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Observing the Use of Insulin Sensitizers for Ovulation Induction among PCOS Women

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Abstract **Original Research Article**

Introduction: In women of reproductive age, PCOS is a prevalent endocrine illness characterized by irregular menstrual cycles, many tiny ovarian cysts, and high levels of androgens. Insulin resistance is one of the leading causes of PCOS. Insulin sensitizers can help increase cells' sensitivity to insulin, allowing them to respond more effectively to insulin and transport glucose into the cells. ***Aim of the Study:*** The study's objective was to evaluate how PCOS women used insulin sensitizer as an ovulation inducer. ***Methods:*** This was a prospective, observational, cross-sectional research at the Manikganj 250 Bedded Sadar hospital, Dhaka, Bangladesh. The study duration was 1 year, from January 2022 to December 2022. During this period, 100 patients with PCOS were selected following the inclusion and exclusion criteria for their participation in this study. ***Result:*** The study population consisted of young individuals with a mean age of 24.91 years, a moderate-to-high body mass index of 26.79 kg/m2, a moderate waist-to-hip ratio of 0.82, high fasting insulin level of 21.00 µIU/mL, high insulin area under the curve (AUC) of 308.32, moderate luteinizing hormone (LH) level of 10.90 mIU/mL, moderate follicle-stimulating hormone (FSH) level of 5.43 mIU/mL, a high LH:FSH ratio of 2.02, and moderate free testosterone level of 2.72 pg/mL. After 4 months of treatment with metformin, 80% of the participants had ovulation induction, with 33% having at least one ovulation, 25% having 2 ovulations, and 6% having 4 ovulations. After continuous treatment with metformin for 16 weeks, the study population had a mean body mass index of 26.22 kg/m2, a moderate waist-to-hip ratio of 0.81, low fasting insulin level of 10.55 µIU/mL, low insulin area under the curve (AUC) of 183.00, low to moderate luteinizing hormone (LH) level of 5.32 mIU/mL, moderate follicle- stimulating hormone (FSH) level of 4.80 mIU/mL, a low LH:FSH ratio of 1.10, and low free testosterone level of 1.33 pg/mL. Comparing the mean ± SD values between pre-treatment and post-treatment findings, it was observed that all mean values had decreased and the difference was most significant in terms of fasting insulin levels, AUC insulin levels, luteinizing hormone (LH) levels, LH:FSH ratio and in free testosterone levels. These findings suggest that metformin can effectively induce ovulation and improve related symptoms in individuals with PCOS. ***Conclusion:*** The study found that metformin, an insulin sensitizer, effectively induced ovulation in 80% of women with PCOS over a 4-month treatment period. Additionally, metformin improved other related symptoms such as insulin resistance, androgen levels and menstrual regularity. The study supports insulin sensitizers as a treatment option for PCOS.

Keywords: Ovulation, Induction, Insulin, Sensitizer, Metformin.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a typical hormonal condition among women of reproductive age [1, 2]. High amounts of male hormones, irregular periods, and problems conceiving are some of its defining characteristics. Insulin resistance, a disorder in which the body's cells do not respond to insulin as intended and cause high blood sugar levels, is frequently present in PCOS patients [3–5]. Up to 10% of women of reproductive age are

affected with PCOS, which is a worldwide health problem. It raises the possibility of type 2 diabetes, heart disease, and numerous cancers in addition to being the primary cause of female infertility [6, 7]. There are various treatment options for PCOS, including lifestyle modifications such as weight loss, exercise, and a healthy diet [8–10]. In cases where these measures are insufficient to regulate menstrual cycles and promote ovulation, medications may be used [10]. Insulin sensitizers increase the body's sensitivity to insulin, which controls blood sugar levels. They are often used to treat conditions such as diabetes and PCOS [11, 12].

Common insulin sensitizer agents include metformin, pioglitazone, and rosiglitazone. These medications work by increasing the uptake of glucose by the body's cells; this can enhance insulin sensitivity and reduce blood sugar levels. Insulin sensitizer agents may be used to induce ovulation in patients with PCOS. Ovulation induction stimulates the ovaries to release an egg and is often used to help patients with PCOS get pregnant [13, 14]. Insulin sensitizer agents can help improve insulin sensitivity, which may help regulate menstrual cycles and promote ovulation. Numerous research has been conducted to look at the usage of insulin sensitizer agents as a method for ovulation induction in patients with PCOS [15]. The use of insulin sensitizers for ovulation induction in women with PCOS has been shown to have several benefits. Evidence suggests that metformin increases ovulation rates and pregnancy outcomes in women with PCOS and may also positively affect weight loss and metabolic parameters [16, 17]. Thiazolidinediones have also been shown to improve ovulation rates and pregnancy outcomes in women with PCOS and may also have a positive effect on weight loss and metabolic parameters [18, 19].

However, insulin sensitizers also have potential side effects that should be considered [12]. Metformin can cause gastrointestinal side effects such as nausea, diarrhea, and abdominal discomfort. Thiazolidinediones can cause weight gain, edema, and an increased risk of heart failure [20, 21]. The use of insulin sensitizers for ovulation induction in women with PCOS has both benefits and drawbacks. On the one hand, these medications can improve ovulation rates and pregnancy outcomes and may positively affect weight loss and metabolic parameters. On the other hand, they can cause side effects such as gastrointestinal upset and weight gain. The decision to use insulin sensitizers for ovulation induction in women with PCOS should be made on an individual basis after a thorough discussion of the risks and benefits with the patient and healthcare provider. About 50% of PCOS patients in a randomized controlled experiment showed that metformin alone helped trigger ovulation [22]. Another study found that the combination of metformin and an aromatase inhibitor was more effective at inducing ovulation than metformin alone, with ovulation rates of up to 84% [23]. Overall, insulin sensitizer agents alone or combined with other treatment methods appear to be effective in inducing ovulation in patients with PCOS. More investigation is required to ascertain the ideal dosage and length of therapy and the medications' long-term effectiveness and safety.

OBJECTIVE

- To observe the effect of insulin sensitizer agents alone for ovulation induction in PCOS women.

METHODS

The location of this prospective observational cross-sectional investigation was the Manikganj 250 Bedded Sadar hospital, Dhaka, Bangladesh. The study duration was 1 year, from January 2022 to December 2022. During this period, 100 patients with PCOS were selected following the inclusion and exclusion criteria for their participation in this study. The participants were given metformin as their insulin sensitizer, at 500 mg dosage, 3 times a day for 4 months. Informed consent was obtained from each participant and ethical approval regarding the study was also obtained from the ethical review committee of the study hospital. All necessary data was collected from hospital records and face-to-face interviews and was analyzed using the SPSS software.

Inclusion Criteria

- PCOS patients.
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Patients under other ovulation induction medication.
- Patients who could not continue medication for 4 months.
- Unable to answer the criteria question.
- Exclude those affected with other chronic diseases etc.

RESULTS

Table 1: Mean ± SD values of baseline characteristics among participants

Baseline characteristics	Mean ± SD
Age (y)	24.91 ± 1.13
BMI (kg/m2)	26.79 ± 0.88
Waist:hip ratio	0.82 ± 0.01
Fasting insulin (µIU/mL)	21.00 ± 2.82
AUC-insulin	308.32 ± 31.75
LH (mIU/mL)	10.90 ± 1.50
FSH (mIU/mL)	5.43 ± 0.45
LH:FSH ratio	2.02 ± 0.19
Free testosterone (pg/mL)	2.72 ± 0.19

The study population comprised young individuals with a mean age of 24.91 years and a moderate-to-high body mass index of 26.79 kg/m2. The mean waist-to-hip ratio was 0.82 and the mean fasting insulin level was 21.00 µIU/mL. The mean insulin area under the curve (AUC) was 308.32 and mean luteinizing hormone (LH) level was 10.90 mIU/mL. The mean follicle-stimulating hormone (FSH) level was 5.43 mIU/mL and the mean LH:FSH ratio was 2.02. The mean free testosterone level was 2.72 pg/mL.

Table 2: Distribution of participants by number of ovulation inductions by the 16th week of treatment

Ovulation induction	n	%
0	20	20%
1	33	33%
2	25	25%
3	16	16%
4	6	6%

Among the participants, only 20% had no record of ovulation by the 16th week of treatment, while 33% had at least one ovulation, 25% had 2 ovulations and 6% had 4 ovulations in the 4 months.

Table 3: Mean ± SD values of characteristics after 16 weeks of treatment among participants

Characteristics	Mean ± SD
BMI (kg/m2)	26.22 ± 0.85
Waist:hip ratio	0.81 ± 0.01
Fasting insulin (µIU/mL)	10.55 ± 1.00
AUC-insulin	183.00 ± 18.38
LH (mIU/mL)	5.32 ± 0.69
FSH (mIU/mL)	4.80 ± 0.47
LH:FSH ratio	1.10 ± 0.11
Free testosterone (pg/mL)	1.33 ± 0.09

After continuous treatment with metformin for 16 weeks, the study population had a mean body mass index of 26.22 kg/m2 and a moderate waist-to-hip ratio of 0.81. The mean fasting insulin level was 10.55 µIU/mL and the mean insulin area under the curve (AUC) was 183.00. The population had low to moderate luteinizing hormone (LH) levels with a mean of 5.32 mIU/mL, moderate levels of follicle-stimulating hormone (FSH) with a mean of 4.80 mIU/mL and a low LH: FSH ratio of 1.10. The population also had low levels of free testosterone with a mean of 1.33 pg/mL.

Table 4: Difference of mean ± SD values from between baseline and after 16 weeks of treatment

Characteristics	Baseline values	Values after 16 weeks of treatment	Difference	P-Value
BMI (kg/m2)	26.79 ± 0.88	26.22 ± 0.85	-0.57	NS
Waist:hip ratio	0.82 ± 0.01	0.81 ± 0.01	-0.01	NS
Fasting insulin (µIU/mL)	21.00 ± 2.82	10.55 ± 1.00	-10.45	<0.001
AUC-insulin	308.32 ± 31.75	183.00 ± 18.38	-125.32	<0.001
LH (mIU/mL)	10.90 ± 1.50	5.32 ± 0.69	-5.58	<0.001
FSH (mIU/mL)	5.43 ± 0.45	4.80 ± 0.47	-0.63	NS
LH:FSH ratio	2.02 ± 0.19	1.10 ± 0.11	-0.92	<0.001
Free testosterone (pg/mL)	2.72 ± 0.19	1.33 ± 0.09	-1.39	<0.001

Comparing the mean ± SD values between pre-treatment and post-treatment findings, it was observed that mean values had decreased in all cases, and the difference after the 16th week was most significant in terms of fasting insulin levels, AUC insulin levels, luteinizing hormone (LH) levels, LH:FSH ratio and in free testosterone levels.

DISCUSSION

The present study discusses insulin sensitizers, particularly metformin, as a treatment option for women with polycystic ovary syndrome (PCOS) to induce ovulation. Women of reproductive age are more susceptible to the prevalent endocrine condition PCOS, characterized by the appearance of several tiny cysts on the ovaries, irregular menstrual cycles, and elevated levels of androgens (male hormones). One of the main causes of PCOS is insulin resistance, which leads to hyperinsulinemia (elevated insulin levels in the blood) and anovulation (absence of ovulation). Insulin sensitizers are medications or supplements that help increase cells' sensitivity to insulin, allowing them to respond more effectively to insulin and transport glucose into the cells. By improving insulin sensitivity, insulin sensitizers can lower blood sugar levels, improve glucose metabolism in individuals with insulin resistance, and potentially reduce the production of androgens, improving symptoms of PCOS such as hirsutism, acne, and weight gain [11, 24, 25]. The baseline characteristics were first measured among the present study participants to observe and later compare any changes made.

The treatment with metformin as the insulin sensitizer continued for 4-months, or 16-weeks, and at the end of the treatment, all but 20% had ovulation induction. It was observed that 6 of the participants had 4 ovulations in this 4- month period. This increase in the ovulation induction among present study participants was supported by findings of previous studies where both ovulation and pregnancy had increased after treatment with metformin [22, 26, 27]. Significant changes were also observed in other variables as well after 16-weeks of metformin treatment. It was observed that due to metformin treatment, fasting insulin and AUC insulin had both decreased significantly, by 10.45 and 125.32 respectively. This finding was supported by multiple other studies that also observed a significant change in the glucose and insulin levels [28, 29] significant decrease was also observed in terms of LH, but not in terms of FSH. LH and FSH are two hormones that play a critical role in ovulation and menstruation.

In PCOS, these hormones are imbalanced, which can lead to irregular menstrual cycles and difficulty ovulating [30, 31]. Studies have shown that metformin can reduce LH levels and increase FSH levels in women with PCOS [32, 33]. This can help to regulate ovulation and improve menstrual regularity. Metformin also impacts androgen levels, which are elevated in PCOS [34]. Lowering the androgen level can help reduce the symptoms of hirsutism and acne commonly observed in PCOS. Although metformin therapy in the current trial resulted in a drop in FSH levels, this decrease was not statistically significant. Overall, the present study showed that insulin sensitizers alone can be an effective medication for ovulation induction in PCOS women and have other benefits.

Limitations of the Study

A modest sample size was used in the investigation, which was done in one hospital. As a result, the outcomes could not accurately reflect the entire community.

CONCLUSION

The current study discovered that the insulin sensitizer metformin works well to induce ovulation in women with the polycystic ovarian syndrome (PCOS). The 4-month treatment resulted in ovulation induction for 80% of participants and also significantly improved other variables such as fasting insulin, AUC insulin, and LH levels. Additionally, metformin has been shown to improve menstrual regularity and reduce symptoms of hirsutism and acne. Overall, the study supports insulin sensitizers as a viable treatment option for PCOS.

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Ethical Approval: The Institutional Ethics Committee granted the study its approval.

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