Role of Metformin in PCOD : A Comparative Study

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Summary

A prospective study was carried out at Purandare Hospital, Andheri, Mumbai and JJ Hospital, Mumbai among 100 PCOD patients with infertility with an objective to study the effectiveness of metformin as an adjuvant with clomiphene citrate (CC) for ovulation induction in these patients. 50 patients were started on tablet metformin (500mg) bd and tablet Chromium Picolinate once a day, which comprised the study group. Ovulation induction in all 100 patients was done with 100mg of CC and follicular scans were done from day 11. IUI was done in patients with successful ovulation on two consecutive days. Ovulation induction was much superior in metformin group in the first cycle itself as compared to control group (96% vs 24%). Patients who failed to ovulate were given 200mg of CC and if required HMG injections (150 IU) on day 4 and day 5. Only 10% patients of control group responded with 66% failure rate. Pregnancy rate was 40% in study group and 16% in control group. Thus metformin along with CC give excellent result for ovulation induction in patients with PCOD.

Introduction

PCOD is the commonest cause of ovarian factor infertility. There is a new appreciation of the role of hyperinsulinemia in the development of PCOD. It is characterised by insulin resistance accompanied by compensatory hyperinsulinemia (elevated fasting blood insulin levels) which has been clearly demonstrated by many investigators (Arthur et al 1999). These patients also have impaired glucose tolerance evidenced by an abnormal GTT (Pratapkumar and Nambiar, 1998). Hyperinsulinemia can be present in both obese and non-obese patients but is more prevalent in obese patients (Dunaif and Shoham 1993).

Hyperinsulinemia causes hyperandrogenism in PCOD by the following mechanism: -

a) Increased insulin levels bind to type I IGF receptors leading to activation of IGF-II and IGF-I factors which cause increased androgen production in theca cells in response to LH.
b) Insulin inhibits hepatic synthesis of SHBG and IGFBP-I leading to increased free levels of testosterone and androstenedione.

Patients of PCOD are also at risk of developing android obesity, abnormal lipid profile, cardiovascular diseases and non-insulin dependent diabetes mellitus.

The traditional treatment with clomiphene citrate (CC) and other hormones is associated with high failure rates. Ovarian drilling, electrocoagulation and wedge resection of ovary are invasive procedures and are frequently associated with formation of post operative adhesions. (Naether et al 1999)

A promising new treatment option for PCOD is metformin, an oral antidiabetic agent given in a dose of

1500-1700 mg/day. It improves insulin sensitivity and causes significant reduction in gluconeogenesis. It reduces levels of insulin, LH and testosterone thus achieving ovulation (Velazquez et al 1997). It facilitates weight loss and reduction of excess body hair and in non-diabetics it does not lower the blood sugar (Diamanti-Kandarakis et al, 1998). It also reduces long term risk of heart disease, stroke and diabetes mellitus by lowering triglycerides and LDL levels and elevating HDL levels. Thus metformin reverses endocrinopathy, restores menstrual cycles and restores fertility.

Materials and Methods

The study was conducted among 100 PCOD patients with infertility attending gynaecology OPD at JJ Hospital and Purandare Hospital, Andheri. The study was done during a 6 months period from Feb 1999 to Nov 1999. They were diagnosed to have PCOD on TVS showing necklace pattern of multiple small follicles. Hormonal profile of FSH, LH and testosterone was done for all patients. Other causes of infertility were ruled out. A record of weight and waist to hip ratio was kept for all patients.

Patients were randomly divided into study group and control group of 50 each. Patients in study group were started on Metformin 500mg bd and tab. Chromium picolinate one daily along with CC 100mg from D3 of menses for 5 days and were given for three months. Patients in the control group were given only CC in similar manner. Follicular studies were done for all patients from D11 and those who achieved a follicle size of 1.8 cm were given injection HCG 10,000IU IM. IUI was done 36 hours after HCG on two consecutive days and tab. Duphaston 10mg daily was given for 10 days as luteal phase support.

Patients in both groups who failed to have follicular maturation were started on 200mg of CC and those who still failed to respond were given injection HMG 150IU on D4 and D5 along with CC and repeat follicular studies were done.

Both the groups were compared in regard successful follicular maturation, failure of follicular maturation, requirement of increased dose of CC and HMG and incidence of pregnancy.

Observations and Results

All the patients were of the age between 20 to 36 years. Seventy percent patients of study group and 64 patients of control group belonged to the age group of 25 to 28 years. Ninety two percent patients of study group and 84% patients of control group had primary infertility and remaining had secondary infertility. Seventy percent patients in the study group and 64% patients in the control group were obese.

Ninety six percent patients in the study group had follicular maturation in the first cycle itself with only 4% failure rate. Whereas only 24 patients in control group had successful follicular maturation with 76% failure rate. Two patients in both the groups had delayed follicular maturation at 20 to 22 days (Table I). In the study conducted by Nestler et al (1998) ovulation induction was carried out in obese women with PCOD using metformin and CC and compared with those who were given placebo and CC. They reported with 90% patients ovulated in the metformin group whereas only 8% ovulated in the CC group.

Only 3 patients in the study group required 200mg of CC as compared to 40 patients in control group. All 3 patients of study group responded in compared to only 5 in control group with 70% failure rate (Table II).

Among 38 patients of control group who were to given CC and HMG injections only 3 patients ovulated 2 had delayed maturation with 66% failure rate (Table III).

Incidence of pregnancy was 40% in study group and 16% in control group (Table IV).

Table I: Follicular maturation in the first cycle

Time in days	Study group		Control group	
	No. of cases	%	No. of cases	%
11-13	40	80	5	10
14-16	5	10	3	6
17-19	2	4	2	4
20-22	1	2	2	4
Failure of maturation	2	4	38	76

Table II : Follicular maturation with 200mg of clomiphene citrate.

Time in days	Study group		Control group	
	No. of cases	%	No. of cases	%
11-13	2	4	1	2
14-16	1	2	1	2
17-19			0	0
20-22			3	6
Failure of maturation			35	70

Table III : Follicular maturation after addition of HMG injections.

Time in days	Control group	
	No. of cases	%
11-13	1	2
14-16	1	2
17-19	1	2
20-22	2	4
Failure of maturation	33	66

Table IV : Incidence of pregnancy

No. of IUI cycles	Study group		Control group	
	No. of cases	%	No. of cases	%
1-2	10	20	3	6
3-4	7	14	2	4
5-6	3	6	3	6
Total	20	40	8	16

In the study group 80% patients lost weight between 1-4kg.

The present study has shown that ovulation induction in patients receiving metformin and CC was much superior as compared to patients receiving only CC and HMG.

In the first cycle itself there was 96% success rate in metformin group and 24% in control group. Only 3 patients required 200mg of CC in study group as compared to 40 patients in control group. Thirty eight patients in control group required HMG along with CC still having failure rate of 66%. This shows that metformin reduces the dose of CC required for ovulation induction and avoids the use of HMG thus reducing the incidence of hyperstimulation and also the cost of the treatment.

Pregnancy rate after IUI was 40% in metformin group and 16% in control group.

As shown in this study metformin and chromium picolinate, both cause weight loss in obese patient which in turn improves ovulation in PCOD patients.

Thus the present study proves that metformin is the safest, cost effective and non invasive method of ovulation induction in PCOD patients and also helps in avoiding invasive procedures in resistant cases. We now have an opportunity of creating a supportive and a preventive health care attitude in anovulatory women which not only corrects specific clinical consequences of anovulation but also reduces major adverse effects on overall health.

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