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PCOS – The Role of Obesity, Hyperinsulinemia and Metformin Therapy

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OBJECTIVE - To study the role of hyperinsulinemia and obesity in polycystic ovarian syndrome (PCOS) and the efficacy of metformin for anovulation resistant to clomiphene citrate (CC). **MATERIALS AND METHOD -** Infertile patients who failed to ovulate with 100 mg CC were recruited. Baseline body mass index (BMI), menstrual cycle pattern and hirsutism were noted and fasting serum insulin, GTT and day 2 FSH and LH were done. Patients were treated with metformin 500 mg three times a day for atleast three months and thereafter BMI, hirsutism and menstrual cycle pattern were rechecked, biochemical tests repeated and patients induced again with CC 100 mg followed by follicular imaging and IUI. Results were analysed by Wilcoxon test. **RESULTS -** Fifty patients were recruited. Fourteen patients were lost for follow-up and two discontinued treatment due to side effects. Hyperinsulinemia was seen in 8.8% of women and 38.2% had normal BMI. Insulin levels and BMI decreased by 38.4% and 5.7% respectively. Seventy nine patients achieved regular cycles and 18.5% became pregnant. **CONCLUSION -** PCOS does not necessarily associate with hyperinsulinemia and elevated BMI. Although metformin does bring about reduction in BMI and regularises cycles, it does not always decrease insulin levels.

Key words : PCOS, metformin, insulin resistance

Introduction

Polycystic ovarian syndrome (PCOS) is the commonest cause of menstrual disorders and anovulatory infertility. Although it was initially described in 1935 by Stein and Leventhal as a rigid syndrome complex of oligomenorrhoea, hirsutism and obesity together with a demonstration of enlarged polycystic ovaries, this viewpoint has undergone a great change.

Way back in 1921, the French physicians Achard and Thiers provided the first description of the relationship between androgen excess in women and disturbances in carbohydrate metabolism which was dubbed "diabetic des femme a barbe" (diabetes of the bearded lady). Although earlier these two conditions, that is PCOS and hyperandrogenemia were considered distinct separate entities, it took us almost 60 years to understand that the two are linked by a common feature – hyperinsulinaemia and insulin resistance.

As our knowledge regarding this rather mysterious and enigmatic condition evolved, newer therapeutic modalities come to light and sometimes even fall by the wayside later on.

Numerous questions have baffled and continue to baffle researchers over time. Is hyperinsulinemia the backbone of PCOS? Does hyperandrogenism cause hyperinsulinemia or is it vice-versa? Is obesity an essential feature or is it only an aggravating factor? Have we found the treatment for PCOS?

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Materials and Method

Fifty patients of infertility (primary and secondary) with PCOS that failed to respond to 100 mg of clomiphene citrate (CC) for five days were recruited for this study conducted from December 1998 to December 2000. Baseline parameters evaluated were body mass index (BMI), menstrual cycle pattern, hirsutism, fasting serum insulin, half hour GTT with 75 gms glucose, DSH, LH, LH:FSH ratio and evidence of insulin resistance (FBS : Insulin=4.5) Patients were treated with 500g metformin three times a day after meals for three months after which they were reevaluated for the above parameters. While continuing metformin, ovulation was induced with CC 100 mg daily from D2 to D6 and follicular imaging done from D11. Success was measured by presence of a 18 mm follicle with subsequent features of ovulation as seen by TVS. Fourteen patients were lost for follow up while two dropped out because of side effects. Results were analysed by Wilcoxon test.

Results

Summary of clinical observations is given in Table I. Most in the patients (62%) were obese while 70.6% were oligomennorrhic. However the correlation between BMI and cycle pattern was not found to be significant ($p=0.57$). Hyperinsulinemia (levels $\geq$ 30µIU /ml) was seen in only 8.8% patients and again corelation of BMI with insulin levels and insulin resistance was not significant ($p=0.7$ and 0.3 respectively). Insulin resistance was however seen in 41.1% of patients; both lean and obese had abnormal carbohydrate metabolism.

Table - I : Summary of Observations

Parameter (n=34)		No.	Percentage
	Normal	13	38.2
	Gr I obesity	17	50.0
	Gr II obesity	4	11.8
BMI (kg/m^2)	Mean BMI	25.0 ± 4.42	
	Range	36.0 – 16.0	
Cycles	Normal	10	29.4
	Oligomenorrhoea	24	70.6
Hirsutism	Present	12	35.3
	Absent	22	64.7
	Mean FSH	5.87 ± 2.45	
	Mean LH	8.4 ± 5.72	
FSH and LH	Mean LH: FSH	1.68±1.32	
	LH:FSH = 2	10	29.4
	LH : FSH normal	31	91.2
Insulin (μIU/ml)	Hyperinsulinaemia	3	8.8
	Mean insulin	20.43 ± 17.09	
	Abnormal insulin level	14	41.2
GTT	Normal	20	58.8
Insulin resistance	FBS/Insulin Ratio = 4.5	14	41.1%
	Mean FBS/Insulin	8.85 ± 9.84	

The effect of metformin on various parameters is shown in Table II. There was an improvement in the BMI in 69.5% of the patients with an overall reduction of BMI by 5.7%. Both lean and obese patients were found to have lost weight. Nineteen out of 24 patients (79.1%) regularized cycles with metformin therapy (p=0.00001).

There was however no change in hirsutism with metformin therapy. Although there was a 9% increase and 14% reduction in the mean FSH and LH values respectively, the change was not statistically significant. All 34 patients with or without hyperinsulinemia had a mean reduction of 38.4% in their insulin levels (p=0.0002). Of the 14 patients (41.2%) with abnormal GTT, 12 (85.7%) had normal GTT values after treatment (p=0.01).

Of the 14 patients (41.1%) with insulin resistance, 12 patients (85.7%) saw a disappearance of insulin resistance (p=0.001) or the mean FBS: Insulin ratio increased by 45.6% (p=0.00001). After metformin therapy, of the 29 patients who achieved regular cycles four continued to have multiple small follicles on TVS. Of the five patients who continued to have oligomenorrhoea, two had good follicles and three had multiple small follicles on TVS (p=0.07). Of the 34 anovulatory patients studied, 27 (97.4%) had ovulation after metformin therapy (p=0.0001). Five pregnancies resulted giving a pregnancy rate of 18.5%.

Discussion

PCOS is a condition which originates possibly at the time of puberty due to an interplay of genetic factors, obesity and post-receptor insulin defect leading to insulin resistance. Fifty percent of women with PCOS

have an android type of phenotype characterized by waist: hip ratio greater than 0.85 as shown by Lefebvre et al[1]. Pasquali et al[2] showed that even a 5% reduction in BMI results in improved insulin sensitivity, menstrual cycle pattern and fertility rates and should be the first line of management in patients with PCOS

Table - II : Results with Metformin Therapy

Parameter (n=34)	Before Treatment	After Treatment	Percentage Change	P value
BMI (kg /m)	25.0±4.43	23.6±4.24	-5.7	0.0001
FSH	5.87±2.45	6.41±3.05	+9.1	0.16
LH	8.40±5.71	7.20±4.29	-14.2	0.59
Mean LH:FSH	1.68±1.32	1.19±0.71	-29.1	0.07
Insulin (μIU /ml)	20.45±17.09	12.59±8.73	-38.4	0.0002
FBS: insulin	8.49±9.84	12.36±10.83	-45.62	0.00001

Table - III : Comparison of insulin levels

Insulin levels (μIU/ml)	Before	After	Percentage change
Kolodziejczyk et al[4]	26.6	16.5	- 37.96
Jean-Charles et al[5]	19.7	21.8	+ 10.65
Pirwany et al[6]	21.0	10.55	- 49.76
Laure et al[7]	17.3	16.9	- 2.31
Ozer and Sadi[8]	21.2	20.8	- 1.88
Nestler et al[9]	17.3	9.0	- 47.97
Study Present	20.45	12.59	- 38.4

This study shows that hyperinsulinaemia is not a common association with PCOS and evaluation of insulin resistance rather than a single insulin value may be a more sensitive indicator. Similar results were also obtained by Lesro et al[3]. However in this study even though the insulin levels were within normal range, a further reduction in levels was associated with therapeutic effect (Table III).

Metformin is a biguanide, which acts principally by suppression of gluconeogenesis in the liver. It enhances the binding of insulin to its receptors and also increases GLUT4, which improves the peripheral uptake of glucose. It is well tolerated with minimal side effects of nausea, vomiting and diarrhea. Lactic acidosis and hypoglycemia are rare. Metformin effectively reduces insulin levels, improves carbohydrate metabolism, regularize cycles and improves fertility rates as seen in this study and also in other studies (Table IV) Vincenzo et al[11] showed that metformin not only brings about spontaneous ovulation in previously anovulatory women, but it also significantly reduces the risk of hyperstimulation by exogenous gonadotrophins. Nestler et al[9] however found metformin ineffective in reducing BMI suggesting that probably some factors also may be responsible and this is where the role of leptins needs to be further defined.

Pregnancy rate of 18.5% with metformin therapy although not much higher than that achieved by other therapeutic modalities for the treatment of PCOS, is comparable to the 19% and 16.6% pregnancy rates in the studies by Velazquez et al[10] and Vincenzo et al[11] respectively.

Insulin resistance and not hyperinsulinemia is characteristic of PCOS and is independent of obesity though the latter does aggravate the existing insulin resistance. Metformin is effective in the treatment of

anovulatory infertile patients with PCOS. It also helps in regularizing menstrual cycles and correcting abnormal carbohydrate metabolism in these patients. Although metformin does seem to be the most logical solution, it may not provide perfect answers to all our questions.

Table - IV : Comparison of the Effects of Metformin

Various studies	Percentage Change in BMI	Cycle pattern percentage of patients who improved	Percentage of Change in LH: FSH ratio
Kolodziejczyk et al[4]	- 4.3	-	+ 18.47
Jean Charles et al[5]	- 3.9	-	-
Pirwany et al[6]	- 1.0	38.8	-
Velazquez et al[10]	- 2.12	95.7	- 45
Laure et al[7]	+ 1.26	68.8	No change
Ozer and Sadi[8]	- 0.33	-	- 3.7
Nestler et al[9]	No change	89.0	-
Present study	- 5.7	79.16	- 28.1

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