Effect of Metformin and Rosiglitazone on Ovulation and Menstrual Cycling in Women with Polycystic Ovarian Syndrome

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A. Background/Study Rationale

Polycystic Ovarian Syndrome (PCOS) is a common reproductive disorder in women. It is estimated that the prevalence in the population is 5%-10%. The syndrome is usually characterized by hyperandrogenism and chronic anovulation. The metabolic abnormalities are quite diverse and include obesity, amenorrhea, infertility, hirsutism, hyperinsulinism and insulin resistance. Women with PCOS are at a particularly increased risk for Type 2 DM and glucose intolerance with combined prevalence of 35-40% for IGT. Hyperinsulinism ultimately results in increasing ovarian steroidogenesis and androgen secretion, lowered sex-hormone-binding globulin (SHBG) and elevated blood levels of androgens. The general thought is that insulin resistance plays a significant role in ovulatory dysfunction in women with PCOS. The exact mechanism of the insulin resistance has not been completely elucidated but several mechanisms have been proposed. One possibility is that the major defect in PCOS is a post-binding defect in insulin-receptor signaling with associated decreased insulin receptor autophosphorylation. Beta-cell dysfunction may also be contributory.

Initially the mainstay of therapy for PCOS was oral contraceptives and antiandrogen agents. However, given that insulin resistance is thought to play such a major role in the pathogenesis of PCOS, insulin-lowering agents such as metformin and thiazolinediones (TZDs) have been studied and used as single agent treatment modalities for this disorder. The exact mechanism by which metformin mediates its effect is not entirely known but it probably works by decreasing hepatic gluconeogenesis ultimately lowering endogenous glucose production. TZDs work primarily by increasing peripheral glucose disposal especially at skeletal muscles and also by decreasing hepatic glucose output.

Several investigators have attempted to look at these drugs individually and evaluate their efficacy in reducing hyperinsulinemia. Valazquez et al conducted the initial study of metformin to treat PCOS. 26 obese women with PCOS were treated with metformin 1.5gm/day for 8 weeks. The treatment resulted in a decrease of serum insulin and free testosterone. Three unexpected pregnancies were reported and 7 women who continued the treatment developed regular periods. The findings were surprising and suggested for the first time that high insulin levels may correlate with the reproductive abnormalities seen in PCOS. A fairly recent study by Moghetti et al was designed to show the long-term effects of Metformin therapy. It was a randomized-controlled trial where 23 women with PCOS were randomized to metformin 500 mg tid or placebo for six months. Then an open-label crossover was continued for an additional six months. Women who received treatment had reduced fasting plasma insulin, increased insulin sensitivity and decreased serum androgens. Fifty Four percent of these women also had improvement in their menstrual patterns. However, there are a few studies that have not shown any benefit with metformin. In a nonrandomized trial Ehrmann et al studied 14 obese, nondiabetic women who were given metformin 850 mg tid for 12 weeks. The researchers found that there was no significant change in serum free testosterone and other androgens with treatment. Also, insulin sensitivity was not improved.

Most of the initial studies analyzing the role of thialozinediones were done with troglitazone as the pilot drug until it was removed from the market after several cases of hepatic failure were attributed to its use. Dunaif et al randomized 25 women with PCOS to a three-month trial of 200 mg or 400 mg of troglitazone. They found that 400 mg troglitazone was most effective in increasing insulin sensitivity and decreasing serum androgen levels. In the PCOS/Troglitazone study group 410 women were randomized to 44 weeks of treatment with placebo or troglitazone 150mg/day or 300 mg/day or 600mg/day. The rates

of ovulation were significantly higher in women taking higher doses (300mg or 600 mg) of troglitazone compared to placebo. Of the patients treated with TZD-600, 57% of the women ovulated more than 50% of the time compared to 12% of controls. Troglitazone also decreased free testosterone in a dose dependent manner. Some researchers are now looking at other TZDs such as rosiglitazone to determine if they too are effective in treating PCOS. Zheng et al conducted an open-label study where 30 patients with PCOS were given rosiglitazone 4mg qd for twelve weeks. At the end of treatment, basal insulin, androgen levels, luteinizing hormone and leptin levels were significantly decreased. The ovulation rate was ~50%.

These studies taken together provide compelling evidence that metformin and troglitazone are effective in ameriolating insulin resistance and its sequelae in women with PCOS. However, the effect of metformin in combination with a TZD and their effects on PCOS have never been studied.

This study was designed to further address the issue of insulin resistance in PCOS and more specifically to address whether the role of TZD and metformin will be additive in lowering insulin levels and thereby improving anovulatory cycles in women with PCOS.

The general hypothesis is that the use of metformin and rosiglitazone in combination will have an additive effect on the increase of ovulation and menstrual cycling in women with PCOS compared to metformin alone.

B. Study Design

The study will be a prospective double blind, randomized study involving 350 number of women with PCOS. 150 patients will receive metformin 850 mg po bid plus placebo and the other half will receive metformin 850 mg po bid and rosiglitazone 2 mg bid. There will be no crossover between groups. The study will have a duration of 12 months.

C. Statistical Analysis

The results will be analyzed by the chi square test to determine whether proportions of subjects meeting the endpoints are different between treatment arms. The study will be done with a power of 80% to detect a difference at an alpha level of 0.05. Based on several studies the power calculation assumes that the ovulatory rate for metformin will be 79% and for rosiglitazone of 50%. A sample size of 350 will find a 10% difference.

Primary Outcome: Restoration of regular ovulation and menstrual cycling.

Secondary Outcomes: Reduction of fasting serum insulin and androgens, change in lipid profile.

D. Study Procedure

Patients with PCOS who are referred to the gynecology clinical practice or reproductive endocrinology clinic will be enrolled in this study. At the time of entry into the study, the women would have to be in the follicular phase of the menstrual cycle determined by serum progesterone <2ng/ml or a menstrual period at least 2 months before. The women will be evaluated for 3 months prior to starting treatment to establish a baseline ovulatory rate and regularity of menstrual cycling. During this time they will undergo initial screening tests after an overnight fast including: glucose, oral glucose tolerance test (OGTT), routine chemistries, complete blood count, liver function tests, TSH, prolactin level, testosterone and free testosterone, LH, FSH, DHEAS, SHBG, fasting lipids (total cholesterol, triglycerides, HDL and LDL), plasma insulin levels. The OGTT will be performed after an overnight 10-12 hr fast after basal blood sample is obtained. A 75 gm glucose load will be administered orally. Blood samples will be obtained at 30, 60, 90 and 120 mins after glucose loading and will be evaluated for glucose and insulin. During the 3 month period, patients will be asked to keep a diary of vaginal bleeding and spotting. A serum progesterone level will be checked every week. Ovulation will be based on progesterone level that

is greater than 8 ng/ml. All samples will be processed at the GCRC Core lab according to standard techniques.

The study drugs will be given after 3 months of baseline evaluation. The patients will be reevaluated at 4 weeks after the beginning of the treatment and then every 8 weeks thereafter. At each visit vitals, weight, basic metabolic labs (chemistries, CBC, LFTs) and a pregnancy test will be obtained. All baseline screening tests including OGTT will be repeated after 6 months and12 months.

Patients will be advised to follow their routine diet and exercise routine. They will also be counseled regarding safe sex practices and will be strongly encouraged to use barrier methods of contraception such as condom or diaphragm.

The patients will also be asked to bring in their medication bottles at each visit so that a pill count can be carried out and new medications dispensed.

E. Study Drugs

Metformin is a member of the class of drugs called biguanides that has been FDA approved for the treatment of Type II DM and has been used as an off-label agent for hyperinsulinemia in PCOS. The drug will be administered as 850 mg po bid, a standard dose. The known side effects include: nausea, diarrhea and abdominal discomfort can be seen in 20% of patients. These effects can be minimized by taking the drug with food. The major adverse effect is lactic acidosis which has a reported incidence of <0.1 case per 1000 patients.

Rosiglitazone is a member of the thiazolinediones a group of drugs that has been approved for treatment of Type II DM. The main side effects are anemia (1.9%), edema (4.8%) and hepatic dysfunction (0.2-0.32%). The study drugs are all available at the hospital formulary.

F. Study Subjects

Inclusion Criteria: The subjects will be women 18-35 years with a diagnosis of PCOS diagnosed by hyperandrogenism defined as free testosterone level greater than the upper limit of normal in our laboratory and chronic anovulation defined as less than 8 menstrual periods per year. These definitions are based on the criteria of the NICHHD conference.

Exclusion Criteria: Prior history of diabetes mellitus, glucose intolerance, hepatic or renal dysfunction, advanced cardiovascular disease, CHF, and pregnancy. Endocrine disorders that are known to cause hyperandrogenism and reproductive dysfunction such as thyroid dysfunction, hyperprolactinemia and congenital adrenal hyperplasia. Also, the use of medications that can affect reproduction or insulin action such as oral contraceptives, fertility drugs and exogenous steroids within 60 days of study.

This study is likely to include an adequate representation of minority groups since most of the participants will be recruited from the Washington Heights Area.

G. Recruitment of Subjects

The patient will be recruited from referrals for PCOS made to the Department of Gynecology Clinical Practice and Reproductive Endocrinology at Columbia Presbytarian Medical Center. Suitable patients will be identified by the primary provider and will be approached for enrollment into the study. Informed consent will be obtained through a meeting with one of the study investigators. The potential risks and benefits of the study will be explained.

H. Confidentiality of Study Data

All subjects will be assigned a unique code number and all data will be stored in a secure location that is accessible only to study investigators.

I. Potential Conflict of Interest

None of the investigators are in any way affiliated with the pharmaceutical companies that produce and market the study drugs.

J. Location of Study

Columbia Presbytarian reproductive endocrinology clinic.

K. Potential Risks

The main risks would be adverse medication side effects. However, close medical follow-up should help to mitigate against these effects. It is highly unlikely that the patients underlying condition will worsen as a result of treatment.

L. Potential Benefits

Participants in this study may or may not benefit. The potential benefit are that subjects will have more regularly ovulatory menstrual cycles, decrease serum androgen levels, serum insulin and improved metabolic profile.

M. Alternative Therapies

None

N. Compensation to Subjects

The study drugs that will be provided free of cost to the study subjects. Barrier methods of contraception such as condoms and diaphragm will be provided upon request.

O. Costs to Subjects

The subjects should not incur any additional costs as a result of their participation in the study.

P. Minors as Research Subjects

None

Q. Radiation or Radioactive Substances

None

R. References

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