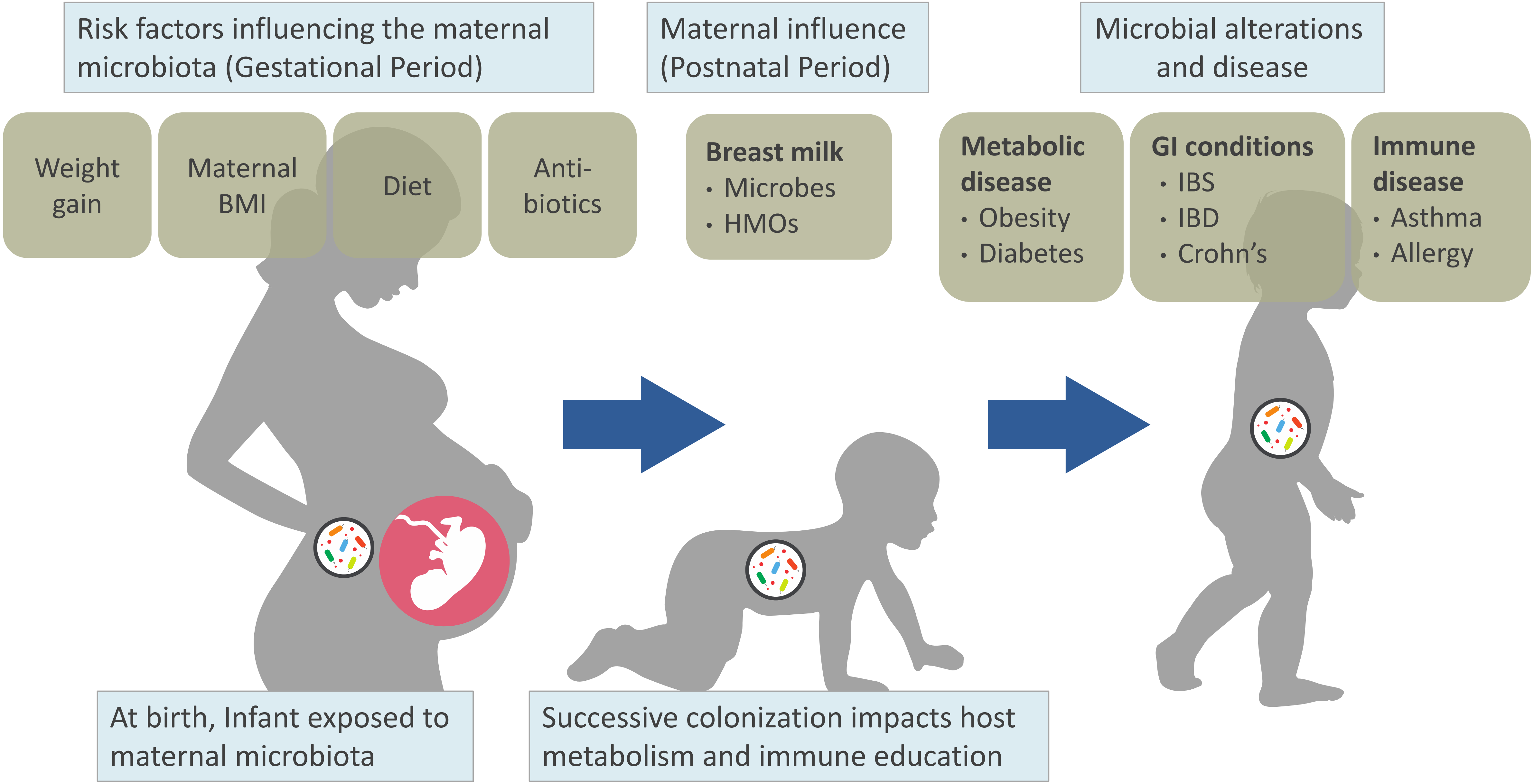

Mulligan CM et al. *J Endocrin.* 2017;235(1):R1-R12.

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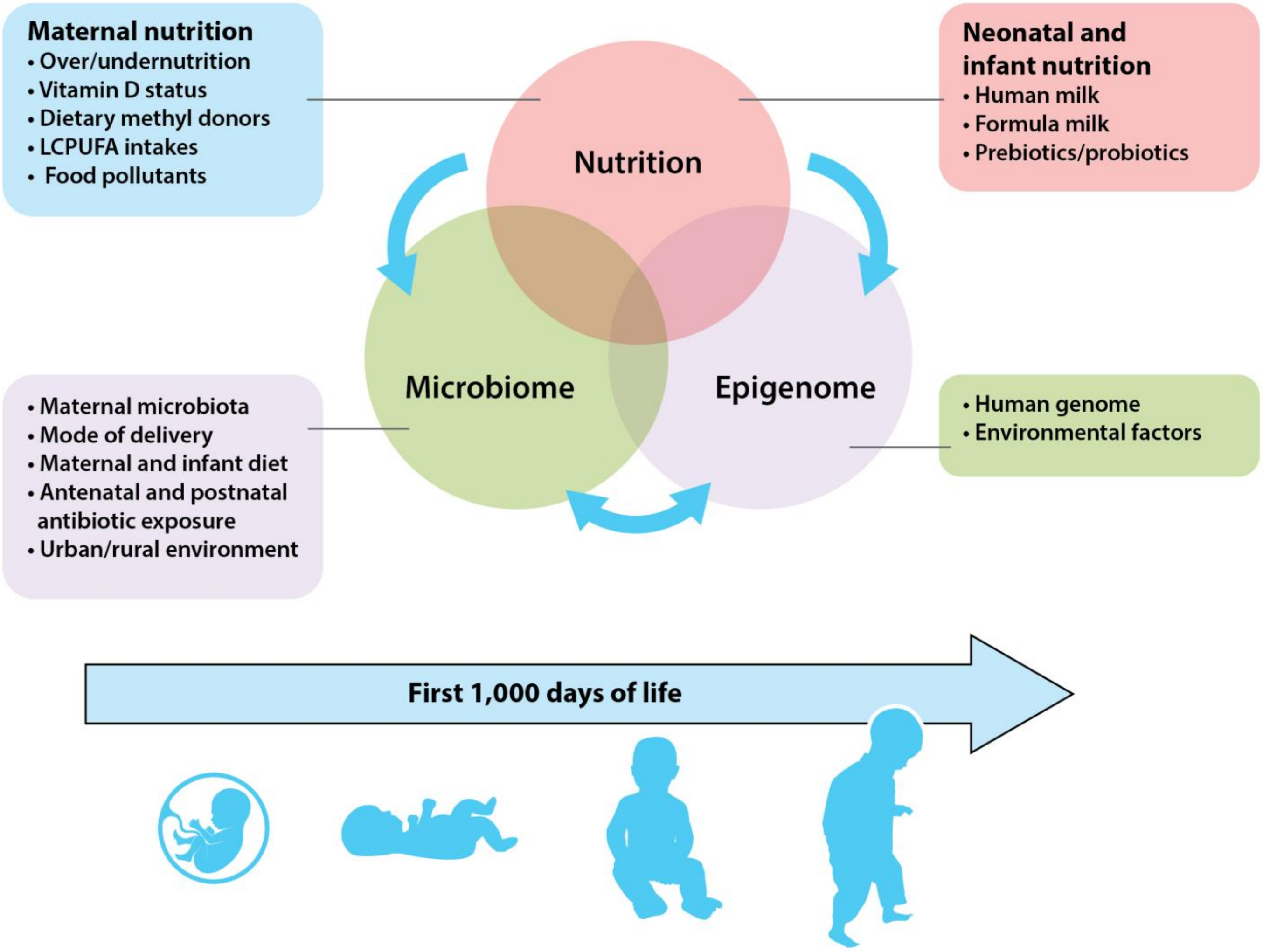
First 1000 Days and Beyond—The Microbiome and Child Growth

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



Shukla SD et al. *Clin Transl Immunology*. 2017;6(3):e133.
Matamoros S et al. *Trends Microbiol.* 2013;21:167-173.
Adlerberth I et al. *Acta Paediatr.* 2009;98:229-238.

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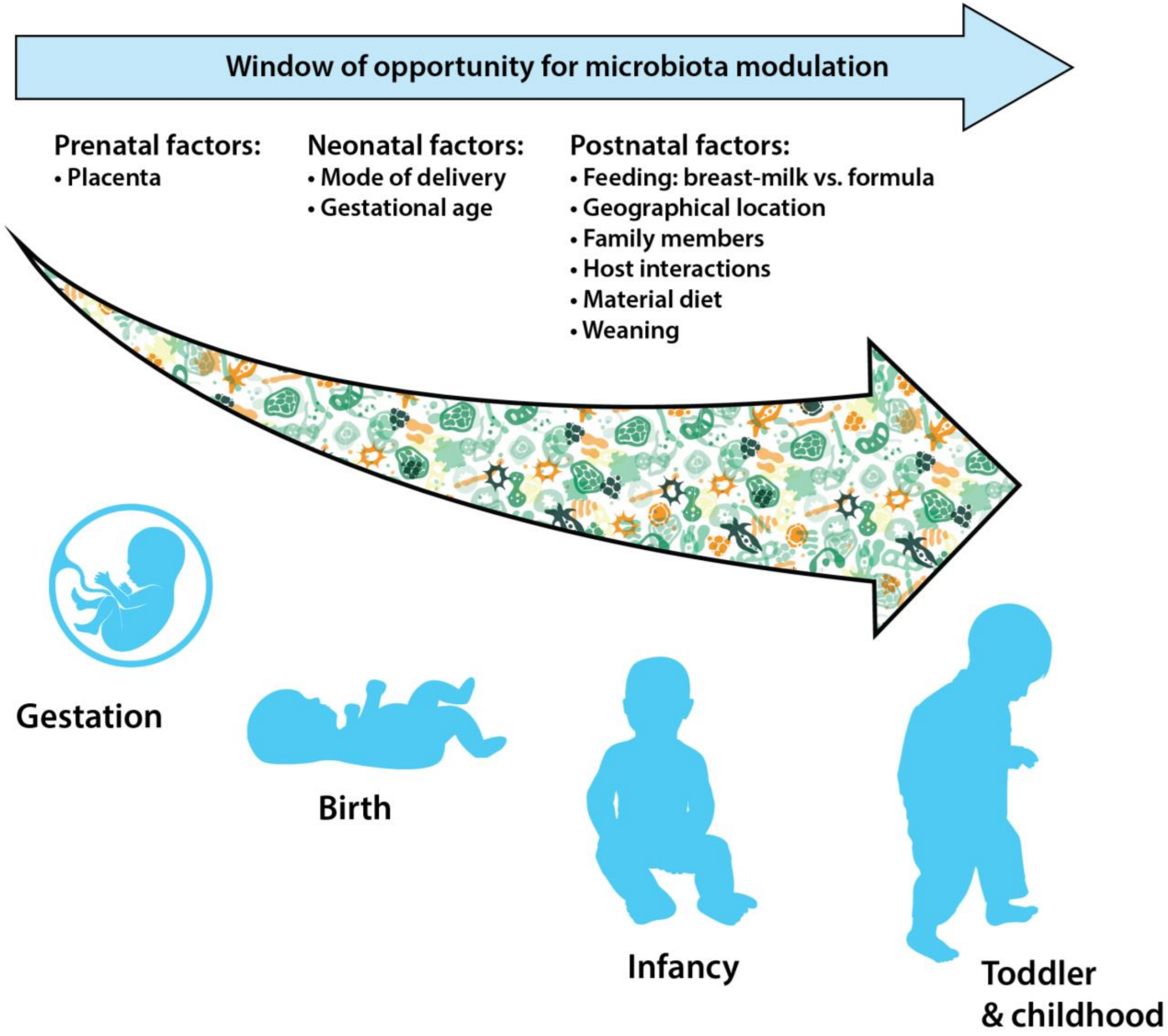

Image adapted from: Milani C et al. *Microbiol Mol Biol Rev.* 2017;8:81.

Windows of Opportunity to Intervene Microbiota-Targeted Therapies From Gestation to Childhood

- 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.

Walker RW et al. *Pediatr Obes*. 2017;12 (Suppl 1):3-17.
Robertson RC et al. *Trends Microbiol*. 2019;27(2):131-147.

Probiotic Usage During Pregnancy

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

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Probiotic Usage During Pregnancy

Study Design	Study Outcome	Reference
In a double blind randomized study, 62 pregnant women from atopic families received either ***Lactobacillus rhamnosus strain GG*** with a daily dose of 2×10^{10} or placebo during the 4 weeks before giving birth and during breast-feeding.	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.	Rautava S et al. *J Allergy Clin Immunol.* 2002;109(1):119-121.
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.	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.	Dotterud CK et al. *Br J Dermatol.* 2010; 163(3):616-623.
1223 pregnant women carrying children at increased risk for allergy were randomized to probiotic capsule containing **$5x10^9$ CFU *LGG*, $5x10^9$ CFU *Lactobacillus rhamnosus LC705, 2x10^8 CFU Bifidobacterium breve Bb99*, $2x10^9$ 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.	The probiotic treatment reduced IgE-associated diseases- **atopic eczema.** *Lactobacilli* and *bifidobacteria* more frequently colonized the guts of supplemented infants.	Kukkonen K et al. *J Allergy Clin Immunol.* 2007;119(1):192-198.
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 $1x10^{10}$ CFU ***Lactobacillus rhamnosus* GG** for 2 to 4 weeks before delivery and 6 months postnatally to their infants.	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.	Kalliomäki M et al. *Lancet.* 2001; 357(9262):1076-1079. Kalliomäki M et al. *Lancet.* 2003; 361(9372):1869-1871.

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Probiotic Usage During Pregnancy

Study Design	Study Outcome	Reference
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 ***Bifidobacterium bifidum BGN4, B. lactis AD011, and Lactobacillus acidophilus AD031***, or placebo in a randomized, double-blind, placebo-controlled trial.	The prevalence of **eczema** during the first 12months of life in infants was significantly lower compared to the placebo group.	Kim JY et al. *Pediatr Allergy Immunol.* 2010;21(2 Pt 2):e386-393.
A mixture of ***Bifidobacterium bifidum, Bifidobacterium lactis, and Lactococcus lactis*** was administered to the mothers of high risk children and also to the offsprings for the first 12 months of life.	Parental-reported **eczema** during the first 3 months of life was significantly reduced in the probiotic treated group.	Niers L et al. *Allergy.* 2009; 64(9):1349-1358.
In a double-blind, randomized, placebo-controlled trial of families with allergic disease, mothers received **L reuteri ATCC 55730** (1 x 10^8 CFU) daily from gestational week 36 until delivery. The infants continued with the same probiotic for one more year.	The probiotic treated group has **less IgE-associated eczema** during the second year.	Abrahamsson TR et al. *J Allergy Clin Immunol*. 2007; 119(5):1174-1180.

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Probiotic Usage During Pregnancy

Study Design	Study Outcome	Reference
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 ***Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14*** of $1X10^9$ 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.	Supplementation of ***L. rhamnosus* GR-1 and *L. reuteri* 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.	Ho M et al. *Taiwan J Obstet Gynecol.* 2016;55(4):515-518.
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 ***Lactobacillus salivarius* UCC118** at a dose of 10^9 colony-forming units or placebo capsule from diagnosis until delivery.	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**.	Lindsay K et al. *Am J Obstet Gynecol.* 2015;212:496.e1-11.

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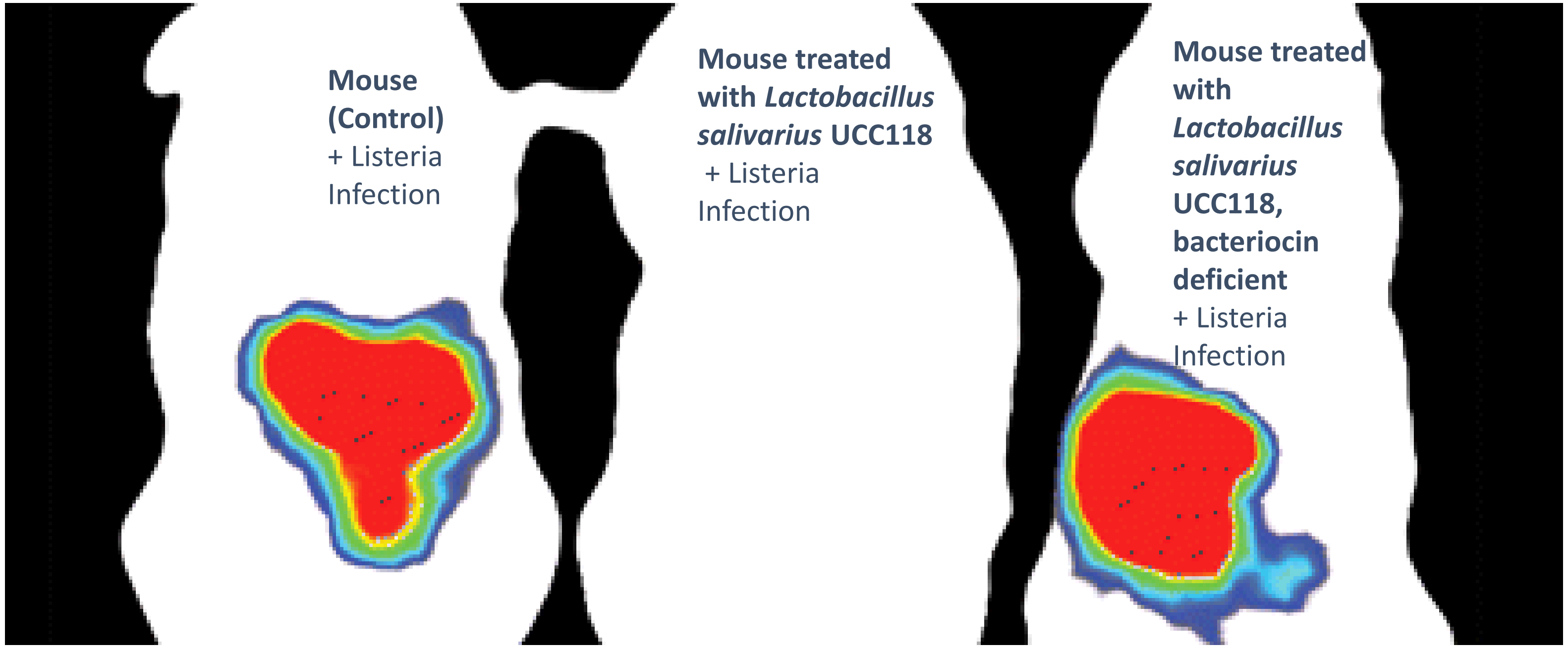
In vivo effectiveness of bacteriocin produced by *L. salivarius* UCC118

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.



Adapted from Corr SC et al. *Proc Natl Acad Sci U S A*. 2007;104(18):7617-7621.

1. Corr SC et al. *Proc Natl Acad Sci U S A*. 2007;104(18):7617-7621.
2. Riboulet-Bisson E et al. *PLOS ONE*. 2012;7(2):e31113.

OB Care & the Affordable Care Act

3 Million Deliveries (Aged 24-25)

February 2018 Outcomes[1]

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 admission**[1].

Our conclusion:
Change what we do during that prenatal care!

1. Daw JR et al. *JAMA*. 2018;319(6):579-587.

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Use What We Have:
9 Months

Control What We Can:
Lifestyle

Assess the Individual:
Always

Preconception—First 1000 Days and Beyond

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How Quickly Can You Turn On or Off Certain Genes?

6 hrs

Bouwens M et al. *Am J Clin Nutr.* 2010;91:208–217.

Assess the Individual:
Why BMI Matters…

A **pre-pregnancy BMI ≥30 kg/m²** 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

Viswanathan M et al. Evidence reports/ technology assessments, No 168. United States: Agency for Healthcare Research and Quality; 2008.

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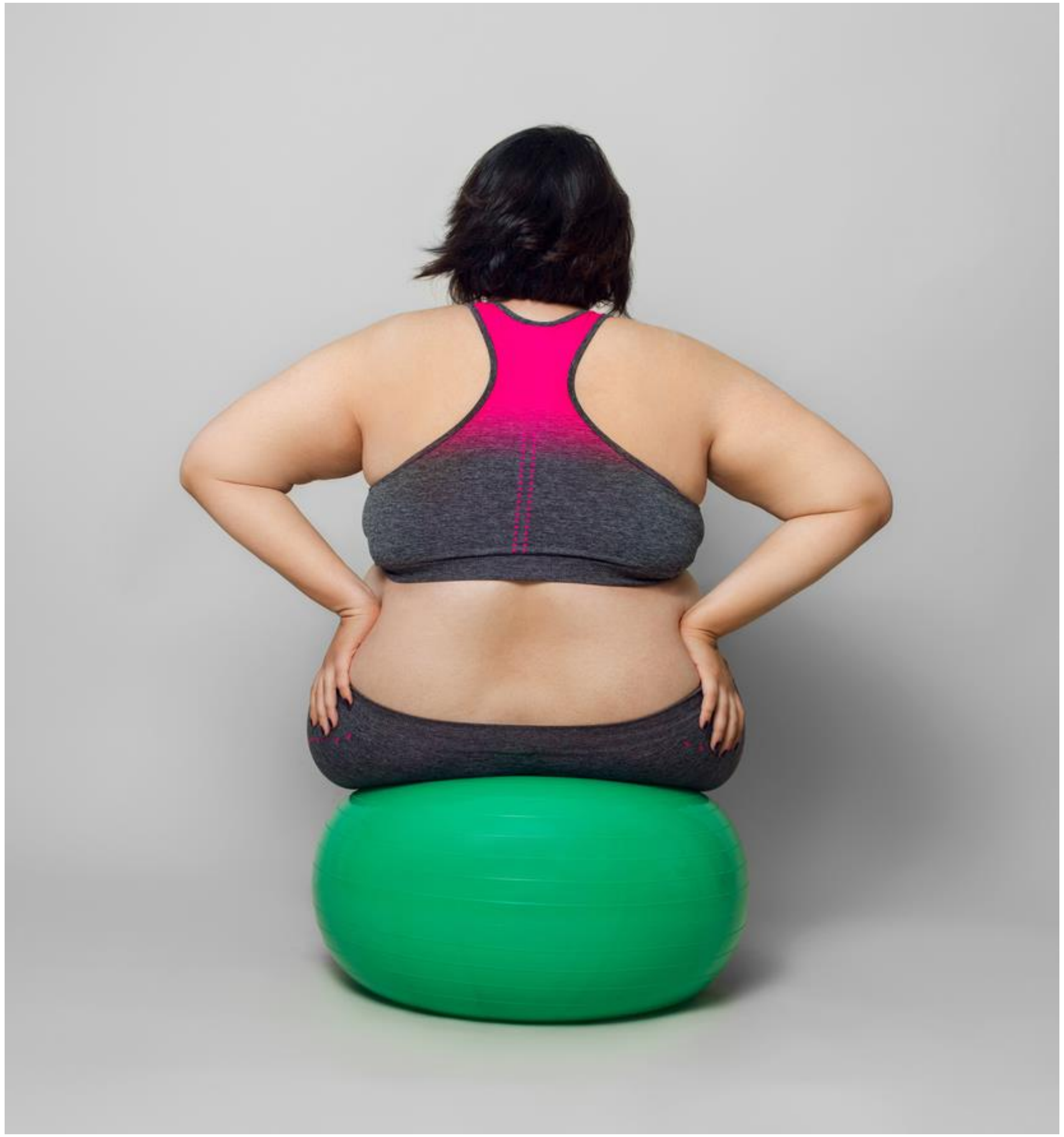
Assess the Individual:
Why Weight & Gain Matters…

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



Krakowiak P et al. *Pediatrics.* 2012;129(5):e1121-1128.

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BMI + Basal Metabolic Rate + Activity + Singleton+

Low Weight Gain	High Weight Gain
Low gestational weight gain is associated with:	**High gestational weight gain is associated with:**
• Higher risk of SGA	• Lower risk of SGA
• Higher risk of preterm birth	• Lower risk of preterm birth
• Lower risk of LGA	• Higher risk of LGA
• Lower risk of macrosomia	• Higher risk of macrosomia
• No difference in cesarean delivery	• Higher risk of cesarean delivery

Goldstein RF et al. *JAMA*. 2017;317(21):2207-2225.

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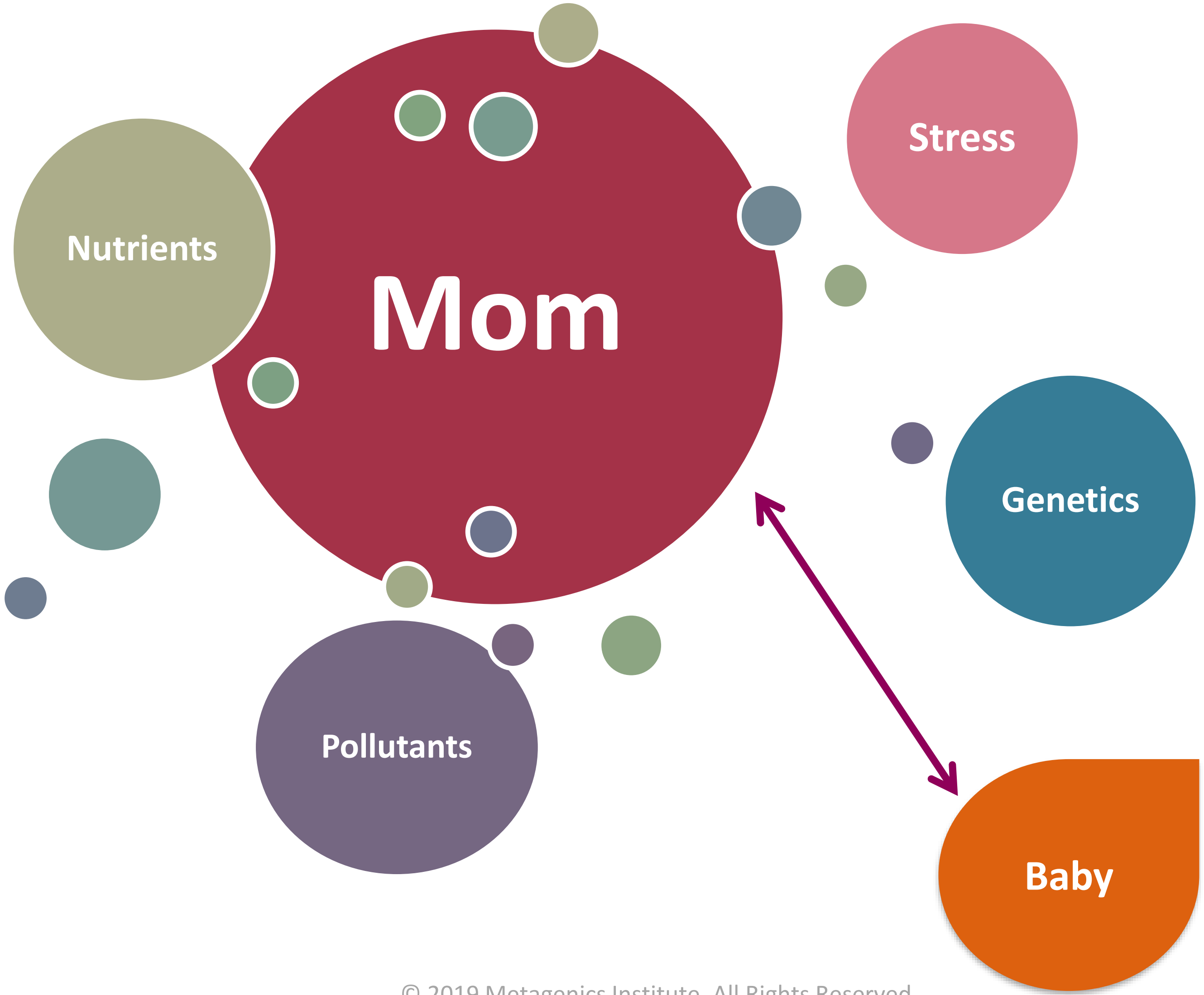
The quality and quantity of the nutrition you eat, the pollutants and stress that you expose your body to while pregnant, all affect the generational health of your family.



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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."

Goletzke J et al. *Am J Clin Nutr*. 2015;102(3):626-632.

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Protein

Animal & Plant-based

Organic, grass-fed & wild caught (cold-water, low-mercury)

Adjust for omnivore, vegetarian, vegan

Quality>Quantity

Fats

High quality, cold-pressed, Omega 6:Omega 3 balance

PUFA*

MUFA*

SFA*

Quality>Quantity

Carbohydrates

Whole, complex & unrefined, fiber-rich

Rainbow of Foods

Flavor diversity

Pro/Prebiotic food

Quality>Quantity

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

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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

Common S_x of Pregnancy-PP	Nutrition & Lifestyle	Bioactives
Nausea	Eating frequency + protein emphasis	Ginger root, B_6
Fatigue	Protein emphasis + iron rich foods & sleep hygiene	Carnitine, iron (vitamin C), vitamin A, B vitamins
Mood Imbalance	Essential fat emphasis-cold water fish + protein emphasis	EPA/DHA, inositol, B vitamins, lavender aromatherapy, turmeric
Hyperemesis		Ginger root
Restless Legs	Magnesium rich foods + electrolyte replenishment	Magnesium
Muscle Cramps	Vitamin C rich foods	Vitamin C
Headaches	Hydrating foods + fluid	CoQ10, carnitine, riboflavin (B_2), magnesium
Constipation	Adequate fiber + hydrating foods/fluid/ kiwi fruit + phytonutrient intake + pre/probiotic rich foods	Magnesium, fiber

1

2

Rydbom, Maternal Needs In Pregnancy: Symptom, Timing, and Management, *GrowBaby*. 2018

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	Common S_X of Pregnancy	Nutrition & Lifestyle	Bioactives
	Insomnia	Limit stimulants sugar/caffeine + support melatonin secretion during daytime	Magnesium
	Heartburn	Limit antagonists: spicy, processed, gluten, dairy, sugar & focus on alkaline rich foods/fluid, positional sitting/laying/eating	
3	**Fatigue**	Protein emphasis + adequate iron rich foods + sleep hygiene	Carnitine, iron (vitamin C), vitamin A, B vitamins
3	**Constipation**	Adequate fiber + hydrating foods/fluid / kiwi fruit + phytonutrient intake + pre/probiotic rich foods	Magnesium citrate
4	**Fatigue**	Protein emphasis + adequate iron rich foods + sleep hygiene + sleep hygiene + resting priority	Carnitine, iron (vitamin C), vitamin A, B vitamins
4	**Mood Imbalance**	Essential fat emphasis-cold water fish + protein emphasis	EPA/DHA, inositol, B vitamins, turmeric, lavender, vitamin D
4	**Mastitis**	Hydration, lymphatic support	SPMs, *L. Gasseri, L. Fermentum, L. Salivarius*

Rydbom, Maternal Needs In Pregnancy: Symptom, Timing, and Management, *GrowBaby*. 2018

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Needs by Trimester	Fetal Development	Maternal Needs
1	**P:** Methionine, cysteine **F:** DHA **M:** Iron, Mg **V:** A, D, B_1, B_2, B_3, B_5, B_6, Folate, B_{12} **Phyto:** Carotenoids	**P:** Carnitine **C:** Soluble & insoluble fiber **M:** Iodine, Iron, Mg, Se **V:** A, C, D, B6 **Phyto:** Ginger
2	**F:** DHA **M:** Boron, Ca, Iron, Mg, Molybdenum, Phosphorous, Zn **V:** A, D, E, B_1, B_2, B_3, B_5, B_6, Folate, B_{12}, **Phyto:** Rainbow, carotenoids	**P:** Carnitine **C:** Soluble & insoluble fiber **M:** Iron, Mg, Zn **V:** A, C, D, B_1, B_2, B_3, B_5, B_6, Folate, B_{12} **Phyto:** Rainbow
3	**F:** EPA & DHA **M:** Copper, Iodine, Iron, Mg, Se, Zn **V:** Choline, A, B_1, B_2, B_3, B_5, B_6, Folate, B_{12} D, E, **Phyto:** Rainbow, carotenoids	**P:** Carnitine **C:** Soluble & insoluble fiber **F:** EPA, DHA, SPMs **M:** Copper, Iodine, Iron, Mg, Se **V:** Choline, A, D, E, B_1, B_2, B_3, B_5, B_6, Folate, B_{12}, **Phyto:** Rainbow **Probiotics:** *L. Gasseri, L. Fermentum, L. Reuteri L. Salivarius, L. Helveticus, B. Longum*
4	**F:** DHA **M:** Calcium, Copper, Iron, Mg, Se, Zn **V:** Choline, A, D, E, B_1, B_2, B_3, B_5, B_6, Folate, B_{12} **Phyto:** Rainbow, lutein, zeaxanthin **Probiotics:** L. Reuteri, L. Rhamnoses	**F:** DHA & SPMs **M:** Iron, Mg **V:** Choline, Inositol, D, B_1, B_2, B_3, B_5, B_6, Folate, B_{12}, **Phyto:** Rainbow **Probiotics:** *L. Gasseri, L. Fermentum, L. Reuteri, L. Salivarius, L. Helveticus, B. Longum*

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

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