Studies The Effects of Finastrides and Diane or Metformin, Diane and Andocur For Treating Subfertile Women with Poly cystic ovary Syndrome

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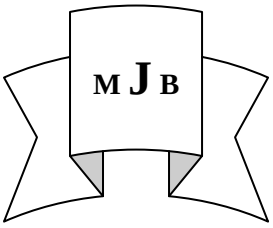


Abstract

Background:
Sub fertility is the inability of a couple to conceive after one year of unprotected coitus in women less than 35 years and six months in women over35 years .It carries significant personal ,social and financial consequences, one half of sub fertility causes due to female causes and one third of the female causes is the an- ovulation and the commonest cause of an-ovulation is the poly cystic ovary Syndrome.

Objective: The aim of this study to evaluate the benefits of Fin strides and Diane versus Metformin, Diane and Andocur on fertility in poly cystic ovary Syndrome with moderate to sever hyperandrogenism.

Patients and Methods:
During a period between first of March 2010 and first of September 2010 a prospective study was performed on 90 patients from infertility centre and outpatient clinic in Babylon Maternity and Paediatrics Teaching Hospital. We divided them into three groups: Group A, 30 women received Fin stride and Diane, Group B,30 women received Metformin,Diane andAndocur while Group C,30 were normal as a control.

Results:
It showed that the commonest age group affected with poly cystic ovary Syndrome were (25-35) years with history of primary infertility and larger body mass index. There is greater reduction in the LH level in both treatment regimes while in prolactin there's little increment after treatment in Group B, it may be due to cyproterone acetate.

Conclusion: Our study showed significant response in both treatment groups A and B support the effect that in poly cystic ovary Syndrome with sub fertility and hyperandrogenism we can use Finstride with Diane or Metformin ,Diane and Andocur to restore fertility.

دراسة تاثير عقار الفنسترايد مع الديان او المتفورمين مع الديان والاندوكيور لمعالجة النساء القليلات الخصوبة المصابات بتكيس المبايض

الخلاصة

الخلفية: ان قلة الخصوبة هي احد المشاكل التي تواجه النساء المصابات بتكيس المبايض نتيجة عدم الاباضة وزيادة الهرمون الدكري ولها تاثير على المراة والعائلة والمجتمع.

غرض الدراسة: تهدف الدراسة لوصف تاثير نوعين من الانظمة العلاجية للنساء المصابات بقلة الخصوبة وتكيس المبايض وزيادة الهرمون الدكري.

المرضى وطرق العمل: اجريت الدراسة للفترة من ادار ٢٠١٠ الى ايلول ٢٠١٠ على ستين مريضة مصابة بقلة الخصوبة وتكيس المبايض وزيادة الهرمون الدكري قسمت الى مجموعة ا ثلاثين مريضة اعطيت الفنسترايد مع الديان ومجموعة ب ثلاثين مريضة اعطيت المتفورمين مع الديان والاندوكيور ومجموعة ج ثلاثين امراة طبيعية كمجموعة سيطرة وتم قياس نسبة الهرمونات قبل العلاج وبعد ستة اشهر.

النتائج: ان معظم المرضى تتراوح اعمارهن بين ٢٥-٣٥ سنة واغلبهن يعانين من عقم اولي وان معامل كتلة الجسم يظهر اختلافا واضحا عن مجموعة السيطرة وكانت هناك زيادة ملحوظة في الهرمون الليوتيني والدكري قبل العلاج للمجموعتين ا،ب وانخفاض ملحوظ فيهما بعد العلاج مع بقاء الهرمون الحويصلي بالمستوى الطبيعي.

الاستنتاجات: تعطى المريضات المصابات بتكيس المبايض وقلة الخصوبة وزيادة الهرمون الدكري الفنسترايد مع الديان او متفورمين مع الديان والاندكيور للحصول على نتائج احسن من ناحية الخصوبة بتقليل الهرمون الدكري واللويتيني.

Introduction

Polycystic ovary Syndrome (PCOS) is one of the most common female endocrine disorders and is thought to be one of the leading causes of female subfertility[1]. It's a heterogeneous condition defined by the presence of two out of three criteria : oligo-and/or an ovulation ,hyperandrogenism (clinical or biochemical),polycystic overies, with the exclusion of other aetiologies. Improvement in life style with combination of exercise and diet is important to improve the prospect of both spontaneous and drug induced ovulation[2].

Finastrides is a synthetic antiandrogen with neither steroid hormone related properties nor affinity for androgen receptors [3]. It decreases symptoms of hirsutism in women with PCOS or idiopathic hirsutism [4].Finastride with rFSH improves ovulation rate in hyperandrogenic anovulatory PCOS women[5]. It's in the FDA category X known to cause birth defects in the developing male fetus [6].

The oral contraceptive pills (Dianette) which contains ethinyloestradiol (30 microgm) in combination with cyproterone acetate(2mg),it has beneficial effects including regulation ofmenstruation,ameluration of hirsutism and acne by reducing ovarian androgen production [7]. Oral contraception can be used alone or in combination with antiandrogen ,gonadotrophin releasing hormone agonists,or insulin sensitizing agents [8]. Cyproterone acetate is an effective antianderogen that inhibits the action of androgens on target organs and has marked progestational effect that suppresses the feedback enhancement of LH and FSH, leading to more effective antiandrogenic effect [9].Metformin is insulin sensitizer used in the treatment of PCOS [10] and recommended for treatment of anovulation [11] ,it lowers glucose level without increasing insulin secretion [12].The usual dose is either 850mg bd or 500mg tds, baseline investigations include an oral GTT, full blood count ,urea and electrolytes and liver function tests. It does not cause lactic acidosis in non –diabetic with normal renal and liver function [2].

Patients and Methods

This prospective clinical trial was conducted during the period from March 2010 to September 2010 in Babylon Maternity and Paediatrics Teaching Hospital from the outpatient clinic and infertility centre. Women with PCOS (60), with control group (30), whose chief complaints were menstrual irregularities and infertility and/or clinical or biochemical signs of hyper-androgenism.Full history and examination were done and written consent of the women after explanation. We excluded women with renal, hepatic and cardiac diseases. Their ages ranged between 18-45 years. We divided them into three groups: Group A (30 women) received Fin astride (5mg/day) and Diane (ethinylestradiol 30microgm with cyproterone acetate 2mg) for the first

21 days of the cycle. Group B (30women) received Diane (ethinylestradiol30 microgram with cyproterone acetate 2mg) for the first 21 days of the cycle+Metformin 850mg twice daily+cyproterone acetate 50 mg/day (Andocur) for the first 10 days of the cycle. Group C (30 women) were normal, married and fertile as a control group. All patients underwent clinical, haematological and biochemical evaluation at baseline and after the end of treatment of six months. Body mass index (BMI) was calculated from the equation: weight (in kilogram) / height (meters)^2. Hormonal assay performed at day two of the menstrual cycle.Hirsutism was clinically evaluated using the Ferriman-Gallawey score (F-G) score: a score greater than 8 was defined as hirsute [13]. Statistical analysis was performed using SPSS program .Mean and standard deviation were used.

Results: We classified our patients into three groups: group A (those who treated with Fin astride and Diane), group B (those who treated with Metformin, Diane and Androcur) and group C were normal (those who are considered as control).

According to the age of the patients, as shown in table (1)the most common age group was (25-35)years which represents the highest percentage of total PCOS patients ,35 out of 60(58%) followed by other groups (15-25) that represents ,19 out of 60(32%) then the lowest percent in the third group ,6 out of 60(10%).

Table 1 Distribution of PCOS patients according to age group

Name of patient's groups	No. of patient in each Age group with percentage.		
	(15-25)years	**(25-35)years**	**(35-45)years**
Group A	11(37%)	17(57%)	**2(7%)**
Group B	8(27%)	18(60%)	**4(13%)**
Total no. (percentage)	**19(32%)**	**35(58%)**	**6(10%)**

In Figure (1) 39 patients out of 60(65%) had history of primary infertility, 18 one was in group A, and 21 was in group B, while the other 21 had history of secondary infertility.

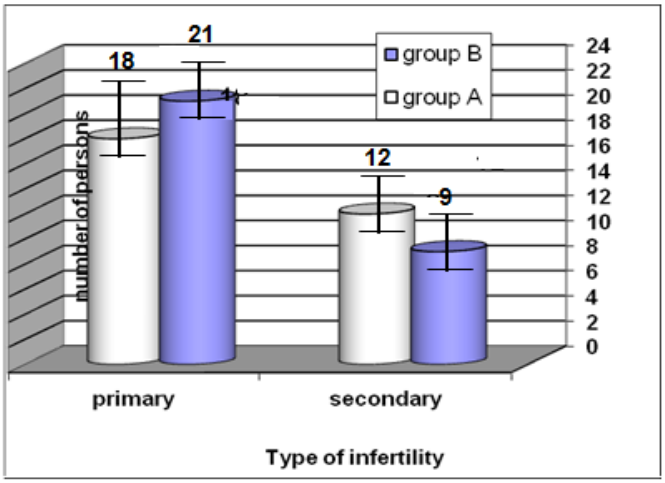
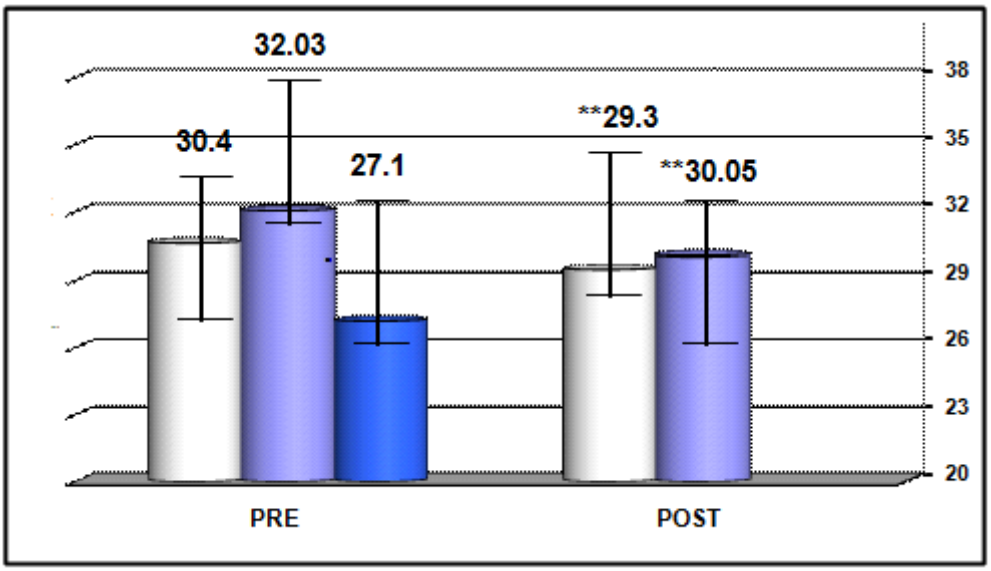


Figure 1 Distribution of PCOS According to type of infertility



** indicate highly significance

Figure 2 Values of BMI in the Three studied groups

Figure (2) shows great differences between patients and control group pre treatment and found highly significant differences p value less than 0.001between pre and posttreatment groups which mean value of BMI in group A was (30.6+_5.1) in group B(32.05+_4.4) while group C was (27.2+_2.4).

Relationship between BMI and Hormones in group A, B, and C.

There is positive significant relationship between BMI , LH, FSH.in group A, p< 0.05, and there is positive non significant relationship between BMI and LH,FSH hormones in group B, with negative significance to LH P<0.05, and positive non significance to FSH in group C. as shown in figure (3):

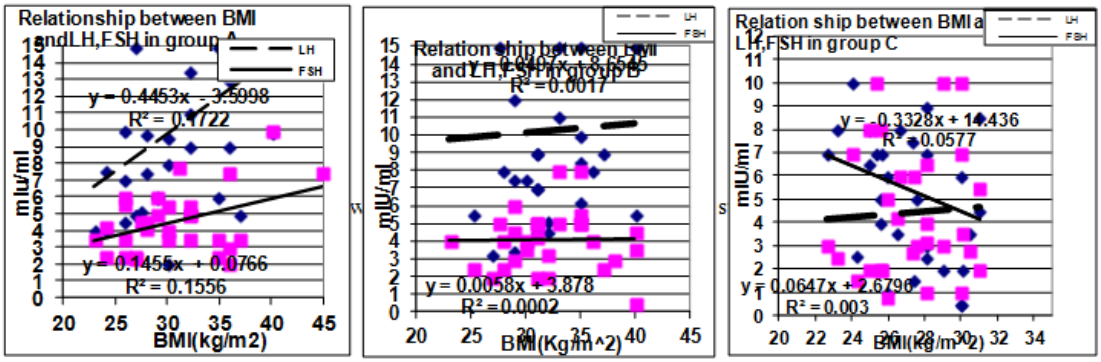


Figure 3 Relationship between BMI, and hormone in the three studied groups.

Ferriman, and Gallwey (F.G) score : Regarding degree of hirsutism there is great difference between patients and control as shown in table (2) and figure (4):

Table (2) Relationship between FG score and hormones in the three groups

Group name	S.Derocs GF±		TestosteroneTotal(ng/ml) pre± S.D	LH pre± S.D(mIU/ml)	FSH pre ± S.D (mIU/ml)
	pre	post			
Group C	6±2.2		0.65±0.24	5.27±3.1	**4.42±2.6**
Group A	10.6±4.4	10.1±3.8	1.24±0.73 *	10.03±5.3*	**4.51±1.7**
Group B	13.11±4.8	9.5 ±2.5	1.37±0.71 **	10.23±5.1*	**4.05±1.5**
*** indicate significance p< 0.05, ** indicate highly significance p<0.001**					

According to the FG score the high degree of hirsutism in the group B are more corrected with Diane and Androcur, and there is significant difference between patients and control as shown in table (2)

LH: The result of LH level had been used as an indicator for PCOS patients compared with control group, but there was significant decrease in this level after treatment in both groups. p< 0.05.as follow:

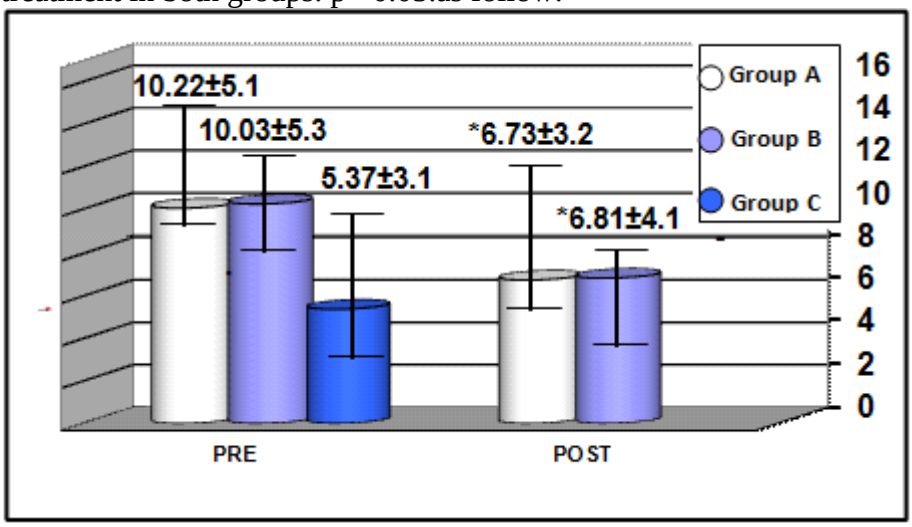


Figure 4 LH level pre and post treatment in patients compared with control

LH/FSH ratio in the three groups: The mean value of LH/FSH ratio reveals highly significant increment after treatment in group A.P< 0.001 and slight increment in group B

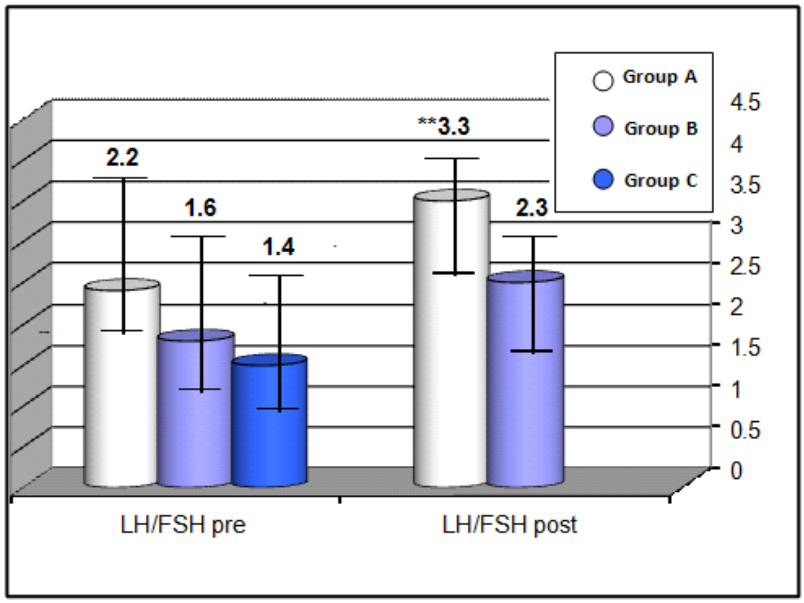


Figure 5 LH/FSH Ratio in patients and Control
**** highly significance**

FSH: There was decreased or normal level of FSH in patient groups pre treatment with highly significant decrement after treatment in group A $p<0.001$, and significant decrement in group B $p< 0.05$.

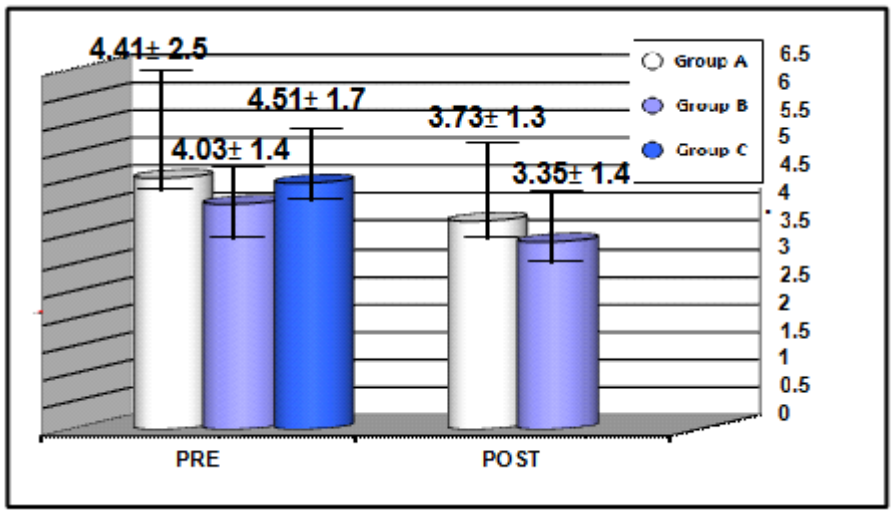


Figure 6 FSH level pre and post treatment in patients compared with control

In our study there's high level of testosterone in patients groups (A, B) show highly significant decrement after treatment $p< 0.001$.The mean value of total testosterone pre treatment in group A and B was equal to (1.25±0.75, 1.38±0.72) while post treatment it equal to (1.05±0.6,1.05±0.56) respectively, compared with control group (0.67±0.26).as shown in figure (7):

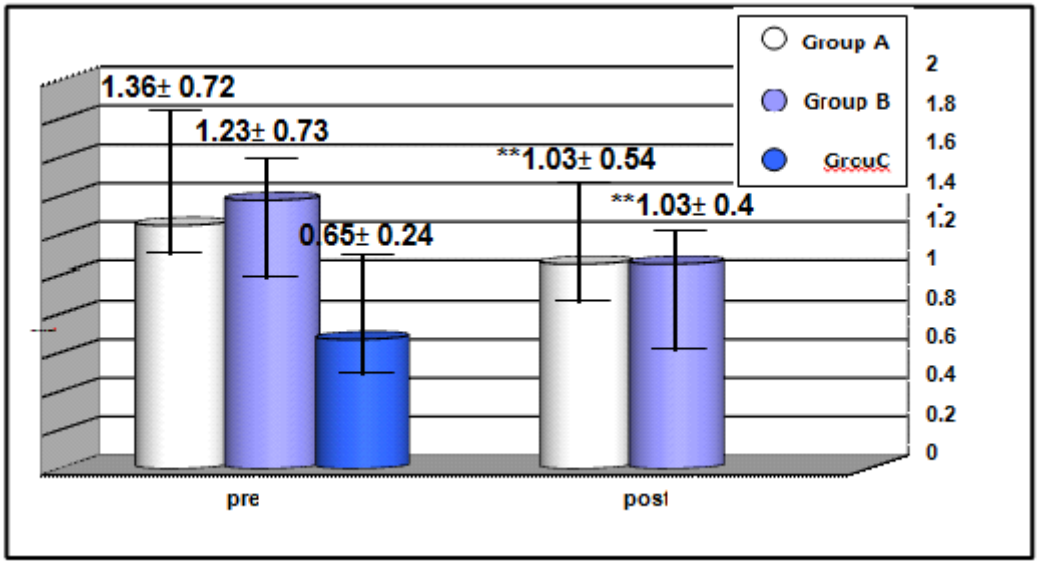


Figure 7 testosterone hormone level pre and post treatment in patient's groups compared with control.
** **highly significance**

Prolactin

There was normal level of prolactin pre treatment with significant increment in group B patients p< 0.05 after treatment. The mean value of prolactin pre treatment in both group A, B was equal to 13±8.3, 11.2±5.5, while post treatment was equal to 12.26±5.7, 14.14±8.8 respectively ,compared with control group 9.52±4.8. as shown in figure below:

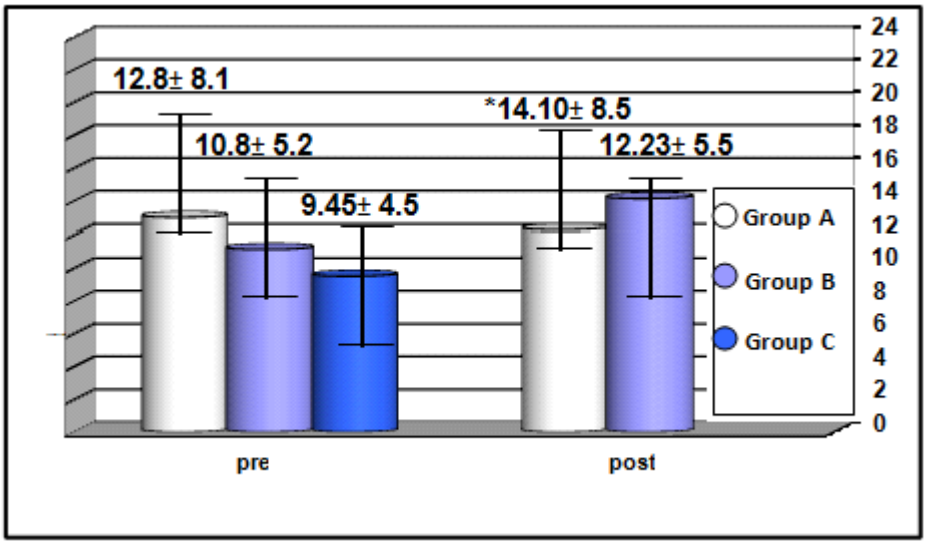


Figure 8 prolactin level pre and post treatment in patient's groups compared with control.
*** significance**

Discussion

In our study we tried to show the effects of two types of treatment : finastride with Diane and (metformin + Diane + antiandrogens (Androcur) and follow up investigations of their Clinical improvement, after 6 month of treatment.

Table (1) shows the distribution of PCOS patients according to their age. The most common age group was ranged between 25-35 (28±2) year, which represent 58% of total number. Followed by (15-25) year with mean of (21±2), 35-45(36±2) year, in a percentage of 32%,10% respectively . And this result agrees with several studies like; Carmina, (14) who mentions that PCOS is the most common endocrinopathy in women, occurring in about 5% of reproductive-aged women. Some cases are also seen in young teenagers. But it is rare above the age of 40 years. Women with PCOS usually present in their mid-20s .Menstrual disturbance is the earliest manifestation, and hirsutism and infertility become apparent later. The evolution of symptoms with age appears to be associated with increase of adiposity [15].

Primary infertility is more common than secondary infertility as shown in figure (1).The percentage of primary infertility was 65%(39/60)18/60 in group A, and 21/60 in group B, whereas that of secondary infertility was 35%.This result was not differ from most studies about infertility which found out that most of PCOS women who had a symptom may ignore it like menstrual irregularities and only they consult when they married and want to conceive as shown in our study.

The role of Finastrides in the treatment of PCOS related infertility without using gonadotrophins with it does not present but we used it for these patients for six months with Diane to prevent getting pregnant during the period of treatment and after stopping it they improve regarding clinical,hormonal, follicular growth and got pregnancy without adding any further medication,we found only one study which agree with our study, done by Tartagni et al,2010 ,who found that the addition of Finastrides to conventional protocol of ovarian stimulation with gonadotrophins can improve ovarian follicular growth in PCOS women who did not respond to previous stimulation with gonadotrophin alone.Tartagni confirms that hyperandrogenism interfere with follicular growth.[5]

The use of insulin sensitizers has many benefits, the decrease in insulin concentration, as a result of improved insulin resistance, may have important effects on hyperandrogenism, metabolic alterations and, particularly, on fertility[16]. With cyproterone acetate/ethinyloestradiol (Diane) has advantages: It regulates the menstrual cycle in the majority of women, spontaneous ovulation can occur rapidly, and normal menstrual rhythm can be achieved within 3 months of treatment [17].

Regarding BMI, figure (2) showed there is a great difference between patients and control pre treatment with highly significant difference after treatment in both groups $p< 0.001$.The mean value of BMI in group A pre treatment was 30.6±5.1, and post treatment was 29.5±4.9, while in group B, pre treatment was 32.05±4.4 and post treatment was 30.06±4.05, compared with control group that equal to (27.2±2.4).Also in figure (3) that describe the relationship between BMI and LH, FSH. In the three studied groups, in which there is positive significant relationship between BMI, LH, FSH. In group A, $p< 0.05$, and there is positive non significant

relationship between BMI and LH,FSH hormones in group B, with negative significance to LH P<0.05, and positive non significance to FSH in group C. This result was consistent with some studies about BMI. Like Balen [18]. So that Metformin promotes weight loss and favorable changes in the lipid profile. In fact: weight loss can significantly improve menstrual cycles and ovulation, thereby favoring pregnancy in otherwise infertile obese PCOS women. Since infertility represents a major complaint of adult PCOS women, weight loss should therefore be encouraged in all obese anovulatory PCOS women wishing to become pregnant, regardless of whether these women are willing to treat their obesity in the long term. This should ultimately increase patient compliance with short-term weight-reducing treatment [16] .

Cyproterone acetate/ethinyloestradiol(Diane) has advantages in that more than 40% of women with facial hair find it clears within 9 months, and many get worthwhile reduction in hair growth elsewhere.

Table (2) shows that the high degree of hirsutism are more corrected with OCP+ antiandrogens. And there is positive significant relationship between FG score and the level of testosterone in group A, with highly positive significant relation in group B. the mean value of FG score in group A and B pretreatment was 10.8±4.3 ,13.13±4.9 respectively while post treatment was 10.2 ±3.8,9.6±2.6 compared with control group 6.3±2.33.

Cyproterone acetate: is an antiandrogen, i.e. it suppresses the actions of testosterone (and its metabolite dihydrotestosterone) on tissues. As part of some combined oral contraceptive pills (Dianette in UK and Diane-35 in other countries) it decreases acne and hirsutism (male-pattern hair growth) [19].

There is a high LH level pre treatment in both patients groups with significant decrement after treatment, as shown in figure (4).The mean value of it pre treatment was 10.05±5.5, 10.25±5.3.respectively, while post treatment was 6.76±3.5, 6.85±4.3 and compared with control mean which equal to5.39±3.3. Regarding FSH, there was a normal level pre treatment compared with control with non significant decrement after treatment in both groups as shown in figure (7) and LH/FSH ratio figure (5) shows that there is significant increment in this ratio pre treatment compared with control with highly significant increment after treatment in group A p<0.001, and significant increment in group B P<0.05. This results were agrees with result of Banaszewska [20] who states that if you have PCOS your pituitary gland secretes higher levels of LH throughout the month instead of just before ovulation and ovulation may fail. Therefore LH/FSH ratios are increased to > 1 in women with PCOS.The ratio of LH to FSH is greater than 1:1.

In this study there is an increment in total testosterone level in some patients figure (7) ,and it remains normal in others so, the mean value of total testosterone pre treatment in group A and B was equal to (1.25±0.75, 1.38±0.72) while post treatment it equal to (1.05±0.6, 1.05±0.56) respectively, compared with control group (0.67±0.26), this result may be due to the hypothesis that says free testosterone is more specific than total testosterone as the results of Harborne [21] who report that in five of seven randomized studies ,in which insulin metabolism, SHBG, and androgens improved.

While Diane significantly decreases serum androgen levels. The combination of OCP s with metformin thus appears to further decrease androgen levels, without any additional effect on insulin sensitivity .By contrast, it is important to outline that patients often complain of hirsutism and other hyperandrogenic features, oral contraceptives have demonstrated their efficacy beyond those on insulin sensitivity. OCP s are the most efficient means of androgen suppression (ovarian as well as adrenal), and nearly any combination OCP s is effective in treating PCOS. This therapy results in lower and static LH levels without surges. The estrogen component stimulates hepatic production of sex hormone-binding globulin that reduces bioavailable androgen and can reduce hirsutism and acne. The progestin component provides competitive antagonism to androgen at its receptors, reducing the action of testosterone at the target organ [22].Treatment with antiandrogens is also effective in PCOS, notably, antiandrogens markedly reduce androgens and improve gonadotropin secretion and hirsutism [23].

The mean level of prolactin hormone in group A pre treatment is 13±8.3, and it is 11.15±5.5 in group B, while in control it is 9.52±4.8 while post treatment it was 12.26±5.7, 14.14±8.8 respectively as in figure (8). Although it is slightly higher than control but it still within normal range. This result may goes parallel with study of Angie(24.) who reveals that Some women with PCOS also have hyper-prolactinemia, while Angela Hywood & Kerry Bone [25] found out that about 25% of PCOS patients exhibit elevated prolactin .Other studies differ from those results and suggest normal level of prolactin.

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