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CLINICAL TRIAL

Treating Inflammation in Polycystic Ovary Syndrome to Ameliorate Ovarian Dysfunction

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Purpose

Polycystic Ovary Syndrome (PCOS) is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. Insulin resistance (IR) is a common feature of PCOS, and the resultant hyperinsulinemia is theorized to promote hyperandrogenism in the disorder. However, 30-50% of women with PCOS who are lean do not have insulin resistance. Women with PCOS also exhibit chronic low-grade inflammation. In PCOS, glucose ingestion activates nuclear factor κB (NFκB), the cardinal signal of inflammation culminating in upregulation of the inflammation pathway within mononuclear cells (MNC). This phenomenon is independent of excess adiposity and is highly correlated with circulating androgens. In addition, in vitro exposure to proinflammatory stimuli is capable of directly stimulating ovarian theca cell androgen production. Nonacetylated salicylates suppress NFκB activation and are well tolerated in humans. The proposed research is a randomized double-blind placebo-controlled study of 90 women with PCOS. Forty-five subjects with PCOS (15 lean without IR), 15 lean with IR and 15 obese) receiving salsalate, a nonacetylated salicylate, at an oral dose of 3-4 gm daily for 12 weeks will be compared with 45 age- and body-composition-matched control women with PCOS receiving placebo. The overarching hypothesis is that inflammation contributes to ovarian dysfunction, independent of excess adiposity or IR. The specific aims are, I: To examine the effect of salsalate administration on the ovarian capacity to secrete androgen and on insulin sensitivity in PCOS. II: To examine the effect of salsalate administration on the inflammatory response of mononuclear cells induced by lipid ingestion and glucose infusion in PCOS. The approach involves evaluation of ovarian androgen secretion in response to human chorionic gonadotropin (HCG) administration and insulin sensitivity during the euglycemic phase of a two-step pancreatic clamp along with ovulation monitoring before and after salsalate administration. The inflammatory response of MNC to lipid ingestion and the hyperglycemic phase of the two-step clamp will also be evaluated during treatment by measuring reactive oxygen species, the mRNA and protein content of inflammation markers, NFκB activation and cytokine release in culture. The investigators expect that women with PCOS receiving salsalate will exhibit decreased ovarian androgen secretion and reduced inflammation regardless of adiposity or IR status. These results will be significant if they show a causal contribution of inflammation to ovarian dysfunction in PCOS, thus improving our understanding of the pathogenesis of PCOS, opening previously unexplored therapeutic avenues that are not necessarily dependent on improving IR, and guiding the design of future studies aimed at determining what interventions will optimally attenuate inflammation in PCOS to reduce medical disease and enhance fertility.

Status	Recruiting

Condition	Polycystic Ovary Syndrome
Phase	Phase 2
Study Type	Interventional
Official Title	Treating Inflammation in Polycystic Ovary Syndrome to Ameliorate Ovarian Dysfunction

Further study details (as provided by National Institutes of Health Clinical Center (CC))

Enrollment	90
Start Date	December 1, 2018

Detailed Description

PCOS is characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology. Obesity and IR are common features of PCOS. Under the current model of pathophysiology of PCOS, the compensatory hyperinsulinemia of IR is the primary driver of hyperandrogenism. This concept was born from the cross-sectional observation that insulin is positively correlated with androgens in obese women with PCOS, and is supported by reports of increased androgen production from theca cells obtained from obese women with PCOS following insulin exposure in vitro4 and increases in circulating androgens in women with PCOS following insulin infusion in vivo. However, these in vitro - in vivo responses were elicited with supraphysiological insulin concentrations. Physiological insulin infusion on the other hand does not augment androgen levels in PCOS. The current model also does not explain the cause of hyperandrogenism and ovarian dysfunction in the 30-50% of women with PCOS who are lean and lack IR. Thus, some other factor contributes to these abnormalities in PCOS. The investigators have shown that ingestion of glucose and saturated fat elicits an inflammatory response from circulating MNC in lean women with PCOS who lack excess abdominal adiposity. The hallmark of this response is increased activation of NFκB, the cardinal signal of inflammation. These findings illustrate the separate and discrete role of MNC in manifesting inflammation in PCOS and that MNC are an excellent model to assess systemic inflammation in PCOS. The investigators have also shown that in PCOS, there is a link between molecular markers of inflammation from MNC and circulating androgens. Chronic suppression of ovarian androgen production does not ameliorate inflammation in lean women with PCOS. However, in vitro exposure of ovarian theca cells to proinflammatory stimuli upregulates CYP17, the androgen producing enzyme and increases testosterone. Salsalate is an inexpensive, safe, well-tolerated, well-understood anti-inflammatory agent that inhibits NFκB activation when used at higher doses. The salsalate dose required to achieve a salicylate level in the upper therapeutic range is dependent on body mass. This is achieved in lean individuals using 3.0 gm/day as the maximum dose recommended in the salsalate package insert. Individuals across the obese range (30-40 kg/m2) require >3.0 gm/day to achieve the same objective. Salsalate and other salicylates have also been shown to decrease IR. However, the ability of salsalate to decrease IR would not be necessary if the beneficial anti-inflammatory effect of salsalate to reduce hyperandrogenism is on the ovaries. In fact, we have shown that in lean insulin-sensitive women with PCOS, salsalate reduces HCG-stimulated ovarian androgen secretion by 44% and normalizes basal testosterone levels. Studies performed by the investigators in MNC also confirm the ability of salsalate to suppress NFκB activation. Together these observations

validate the use of these measurements as endpoints to assess the effects of salsalate to probe the pathophysiology of PCOS. Salsalate raises circulating insulin due to its ability to decreased insulin clearance from the liver which confounds the assessment of insulin sensitivity from post-treatment hyperinsulinemic-euglycemic clamp studies. Performance of a novel minimal model-based analysis from an insulin-modified frequently-sampled intravenous glucose tolerance test (FS-IVGTT) is able to address this confounding factor. With this approach, hepatic and extrahepatic insulin clearance can be estimated before and after salsalate treatment to obtain measures of insulin sensitivity that take into account the salsalate-induced alteration in insulin clearance. In this context, the rationale for the proposed study revolves around the concept that in PCOS, inflammation contributes to ovarian dysfunction independent of excess adiposity or IR, and may also improve insulin sensitivity when IR is present. The investigators will undertake a 12-week randomized, double-blind, placebo-controlled trial to test the link between inflammation and ovarian androgen secretion in PCOS unrelated to IR. If this study of pathophysiology demonstrates beneficial effects, this will pave the way for developing novel therapies for ovarian dysfunction in PCOS. The main objective of this proposal is to evaluate the ability of salsalate to reduce ovarian androgen secretion, induce ovulation and decrease lipid-stimulated inflammation independent of body composition and IR in women with PCOS; and to also improve insulin sensitivity in IR women with PCOS. Effects of salsalate will be assessed based on the following aims: Specific Aim 1. To examine the effects of salsalate administration on the ovarian capacity to secrete androgens, menstrual function, and insulin sensitivity in PCOS. The hypothesis for this aim is that salsalate treatment will decrease HCG-stimulated ovarian androgen secretion and induce ovulation in women with PCOS regardless of body composition or IR status; and may also improve insulin sensitivity in IR women with PCOS. The investigators will test this hypothesis in a randomized double-blind placebo-controlled study. The ovarian androgen response to HCG administration will be evaluated in women with PCOS (15 lean with IR, 15 lean without IR and 15 obese) before and after administration of a therapeutic salsalate dose for ~12 weeks compared with women with PCOS receiving placebo for ~12 weeks (15 lean with IR, 15 lean without IR and 15 obese). Ovulation monitoring and assessment of insulin sensitivity during FS-IVGTT will be performed before and after salsalate or placebo administration. It is anticipated that salsalate will reduce HCG-stimulated ovarian androgen secretion, induce ovulation regardless of body composition or IR status when compared with placebo. It is also anticipated that salsalate will increase insulin sensitivity in IR women with PCOS compared with placebo. Specific Aim 2. To examine the effect of salsalate administration on the inflammatory response of mononuclear cells induced by lipid ingestion in PCOS. The hypothesis for this aim is that salsalate administration will down-regulate inflammatory signal transduction and cytokine production within MNC following lipid ingestion in women with PCOS regardless of body composition or IR status. The investigators will test this hypothesis using the study design described in Aim 1. The inflammatory response of MNC to a cream challenge test will be evaluated in women with PCOS before and after salsalate treatment. It is anticipated that lipid-induced inflammation will decrease with salsalate use regardless of body composition or IR status when compared with placebo.

Eligibility

Minimum Age Eligible for Study:	18 Years
Maximum Age Eligible for Study:	40 Years
Genders Eligible for Study:	Female

Criteria

Inclusion Criteria: - Diagnosis of PCOS based on the presence of hyperandrogenism (skin manifestations of androgen excess such as hirsutism, acne or temporal balding – or –elevation of at least one serum androgen [i.e. total testosterone, free testosterone, androstenedione or dehydroepiandrosterone-sulphate] using predetermined local laboratory cutoffs), oligo/amenorrhea and evidence of withdrawal bleeding after progestin administration. - 18-40 years of age. - Good health as evidenced by medical history, physical examination and gynecologic examination within 30 days prior to starting the study. - Willingness to provide informed consent according to the guidelines of the University of Illinois at Chicago (UIC) Institutional Review Board (IRB). - Willingness to use double-barrier contraception such as condoms and topical spermicide (foam, cream or gel), condom and diaphragm, diaphragm and topical spermicide or sponge with topical spermicide if sexually active. Use of a non-hormonal intrauterine device (IUD), or permanent sterilization of the subject or her partner (i.e. tubal ligation or vasectomy) is also acceptable in all instances. Exclusion Criteria: - Hyperprolactinemia. - Uncontrolled thyroid disease. - Evidence of Cushing's syndrome, nonclassic congenital adrenal hyperplasia or a hormone producing tumor based on physical findings and serum androgen levels on initial screening. - Known or suspected pregnancy. - Regular vigorous physical activity during previous 6 months. - Use of any medications known to affect carbohydrate or sex hormone metabolism such as oral contraceptives, progestins, glucocorticoids or insulin sensitizing agents within 30 days of beginning the study. - Acute or chronic inflammatory illnesses (e.g. upper respiratory infection, asthma, rheumatoid arthritis or systemic lupus erythematosus). - Type 1 or type 2 diabetes mellitus defined as having a fasting glucose >126 mg/dl and/or a 2-hour postprandial glucose >200 mg/dl. - Regular smoking defined as more than 2 cigarettes a month, or any smoking within 30 days of beginning the study. - History of any illness exacerbated by salicylate use (e.g. peptic ulcer hepatic or renal disease, anemia, thrombosis, coagulopathy, congestive heart failure, hypertension or gout). - Allergy to salicylate or dairy products. - Medication use interacting with salicylates such as anti-platelet drugs (e.g. cilostazol, clopidogrel), anticoagulants (e.g. enoxaparin, heparin, warfarin), corticosteroids (e.g., prednisone), certain diabetes drugs (e.g. sulfonylureas such as glyburide), certain anti-seizure drugs (e.g. phenytoin, valproic acid), cidofovir, cyclosporine, drugs for gout (e.g. probenecid, sulfinpyrazone), anti-hypertensives (e.g. angiotensin converting enzyme inhibitors such as captopril, angiotensin II receptor antagonists such as losartan, and beta blockers such as metoprolol), drugs that affect the acidity of urine (e.g. ammonium chloride, acetazolamide), lithium, methotrexate, oral bisphosphonates (e.g. alendronate), pemetrexed, selective serotonin reuptake inhibitor antidepressants (e.g. fluoxetine, sertraline), tenofovir, and diuretics (furosemide, hydrochlorothiazide, spironolactone).

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT03229408

Locations

Frank González

Status:	Recruiting
Facility:	Chicago, Illinois, 60612, United States

Sponsors and Collaborators

University of Illinois at Chicago

More Information

Principal Investigator's career profile (https://www.doximity.com/pub/frank-gonzalez-md)

Other Publications

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