COVER PAGE

Evaluation of Kisspeptin Glucose-Stimulated Insulin Secretion With Oral Glucose Tolerance Test

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Inclusion/Exclusion Criteria:
No PI concern about study subject appropriateness for study
History:

- over the age of 17,
- normal pubertal development
- stable weight for previous three months,
- no active illicit drug use,
- no history of a medication reaction requiring emergency medical care,
- no difficulty with blood draws.
- no history of hypertension, diabetes, heart disease, high cholesterol, cancer, or clotting disorders.
- no history of chronic disease that has required hospitalization
- no recent use of prescription medications which interfere with metabolism or reproduction (recent = within 5 half-lives of the drug), unless specified in the protocol (see below re: hormonal methods of birth control). Use of levothyroxine or seasonal allergy medications is acceptable,
- no history of diabetes in a first degree relative,
- Use of contraceptive pills and IUDs are acceptable if subject has been on them for >4 weeks at time of screening.
    - If applicable, subjects must be on this method of birth control 4 weeks prior to first clinical research center visit and continue use of it throughout all study procedures.

Physical examination:

- systolic BP < 140 mm Hg, diastolic < 90 mm Hg,
- normal body mass index (BMI between 18.5-25)
- regular menstrual cycles

Laboratory studies: (per MGH reference ranges)

- normal hemoglobin, unless hypogonadal then no lower than 0.5 gm/dL below the lower limit of the reference range for normal women (as men and women with hypogonadism have lower hemoglobin levels off of treatment)
- hemoglobin A1C < 6.5%
- BUN, creatinine not elevated
- AST, ALT < 3x upper limit of normal
- no hyperlipidemia by fasting lipid panel
- negative serum pregnancy test (for all women)

<u>Subject Protocol</u>

<u>Screening</u>
Healthy subjects who may have higher risk of a reaction to kisspeptin will be excluded. These include subjects who have a history of a severe allergic reaction, or who have abnormal physical exam or laboratory findings.

<u>Study Visits</u>
Clinical research center visits will only be done at MGH. Following screening and eligibility determination, women will undergo the following protocol:

i) DEXA scan (can be combined with any other visit)
ii) admission to Clinical Research Center:
    a. frequent blood sampling
    b. standard dinner meal
    c. appetite questionnaires (before and during infusion)
    d. 12 hour fast
    e. kisspeptin administration (infusion) or placebo administration (infusion)
    f. undergo a oral glucose tolerance test
    g. frequent blood sampling to assess response to kisspeptin

h. questionnaire on hunger and satiety
iii) follow-up within 72 hrs of discharge (phone or email)
iv) second admission to Clinical Research Center (as above)
v) follow-up within 72 hrs of discharge (phone or email)

Risks
The risks involved with this study are associated with the administration of study drugs, frequent blood sampling, and DEXA scan. There are no known risks associated with kisspeptin administration.

Blood Draws, including IVs:
There is a slight discomfort associated with the placement of IV lines and a small risk of infection at blood draw sites. Subjects may faint from blood drawing or develop bruise or irriation at the site of the blood draw. An IV line may fail and a replacement IV will be placed, if possible. In addition, it is possible that subjects could develop anemia and related fatigue from blood-drawing. Subjects will be instructed to avoid donating blood or having large blood draws for 8 weeks after the overnight studies.

DEXA Scan:
As a result of your participation in this study you will be exposed to radiation from the whole body DEXA scan. Please note that this radiation is not necessary for your medical care and is for research purposes only.

The total amount of radiation exposure you will receive from taking part in this study is equal to a whole body exposure of about 8.40 microSieverts (μSv). A μSv is a unit of radiation dose. This amount of radiation is about the same as you would normally get in 1 day from natural background sources from the earth and the sky. Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses used in this study is a slight increase in the risk of developing cancer later in life.

Oral Glucose Tolerance Test: The drink may taste very sweet making it hard to drink. Subjects may feel sick after drinking the glucose liquid and may vomit. There is a risk of hypoglycemia or symptoms of hypoglycemia without low blood sugar levels. These symptoms include weakness, hunger, sweating, and feeling nervous or restless. If subjects develop these symptoms during the test, their blood glucose level will be checked by glucometer. If the level is <60 mg/dL with symptoms, the subjects will be provided with glucose tabs and the study will be stopped.

Statistical Analysis Plan:

For OGTT, these estimates were generated using published data on reproducibility available for the primary endpoint[1]. In addition, the oral glucose insulin sensitivity index (OGIS) declines by 17% when comparing individuals with obesity to those who are lean, and by 26% when comparing individuals with impaired glucose tolerance to those without[2]. Therefore, with a clinically meaningful change of 10%, completion of these studies with 10 individuals under each condition is anticipated to provide a well-powered study.

References
1. Gordon BA, Fraser SF, Bird SR, Benson AC. Reproducibility of multiple repeated oral glucose tolerance tests. Diabetes research and clinical practice 2011;94:e78-82.
2. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes care 2001;24:539-48.