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Efficacy of Pretreatment of Insulin Resistant PCOS Patients by Metformin Alone vs Metformin Plus Myo-Inositol before Induction of Ovulation

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Abstract

Objective: The aim of this study was to explore the efficacy of pretreatment of insulin resistant PCOS patients by metformin alone and by metformin plus myo-inositol (MI) before using oral ovulation inducing agents for induction of ovulation.

Materials and methods: This prospective experimental study was conducted in Infertility Care and Research Center (ICRC) Ltd between January and December 2018. One hundred and sixty insulin resistant (PCOS) patients of primary infertility, who failed to ovulate by tab letrozole 10 mg/day for 5 days and tab glucocorticoid 0.5mg every alternate day for 5 days, were recruited for insulin sensitizer drug. By using lottery 80 patients received only metformin for 12 weeks and 80 patients received both metformin and MI with folic acid for 12 weeks. After 12 weeks, we gave same drugs for ovulation induction at which patient was resistant before using insulin sensitizers. Follicular tracking was done to observe ovulation. Patients were advised for timed sexual intercourse. Viable pregnancy was confirmed by observing cardiac pulsation by ultra-sonogram. Student's t test and Chi square test were done for statistical analysis. A p value of <0.5 was considered as significant.

Results: Ovulation rate was (77.50% vs 43.00%) and pregnancy rate was (43.75% vs 25.00%), which was significantly higher in metformin and myo-inositol group than metformin only group (p <0.05).

Conclusion: Myo-inositol supplement along with metformin is effective in promoting ovulation in insulin resistant PCOS patients.

Keywords: PCOS; Insulin Resistance; Metformin; Myo-Inositol

Abbreviations: MI: Myo-Inositol; ICRC: Infertility Care and Research Center; PCOS: Polycystic Ovarian Syndrome; CC: Clomiphene Citrate; IR: Insulin Resistance; DCI: D-Chiro Inositol; FF: Follicular Fluid; OHSS: Ovarian Hyper Stimulation Syndrome.

Introduction

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine, reproductive and metabolic disorder, which affects 5-10% of women of reproductive age [1]. The commonest symptoms are oligomenorrhoea and amenorrhoea due to

anovulation. Anovulation resulting in infertility in most of the married women. Diagnosis is based on oligo or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries on ultrasound. According to Rotterdam consensus, any two of three are diagnostic [2]. Though the exact pathogenesis of PCOS is still remains unclear, insulin resistance (IR) and subsequent hyperinsulinemia leading to hyperandrogenism are considered primary triggers in this syndrome [3-5]. Almost 50-70% of PCOS women are insulin resistance [6] and hyperinsulinemia occurs in roughly 80% of PCOS obese women and in 30-40% of PCOS lean women [7]. Life style modification in the form of dieting and exercise improve the metabolic environment and spontaneous ovulation may occur in infertile PCOS. But majority need ovulation inducing drugs for ovulation to take place.

Almost 75-80% patients respond to 1st line ovulation inducing agents like clomiphene citrate (CC) and letrozole. Women who fail to ovulate after maximum dose of CC (150 mg/day) are considered as clomiphene resistant [8]. In women with PCOS, the rates of CC resistance are around 10-30% [9]. By HOMA test it is found that CC resistant patients are insulin resistant [10]. By the same way it is also found that patients who fail to ovulate with maximum dose of letrozole (10 mg/day) are insulin resistant (Unpublished data).

Hyperinsulinemia and IR has been shown to play a pivotal role in endocrine and metabolic abnormalities of PCOS [11,12]. Insulin affects the androgenic state directly by interfering with metabolism of ovarian androgens and also indirectly by decreasing circulating SHBG levels [13]. Several insulin sensitizing agents are recommended to ameliorate these endocrine and metabolic abnormalities, which facilitate ovarian folliculogenesis and minimizes long term health hazard of PCOS [14].

Among these drugs metformin is the most used and studied drug, which is though effective in reducing androgen levels and restoring ovulation in women with PCOS [15,16] but associated with gastrointestinal discomfort like bloating, nausea and diarrhea [17,18]. Myo-inositol (MI) and D-chiro inositol (DCI) are insulin-sensitizing agents recently used for the treatment of PCOS. MI is now considered as a further insulin-sensitizing supplement. Different studies including one meta-analysis have shown that MI alone or combined with DCI improves the metabolic profile of women with PCOS [19,20]. Unfer, et al. [21] found that the concentration of MI, and the ratio of MI to DCI, decreases and confirm the occurrence of an imbalance between MI and DCI levels in the follicular fluid (FF) of PCOS patients in comparison to FF of normal women. So, the ovarian FSH resistance may be caused by intraovarian depletion of MI. According to Dinicola et al pre-treatment with oral administration of MI to PCOS women in controlled ovarian hyperstimulation reduces the units of FSH required, lowers the risk of ovarian hyperstimulation syndrome (OHSS), and improves oocyte and embryo quality [22].

Considering the well tolerability, lower side effects and beneficial effect of MI supplementation in PCOS before ovulation induction and controlled ovarian hyperstimulation it can be used as it improves oocyte and embryo quality and decreases FSH resistance, by making the ovary more sensitive to FSH. The mechanism of action of metformin and MI is different. Metformin reduces the glucose absorption and gluconeogenesis and MI activates PI3 kinase and opens the door for glucose entry into the cell. Both the drugs reduce insulin level of blood. In a comparative study it is shown that both treatments improved the glyco-insulinemic features of obese PCOS patients, but only metformin seems to exert a beneficial effect on the endocrine and clinical features of the syndrome [23].

When oral drugs fail to produce mature follicle due to insulin resistance, application of gonadotropin or laparoscopic ovarian drilling can help these women. Gonadotropin is expensive and there is risk of development of ovarian hyperstimulation syndrome (OHSS) and laparoscopic ovarian drilling is invasive. To avoid gonadotropin and laparoscopic ovarian drilling effective insulin sensitizers are definitely beneficial for patients. We tried to explore the efficacy of combined metformin and MI in folliculogenesis in insulin resistant PCOS patient. So, purpose of this study was to explore the beneficial effect of MI in addition to metformin instead of metformin alone in PCOS patient who does not ovulate with 1st line ovulation inducing agents.

Materials and Methods

This experimental study was conducted in Infertility Care and Research Center (ICRC) Ltd between January and December 2018. By following Rotterdam criteria, we diagnosed PCOS by oligomenorrhoea and ultrasonographic polycystic ovaries [2]. We started with 5 mg letrozole per day from D3 to D7 of the cycle and monitored the patient on D12 and onwards to observe folliculogenesis and ovulation. If no follicle attained the size of 17 mm by D16 we increased the dose by 2.5 to 5 mg in next cycle depending on response of 5 mg daily. If patient did not develop any mature follicle by 10 mg letrozole per day, we considered her as insulin resistant. In our previous study by HOMA test it is found that all CC resistant patients are insulin resistant [10].

By the same way it is also found that patients who fail to ovulate with maximum dose of letrozole (10 mg/day) are insulin resistant (Unpublished data). Before going for insulin sensitizers, we added tab glucocorticoid 0.5 mg every alternate day from D2 of the cycle for 5 days to reduce free

androgen level. In our previous study ovulation rate was 65% more when glucocorticoids were added with letrozole due to reduction of adrenal origin of androgen [24]. In-spite of that when patient did not ovulate, we recruited them for insulin sensitizer.

Within the study period by excluding hypothyroidism and diabetes mellitus we recruited 160 such patients of primary infertility for insulin sensitizers, whose partners' semen parameters were normal. By using lottery 80 patients received only metformin at a dose of 1500 to 2500 mg daily in divided doses according to BMI for 12 weeks and 80 patients received both metformin at the same schedule and MI (Inofem sachets, EP Establo Pharma, Poland) 2 gm. daily with 200µg folic acid for 12 weeks.

After 12 weeks we gave same drug for ovulation induction at which patient was resistant before using insulin sensitizers (Letrozole 10 mg daily for 5 days and glucocorticoid 0.5 mg every alternate day for 5 days). MI was omitted after 12 weeks but metformin was continued with same doses. Follicular tracking was done on D12 and onwards. Ovulation was confirmed by observing absence of previously observed mature follicle (s) (rupture of the follicle) by ultra-sonogram. Results were compared between two groups. Our main outcome measures were ovulation and pregnancy. So, no biochemical tests were done before and after treatment. When ovulation was confirmed with letrozole and glucocorticoids we continued the same regimen for next 5 cycles to complete 6 ovulatory cycles. Patients were advised for timed sexual intercourse and for pregnancy test in case of missed period either by pregnancy test kit or by βhCG as per patient's convenience. Viable pregnancy was confirmed by observing cardiac pulsation by ultrasonogram. Informed consent was taken from all patients and ethical permission was taken from ethical committee of ICRC. Student's t test and Chi square test were done for statistical analysis. A p value of <0.5 was considered as significant.

Results

Age and BMI of the patients were similar in both groups (Table 1). Ovulation rate was (77.50% vs 43.00%) and pregnancy rate was (43.75% vs 25.00%) in metformin + MI and metformin only group respectively, which is significantly higher in metformin and MI group than metformin only group, p <0.05 (Table 2). Two patients of metformin +MI group got pregnant at the end of the 3rd month before giving stimulation by letrozole and glucocorticoids.

Parameters	Metformin Mean ± SD	Metformin plus myo-inositol Mean ± SD	p-value
Age (Yrs)	26.47±2.98	27.12±2.32	0.125
BMI (Kg/m^2	23.63±2.16	24.23±2.24	0.956

Table 1: Patients characteristics.

Discussion

Though pathogenesis of polycystic ovarian syndrome still remains unclear, certain aetiological factors are demonstrated to be involved. Insulin resistance and compensatory hyperinsulinemia play pivotal role in this syndrome [7,25-27]. Insulin directly increases the ovarian production of androgen and indirectly reduces hepatic SHBG synthesis, resulting in hyperandrogenemia, the most important barrier for folliculogenesis [28,29]. Though androgen is responsible for FSH receptor amplification at a low dose and beneficial for proper folliculogenesis, high androgen level causes follicular atresia.

PCOS has multidimensional health hazard through endocrine and metabolic derangement. Anovulation and infertility are the commonest effect of PCOS in reproductive age. Studies proved that different insulin sensitizing agents rebalance the endocrine and metabolic profiles of these patients, ameliorating insulin resistance. By reverting pathology and reducing free testosterone level by increasing SHBG; they can restore ovulation capability.

Two inositols (MI and DCI) acting as insulin sensitizers have been demonstrated to positive influence, ameliorating their endocrine and metabolic profile both alone and in combination [30-35]. Metformin also significantly improves insulin sensitivity, menstrual cyclicity and restores spontaneous ovulation in many cases [20,36]. The mode of action of three agents (MI, DCI and metformin) is different. Metformin reduces intestinal absorption of glucose, reduces hepatic gluconeogenesis, increases glucose uptake by some peripheral tissues, DCI promotes glycogen synthesis and MI supports glucose entry into the cell [37]. All can be used individually or in combination to get additive effect.

Benelli et al described significant improvement of endocrine and metabolic derangement after combined therapy by MI and DCI [38]. Though DCI supplementation alone is not recommended by a recent study showing that the oocyte quality and ovarian response have been progressively worsened by the increased dose of DCI. High dose of DCI has been toxic to ovaries and oocyte maturation [39]. PCOS patients are deficient of MI and MI deficiencies are correlated

with many IR conditions [39]. The improvement of insulin sensitivity and the reduction of serum insulin demonstrated by MI supply are of paramount importance for ameliorating the clinical features of women with PCOS [40].

MI is generally well tolerated in therapeutic doses, with minor side effects reported at higher concentration [41]. Due to it's reported many positive effects we used MI for insulin resistant patients. In our situation MI is not locally produced and imported from outside. So, it is a bit expensive for our poor population. Metformin is available locally and much cheaper drug. When metformin is not enough for correcting metabolic defect and ovulation does not take place by oral ovulation inducing drug, patient needs either Gonadotropin or laparoscopic ovarian drilling. Gonadotropin again is expensive, needs monitoring and meticulous judgment for application. On the other hand, ovarian drilling needs surgery, which is invasive and expensive. So, for poor community before going for expensive drug or surgery it is very important to make the patient ovulatory by correcting metabolic defects.

We found that a group of patients do not respond to maximum dose of oral ovulation inducing agent along with metformin and glucocorticoids. That is why we tried to correct metabolic defect by applying MI. As MI is also a bit expensive than metformin we added 2 gm MI daily along with metformin to reduce the dose and price of MI instead of recommended 4 gm by other authors [42,43]. We compared the effect of this low dose of MI along with metformin and only metformin after failure of ovulation by Letrozole and glucocorticoids. It is found that after applying MI with metformin for 12 weeks patients' response to previous drugs were highly satisfactory.

We did not evaluate endocrine and metabolic profile after treatment with Metformin and MI. Because it is well established by many studies that endocrine and metabolic profile improved after treatment with metformin or MI [19-23,38,44,45]. Our main outcome measures were ovulation and pregnancy. So, we did not look for biochemical tests. By introducing simple drugs we observed ovulatory status. We also did not find out insulin resistance as we explored in our previous study that 100% CC resistant (CC 150 mg daily for 5 days) patients are insulin resistant by HOMA test [10]. We also observed that letrozole resistant (Letrozole 10 mg daily for 5 days) patients are also insulin resistant by HOMA test (Unpublished data). So, in this study when we did not get any mature follicle by ultrasonographic follicular tacking by using letrozole 10 mg daily for 5 days, we considered it as insulin resistant. After pretreatment by MI plus metformin and by only metformin, it is found that in both groups ovulation rate was increased but it was significantly higher in metformin and MI combination group (Table 2).

Parameters	Metformin N %	Metformin plus Myo-inositol N %	P value
Ovulation	35 43.00	62 77.50	0.000
Pregnancy	20 25.00	35 43.75	0.012

Table 2: Response to treatment.

All PCOS patients do not need insulin sensitizing agents. Treatment should be directed at specific metabolic or reproductive problems [17]. We used to solve metabolic problem when patients did not respond to oral ovulation inducing agents. Both ovulation and pregnancy rate were significantly higher when we used both metformin and MI as pre-treatment for short time. Ovulation rate was 77.50% vs 43.00% and pregnancy rate was 43.75% vs 25.00% in metformin plus MI vs only metformin respectively. Both are significantly higher in metformin and MI group than metformin only group ($p<0.05$). Two patients of Metformin +MI group got pregnant spontaneously without induction at the end of the 3rd month of therapy. In metformin and MI group pregnancy rate was 43.75% among all and it was 56.45% among ovulatory group.

The cost of metformin is 360-600 BDT (4.2-7.1 USD) per month and that of MI 2 gm is 3100 BDT (37 USD) per month. To get satisfactory result if we could reduce the cost of MI (by using 2 gm along with metformin instead of recommended 4gm) it would be very helpful for our poor patients. By using MI we could avoid more expensive gonadotropins as well. So, this step by step use of drugs for PCOS patients is very effective to make the patient ovulatory and pregnant and it saved money for a large number of patients. Though it takes time but for PCOS patient it is not problematic as ovarian reserve is very high (AMH is 11.1 ng/ml, ranging from 3-17.1ng/ml) and patients are generally young as irregular menstruation forced them to come to doctor. In conclusion it can be said that myo-inositol supplement is effective in promoting ovulation in PCOS patients with insulin resistant. By eliminating the necessity of gonadotropin it can reduce the cost of the treatment.

Disclosure

None

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