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Research Protocol

A New Approach to the Conservative Treatment of Endometrial Hyperplasia without Atypia

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Introduction

Endometrial hyperplasia (EH) is defined as an irregular proliferation of the endometrial glands with an increase in the gland to stroma ratio when compared with proliferative endometrium. The revised 2014 World Health Organization (WHO) classification is recommended. This separates endometrial hyperplasia into two groups based upon the presence of cytological atypia: i.e. (i) hyperplasia without atypia and (ii) atypical hyperplasia [1,2].

EH develops when estrogen, unopposed by progesterone, stimulates endometrial cell growth by binding to estrogen receptors in the nuclei of endometrial cells [1].

Endometrial hyperplasia is a precursor for developing endometrial cancer. The incidence of EH is estimated to be at least three times higher than endometrial cancer and if left untreated it can progress to endometrial cancer [3]. Although the risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years, 20% of cases of endometrial hyperplasia without atypia are progressed as atypical endometrial hyperplasia and more than > 25% of cases of atypical EH are progressed as endometrial cancer, which is the most common gynecological malignancy in the Western world [1].

Endometrial hyperplasia is associated with multiple identifiable risk-factors and assessment should aim to identify and monitor these factors. Known risk-factors for endometrial hyperplasia reflect this etiology: increased Body Mass Index (BMI), anovulation, perimenopause, PCOS, estrogen-secreting ovarian tumors and drug-induced endometrial stimulation [1]. Its also important that inflammation may work in conduction with or in addition to estrogen exposure in the development of endometrial hyperplasia. And while estrogenic stimulation of the endometrium is believed to be the main etiological risk-factor for developing this condition, other elements, such as immunosuppression and infection may also be involved [3].

The most common presentation of endometrial hyperplasia is abnormal uterine bleeding. This includes: heavy menstrual bleeding, intermenstrual bleeding, unscheduled bleeding on HRT and postmenopausal bleeding [1].

Diagnosis of endometrial hyperplasia requires histological examination of the endometrial tissue. Endometrial surveillance should include endometrial sampling by outpatient endometrial biopsy. Diagnostic hysteroscopy should be considered where outpatient sampling fails or is nondiagnostic. Transvaginal ultrasound may have a role in diagnosing endometrial hyperplasia in pre- and postmenopausal women [2,4].

Most current guidelines recommend hormone therapies for treatment of endometrial hyperplasia, which includes the use of local (LNG-IUS) and oral progestogens, GnRH or its analogues or their combination and surgical treatment - when traditionally hysterectomy is performed. The selection criteria for treatment options are based on patient age, health, the presence of cytological atypia and fertility status [1,5].

Objective of the Study

The endometrium has a balanced cytokine system with numerous correlations at the proliferative and secretary stages of the menstrual cycle. Inflammation is one of the important factor in the most hyperplasia conditions. Cell type specific up-regulation of pro-inflammatory genes and down-regulation of anti-inflammatory genes is a hallmark of the onset of an inflammatory reaction.

Recent studies are focused on the effect of anti-estrogens, aromatase inhibitors and different kind of pro-and anti-inflammatory cytokines to the pathogenesis of endometrial hyperplasia.

That's why, our attention was drawn to frequency of 25(OH) vitamin D deficiency with patients and anti-inflammatory and anti-peroxidation effects of above cited vitamin, which affects and reduces to the production of pro-inflammatory cytokines, suppresses of prostaglandin action, inhibits of P38 stress kinase and NF-kB signaling, decreases the expression of aromatase and impacts by the optimizing metabolic status [6-8].

These factors were taken into consideration and we aimed to study the impact of vitamin D3 supplements in clinical outcomes to the women with diagnosed endometrial hyperplasia.

Methods

For our randomized, placebo-controlled study we have selected total 32 patients (25.9 +/- 10.1 years of age) with diagnosed endometrial hyperplasia without atypia, whose serum 25(OH)D_3 levels varied from 20.1 +/- 10.1 ng/ml. BMI was ranged between (30.1 +/-10.5 kg/M^2).

We were diagnosing endometrial hyperplasia by TVS control by using GE Voluson E8, which was later confirmed with the result of endometrial Pipelle biopsy.

After the end of treatment we made again TVS to evaluate the results.

The research was conducted in the late proliferative phase of the menstrual cycle at the both stages.

We were determining the level of 25(OH)D_3 vitamin in the blood serum before and after the end of treatment.

The randomization of patients conducted randomly by two groups: study group (n = 17), in which patients were given 50.000 IU dose of vitamin D3 weekly during 16 week and placebo group (n = 15).

Among the study groups there was no difference between age, BMI and between the quantity of pregnancy and childbirth.

Results

After 16 weeks, unlike a placebo group, the study group patients had increased serum 25(OH) vitamin D levels (+11.0 ± 10.6 vs. +1.9 ± 8.1 ng/mL, $P < 0.001$). Herewith, in 14 (82%) patients of research group had reduced thickness of endometrium (-3.0 ± 1.5 mm. $P < 0.001$), in 3 (18%) patients the indicator of previous treatment was maintained unlike the placebo group, where in 11 (73%) patients had the increase of thickness of endometrium (+2.0 ± 1,5 mm. $P < 0.001$) and it became necessary to do repetitive biopsy and then other types of intervention, in accordance with the results. The results in 4 (27%) patients were not changed.

Conclusion

Use of the supplements of vitamin D3 had the positive effects in women diagnosed with EH and vitamin D3 deficiency. Due to the results of the study, we are able to say that vitamin D3 may plays a role in decreasing the complications associated with endometrial hyperplasia.

In addition, we could conclude that a new approach of using vitamin D_3 requires further observations and clinical researches, what may change the policy of the treatment of EH.

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