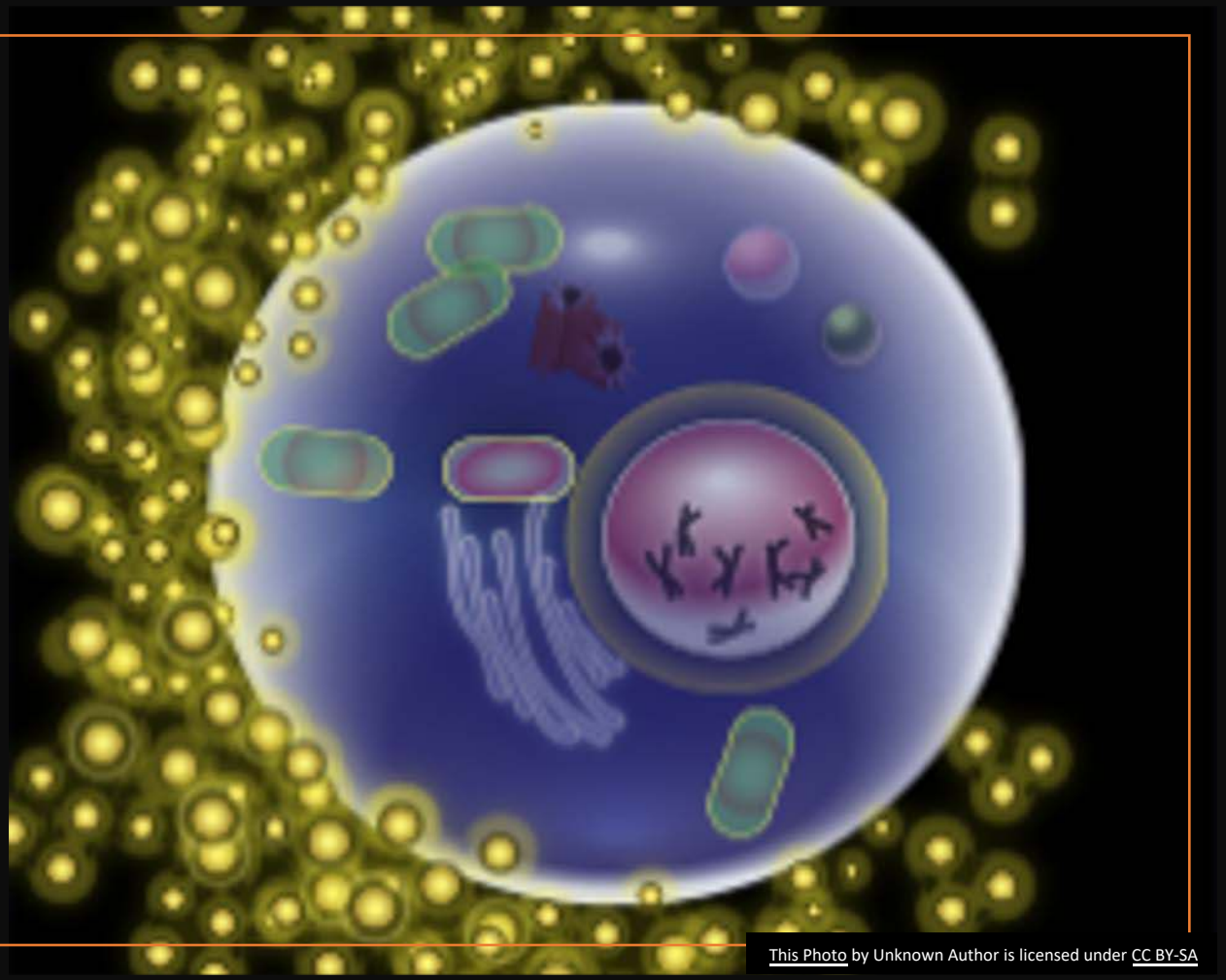
Optimizing Oocyte Quality

Presented by Dr. Jennifer Fitzgerald, ND

Conceive Inc. Toronto, Ontario



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Presentation Outline

- Primordial oocyte development review
- Factors affecting oocyte quality
- Mitochondria function and oocyte quality
- Mitochondrial nutrients and antioxidants for oocyte quality

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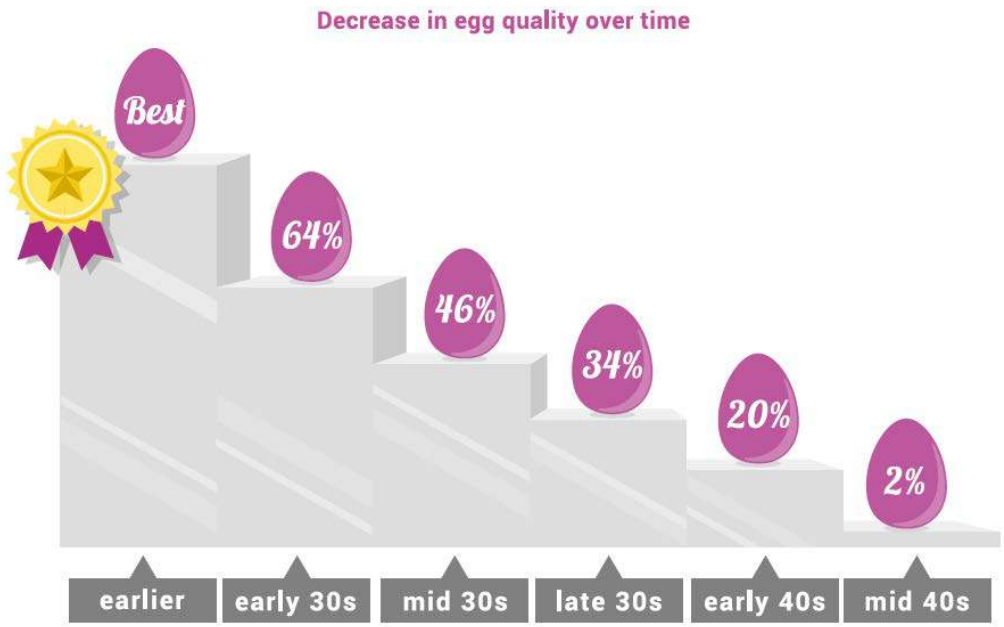
Egg Quality Basics

- Female fertility peaks at age 25, and after age 35 suffers a rapid decline.
- Oocytes take approximately 100 days to mature. During this time they are incredibly vulnerable to their environment.
- Quality of oocytes can depend on:
  - Age***
  - Nutritional status
  - Environmental exposures
  - Stress – HPA axis
  - Genetic variables



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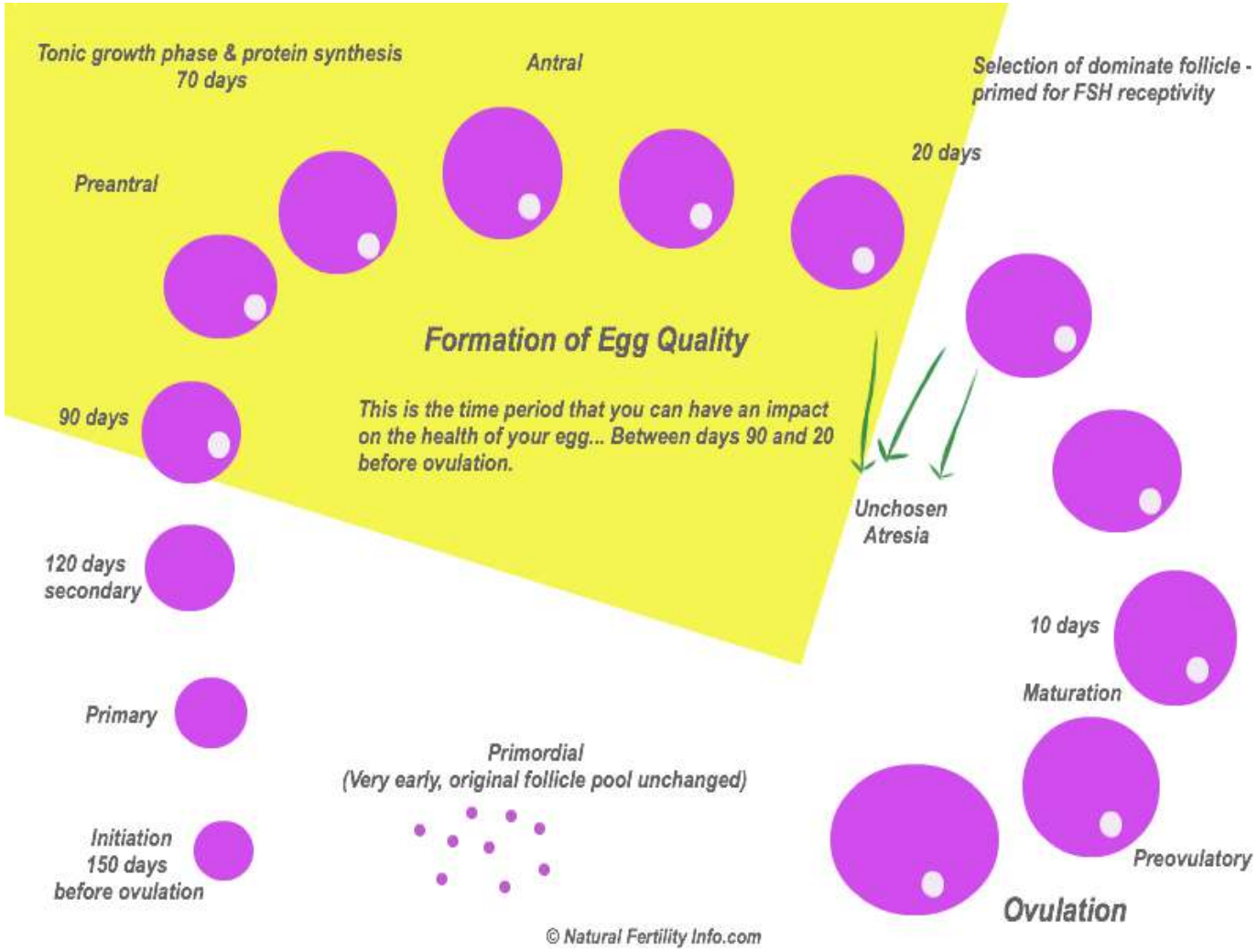
100 Days of Follicular Development



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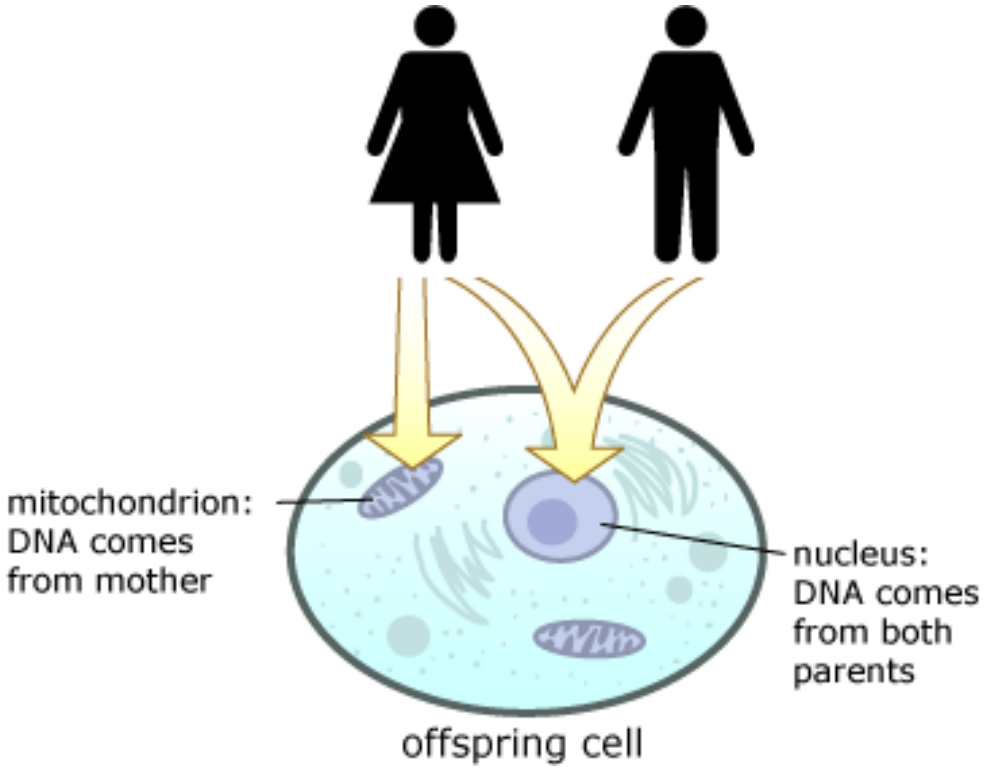
Oocyte Vulnerability

- Oocytes contain 200,000-500,000 mitochondria
- mtDNA is especially sensitive to damage, and mutates 17X faster than nDNA
- Damaged mitochondria replicate faster
- Lack of protective histones, efficient DNA repair enzymes, introns
- ALL mitochondrial are of female origin: the oocyte passes 100,000+ mitochondria to the next generation (sperm typically contain less that 100 mitochondria).
- Bentov et al, 2010



https://evolution.berkeley.edu/evolibrary/images/news/mitochondrialdna.gif

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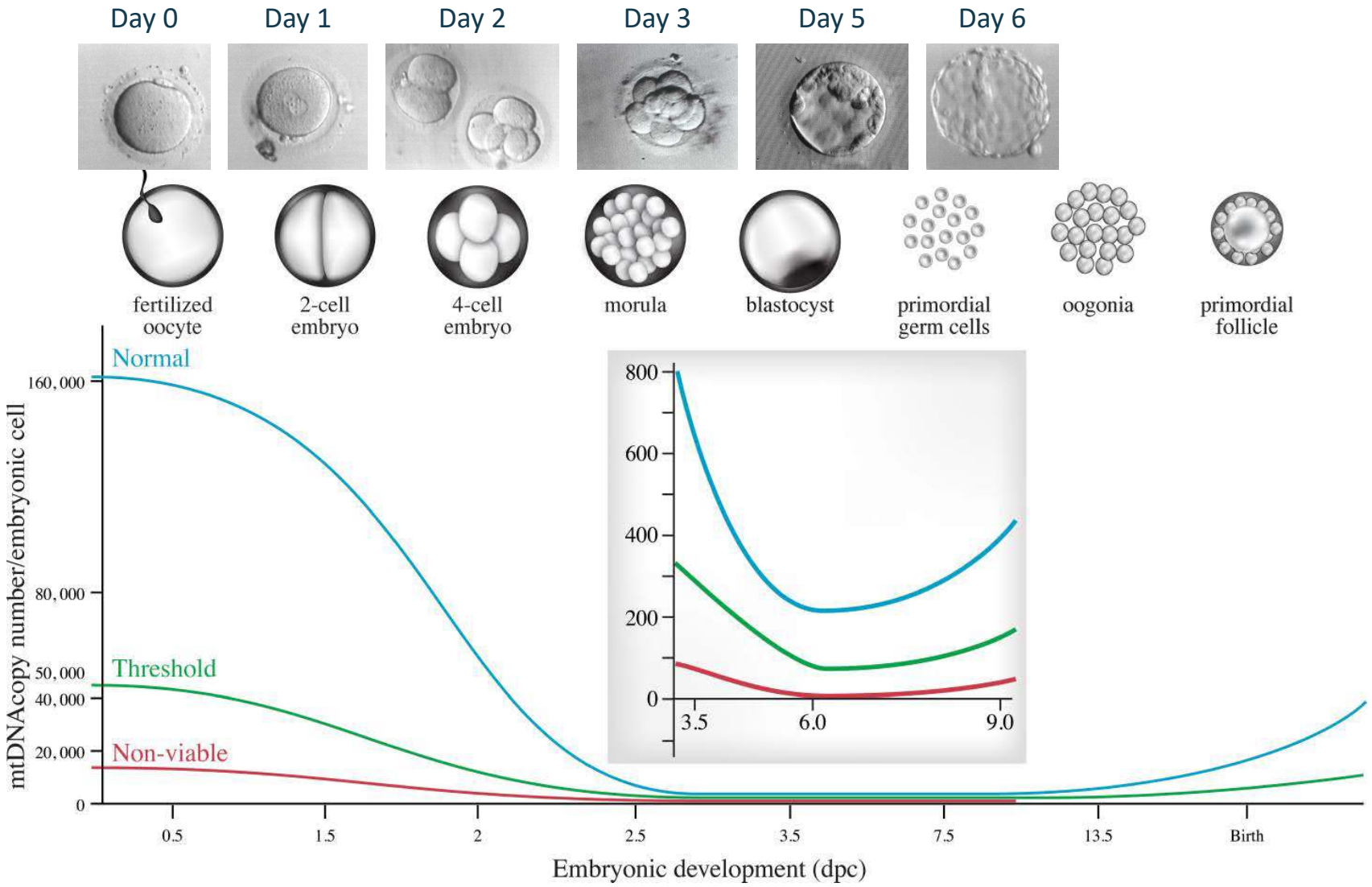
Mitochondria and Embryo Development



- Adapted from Wai et al., 2010

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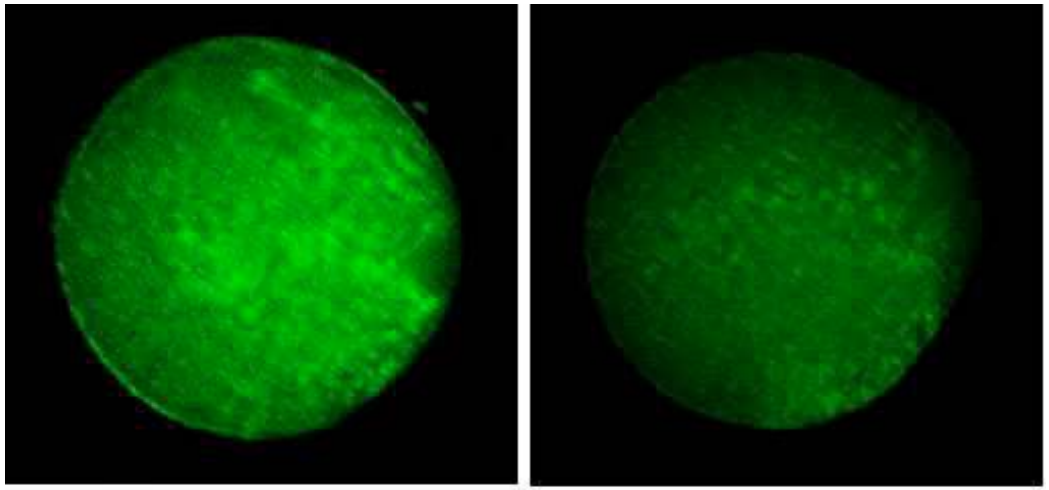
Aging and mtDNA Mutations

- Decreased efficiency of mitochondrial electron transport
- Decreased energy (ATP) production
- Increased production of ROS
- Damage to essential cell proteins, lipids, DNA
- Increased susceptibility to apoptosis



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Nutritional Status Effects mtDNA

- **Deficiencies and excesses**
- **Malabsorption, celiac, ileostomy**
- **Vegetarianism/Veganism/Keto/Fasting**
- **Obesity**
- **Low BMI or adipose %**
- **Ultimate damage to mitochondrial function/replication**

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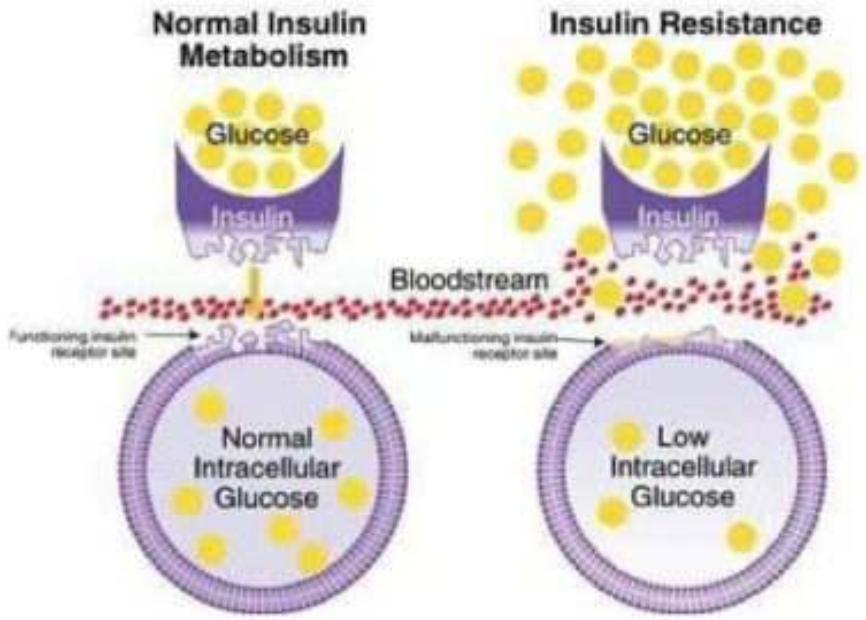
Insulin Resistance and Oocyte Quality



- HOMA-IR, OGTT
- PCOS, PCO, or neither
- Metformin – interferes with complex I-II of the ETC, lowers ATP.
- IR impairs mitochondrial function and increase rates of aneuploidy (Tatone et al 2008, Wang 2010)
- AGEs associated w/ reduction in number of oocytes retrieved, fertilized and good quality embryos, ongoing Pregnancy rate 23% vs 3.4% (Jinno, 2011)

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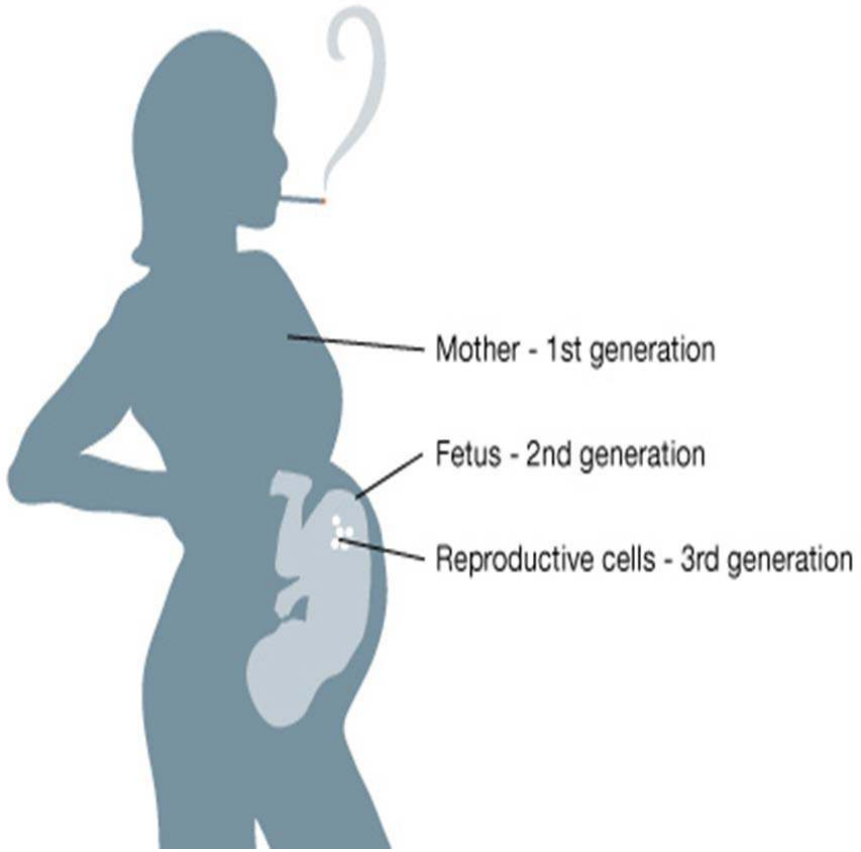


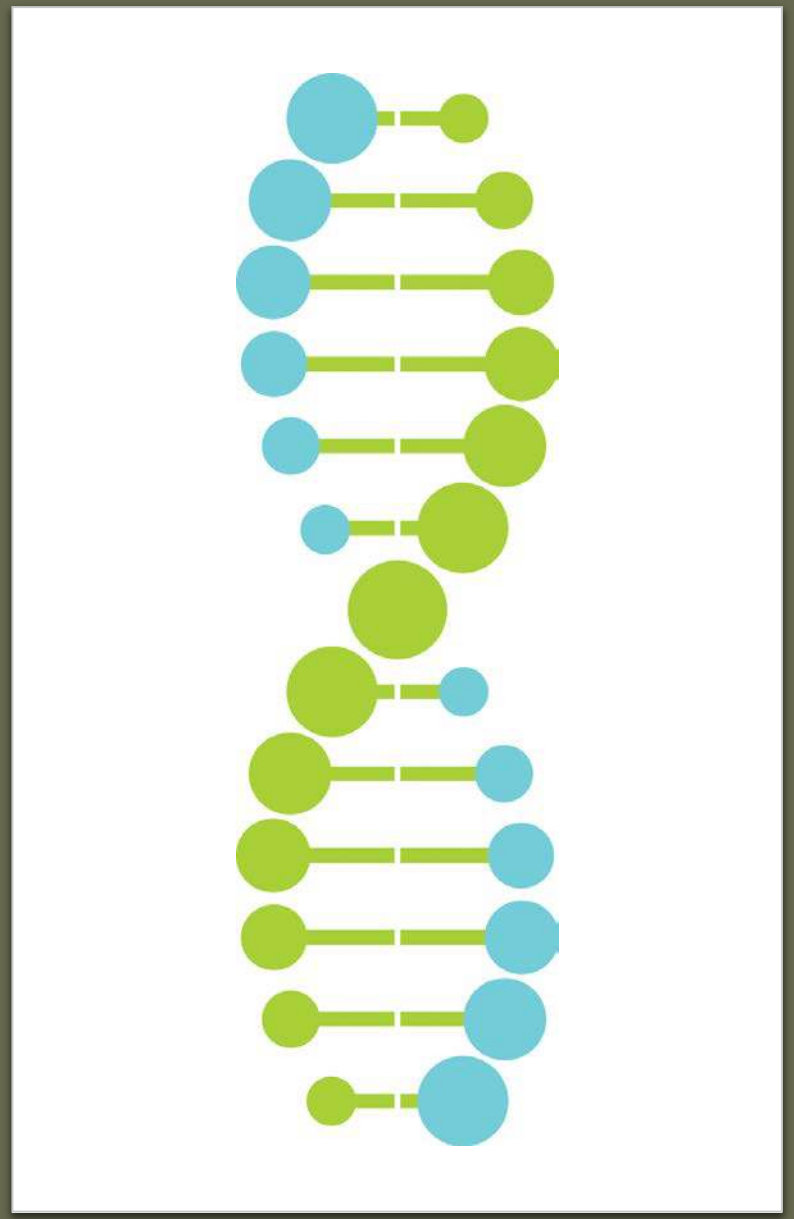
Environmental Factors and Exposures

- Over **800 chemicals** daily, many are **endocrine disruptors**
- BPA
- Phthalates
- Dioxins, polycyclic aromatic hydrocarbons
- Heavy metals
- Organophosphate pesticides
- Social toxins
- Medications
- 200 toxic elements found in cord blood

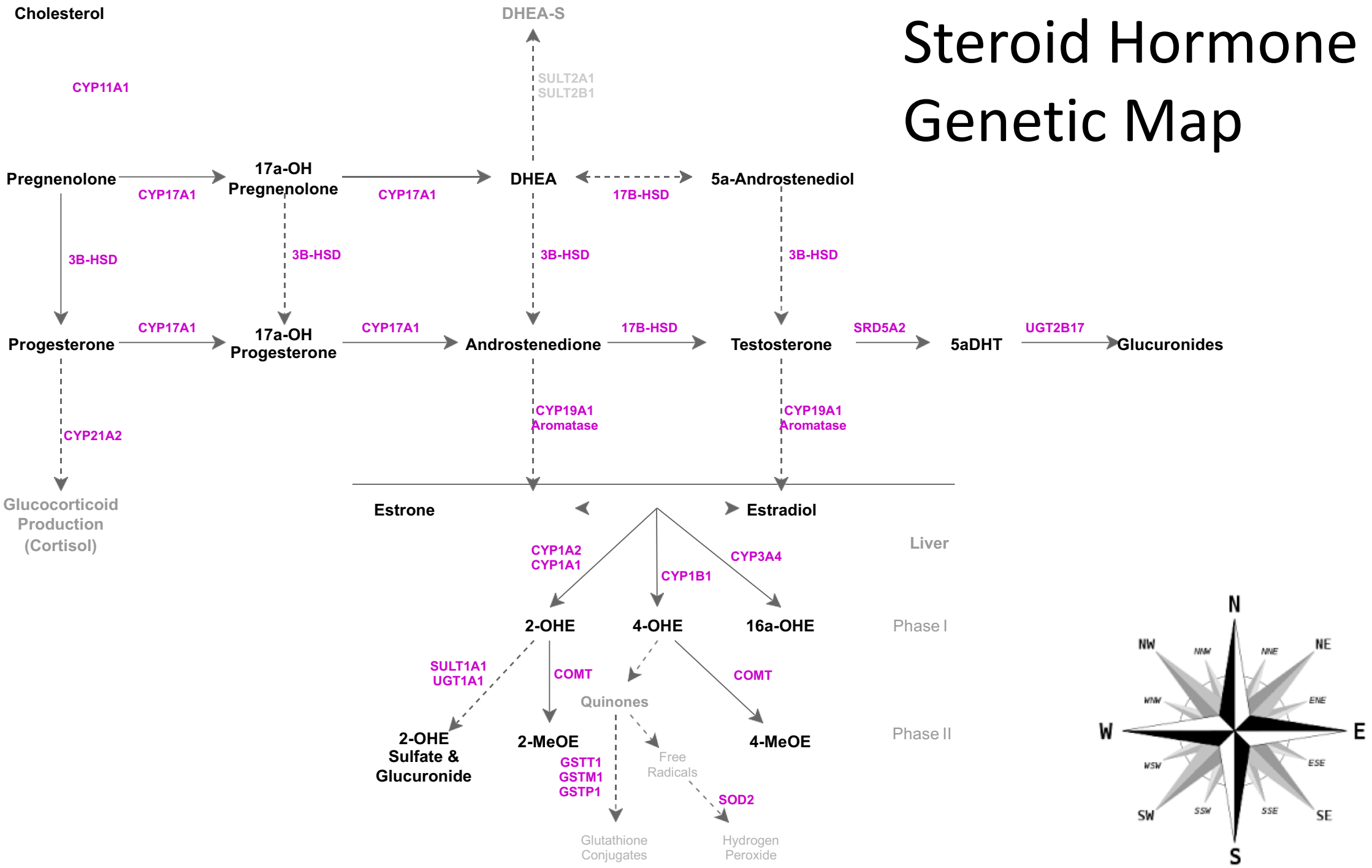
- Exposure assessment and reduction education

Genetic Factors

- Modifiable vs unmodifiable genetic risk factors
- Unique genetic variables
- Ongoing research on effects of SNP's on oocyte quality and fertility.
  - Nutrients: BCMO1, NOS, SOD, FUT2, MTHFR, FTO, etc
  - Detox/hormone: CYP17A1, GST(M/P/T), COMT
  - Methylation: MTHFR, PEMP
  - Immune:SIRT1, PGC-1α, IL-6, TNF – many more.
  - Antioxidant: SOD2, NQ01, CRP. APOE

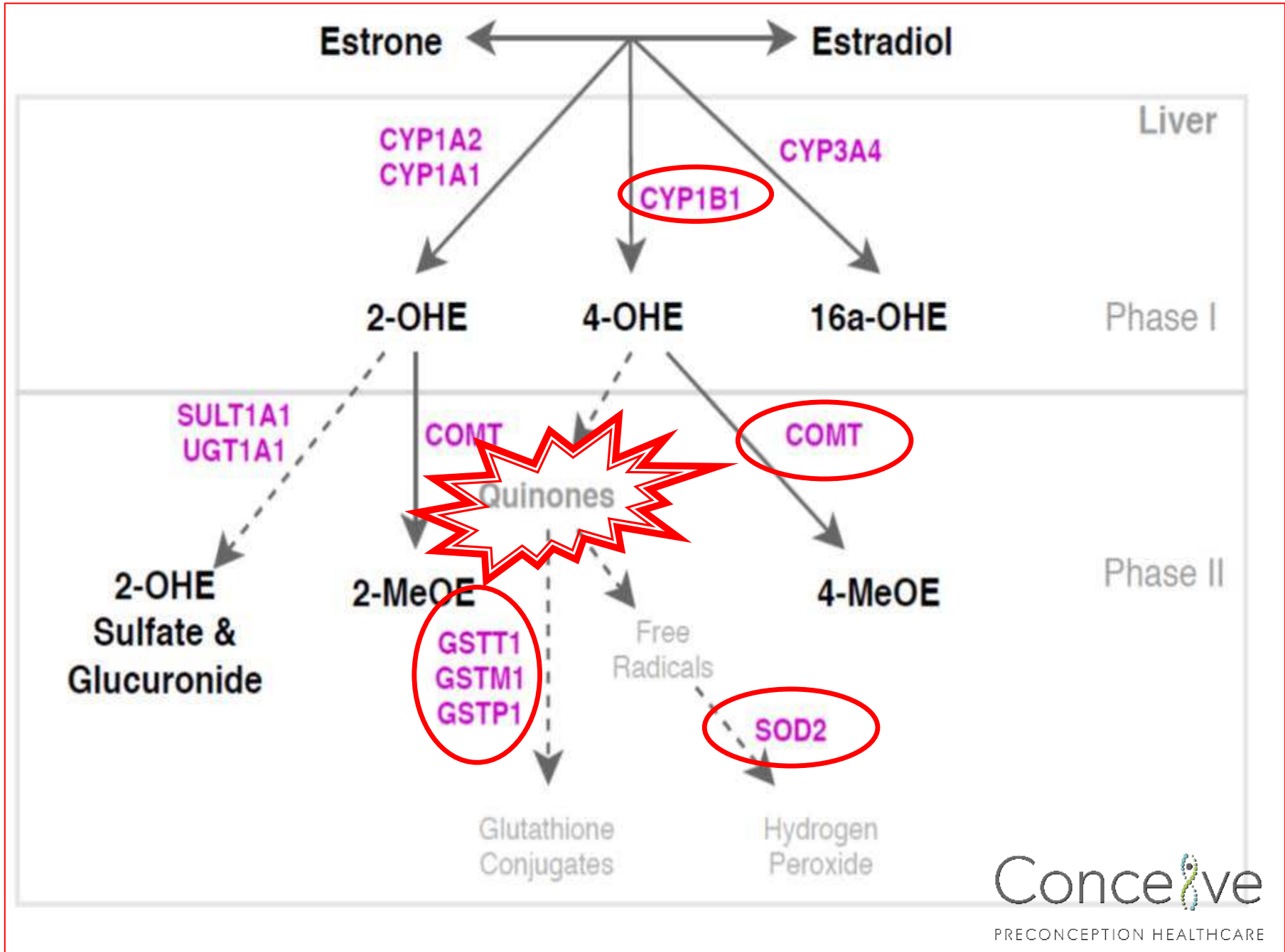


Steroid Hormone Genetic Map



Estrogen Metabolism

SNP trends that affect egg quality



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Assessing Oocyte Quality

- **Day 3 hormones: FSH, LH, E2, prolactin, AMH**
- **Other hormones: Progesterone (post-ov), prolactin, thyroid, androgens**
- **U/S, AFC, ovarian size/volume, cysts**
- **Nutrient testing: ferritin, vit a, b12, d, beta carotene, homocysteine, glucose, insulin, HOMA-IR**
- **Micronutrient testing**
- **Dutch Test (8-OHdG)**
- **Organic Acid Testing**
- **SNP testing**
- **IVF (incl spindle view and other advanced technologies)**
- **Other**

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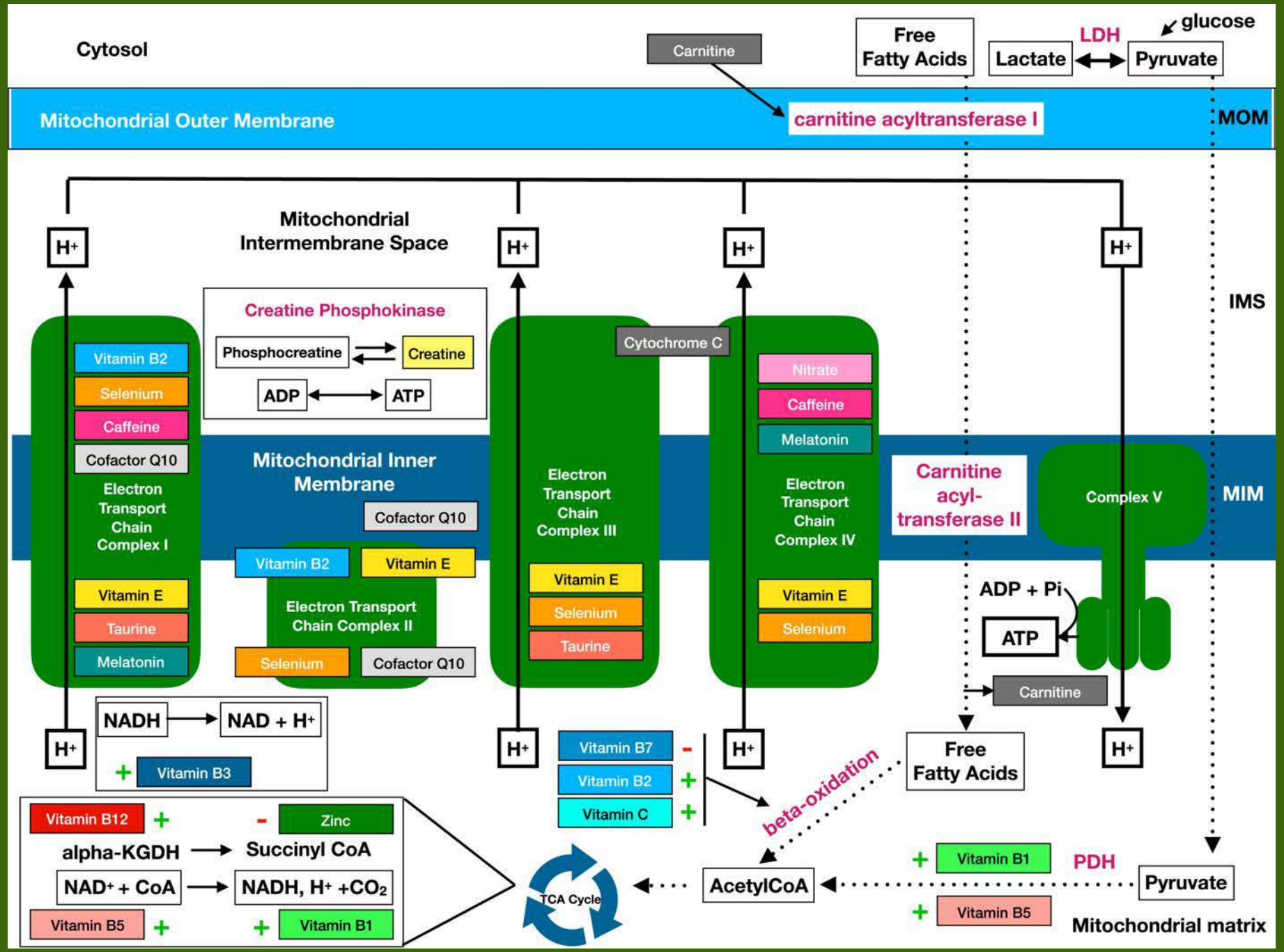

What to do?

Mitochondrial Nutrients and Cofactors

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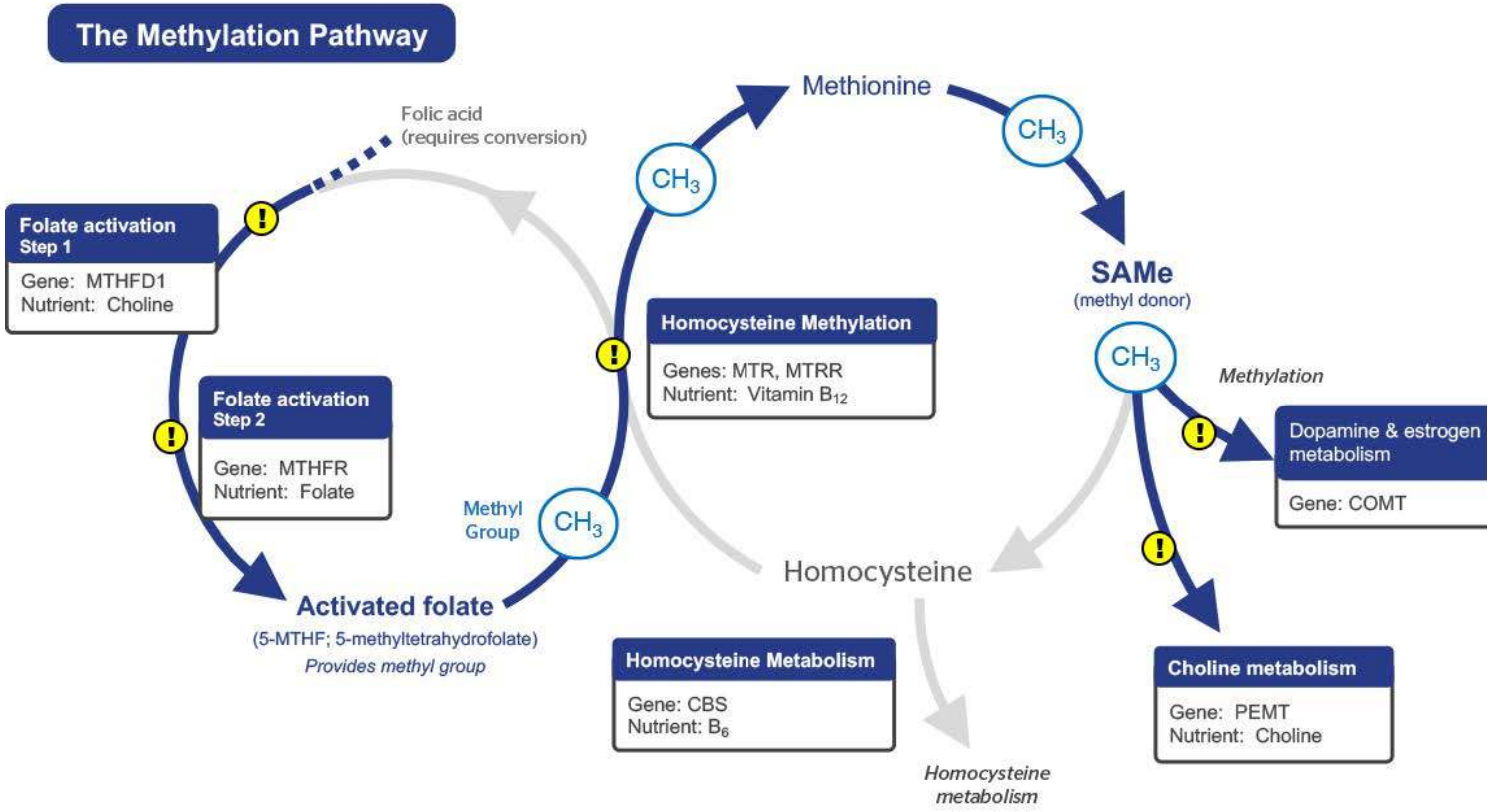

B Vitamins

- PHD Complex: CoA (from B5), NAD+ (contains B3), FAD+ (contains B2), ThPP (thiamine pyrophosphate, contains b1)
- Krebs: B1, B2, B3, B5
- ETC and electron shuttle: B2, B3
- Methylation cycle (folate, B12)

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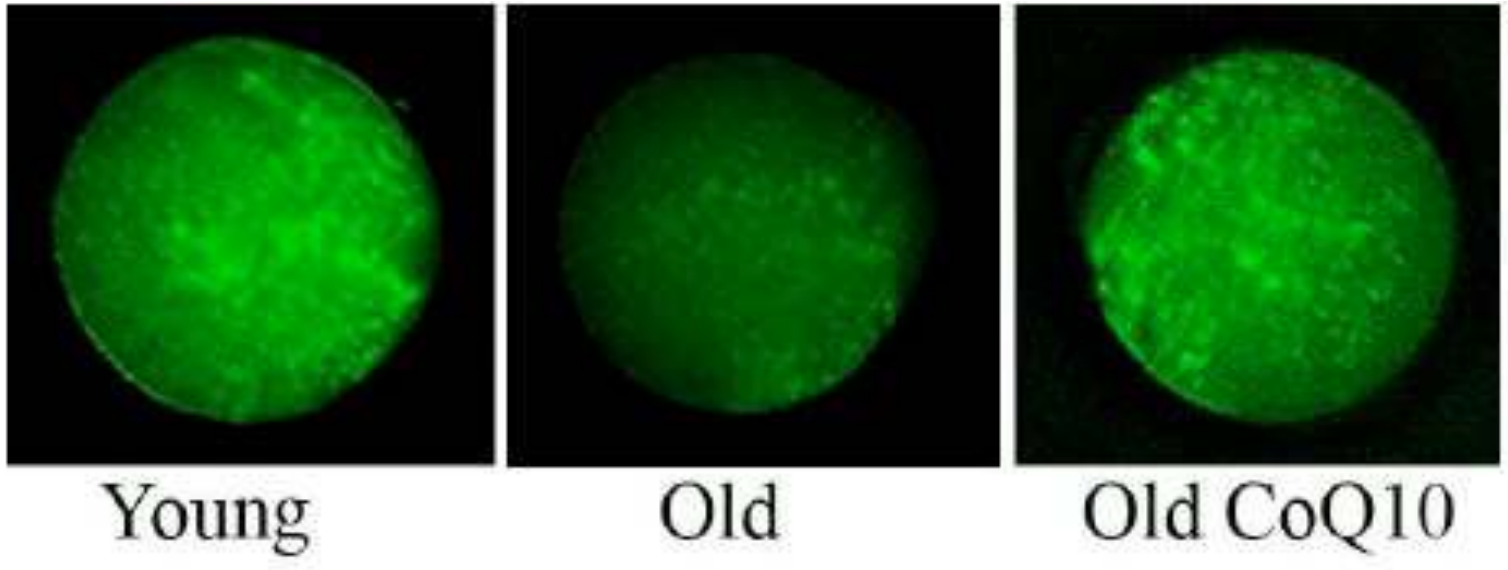
CoQ10 and Aged Murine Ovaries

- CoQ10 improved egg numbers and quality, embryo quality and pregnancy outcome.
- ATP spike at time of chromosomal separation
- Several animal studies suggest CoQ10 protective to oocyte reserve, restores mitochondrial function, improves embryo cleavage and blast formation.



Burstein, 2009

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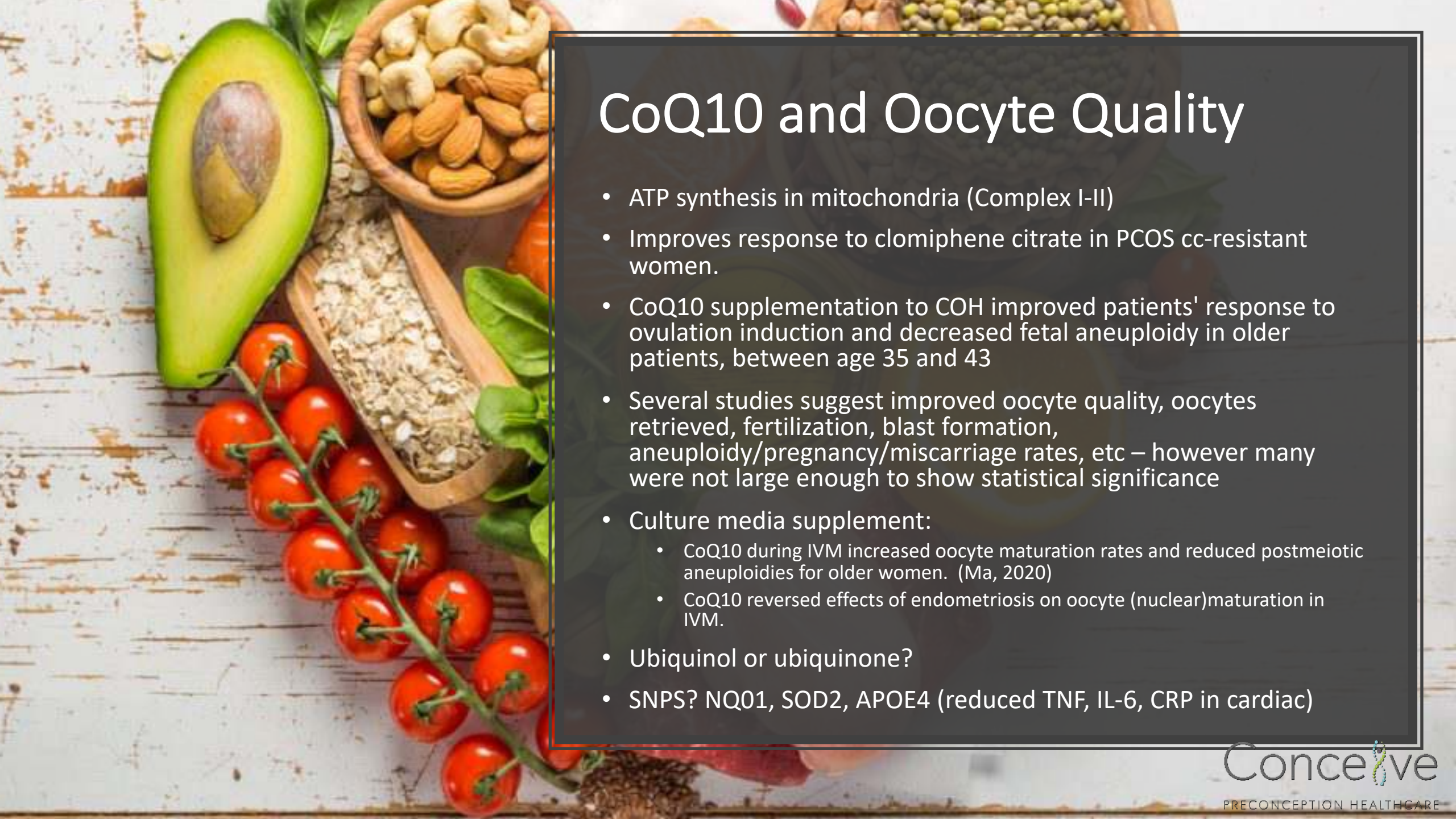

CoQ10 and Oocyte Quality

- ATP synthesis in mitochondria (Complex I-II)
- Improves response to clomiphene citrate in PCOS cc-resistant women.
- CoQ10 supplementation to COH improved patients' response to ovulation induction and decreased fetal aneuploidy in older patients, between age 35 and 43
- Several studies suggest improved oocyte quality, oocytes retrieved, fertilization, blast formation, aneuploidy/pregnancy/miscarriage rates, etc – however many were not large enough to show statistical significance
- Culture media supplement:
  - CoQ10 during IVM increased oocyte maturation rates and reduced postmeiotic aneuploidies for older women. (Ma, 2020)
  - CoQ10 reversed effects of endometriosis on oocyte (nuclear)maturation in IVM.
- Ubiquinol or ubiquinone?
- SNPS? NQ01, SOD2, APOE4 (reduced TNF, IL-6, CRP in cardiac)

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PQQ (Pyrroloquinoline Quinone)

- Vital for mitochondrial synthesis and function
- Strong, continuous cycling AO
- Spontaneous regeneration of new mitochondria
- Activates AMPk (enzymatic master regulator of energy metabolism).
- Synergistic with Co-Q10 in managing electron transport, protecting mitochondrial membranes and DNA from oxidative damage
- Reynolds et al, 2013.
  - 0% vs 30% degeneration
  - 50% reduction in abnormal meiotic spindle development
- Logsdon, 2018
  - Improved number of hatched embryos in aging females, and mitochondrial energy in 2 cell embryo.

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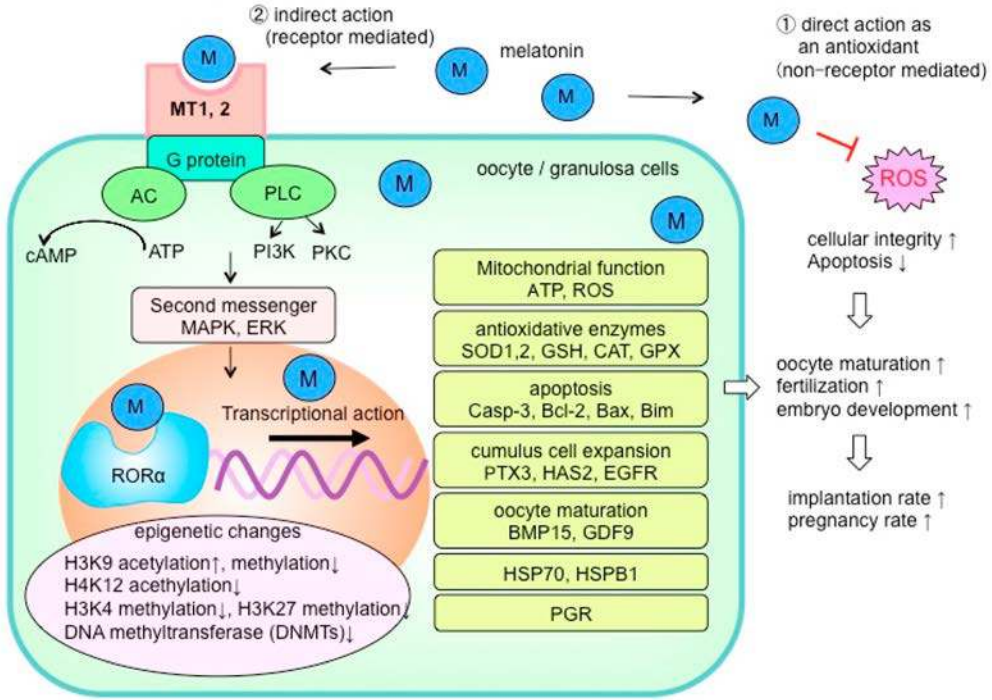
Melatonin

- Regulates biological rhythms, reproduction, immune response, apoptosis, metabolism, antioxidant.
- Stimulates several antioxidative enzymes
- Concentrates in follicular fluid, levels increase as follicle grows.
- Studies indicate melatonin increases egg and embryo quality, fertilization rate, and pregnancy rate.
    - Tamura et al, melatonin given from beginning of IVF cycle, average of 65% of oocytes retrieved creating good quality embryos vs 27% in the previous cycle.
- Espino et al, 2019. Melatonin supplements reduced oxidative balance in FF, improved oocyte quality, and slightly increased CPR/LBR.



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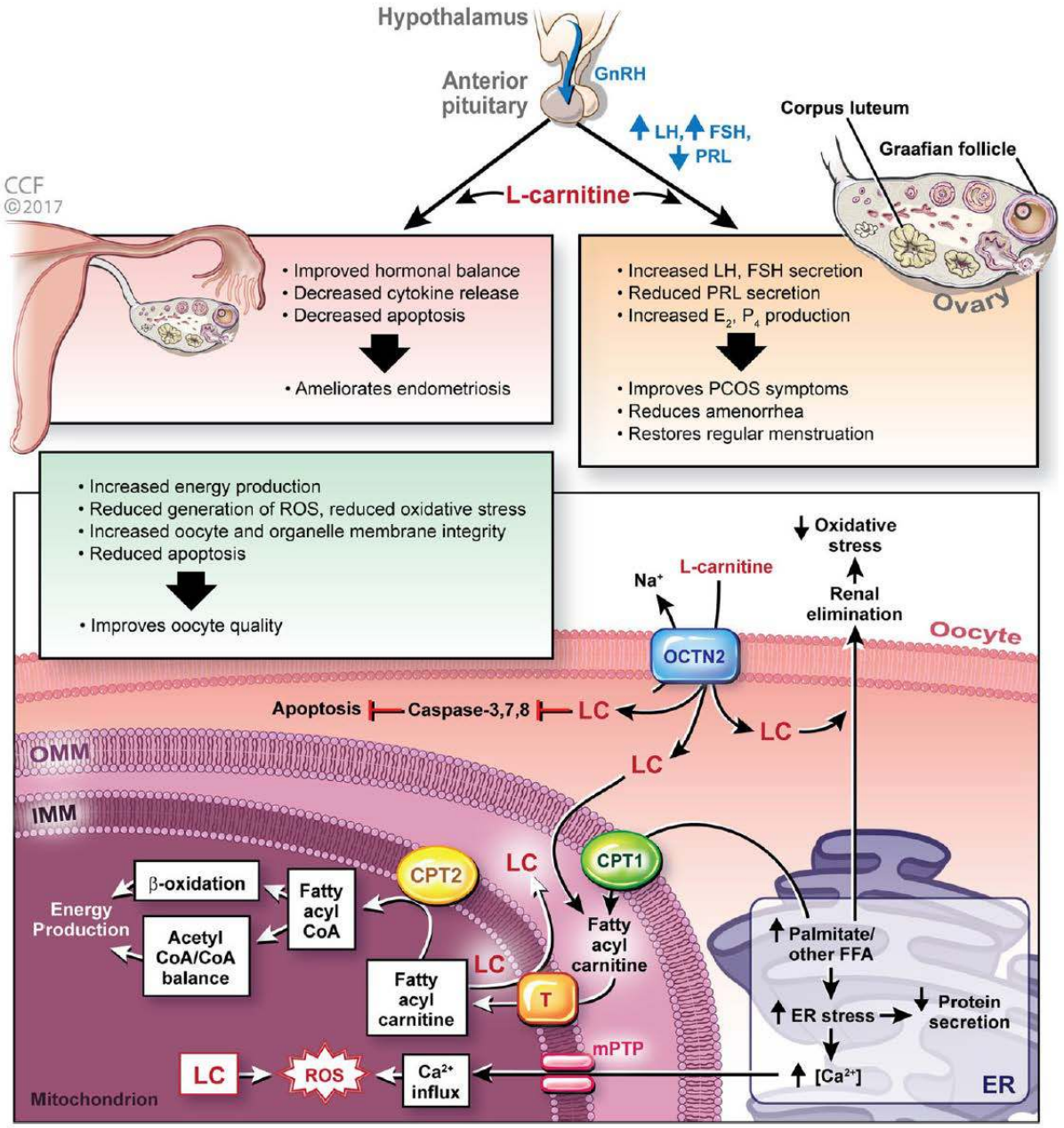
Carnitine (ALC, LC)



- From diet/supplements or lysine methylation in Kd
- Increased b-oxidation of long chain FFA
- Maintain CoA/Acetyl CoA ratio for ATP production
- Vit E sparing effect
- Reduction of OS
- Antioxidant
- Anti-apoptotic effects
- Anti-inflammatory effects (TNF alpha, IL-2, IL-6, IFN, etc.)
- LC improved blood glucose and insulin resistance, lower LC associated w/ higher androgens, LH, LDL and fasting insulin than controls (Fenkci, 2008)
- Improved response to clomid AND gonadotrophins, 64% had improved follicular growth, improved ET, and 20% positive preg test. (Latifian, 2015)

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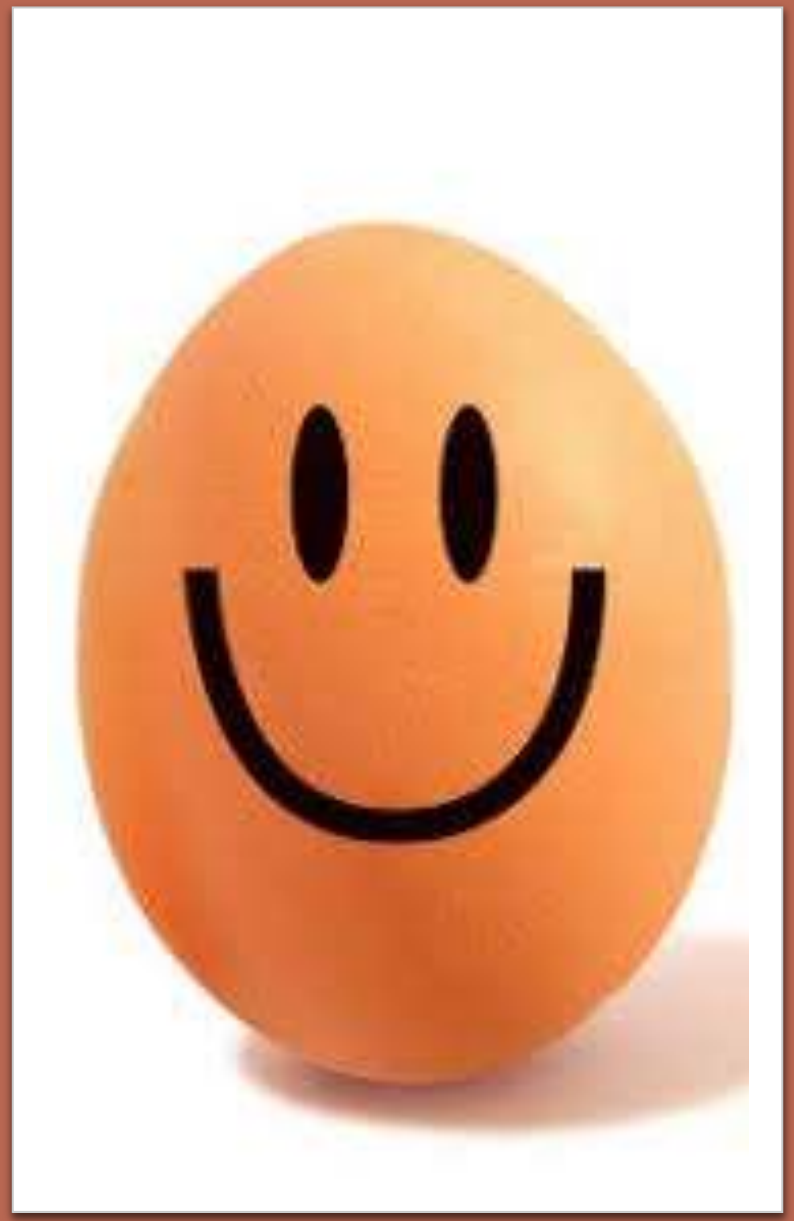

N-acetyl cysteine

- Protects mitochondria from oxidative stress
- Several papers highlight NAC's effects on detoxification of harmful substances including organophosphates, BPA, lead, aluminium.
- 1800 mg/d improve oocyte and embryo quality in PCOS patients in IVF2.
- 600 mg qd lowered FF homocysteine and improved oocyte yield and CPR in ICSI cycles (Hebisha, 2015).
- NAC and LC protected meiotic abnormalities in oocytes exposed to FF from women with mild endometriosis (Giorgi, 2015).

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Vitamin D

- 80% of my patient population below reference range
- Deficiency is related to subfertility, endometriosis, fibroids, PCOS, preeclampsia, preterm delivery, gestational diabetes, and bacterial vaginosis.
- Increased estrogen, estrone, progesterone, insulin-like growth factor binding protein 1 in ovary.
  - 17β-HSD, *3*β-HSD and Aromatase (thereby regulating androgens)
- High Vit D in FF paired with VDR and CYP24A1 expression in healthy sperm may facilitate selection and fertilization (Hansen, 2016).

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Vitamin D and Oocyte Quality

- AMH production in adults may be regulated by Vit D.
  - Deficiency changes expression and serum concentration
  - Secreted by granulosa cells
  - Supplementation prevented seasonal variation
- In IVF: increase in top quality embryos and, blastocyst transfer was higher in women with sufficient levels of 25(OH)D. Implantation rate also improved (Paffoni, 2019).
- Also lowers risk of pre-eclampsia (w/ Ca), improves mean birth weight.

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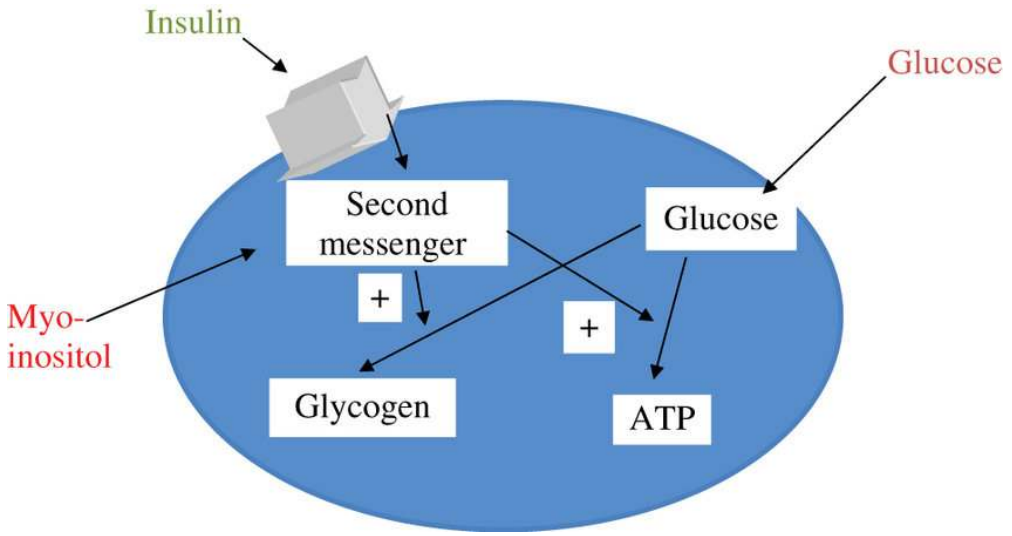
Beta Carotene and Vitamin A

- Beta carotene to Vit A via BCM01
- BC: Concentrates in ovary, estrogen blocking effects, delays/impaired oocyte maturation (Murphy, 2017)
- Vit A: Early follicular recruitment, early embryogenesis
- Fetal folliculogenesis - triggered by retinoic acid (Bowels et al 2007)

Inositol

- Insulin sensitizer, 2nd messenger for FSH, TSH
- Significantly higher MI in FF of good quality oocytes (Chiu et al, 2002)
- Improves oocyte maturation, fertilization, and embryo development
- Poor responders: Increased good quality oocytes and improved pregnancy rate
- PCOS: Increased oocytes retrieved, ET's and good quality embryos, decrease in immature oocytes, reduction in days/units of FSH and lowered rates of OHSS.
- MI – most studied, most effects on ovary/oocye
- DCI – 40:1, strong insulin sensitizer, androgens, T2DM, CV markers



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In Summary

- Preconception care is key, especially in a world of aging parents.
- It is clear there is a role for antioxidants in female oocyte quality
- Limitations include the longevity of humans. For some agents, supplementation may be required for months to years for improvement.
- Integrating with ART is important regardless of age. IVF, even with the best of prognosis, still fails to produce a baby most of the time.

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