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Study of Metformin in Polycystic Ovarian Syndrome

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Abstract: *Polycystic ovarian syndrome (PCOS) is a common hormonal disorder among women of reproductive age and is a leading cause of infertility. Insulin resistance and hyperinsulinemia play a key role in pathophysiology of PCOS . Recognition of hyperinsulinemia has led to the intervention of Insulin sensitizing drugs to play a key role in the management of PCOS . Hence the present study was undertook to measure the efficacy,and safety of insulin sensitizing drug metformin in reversing the metabolic and endocrine disturbances in fifty women with polycystic ovarian disease. Metformin 500 mg thrice daily was given until the cysts disappeared which was taken as the end point of the study. Follicular studies were done to check the effect of metformin on ovulation . Significance was tested by paired t test and p value calculated .Metformin was found effective in regressing polycystic changes in ovary,regularization of menustral cycles and improving ovulatory cycles . The present showed that metformin has a beneficial role in effective management of PCOS.*

Keywords: *Metformin, PCOS.*

I. Introduction

Polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation (HA),[1] or Stein–Leventhal syndrome,[2] is one of the most common endocrine disorders among women.

symptoms and signs of PCOS are very heterogenous.The disease presents with any of the following combination features like menustral irregularities (irregular menustral cycles,amenorrheoa),signs of hyperandrogenism(hirsutism,acne,alopecia),a characteristic polycystic appearance of ovaries on ultrasound examination and endocrine disturbances involving high serum concentration of leutinizing hormones and androgens.

A link between disturbed insulin action and PCOS was first highlighted in 1980[3].Insulin resistance and compensatory hyperinsulinemia play an important role in pathophysiology of PCOS.Insulin resistance is the lack of cellular sensitivity with respect to glucose metabolism.

The endocrine manifestations of hyperinsulinaemia are of hyperandrogenaemia leading to anovulation, reproductive failure and skin stigmata(acne,alopecia,hirsutism).In addition hyperinsulinaemia is associated with metabolic disturbances like type 2 diabetes mellitus,dyslipidaemia ,hypertension,and elevated plasma plasminogen activator-1 concentrations,all of which are risk factors for cardiovascular disease.

Regression of the symptoms of PCOS is achieved by reducing hyperinsulinaemia .Hence recognition of this hyperinsulinaemia has led to the intervention of insulin sensitizing drugs to play a key role in the management of PCOS.Among the available insulin sensitizing agents metformin is widely used drug.c linical trails with metformin have recorded a wide range of benefits[4]

II. Objectives

To study the efficacy and safety of metformin in regularization of menustral cycles and regression of cysts in polycystic ovarian disease

III. Methodology

The study was performed on 57 women with PCOS in the out patient department of obstretics and gynaecology,government general hospital, Guntur. Before starting the study the ethical committee approved the protocol.Written and informed consent was obtained from each patient.

Selection of patients: was done by standard diagnostic assessments:

1. History- taking specifically for menustral pattern (oligomenorrhoea,amenorrhoea), features of hyperandrogenism (hirsutism,acne) .

2. Gynaecologic ultrasonography- According to Rotterdam 12 or more follicles should be seen in an ovary on ultrasound examination. The follicles are oriented in the periphery giving the appearance of 'string of pearls'.Polycystic ovaries are defined as 12 or more follicles in at least 1 ovary measuring 2-9mm volume of >10cm3

3. Biochemical tests-

- Serum level of leutinizing hormone is elevated.The elevated level of LH:FSH ratio > 1.5-3 is an indicator of PCOS.
- Reversible estradiol :estrone ratio .Estrone level is markedly elevated in PCOS
- Sex hormone binding globulin is elevated in PCOS
- Adrostenedione is elevated.
- 2-Hour oral glucose tolerance test (GTT) in women with risk factors (obesity, family history, history of gestational diabetes) may indicate impaired glucose tolerance (insulin resistance) in 15–33% of women with PCOS. Frank diabetes can be seen in 65–68% of women with this condition. Insulin resistance can be observed in both normal weight and overweight people.

50–80% of people with PCOS may have insulin resistance at some level.

Inclusion criteria:

1. Age: 15-30 yrs
2 .Women with irregular menustrual cycles and evidence of polycystic ovaries on ultrasound

Exclusion criteria:

Other causes of chronic anovulation
1. Hyperprolactinemia
2. Hypothyroidism
3. Congenital adrenal hyperplasia

Procedure : 57 women who had polycystic ovaries on ultrasound were selected for the study.Detailed menustrual history regarding age of menarche, menustrual cycle and period of infertility were obtained from every patient.Each patient was questioned about past and family history of diabetes mellitus and hypertension.Body weight and height were estimated to calculate body mass index.Clinical examination with special reference to hirsutism was done.Investigations like ultrasound,fasting blood glucose, and thyroid stimulating hormone levels were done. Among 57 women seven women discontinued due to incompliance.So 50 women were taken into study.These 50 women were given metformin 500mg once daily for one week,followed by twice daily in the second week,and then thrice daily from third week to avoid incomplaince.ultrasound examination was done every month to note the disappearance of cysts and evidence of ovulation was seen by follicular study from day 11to day 21 alternately .Results were tabulated ,significance was tested by paired t test and p values.Results were shown graphically also.

IV. Results

Metformin was well tolerated by all patients. Among 50 patients 18 patients were between 15-25 yrs and 32 patients were between 26-32 yrs. So the incidence of PCOS is more at the age of 15-25 yrs.

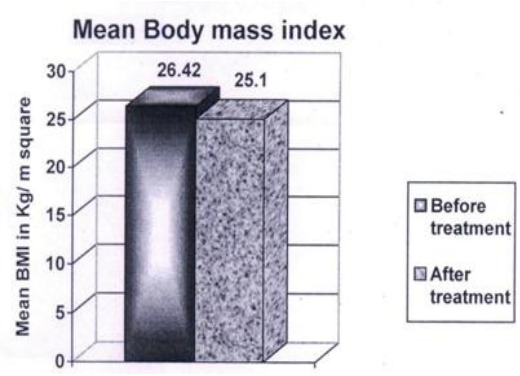
AGE DISTRIBUTION

Age(Yrs)	No. of Patients(n=50)
15-25	18
26-35	32

Body Mass Index: The BMI mean±(SD) before treatment was 26.42kg/m2±(2.52) and after treatment it reduced to 25.1kg/m2 ±(2.59)(p>0.05).

MEAN BODY MASS INDEX

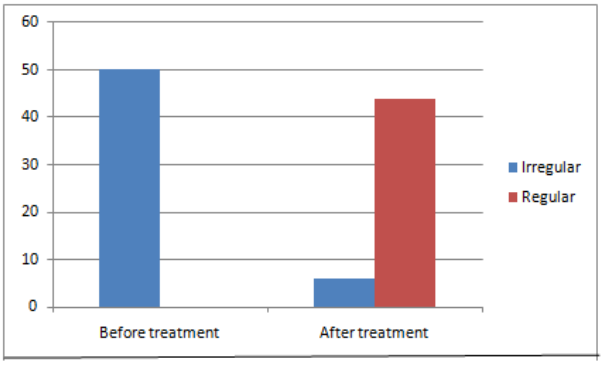
BMI(Kg/m2)	BEFORE TREATMENT	AFTER TREATMENT
mean±SD	26.42±2.52	25.1±2.59



Menustrual Cycles: Among 50 (100%) patients who had irregular periods , 44%(88%) patients showed improvement in menustral cycles.

MENUSTRUAL CYCLES

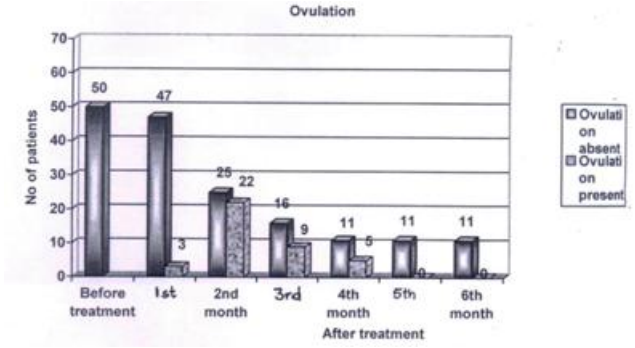
MENUSTRUAL CYCLES	BEFORE TREATMENT	AFTER TREATMENT
Irregular	50	6
regular	0	44



Ovulation: Among 50 patients ovulation was seen in 39 (78%) patients at the end of the first month out of 50 patients ovulation was seen in 3 patients .at the end of the second month out of 47 patients ovulation was seen in 22 patients .at the end of the third month out of 25 patients ovulation was seen in 9 patients. At the end of 4 th month out of 16 patients ovulation was seen in 5 patients.in the 11 patients there was no ovulation at the end of 6 months.

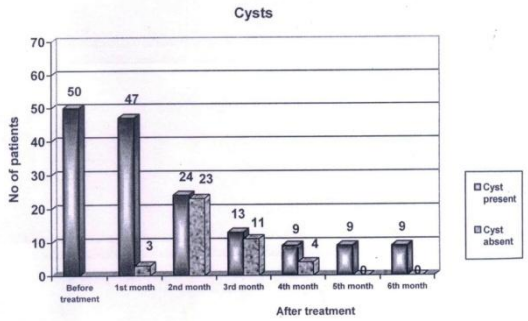
Ovulation

	Before treatment	After treatment						
	(n=50)	1 month (n=50)	2 month (n=47)	3 month (n=25)	4 month (n=16)	5 month (n=11)	6 month (n=11)	Total number of patients at the end of the study (n=50)
Ovulation absent	50	47	25	16	11	11	11	11
Ovulation present	0	3	22	9	5	0	0	39



Cysts: Among 50 patients 41 patients (82%) patients showed disappearance of cysts .At the end of 1st month out of 50 patients cysts disaapeared in 3 patients . At the end of 2 nd month out of 47 patients cysts disappered in 23 patients .At the end of 3 rd month out of 24 patients cyst disappeared in 11 patients. At the end of 4 th month out of 13 patients cyst disappeared in 4 patients.in patients cyst did not disappear at the end of 6 month.

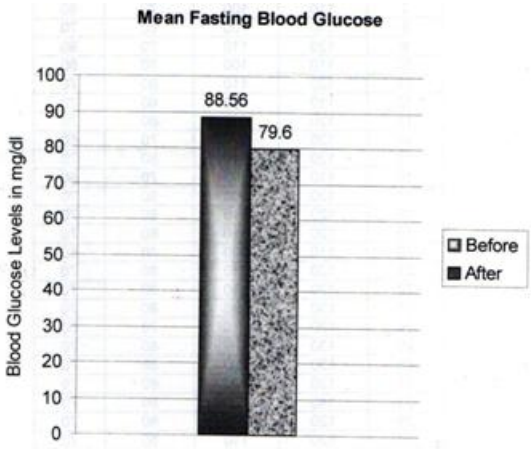
	Before treatment	After treatment						
	(n=50)	1 month (n=50)	2 month (n=47)	3 month (n=24)	4 month (n=13)	5 month (n=9)	6 month (n=9)	Total number of patients at the end of the study (n=50)
Cyst present	50	47	24	13	9	9	9	9
Cyst absent	0	3	23	11	4	0	0	41



Fasting Blood Glucose: The fasting blood glucose mean±(SD) before treatment was 88.56mg/dl ±(8.59) and after treatment it reduced to 79.58mg/dl ±(6.92)($p<0.001$,highly significant).

MEAN FASTING BLOOD GLUCOSE

Fasting blood glucose mg/dl	Before treatment	After treatment
Mean±SD	88.56±8.59	79.6±6.92



V. Discussion

The results in the present study suggested that metformin has an effective role in the management of PCOS. In the study metformin improved the regularization of menustrual cycles in 88% of previously amme-norrheic women with PCOS. These results were consistent with those of Glueck,C.J.,Wang,P.,Fontaine,R.et al.[5]who concluded in their study that metformin resumed normal menses in 91% of previously ammenorrheic women.

The cycles became ovulatory after metformin treatment in 78% women with previous anovulatory cycles.These results were consistent with that of of Moghetti P,Castello R, Negri C, Tosi F,PerroneF,CaputoM.et al[6].(J.Clin Endocrinol Metab 2000;85:139-46).

In their study they concluded that metformin showed 79% improvement in ovulation.

The above results show that metformin had a promising role with regression of polycystic ovarian

changes ,regularization of menustrual cycles and resumption of ovulation in the management of PCOS.

VI. Conclusion

Insulin resistance plays a key role in the pathogenesis of PCOS,altering the endocrine and metabolic disturbances.In this regard insulin sensitizing drugs like metformin show promising results in reversing this endocrinopathy and improvement in the metabolic disturbances.50 patients were recruited in the study.Metformin 500mg thrice daily was given until the cysts disappeared which was taken as the end point of the study.Follicular studies were done to check the effect of metformin on ovulation.Significance was tested by paired t test their p value was calculated. Results were represented graphically.

Metformin was found to be effective in regressing polycystic changes in ovary , regularization of menustrual cycles and improving ovulatory cycles .

In conclusion metformin has a beneficial role in the management of PCOS

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