

NUTRITION GENOME

12 WEEK PRACTITIONER TRAINING



WEEK 12, TOPIC 2: GENETIC SUSCEPTIBILITIES TO INFERTILITY

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It has been estimated that 7.4% of women and their husbands in the United States are infertile and that the number of infertile people in the world may be as high as 15%.

When under the age of 30, a woman's chances of conceiving may be as high 71%; when over 36, it may only be 41%. The number of infants born begins to exponentially decrease after the age bracket of 35–39. For women, having extremely low amounts of body fat and excessive exercise are associated with ovarian dysfunction and infertility. Approximately 20.7% of infertile women seeking intrauterine insemination (IUI) had also been diagnosed with an eating disorder. **Studies (*Refer to online article for study link)* have found that folate, vitamin B6, vitamin C, vitamin D, vitamin E, iodine, selenium, magnesium, iron, and DHA might have a positive impact on infertility treatment on female fertility.

Infertility in males is often the result of reduced sperm count, abnormal sperm quality (e.g., reduced motility and altered morphology), or altered levels of sex hormones (e.g., reduced testosterone). In the last 10 years in the researchers have discovered that oxidative sperm DNA damage has a critical role in the etiology of poor semen quality and male infertility. **Approximately, *30-80% (*Refer to online article for study link) - of infertility cases are caused by oxidative stress and decreased levels of seminal total antioxidant capacity.**

One of these studies that stood out was conducted in the Czech Republic regarding men living in two different locations, one more polluted than the other. Men who were exposed to higher levels of air pollution were more likely to experience abnormal sperm morphology, decreased motility, and an increased chance of DNA fragmentation. In a study including 950 men conducted by stress levels such as their job, life events, and even social strain were seen to have a significant negative impact on sperm density, total sperm counts, forward motility, and morphology.

The most recent research shows that the reasons for infertility are heavily weighted towards having children later in life, stress and high toxicity levels from polluted air, heavy metals, pesticides, herbicides, phthalates, dioxins, and other sources of chemicals. The risk of developing female and male infertility has also been associated with gene polymorphisms that decrease the activity of enzymes involved in systemic oxidative stress.

To prevent trying to cover every angle of infertility, this post will focus on the gene polymorphisms associated with heavy metals, chemicals, and oxidative stress. However, I first want to address research on the other genes associated with infertility and miscarriages.

MTHFD1, DHFR, MTHFR 677, SLC19A1, Infertility and Miscarriages

All of the genes associated with folate metabolism are going to be relevant for fertility and pregnancy. Here are a few studies.

- *A meta-analysis* of a Russian population found an association between male infertility and variants in MTHFR 677 and MTHFD1.
- Women who are MTHFD1 1958 AA homozygous have a 1.64-fold increased risk of having an unexplained second-trimester loss compared to women who are MTHFD1 1958AG or 1958GG.
- MTHFD1 encodes for folinic acid, and variants have also been *significantly* associated with nonsyndromic cleft lip and palate in South Indian subjects.
- MTHFR 677 has numerous studies that show conflicting results regarding miscarriages. This is because other folate genes, synthetic folic acid intake, DHFR gene function, MTHFD1 gene function and dietary folate intake all need to be assessed. A 2017 *study* did not find that variants in MTHFR 677 were associated with infertility in men or women. Variations in MTHFR have been *associated* with preeclampsia.

(**Refer to online article for study link*)

It is important for your patients to understand that folate-rich foods contain the whole spectrum of folate compounds and are going to be the superior source for optimal folate metabolism.

The Thyroid Genes, VDR and Infertility

Thyroid dysfunction can affect fertility in various ways including luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalances. In a *study* of 394 infertile women, 23.9% were hypothyroid with a TSH greater than 4.2. After treatment for hypothyroidism, **76.6% of infertile women conceived within 6 weeks to 1 year.**

While the DIO1 gene does not affect TSH levels, a homozygous gene can indicate that the thyroid may need more attention due affecting the deiodination of T4 into T3. Hypothyroidism affects MTHFR function, so a combination of variants in MTHFD1, MTHFR, DHFR and SLC19A1 and poor thyroid function would be highly relevant. Iodine, selenium, B2, magnesium, A, D and zinc are the most relevant nutrients for thyroid health.

A study consisting of 154 women with endometriosis-associated infertility and 347 controls found a significant association with the Vitamin D receptor gene (VDR) rs1544410 and rs222857 minor alleles and endometriosis-associated infertility.

NOS3, F5 Gene and Miscarriages

Review the post on *Nitric Oxide Genes and Inflammatory Disorders* for a further understanding on how to optimize the nitric oxide genes. Researchers believe nitric oxide can help prolong fertility in women, prevent genetic abnormalities during early embryo development, prevent Down Syndrome and spontaneous miscarriages, and other issues associated with pregnancies among older women.

One *study* found that women who had variants in the NOS3 gene (Cardiovascular Section) were more likely to experience multiple miscarriages due to low endothelial nitric oxide levels, affecting blood flow to the uterus and fetus.

The risk of having at least two miscarriages or infertility problems was 2.5 times greater for individuals with variants in the Factor V Leiden gene (F5 gene in the Cardiovascular section) versus controls.



MTHFR 1298, Heavy Metals and Infertility

People who have the homozygous variants in MTHFR 1298 are much more susceptible to the harmful effects of heavy metals including lead, aluminum, and mercury. This may explain why men with the homozygous (C/C) MTHFR A1298C genotype had a **statistically* high significance for infertility.

Vitamin C, B1, and B6 deficiencies have also been reported to enhance sensitivity towards cadmium and lead toxicity. Review the NBP3 gene for B6 and SLC23A1, GSTM1 and GSTP1 gene for vitamin C requirements.

Lead

Lead interrupts the hypothalamic-pituitary axis and has been reported to decrease overall fertility. Lead may alter sperm quality in men, and cause irregular menstruation, induce preterm delivery, and cause miscarriage, stillbirth, and spontaneous abortion in women. **Vitamin C lowers lead levels in the body while calcium blocks its uptake, and this may be one of the mechanisms by which vitamin C helps fertility along with lowering oxidative stress levels.**

Aluminum

Research* from scientists in the UK and France suggests that human exposure to aluminum may be a significant factor in falling sperm counts and reduced male fertility. Aluminum in the food supply comes from medications, antacids, water, food additives, and contamination by aluminum utensils and containers. As one study accurately states “the real scientific question is not the amount of aluminum in foods but the availability of the aluminum in foods and the **sensitivity of some population groups to aluminum.”

Malate and citrate both bind and remove aluminum from the body, making magnesium malate/citrate supplementation a great addition for MTHFR 1298 homozygous genotypes. Apples contain pectin and malic acid, making them an excellent detoxifying food for aluminum and lead.

Mercury

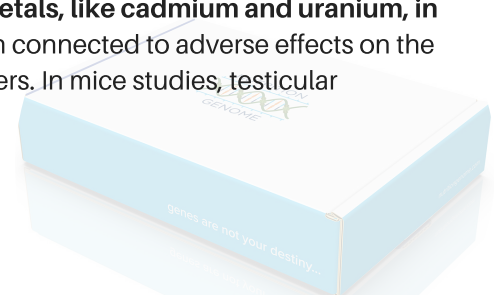
Mercury can precipitate pathophysiological changes along the hypothalamus-pituitary-adrenal and gonadal axis that may affect reproductive function by altering the circulating levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin, estrogen, progesterone, and the androgens. Reduced fertility among dental assistants with occupational exposure to mercury has been found in research. Studies in Hong Kong demonstrated that increased mercury levels were associated with infertility in both men and women.

In males, mercury can have adverse effects on spermatogenesis, sperm count, and testicular weight. Evidence also exists linking mercury with erectile dysfunction. In females, mercury has been shown to inhibit the release of FSH and LH from the anterior pituitary which in turn can affect estrogen and progesterone levels leading to ovarian dysfunction, painful or irregular menstruation and premature menopause. There is also good evidence linking mercury with menstrual disorders including abnormal bleeding, short, long, irregular cycles, and painful periods.

Mercury is associated with the fetotoxicity which can present as miscarriage, spontaneous abortions, stillbirth, and low birth weights.

SNPs for Cadmium Detoxification

Exposure to cadmium occurs through plant-derived foods and certain seafood, as well as from tobacco smoke. Non-organic agriculture uses high amounts of synthetic organophosphates which end up in our food, creating a very high phosphorus content. **Synthetic phosphorus concentrates the amounts of heavy metals, like cadmium and uranium, in non-organic soils and food.** Even at low levels, cadmium exposure in adults has been connected to adverse effects on the kidney, bone, cardiovascular system, reproductive system and hormone-related cancers. In mice studies, testicular necrosis, low libido, and infertility have occurred from cadmium exposure.



The half-life of cadmium can be pretty long, 10–30 years. **Low iron levels are associated with a higher absorption of cadmium, and since women are more prone than men to have low iron status, they are more at risk for accumulation.** Low zinc levels are also associated with elevated cadmium levels. Low levels of iron and zinc can be common in the female population.

Researchers are still attempting to narrow down the most relevant SNPs in regards to cadmium detoxification. Genes that are related to iron and zinc metabolism and glutathione appear to be the most relevant.

Dioxins and Infertility

We have discussed the dioxin TCDD in previous training posts, and how it severely harms the BRCA genes for DNA repair. In 1976, an explosion near Seveso, Italy resulted in the highest TCDD exposure known in residential populations. Twenty years later, a retrospective cohort **study* called the Seveso Women's Health Study was conducted on this population. **They found that for every 10-fold increase in serum TCDD, they observed a 25% increase in time to pregnancy (more than 12 months).**

One **study* reviewed sperm contamination by the dioxin polychlorinated dibenzo-p-dioxins/furans in 168 infertile and 49 fertile men. In the sperm of infertile men, **the content of dioxins and furans was 2.2-2.3 times higher than infertile donors.**

As mentioned in the post **DNA Damage, Protection and Repair*, dioxins accumulate the most in the fat of animals from their feed and goes up with the food chain. Patients need to be cognizant of the source of their animal fat. Research has found that resveratrol was most effective at preventing TCDD-induced DNA strand breaks.

The Antioxidant Genes and Infertility

Researchers looked at polymorphisms in antioxidant genes that are more susceptible to sperm DNA damage and male infertility including GPX1, CAT, PON1, NQO1, SOD2, and SOD3) in 580 infertility cases and 580 controls from a Chinese population-based case-control study. **The results indicated that the PON1 (rs662) and SOD2 Val16Ala (rs4880) variant genotypes were associated with a significantly higher risk of male infertility.**

The PON1 gene detoxifies pesticides. Organophosphate pesticides are known factors involved in male infertility. Men working in agricultural regions and greenhouses which use pesticides have higher concentrations of common pesticides in their urine and a **60% decrease in sperm concentrations.**

In one small **study*, six women with a history of unexplained infertility or early miscarriage had also failed to normalize red blood cell magnesium levels after 4 months of 600mg magnesium supplementation daily. They were compared with six age-matched women with a history of unexplained infertility or miscarriage who did normalize their RBC-Mg levels on magnesium supplementation. **The six non-normalizers had significantly lower glutathione levels than the six normalizers.**

After a further two months of 200 micrograms daily oral selenium as selenomethionine and oral magnesium supplements, all six women who could not raise their magnesium levels were able to normalize their magnesium and RBC-selenium levels. **All 12 previously infertile women have produced normal healthy babies all conceiving within eight months of normalizing their RBC-Magnesium levels.**

It is important to review and optimize the genes GSTM1, GSTP1, GPX1, CTH, PON1 and SOD2 for your patients experiencing infertility.



Applying Nutrigenomics for Heavy Metals

- Zinc competes for binding sites with cadmium and lead, and a higher intake of zinc increases the detoxification of cadmium. Zinc has also been found to alleviate oxidative stress by cadmium and lead by inducing copper/zinc SOD enzyme function. **Therefore, SOD3 gene function may be relevant for these patients.**
- Selenium is a cofactor of the **glutathione gene GPX1** and reduces oxidative stress from cadmium and lead, while also increasing detoxification of both.
- Calcium and magnesium have also been found to protect against cadmium and lead toxicity by competing for intestinal absorption and prevent heavy metal-induced tissue damage by competitive binding to active sites of the enzymes. **Look for medications like PPI's that deplete calcium, and higher needs for magnesium like COMT, MAT1, MTHFR 1298, NOS3, stress and other magnesium depleting habits.**
- Royal jelly protects against cadmium-induced genotoxicity and oxidative stress in mice, while also being a dietary source of BH4 for MTHFR 1298.
- Folate lowers blood mercury levels and selenium blocks mercury uptake, making MTHFR, MTHFD1, SLC19A1, GSTM1, GSTP1, GPX1 and CTH relevant.

Further Research on Nutrition and Heavy Metal Detoxification and Protection

Tomatoes have been shown to significantly reduce the accumulation of heavy metals (cadmium, lead, and mercury) in the liver of rats. Berries, onions, garlic and grapes have all been studied in research to be effective at reducing and protecting against heavy metals.

Spirulina and chlorella has been found to attenuate cadmium or lead toxicity in the liver, kidney, and brain of animals. The probiotic *L. plantarum* CCFM8610 is able to bind to cadmium and protected mice from acute and chronic cadmium toxicity via its intestinal sequestration and antioxidant effects. *L. plantarum* also decreased lead levels in the blood and tissues and prevented lead-induced oxidative stress.

A short pilot human study published in the peer-reviewed journal *Phytotherapy Research* found that citrus pectin resulted in significant increases in the urinary excretion of lead, arsenic, cadmium, and mercury.

The probiotic strain *L. rhamnosus* from yogurt lowered heavy metal levels in at-risk populations of pregnant women and in children in Tanzania. The results showed that blood levels of mercury and arsenic of pregnant women increased in the control groups but remained stable in the probiotic group, indicating a protective effect of *L. rhamnosus* consumption.

Pharmacogenomics and Infertility

Numerous medications have been linked to infertility, however, it is reversible once stopping the drugs. These include anabolic steroids, antiandrogens, antibiotics, antiepileptics, antihypertensives, anti-inflammatory 5-ASA, antimalarials, antimetabolites, anti-estrogens, anti-progestins, antipsychotics, antischistosomes, corticosteroids, testosterone, H2 blockers, anesthetics, methadone, NSAIDs (Tylenol, Aspirin etc.) and Cox-2 inhibitors.

Summary

The following is a summary of the genes to address for your patients with infertility and miscarriages.

See next page for gene breakdown:



Infertility



Miscarriages

