STUDY OUTLINE

TITLE: Evaluation of Vitamin D With And Without Hormonal Contraception on Sexual Function in Women With Polycystic Ovary Syndrome

INVESTIGATORS: Steven R. Lindheim, MD, MMM; Lisa Kellar, MD; Logan Havermann, Michelle Durrant, MD; Rose Maxwell, PhD

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SUMMARY:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among reproductive age women with a prevalence as high as 15%. The clinical symptoms of PCOS including menstrual dysfunction, infertility, hirsutism, alopecia, acne, and the possible increased risk of diabetes and cardiovascular disease have been reported to be significant contributors to psychological morbidity and impact health-related quality of life. For women with PCOS, the changes in physical appearance and the associated mood disorders appear to be deleterious for sexual function.

Vitamin D deficiency (<20 ng/ml serum concentration of 25[OH]D), which affects from 67% to 85% of women,[4] is closely linked to symptoms of PCOS. The main physiologic role of vitamin D is to regulate calcium and phosphorus homeostasis and to promote bone health. Although there has been an increase in awareness of the importance of sexual dysfunction and QoL in women with PCOS, few studies have evaluated the outcomes of treatment for PCOS upon sexual and subjective health status of women.

The goals of this study are:

1. To evaluate the prevalence of sexual dysfunction (SDy) in women with Polycystic Ovarian Syndrome (PCOS)

2. To determine the effects of Vitamin D therapy, with and without hormonal contraceptives, on SDy in women with PCOS in the absence of depression.

METHODS:

The study will enroll 60 women diagnosed with PCOS and reporting SDy at the Wright State Physicians (WSP) OB-GYN Practice and the WSP Family Medicine Practice.
All participants will take vitamin D 600IU/day and will choose between hormonal and non-hormonal contraceptive methods (target of 30 participants in each group). Participants will complete three study visits (Initial, Month 3, and Month 6). Vitamin D levels will be drawn at the beginning of the study and again at 3 and 6 months after initiation of vitamin D therapy. Each participant will be asked to complete the Female Sexual Function Index (FSFI) and the Beck Depression Inventory (BDI) prior to initiation of treatment and again at 6 months.

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BACKGROUND:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among reproductive age women with a prevalence as high as 15% using Rotterdam diagnostic criteria.[1] PCOS is a heterogeneous clinical disorder characterized primarily by chronic anovulation and hyperandrogenism.[2] A number of other metabolic and health complications are associated with PCOS including obesity, insulin resistance, dyslipidemia, type 2 diabetes, cardiovascular disease, and endometrial cancer.[3]

The clinical symptoms of PCOS including menstrual dysfunction, infertility, hirsutism, alopecia, acne, and the possible increased risk of diabetes and cardiovascular disease have been reported to be significant contributors to psychological morbidity and impact health-related quality of life (HRQoL)[4,5] including depression and anxiety,[6,7] suicide attempts,[8] body dissatisfaction,[9] eating disorders,[10] lower overall health-related quality of life[11] and diminished sexual satisfaction.[12,13]

For women with PCOS, the changes in physical appearance and the associated mood disorders appear to be deleterious for sexual function.[6] Previous research in this area is scant, and what has been done reveals a large number of women with PCOS (60%) reporting sexual dysfunction and that the domains of desire and arousal are most commonly affected (in 98% - 99% of cases). Using the Changes in Sexual Functioning Questionnaire (CSFQ), others have reported that women with PCOS were similar to control women in the number of sexual thoughts and fantasies and in the frequency of sexual intercourse, but differed significantly with lower orgasm/completion scores than control women.[13] The existing research is limited by the study populations used, which have consisted of infertile women with PCOS who have a high prevalence of sexual dysfunction that may be more related to infertility and not an underlying sexual dysfunction, and by the possible impact of depression and psychotropic medications on sexual dysfunction.

Vitamin D deficiency (<20 ng/ml serum concentration of 25[OH]D), which affects from 67% to 85% of women,[4] is closely linked to symptoms of PCOS. Observational studies have shown that lower 25[OH]D levels are associated with insulin resistance, ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity, and elevated cardiovascular disease risk factors[14] as well as decreased HRQoL and depression in select

populations.[15] Nonetheless, there is limited research exploring the implications of vitamin D status and replacement on HRQoL issues including SDy.

The main physiologic role of vitamin D is to regulate calcium and phosphorus homeostasis and to promote bone health. However, accumulating evidence suggests that vitamin D deficiency may also be an important factor for many other diseases. Several mechanisms of action have been proposed to explain the association between vitamin D and depression.

The role of calcitriol or 1,25 dihydroxy cholecalciferol, the bioactive form of vitamin D, in brain tissue has been confirmed by the presence of vitamin D receptors (VDRs) and hydroxylases in various brain regions. One area where VDRs and hydroxylases have been found in the amygdala, the center of the limbic system, where behavior and emotions are regulated.[16] In addition, Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development,[16] making it biologically plausible that vitamin D might be associated with HRQoL and SDy.

Although there has been an increase in awareness of the importance of sexual dysfunction and QoL in women with PCOS, few studies have evaluated the outcomes of treatment for PCOS upon sexual and subjective health status of women. Therapy has been directed at treating the physical symptoms produced by chronic anovulation, hyperandrogenism and metabolic disturbances associated with insulin resistance of PCOS. Treatment for PCOS has included oral hypoglycemic agents, laparoscopic wedge resection, and cosmetic procedures, such as laser hair removal, but the mainstay remains combined hormonal contraception.

The specific contribution of estrogens and progestogens in oral contraceptives is not fully understood, particularly the latter as it has variable potency and androgenicity. In general, the most commonly used progestins are the 19-testosterone derivatives. Newer oral contraceptives, such as drospirenone, norgestimate, and desogestrel, contain less androgenic progestins. Drospirenone is a 17-alpha spironolactone derivative progestin with antiandrogenic and antimineralocorticoid activity. Studies have shown various benefits of combined hormonal contraceptives for PCOS patients who are not pursuing fertility, e.g., management of endocrine and metabolic profiles, androgen levels, and endometrial cancer.[5]

Vitamin D supplementation has also been reported to improve glucose metabolism and menstrual frequency in PCOS women[17] and since Vitamin D deficiency is closely linked to PCOS and depression, its supplementation has been suggested to possibly play an important part in the treatment of PCOS and HRQoL and perhaps SDy.[18]

As such, the goal of this study is to evaluate the prevalence of sexual dysfunction and assess the impact of treatment using oral contraceptives with Vitamin D on SDy in absence of depression. We anticipate this may provide a new treatment strategy in SDy issues for women with PCOS.

OBJECTIVES:

1. To evaluate the prevalence of sexual dysfunction (SDy) in women with Polycystic Ovarian Syndrome (PCOS)

2. To determine the effects of Vitamin D therapy, with and without hormonal contraceptives, on SDy in women with PCOS in the absence of depression.

METHODS:

The study will enroll 60 women diagnosed with PCOS and reporting SDy at the Wright State Physicians (WSP) OB-GYN Practice and the WSP Family Medicine Practice.

All participants will take vitamin D 600IU/day (as recommended by the National Institutes of Health's Office of Dietary Supplements) and will choose between hormonal and non-hormonal contraceptive methods (target of 30 participants in each group). Participants will complete three study visits (Initial, Month 3, and Month 6). Vitamin D levels will be drawn at the beginning of the study and again at 3 and 6 months after initiation of vitamin D therapy. Each participant will be asked to complete the Female Sexual Function Index (FSFI) and the Beck Depression Inventory (BDI) prior to initiation of treatment and again at 6 months.

Inclusion / Exclusion Criteria:
Women will be included in the study if they meet the following inclusion criteria and none of the exclusion criteria listed below:

Inclusion criteria:

1) Are reproductive age from 18-40 years old;
2) Have a diagnosis of PCOS using the revised 2003 Rotterdam European Society for Human Reproduction (ESHRE) criteria in which the following are present:
    a) Oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (fewer than 3 cycles in the past 6 months);
    b) Either clinical signs of hyperandrogenism (hirsutism with a Ferriman-Gallwey score of more than 7 or obvious acne or pronounced alopecia) or an elevated total testosterone (>2.0 nmol/L); **or**

c) Poylcystic appearing ovaries.

3) Report SDy according to the FSFI; and
4) Have no evidence of severe depression as measured by the BDI >30.

Exclusion criteria:

1) Patients with chronic medical illness, such as, diabetes mellitus, hypertension and previous venous embolism
2) Are taking any prescription medications for at least 3 months prior to entering the study, with the exception of allergy and occasional pain medications
3) Have other etiologies of anovulation and hyperandrogenism (e.g., Cushing's, thyroid dysfunction, elevated prolactin levels, signs of congenital adrenal hyperplasia)
4) Have any contraindications to hormonal contraception

Recruitment:

Participants will be recruited from the Wright State Physicians Obstetrics and Gynecology and Family Medicine practice offices. The opportunity to be involved in this research project will be approached at their clinic visit with the physician if the patient meets selection criteria. A consent form will be given and the study will be discussed.

In addition, print advertisements will be placed in the local Reach magazine to recruit patients in the Dayton area.

Stipends:

Participants will receive a stipend in the form of a MasterCard gift card for their time and travel. After each completed study visit the participant will be provided with a gift card -in the amounts as follows: $50 at Visit 1 and Visit 3, and $35 at Visit 2 for a maximum per patient compensation of $135.

HUMAN SUBJECTS PROTECTION:

The PI is responsible for protection of human subjects. This protocol will be reviewed by the WSU Institutional Review Board. Only subjects who meet study eligibility criteria will be enrolled. All eligible participants will have the study explained to them. The informed consent process will be conducted appropriately and the informed consent will be obtained prior to proceeding with any study procedures.

The primary physician or the Principal Investigator and research associates will be the individuals obtaining informed consent from patients. They will be uniform in their explanations of the nature of the study to all patients who fit the selection criteria. Those patients interested in

participating will be given time to read over the informed consent. The patients will be asked either in the clinic to be involved in the study. After the informed consent is reviewed by the patient any remaining questions will be answered.

Adverse events will be reviewed and evaluated by the PI throughout the study. In the event that any additional diagnoses are obtained during this study, the primary physician for the patient will be notified. It will be their responsibility to notify the patient of these diagnoses and any changes to management that may result.

Subjects' confidentiality will be protected. Participants will be assigned a unique identification (ID) number for the study that will be used on data collection forms rather than subjects' names. Only the minimum data necessary to conduct the study and meet the objectives will be collected. Data will be stored in a secure database (REDCap[19]) that uses a unique username and password for each team member. Data will be de-identified prior to analysis.

SIGNIFICANCE OF THE STUDY IN RELATION TO HUMAN HEALTH (BENEFITS):

PCOS is the most common reproductive endocrine disorder that has a number of health quality of life issues. The benefit of this study will be to identify SDy which is often overlooked and may potentially be helped with Vit D and/or birth control.

POTENTIAL HAZARDS (RISKS):

The study questionnaires may evoke stressful feelings taking a psychosocial questionnaire. In addition, there are rare potential risks related to OCPs including deep venous thrombosis, and stroke.

Serious side effects of vitamin D include allergic reactions, swelling of the face, throat, and tongue, dizziness, irregular or racing heart beat, dry mouth, headache, vomiting, weakness and lack of energy, and fatigue

The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

ESTIMATED PERIOD OF TIME TO COMPLETE STUDY:

We estimate data collection, data analysis, and abstract writing to require approximately 18-24 months. Preparation of the manuscript will require an additional 6-9 months.

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