Welcome to Presentation of Thesis Proposal

Title

Comparison of Myoinositol and Metformin versus Metformin Alone on Glycaemic Control and Menstrual Cycle in Women with PCOS at Rajshahi Medical College Hospital

Submitted by

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INTRODUCTION

Introduction

- The Polycystic Ovarian Syndrome (PCOS) is one of the common endocrine disorders among women of reproductive age.
- It is a diverse multisystemic condition affecting women of reproductive age and characterized by anovulation (oligomenorrhoea/ amenorrhoea), hyperandrogenism (hirsutism, acne, alopecia) and Insulin Resistance (IR) (Bozdag et al., 2016).
- It may be due to intrauterine androgen exposure, post-natal insulin resistance and hyperinsulinemia (Norman et al., 2007).

Introduction Cont..

- IR and resulting hyperinsulinemia play a key role in the pathogenesis of anovulation and hyperandrogenism, contributing to a range of metabolic disorders like obesity, type 2 diabetes mellitus, hypertension and gonadal dysfunction.
- Most PCOS patients have menstrual irregularities such as oligomenorrhea or abnormal uterine bleeding. Approximately 75% of PCOS individuals have clinically evident menstrual abnormalities.
- Polycystic ovarian syndrome (PCOS) is associated with insulin resistance. So, insulin sensitizing drugs are therefore used in the treatment of PCOS (Conway et al., 2014).

Introduction Cont..

- Metformin was the first insulin sensitizing drug and it showed a reduction in circulating androgen levels, significant reduction in the body weight, improvement in menstrual regularity and promotes peripheral insulin sensitivity.
- On the other hand, Myoinositol (MI) is a naturally occurring insulin sensitizer found in citrus fruits and beans. Among the numerous inositol isomers, Myoinositol (MI) and D-Chiro Inositol (DCI) are known to have insulin-simulating properties and are considered beneficial in managing PCOS.

Introduction Cont..

- As insulin sensitizers, both metformin and MI correct the metabolic and hormonal parameters, eventually leading to improvements in menstrual irregularities and hyperandrogenism and aiding in conception.
- However, studies have shown variable responses to these treatments (Agrawal et al., 2019).
- Metformin has been found to significantly decrease fasting glucose and insulin levels in PCOS patients but is associated with gastrointestinal side-effects (Lashen, 2010; Mansfield et al., 2003).

Introduction Cont..

- Literature has also shown that myoinositol has a beneficial effect in PCOS patients due to its action on insulin sensitivity.
- However, the main drawback is its expense and the usual dosage studied is 2-4 grams per day (DiNicolantonio and H O'Keefe, 2022; Facchinetti et al., 2016).
- Hence, the objective of the study will be to compare the efficacy of insulin sensitizers Metformin and Myoinositol plus Metformin in controlling blood glucose level and menstrual pattern in PCOS patients.

RATIONALE

Rationale

- PCOS is a complex heterogenous endocrine disorder affecting women of reproductive age group.
- It is the most common cause of female infertility due to endocrinological disorder and characterized by a combination of hyperandrogenism, chronic an-ovulation and irregular menstrual cycle.
- Patients with PCOS have multiple metabolic disturbances such as diabetes mellitus, cardiovascular disorders and metabolic syndrome. Menstrual irregularity is one of the most common presenting complain of PCOS.

Rationale Cont..

- Due to complexity of this disorder and various controversies of its treatment, different management regimen has been proposed over last three decades.
- Insulin sensitizing drugs are used in the treatment of PCOS and Metformin (MET) is the first insulin sensitizing drug to be used in PCOS to investigate the role of insulin resistance in the pathogenesis of the syndrome.
- Metformin is a well-known insulin sensitizer and prescribed in PCOS due to positive effects on insulin resistance and cycle length.

Rationale Cont..

- But supplement of MET to lifestyle intervention has no additional effect on insulin sensitivity in PCOS and weight loss is the main mechanism for decreased insulin resistance and the drug has gastrointestinal adverse effects.
- Recently, new insulin sensitizers containing inositol have been suggested in the treatment of patients with PCOS. Myoinositol (MI) can improve insulin sensitivity and menstrual pattern.
- In addition, Myoinositol intake improves reproductive axis functioning in patients with PCOS.

Rationale Cont..

- MI is a second messenger in the follicle-stimulating hormone signaling pathway and it's deficiency is related to ovulatory dysfunction in PCOS and is responsible for the glucose uptakes which in turn increase insulin sensitivity.
- In contrast to Metformin, no side effects have been reported following treatment with myoinositol.
- Currently there is no study in Bangladesh focusing the efficacy and safety of Metformin and Myoinositol on PCOS.
- Therefore, the aim of this study will be to compare Myoinositol plus Metformin and Metformin alone on glycemic control and menstrual pattern in patients with PCOS.

Research hypothesis

- Myoinositol plus Metformin are more effective and safer in controlling glycaemic index and improving menstrual pattern than Metformin alone.

OBJECTIVES

General Objective

- To assess and compare the efficacy and safety between Myoinositol plus Metformin and Metformin alone group in controlling glycaemic index and improving menstrual pattern.

Specific objectives

- To assess the efficacy in terms of controlling glycaemic index and improving menstrual pattern in Myoinositol plus Metformin group.
- To determine the efficacy in terms of controlling glycaemic index and improving menstrual pattern in Metformin alone group.
- To assess the Gastrointestinal adverse effects in Myoinositol plus Metformin group.

Specific objectives Cont..

- To determine the Gastrointestinal adverse effects in Metformin alone group.
- To compare the efficacy between Myoinositol plus Metformin and Metformin alone group.
- To compare the safety between Myoinositol plus Metformin and Metformin alone group.

METHODS AND MATERIALS

- **Study design:** The study will be a randomized controlled trial.
- **Place of study:** This study will be conducted in the Department of Obstetrics & Gynaecology, Rajshahi Medical College Hospital, Rajshahi.
- **Period of study:** The study will be done in a one and years from January 2025 to June 2026.

- **Data collection place:** Data will be collected from the outpatient Department of Obstetrics & Gynaecology, Rajshahi medical college hospital, Rajshahi.
- **Study population:** All PCOS women with improper glycaemic control and menstrual irregularities will be the study population. Study population will be again divided into 2 groups

- Intervention Group: Women who will receive Tab Myoinositol 2g plus Tab Metformin 500 mg two times daily for 12 weeks.
- Control group: Women who will receive Tab Metformin 500 mg two times daily for 12 weeks.

Inclusion criteria

PCOS Women who will give consent to participate in the study with following characteristics will be included:

- Diagnosed PCOS women according to the Rotterdam criteria with improper glycaemic control and menstrual irregularities.
- Age 18-40 years.
- Before study entry, pausing will be required for Metformin and oral contraceptive pills for at least one and three months, respectively.
- No woman will be under Myoinositol before the study.

Exclusion criteria

- Pregnancy.
- Patients will be already under other drug treatment for PCOS.
- Deranged kidney or liver function tests.
- Hyper-prolactinemia.
- Cushing’s disease.

Exclusion criteria Cont..

- Congenital adrenal hyperplasia.
- Androgen secreting neoplasia.
- Thyroid disorders.
- Known hypersensitivity to Myoinositol.
- Inability to come for follow-up.
- Women who will not give consent to participate in the study.

Sample size determination

- Sample size will be determined using hypothesis testing for the difference between two proportions Haque, (2021) as follows:
- Thakur et al., (2020) in their study observed that the proportion of menstrual irregularity after treatment with Metformin was 63.15% and after treatment with Myoinositol was 33.3%. So, the sample size at 5% level of significance at 80% power could be calculated using the formula.

$$n = \frac{p_1(100-p_1)+p_2(100-p_2)}{(p_1-p_2)^2} X (Z_\alpha + Z_\beta)^2$$

Sample size determination Cont..

Here

- n = Minimum required sample size to ensure the validity of the findings
- p_1= Proportion of menstrual irregularity after treatment with Metformin = 63.15%
- p_2= Proportion of menstrual irregularity after treatment with Myoinositol = 33.3% (Thakur et al., 2020)
- Z_α = Z-value at 5% level of significance = 1.96
- Z_β = Z-value at 80% power = 0.85 (when $\beta = 0.2$)

Sample size determination Cont..

$$n = \frac{63.15\,(100-63.15)+33.3\,(100-33.3)}{(63.15-33.3)^2} X (1.96 + 0.85)^2$$

$$= \frac{2327.08+2221.11}{891.02} X 7.89$$

$$= 40.27 \text{ (approximately)} = 40$$

Therefore, the calculated sample size is 40 in each group. However, considering an estimated 10% drop-out for 3 months follow up, a total of (40+4) = 44 patients will do suffice in ensuring validity of the study findings. However, 44 PCOS women will be included in each group in the study.

Sampling technique

- Systematic random sampling technique will be used to select total 88 PCOS women who will fulfill the inclusion and exclusion criteria during the data collection period.

- From record book survey, it is clear that everyday average 2 PCOS women attended in the outpatient Department of Obstetrics and Gynaecology, Rajshahi Medical College Hospital, Rajshahi.

- So, counting 6 days in a week, 48 PCOS women come in a month.

Sampling technique Cont..

- If I will want to collect sample within six-months, sampling interval will be k=288/88=3.27=3.

- So, every third PCOS patient will be enrolled in the study. Then at the same time each PCOS patient will be randomly allocated into intervention or study group.

- First PCOS patient will be selected by simple lottery method. Then every third patient will be being allocated into intervention and control group until 44 desired patients in each group.

Variables will be used in the study

Independent variables

- Age
- Residence
- Educational status
- Occupational status
- Height
- Weight
- Monthly family income
- Treatment used in PCOS

Dependent variables

- Fasting blood sugar
- 2 hours after blood sugar
- HbA1c
- Menstrual cycle length

OPERATIONAL DEFINITIONS

Operational definitions

- **PCOS:** Reproductive age women who will meet the diagnostic criteria for PCOS will be included in PCOS group. Polycystic ovaries (PCO) will be determined by abdominal ultrasound. Diagnosis of PCOS will be established based on Rotterdam 2003 consensus. PCOS will be confirmed when two out of three criteria will be fulfilled.
- 1. Oligo and/or anovulation.
- 2. Clinical and/or biochemical signs of hyperandrogenism.
- 3. Polycystic ovarian morphology observed through ultrasound, after excluding other related disorders.

Operational definitions Cont..

Efficacy: In this study, efficacy will be measured by

- Glycemic control (Fasting and 2 hours after blood sugar, HbA1c).
- Improvement of menstrual regularity (measured by cycle length).

Operational definitions Cont..

- **Timing of blood collection:** Blood samples will be drawn in the morning after an overnight fast in the follicular phase in menstruating women.

- **Blood analysis:** Fasting plasma glucose will be analyzed by ultraviolet hexokinase analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland).

Operational definitions Cont..

- **Assessment of menstrual cycle length:** Menstrual cycle length will be assessed by self-report in a menstrual cycle calendar.

- **Safety:** Mainly gastrointestinal (GI) side effects will be considered for assessment of safety and measured by feelings of nausea, abdominal pain, vomiting, diarrhea and appetite changes.

Detailed study procedure

- This randomized controlled trial will be conducted in the Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi after obtaining approval from the Ethical Review Committee, Rajshahi Medical College, Rajshahi.

- A total of 88 women aged 18 to 40 years with signs and symptoms of PCOS (according to Rotterdam Criteria) attending in the OPD will be included in the study after obtaining consent from them.

Detailed study procedure Cont..

- A detailed history regarding menstrual cycles, gynaecological complaints, hirsuitism, acne, acanthosis nigricans will be collected and noted in the proforma.

- All the patients will be subjected to pelvis ultrasonography and the size, number of follicles and volume of both ovaries will be noted. At the time of enrollment, fasting and 2 hours after blood sugar will be performed.

Detailed study procedure Cont..

- PCOS women will be divided into two groups (Intervention and study groups) on the basis of whether they will receive Tablet Myoinositol plus Metformin or Metformin alone through randomization and each group consisting of 44 women.

- Out of the 88 PCOS women, 44 patients will receive Tab Myoinositol 2g plus Tab Metformin 500 mg two times a day for 12 weeks (intervention group) and the other 44 will receive Tab Metformin 500 mg two times daily for 12 weeks (control group) which were prescribed by the consulting physician.

Detailed study procedure Cont..

- At baseline, participants will be matched according to BMI, age and phenotypes of PCOS.

- A fasting venous blood sample will be taken on day two of menstruation and sent for biochemical investigations for blood sugar and HbA1c and menstrual history will be assessed.

- These patients will be called after 3 months and again subjected to blood sugar, HbA1c and menstrual history.

Detailed study procedure Cont..

- Any reported adverse drug reactions will be also noted.
- Then the efficacy and safety of Myoinositol plus Metformin Vs Metformin in the PCOS patients will be compared.
- The violation of protocol will be recorded and the data will be analyzed on the intent-to-treat basis.

Data collection tools

- Data will be collected using a semi-structured questionnaire (research instrument) containing all the variables of interest, measuring tape, weight measuring machine and transabdominal ultrasonography machine.

Statistical analysis

- All data will be analyzed by using the 'Statistical Package for Social Sciences (SPSS)' software, 24-version.

- Categorical variables will be summarized by using numbers and percentages while continuous variables will be summarized by means ± standard deviation (SD).

- An independent t-test will be used to compare continuous variables with two categories and a chi-square test will be used to compare categorical variables. A p-value < 0.05 will be considered statistically significant for all tests.

Utilization of the study

- The data generated from the study might be useful for choosing appropriate treatment option for the women of PCOS in controlling blood sugar and regulating menstrual pattern.

Ethical Implications

- Permission will be taken from the Institutional Review Board (IRB) of Rajshahi Medical College (RMC), Rajshahi before data collection. Keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects 1964, revised in 2013, all the study subjects will be informed verbally about the study design, the purpose of the study and potential benefits derived and risks involved from the study. They will also be assured that they will have full rights to withdraw themselves from the study at any time for any reasons what-so-ever. Patients who will give informed consent to participate in the study will be included as study sample.

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Thank You