

Use of Metformin in Women with Polycystic Ovary Syndrome with Impaired Fertility

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Abstract: *Many studies based on the role of IR in PCOS have demonstrated the possible role of insulin-sensitizing agents, particularly Metformin, in the treatment of PCOS. A series of studies in women with PCOS, indicated that Metformin reduced insulin resistance and increased ovulation and pregnancy without, or sometimes with, clomiphene citrate (CC) (4, 5). However, Metformin's exact role in managing women with PCOS has been quite controversial. In a group of women with PCOS and impaired fertility (76) presenting in our gynecological clinic, we have seen the different treatments used by the gynecologist and have concluded that in 80 % of them Metformin is used alone or with contraceptives (38 %). Metformin was a treatment of choice especially in overweight or obese women and this is concordant with high IR in this group. However, we have no sufficient data on ovulation or pregnancy rate improvement. We concluded that further investigations are necessary to determine if Metformin has a role in the reproductive or only metabolic aspect of PCOS.*

Keywords: PCOS, insulin resistance, therapy

1. Introduction

Good evidence supports the hypothesis that decreased peripheral insulin sensitivity (or insulin resistance) and related hyperinsulinemia are pivotal in the pathogenesis of the polycystic ovarian syndrome. (1). Peripheral insulin resistance is most evident in overweight patients but obesity and polycystic ovarian syndrome each seem to have a separate and synergistic relation with insulin resistance. (1) The exact mechanism (s) for insulin resistance is uncertain, but a post-receptor defect in adipose tissue has been identified. (1) Besides insulin resistance in other organs, ovaries remain sensitive to the action of insulin, and both with insulin-like growth factor-1 have stimulatory effects on thecal androgen production. (2) This is evident in some lean women with polycystic ovarian syndrome, who may not have insulin resistance and hyperinsulinemia, but an enhanced ovarian sensitivity to insulin. Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin-like growth factor-1 binding protein. A reduction in sex hormone binding globulin leads to an increase of the biologically available free testosterone. Eventually, it became clear that insulin resistance is a common feature in the disorder and is not directly related to obesity (3)

Many studies, based on the role of IR in PCOS, have demonstrated the possible role of insulin-sensitizing agents, particularly Metformin, in the treatment of PCOS. Metformin is a biguanide that lowers blood glucose levels in hyperglycemic individuals with type-2 diabetes mellitus but has no effect on glucose levels in normal subjects. A series of studies in women with PCOS, indicated that Metformin reduced insulin resistance in women with PCOS and increased the ovulation and pregnancy without, or sometimes with, clomiphene citrate (CC) (4, 5). However, the exact role of Metformin in the management of women with PCOS has been quite controversial.

Aim of Study

In a group of women with PCOS and impaired fertility presenting in our gynecological clinic we have seen the different treatment used by the gynecologist and to determine the importance of Metformin, alone or in combination with other drugs according the PCOS characteristic.

2. Material and Methods

We examined the different treatments that are used by our gynecologist in women with PCOS and impaired fertility in our clinic. We have seen this according the BMI (normal weight, overweight, or obese) and the insulin resistance, and the combination of Metformin with other drugs. The insulin resistance is determined by calculation of HOMA (Homeostasis Model Assessment, HOMA) index. The classification of PCOS is made according to 2003 Rotterdam and NIH 2012 criteria. (6)

3. Statistics

SPSS software was used for statistical analysis. Continuous data were assessed for normal distribution using the Shapiro-Wilk test. Student T-test or Kruskal-Wallis were used to compare continuous variables based in whether they followed a normal or not normal distribution. Dichotomous variables were compared with a two-tailed Chi-square or Fischer exact test where appropriate. P-value <0.05 was considered statistically significant.

4. Results

76 women aged between 23 and 38 were recruited. Mean age was 29.53 ± 4.3 years old. The mean menarche age was 13 ± 0.9 years old. 92% of the women had irregular cycle. The mean length of a cycle was 40 ± 22 days ranging from 25 to 180 days. The mean number of months in amenorrhea was 3.4 ± 2.2 months, ranging from 2 to 12 months. Hirsutism was present in 51% of the sample, acne in 38% and PCO

morphology in 100% of the patients. 43 % of the sample had all 3 diagnostic criteria of PCOS and, 56.6% has two diagnostic criteria fulfilled. The phenotype distribution is shown on Table 1.

Table 1: Distribution of PCOS phenotypes

	n	%
Phenotype A (HA+OA+PCOM)	33	43.4
Phenotype B (HA+OD)	0	0
Phenotype C (HA+PCOM)	6	7.9
Phenotype D (OA+PCOM)	37	48.7

32 patients had difficulty conceiving and the mean time trying for pregnancy was 2.7 years, ranging from 4 months to 8 years.

The mean HOMA-IR was 5.9 ± 1.7 and considering a cut-off of 2.5 for insulin resistance, all patients had insulin resistance. Only 3.9% had a HOMA-IR < 3, 55.3% had a HOMA-IR between 3-6.5 and 40.8% had severe insulin resistance with a HOMA-IR > 6.5%

In our sample of 76 women with PCOS n= 61 (80%) were treated with Metformin, and the mean dose of Metformin was $804 \text{ mg} \pm 237$, ranging from 500 to 1700 mg.

Table 2: Metformin use in women with PCOS and insulin resistance

	HOMA-IR			
	< 3	3	- 6.5	>6.5
Metformin use	33.3%		72.5%	100%

We have these results in women using Metformin according to HOMA-IR; in normal IR (HOMA<3), MT was used in one-third (33.3%), and in the groups with high IR, it was respectively used in 72.5 % with intermediated HOMA, and in all (100%) with severe IR (> 6.5) (Tab 2)

Table 3: Metformin use in women with PCOS according to BMI

	BMI		
	Normal	Overweight	Obese
Metformin use	25%	81.8%	100%

In PCOS women with normal weight (n= 4) all had a moderated IR (HOMA-IR between 3 and 6.5) and only one patient was treated with Metformin.

All obese patients with a BMI above 30 were treated with Metformin and 80% of them had severe insulin resistance with a HOMA-IR >6.5. In the group of normal weight 1 (25%) used Metformin, but in the other groups the metformin treatment was higher, respectively 81 % of overweight women and 100 % of obese.

Oligomenorrhea was present in 92 % of the women with PCOS. However, only 42% of women were previously treated with oral contraceptives. 50% of women not having a regular cycle were not taking oral contraceptive. 3.4% were taking myoinositol. 31.6% were taking both Metformin and oral contraceptive, 10.5% were taking spironolactone.

5. Discussion

In this study we have demonstrated that most of women with PCOS treated by gynecologist had used for a period Metformin (80 %), because in all women we have IR from moderated to high HOMA. The Metformin was used even in women with HOMA < 3, but it was used in a higher percentage in the overweight (81.8 %) and obese (100 %).

There are many studies that confirm that use of Metformin has a good impact in lowering IR but the role in ovulation induction, pregnancy, live-birth rate, and miscarriage are discordant.

Several studies demonstrated that Metformin is associated with a statistically significantly higher ovulation rate compared with placebo (7-9, 12). There is a limited group of smaller studies showing no benefit (11) or only non-statistical improvement in ovulation (13).

The existing randomized trials examining clinical pregnancy rate in patients treated with Metformin vs placebo fail to detect any improvement with Metformin (7-11, 14-16). However, a large meta-analysis was suggestive of a modest improvement in clinical pregnancy rate (17).

In our study resulted that in PCOS women Oligomenorrhea was present in 92 % of cases, but only 42% of women were previously treated with oral contraceptives. This could be related mainly to cultural barriers on starting oral contraceptives. The combination of oral contraceptive with Metformin was used only in 31.6% of PCOS women.

There are studies that assessed ovulation, clinical pregnancy rate, and/or live birth in patients treated with Metformin vs CC (10, 11, 17-22) and most of them demonstrated that CC is superior to Metformin in the achievement of both ovulation and pregnancy (18, 21). Only one RCT indicated that Metformin was associated with statistically improved outcomes compared with CC. (20).

A systematic review stratified meta-analysis of Metformin vs CC in participants according to BMI but the results were opposite one in favor of Metformin (20) and other to CC (10).

There is fair evidence from one large, well-designed RCT that Metformin alone is less effective than CC alone for the achievement of ovulation induction, clinical pregnancy, and live birth in women with PCOS.

Concerning letrozole alone there is a RCT comparing letrozole with CC for ovulation induction in women with PCOS demonstrated that letrozole was superior (22, 23). Since that time, the use of letrozole for ovulation induction has increased in this population and is a reasonable first-line agent for ovulation induction in women with PCOS.

6. Conclusion

In our study we found that Metformin was used in a high percentage of women with PCOS, and the combination with contraceptives also. Metformin is mainly used more in

overweight and obese women. However, we have no data for the improvement of the PCOS characteristic and further investigation are necessary to determine if Metformin has a role in reproductive or only metabolic aspect of PCOS.

Disclosure

The author has nothing to disclose.

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