NATUROPATHIC DOCTOR NEWS & REVIEW

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Thyrotropin

Using the Marker to Manage Autoimmune Thyroiditis

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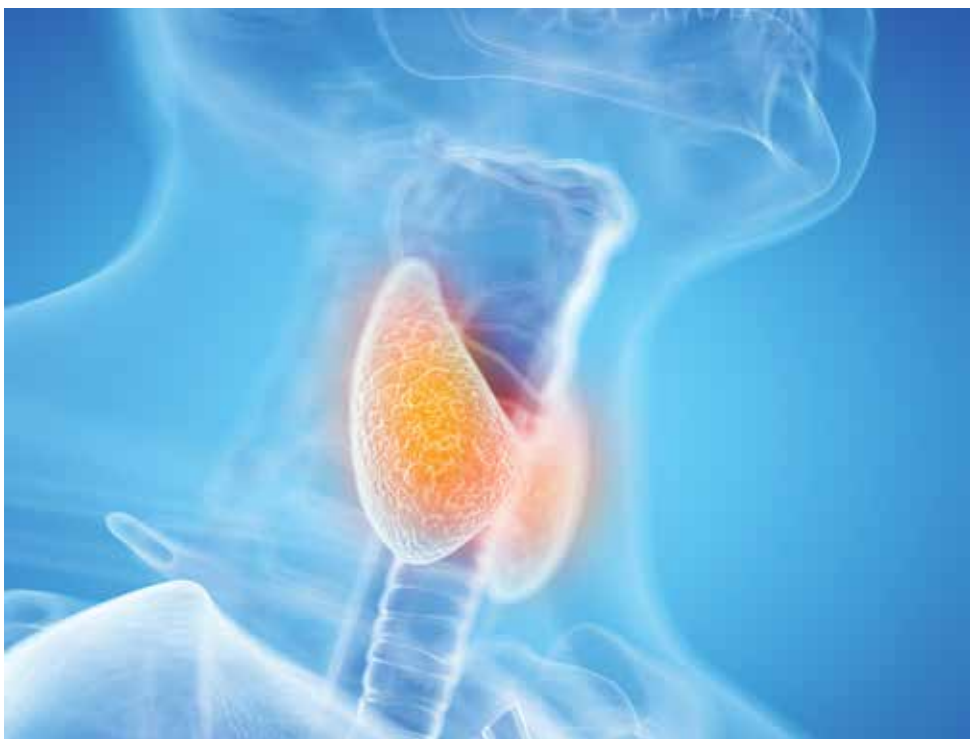

Thyrotropin, also known as thyroid-stimulating hormone (TSH), is the signal secreted from the thyrotrophic cells of the anterior pituitary in response to the release of thyrotropin-releasing hormone (TRH) by the hypothalamus. Thyrotropin acts as a proliferative signal to target cells primarily in the thyroid gland, but also non-thyroidal target cells, including osteocytes, vascular endothelial cells, and hepatocytes.

Clinically, most physicians are aware of thyrotropin mainly through its diagnostic role in thyroid disease. Autoimmune thyroiditis is the most common reason for hypothyroid disease in developed countries, with a prevalence of up to 10%.[1]

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Botanical Insights

Herbal Sexual Tonics for Men

Help or Hype?

JILLIAN STANSBURY, ND

Health food stores often have an entire section of products dedicated to enhancing the libido, improving erectile function, and boosting low testosterone, sometimes located right next to the pills that help you gain muscle mass and "burn" fat. Low testosterone levels are frequently demonstrated with modern lab testing, especially in the elder decades of a man's life, and many symptoms – including low libido, loss of muscle mass, poor stamina, and infertility – have been treated with herbal medicines since ancient times. Many such herbs are now being shown to support healthy testosterone levels, including the well-known *Panax ginseng* of Asian traditional medicine and *Lepidium* (maca) root in the traditional medical system of the Andean peoples.

This review will briefly summarize

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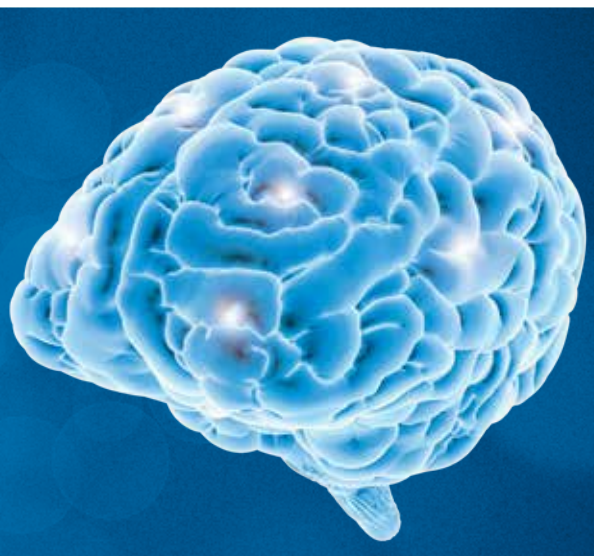

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It is characterized by an immune system attack on the thyroid that systemically damages the gland. Roughly 40-50% of those with autoimmune thyroiditis will have measurable thyroid antibodies, and in most affected individuals the disease progresses to clinical hypothyroidism and atrophic or goitrogenic thyroiditis.

In this article we will move beyond the use of thyrotropin as a marker for hormone production and explore the importance of thyrotropin regulation in the management of autoimmune thyroid disease.

Diagnosis of Hypothyroidism

The conventional definition of hypothyroidism is an elevated serum level of thyrotropin along with low serum levels of thyroxine (T4). Symptoms may include (though are not necessary for diagnosis): thyroid enlargement (goiter), fatigue, infertility, dry skin, cold intolerance, voice changes, and – most importantly – a generalized slowing of metabolic processes (eg, constipation, weight gain). None of these symptoms is pathognomonic for hypothyroidism; thus, serological confirmation must be made in order to arrive at a diagnosis.

Many in the early stages of autoimmune thyroiditis may have the clinical presentation of hypothyroidism but lack the serologic findings of thyrotropin elevation and/or T4 or T3 suppression.[2] The term "subclinical hypothyroidism" has been used in functional medicine to describe this state, yet this is a misuse of the term. Subclinical hypothyroidism is a partial hypothyroid state defined by a lack of hypothyroid symptoms (subclinical), an elevated thyrotropin, and a normal T4 or free T4 level.[3]

The goal of therapy should be to lower thyrotropin production to optimal levels. This will reduce stress on the thyroid (and thus reduce thyroid gland size), ameliorate symptoms of the disease, and – most importantly – prevent iatrogenic thyrotoxicosis that can result from overtreatment.

Causes of Autoimmune Thyroid Disease

In the state of hypothyroidism, elevated thyrotropin levels signal the thyroid gland to produce more T4 via increased iodine uptake. Additionally, thyrotropin acts as a cell growth stimulant and an endothelial growth factor. These effects increase the surface area and the volume of the thyroid gland, which can lead in some cases to changes such as nodules, calcifications, and goiter.[4] These structural changes are clinically undesirable in that they can cause symptoms such as hoarseness, difficulty swallowing, and a sensation of a lump in the throat. For these reasons, reducing thyrotropin to optimal levels can, by itself, prevent and sometimes reverse structural pathology and often improve patients' clinical manifestations.

Thyroid antibodies are produced within the thyroid tissue. These antibodies destroy healthy tissue via apoptosis and can prevent the iodination of thyroglobulin into active thyroid hormone. It has been demonstrated that with the complete removal of the thyroid or proper management of hypothyroidism with thyroid replacement therapy, the serum antibody concentrations decrease.[5]

Common Causes of Thyroid Antibody Production

Autoimmune thyroid disease appears to be a perfect storm of events that occur as a result of genetics, toxicologic exposure, chronic immunologic stressors, and acute infectious disease.

Infections can cause the production of thyroid antibodies through molecular mimicry. Epstein-Barr virus (EBV), hepatitis C, and other infections can precipitate the production of thyroid antibodies.[6]

Genetics predisposes individuals to autoimmune thyroiditis. There is sufficient data suggesting that autoimmune thyroid disease clusters among family members; for example, having a first-degree relative with the disease increases the chances of developing it.[7]

Acute stress can also precipitate the immune system to produce thyroid

antibodies. This could be a result of an acute spike of cortisol,[8] and might explain the 15% increase in thyroid dysfunction during pregnancy.[9]

After the delivery of a child, physiological changes occur in the woman's body. The immune system undergoes suppression right before delivery, and upon its return is usually a little overactive.[10] This can activate the faulty mechanisms that create autoimmune thyroid disease.

Management of Autoimmunity

Along with structural harm to the thyroid, continued stimulation of thyroid hormone production by elevated thyrotropin exacerbates the immune response against thyroperoxidase and thyroglobulin.[5]

It has been argued that thyrotropin elevation above 2.5 or 3.0 µIU/mL may perpetuate the autoimmune process that can lead to hypothyroidism. This phenomenon has been called the hypothyroid-autoimmune loop and can be one of the reasons for benefit from thyroid replacement in the early stages of Hashimoto's thyroiditis.

> Coffee can impair absorption of T4 by up to 36%, even when consumed many hours after thyroid medication is ingested.

Conservative initiation of thyroid replacement, with the goal of reducing thyrotropin levels, should be the first line of treatment. A dose of approximately 1.6 µg/kg body weight per day (eg, 112 µg/day of levothyroxine or its equivalent in a 70-kg adult) is usually sufficient to begin reduction of serum thyrotropin levels.[11] Importantly, lean body mass is a better measure than total body weight in the initiation of treatment; for this reason, conservative treatment (ie, a low standard dose of about 25-88 µg of levothyroxine or its equivalent) is preferred over dosing based on symptoms, laboratory findings, or the practitioner's prior clinical experience.[12] Although this is a good starting point, it is worth mentioning that pregnancy, gender, and age should be considered when initiating thyroid hormone treatment.[13] It is recommended that autoimmune thyroiditis in these patient populations be referred to practitioners with added training or experience treating the condition.

Thyroid medication should be taken on an empty stomach, ie, 1 hour away from food or coffee. A study by Benvega et al demonstrated that coffee can impair absorption of T4 by up to 36%, even when consumed many hours after thyroid medication is ingested.[14] For this reason, patients should be encouraged to abstain from food (especially bran, oatmeal, and other high-fiber foods) and beverages other than water (especially orange juice, coffee) when taking thyroid medication.

As soon as 2 weeks after initiating thyroid replacement therapy, symptom reduction may be seen for subjective symptoms such as fatigue or mood alterations. First, serum thyroid hormone levels increase, and then thyrotropin levels begin to drop. Because of this delay, thyrotropin levels should not be expected to normalize until at least 6 weeks after initiating treatment. If thyrotropin levels are not properly suppressed (lower limit=0.4 µIU/mL) after 6 weeks of treatment, conservative increases of thyroid hormone, in the range of 12 µg to 25 µg of levothyroxine per day, should be considered, and the patient retested after another 6 weeks.

Because of significant intra-individual variation in thyroid hormone parameters, including thyrotropin, it has been suggested that population-based reference ranges may be of limited use. Erden et al, who examined such fluctuations in serial measurements of healthy Turkish subjects every 2 weeks for 6 weeks, observed mean serial blood measurements of TSH in a range of 0.36-1.91 µIU/mL.[15] Based on these findings and our own clinical experience, we recommend an optimal TSH range of 0.5-1.5 µIU/mL. This range helps prevent both over-prescribing of thyroid hormones and potential thyrotropin over-suppression; it also gives us some room to help suppress thyrotropin in patients with nodules.

Avoiding Overdosing of Thyroid Hormone

Conservative management of autoimmune thyroid disease is important in preventing iatrogenic hyperthyroidism. The most common symptoms of this are anxiety, worsening of fatigue, osteopenia, cardiac disease, and even death.[16]

Subclinical hyperthyroidism is a state in which patients have a mildly or completely suppressed thyrotropin (ie, <0.4 µIU/mL), no elevations in T3 or T4 hormones, and no apparent clinical symptoms. Patients in this group are shown to have higher risks for atrial fibrillation, heart failure, bone fractures, spontaneous progression to overt hyperthyroidism, and all-cause mortality.[17] Similar risks are documented in cancer patients who are prescribed exogenous thyroid replacement with the goal of complete thyrotropin suppression.[18] For these reasons, thyrotropin should

be closely monitored. Suppression of thyrotropin below <0.4 predisposes patients to increased risk of arrhythmias as well as bone fractures.[19]

Thyrotropin suppression appears to promote the same type and rate of sequelae regardless of whether it is caused by endogenous thyroid secretion or exogenous thyroid hormone ingestion. Furthermore, exogenous thyroid hormone ingestion produces similar adverse effects regardless of whether the therapy is T4-based, T3-based, combination, natural desiccated thyroid, compounded, or an OTC thyroid glandular.

It is worth noting that the risk of thyrotropin suppression is not attenuated by monitoring basal body temperature or serum levels of free T3 or total T3. Basal body temperature is regulated in part by thyroid hormone; however, thyrotoxicosis does not lead to a predictable, linear rise in basal body temperature.[20] Normal T3 levels correlate with earlier states of thyrotoxicosis compared to T3 elevation, but even the early stage carries risks.

Conclusion

There is much confusion about the proper management of autoimmune thyroid disease. As we explain in this article, proper management aims to reduce symptoms, lower the risk of onset of autoimmune comorbidities, and manage structural pathology. The treatment and appropriate dosing should be guided by serological analysis, with special focus on and interpretation of thyrotropin levels and appropriate suppression of this very important hormone. Treatment should be conservative and special care should be taken to avoid complications that could arise from iatrogenic hyperthyroidism caused by excessive administration of replacement thyroid hormone.

Exogenous thyroid hormone ingestion produces similar adverse effects regardless of whether the therapy is T4-based, T3-based, combination, natural desiccated thyroid, compounded, or an OTC thyroid glandular.

Guillermo Ruiz, NMD, is a graduate of the Southwest College of Naturopathic Medicine. Dr Ruiz aims to use his research to advance naturopathic medicine using an evidence-based approach, and he focuses on finding evolutionary connections between our modern and traditional healthcare systems. He currently practices at Integrative Health in Scottsdale, AZ, under the mentorship of Dr Alan Christianson. Dr Ruiz specializes in endocrinology, autoimmune disease, and GI health. His hobbies include researching, learning, practicing, and teaching the benefits of adhering to an appropriate evolutionary diet.

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the research on these classic reproductive tonics, as well as review the evidence supporting the ability of *Epimedium, Eurycoma,* and *Tribulus* to boost low testosterone levels. In practice, the herbs which improve circulation, such as maca and small amounts of yohimbe, might be used for those with erectile dysfunction due to vascular weakness. Those herbs that boost DHEA and androgens, such as *Epimedium, Eurycoma,* and *Tribulus*, might be combined with the classic adaptogens and used for men with erectile dysfunction that presents along with loss of muscle mass and general vitality.

Popular Herbs

Ginseng

Panax ginseng (ginseng) is one of the best-known sexual and reproductive herbs, used for centuries as an anti-aging and longevity tonic; the roots are purported to help maintain sexual function into old age. *Panax*, which is widely used by herbalists as an adrenal tonic, may also improve low sperm counts and low testosterone levels in men. Animal and clinical investigations suggest regular use of *Panax ginseng* can enhance spermatogenesis, support fertility, enhance libido, and increase erectile function.[1] The herb may also improve sperm survival rate, motility and quality.[1] In rats, *Panax ginseng* has been shown to protect testicular Leydig cells from suppression by dexamethasone (a synthetic glucocorticoid), thereby protecting or restoring diminished testosterone synthesis.[2]

The ginsenosides, which are steroid-like compounds, are credited with traditional adaptogenic activity and are shown to bind glucocorticoid receptors. These compounds may also promote endothelial nitric oxide production in the vasculature.[1] In animal models of metabolic syndrome, *Panax* has been shown to improve erectile function related to enhanced circulatory and metabolic parameters, including ameliorating dysfunction of the cavernous nerves of the penis and endothelial cells, smooth muscle fibrosis, reduced nitric oxide production, and reduced cyclic guanosine monophosphate (cGMP).[3] Ginseng also promotes the release of luteinizing hormone from the pituitary, which in turn may help boost serum testosterone.[1] *Panax* is considered a warming herb, since it can sometime cause heat symptoms in the body; it is therefore most indicated for those with cold or neutral constitutions. *Panax* is specifically indicated for exhaustion and endocrine imbalances that follow long-term overwork and stress.[4]

Maca

Lepidium meyenii (maca) is a small turnip-like tuber in the crucifer family, which grows exclusively at high elevations in the Andes. The tuber has been cultivated since Incan times, and is dried and eaten as a food staple in the Andean diet in areas where few other vegetables thrive at such an extreme altitude. Maca powder has an agreeable flavor and is easy to stir into oatmeal, applesauce, or used in smoothies. Traditionally, dried maca tubers are cooked in soups or are ground into a flour and used in a variety of baked goods; the herb is believed to improve energy and stamina, fertility, heart function, mood, and longevity.

In menopausal women, maca consumption has been found to offset libido impairments induced by antidepressant medications.[5] Although maca has a reputation for stimulating the libido, the plant has not been shown to activate androgen receptors or increase androgen levels, and, in fact, may block them.[6] Thus, any erectile-supportive actions of maca may be due to circulatory enhancement rather than testosterone-boosting effects.

Lepidium tinctures are available and can also be included in formulas for male and female infertility and to support general reproductive health. Early herb texts claimed *Lepidium* to be specific for breast pain when the pain was squeezing or lancinating in quality; these texts also reported maca as helpful for menorrhagia. Maca's antioxidant and anti-inflammatory properties, as well as circulatory effects via nitric oxide production, make it a promising cardiovascular agent.[7-10] The herb has also been shown to increase sperm count and motility.[11]

Being a crucifer, maca roots and commercial maca products (eg, powders, tinctures, encapsulations) contain glucosinolates that may help optimize metabolism of hormones and protect hormone-sensitive tissues from carcinogens. Glucosinolates liberate sulforaphane upon heating, which may be more prominent when consuming cooked maca tubers, as in the traditional diet of the Andean people, and absent in tinctures or simple dried powders. Fatty acids and macamides are additional constituents that are credited with anti-inflammatory effects.[12]

Yohimbe

Pausinystalia yohimbe (yohimbe) is an African tree species whose bark is traditionally used to treat erectile dysfunction. Modern research has shown the alkaloid, yohimbine, to promote penile vasodilation via alpha-2 adrenergic blockade.[13] Yohimbe was referred to as "herbal Viagra" following the FDA's approval of yohimbine as the first plant-derived drug for treating erectile dysfunction in the late 1980s. Yohimbine and related alkaloids also inhibit monoamine oxidase,[14] which causes serotonin and epinephrine to increase in the brain.

The adrenergic activity of yohimbine can result in many side effects, including nervousness, anxiety, insomnia, headaches, panic attacks, increased frequency of urination, and possibly hypertension.[15] However, small amounts combined with more nourishing herbs may improve erectile function by enhancing penile

circulation. The herb is also reported to enhance sexual sensation and improve orgasmic function by increasing adrenergic signaling in pelvic ganglia.[16] The simultaneous use of phosphodiesterase inhibitors may increase the efficacy of yohimbine for erectile function, but can also promote side effects such as changes in visual perception, rhabdomyolysis, dyspepsia, headache, or back pain.[17] Due to potential toxicity, yohimbe should be avoided by individuals with advanced circulatory disease (eg, diabetes or metabolic syndrome) to avoid inappropriate adrenergic blockade.

Damiana

Turnera diffusa aphrodisiaca (damiana) is a shrub that is native to the United States. *Turnera* has a folkloric reputation for enhancing libido, thus earning the species name *aphrodisiaca.* Although the aphrodisiac claims may be exaggerated and with sparse corroborating scientific research, the plant has been shown in aging rats to increase sexual activity.[18] *Turnera* has been traditionally used to treat menstrual and pregnancy disorders, incontinence in the elderly, fatigue, and anxiety. *Turnera* is in the Passifloraceae family – a family noted for its calming, relaxing, and GABAergic activity. Anxiolytic effects have been demonstrated in modern research.[19] In keeping with folkloric tradition, *Turnera* may improve sexual function and libido when suppressed by stress and anxiety, and help improve the mood in cases of nervous debility.

Turnera has not been widely studied, but anti-cancer effects in breast cancer have been reported, and the herb is credited for general anti-inflammatory action combined with estrogenic, yet aromatase-inhibiting, actions.[20]

> The aphrodisiac effect of *Tribulus* may be more attributable to endothelial effects, such as that of nitric oxide, than to androgenic effects.

Tribulus

Tribulus terrestris (puncture vine) was used in ancient India and the Middle East, where it was said to boost the libido in both sexes; in the humorist school of medicine in Iran it was said to affect all 4 humors, thereby addressing all possible underlying causes of low libido and sexual dysfunction. *Tribulus* has been used in many traditional healing systems for low libido, sexual debility, erectile dysfunction, premature ejaculation, low sperm count, prostatitis, male and female infertility, as well as for other medical complaints, such as diabetes, kidney stones, and heart disease. Both the fruits and roots of T*ribulus* are used medicinally, with many effects credited to steroidal saponins including spirostanol and furostanol, as well as anti-inflammatory flavonoids.

While popular claims regarding the herb's power to enhance sexual function may be exaggerated and sensationalized, *Tribulus* has been shown to improve erectile function via circulatory enhancement and to increase libido in postmenopausal women.[21] The saponin in *Tribulus*, protodioscin – also found in *Dioscorea* (wild yam) – may support testosterone production,[22] possibly via conversion into DHEA upon ingestion,[23] in both men and women. One study found *Tribulus* to support DHEA levels in women, which was associated with increased sexual satisfaction, and to promote penile circulation and libido in male animals.[24] However, the research has been mixed. Although some studies have shown the ingestion of protodioscin and other steroidal saponins to increase testosterone in men but not in women, other studies have shown no significant effects of the herb on testosterone levels in either gender. The aphrodisiac effect of *Tribulus* may thus be more attributable to endothelial effects, such as that of nitric oxide, than to androgenic effects.[25] Animal studies suggest that *Tribulus* may support the maturation of ovarian follicles.[26] Its specific actions in the ovary may make it useful in PCOS, reducing inappropriate folliculogenesis and the tendency to form ovarian cysts.[27]

Horny Goatweed

Epimedium grandiflorum, koreanum, brevicornu (horny goatweed) are some of hundreds of species of *Epimedium*; many are referred to as horny goatweed in the West. *Epimedium brevicornu* is a commonly used species that goes by the common name *yin yang huo* in Traditional Chinese Medicine, where it has been used to treat infertility, erectile dysfunction, and low libido. Many *Epimedium* species also have a long history of use in the treatment of estrogen deficiency-related diseases such as osteoporosis,[28,29] as well as to support sexual function and fertility in both sexes.[30]

Modern research shows *Epimedium* to support spermatogenesis when suppressed by hormonal imbalance or oxidative stress in the testes.[31] The herb contains the isoprenylated flavonoid glycosides, icariin and epimedin, which have been shown to inhibit bone resorption and improve erectile function in animal models of aging.[32] Icaritin, the aglycone of icariin, has estrogenic

properties and stimulates estrogen-driven cells,[32] and may promote estrogen biosynthesis in human ovarian cells.[33]

Icariin and related flavonoids may also have significant anti-inflammatory and immunoprotective effects. Even though these compounds appear to be estrogenic, the flavonoids may induce apoptosis in cancer cells, including drug-resistant cancers.[34] One study reported *Epimedium* to increase the sensitivity of breast cancer cells to radiation therapy,[35] and another study showed purified icaritin to have antiproliferative effects in endometrial cancer, due to estrogen receptor modulation.[36] The flavonol, icariin, has also been shown in rats to promote nitric oxide synthesis,[37] which may enhance penile circulation and erectile function due to vascular effects.

Tongkat Ali

Eurycoma longifolia (tongkat ali, also known as Long Jack) is regarded as an aphrodisiac and energy tonic in Southeast Asia; it is also a major export of Malaysia, including beverages that combine the decoction with coffee, canned drinks, and various medicinal preparations. The common name "tongkat" means the "stick of a man," referring to an erect penis, and "ali" means aphrodisiac. The plant itself is a large shrub; it is the roots that are used traditionally as an anti-aging and sexual tonic.

Root decoctions yield various quassinoids (including eurycolactone, eurycomalactone, eurycomanol, eurycomanone, and eurycomaoside) and triterpenes, all of which contribute to *Eurycoma's* ability to improve strength and stamina.[38] Animal studies suggest that these and other compounds in *Eurycoma* may promote testosterone production and sperm parameters via androgenic effects.[39] Other animal studies show *Eurycoma* root extracts to promote steroid synthesis, possibly via enhancement of ATP production and cell membrane signaling cascades in gonadal cells. *Eurycoma longifolia* tincture has been shown in animals to increase erectile function and sexual activity.[7] Human studies suggest that *Eurycoma* can increase semen volume and sperm motility and morphology, as well as pregnancy rates in female partners.[40]

Androgen promotion by *Eurycoma* may also reduce bone resorption,[41] thus help in the treatment of osteoporosis related to androgen deficiency. Even though the herb promotes androgenic effects in human males, it does not appear to cause prostatic hypertrophy; in fact, anti-cancer and anti-inflammatory effects in the prostate have been reported.[42] Furthermore, while *Eurycoma* has been found to increase testosterone levels in aged or hypogonadal men, use of the herb by endurance athletes was not shown to alter the urinary testosterone:estrogen ratio.[43] It is thus not considered to be a doping agent and is presently not prohibited by athletic associations.

The herbal medicines discussed in this article can help prevent hormonal decline, reduce oxidative stress in the vasculature, and support endocrine function when used long-term.

Summary

In summary, the research on these plants supports their traditional usage for hormonal production, circulatory enhancement, and maintaining sexual function into one's elder years. However, the marketing of such herbs may make them out to be tools that may yield rapid or sensational improvements in libido, stamina, and erectile function, which are sensationalized claims. Like adaptogens that can tone the hormonal regulatory pathways gently, over months and years, the herbal medicines discussed in this article can be agents to prevent hormonal decline, reduce oxidative stress in the vasculature, and support endocrine function when used long-term.

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HPV Vaccine & Infertility

No Link

MAX COHEN, ND

A research paper by Delong was recently published that has generated considerable attention, especially in online environments where vaccine misinformation tends to thrive. This research makes a bold claim, which is that a decline in fertility rates is due in part to vaccination against certain strains of the human papillomavirus (HPV).[1] Delong's claim was based on NHANES data for 2007-2014 revealing fewer pregnancies among vaccinated women compared to women not receiving the vaccine. Although these correlations can appear worrisome at first, they do not prove cause and effect. Nevertheless, this paper has led to increased concerns that the HPV vaccine is in some way dangerous. Before exploring why the data do not support this claim, let's briefly review HPV and the HPV vaccine.

Human Papillomavirus

HPV is an extremely common infection, usually acquired from sexual activity. It is estimated that at least three-quarters of the US population will contract some form of HPV in their lifetime.[2] This usually happens during adolescence, when many people first become sexually active. The symptoms of HPV infection can range from nothing, to genital warts, to genital/oral cancers. It's impossible to tell if you will develop cancer from an HPV infection, and these cancers can take 10+ years to develop.[3] Some strains of the virus are more likely to cause cancer than others, and these strains are the focus of vaccination efforts.

There are over 10 000 cases of HPV-associated cancers per year in the United States[4] (and over 500 000 worldwide[5]), and that doesn't count the roughly 300 000 pre-cancer diagnoses (abnormal cells found on a Pap test, which requires additional testing or surgical procedures to evaluate), or the nearly 30 000 non-cervical cancers caused by HPV each year.[4] Eighty-eight percent of these cancers are *preventable with vaccination*.[4] You cannot develop cancer from an infection you did not contract.

The HPV Vaccine

There have been several HPV vaccines, but all of them use selected naturally-occurring proteins from up to 9 different high-risk HPV strains.[6] Like any vaccination, a small amount of antigen helps the body create an immunity against these versions of the virus. By introducing the immune system to these viral proteins, it is able to recognize and neutralize the virus if that person is ever exposed. This is only effective *before* an exposure, which is why the vaccine is recommended for ages 11-12[7]; it was recently approved for adults up to age 45.[8] The vaccine is extremely effective: nearly 100% of those vaccinated will become immune to high-risk strains of HPV and the cancers they cause.[6]

HPV Vaccine & Fertility

Strong claims require equally strong evidence. So do any data support the researcher's claim that vaccination could lead to reduced fertility? The answer is no. Using population-level epidemiological data to evaluate this claim is reasonable. I will note that while I am not an epidemiologist, neither is the author of the paper in question, which should raise immediate concern about the validity of these findings.

Delong's rationale for this study includes Vaccine Adverse Event Reporting System (VAERS) database entries for POI. There are significant problems with using VAERS data in this way, as I will discuss shortly. For the data analysis, Delong utilized 2 publicly available datasets from the Centers for Disease Control and Prevention (CDC). VAERS is neither designed nor able to show causal links between vaccines and adverse events, but rather serves as a collection of unverified reports provided by healthcare providers or patients. The events do not even need to be health related. As an example, "car accident 2 days after receiving vaccine" was reported to VAERS, and can be found in the system. VAERS is simply a database, without any ability to determine causality.

VAERS is valuable as a detector of potential safety signals. For example, if I administered a vaccine to a patient with chronic migraines, and the following day the patient developed a severe headache with concomitant light and sound sensitivity, this would be reported to VAERS. But did the vaccine cause the migraine? We don't know. If the report of a headache existed in isolation, it is very unlikely that the vaccine in-and-of-itself *caused* the migraine. If other healthcare providers around the country all started reporting severe headaches after vaccination, the information would start to compile in the database and a potential safety signal would be detected and reported.

A real-world example of this was a previous version of the oral rotavirus vaccine. This vaccine, while effective at preventing dehydration from diarrhea caused by rotavirus, was also found to cause intussusception (telescoping of the intestines – a potentially deadly condition) at the *same rate* of actually contracting the rotavirus infection.[9] This safety issue was detected by VAERS, and the CDC suspended use of the vaccine until further investigation could be completed. After case-control studies confirmed a correlation, the vaccine was quickly removed from the market.[9]

A Close Look at the Data

Back to the research question at hand. Delong's study[1] presumes that VAERS reports of premature ovarian insufficiency (POI) following vaccination are the reason for reduced birth rates in a population vaccinated against HPV. POI is a rare condition in which the ovaries fail before age 40, causing menopause at a much earlier age than normal. There is *no known association between HPV vaccination and infertility/POI*, and numerous high-quality studies looking at short- and long-term outcomes have supported this conclusion.[10-12]

Although these correlations can appear worrisome, they do not prove cause and effect.

Furthermore, like all vaccines, the HPV vaccination is comprised of naturally occurring HPV proteins. It thus follows that if POI were caused by the vaccine, one would assume that wild-type HPV infection must also be capable of causing POI at or above the rates seen in a vaccinated population. This is, of course, not the case: background levels of POI occur in up to 1% of the female population under 40 years of age[13] regardless of vaccine status, and POI is not a known effect of HPV infection.

In fact, the HPV vaccine appears to *improve* fertility in women with a history of sexually transmitted infections (STI).[12] STIs are a known risk factor for reduced female fertility, and HPV has also specifically been shown to reduce the quality of sperm.[12] Preventing infection through vaccination would thus be expected to have either no effect on fertility or to improve it.

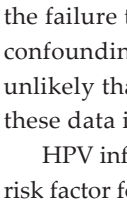
In fact, the HPV vaccine appears to *improve* fertility in women with a history of STIs.

Additionally, individuals with higher socioeconomic status tend to have fewer children,[14] and also have greater access to health care. As such, these individuals are more likely to have received HPV vaccinations and other preventive care. This is compounded by the well-recognized fact that the fertility rate has been dropping over the last 30 years due to a confluence of many factors,[15] but did not see a sudden new decline with the introduction of the HPV vaccine. Delong's study does not address whether the individuals in the analysis were using contraception. These confounders are not adequately accounted for, and depending on the covariate analysis, the researcher found only intermittent statistical significance. This strongly suggests that there is no correlation between HPV vaccination and POI/infertility. Further, the failure to account for so many confounding variables makes it highly unlikely that the study's interpretation of these data is valid at all.

HPV infection is a well-documented risk factor for cervical and oropharyngeal cancers, and with the advent of the HPV vaccine, this risk is now modifiable. Primary prevention of these conditions via vaccination offers a significant reduction in morbidity/mortality and reduces the need for surgical interventions such as loop electrosurgical excision (LEEP) or cervical conization. Preventing cancer is always preferable to treating it!

The Bottom Line

Concerns that HPV vaccination can induce infertility or POI are unfounded and should not be a factor in vaccine counseling. There is ample evidence that the HPV vaccine is safe. Clinicians should encourage this vaccine for its robust efficacy at preventing infection from high-risk HPV subtypes and the cancers these viruses cause.



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Estrogen Dominance in Women

SERENA GOLDSTEIN, ND

Young girls today are developing breasts and starting their periods earlier than in previous generations. High estrogen levels are a likely key contributor to this premature development in girls. Excess estrogen over time places women at risk for hormonal issues such as early menopause and breast cancer. Early sexual development also increases risk of precocious sexual activity as well as psychological challenges such as eating disorders, depression, and substance abuse. There is no one cause of high estrogen levels. Studies suggest that emotional stress associated with growing up in households with high levels of conflict, early sexual abuse, or the absence of a girl's biological father, can raise estrogen and promote early puberty.[1] Other contributors most likely include increasing body mass index (BMI) in the general population, dietary and lifestyle factors, and environmental estrogens. Indeed, estrogen dominance is not only a significant risk factor among girls, but also women in general. Along with estrogen-related cancers, excess estrogen increases risks of uterine fibroids, ovarian cysts, endometriosis, premenstrual syndrome, fibrocystic breasts, painful or heavy periods, and a more difficult perimenopausal transition.

Women have 4 reproductive hormones that are in constant flux (estrogen, progesterone, luteinizing hormone, and follicle-stimulating hormone), along with a generally steady level of testosterone. As a result, when certain concerns arise, especially in a premenopausal woman, any or all of these hormones may be affected to varying degree; in turn, hormone disruptions can also potentially imbalance other processes, due to the complexity of hormone regulation in the body. Estrogen dominance is one of the more common conditions among women. It can result from both normal physiology and environment/lifestyle, and contributes to a myriad of signs and symptoms. Rather than just replacing a hormone here and there, a more effective approach is to identify and address the underlying causes of hormone imbalance.

A Brief Review of Estrogen Physiology

Estrogen, which is made in the ovaries, adrenal glands, and adipose, is the main sex hormone in women. Estrogen is important for early development of primary and secondary sex characteristics, as well as embryonic and fetal development of brain networks. Estrogen also plays a major role in puberty onset, fertility, and the menstrual cycle, and helps protect against bone fractures, cardiovascular disease, and Alzheimer's disease.[2] At the beginning of the follicular phase of a woman's menstrual cycle, hormones in the hypothalamus signal pituitary release of follicle-stimulating hormone (FSH), which promotes the development of follicles in the ovary. These follicles predominantly produce estradiol, which thickens the endometrium. Estradiol levels rise sharply during the last few days before ovulation, reaching their maximum 1 day before the luteinizing hormone (LH) surge, and then rapidly decline. Assuming no fertilization, the corpus luteum post-ovulation produces increasing amounts of progesterone (and a slight rise in estradiol), and both hormones then decrease steadily in the week prior to menses. A new cycle begins. Once fully menopausal, circulating levels of both estrogen and progesterone fall to low levels.[3] Estrogen deficiency in menopause causes LH and FSH levels to increase, with the latter remaining high well into menopause.[4]

The 4 forms of estrogen include 17β-estradiol, estrone, estriol, and estetrol (E4, aka human fetal steroid estetrol, which is only synthesized during pregnancy by the fetal liver; E4 is being explored as a possible form of hormone replacement therapy, as it antagonizes estradiol).[5] Estradiol (E2) is the most potent estrogen and is the predominant estrogen in non-pregnant females of reproductive age; E2 is synthesized primarily in the ovaries, can be aromatized from testosterone, and can be converted in the liver to estrone and estriol. Estrone (E1) is also produced in peripheral tissues (ie, adipocytes) via aromatization from androstenedione. E1 is weaker than E2 and is the main form of estrogen after menopause, although small amounts of E2 continue to be produced. Estriol (E3) is the least potent estrogen (1000 times less potent than E2) and plays a large role in pregnancy, as it is produced by the placenta. E3 can also be formed from E1 through 16α-hydroxylation.[2]

E1 and E2 break down into metabolites called 2-hydroxy (OH)-estrone, 4-OH-estrone, 16α-OH-estrone, 2-OH-estradiol, and 4-OH-estradiol. The "2" form is considered protective against cancer, since it doesn't stimulate cell growth, whereas the "4" and "16" forms are potentially deleterious; the former can develop as a result of environmental toxin exposure and damage DNA, while the latter has stronger estrogen activity and can be at higher concentrations in obese women.[6] The protective 2-OH-estrone and 2-OH-estradiol metabolites are converted to 2-methoxy (Me)-estrone- and 2-(Me)-estradiol, respectively, by the enzyme, catechol-O-methyltransferase (COMT), which serves to suppress tumor cell proliferation and angiogenesis. COMT is also required to convert 4-(OH)-estrone and 4-(OH)-estradiol to 4-(Me)-estrone and 4-(Me)-estradiol, respectively, which are actually protective metabolites that help prevent oxidative metabolism of E2 and DNA damage. If COMT is deficient or its function is compromised due to genetic mutations, then variations of the "2" and "4" metabolites can have the opposite effect of being pro-inflammatory free radicals.[6] Further conjugation by glucuronidation or sulfation facilitates safe removal of estrogens.

Estrogen receptors (alpha and beta subtypes) are present in many organ systems throughout the body. In women, estrogen receptor-alpha (ERα) is predominant in the mammary gland, thecal cells of the ovary, uterus, bone, liver, and adipose tissue, and plays more of a role in regulating metabolism.[7] The estrogen receptor-beta (ERβ) is located mainly on the granulosa cells of the ovary, colon, and adipose tissue. ERβ has a larger role in the immune and central nervous systems and opposes the ERα-driven hyperproliferation in tissues such as the breast and uterus. Both ERα and ERβ receptors are also present in men.[7]

Along with estrogen-related cancers, excess estrogen increases risks of uterine fibroids, ovarian cysts, endometriosis, PMS, fibrocystic breasts, painful or heavy periods, and a more difficult perimenopausal transition.

Estrogen Modifiers & Effects

Just as there are many ways that estrogen can be made and metabolized, there are many ways for these processes to be thrown off that contribute to hormonal imbalances. Most estrogen is held in reserve by being bound to hepatic sex hormone-binding globulin (SHBG) or (more weakly) to albumin. Thus, concentrations of SHBG are important determinants of bioavailable estrogen in the body. High SHBG concentrations have been associated with factors such as a high carbohydrate diet (35-40%), while low concentrations of SHBG have been linked with elevated prolactin, hyperinsulinemia, and obesity. Low SHBG results in greater amounts of free, unbound estrogen.[8]

Elevated estrogen increases thyroid-

binding globulin, which has the effect of binding more thyroid hormone.[9] Reduced amounts of unbound thyroid hormone results in slower metabolism and reduced energy expenditure (increasing the risk of weight gain), reduced lipolysis (increasing the risk of hyperlipidemia), and reduced gluconeogenesis (raising the risk of hypoglycemia).[10] Keep in mind that the thyroid is strongly affected by stressors on the body (external or internal), in areas such as autoimmunity and activation of T3 from T4.[11]

As mentioned, the metabolism of E1 and E2 into favorable metabolites occurs via methylation. Certain genetic variants of COMT (such as the Val/Met polymorphism that reduces enzyme function) can affect how efficiently these estrogens are metabolized. This same polymorphism can impact the degradation of dopamine, an excitatory neurotransmitter. Women with the Val/Val genotype have been shown to have greater COMT enzyme activity, hence lower dopamine levels, compared to women with the Met/Met genotype, who have been shown to have higher dopamine levels and impaired executive functioning as a result.[12] Because COMT also metabolizes estrogen, women with the Met/Met genotype and high estrogen may be at particular risk of impaired cognitive function in menopause.[12] More studies are needed to confirm this.

Gut health can also influence estrogen metabolism and levels, as some bacterial species possess the enzyme beta-glucuronidase, which can reactivate the hormone. Estrogen that isn't bound to SHBG is conjugated through phase 2 detoxification pathways, such as glucuronidation, and is then eliminated through the kidneys and gastrointestinal tract. However, too much bacterial beta-glucuronidase activity in the intestine can cause deconjugation of estrogen. This results in increased reabsorption of free estrogens into the body, potentially contributing to the development of estrogen-related cancers of breast, ovary, or endometrium.[13]

Additional Sources of Estrogen

Environmental estrogens also contribute to overall estrogenic activity in the body, including the estrogens added to meats and dairy products,[14] phytoestrogens in soy, and especially xenoestrogens, which are non-physiological compounds that bind ERα receptors and can evoke estrogen responses in the body as well as interfere with endogenous estrogen actions.[15] Xenoestrogens are common in a wide variety of cleaning and beauty products (eg, parabens), plastics (eg, BPA, phthalates), pollution, and pesticides (eg, DDT, DDE), and artificial preservatives.[16] Feminine hygiene products, such as tampons, used to be composed of more synthetic fibers, which can alter the vaginal pH and environment; now they are comprised of a single synthetic fiber and are mostly cotton.[17] However, they also now contain trace amounts of dioxins (chemical byproduct of bleaching) that can be absorbed directly by the vulva without being metabolized. This constitutes a significant exposure, considering that a woman might be exposed to over 10 000 tampons during her lifetime.[17] Switching to an organic pad or tampon or to a non-chemical alternative can help reduce this exposure.

Hormone Testing

Hormone testing can be done using blood, urine, or saliva.[18] A serum test is convenient if you want to also evaluate organ systems that might be related to an estrogen imbalance; examples of useful blood tests include thyroid, vitamin D (precursor to sex steroids), CBC, CMP, iron, hemoglobin A1c, and possibly DHEA-S and SHBG. However, estrogen and progesterone may be best measured by urine and saliva because these tests measure the "free" (unbound) form of the hormones, ie, that fraction of hormone that is acting on the body; levels of total (free + bound) hormone in the blood can sometimes be falsely high or normal. Hormones are also pulsatile; since serum represents a snapshot in time, it's difficult to discern if a lab value is at its high or low point.

In contrast to most hormone blood tests, salivary testing measures the free hormone and specimens can be collected throughout the day, thus lending more versatility and clinical value to the result. Salivary testing is also helpful in evaluating cortisol levels throughout the day if indicated, to gain an understanding of the patient's stress levels. Limitations can include a patient being unable to produce adequate saliva.[18]

Urine tests are also useful for measuring hormones, either at a single point in time or in a 24-hour collection, to evaluate a patient's natural rhythm. A 24-hour collection also provides insight into the various estrogen metabolites and liver function, which may point to specific paths for treatment. Limitations can include dehydration or excessive fluid intake.[18]

Finally, consider genetic testing (cheek swab) for COMT, to gain insights into estrogen metabolism and mood and to help guide your treatment.

Therapeutic Approach

As discussed, there are many possible reasons for why a woman is estrogen dominant, as well as multiple factors that can exacerbate estrogen excess. We therefore need a multi-systems approach in our treatment. A patient's personal and family history, along with a thorough analysis of her environment, will help you identify the most significant obstacles to cure. In addressing the root cause of disease in a multi-factorial condition can be proverbially like peeling the layers off an onion. From there, a treatment plan can more easily come into view, often focused around nutrition, proper sleep, a healthful

lifestyle, and certain combinations of supplements to help expedite healing and balance hormones.

Nutrition

Fruits and vegetables are great sources of fiber, vitamins, and minerals that support both estrogen metabolism and gut health and help prevent cancer. The American Institute of Cancer Research estimates that at least 5 servings of fruits and vegetables per day can reduce cancer rates by as much as 20%.[19] Cruciferous vegetables, in particular, have been shown to protect against cancer more effectively than total intake of fruits and vegetables.[19] Crucifers contain glucosinolates, selenium (also helpful for thyroid), sulforaphane, and indole-3-carbinol, all of which promote healthy estrogen metabolism, protect against reactive oxygen species, and optimize phase 1 and phase 2 detoxification pathways in the liver.

Soy is a type of phytoestrogen, a naturally-occurring plant compound that is structurally and functionally similar to estrogens and their metabolites. For this reason, soy is a controversial food group in terms of estrogen-related conditions; its phytoestrogen compounds mimic estrogen but it has also been a long-time staple in the traditional Asian diet and has been credited for Asians' historically lower rates of menopausal symptoms, hormone-dependent cancers, obesity, diabetes, and cardiovascular disease compared to Western populations.[20,21] Until we know more about the extent to which soy isoflavones can counteract excessive estrogen or harmful estrogen metabolites (ie, 4-OH-estrogen), it might be best to err on the side of low-to-moderate consumption of soy, especially for a patient with a strong history of estrogen-related concerns.

Supplements

One of the most powerful ways to counteract estrogen dominance is by boosting progesterone concentrations. *Vitex agnus-castus* (chasteberry), which acts directly on the pituitary, is an especially effective way to do this. Chasteberry inhibits the secretion of FSH, which helps prevent increases in estrogen. It also promotes LH secretion, which supports corpus luteum production of progesterone. The herb also indirectly supports progesterone production by enhancing dopamine production by the pituitary. Dopamine inhibits prolactin, a hormone that can reduce progesterone production by suppressing the corpus luteum.[22]

Calcium-D-glucarate, which is produced naturally in small amounts from dietary glucaric acid but is also available as a supplement, inhibits the bacterial enzyme beta-glucuronidase that reactivates estrogen in the colon. Calcium-D-glucarate helps counteract estrogen dominance, reducing the risk of hormone-sensitive cancers such as prostate, breast, and colon; it also appears to lower cholesterol.[23] Glucaric acid is found naturally in many fruits and vegetables, eg, apples, oranges, and cruciferous vegetables.[23]

Indole-3-carbinol (I3C) and diindolylmethane (DIM), I3C's metabolite, which are found naturally in cruciferous vegetables and are also available in supplement form, induce cytochrome P450 enzymes to produce the beneficial 2-OH-estrogens. One study demonstrated that 500 mg/day of I3C for 1 week significantly increased 2-OH-estradiol levels, an outcome that can help counter estrogen-dependent disorders.[24]

A healthy liver is critical, since it is the organ that handles the bulk of detoxification of xenobiotics, metabolism of estrogen and other hormones, and the conversion of inactive to active thyroid hormone. *Silybum marianum* (milk thistle) is one of our most useful liver botanicals, as it not only provides support for detoxification pathways and regeneration of hepatocytes, but also has anti-cancer properties.[25]

Sleep

We are in a day and age of constantly being on the go, where the phrase "I'll sleep when I'm dead" is well known; it also reflects the pervasive lack of quality sleep. Sleep duration has decreased about 1.5-2 hours over the past 50 years.[26] Prioritizing sleep has multiple beneficial effects on our hormones, including inhibiting corticotropin-releasing hormone, optimizing TSH release, and regulating appetite and satiety via leptin and ghrelin release.[26]

Conclusion

We can clearly take many steps to remove toxic burden from our environment, both physically and emotionally. Adopting a toxin-free lifestyle, cultivating supportive relationships, supporting gut health, and emphasizing a healthful diet can all help counter estrogen dominance; these measures will also improve thyroid and adrenal health, balance blood sugar, and promote a healthy weight. Key supplements can help in achieving this balance, but are meant to supplement, not to replace, an unhealthful lifestyle. Your patients' hormonal issues did not occur overnight. Working with them long-term helps healthy habits be put into place so that everything they do can also double as prevention.

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Estrogen Dominance

When an Unhealthy Gut Estrobolome is to Blame

CARRIE JONES, ND, MPH

It is well established that elevated estrogen can pose many problems for both men and women. Not only can it result in estrogen dominance symptoms; if not properly detoxified, it increases the risk of several cancers. When patients present with elevated laboratory levels of estrogen and/or have symptoms related to excess estrogen, strategies often include supplements such as diindolylmethane (DIM) or indole-3-carbinol (I3C). While DIM and I3C can be effective at lowering estrogen levels, they only impact phase-1 of estrogen metabolism. Frequently overlooked are the phase-2 and -3 processes that play major roles in the safe excretion of this hormone. It is critical to consider all phases of metabolism, including the intestinal microbiome's important role in facilitating proper excretion of estrogen metabolites; impairments in this step can have a significant effect on the patient's health. By having a clearer understanding of each step and making sure to focus on proper gut health, practitioners can help mitigate potential risks in the future.

> The estrogen glucuronide conjugate can become the target of gut bacteria during phase 3.

Estrogen Metabolism

Phase-1 Detoxification

Estrone (E1) and estradiol (E2) are the primary estrogens in the body. Primarily in the liver, they both undergo hydroxylation by members of the cytochrome P450 (CYP450) enzymes, which attach a hydroxyl (-OH) group to the estrogen.

- 2-hydroxyestrone (2-OH) is formed primarily through CYP1A1
- 4-OH is formed primarily through CYP1B1
- 16α-OH is formed primarily through CYP3A4

This group is known collectively as phase-1 estrogen metabolites, although they can be rather reactive themselves.[1] Among the 3 metabolites, the 2-OH metabolite is generally considered the "safest" and the predominantly preferred metabolite because of its weak binding capacity to the estrogen receptor and its modest proliferative effects. In contrast, the 16α-OH metabolite can bind strongly to the estrogen receptor and has quite strong proliferative effects. However, it is important to keep in mind that estradiol itself is inherently proliferative. If an unhealthy microbiome allows for increased reabsorption of E2 into the general circulation, the effects will be much more impactful on the body than those of 16α-OH. The 4-OH metabolite has the potential to promote high cancer risk if it is unable to proceed through phase-2 detoxification.[1] In such a case, 4-OH can head down a different pathway to become the free radical, 3,4-quinone, that reacts with DNA and forms depurinating estrogen DNA adducts.[2,3]

Phase-2 Detoxification

The phase-1 estrogen metabolites, 2-OH and 4-OH, are inactivated in Phase-2 detoxification primarily by methylation via the enzyme catechol-O-methyltransferase (COMT).[4] Other phase-2 pathways include sulfation and glucuronidation. Importantly, it is the estrogen glucuronide conjugate (from glucuronidation) that can become the target of gut bacteria during phase 3, as discussed in the next section. Phase-2 metabolites are relatively inert and water-soluble, which allows them to be easily excreted via the kidneys as well as the gastrointestinal tract. Phase-1 and phase-2 detoxification can thus be evaluated using urine hormone testing. Following phase-2 metabolism, the inactive metabolites that are transported to the bile then enter what is colloquially known as phase-3 detoxification in the intestine.

Phase-3 Intestinal Detoxification

For the estrogen that is conjugated or "packaged up" and delivered to the bile for "safe" excretion, a healthy intestinal tract is critical in order to minimize reabsorption of the hormone. Unfortunately for many, this is not always the case. In a 2016 study, women were injected with radio-labeled estrogen. These estrogens were expected to be found in their conjugated (detoxified) forms in the subjects' feces. Surprisingly, researchers found that 65% of the estradiol had reversed to its unconjugated (active) form, which can be easily reabsorbed from the intestine.[5] It turns out that high levels of the bacterial

enzyme, beta-glucuronidase, made by an unhealthy estrobolome, was to blame.

The Estrobolome

What is the estrobolome? It has been described as "the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens, [and which] acts on conjugated estrogens and estrogen metabolites, with downstream physiologic effects."[6] Much like the rest of the microbiome, the estrobolome is easily influenced by factors such as diet, lifestyle, antibiotic use, history of vaginal delivery (or not), age, and alcohol use.[5,6]

While the Human Microbiome Project found over 50 species of gut bacteria that can encode for beta-glucuronidase, they can be grouped into 4 main phyla: Bacteroidetes, Firmicutes, Verrucomicrobia, and Proteobacteria.[7] Beta-glucuronidase has a bad reputation. However, the enzyme has an important role in breaking down complex carbohydrates and facilitating the reabsorption of bilirubin and flavonoids.[8] Much like the Goldilocks story, humans need just the right balance.

Unfortunately, estrogen-dominance symptoms like PMS or menorrhagia are not the only potential problems associated with elevated beta-glucuronidase levels. Studies have shown that obesity, metabolic syndrome, estrogen-related cancers, uterine hyperplasia, endometriosis, infertility, cognitive function, and cardiovascular disease may all be directly impacted.[9] This is why appropriate testing and treatment is so important to a person's overall health.

Many stool companies testing for bacteria, candida, parasites, and gastrointestinal inflammation also measure fecal beta-glucuronidase levels. Treatment for borderline-elevated or elevated levels centers around key factors such as lifestyle modification and appropriate supplementation, as well as addressing any other intestinal imbalances.

Treatment

As the popular saying goes, we are what we eat and absorb. Therefore, advise patients to work on eliminating or reducing sugar and processed foods or other choices commonly considered part of the "standard American diet." Focus on a diet rich in organic vegetables, fruit, and fiber. Research has shown that a shift in the diet can induce microbial shifts within 24 hours![10] This means those fried fatty foods eaten yesterday can have a direct impact on the microbiome – including the estrobolome and estrogen reabsorption – today.

Be mindful of antibiotic use and work to reduce or eliminate toxicant exposure, as both have a direct impact on the microbiome.[11-14] Advise patients to read labels, minimize use of plastic water bottle and food containers (especially when heated), decline the thermal receipts printed at stores, filter drinking water, opt for organic food whenever possible, consider an air filter for the house if necessary, and to be mindful of what they put on their bodies and use in their homes and out in their yards.[12-15]

Honestly discuss alcohol consumption with your patients, as it has an impact not only on the gut microbiome but also on the ability of the liver to properly detoxify circulating estrogens (and endocrine-disrupting chemicals); these impairments can contribute to estrogen dominance symptoms and/or an increased risk of estrogen-related cancers.[16-19]

Consider supplementation with prebiotics and/or probiotics to help with dysbiosis while also addressing any infections that might have been revealed by stool testing.[10] Lastly, the supplement calcium-D-glucarate is a known beta-glucuronidase inhibitor, allowing estrogen to remain conjugated or "packaged for excretion" and safely eliminated from the body. The typical dosage of calcium-D-glucarate is 1500-3000 mg/day; however, animal research tends to use 100-200 mg/kg, which may indicate that traditional dosing for humans is on the low side.[20,21] Nevertheless, every little bit does help. Currently, there are no known toxic effects of calcium-D-glucarate in animal studies.[20]

Focusing on gut health has always been a mainstay in naturopathic practices, and with estrogen issues, it is no different. By understanding the detoxification process from start to finish, practitioners can further tailor individual treatment plans for their patients and help eliminate or reduce risk.

References 8-21 available online at ndnr.com

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Antioxidants & Male Infertility

Can Supplements Make a Difference?

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Modern couples are attempting to procreate in a world of toxins and dietary and lifestyle habits that produce an overabundance of reactive oxygen species (ROS); antioxidant defenses are burdened as a result. Toxins (eg, bisphenol-A and pesticides in food), aging, psychological stress, obesity, poor nutrition, reduced physical activity, high intake of caffeine, high scrotal temperature, and mobile telephone use all cause an uncontrolled release of ROS, and all have been implicated in the etiology of infertility.[1-3] With increased exposure to all of these factors, it is therefore not surprising that, globally, 15% of modern couples (48.5 million) are infertile.[4]

A couple is considered infertile if they are unable to conceive after at least a year of regular, unprotected intercourse. Male infertility is thought to be responsible for 50% of overall cases.[4] Although the cause of some cases of male infertility has been identified, such as varicocele, cryptorchidism, and hypogonadism, many cases of infertility remain idiopathic. In more than 25% of cases, no explanation can be found for an abnormal semen analysis.[5]

ROS: A Driving Force

Molecular-level research directed at identifying the causes of idiopathic male infertility has deemed oxidative stress to be an important contributor.[6] ROS have been found to be higher in subfertile men,[5] and are elevated in up to 40% of infertile men.[7] These high levels were not observed in fertile men.[7] Balanced levels of ROS are required for some sperm functions, including fertilization of the egg.[8] However, uncontrolled generation of ROS harms sperm function,[9] leading to DNA damage,[10] impaired motility,[11] and defective membrane integrity.[12] Spermatozoa are especially vulnerable to oxidative damage on account of the presence of large quantities of plasma membrane polyunsaturated fatty acids.[5] Modern males are subjected to an onslaught of oxidative stress, which may be a primary reason why sperm counts in men have progressively declined since the 1930s.[13] Specifically, in the 1930s, only 15% of men had a sperm count <40 million/mL, whereas by the 1990s to 2000, that percentage increased to 40%.[13] Average sperm count normally ranges from 45 to 65 million/mL.[14] However, a series of European studies of men between 18 and 25 years old from 7 countries found that, depending on the country, approximately 20% of young men had a sperm count <20 million/mL and approximately 40% had a sperm count <40 million/mL. This latter level is thought to be the threshold below which fertility diminishes.[14]

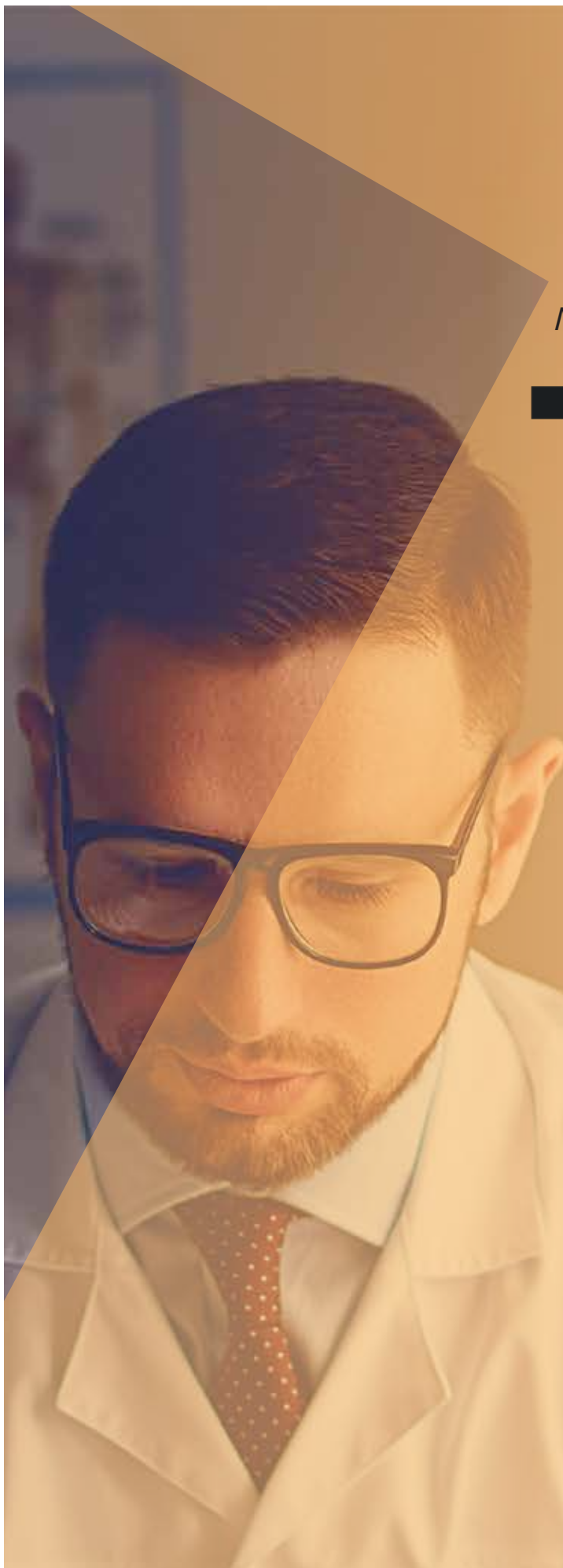
> Reducing oxidative stress may reduce DNA fragmentation, increasing the likelihood of conception.

One mechanism by which oxidative stress leads to infertility may involve sperm DNA fragmentation, which is a strong indicator of the ability to conceive – even more so than conventional semen markers.[15] Men who have high DNA fragmentation levels are significantly less likely to conceive, either naturally or through intrauterine insemination or in-vitro fertilization (IVF).[15] Oxidative stress is the primary reason why DNA fragmentation occurs in spermatozoa.[15] Reducing oxidative stress may therefore reduce DNA fragmentation, increasing the likelihood of conception.[15]

Antioxidants & Fertility

Evidence indicates that antioxidant supplementation can play a valuable role in mitigating various aspects of oxidative damage in human sperm. In a prospective clinical trial, Arafa and colleagues studied 101 infertile men who had an abnormal semen analysis.[16] The men were given an antioxidant supplement containing L-carnitine, coenzyme Q10 (CoQ10), lycopene, N-acetyl L-cysteine, vitamins E, A, D3, C, K, and B-complex, iodine, selenium, zinc, copper, manganese, chromium, molybdenum, grape seed extract, benfotiamine, and L-arginine 3 times per day. At the end of the 3-month study, sperm count increased by 33%, progressive motility increased by 122%, and normal morphology increased by 62%. Furthermore, DNA fragmentation decreased by 20%, and oxidation-reduction potential decreased by 44%.[16]

A collection of other research over the years has added to the body of evidence



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that antioxidant supplementation can improve sperm health. Abad and associates found that a combination of L-carnitine, CoQ10, zinc, selenium, and vitamins E, B9, and B12, administered for 3 months to 20 infertile patients diagnosed with asthenoteratozoospermia (reduced sperm motility), led to significantly improved DNA integrity.[17] Furthermore, the proportion of highly DNA degraded sperm was lower after the antioxidant supplementation.[17] Semen analysis revealed a pronounced increase in sperm concentration, motility, vitality, and morphology.[17] One review of the medical literature showed 20 out of 32 studies observing significantly improved sperm motility after antioxidant use.[5] Other studies have demonstrated that CoQ10 alone,[18] N-acetylcysteine with selenium,[19] or selenium with vitamin E[20] significantly improved various sperm parameters, including morphology, motility, and density. Some of these nutrients, such as CoQ10, have also been found to improve pregnancy rate.[21]

In a 3-month study, L-carnitine plus acetyl-L-carnitine were administered twice daily, along with the anti-inflammatory drug cinnoxicam every 4 days, to 33 infertile men.[22] The men and their partners were using intracytoplasmic sperm injection (ICSI) as a fertility treatment due to severe idiopathic oligoasthenoteratospermia. Of the 33 men, 22 had a reduced frequency of aneuploid sperm (spermatozoa with chromosomal abnormalities) and improved sperm morphology after supplementation combined with the drug. Use of L-carnitine, acetyl-L-carnitine, and cinnoxicam was also significantly associated with increased numbers of biochemical pregnancies, clinical pregnancies, and live births.[22]

The beneficial effects of antioxidants are due to their ability to directly scavenge ROS. For example, vitamin C, the principal antioxidant in seminal plasma, inhibits the formation of ROS from a number of sources and also helps recycle oxidized vitamin E.[3] In sperm plasma membranes, vitamin E is also known to directly neutralize ROS.[3]

Conclusion

An abundant amount of research ties an overproduction of ROS to male infertility. Resolving the oxidative stress that ensues after ROS overproduction through the use of antioxidant supplements can improve many aspects of sperm health, including motility and morphology, and may even increase the rate of pregnancy and live births. In couples ultimately able to conceive, reducing oxidative stress can also improve cellular integrity of the next generation from conception onwards into childhood and beyond.

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GMO Crops & Glyphosate

Detrimental Effects on Health

HUMAIRA QURAISHI, ND, MS

An historic event took place in August of 2018 when Dewayne Johnson won his lawsuit against Monsanto; he was granted "$39.2 million in compensatory damages and $250 million in punitive damages."[1] Johnson, a 46-year-old gardener, developed non-Hodgkins lymphoma after continuous use of Monsanto's most popular commercial weed killer. Thus far, this was the first case against Monsanto to go to trial, as well as the first case won. Thanks to this trial, Monsanto's classified documents were scrutinized, and they revealed that the company knew of the product's potential harmful effects on health. Not only has Monsanto neglected to acknowledge these side effects, the company has also targeted researchers who write negatively about glyphosate and genetically modified organisms (GMOs).

Critical Data & Monsanto's Cover-ups

Researcher Gilles-Eric Séralini published a study in 2012 that showed that rats fed glyphosate – the active ingredient in Monsanto's weed killer – in their drinking water developed tumors, even at low amounts.[2] His research was later retracted by the journal because "it did not meet scientific standards,"[3] even though there was no evidence of it being scientifically invalid. Séralini took these accusations to court in 2 separate cases, and won. In both cases, the court ruled that the individuals accusing Séralini, one of whom was an ex-employee of Monsanto who had begun working for the journal, were guilty of public defamation and forgery.[2] Séralini went on to republish his article in another journal.[4]

Meanwhile, previous research[5] on health effects of GMOs by another investigator, Joël Spiroux de Vendômois, was also targeted by Monsanto. Thanks to court order, Vendômois was able to obtain Monsanto's data, which gave his study credibility regarding chronic and subchronic toxicities. Vendômois and his team discovered within Monsanto's documents hepatorenal differences in rats which, in a 90-day trial, consumed 3 GM corns: MON 863, Mon 810, and NK 603, all owned by Monsanto.[5] Other toxicities included increases in weight and plasma triglycerides in female rats that consumed MON 863; increase in heart weight in males given NK 603; and early signs of chronic nephropathy in Sprague Dawley rats fed MON 863 (though not with MON 810 and NK 603).[5] In his article, Vendômois also outlined issues with Monsanto's data, and included the following observations:

1) Ninety-day studies on rats are not long enough to evaluate for chronic side effects by pesticides

2) There were too many controls – "out of 400 rats, there were only 80 eating GMOs." This means the study was only based on 320 control animals, giving the impression that GMOs do not pose any risks, since the majority of the rats were unaffected.

3) A regulatory health test was performed only once for each GMO product. This means that the evaluation process was not scientifically up to standards, even for a 90-day trial.

The German Appeal Court, after concerns in Europe over GMO MON 863, allowed public access to Monsanto's raw data.[6] After review of the data, Séralini et al discovered that Monsanto neglected to show data with even the slightest negative results from MON 863 maize and had suggested that it was safe to consume. "The disturbing oversight runs false negative results and a risk of health consequences for millions of people and animals."[6] Séralini and his team also found "significant effects were concentrated in livers and kidneys as main detoxification organs reacting in cases of food/chemical contamination."[6] Once again, Monsanto failed to mention significant side effects of GMOs, including: "significant increase in blood glucose of 10% in GM-fed females, in triglycerides of 24-40%, overweight livers and enhanced liver/brain ratios (7%), small but significant body weight gain (3.7%), and disturbed kidney parameters."[6] Sounds like metabolic profiles.

Since early findings of hepatotoxicities in Sprague Dawley rats, a 2-year study was conducted on these rats using NK 603 maize and Monsanto's glyphosate-containing herbicide.[7] Researchers used 3 different concentrations of both residues. NK 603 was administered with or without the weed killer in the feed at 11%, 22%, and 33% concentrations, while the weed killer, alone, was administered in drinking water with concentrations at 0.1 ppb (regular tap water), 400 ppm

(max level allowed in GMOs), and 0.5% (half the agricultural dose). At 15 months, the female rats showed marked liver and kidney dysfunction.[7] Testosterone and estradiol levels also appeared to be elevated. By the end of the 2-year experiment, researchers noted male rats to have more severe hepatorenal deficiencies compared to females. However, females who consumed 0.1 ppb of the weed killer were seen to have more mammary tumors, which led to premature deaths.[7] Despite the evidence of toxicity, the results were "immediately dismissed by persons involved in the products' authorizations, or in collaborations with biotech industries."[7] Studies that have been conducted by Monsanto and their collaborators have all been classified as confidential, thus preventing other researchers and the general public from seeing the results unless allowed by court order.[7]

GMOs & Glyphosate: Cellular Effects

Seeing these side effects and tumors in animal models, one must also consider the biological and biochemical impact of both GMOs and glyphosate on the cellular level. How might the mitochondria react to GMOs? Mitochondria are not only critical to ATP production; they also have important roles in cell signaling, apoptosis, and inflammation. Alex Vasquez, DO, ND, DC, has compiled a variety of evidence correlating mitochondrial dysfunction with metabolic syndrome, type 2 diabetes, and hypertension.[8]

Glyphosate acts as a chelator and binds to many minerals, leading to nutritional depletion in plants and, later, in animals and humans.[9] One of these minerals is manganese, which is very important to the mitochondria. Manganese plays a role in cell survival and regulating enzymes like manganese superoxide dismutase (Mn-SOD), which helps protect the mitochondria and surrounding cells from oxidative damage.[10] As explained by Dr Vasquez and MIT research scientist Stephanie Seneff, PhD, the combining of solvents and the glyphosate in Monsanto's weed killer can particularly predispose to mitochondrial dysfunction, as the solvents impair the mitochondrial membrane, allowing glyphosate to penetrate the organelle and bind to manganese [11] Because manganese is so critical to the function of Mn-SOD, a deficiency of manganese can promote intracellular oxidative damage and inflammation, in turn raising the risk of chronic health conditions.

If causing damage to the mitochondria isn't bad enough, Dr Seneff describes glyphosate as also causing DNA damage, interrupting amino acid balance, removing trace minerals, and impairing detoxification pathways. As she stated in an interview with Dr David Perlmutter, "Epidemiological evidence supports strong temporal correlations between glyphosate usage on crops and a multitude of cancers that are reaching epidemic proportions, including breast cancer, pancreatic cancer, kidney cancer, thyroid cancer, liver cancer, bladder cancer, and myeloid leukemia."[12] Séralini and Vendômois found the maize GMO, MON 863, to have metabolic effects including "direct or indirect insertional mutagenesis."[5] An example is the insertion

> The combining of solvents and the glyphosate in Monsanto's weed killer can particularly predispose to mitochondrial dysfunction.

of the transgene producing the insecticidal Cry1Ab toxin, leading to "synthesis of new RNA products encoding unknown proteins or/and to metabolic pathways variations which caused up to 50% changes in measured osmolytes and branched amino acids."[5] Another such study, published in *The Lancet Oncology*, found occupational exposure to Monsanto's herbicide and its solvents in the United States, Canada, and Sweden to have a positive association with non-Hodgkin's lymphoma.[13]

There is also evidence, from a 2012 animal study by Séralini et al, suggesting that GMO maize and Monsanto's weed killer causes infertility and hormonal imbalance by disrupting the enzyme aromatase that produces estrogen.[2] In the study, rats fed the glyphosate herbicide alone in water, rats fed corn sprayed with the herbicide, and rats fed GM maize treated with the herbicide, all showed higher levels of estrogen.[2] They also displayed large mammary tumors – tumors that are known to be estrogen-dependent and shown to be significant at even the lowest dose of the Monsanto's weed killer. "[I]n females, the androgen/estrogen balance in serum was modified by GM maize and [glyphosate] treatments,… and for male animals at the highest [glyphosate]-treatment dose, levels of estrogens were more than doubled."[2] The Natural Fertility Info organization stated the following: "The recent study prompted the largest healthcare organization in the U.S. Kaiser Permanente, to release warnings to limit consumption of GM foods."[14] Assuming similar effects in humans, this increase in estrogen levels leads to many issues in fertility, including ovulation, polycystic ovarian syndrome, endometriosis, fibroids, and low sperm count.[14] Rising estrogen levels is resulting in earlier puberty. Research published in the journal *Pediatrics* revealed that 15% of girls worldwide are beginning puberty by the age of 7."[15]

False Promises

According to Emily Cassidy, a research analyst for Environmental Working Group, GMOs were supposed to help global food security because the demand for food is expected to double by 2050 compared to what it was in 2005.[16] However, recent evidence indicates "GE crops have not increased crop yields enough to significantly contribute to food security."[16] Cassidy also found that in Africa, traditional breeding techniques have produced more crops compared to genetic engineering.[16] It also takes more money to produce genetically engineered (GE) crops: "industry-supported research found that it can take more than $100 million to research and develop a simple [GE] variety," whereas, it takes only $1 million to create a new variety using traditional breeding techniques.[16] Unfortunately, 75% of the processed foods in the United States contains genetically engineered ingredients. What's worse, because of herbicide resistance, "superweeds" are causing farmers and manufacturers to use more glyphosate. Between 1996 and 2011, glyphosate usage increased by 527 million pounds, an increase of about 11%.[16]

GMOs were created to endure and/or produce 1 or more insecticides.[5] GMO crops made to withstand heavy use of glyphosate are labeled "RoundUp Ready." Ninety percent of cotton, corn/maize, soy, canola, and sugar beets sold in the United States are genetically modified.[17] Farmers are able to spray these crops in order to kill the weeds because the crops are not affected by the herbicide. However, the residue of the herbicide still remains on the food.[18] Think about this: if the residue remains on the food, how likely is it going to remain in our bodies, considering factors such as 1) not cleaning produce properly; 2) hooverizing instead of fletcherizing foods; and 3) digestive concerns, such as leaky gut, which allow more penetration of the pesticide/mutated genes into the body. Glyphosate has also been shown to deplete nutrients, which results in deficiencies.[19] For 60 years, "the USDA has been tracking the nutrient density of 43 crops … USDA data shows a progressive and alarming rate of decline in nutrition since the 'green revolution' began in the 1940s."[19]

Closing Comments

If the poison is still present, the genes are still active,[20] and genetic modification reduces the nutritional density of foods, then GMOs and glyphosate herbicides can have more severe and chronic effects on our health than we already know. In 2015, the World Health Organization labeled glyphosate as "probably carcinogenic in humans."[21] When an Indian research team in 2010 found significant biological effects of their new Bt insecticide on 3 different mammals within a short period of time, they decided to study its chronic effects on heath rather than commercialize the toxin.[5] If they stepped up to study these insecticides' effects of health, then why can't we? There is momentum in the organic revolution, but many are hesitant to obtain organic produce, due to hidden or deficient evidence or the cost of organic goods. However, if we can bring more evidence forward, increase awareness of health concerns associated with GMOs and glyphosate, and teach our communities how to grow and effectively use organic produce, our health will be in much better shape. This begins with us whenever we recommend nutritional protocols and non-GMO supplements to our clients and patients – Docere.

References available online at ndnr.com

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Rosa canina

A Potential Herbal Preventive for Post-C-section UTI

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Urinary tract infection (UTI) is a common ailment in female-bodied individuals. Certain populations are at an increased risk for UTI, including, but not limited to, pregnant and postpartum women.[1] Due to catheterization, there is an increased risk of bacteriuria in post-Cesarean section (CS) patients.[2] Current standards of care for acute, uncomplicated cystitis call for the use of an antibiotic such as nitrofurantoin and/or trimethoprim-sulfamethoxazole, both of which are excreted in breast milk.[3,4] Though the amount excreted is relatively low, the presence of antibiotics in breast milk has the potential to alter bowel flora in neonates.[4] Currently, the World Health Organization recommends avoiding nitrofurantoin while breastfeeding infants less than 1 month of age.[4] Given the increased risk of UTI in post-CS patients and concerns about neonatal exposure to antibiotics, there is a need for alternative interventions for preventing UTIs.

In a recent randomized controlled trial conducted by Seifi et al (2018), researchers investigated the effectiveness of *Rosa canina* fruit in preventing UTIs following CS.[1]

Rosa canina is a wild plant whose fruits, known as rose hips, are widely used for their immune-modulating and antioxidant properties. They contain high amounts of vitamin C, in addition to vitamins A, B1, B2, B6, D, E, and K.[5] They are also rich in carotenoids, including lycopene and β-carotene. In the Seifi et al study, the 400 subjects were patients in the postpartum period following CS, who were matched socioeconomically.[1] For the 20 days following surgery, the intervention group (n=200) was administered *Rosa canina* fruit (500 mg standardized capsules, twice daily by mouth), and the control group (n=200) was administered a placebo consisting of cornstarch capsules (twice daily by mouth).

The subjects were assessed for UTI at 7-10 and 20 days post-surgery, based on symptom evaluation and urine culture.[1] The primary outcome was the incidence of any UTI (asymptomatic or symptomatic) up to 20 days postpartum. In our paper, the methods, results, and conclusions of the Seifi et al study were analyzed in order to answer the following clinical question: "What is the effectiveness of *Rosa canina* in preventing UTI in post-CS patients?" In order to be inclusive of trans men and gender-non-conforming individuals, this paper was written using gender-neutral language.

Methods

The study of interest was located on PubMed, using the search term "Urinary Tract Infections," and with the following filters applied: Clinical Trial, Humans, 5 years, and Complementary Medicine.

Results

At 7-10 days post-CS, 4 subjects in the experimental group developed a UTI, as compared with 17 in the control group (odds ratio=0.22).[1] At 20 days, the numbers were 8 and 23, respectively (OR=0.32).

Seifi et al listed no statistical analyses beyond odds ratios. Unfortunately, odds ratios are not always the most accurate reflection of treatment effect. As stated by Schechtman, "An odds ratio will always exaggerate the size of the effect compared to a relative risk."[6] Consequently, we made our own calculations:

Among subjects who developed a UTI, Absolute Risk Reductions (ARRs) and Relative Risk Reductions (RRRs) were modest: ARR=0.066 at 7-10 days, and 0.078 at 20 days; 0.5<RRR<1. The Number Needed to Treat (NNT) was somewhat high at both 7-10 days and 20 days: NNT=15 at 7-10 days; NNT=13 at 20 days.

The most significant results were found in the outcome of asymptomatic bacteriuria. At 7-10 days post-surgery, the RRR was 0.69 and the ARR was 0.046, with an NNT of 22. The 20-day mark is where this intervention demonstrated the most benefit: RRR=0.838; ARR=0.8; NNT=12 (p=0.006).

In contrast, the outcome of cystitis (symptomatic) was equivocal. At the 7-10-day follow-up, 2.6% of the control group developed cystitis, in comparison to 0% of the experimental group (RRR=1).[1] However, at the 20-day follow-up, the incidence of cystitis was actually increased in the experimental group in comparison to the control group, albeit to a small degree (1.6% vs 0%, respectively).

The researchers' clinical question was answered through the study's final results. Although the results were not overwhelmingly positive, the researchers did show that *Rosa canina* was mildly effective at preventing UTIs in post-CS women.

Discussion

For the outcome of any UTI (asymptomatic or symptomatic), the absolute numbers

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in this study looked encouraging, as the development of a UTI was significantly lower among subjects taking *Rosa canina* compared to those taking placebo. However, the AARs are not staggering, and the RRRs are greater than 0.5 but less than 1. The NNT for both points in time is somewhat high; the NNT of 13 at 20 days is not quite low enough to warrant prophylactic treatment with *only* this intervention. The most promising results of the study were found in the outcome of asymptomatic bacteriuria, especially at the 20-day mark.

Since the subjects with asymptomatic bacteriuria received prophylactic antibiotic treatment, there was a reduction in symptomatic cystitis in both groups. The low incidence of symptomatic UTIs may have been one reason that *Rosa canina* didn't appear to be effective for symptomatic cystitis, even though it did appear to be relatively effective for asymptomatic bacteriuria. It is also likely that larger subject groups and a longer treatment time-frame may be necessary to detect any significant effects of this treatment on cystitis incidence.

Overall, this was a well-designed and thorough study. The randomization process was clearly stated ("block randomization with block sized 4 and 6 and allocation ratio of 1:1") and was performed by someone who was not involved in the sampling or data analysis.[1] It was also triple-blinded, involving blinding of clinicians, participants, and analysts. A thorough demographic survey was conducted at the start of the study, and no significant differences were observed between the 2 groups, aside from spouse education (p=0.006).

The most promising results of the study were found in the outcome of asymptomatic bacteriuria, especially at the 20-day mark.

There are 3 major limitations to this study. First, despite the authors explicitly stating they would perform an intention-to-treat analysis, they did not. During the course of the study, 8% of the intervention group and 5.5% of the control group had discontinued follow-up.[1] The statistical analysis only included the remaining subjects, raising the possibility of attrition bias. However, the attrition rate was slightly lower in the placebo group, and the satisfaction rate was nearly equal by the end of the study. This suggests that the cornstarch capsules were relatively effective as placebo. Second, as the researchers acknowledge in their paper, the trial period should have been closer to 40 days in order to more adequately represent the postpartum period (in which UTI risk is still relatively high). Third, the way in which patients were screened and treated for asymptomatic and symptomatic UTIs did not mirror clinical practice. During the course of the study, they screened subjects for the presence of pathogenic bacteriuria. Subjects with detected uropathogens were treated for 7 days with antibiotics (either cephalexin 500 mg or nitrofurantoin 100 mg). In clinical practice, patients would only be treated for a UTI if they presented with symptoms. This prophylactic treatment of asymptomatic subjects may have decreased the apparent effectiveness of *Rosa canina* in treating symptomatic cystitis.

Conclusions

Rosa canina fruit may help prevent UTIs in post-CS patients. While the Seifi et al study did show a statistically significant reduction in urethral bacteriuria in post-CS patients, its effectiveness in preventing cystitis in this population is unclear at best. Further studies should investigate the effectiveness of *Rosa canina* in preventing UTIs in postpartum women throughout the full postpartum period (that is, up to 40 days postpartum and/or post-CS) as well as in other high-risk populations, including patients with urinary catheterization and postmenopausal women. Additional research on other safe botanical medicines for post-CS and postpartum people is also warranted.

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Kris Somol, ND, has spent 20 years in the healing profession and 10 years as a public educator on botanical medicine. She has written articles for the *Seattle Times* and has been consulted for multiple online publications. She is a lecturer on women's health, pediatrics, and more. Dr Somol is an adjunct faculty member at Bastyr Center for Natural Health, where she sees patients in private practice. She received an ND degree from Bastyr University and a BA in Russian language and literature from Wesleyan University. She has served as secretary on the board of directors for the Washington Association of Naturopathic Physicians.

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Biopharma & Biomedicine

The Stacked Deck

DAVID J. SCHLEICH, PHD

The monolith that is the biomedicine industrial complex in America costs hit 18.2% in 2018, regardless of the irrefutable data about growing chronicity and the poor health of young people and boomers alike. (Statistics Portal, 2019) The European Union average is about half that. (Nuffield Trust, 2017) In fact, projected annual US per capita health-spending will reach almost $12K this year. (Kamal et al, 2018) This profitable US juggernaut shuffles with impunity through the retail corridors of the health industry in America, yanking from every shelf anything with a potential sustainable cash flow, and dismissing competing groups and ideas that get in its acquisitive way.

Despite Section 2706 in the post-ACA world, 2 biomedicine players – the AMA and the biopharmaceutical industry – have consistently challenged other professional groups and producers, even when they have something to contribute. The evidence of detraction about nutrition, smoking, spirituality in medicine, and even the energetics of homeopathy and Chinese medicine, are stacked on high over the decades, notwithstanding continuing growth in public use. (NCCIH, 2018) Yet, in recent years, allopathic medicine's newest acceptance of the dangers of inflammatory foods such as wheat, and the potential of mind-body medicine, long valued and protected in practice by the heterodox professions, are newly monetized and celebrated.

In the middle of such a turbulent, competitive health services marketplace, the educational leaders of non-MD professional bodies have been looking closely, yet again, at the stacked deck of biopharma and biomedicine. They are noticing (with more *realpolitik* in those same backpacks) the not so subtle migration of branding language from natural medicine into "integrative medicine." Integrative medicine, as a moniker, is less affronting than its predecessor, "complementary and alternative medicine." At least there is in the terminology a sense of things coming together. The sheer size and arrogance of mainstream biomedicine, however, continues to assimilate whatever it chooses, not apologizing or even acknowledging its earlier positions on, say, "food as medicine." I have characterized the dominant, orthodox profession more than once as "clever rascals."

This play for natural medicine principles and practice has already affected both camps, though. The professional agencies of non-MD professions are inclined not to rock the boat, wanting to build value propositions into interprofessional collegiality and stake a claim in the healthcare terrain. Those entering the medical professions are confused by the contrary imperatives of groups both claiming the high ground in mind-body medicine or food as medicine, for example. The "heterodox professions," as Hans Baer called them 2 decades ago (Baer, 2001), drift toward the more orthodox. On the one hand, research into natural medicine protocols, theories, therapeutic order, and clinical practice grows; however, on the other, the inclusion of pharmacy and the proliferation of testing constitute a worrying blend to many traditional naturopathic and natural medicine practitioners. For many biomedicine professionals, for example, "prevention" means more tests sooner, rather than powerful lifestyle choice changes which span a lifetime and affect everything from life/work balance to food choice. While the allopathic mainstream adds momentum to its assimilation of modalities and approaches to treatment long eschewed by their political and regulatory arms, and often in the name of "new" science, the healthcare landscape is the worse as a minefield of competition and confusion proliferates, especially for

For many biomedicine professionals, "prevention" means more tests sooner, rather than powerful lifestyle choice changes which span a lifetime and affect everything from life/work balance to food choice.

the consumer. The tension is palpable, especially in the southeast United States, where the data about health markers are grim. Other regions of the country progressively enhance choice as one way to slow down the juggernaut. As a case in point, within the last decade the following states have added naturopathic medicine to the available choices of citizens: Minnesota, Colorado, North Dakota, Maryland, Massachusetts, Rhode Island, and Pennsylvania. Legislation is pending in North Carolina and New York, and is planned in 13 more states from one coast to the other.

The Essence of the Mater

Just what is the *essence* of this sharpening tension, then, characterized as it is by sorties into areas of nutrition and mind-body medicine long studied and successfully practiced by what have long been considered heterodox groups? How is it that the non-material elements in health outcomes are now more acceptable to the reductionist medical paradigm? It's all in the evidence, not just the cost.

Perhaps a helpful descriptor in our deliberations about this process of assimilation is the word "quintessence," rather than essence. The former word comes from the Latin words *quinta* and *essential*, meaning: *5 elements*. When ancient Greek philosophers were contemplating what the universe was made of, they settled on 4: *earth*, *air*, *fire*, and *water*. Later physicists and mathematicians added a fifth, less familiar essence, or element – *dark matter*. However, even they, buoyed by the tools of science (as the heterodox professions have also been doing robustly and more often in the last 2 decades), are still not sure, for example, what dark energy and dark matter are ultimately all about, or exactly how to quantify the biopsychosocial factors that convert thought and emotion to physical response and health outcomes. Even so, Einstein and others, such as Vesto Slipher and Edwin Hubble, worked up their formulae into which they injected, as needed, something called the "cosmological constant" – which has proven to be anything but constant. Einstein was the first to use the Greek symbol, lambda (λ), to account for it in his calculations. He knew, and investigators ever since have known, that the value of lambda keeps shifting. Naturopathic doctors, as a profession, have long welcomed λ and all it implies. This development in the therapeutic order is promising.

Five Elements of Naturopathic Medical Curricula

Important in the realpolitik of what is happening in health care worldwide, however, and to which naturopathic and other heterodox medical educators are paying increasing heed, are the rapidity, volume, and persistence of scientific innovation, patient centricity, evidence, big data, and emerging technology. However, before we drill more deeply into the detail of these variables, let us review what we've been working with all these years as we have shaped and delivered naturopathic medical education in that testy terrain.

Four key elements of accredited naturopathic medical curricula around North America are well known:

- *traditional theoretical content* (our roots, reflected broadly in the writings of the early naturopathic profession)
- *emerging content* incrementally built over time and nourished by advancing clinical practice (which in turn finds its way into our classrooms via teachers and texts), naturopathic medical research (which translates into new approaches, modalities, tools, and techniques communicated by studies, seminars, lectures, CEUs, and the like)
- *required competencies* reflecting the politics and requirements of professional practice, public policy, and regulatory frameworks
- *flexibility and affordability of delivery*

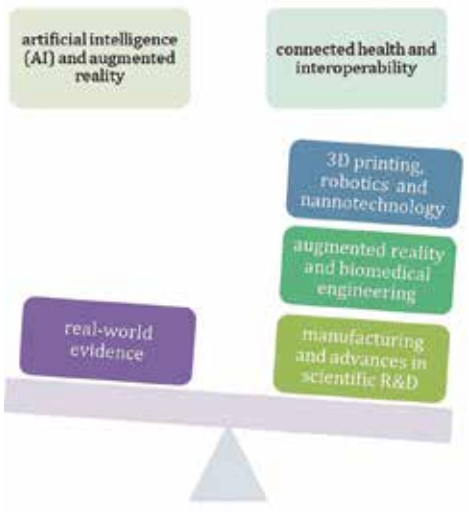
The Fifth Element

A fifth element of sociopolitical pressure also has to be adjusted every once in a while to keep pace with the constant change in the direction, shape, and size of the curriculum universe. This, in turn, affects and contains the profession by virtue of producing graduates whose skills have to translate into effective practice. For example, naturopathic physicians are primary care professionals in a number of states. That recently earned status brings with it accountabilities and new tools. That fifth element, in curriculum design terms, can be understood from another perspective, rather than by mere content and skill development reaction to legislative and public policy changes.

Donald Schon's landmark work, *The Reflective Practitioner* (Schon, 1987) is particularly useful in navigating those intersecting waves of regulation, tradition, and competition which hit the beachheads of the heterodox professions in different jurisdictions at different times. Collectively, these elements and Schon's version of a "lambda" help describe naturopathic medical education as it manifests in our degree programs. In this regard, Schon's work verifies that the tiers of professional curriculum *repeat* in all professions, ours included: basic sciences, applied sciences, and a practicum (Figure 1). Schon insists that no profession evolves in civil society without navigating these phases. The great challenge in all of this is that the form and content elements of the curriculum itself vary not only over time, but also from venue to venue in concert with the accreditation standards of the particular professions accreditor.

Figure 1. **The 5 Formative Elements of Naturopathic Medical Curriculum**

Figure 2. **Factors Affecting the Future of Medicine in America**



Schon contended that the phases of professional education repeat across an entire spectrum of occupations. In addition to pointing out the inevitable pressure of science in all professional preparation, Schon explains that the basic and the applied versions of the scientific content of curriculum occur in that order, followed by actual hands-on experience. Part of the context and background of the development of the curriculum of the naturopathic profession has been a sometimes divisive and always challenging debate about the "yearning" which many of the heterodox professions experience in their professional schools, namely, a "yearning for the rigor of science-based knowledge and the power of science-based technique" (Schon, 1987, p.9). Making the process even more unstable, as pointed out by Susan Lieff (2009), is that "the time lag between needs assessment and implementation of faculty development curricula assumes a certain stability of participants' individual and contextual needs that may not reflect the often complex and shifting priorities in health professional schools."

As Schon contended later (1995), "the greater one's proximity to basic science, the higher one's academic status." Professional schools of medicine, in this regard, could easily set out to train healers and socialize them into a profession, but end up with biotechnical problem-solvers and not healers/physicians at all, with their art and science in hand. Routinely, the schools of medicine followed a sequence that immersed the student in basic and applied medical sciences and then in supervised clinical practice, all the while proclaiming "evidence-base." This fascinating polarity has hugely influenced the development of naturopathic medical education in North America too.

The hegemony of Western medicine, Schon would maintain, has been sustained for a long time in this form, without overt coercion, via regulatory frameworks with vested interests and the accompanying power relationships. Ideas about "power and resistance" and what Schon describes as "zones of indeterminacy in practice that call for artistry but are bound by institutional commitments" (1987, p.115), may account for some of the eventual divergence from original curriculum intentions at our schools. In any case, it seems the "outline of professional preparation" (Schon, 1995) was as much the form of "requirements" for the naturopathic students at CNME-accredited schools as for any allopathic medical student. In the end, naturopathic doctors have to go through "board exams" which are far away from clinical ecology and closer and closer to applied biological science. Ours is a stretchy universe of expanding curriculum. Lots of dark matter and dark energy out there.

Joining the Higher-Ed Mainstream

Hanna (2000) gives us an insight into the other variables that have been influencing our participation in the mainstream. He writes, "The university will be less inclined to base important decisions about programs and priorities strictly upon considerations of content and program quality" (Hanna, p.93) and more upon "what students, the adult marketplace and the university's publics generally say they want from their university." Earlier, Hanna set out what those new models would look like, basing them on analysis of trends observed in emerging organizational practice (Hanna, 2000, p.94):

- extended traditional universities
- for-profit, adult-centered universities
- distance education/technology-based universities
- corporate universities
- university/industry strategic alliances
- degree/certification competency-based universities
- global multinational universities

Hanna's discussion of "extended traditional universities" builds on the work of Berquist (1992) and pretty much reinforces a notion that has evolved in our time, which is this: a time of transformation when the "traditional, content-based organization and decision-making within the university" (Hanna, p.99) will have to respond to a competitive higher-education environment – one in which our naturopathic colleges and naturopathic programs in small, comprehensive universities will also have to thrive, especially in view of emergent pressures such as AI, robotics, and "connected health."

Among other powerful and interprofessional meta-themes in the normative medical curriculum is the study of what the goal of professional preparation for medical practitioners is. We accept that the medical profession's purposes are as economically motivated as health-oriented; nevertheless, the very question of *what health is* arises when public policy permits disproportionately commodified systems as have evolved in North America. The nature of the US mainstream medical system presents with serious academic, economic, philosophical, and clinical questions, affecting naturopathic medical education structures at CNME-accredited schools and related medical curricula in the allied professions. Because of its curriculum content and design history, naturopathic medicine is uniquely positioned to cope with the wide array of factors rapidly reshaping the monolith referenced earlier (Figure 2).

Ours is a stretchy universe of expanding curriculum. Lots of dark matter and dark energy out there.

Reflection in Action

Appropriately, then, Schon's notion of "reflection-in-action" is very useful to get at what our education leaders are constantly forming in classroom and clinical curricula. As Schon states (1987), it is very difficult to separate identity from professional role. Naturopathic medical education is inevitably aligned with scientific professionalism and responds increasingly to this taxonomy of factors. Biomedicine and biopharma's stacked deck has been a "guild-like" monolith in health design and delivery, but with diminishing credibility as efforts continue to co-opt holism and "natural" health systems and treatment. This pattern can be seen in the history of allopathic medicine and related industries since the time of Flexner (1910). Schon reminds us that "the relative status of the various professions is largely correlated with the extent to which they are able to present themselves as rigorous practitioners of a science-based, professional knowledge and to embody in their schools a version of the normative professional curriculum" (1987, p.9).

Krause's contentions (1999) add some light to this multi-faceted conversation. His ideas help us to see that as naturopathic medicine continues to achieve social closure, as a profession its confrontation of that "guild power" could inexorably apply as much to the naturopathic profession as to any other group which strives to create institutions around its work. Power comes, Krause says, through dimensions of power over association, workplace, and market. Added to these is power over the relation to the state. The naturopathic profession increasingly fits into this political and social process quite handily. The fifth element keeps popping up no matter what we do.

We may yet have to dust off Schon's "lambda" more than once in order to avoid the damage this accumulating muddle can cause to our roots and traditions. In the era of evidence-based medicine, the uncertainty about whether the 5 elements of curriculum are producing amazing naturopathic doctors rather than a subspecialty of holistic physicians is no small question. Even so, the game persists, and as we face the stacked deck of those who control the main turnstiles and cash flow of health care, the quintessential nature of naturopathic medicine may yet be figured out.

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Early Peri-Menopause

A Non-HRT, Alternative Approach

Dr. Christine Chen, ND, MSc, RPh

When a middle-aged woman visits your office with unexplained weight gain, sleep disturbances, fatigue, palpitations, shortened menstrual cycle lengths, new heavy/longer menstrual flow, premenstrual syndrome (sore and swollen/lumpy breasts, night sweats, mood swings), and worsened migraine/headaches, what's the first thing that comes to your mind?

While hypothyroidism and clinical depression need to be ruled in/out, "perimenopause" is the most likely cause of all the above-mentioned symptoms.

Perimenopause describes the period of time before and after the final menstrual period (FMP). It is the transition from reproductive years to the early post-menopause and could last between 6-10 years (Table 1).

Vasomotor symptoms (VMS) (ie. hot flash and night sweats) are not common in the early stage of perimenopause (Table 1) due to the still elevated levels of estrogen, and if present, are often fairly mild and occur in a cyclic, regular fashion right before each period (ie. when estrogen levels are relatively low).

Not all women experience the same perimenopausal symptoms, but most symptoms are the result of drastic changes in estrogen-progesterone ratios. In the early stage of perimenopause (Table 1), estrogen levels are usually elevated while the progesterone (P4) levels are lowered due to the declining function of the corpus luteum. Patients with low progesterone may have periods as early as 3-4 days after ovulation.

Many patients may also experience a phenomenon called "luteal-out-of-phase" (LOOP). LOOP is when an estrogen spike happens either in the follicular phase triggering early ovulation (ie. shortened cycle of <21days) or in the luteal phase triggering another ovulatory episode consequently prolonging the luteal phase (ie. lengthened cycle of >40 days).

A Non-HRT Approach to the Early Stages of Perimenopause

The treatment approach to the early stages of perimenopause should include promoting progesterone secretion, lowering estrogen levels, and facilitating the metabolism of toxic catechol estrogens (4-OH and 16-OH) to the protective form (2-OH). Collectively, we can help to not only ease the perimenopause symptoms, but also reduce the risk of complications from high estrogen levels, such as fibroids, breast cancer, and endometrial cancer.

While bioidentical progesterone (P4) is widely used as the firstline treatment for perimenopause, it is not always the best approach in the early stage when the corpus luteum is still capable of maintaining adequate levels of progesterone. Rather, we should consider natural means to promote endogenous progesterone secretion and reduce elevated estrogen levels to bring balance to the estrogen-progesterone ratio.

Both the metabolism and detoxification of estrogen need to be facilitated for the entire menstrual cycle to reduce the overall estrogen dominance. Utilizing compounds such as diindolylmethane (DIM) and indole-3-carbinol (I3C) could help promote estrogen metabolism to the protective2-a-OH-estrogens while reducing the 16-a-OH (highly estrogenic) forms. DIM is the bioactive form of I3C. While I3C is converted to DIM in contact with stomach acid, the conversion rate is only about 60%. In addition, d-glucarate has been shown to promote the excretion process of estrogenic metabolites by inhibiting beta-glucuronidase – a bacterial enzyme that recycles toxins and hormone metabolites back into the blood stream.

Supplementing high-dose Vitex (4-6g dried herb per day) in the luteal phase of early perimenopause can help increase the progesterone (P4) levels via its action on the hypothalamus-pituitary-ovary(HPO)-axis. Combined with DIM, Vitex can help re-balance the estrogen-progesterone ratios and in turn reduce the flow as well as restore regular and normal-length cycles.

Sex Hormones, The Adrenals, and Thyroid

The body's endocrine systems work in a complicated and interconnected fashion. The drastic changes in P4 and estrogen levels in early perimenopause, therefore, can put burdens on other endocrine systems like the Hypothalamus-Pituitary-Adrenals(HPA)-axis and thyroid.

HPA-Axis support is important because 1) elevated estrogen levels during perimenopause stimulate stress hormones and neurotransmitters like cortisol, ACTH, and norepinephrine – amplifying hormonal responses to stress, and further aggravating the severity of VMS, and 2) the adrenal glands take over as the main source of sex hormones after menopause.

The decline of P4 levels in early perimenopause, on the other hand, would result in increases in thyroid-binding globulins and in turn decreases in thyroid hormone activity.

Adaptogenic herbs, such as cordyceps, ashwagandha, rhodiola, and eleuthero, can be implemented to not only stabilize the amplitude of cortisol fluctuations improving energy and sleep, but also support thyroid function and the body' metabolic rate.

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A non-HRT approach to early peri-menopause is a worthy first-line treatment considering the body is still capable of producing estrogens and P4, and a little assistance in bringing everything into balance might be all that's needed to facilitate a smooth transition to later stages of peri-menopause.

Table 1. Proposed stages from reproductive years to post-menopause: clinical and hormonal characteristics

	Reproductive			Menopausal Transition		Post Menopause		
			Early Perimenopause		Late Perimenopause			
	Early	Peak	Late	Early	Late	Early		Late
Duration	Variable			variable	1-3 years	2 years (1+1)	3-6 years	remaining lifespan
PRINCIPLE CRITERIA								
Menstrual Cycles (MC)	Variable to regular	Regular	Regular	Subtle changes in flow and/or length	Variable lengths persistently >=7 day difference from reproductive years	Interval of amenorrhea of >=60days		
Flow	Variable	Variable	Variable	Increased or the same	Increased	Increased or less, often alternating		
MC-related symptoms				↑PMS	↑↑PMS, intermittent dysmenorrhea	↓PMS, but erratic menstrual cramps		
Vasomotor Symptoms					Unlikely. If present, mild & cyclic	Still cyclic, less predictable, onset in daytime	Erratic & ↑intensity	
Hormonal				Variable FSH, ↑E2, normal LH, ↓P4	↑FSH, ↑↑E2, ↓↓P4	↓ alternating with ↑E2, ↑FSH, ↓↓P4	↓E2, ↓↓P4, ↑FSH	↓↓E2, ↓↓P4, FSH stabilizes

↑elevated; ↑↑very high; ↓low; ↓↓very low
E2 - estradiol; P4 - progesteroe; FSH - follicular stimulating hormone; LH - luteinizing hormone

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