This study predates but predicts the use of glucophage, exercise and diet for the treatment of PCO.

EFFECT OF WEIGHT LOSS ON OVARIAN AND ADRENAL ANDROGEN SENSITIVITY

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Subjects:  20 (10 Obese, 10 Normal Body Weight)

Expected Starting Date:  March 1, 1987
Duration:  Six Months
Background:

Polycystic Ovarian Syndrome (PCOS) as described by Yen\(^1\) has been found to occur in many patients who are obese during the perimenarchal period. These patients develop an increase in ovarian and/or adrenal androgens as part of PCOS. Additionally, obesity appears to be associated with an elevation in insulin\(^2\) and insulin-like growth factor-I, both of which appear to stimulate ovarian androgen production in vitro\(^3\). Insulin also appears to increase androgen production in vivo\(^4\).

It is hypothesized that obesity may increase insulin and IGF-I, which, by the mechanism outline above, increase androgen production by both the ovaries and the adrenal glands. We hope to determine the effect of weight loss in obese individuals on androgens produced by the ovaries and the adrenal glands and answer the following questions:

1. Does obesity increase the baseline and post-prandial insulin and IGF-I concentrations, and is this reversible with weight loss?
2. Is this increase in insulin and/or IGF-I associated with an increase in androgens produced by either the ovaries or adrenal glands and is this reversible with weight loss?
3. Is weight loss associated with the normalization of LH pulses in pituitary sensitivity, further demonstrating a reversal of the PCOS?
4. Is the normalization of LH secretion associated with changes in insulin and IGF-I, steroids,
or some combination of these factors?

Materials and Methods:

Population: Ten premenopausal women 50 lbs. or more above ideal body weight (> 140% IBW), participating in the Optifast(R) program at Hampton General or the VAMC will be recruited, along with 10 normally cycling, normal weight, paid volunteers. Normal and obese volunteers will undergo baseline testing, and the latter will be retested after 12 weeks of the Optifast(R) supplemented fast, and again when calories have returned to the maximum allowed. The participants will have an 18 g 1-i/4 inch Teflon catheter inserted into a forearm vein (KVO 0.9% NaCl) for the following sequential studies:

1. a three hour oral glucose tolerance test (100 gm glucose)

2. a one hour cosyntropin (1 mg ACTH analog)

3. a gonadotropin-releasing hormone stimulation test (100 mcg GnRH).

Blood samples will be obtained every 15 minutes for LH, every one-half hour for GH, insulin and
IGF-I, and every hour for FSH, 17-OH progesterone, progesterone, testosterone, androstenedione, cortisol and DHEA (with an additional 30 minute sample after ACTH). A single determination for free testosterone, DHEA-S estradiol, estrone and prolactin will be made on the basal sample. Total blood withdrawal for each 5 hour session is 200 ml, with a maximum individual sample of 20 ml, and most samples ranging from 1 ml (LH alone) to 5 ml.

At the end of 5 hours, 5,000 units of hCH will be administered IM. Study participants will return in 24 hours for one blood sample of 20 ml (testosterone, free testosterone, androstenedione, DHEA, progesterone, 17-OH progesterone).

No side effects or adverse reactions, other than those detailed in the consent form, are expected.

OUTCOME:

It is expected that I + IGF-I will correlate directly with weight, and these will fall with weight loss. From previously cited data, we also expect ovarian (post-hCG) and adrenal (post-ACTH) androgen secretion to fall and be statistically correlated with weight loss. Furthermore, this should apply to all women, although perhaps in varying degrees. If these changes are not observed, especially in those with PCOS, the hypothesis that obesity-related PCOS is initiated by I/IGF-I-induced excess androgen production may be seriously questioned.
Bibliography


CONSENT FORM: EFFECT OF WEIGHT LOSS ON OVARIAN AND ADRENAL ANDROGEN SENSITIVITY

I understand that I have been asked to participate in a clinical research study by Drs. David Kreiner, Donald Richardson, Timothy Morek, and Zev Rosenwaks. The study is designed to evaluate the impact of body weight on insulin and insulin-like growth factor I (IGF-I), nutritional and weight-related hormones, and their effects on androgen (male) hormone production by the ovary and adrenal glands.
The study entails inserting a plastic catheter or butterfly needle into an arm vein to take blood samples for 5 hours 200 ml (one-half (1/2) pint) of blood will be withdrawn at each session. During these 5 hours, four tests will be done: an oral glucose (sugar by mouth) tolerance test, and ACTH, GnRH and hCG stimulation tests.

Adrenocorticotropic hormone (ACTH) is responsible for stimulating the adrenal gland, gonadotropin releasing hormone (GnRH) is responsible for stimulating the ovary-stimulating hormones from the pituitary gland, and human chorionic gonadotropin (hCG) is a hormone which directly stimulates the ovary. ACTH and GnRH will be administered by the intravenous catheter, and the hCG by an intramuscular injection. These tests will be repeated after 12 weeks of Optifast and again when calorie intake has been normal for 12 weeks.

The possible side effects of these tests include nausea from the sugar-water mix during the oral glucose tolerance test, and pain from ovulation and an early or abnormal period after hCG. ACTH and GnRH have no side effects. Potential complications of taking blood samples and administering intravenous medications other than the potential side effects of the medication already outlined include dizziness, fainting, bleeding, infection, clotting or a painful bruise.

A complete history and physical examination pre- and post-therapy will be performed along with frequent examinations of my vital signs during the administration of the medication.
The benefit to me, in addition to the $100.00 compensation, may be finding that weight loss has a positive or therapeutic effect on the hormones which relate to diabetes, infertility, irregular menstrual cycles, and excess hair growth. The study also may benefit others by gaining information about the potential effects of body weight and weight loss on male hormone production in the ovaries and adrenal gland.

I understand that participation in this clinical study is voluntary, and is only open to healthy patients who are premenopausal and not on any hormone therapy.

If I elect not to participate in this study or if I choose to withdraw from this study at any time I will not incur any penalty or loss of benefits to which I am otherwise entitled.

These procedures and risks have been explained to me by

______________________________________.

I understand that the results may be published but that my identity will not be disclosed without my separate written consent. At all times strict confidentiality will be maintained.

I understand that if I have any questions, comments or concerns about this study or the informed consent process. I may write to or call Dr. David Kreiner at (804) 446-8916.
I am advised that if injury should result from my participation in this research project, the V.A. and EVMA provides no insurance coverage, compensation plan or premedical care plan to compensate me for such injuries. In the event I believe that I have suffered injury as a result of my participation in any research program. I may contact Dr. Robert McCombs, an employee of EVMA, at (804) 446-5804, or Dr. Joseph Regan, 722-9916, (V.A.) extension 655.

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SUBJECT                                                                                                              DATE

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WITNESS                                                                                                             DATE

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INVESTIGATORDATE