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FACTORS AFFECTING METFORMIN AND CLOMIPHENE'S REPRODUCTIVE EFFICACY IN PCOS WOMEN

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FACTORS AFFECTING METFORMIN AND CLOMIPHENE'S REPRODUCTIVE EFFICACY IN PCOS WOMEN

Abstract

Polycystic Ovarian Syndrome (PCOS) is a heterogeneous multifactorial disorder in which the ovarian dysfunction is the main cause of an ovulatory infertility. Metformin and Clomiphene Citrate (CC) are two effective drugs to induce ovulation in these patients. The study aimed to ascertain the effect of obesity, serum insulin and free testosterone levels on fertility success with metformin and CC as first line approaches in PCOS. This clinical study was a retrospective multicenter cohort study conducted in nine gynecology and endocrinology clinics. It included (61) PCOS women, aged (18-32) years, having desire to conceive, and free from the study medications for more than six months. Patients were divided to metformin receiving and CC receiving groups. Main outcomes of measure were; pregnancy rate, and improvement in PCOS as detected by ultrasound on their second visit. Results showed that CC was more effective in non-obese users (P0.05). Overall improvement was affected by Serum Free Testosterone (SFT) in both study groups (P>0.05). Metformin was effective regardless of patient's SFT levels, while CC was effective in patients with high SFT levels. There was a significant association between obesity and pregnancy rate in metformin users (P0.05). However, CC was less effective than metformin in overall improvement (OR=0.53, P>0.05,) suggesting metformin as the possible drug of choice regardless to obesity, serum insulin and SFT levels.

Keywords

Polycystic Ovarian Syndrome (PCOS), Obesity, Serum Free Testosterone, Clomiphene, Metformin.

1. INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a heterogeneous multifactorial disorder characterized by polycystic ovaries, hyperandrogenism and ovulatory dysfunction (Rotterdam ESHRE/ASRM group, 2004). Chronic oligoanovulation is one of the pivotal features of the PCOS, whose related ovarian dysfunction is the main cause of anovulatory infertility (Hull, 1987; Azziz et al, 2004). Several approaches have been proposed to induce ovulation in women with PCOS (Palomba et al, 2004). Clomiphene citrate (CC) and metformin are two effective drugs used to induce ovulation in those patients (Palomba et al, 2007). Clomiphene citrate was the first agent used for ovulation induction's experiments in oligomenorrheic women. It has been proven effective in ovulation induction for women with PCOS and should be considered as the first-line of therapy (Saha, Kaur & Saha, 2012).

Insulin resistance (IR) and secondary hyperinsulinemia affect approximately 65-70% of women with PCOS. This could be due to; genes related to insulin resistance in PCOS, family history of diabetes mellitus type II, or even obesity (Palomba et al, 2005; Palomba, Pasquali, Orio & Nestler, 2009). Many PCOS women are obese (Body Mass Index (BMI) of 30 kg/m² or more) (Loret do Mola, 2009), which further exacerbates their IR (Johnson, Bontekoe & Stewart, 2011).

Metformin likely plays its role in improving ovulation induction in women with PCOS via several mechanisms. Metformin reduces insulin levels, thus altering insulin's effect on ovarian androgen biosynthesis and resulting in a reduction of ovarian gluconeogenesis. In addition, metformin decreases hyperandrogenism, theca cell proliferation, and endometrial growth (Shaw et al, 2005; Nestler & Jakubowicz, 1996).

It is still unclear whether CC or metformin should be initially administered to induce ovulation in PCOS patients. In a meta-analysis done by Palomba et al., the Odds ratio (OR) between CC and metformin was 1.22 for pregnancy rate (Palomba et al, 2009). In another study, Legro et al. reported that CC alone resulted in significantly greater live birth rates than metformin alone, with percentage of 22.5% and 7.2% respectively (Lergo et al, 2007). As long as multiple births were only seen with CC therapy, it was suggested by the data of the PPCOS trial that if the goal of infertility treatment is to achieve a singleton gestation, CC may not be successful (Barbieri, 2007). On the other hand, the side effects of metformin are mainly gastrointestinal, although the sustained release preparation may have an overall lower rate of side effects (Mathur, Alexander, Yano, Trivax & Azziz 2008).

A number of pre-specified factors were identified in determining the clinical parameters that may predict prognosis or chance of success between metformin and CC in PCOS patient groups. Body mass index was stated in the UK National Institute of Clinical Excellence (NICE) and Society of Obstetricians and Gynecologists of Canada (SOGC) Guidelines to be an important factor, with a recommendation that metformin was advisable to be used in PCOS women having visceral obesity (Saha et al, 2012). In previous Randomized Controlled Trials (RCTs), obese women had a particularly poor response to metformin (Lergo et al, 2007; Zein, Jamaluddine, Ibrahim & Norman, 2009), whereas in another trial on non-obese women, they favored metformin (Hull, 1987).

Hyperinsulinemia is condition which is demonstrated by elevated insulin levels on a 2-hour 75-g load glucose tolerance test. It is an important parameter used to decide whether or not to initiate metformin therapy in women with PCOS. This is because metformin has a better predictable response than CC in hyperinsulinemic PCOS women due to its insulin sensitization (Barbieri, 2007).

There exist only a limited number of studies showing the relationship between serum free testosterone (SFT) and the response to CC or metformin in PCOS. However, a higher level of SFT, as an index for PCOS severity, may predict a better response to clomiphene, as long as CC could be more effective for cases intractable to treatment (Johnson et al, 2011).

Due to the lack of comprehensive documentation about PCOS in Lebanon, this retrospective multicenter study was conducted to get more insight on main factors predicting fertility success with the commonly prescribed medications, metformin and CC. In addition, the study also compared, in clinical settings, the efficacy of these two drugs in PCOS patients having desire to conceive.

2. METHODOLOGY

This retrospective multicenter cohort study, approved by the Institutional Review Board of Beirut Arab University, was conducted in Lebanon during 2011-2012. Total of one hundred thirty five PCOS patients' medical profiles from nine Gynecology and Endocrinology private outpatient clinics were reviewed. Sixty-one out of the 135 profiles had the adequate data to be eligible for this study. The included medical profiles for patients were from 2009 – 2011, and were screened for the following data; the demographic data (age on presentation, weight, height and BMI), the gynecological history (number of pregnancies, number living birth and abortions before enrolment), previous use of study medications (since more than 6 months), laboratory tests (such as FSH, LH, serum Insulin and free testosterone) and diagnostic procedures (such as ovarian ultrasound imaging on presentation and on their second visit at least four months after presentation).

The inclusion criteria in this study included; married patients diagnosed with PCOS (regardless of the etiology), patients aged eighteen years and above, patients who have been presented for at least one follow up visit, and finally patients who were free from study medications in the last six months and did not receive other ovulation induction medications (human chorionic gonadotropin). The patients in metformin group received metformin in a range of 500-2550 mg orally daily. The CC group patients received 50 mg orally twice daily for five days, starting from the fifth day of the menstrual cycle and repeated for maximum of 3 cycles. The exclusion criteria in this study included; menopausal patients, pregnant PCOS patients, and all patients having androgen excess secondary to any cause other than PCOS related hyperandrogenism or obesity.

The reproductive outcomes in this study were of concern, including; pregnancy rate (number of patients who became pregnant on the second visit (first follow up visit)), and improvement in polycystic ovaries (number of non-pregnant patients who had a decrease in the number of ovarian cysts on the second visit). These outcomes of measure were based on comparing the ultrasound imaging data done for each patient on presentation with the ultrasound done on their first follow up visit (at least four months after getting the prescription of metformin or CC on presentation). This comparison helped in detecting any improvement in PCOS, taking into consideration the factors likely to have a differential influence on the likelihood of success between the two medications, such as weight, serum insulin and free testosterone levels.

Data were statistically analyzed using "Megastat" program for excel (version 8.9). The mean, standard deviation (SD), percentage and Odds ratio (OR) were calculated when appropriate. The study groups showed normal distribution, thus the parametric Student's t test was used to compare between the study groups. The Chi square test was also used whenever appropriate and the results were considered significant at $P<0.05$, with a Confidence Interval (CI) of 95%.

3. RESULTS

Both CC and metformin groups presented with comparable age. However, CC users were older than metformin users and had more past history of pregnancy, live birth delivery and abortion. Most of the CC group were non-obese, having normal serum insulin level, Luteinizing hormone/Follicle Stimulating Hormone [LH/FSH] <2, but had high SFT level. On the other hand, obesity and hyperinsulinemia were more common in metformin users; they also had LH/FSH around 2, and almost normal SFT level (as indicated in Table 1).

Table 1: The Baseline characteristics in the two study groups

Variable	CC group (n=22)	Metformin group (n=39)	OR	P value
Age (year) ---mean(SD)	26.04 (4.97)	23.49 (3.89)		> 0.01
BMI (Kg/m²) ---mean(SD)	26.6 (4.11)	29.25 (5.037)		> 0.1
Gynecological History ---no (%)				
Pregnancy	12 (56%)	6 (15%)	6.6	< 0.001
Live birth	11 (50%)	2 (5%)	18.5	< 0.001
Abortion	3 (14%)	4 (10%)	1.38	> 0.5
Lab data ----mean (SD)				
Serum insulin ----µU/ml	7.91 (4.31)	12.13 (4.71) [a]		< 0.01
LH/FSH	1.58 (0.379)	1.85 (1.105) [b]		< 0.01
SFT ---pg/ml	7.46 (4.67)	2.22 (1.265) [c]		< 0.001
Ultrasound imaging showing polycystic ovaries ---no(%)	22 (100%)	39 (100%)		

NB: [a] n=36, [b] n=32, [c] n=21. CC= Clomiphene citrate; OR= Odds ratio; BMI= Body mass index; LH/FSH= Luteinizing hormone/ Follicle stimulating hormone; SFT= Serum free testosterone.

Depending on the overall improvement (pregnancy and/ or a decrease in number of ovarian cysts) as detected by ultrasound on the second visit, CC was more effective in its non-obese users than obese ones (OR=10, P< 0.05) (as shown in Fig 1). Metformin showed efficacy in both obese and non-obese users (OR=1.06, P> 0.05), and was more effective than CC in obese category (OR=5.83, P< 0.05) (as shown in Fig 2 and Fig 3, respectively).

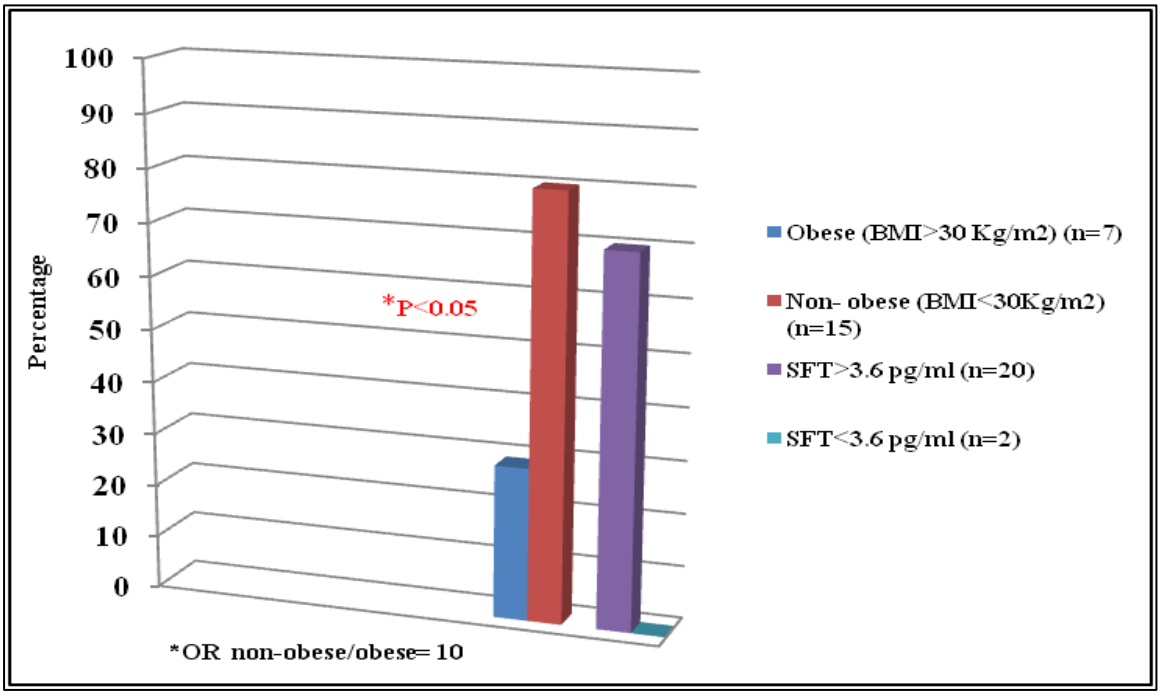

Fig.1: Percentage of overall improvement as detected by ultrasound in CC group according to obesity and SFT level.

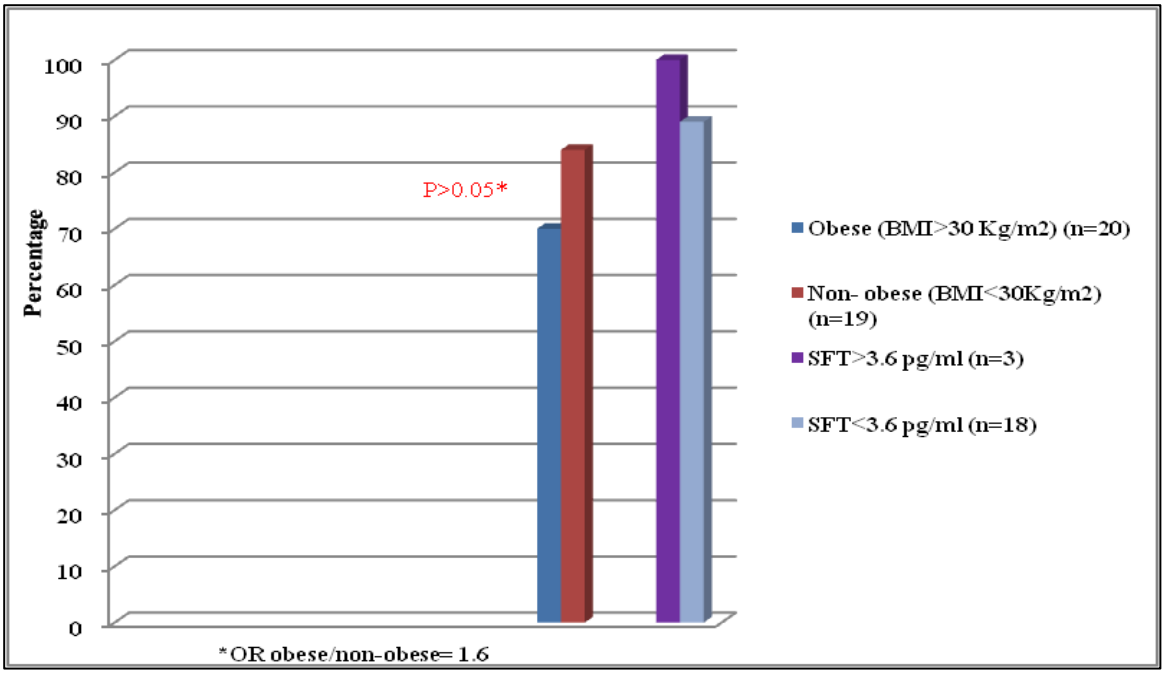

Fig.2: Percentage of overall improvement as detected by ultrasound in metformin group according to obesity and SFT level.

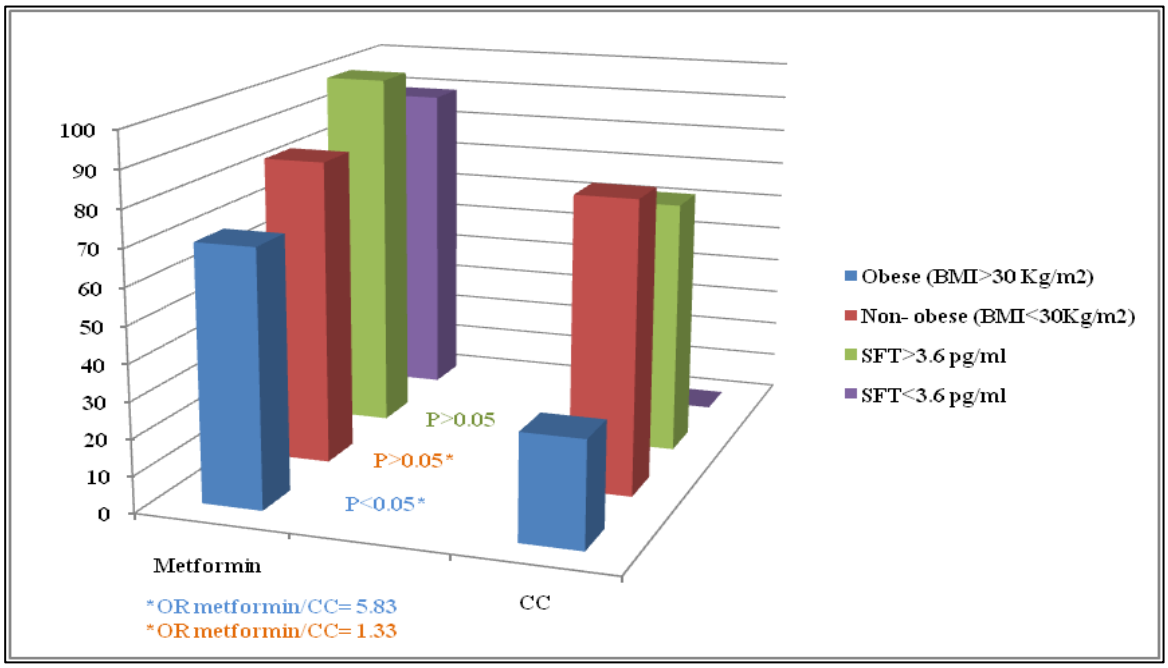

Fig.3: Comparison of the overall improvement percentages as detected by ultrasound between both study groups.

From the basic characteristics of PCOS patients in metformin group, 18 out of 21 patients, whose SFT level was available, had SFT <3.6 pg/ml. Interestingly, metformin was effective in patients with high and normal SFT levels (100% vs 89%) (as shown in Fig.2) . Clomiphene Citrate was more effective in patients with SFT >3.6 pg/ml (as shown in Fig. 1). In patients having high SFT there was no significant association in overall improvement between metformin and CC (P>0.05) (as shown in Fig. 3). On the other hand, in those having normal SFT, 89% of metformin users showed overall improvement, while CC failed to induce improvement in the only two patients who used CC and had normal SFT level (as shown in Fig. 2 and Fig. 1, respectively).

In order to get further description of metformin patients' characteristics and its impact on the outcome (taking into consideration the obesity and serum insulin), 36 of metformin patients whose serum insulin level was available were divided into obese and non-obese groups. Each of these groups was subdivided according to serum insulin level. There was a significant association between obesity and pregnancy in those having serum insulin>10µU/ml and those having serum insulin<10µU/ml (OR=0.02, P< 0.05, and P<0.05, respectively), in which metformin was more effective in inducing pregnancy in non-obese patients. On the other hand, there was no significant association between obesity and overall improvement in those having serum insulin>10µU/ml and those having serum insulin<10µU/ml (P>0.05) (as indicated in Table 2).

Table 2: Patients' outcome as detected by ultrasound imaging in metformin users according to BMI and serum insulin level*

Serum Insulin	BMI		Pregnant	Improved	Overall improvement	No improvement
>10 µU/ml [a]	>30 Kg/m^2	15	1	10	11	4
	<30 Kg/m^2	11	9	2	11	0
<10 µU/ml [b]	>30 Kg/m^2	5	0	3	3	2
	<30 Kg/m^2	5	4	0	4	1

BMI= Body mass index. *n=36

[a] P< 0.05 for the association between obesity and pregnancy (OR=0.02). P>0.05 for the association between obesity and overall improvement.

[b] P< 0.05 for the association between obesity and pregnancy. P>0.05 for the association between obesity and overall improvement.

The comparison of metformin and CC's outcomes in the study sample showed no difference between metformin and CC in inducing pregnancy (OR=0.83, P>0.05). Clomephene Citrate was less effective than metformin in overall improvement as detected by ultrasound on the second visit (OR= 0.53, P>0.05) (as indicated in Table 3).

Table 3: Outcomes of measure in the two study groups

Variable	CC group (n=22)	Metformin group (n=39)	OR	P value
Pregnancy ---no(%)	7 (32%)	14 (36%)	0.83	NS
Overall improvement ---no(%)	14 (64%)	30 (77%)	0.53	NS

CC= Clomiphene citrate; OR= Odds ratio; NS= non significant.

4. DISCUSSION

In this study (as indicated in Table 1), PCOS patients using CC had more past history of pregnancy, live birth delivery and abortion than metformin users due to their older age. Patients prescribed CC were almost non-obese, and most of them presented with around normal serum insulin levels. Obesity was more prominent in the metformin group, and the patients were mainly hyperinsulinemic since obesity is a contributing factor in developing hyperinsulinemia and IR (Tsilchorozidou, Overton & Conway, 2004).

In CC group, SFT was mainly higher than 3.6 pg/ml. The mean was 7.46pg/ml for SFT and 1.58 for LH/FSH. This high testosterone level is due to a primary ovarian hyperandrogenism in the non-obese PCOS patients (Nelson, Legro, Strauss & McAllister, 1999). On the other hand, metformin users had mainly a normal SFT level and a mean LH/FSH of 1.85. The normal SFT level can be reflected by the extraglandular aromatization of excessive circulating androgen to extraglandular estrone (Kasper et al, 2005, p2204-2205).

In the review of the impact of obesity on the outcome in both groups, CC was more effective in its non-obese users than obese ones (OR= 10, P<0.05) (as shown in Fig.1). On the other hand, obesity had a non-significant association with the overall improvement in metformin group (P>0.05) (as shown in Fig.2).

In non-obese patients, there was no difference in overall improvement in both groups (P> 0.05) (as shown in Fig. 3). This is compatible with Johnson et al. finding which stated that there was no evidence of significant differences in outcomes for those with BMI≤32 kg/m2, whether treated with metformin or CC (Johnson et al, 2011).

This study supports that SFT can be considered as a criterion for selection between the two drugs, because most of CC patients had a high SFT level and the drug showed efficacy in the overall improvement of this category. Previous trials also support that a higher level of free testosterone, as an index for PCOS severity, may better predict the response to CC (Johnson et al, 2011), which can be due to the improvement in the primary ovarian hyperandrogenism. Moreover, most of metformin patients had a normal SFT level. The drug was effective in their overall improvement regardless of SFT level because metformin helps in decreasing glucose intolerance, hyperinsulinemia, hyperandrogenism and ovulatory dysfunction associated with PCOS (Saha et al, 2012; Nestler et al, 1996). However, there was no difference between CC and metformin in overall improvement (P>0.05) in PCOS patients having high SFT levels. Also, metformin was more effective than CC in patients having normal SFT levels.

Metformin was effective in obese and non-obese patients regardless of their serum insulin level, yet it induced pregnancy in the non-obese patients rather than the obese ones (as indicated in Table 2). This is compatible with the insulin sensitization effect of metformin in case of hyperinsulinemia, and Johnson et al's outcome in which women with lower BMI may respond better to metformin than obese women (Johnson et al, 2011). In addition, our data proves the necessity of metformin's usage with the lifestyle modification (structural exercise, low glycemic index diet, hypocaloric diet, etc..) to improve the outcome in obese patients. This outcome supports the SOGC recommendations in that lifestyle modifications should be the first-line option for overweight and obese PCOS women because it has been proven effective in achieving pregnancy in these women (Saha et al, 2012).

There was no significant difference between metformin and CC in this study regarding pregnancy induction (P> 0.05, OR=0.83), while metformin was more effective than CC in overall improvement as detected by ultrasound on the second visit (P> 0.05, OR of CC/metformin= 0.58) (as indicated in Table 3). This was compatible with findings of Palomba et al.'s meta-analysis, in which no significant difference was observed in pregnancy rate between CC and metformin (OR= 1.22, 95% CI: 0.23 to 6.55) (Palomba et al, 2009). On the other hand, a previous prospective randomized clinical trial also showed that the pregnancy rate was significantly higher in metformin group than CC group (15.1 vs. 7.2%, P <0.001) (Palomba et al, 2005).

The observations above give rise to important questions in terms of managing infertility in PCOS: Do these factors really affect the higher clinical response to either metformin or CC? Can metformin really replace CC in clinical practice for all PCOS patients due to its safer characteristics as a drug?

We consider our work as a highlighting study for the mentioned facts and supporting to previous clinical trials. Our sample size is considered reasonable as PCOS has a prevalence of 6-10% as indexed by country. Further prospective studies on larger population are recommended to solve these questions. The conservative number of patients in each group may be considered as a limitation to this study because there was a difficulty in finding complete medical profiles containing the needed data for the study. This is attributed to incomplete documentation issues in the clinics; in addition, due to financial issues in the society, as some of the patients were not able to perform all of the laboratory tests.

5. CONCLUSIONS

A- Serum free testosterone levels, serum insulin levels, and obesity can be considered as factors to select between metformin and CC, and as predictors for the overall improvement in PCOS patients.
B- Clomiphene Citrate is preferred for non-obese PCOS patients having high SFT levels.
C- Metformin was effective in all patient categories (taking into consideration the BMI, serum insulin and SFT levels); and can be considered as the drug of choice for all PCOS patient categories.
D- Metformin must be used with lifestyle modification in overweight and obese PCOS patients.
E- There was no difference between metformin and CC in inducing pregnancy.
F- Metformin was superior to CC in terms of overall improvement.

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