Natural Approaches to Fertility Enhancement

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Physiology basics

- Maximum oocytes: 6–7 million (at 20 weeks of gestation)
- 1–2 million oocytes at birth→ 300,000–500,000 at puberty→ 25,000 at age 37 years→ 1,000 at age 51 years
- Fecundity decreases gradually but significantly beginning approximately at age 32 years; more rapidly after age 37 years
- Reflects primarily a decrease in egg **quality** plus a gradual increase in the circulating level of FSH and decreases in circulating AMH and inhibin B concentrations

Infertility: Definition

Failure to achieve pregnancy within 12 months of unprotected intercourse in women younger than 35 years or within 6 months in women older than 35 years

Affects up to 15% of couples

Offer workup after 6 months to those older than 35

Perhaps sooner if older than 40 or known risk factors in younger women (endometriosis, PCOS)

Can our fertility predict our mortality?

- Twin study: 14,000 twins (55% female, 45% male) over 20+ years
- Longer "time to pregnancy" also had the highest mortality (esp. women)
- Women who took 18+ months to conceive had overall mortality rate 46% higher than those who conceived in 2 months or less, and were hospitalized 21% more often
- Think of fertility as a vital sign

Hum Reprod. 2021;36 (8): 2309-2320

Preconception Screening Tests

- Hormones
  - FSH, LH, Testosterone, Cortisol, DHEA(s), prolactin
  - Maybe: AMH (antimullerian hormone), estradiol, progesterone
- Thyroid
  - TSH, free T4, free T3, reverse T3, thyroid peroxidase abx, thyroglobulin abx, thyroid stimulating immunoglobulin
- Metabolism
  - CBC, Comprehensive Metabolic Panel, Hemoglobin A1C, fasting insulin, HS-CRP, lipid panel with fractionation (particle size)

Essential components of an initial workup

- Review of the medical history
- Physical examination
- Areas of concern
  - ovarian reserve
  - ovulatory function
  - structural abnormalities
- Imaging
  - tubal patency (hsg or sonoshysterogram)
  - pelvic pathology
  - assess ovarian reserve (u/s)

"Unexplained infertility": ACOG definition

- As many as 30% of infertile couples
- Definition of infertility is met
- Basic infertility evaluation is performed
- All the test results are normal
- At a minimum, these patients should have evidence of:
  - ovulation
  - tubal patency
  - normal semen analysis

"Unexplained infertility" actually consists of :

- Poor gut health
- Nutritional insufficiencies/ deficiencies
- Toxic exposures
- Altered immune function
- Luteal phase defect/ low progesterone
- Thyroid dysfunction
- Oxidative Stress
- Inflammation
- Energy production/ mitochondrial function
- Adrenal dysfunction
- Chronic infections

"Unexplained infertility": Poor gut health

- Leads to nutritional deficiency, leading to poor egg quality or poorly functioning placenta
- Symptoms:
  irregular bowel movements, constipation/diarrhea, bloating, excess or foul gas, belching, halitosis
- History of antibiotic use, H Pylori

"Unexplained infertility": Poor Gut Health Testing

- Comprehensive stool testing
- Evaluate pancreatic and bile/gallbladder function
- Include testing for betaglucuronidase
- SIBO test

Endometrial microbiome

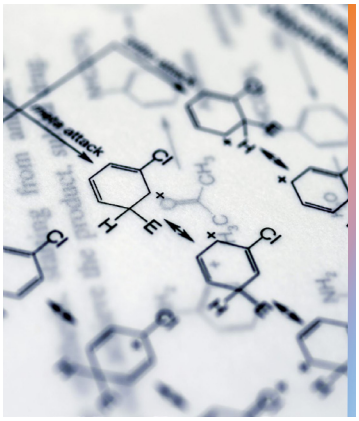
- Varies with the menstrual cycle
- Modulates immune function, impacts implantation
- Higher levels of lactobacillus associated with improved outcomes
  - Lactic acid, maintains lower ph in uterus for improved implantation
- Higher levels of gardnerella, prevotella associated with complications
- Impacted by:
  - Gut microbiome
  - Oral microbiome
  - Vaginal microbiome
  - Contraceptive devices
  - Microorganisms on sperm
  - Hormones

"Unexplained infertility": Testing for Nutritional Issues

- Organic Acids
  - Malabsorption, dysbiosis markers
  - Cellular energy, mitochondrial markers
  - Neurotransmitters metabolites
  - Markers of vitamin cofactors
  - Detoxification markers
  - Oxalate markers
- Amino Acids
  - Essential and nonessential
  - Markers of methylation pathways
- Oxidative stress markers
  - Lipid peroxidases
  - 8 OHdG
- Comprehensive Urine Elements
  - Nutrient elements
  - Toxic elements
- Omega Check
  - Conventional/ national labs
  - Essential for egg quality

"Unexplained infertility": toxic exposures and altered detoxification

- Take a good history of chemical exposures at work, home
- Dental history—mercury amalgams, caps/implants, dental whitening products
- Well water or municipal
- Mold exposure?
- Symptoms
  - Fatigue, brain fog
  - Irregular periods
  - Poor sleep
  - Skin eruptions



"Unexplained infertility": Detoxification issues Testing

- Organic acids
- Hormone detoxification panels
- Mold and mycotoxin testing
- Microbial organic acids
  - Includes beneficial and harmful bacteria, yeast/fungal organisms
- Glyphosate
- Estrogen metabolism testing
- Genetic snps

"Unexplained infertility": Altered Immune Function

- Frequent illness
- Joint pain
- Myalgia
- Skin eruptions
- Autoimmunity
- Fatigue
- Brain fog
- Lyphadenopathy

"Unexplained infertility": Altered Immune Function Testing

- SED rate
- hsCRP
- Autoimmune panel
  - ANA, thyroid peroxidase abx, thyroglobulin abx, thyroid stimulating immunoglobulin, DsDNA abx, RF, anticardiolipin abx, etc
- cytokines

"Unexplained infertility": Luteal Phase Dysfunction/ low progesterone

- PMS/ PMDD
- Short cycles
- Heavier periods
- Poor "stop and start" pattern to bleeding
- Fatigue, brain fog
- Weight gain
- Breast soreness premenstrually

"Unexplained infertility": luteal phase defect/ low progesterone: Testing

- Might need no testing at all: work from symptoms alone
- LH>FSH implies poor hormone balance
- Urine hormone panels
- Adrenal testing (blood, urine, saliva)
- Prolactin

"Unexplained infertility": Thyroid Dysfunction

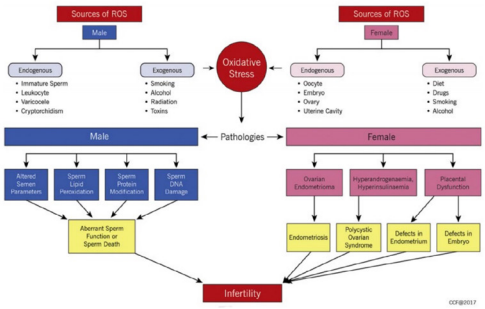
- Irregular periods
- Weight gain or loss, unexplained
- Crushing fatigue
- Agitation
- Palpitations
- Changes in bowel habits
- Sensation of constant sore throat
- Goiter
- Low/suboptimal thyroid function prevents appropriate granulosa cell function (increased anovulatory cycles)

"Unexplained infertility": Thyroid Dysfunction Testing

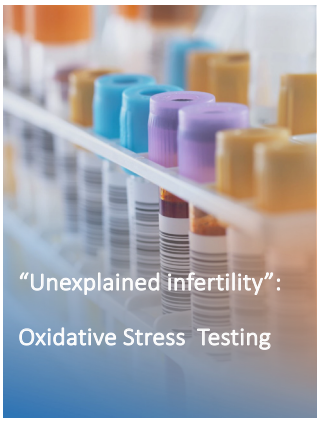
- TSH
- Free T3
- Free T4
- Reverse T3
- Thyroid peroxidase antibodies
- Thyroglobulin antibodies
- Thyroid stimulating immunoglobulin
- Note:
  - Check antibodies even if hormone levels normal
  - Thyroglobulin antibodies made once damage to thyroid has occurred, implies longer course of disease
  - All three antibodies can be made at once, so check them all

"Unexplained infertility": Oxidative Stress

- Weight gain or loss
- Fatigue
- Allergies
- Skin eruptions



Reprinted from Reproductive BioMedicine Online, Vol. 34, Roychoudhury, S., Agarwal, A., Virk, G., & Cho, C.-L., Potential role of green tea catechins in the management of oxidative stress-associated infertility, Pages 487-498, Copyright 2017, with permission from Reproductive Healthcare Ltd.



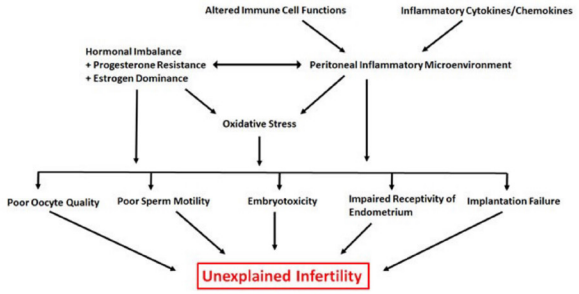
"Unexplained infertility": Oxidative Stress Testing

- Lipid peroxidases
- 8 OHdG
  - IVF studies: level in follicular fluid is negatively correlated with number of eggs retrieved and quality of embryos produced
  - Appears to be elevated in follicular fluid of those with subfertility and endometriosis
  - Associated with damage to mitochondria

"Unexplained infertility" Inflammation

- Fatigue
- Allergies
- Skin eruptions
- Joint pain
- Myalgia
- Associated with autoimmunity
- Leads to other pathways of damage to fertility
- Elevated BP or swelling
- Periodontal dz
- Bloating/ abdominal pain
- Headaches
- Menstrual cramps, endometriosis

- Testing is similar to immune dysregulation testing

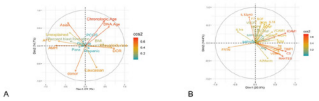


Miller JE, Ahn SH, Monsanto SP, Khalaj K, Koti M, Tayade C. Implications of immune dysfunction on endometriosis associated infertility. *Oncotarget*. 2017;8(4):7138-7147. doi:10.18632/oncotarget.12577

Inflammation – the real driver of accelerated ovarian aging?

July 2021 pilot study published in *Fertility & Sterility*

- Participants included 40 women undergoing ovarian stimulation and embryo cryopreservation. A 46-cytokine serum assay was performed in a subset of 20 patients.
- Circulating inflammatory cytokines were independent correlates of diminished ovarian reserve → the most positively correlated cytokines being stem cell factor and interleukin-18
- IL-18 outperformed actual chronological age by 10 fold in the prediction of DOR.
- Biological age had a stronger association with DOR than chronological age, but still was out-performed by cytokines in terms of prediction abilities.



Murugappan G, Huang H, Grawe A, et al. Inflammatory proteins as predictors of diminished ovarian reserve. *Fertility and Sterility*. 2021;116(1). doi:10.1016/j.fertnstert.2021.05.002

Inflammation contributes to….

- Insulin resistance
- Luteal phase dysfunction
- Endometrial receptivity
- Endometriosis
- PCOS
- Premature ovarian insufficiency

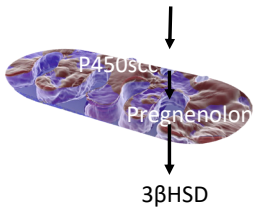
Inflammation: root causes

- Food triggers
- High glycemic load meals
- Insulin resistance
- Underlying infections
- Toxins
- Metabolic endotoxemia/leaky gut
- Chronic stress

"Unexplained infertility": Mitochondrial Dysfunction and Energy Production

- Fatigue
- Myalgia
- Mood disorders
- Irregular periods
- Blood sugar dysregulation

Getting cholesterol to the inner membrane of the mitochondria is the rate limiting step in hormone production



This implies healthy mitochondria are essential to normal hormone production!

"Unexplained infertility": Mitochondrial Dysfunction and Energy Production Testing

- Organic acids can imply disruption
  - Lactate, pyruvate; plasma amino acids
- Any hormone imbalance noted on testing implies disruption
  - All hormones made from cholesterol in the mitochondria
- Blood sugar regulation
  - Fasting glucose
  - Fasting insulin
  - Hemoglobin A1C
    - Make sure the A1C and fasting glucose "match"
  - HOMA-IR

"Unexplained infertility": Adrenal Dysfunction

- Fatigue
- Myalgia
- Mood disorders
- Irregular periods
- Blood sugar dysregulation
- Poor sleep
  - Altered circadian rhythm due to choice or work

Chronic stress

- Stress induced levels of glucocorticoids in the ovary impair egg cell function
- IVF studies:
  - Fluid from follicles containing eggs that did not fertilize had levels of cortisol significantly higher than in the fluid from follicles containing successfully fertilized egg cells

"Unexplained infertility": chronic stress testing

- Salivary cortisol
  - (with cortisol awakening response)
- Urine DHEA(s)
- If doing serum, get cortisol am and DHEA am
  - Must be drawn fasting and prior to 9am. No gym first!
  - Will give you a snapshot of which phase of adrenal dysfunction they are in
  - Serum cortisol can be misleading if they are scared of blood draw!

"Unexplained infertility": Chronic Infections

- Fatigue
- Myalgia
- Joint pain
- Mood disorders
- Frequent illnesses
- Chronic/ subacute vaginitis

"Unexplained infertility": chronic infections testing

- A bigger problem for male infertility
- Reliable Lyme panel
  - Additional testing for co-infections
- Vaginal / cervical PCR
  - Chlamydia
  - Gonorrhea
  - Atopobium, guardnerella
- Specialty vaginal microbiome

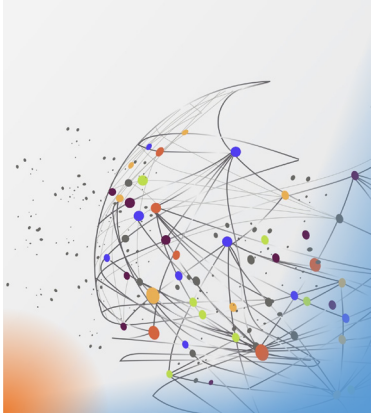
Miscellaneous: homocysteine

- Elevated homocysteine increases chance of neural tube defect
- Impairs growth and function of blood vessels in the placenta
  - IUGR, preeclampsia
- Impacts sperm: causes oxidative stress, decreasing sperm motility and depleting antioxidants in seminal fluid
- Check methylation status (blood test)

Specific to Men

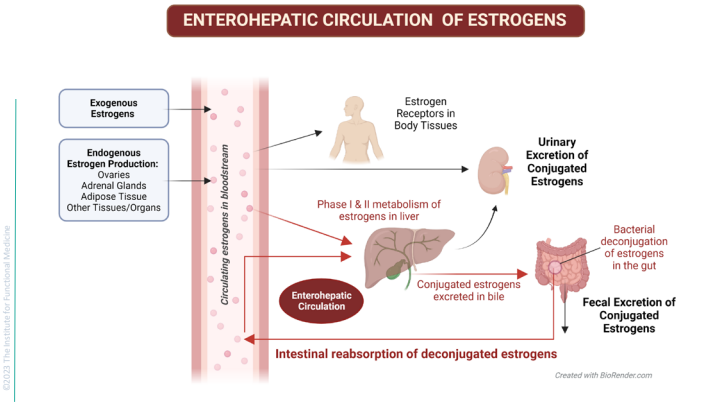
- 90% from low sperm count or quality
- Anatomic abnormalities
  - Bilateral obstruction of the vas deferens
  - Epididymitis
  - Varicocele
  - Retrograde ejaculation
- Endocrine issues
  - Congenital GnRH Deficiency (Kallmann syndrome)
  - Hemachromatosis
  - Head trauma
  - Intracranial radiation
  - Testosterone supplementation
  - Hyperthyroidism
- Toxins
  - Insecticides, fungicides, pesticides, smoking, excess alcohol, Agent Orange
- Cannabis

Treatment Suggestions



Gut Health

- Demulcents
  - Soothe mucosal lining
  - Marshmallow, slippery elm, aloe
- Carminatives
  - Stimulate bile production
  - Improve peristalsis
  - Fennel, chamomile, ginger, peppermint, wild yam
- Fermented foods
- Pre- and Probiotic foods
- If SIBO, antibiotics



Beta Glucuronidase

- Induced by abnormal microbiome
- Typically with a history of constipation
- Reactivates estrogen breakdown products
- Ovaries don't know this is going on, so not increasing progesterone to compensate!

Carotenoids: Reduce Serum B-glucuronidase Activity

Alpha-carotene:
- Pumpkin (highest)
- Carrot
- Winter squash
- Red peppers
- Collards
- Dandelion greens
- Spinach
- Turnip greens
- Cantaloupe
- Cilantro
- Thyme
- Romaine lettuce
- Tomato
- Swiss chard
- Apple
- Avocado

Beta-carotene:
- Sweet potato (highest)
- Kale
- Carrot
- Turnip
- mustard greens
- Spinach
- Butternut squash
- Herbs: basil, parsley, marjoram, oregano, sage, coriander, thyme
- Lettuce: Romaine, green leaf
- Collard greens
- Red hot chili peppers
- Dandelion greens
- Pumpkin

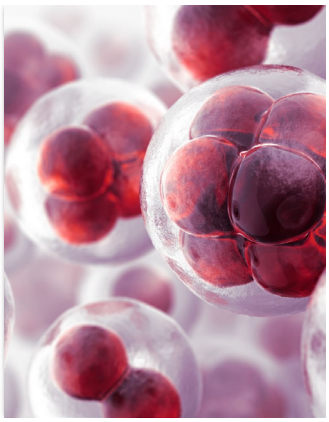
Other B-Glucuronidase Inhibitors

- Silymarin (milk thistle extract)
- Reishi (ganoderma lucidum)
- Licorice (glycyrrhizin)
- Lactic acid probiotics: lactobacillus acidophilus, L. rhamnosus GG, Bifidobacteria
- Prebiotics: inulin
- Caloric restriction
- Lacto-vegetarian diets reduces the level

Plant Med 2000;66(1):40-3. Arch Pharm Res 2005;28(3):325-9. Cancer Lett 1990;54:1-8

Iron

- Improves oxygen delivery to uterus and ovaries
- Improves egg quality
- Required by granulosa cells (which support follicles)
- Improves endometrial lining
- Dandelion, nettle, yellow dock, parsley, amaranth



Nutrition for Ovarian Aging

- **Vitamin C and E**—antioxidants
  - Animal studies: reduces aging effects on ovarian reserve and improves egg quality
- **NAC**—reduces oxidative stress
  - Improves egg quality, embryonic development
  - Improves cervical fluid
- **Curcumin/turmeric**
  - Increases number healthy follicles
  - Improves ovarian blood flow
  - Protects ovarian reserve
- **CoQ10**—antioxidant, mitochondrial support
- **Quercetin**—antioxidant, slows follicular atresia

Nutritional Issues

- Look for unspoken disordered eating patterns
- Is it financial?
  - www.leannebrown.com Free downloadable book: "Good and Cheap"

Pomegranate

- Vitamin C, polyphenols, phytoestrogens
- Anti-inflammatory, enhances endometrial thickness
- Improves implantation (rat study)

- *Biomedical and Pharmacology Journal*, 2015, 8(2), 971–977

Improving Mitochondrial Function

- Improve blood sugar stability
- Regular moderate exercise
- Avoid toxins
- Deal with inflammation
- Sleep

- Specific nutrients
  - Coq10
  - Resveratrol
  - Alpha Lipoic Acid
  - N-acetylcysteine
  - L carnitine
  - Melatonin
  - Curcumin/ Turmeric
  - Green tea / EGCG

Vitex for hormone balance

- Flavonoids increase the release of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) from vascular endothelium to increase endometrial blood flow
- Isoflavones reduce the release of the prolactin and FSH hormones by affecting the HPG axis
- Improves progesterone production

- *African Journal of Traditional, Complementary and Alternative Medicines*,2012, 9(4), 584–590.

Nigella sativa for hormone balance

- Long-term use of *N. sativa* can reduce testosterone levels, exerting a negative feedback on LH.
- May reduce LH dominance over FSH by inhibiting nitric oxide and leptin-releasing neurons that are directly involved in the synthesis of LH from the anterior pituitary gland
- Mouse study

- *International Journal of Reproductive BioMedicine*, 2020,18(9), 733.

Optimal pelvic blood flow

- Acupuncture
- Nitrous Oxide production
  - Beets
  - Garlic
  - Leafy greens
  - Pomegranate
  - Watermelon
- Massage/manual therapy, exercise, reflexology
- Hydration

Inflammation modulators

- Omega three fatty acids
- Turmeric/curcumin
- Bromelain
- Quercetin
- Specialized pro-resolving mediators (SPMs)
- Resveratrol
- (and a host of plants!)

Chronic Stress

- Adaptogens
- Nervines
- Meditation
- Mindfulness practices
- Heart rhythm variability manipulation

Ashwaganda (Withania somnifera)

- Increased gonadotropin release and improved oogenesis
  - Action on HPAG axis, improved estrogen balance
- Via GABA mimetic properties
- (mouse study)

- *Phytotherapy Research*, 2010, 24(8), 1147–1150

Maca (Lepidium peruvianum)

- Member of the Brassica family
- Action directly on HPAO axis
- Contains glucosinolates
- Modulates estradiol, progesterone, FSH, ACTH

- Front Pharmacol. 2024 Feb 19;15:1360422.

Nervines

- Calming
- Improve sleep
- Improve adrenal function indirectly
- Examples
  - Lavender
  - Chamomile
  - Lemon balm
  - Passionflower
  - Milky oats (Avena sativa)
  - Skullcap
  - Catnip

Meditation

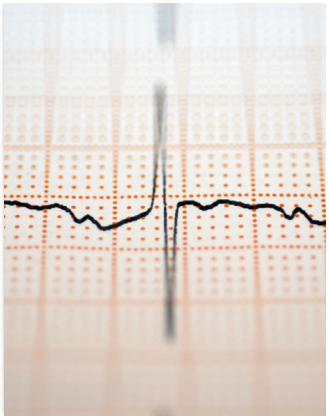
- Regulates HPAG axis
- Improves sleep
- Increases pregnancy rates for IVF cycles

Behav Res Ther. 2016 Feb;77:96-104.

Heart Rhythm Variability Manipulation

- Decreased HRV is indicator for poor IVF outcome
- HRV can be directly improved by focused shift in emotional regulation
  - Research from the Institute for Heartmath

- PLoS One. 2018 Mar 12;13(3):e0193899. doi: 10.1371/journal.pone.0193899



DHEA

- Enhances mitochondrial energy production
- Improves egg maturation
- May slow follicular aging in low ovarian reserve
- Lowers chance of aneuploidy so fewer pregnancy losses
- IVF: higher quality embryos, improved pregnancy rates

- 25-75 mg daily (often need less to get into optimum range)

- Reprod Biol Endocrinol. 2011 May 17;9:67.

Thyroid function

- Adjust thyroid meds as needed for optimal range
- + antibodies with normal function: work to modulate immune function
  - Don't start thyroid meds right away
  - Selenium, D, myoinositol
  - Immune amphoteric herbs (eg: licorice, tulsi, turmeric)
  - Mushrooms
    - Reishi
    - Shitake
    - maitake

High 8-OHdg

- Decreased by melatonin supplementation
  - 3 mg oral cycle day 5-midcycle or lower dose (0.3mg) daily

High Toxic Load

- Decrease exposure (personal care products, cleaners, work, dental)
- Hydration
- Daily bowel movements
- Regular sweating
- Cruciferous veggies and phytonutrients to support liver detox pathways
- Alterative Herbs
  - Violet
  - Burdock
  - Cleavers
  - Nettles

Melatonin

- Downregulates HPA Axis
- Decreases aromatase expression and activity
- Therefore decreases circulating estrogens
- Decreases 17 beta dehydrogenase (decreases androgen production)
- Increases activity of sulfotransferase
- Much on the market is synthetic; look for a good plant based source

- Curr Cancer Drug Targets. 2008 Dec;8(8):691-702

Melatonin, continued

- Increases follicular growth rate
- Improves oocyte quality
- Increases number of quality embyros with IVF
- Enhances the repair of double-strand breaks via the non-homologous end joining (NHEJ) pathway to protect oocytes from the accumulation of DNA damage during prophase arrest
- Protects the ovaries from chemotherapy induced damage, (mouse study)
- Inhibits ovarian granulosa cell apoptosis and maintains anti-Müllerian hormone (AMH) expression (mouse study)

- Antioxidants 2023, 12, 1601. https://doi.org/10.3390/antiox12081601 (this is a great review paper!)

Treatment Specific to Men

- Acupuncture improves sperm quantity and motility
- Saffron improved motility
- Ashwagandha improved pregnancy rate
- Nutrients: zinc, vitamin C, vitamin E, co q 10

- Health Sci Rep. 2024 Jun 24;7(6):e2118.

GrowBaby Health

(growbabyhealth.com)

- Specific genetic nutritional markers
  - Methylation
  - Vitamin B12 transport
  - Melatonin receptor
  - Insulin secretion
  - Vitamin D metabolism
- Targeted nutrition and lifestyle interventions based on results
- Working with 50% Medicaid population for their study
- Midstudy results (N=16) NNT = 10.3
  - Preterm births 0%
  - SGA 0%
  - Preclampsia 0%
  - GDM 6%
  - LGA 12%
  - c/section birth 12%
  - Estimated savings $650K

Bao Mai

- TCM: Channel that connects heart to uterus
- Translates as "Uterus Vessel"
- When heart qi does not descend to the uterus, causes infertility and amenorrhea
- When emotions not processed properly, qi and blood flow changes and menstrual irregularities arise

- Worry → anovulation (heart blood and/or yin deficiency, heart qi stagnation)
- Overwork → amenorrhea (heart yin deficiency, heart Qi stagnation or rebellious heart Qi)
- Sadness → menorrhaghia (heart yin deficiency with floating yang or Qi stagnation)

Things to discuss with every woman of reproductive age considering pregnancy

- Stop smoking
- Stop alcohol
- Move daily
- Clean up diet
- Limit/ stop sushi, tartare
- Get off antacids/ PPI's
- Get restful sleep
- Improve gut health
- Stop/limit hair treatments/ color
- Start a prenatal vitamin
- Get a pelvic exam and pap
- Get a full medical evaluation/ labs
- Start discussing any age-related factors (genetic testing)
- Discuss personal preferences of risks they are willing to incur re: place of delivery
- Discuss what life will be like with a baby

Thanks for your attention