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Hypovitaminosis D and high serum TGFβ3, important biomarkers for uterine fibroids risk

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Uterine fibroids (UFs, AKA: leiomyoma) are the most common benign tumor in the uterus that affect more than 80% of women by age 50. UFs usually cause several symptoms including heavy menstrual bleeding, pelvic pain, subfertility, recurrent pregnancy loss, preterm birth, and other pregnancy-related complications. At present, hysterectomy is the mainstay treatment option for UFs which leading to a huge economic burden in the Unites States and worldwide. The estimated annual cost for treatment of UFs in the United States is approximately $34 billion (1).

Due to high prevalence, negative health impact, and enormous economic burden, primary preventive strategies as well as novel treatment options for UFs are urgently needed particularly in younger women who want to preserve their fertility. Although, several alternative therapeutic options such as myomectomy, uterine artery embolization, GnRH analogs and selective progesterone receptor modulators are becoming increasingly available, these methods have some limitations such as serious side effects, high expense, also some might be incompatible with future pregnancy. Thus, an ideal therapeutic option for prevention and treatment of women with symptomatic UFs should be one have low risk, cost effective, high efficacy, would not preclude future fertility and safe for long-term use.

Race also plays an important roles in UFs risk. African American women have three-four times higher incidence of UFs, higher surgery at younger age, multiple larger fibroids, as well as severer complications than Caucasian women (2). The etiology of this racial/ethnic

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disparity is still not fully understood. In 2010, Halder et al. reported at SGI/SRI meeting for the first time that vitamin D deficiency is a novel risk factor for UFs in a cohort of African American and Caucasian women from southern US states (2, 3). Their observation was subsequently confirmed independently in two distinct populations from central Europe and eastern USA (2). Vitamin D deficiency is present in almost all races, however particularly prevalent in African Americans have likely due to their darker skin pigmentation (2). Thus, this important observation can at least provide partial explanation for that high ethnic disparity of UFs in women of color. Vitamin D play roles as an anti-proliferative and anti-inflammatory agent, and it is present in oily fish, cod liver oil, and many dairy products, while the main source of vitamin D is sun exposure. Serum levels of vitamin D (25-hydroxyvitamin D3) is the major circulating form of vitamin D which is an index of vitamin D status in human body. The normal levels of circulating 25-hydroxyvitamin D3 [25(OH) D3] is 30–80 ng/ml (2). Vitamin D deficiency can be defined when serum levels of 25(OH)D3 falls below 20 ng/ml, and insufficiency at levels between 20-30 ng/ml. However, 25(OH)D3 is biologically inactive and require to be activated by hydroxylation in the kidney, and likely other organs as well, by the enzyme 1α-hydroxylase the biologically active 1α, 25-dihydroxyvitamin D3 (1α, $25(OH)_2D3$) which can binds and signal through its vitamin D receptor (VDR). Vitamin D can modulate gene expression in a tissue-specific manner that can lead to inhibition of cellular proliferation, differentiation, and apoptosis, among a plethora of other cellular effects (2).

Recently, numerous studies have evaluated the effect of vitamin D3 on uterine fibroid cells, and showed that vitamin D3 inhibits cell proliferation through various mechanisms including inhibition of PCNA, Cyclin D1, Cdk1, Bcl2, and suppression of COMT activity in human fibroid cells (2). Elevated expression of estrogen and progesterone receptors (ER-α, PR-A, and PR-B) was also confirmed in human UFs, and treatment with vitamin D3 inhibited those receptors in human uterine fibroid cells. It has also been established that administration of vitamin D3 or paricalcitol, a potent VDR activator, effectively inhibits human uterine fibroid cell proliferation *in vitro* and shrinks fibroid tumor lesions in well-established preclinical animal models (2). Thus based on available published literature, it is evident that vitamin D and other VDR agonists might be potent anti-tumor/anti-inflammatory agents that can be considered as non-surgical orally-administered therapeutic options for the effective, safe and long-term medical treatment and/or prevention of UFs. However, well-designed human therapeutic and preventative clinical trials are yet to confirm the utility of vitamin D in patients with symptomatic uterine fibroids.

The transforming growth factor beta (TGFβ) is known as multifunctional cytokines that has three isoforms such as 1, 2, and 3. TGFβs play key role in the regulation of cell growth and proliferation, differentiation, as well as tissue remodeling. These processes can play role in the development of tissue fibrosis. UFs is characterized by excessive production and deposition of extracellular matrix (ECM). It has been well-established that the level of TGFβ3 is elevated three to five times in human UFs as compared with adjacent normal myometrium (2). Moreover, elevated levels of TGFβRII were also observed in UFs as compared with adjacent normal myometrium. TGFβ3 isoform plays pivotal role in the synthesis of many of the ECM proteins that are associated with tissue fibrosis. TGFβ3 stimulates the synthesis of collagen type 1, fibronectin as well as ECM associated

proteoglycans, while treatment with vitamin D3 reduces these ECM associated collagen type 1, fibronectin, as well as plasminogen activator inhibitor-1 (PAI-1), which are well-known TGFβ-regulated genes. Study also suggested that administration of vitamin D3 potentially reduced TGFβ3-induced Smad activation as well as reduction of TGFβ3-dependent key profibrotic factors in human uterine fibroid cells (4). Interesting, in their manuscript in this issue of *Fertility and Sterility*, Ciebiera et al. demonstrate that higher BMI, family history, lower serum vitamin D and higher concentrations of serum TGFβ3 as significant risk factors for UFs in an independent cohort from Poland (5). The manuscript is impactful since the authors included detailed epidemiological data to establish the risks of development of human UFs, and emphasize the role of vitamin D deficiency and increased TGFβ3 serum concentrations as established risk factors and viable biomarkers for UFs. In that article, the authors presented data from a total of 188 Caucasian subjects, of which 105 were fibroid subjects and 83 were normal subjects who have no pathological evidence of UFs (5). The significant association between lower serum levels of vitamin D and UFs occurrence in an independent unique cohort from Eastern Europe suggest that such an association is a global phenomenon. Additionally, the higher serum concentrations of TGFβ3 is interesting as it is consistent of the well-established local effects TGFβ3 in uterine fibroid tissues. Previous studies have established elevated levels of TGFβ3 mRNA in UFs than adjacent normal myometrium, and in this manuscript, authors report increased serum concentrations of TGFβ3 in UFs patients suggest that this cytokine affect fibroid development in an autocrine, paracrine as well as endocrine manner. However, a direct causality between vitamin D deficiency and increased serum concentrations of TGFβ3 is not yet established. As the authors mentioned that TGFβ3 is a non-specific marker, and thus it is imperative to establish the serum concentration of TGFβ3 in a larger population to establish this statement. These novel biomarkers for UFs risk conceivably revive the concept of UFs prevention in high risk population. Combining these easily measurable serum biomarkers with other anthropometric (high BMI), strong family history and racial tendencies (African ancestry) constitute a reliable screening tools to identify women at higher risk for future development of symptomatic UFs. In turn these pre-symptomatic women can potentially be offered preventative measures such as regular imaging evaluation, correction of vitamin D deficiency as well as other preventative measures (2). While novel therapeutic products are being developed for oral and localized UFs treatment which will no doubt provide useful tools in the armament against this major clinical challenge, we believe that such highly prevalent disease with clear easily detected risk factors is a ripe candidate for an ambitious cost-effective prevention strategy.

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