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Vitamin D - A Prohormone Essential to Female and Reproductive Health

Vitamin D deficiency is a global health problem that uniquely impacts women and female health. This essential prohormone has in recent studies been shown to be uniquely beneficial in multiple areas of female health and reproductive function.

Vitamin D an Important Prohormone

Vitamin D deficiency has been described as a global health problem with nearly one-billion people living with abnormally low levels of this vitamin - a critical component of human health and wellbeing.

Vitamin D is commonly referred to as "the sunshine vitamin." But less commonly known is the unique nature of this vitamin in the sense that it is actually a fat-soluble prohormone produced by the body in response to sunlight. A prohormone is a substance the body converts into an active hormone, which then acts as a messenger to uniquely stimulate target tissues and cells within the body calling them to a certain, predetermined and functional action.

Vitamin D is well known for its critical role in healthy bone growth and development. However, receptor sites specific and responsive to the hormonal effects of vitamin D are present in numerous tissues and cells throughout the body extending the benefits of vitamin D beyond mere bone health. In fact, the prohormonal effects of vitamin D have been clearly shown to play an important role in multiple aspects of human health and disease progression.

For example, Vitamin D deficiency has been linked to numerous illnesses including:

- Dental disease
- Muscle weakness
- Autoimmune issues
- Infections
- Cardiovascular disease

- Cancer
- Diabetes
- Neurologic dysfunction
- Physical ailments
- Mood disorders

25-hydroxyvitamin D (25(OH)D) is the major circulating form of vitamin D in the body and the most widely used indicator to evaluate a person's dietary exposure and endogenous production. Serum concentrations of 25(OH)D can be measured to determine a person's vitamin D status.

There is currently no consensus on optimal vitamin D levels, but a level less than 20 ng/mL is generally regarded as vitamin D deficiency. A 25(OH)D level between 20 to 30 ng/mL is classified as vitamin D insufficiency.

Levels less than 20 ng/mL should be avoided due to a higher rate of parathyroid hormone production, which triggers the elimination of calcium from bone resulting in bone loss and higher fracture risks.

Vitamin D Uniquely Impacts Female Health

Vitamin D deficiency is an important - and unfortunately often overlooked - female health issue with a significant number of women deficient in vitamin D.

It has been estimated that an astounding 45% to 90% of all reproductive age women are deficient in vitamin D.

Vitamin D is critical to female health as receptors for this prohormone are present in large numbers throughout the entire female body playing an important role in healthy ovarian, endometrial, and placental function.

Examples in the medical literature illustrating the impact of vitamin D on female health include the following:

- Vitamin D deficiency has been associated with pre-eclampsia in pregnancy - a complicated and dangerous disease associated with underlying placental dysfunction and elevated blood pressures, which can have a significant and detrimental impact on the health of the mother and her baby.

- Evidence suggests vitamin D plays an important role in the maintenance of a healthy pregnancy by supporting fetal calcium levels and promoting normal birth weight.

- Vitamin D supplementation has been shown to reduce prostaglandin production within the endometrial tissues exerting an anti-inflammatory effect resulting in a decrease in cyclical pelvic pain.

- Recent studies have shown that Vitamin D deficiency may play a role in the development of uterine fibroids - a common, and often benign, tumor impacting a large number of women. Uterine fibroids are a major gynecologic issue as related symptoms, such as heavy menstrual bleeding, are a major reason for women to undergo a hysterectomy (surgical removal of the uterus) in the United States. Highlighting the impact of vitamin D on uterine fibroid tumors, a recent 2021 study by Suneja et al. concluded that vitamin D supplementation resulted in a significant reduction in the symptoms related to uterine fibroids. The authors of the study revealed a remarkable 30% reduction in menstrual blood loss; an approximately 44% decrease in cyclical pelvic pain; a 35% reduction in general pelvic pain, and a 50% reduction in backaches in women supported with vitamin D supplementation. In addition, the authors revealed a 6% reduction in uterine volume and a 11% decrease in fibroid size. For this study, vitamin D deficient women were provided 60,000 international units (IU) of vitamin D3 weekly for 8 weeks followed by 60,000 IU every 2 weeks for an additional 8 weeks.

- Studies have shown an association between vitamin D deficiency and breast cancer, the most common malignancy impacting women in the United States. And several studies have shown the benefits of vitamin D supplementation and breast cancer risk reduction. In one such study, published by McDonnell et al. in 2018, women with a vitamin D level at or above 60 ng/mL had a 82% lower risk of breast cancer when compared to those with vitamin D levels below 20 ng/mL. Specifically, the authors concluded higher 25(OH)D levels were associated with a dose-response decrease in breast cancer risk with levels greater than 60 ng/mL being identified as the most protective.

Vitamin D Deficiency and Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is the most frequent - and one of the most well known - endocrine disorders impacting nearly 10-15% of reproductive age women.

PCOS is a disorder that affects multiple systems and is characterized by ovulatory dysfunction, hormonal abnormalities, and a unique polycystic ovarian morphology of the ovaries.

Secondary to the impact PCOS has on healthy ovulation - nearly 25% of women with PCOS fail ovulation medications resulting in multiple treatment rounds in couples experiencing infertility and desiring pregnancy.

PCOS is also related to a broad constellation of gynecologic, reproductive, and health-related issues including - ovulatory abnormalities; irregular cycle lengths; abnormal bleeding patterns; endometrial hyperplasia and cancer; infertility; miscarriage; endometriosis; premenstrual tension syndrome; acne; abnormal hair growth; insulin resistance; glucose abnormalities; diabetes; obesity; and androgenic hormone dysfunction.

In addition, it is well documented that PCOS and vitamin D deficiency have multiple overlapping metabolic similarities including obesity and insulin resistance; and approximately 44% of women with PCOS have vitamin D deficiency.

In my reproductive medicine practice, it is quite common to encounter women with PCOS who have not been thoroughly evaluated or potentially treated for vitamin D deficiency, echoing the need for more education regarding this issue in women experiencing the negative fertility impacts associated with PCOS.

Vitamin D, PCOS and Reproductive Health

There has been a growing body of medical literature showing the importance of the prohormone vitamin D in human reproduction and the maintenance of health fertility in women with PCOS.

First, it is important to appreciate that vitamin D deficiency has a uniquely negative impact on women with PCOS. For example, recent studies have shown vitamin D deficiency in women with PCOS " . . . is related to menstrual irregularity, altered follicular development, ovulatory dysfunction, metabolic alterations, and decreased pregnancy rate." [7]

Each one of these negative factors are directly-related to the fertility and reproductive issues women with PCOS face at a significantly higher rate than women with normal fertility. Accordingly, it would make sense then that adequate correction of vitamin D in women with PCOS could result in improvement in these issues and promote healthy fertility.

Recent studies have certainly been encouraging and bolster the positive benefits of vitamin D support in women with PCOS, while also continuing to add to our understanding of the potential negative effects vitamin D deficiency may have on PCOS.

For example, in a 2017 study performed by Fang et al. the authors revealed that Vitamin D supplementation in women with PCOS significantly improved ovarian function via follicular development and a higher number of dominant follicles. In addition, when vitamin D support was combined with metformin - a prescription medication that decreases blood glucose levels - the regularity of menstrual cycles were improved.

Butts et al. revealed in a 2018 article that women with PCOS and vitamin D deficiency had lower ovulation rates, pregnancy rates, and a 40% lower chance of live birth than those who were not deficient. Importantly, the study found an association between vitamin D deficiency and miscarriage. The study specifically found that women with vitamin D deficiency were 60% more likely to experience a pregnancy loss than subjects with normal vitamin D levels. The impact of vitamin D deficiency on miscarriage rates was attributed to all women regardless of infertility or PCOS diagnosis - indicating the potential importance of healthy vitamin D levels in the support and maintenance of early pregnancy.

In addition, vitamin D deficiency in women with PCOS can negatively affect markers of ovarian reserve such as Anti-Mullerian Hormone (AMH) levels. AMH is a protein that is produced by the cells surrounding the ovarian follicles. This follicle-specific protein is secreted in the blood and can be directly measured as a way of monitoring ovarian reserve. Researchers have shown that the gene responsible for AMH expression is responsive to vitamin D, and AMH levels are directly correlated to 25(OH)D levels. In women with PCOS, vitamin D supplementation has been shown to normalize AMH levels resulting in improved follicle formation, positively impacting ovulation, and correcting a key abnormality of PCOS-related fertility issues.

True Health Matters Summary

Vitamin D deficiency is a global health problem that uniquely impacts female health, and should be assessed in all women due to its myriad of health benefits. In addition, emerging data reveals the impact vitamin D has on multiple reproductive issues including improving ovarian follicular growth, the formation of a dominant follicle, and menstrual cycle regularity in women with PCOS; assisting in normalization of AMH levels related to ovarian reserve; and potentially decreasing early pregnancy loss.

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