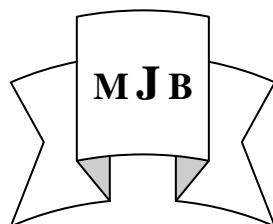


Use of Finasteride- Oral Contraceptive Pill Combination in the Treatment of Polycystic Ovarian Syndrome Related- Infertility

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a common endocrinopathy characterized by oligo-ovulation or anovulation, signs of androgen excess, and multiple small ovarian cysts. PCOS is thought to be one of the leading causes of female subfertility.

Aim of the study: Evaluate the activity of finasteride - OCP combination in treatment of PCOS related infertility.

Patients and Methods: Thirty nine infertile married women at reproductive age were involved in this study; they all were complaining infertility due to PCOS. The diagnosis of PCOS was established depending on the presence of at least two out of three of Rotterdam criteria. The Patients were treated with finasteride 5 mg daily concomitantly with an oral contraceptive pill (OCP) continuously for 2 months.

Results: The present study, found that the percentage of patients responded to the treatment with finasteride-OCP combination was (35.89%). The mean number of mature follicles, endometrial thickness & pregnancy rate per patient were (1.21 ± 0.42) , $(7.26 \pm 1.1 \text{ mm})$ & (21.42%) respectively, whereas miscarriage rate was (0.0 %).

Conclusion: The oral finasteride-OCP combination had a good promising effect in the treatment of PCOS related infertility.

Keywords: Finasteride, Oral contraceptive pill, Polycystic ovary syndrome, Infertility

الخلاصة

خلفية البحث: إن متلازمة تكيس المبايض (Polycystic ovarian syndrome) هي من الاضطرابات الهرمونية الشائعة التي تتمثل بقلة أو عدم الاباضة (التبويض) (oligo-ovulation or anovulation)، تمتاز متلازمة تكيس المبايض بعلامات زيادة الهرمون الذكري الاندروجين (androgen) ويوجد اكياس صغيرة متعددة في المبيض. يعتقد إن متلازمة تكيس المبايض هي واحدة من الأسباب المؤدية إلى قلة خصوبة الإناث.

المرضى وطرق البحث: شملت الدراسة ٣٩ امرأة في عمر الإنجاب متزوجة وغير قادرة على الإنجاب (عقيمة).

لقد تم اعتماد معايير روتردام (Rotterdam criteria) في تشخيص متلازمة تكيس المبايض لدى تلك النساء اللواتي شاركن في هذه الدراسة وذلك بحضور على الأقل إثنان خارج ثلاثة من هذه المعايير لديهن . تناولت المريضات حبوب بالفيناسترايد ٥ ملغ مرة واحدة في اليوم وتناولت معه وبشكل متزامن حبوب مانع الحمل لمدة شهرين متتاليين.

النتائج: لقد بينت هذه الدراسة إن النسبة المئوية للمريضات اللواتي استجبن للعلاج بالفيناسترايد مع حبوب منع الحمل كانت (٣٥.٨٩ %)، وإن متوسط عدد البيوض ، سمك بطانة الرحم ومعدل الحمل كانت (1.21 ± 0.42) و $(7.26 \pm 1.1 \text{ mm})$ و (٢١.٤٢ %) على التوالي فيما كان معدل الإسقاط (٠.٠%).

الاستنتاجات: إن للفيناسترايد دور واعد في علاج العقم عند النساء المصابات بمتلازمة تكيس المبايض.

كلمات المفتاح: فيناسترايد ؛ حبوب منع الحمل ؛ متلازمة تكيس المبايض؛ عقم

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders that affects approximately 5-10% of pre-menopausal women [1,2], and it is a leading cause of infertility in these women.[3,4] PCOS is a syndrome with unknown etiology, characterized by hyperandrogenism which may be clinical (particularly hirsutism and acne) and / or biochemical (hyperandrogenemia), and chronic anovulation.[2,5] However, PCOS includes a wide spectrum of signs and symptoms (obesity, polycystic ovary), pathology, and laboratory findings. Recent studies have shown that women with PCOS are frequently insulin resistant and at increased risk of developing glucose intolerance or non insulin-dependant diabetes mellitus in the third and fourth decades of their life. [2,6]

A proposed mechanism for anovulation and elevated androgen levels suggests that under the increased stimulatory effect of LH secreted by the anterior pituitary, stimulation of the ovarian theca cells is increased. In turn, these cells increase the production of androgens (eg, testosterone, androstenedione). Because of a decreased level of FSH relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens, and this led to ovarian follicular arrest in the preantral stage (estrogen is critical to the development and selection of a dominant follicle) and also had increased central stroma due to excessive thecal and stromal hyperplasia from the disordered gonadotropin exposure. Also hyperinsulinemia appears to lead to hyper production of ovarian androgens and to an increase in serum free-

testosterone concentration and peripheral androgen action by decreasing the serum sex-hormone-binding globulin concentration (SHBG).[7,8,9] Chronically elevated LH and insulin resistance are 2 of the most common endocrine aberrations seen in PCOS. [10,11]

Drugs that block male hormones can protect women with PCOS from developing diabetes, heart attacks, obesity and masculinizing traits such as hirsutism, acne, and large muscles and bones and that progesterone can protect them from uterine cancer [12-14]. Also the antiandrogens can lower cholesterol [15] and help the ova to pop from the ovaries. [16,17]

Finasteride, has been approved by Food and Drug Administration (FDA) for treatment of androgenetic alopecia in men.[18] The largest application of finasteride consists in treating benign prostate hyperplasia, in women finasteride has been used in some control trials for treatment of hirsutism.[19] Finasteride is a preferential, competitive inhibitor of the intracellular, 5 α -reductase isoenzyme Type II which converts testosterone into dihydrotestosterone (DHT), a more potent androgen [20-22], as well as liver, and is responsible for two-thirds of circulating DHT.

Finasteride is in the FDA pregnancy category X, it is known to cause birth defects in a developing male baby. Thus women who are or who may become pregnant must not handle crushed or broken finasteride tablets and it should be taken with an oral contraceptive pill (OCP) by woman who may become pregnant. [23]

Finasteride is known to affect blood donations, and potential donors are

typically restricted for at least a month after their most recent dose. [24] Combined OCP may reduce insulin and glucose tolerance in women with PCOS. [35, 36] A combination of cyproterone acetate and ethinylestradiol (Dian) can be used as contraceptive. Cyproterone acetate is a synthetic androgen receptor antagonist that has a weak progestational and glucocorticoid activity [31, 34], thus it is less likely to affect insulin tolerance because the more potent progestin may cause progressive decreases in carbohydrate tolerance, and weight gain is more common with OCP containing androgen-like progestins, while cyproterone acetate has antiandrogenic effect [37].

Aim of the study was to evaluate the activity of finasteride - OCP combination in treatment of PCOS related infertility.

Patients and Methods

The study was conducted during the period from September 2010 to May 2011. The Ethics Committee of the Al-Nahrain medical college approved this study. Thirty nine married women were taken from two sources (the infertility center of maternity and pediatrics teaching hospital and from those who referred from out patient clinics to the hospital in Hilla city, Babylon Province, Iraq). The range of their age was between 18-35 years, they all complaint PCOS related infertility. In these women PCOS was diagnosed when each of them had at least 2 out of 3 of Rotterdam criteria. Diagnosis of PCOS

based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS. [25]

A two-month washout period before treatment with finasteride was used to eliminate the effect of any post-treatment. In PCOS amenorrhoeic women withdrawal bleeding was induced by using dydrogesterone 10 mg tablets daily for 10 days.

Thirty nine women received finasteride tablets 5mg daily (Propecia; Novartispharma AG, USA) plus an ethinylestradiol and cyproterone acetate (Diane-35; Schering AG, Germany) [23] as a contraceptive pill for 2 months starting from the fifth day of a spontaneous or dydrogesterone (Duphaston Solvay pharmaceuticals B.V., Holland) induced menstrual bleeding. Good response was achieved when at least one mature follicle became ≥ 17 mm in diameter [26,27], follicular maturation monitoring after 2 months of treatment was followed by transvaginal ultrasound on cycle day 12. When the optimal follicle size was reached timed intercourse was advised after 24 hours and every other day. [28] Chemical pregnancy was assessed by measurement of β -hCG and clinical pregnancy by detection of fetal heart beat on sonography. Follow up of pregnancies achieved with finasteride was continued until they ended with full term delivery.

Results

Table (1) shows number of women and their clinical and hormonal characteristics on which the diagnosis of PCOS was determined according to Rotterdam criteria.

Table 1 Clinical and hormonal characteristics of the patients pretreatment with finasteride-OCP combination.

Variables	Value
Number of women	39
Age Mean (Range) (years)	25.10 ± 5.25 (18-35)
Mean duration of infertility ± SD (Years)	2.64 ± 0.44
Primary infertility (%)	66.66%
Secondary infertility. (%)	33.33%
Irregular cycle (%)	100%
Regular cycle (%)	(0)
BMI	30.4 ± 5.2
Present Hirsutism (%)	94.6%
Absent Hirsutism (%)	5.4%
Positive US (%)	94.73%
Negative US (%)	2.26%
LH (mIU/ml)	6.90 ± 4.24
FSH (mIU/ml)	5.60 ± 1.43
LH/FSH ratio	1.28 ± 0.772
Testosterone (ng/ml)	0.99 ± 0.95
PRL (ng/ml)	23.38 ± 10.49
TSH (mIU/ml)	1.67 ± 0.83

BMI=Body Mass Index; LH=Luteinizing Hormone; FSH=Follicle Stimulating Hormone; TSH= Thyroid Stimulating Hormone; PRL= Prolactin

Table (2) shows post treatment results with finasteride–OCP combination. At day 12 of menstrual cycle transvaginal ultrasound appears that among the 39 women treated with finasteride–OCP combination, only 14 women responded to the treatment as they resulted in 1 or 2 mature follicles, the

mean number of these follicles was 1.21 ± 0.43 and the mean of endometrial thickness was 7.26 ± 1.1 mm. Three pregnancies had occurred among the 14 responded women. The 3 pregnancies were ended with full term delivery.

Table 2 Post treatment results with finasteride-OCP combination.

Variables	Value
Total patients No.	39
*Responded patients NO. (%)	14 (35.89)
NO. (%) of patients with 1 MF	11(78.57)
NO. (%) of patient with 2 MF	3 (21.42)
Mean NO. of mature follicle \pm SD	1.21 \pm 0.43
Mean size of mature follicle \pm SD	20.26 \pm 3.66
ET Mean \pm SD (mm)	7.26 \pm 1.1
Pregnancy Rate / Patient (%)	21.42 (3 /14)
Miscarriage rate	0%

F= Finasteride; * = Resulted in one or more mature follicles \geq 17 mm; ET = endometrial thickness

Discussion

Reduction of ovarian androgen production not only improves ovulation and pregnancy rates, but also reduces spontaneous abortion rates.[29] Testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-alpha reductase (5 α -R). DHT is a more powerful androgen than testosterone as it has a much higher affinity for the androgen receptor.[30,31] Finasteride is an inhibitor of 5 α -R by being an aza analog of testosterone, thereby initially binding to 5 α -R similarly to testosterone.[32] Up to knowledge the role of finasteride in the treatment of PCOS related infertility had been investigated only by one study done by Tartagni *et al.*(2010)[33], who add finasteride to conventional protocol of ovarian stimulation with gonadotropin and found that finasteride can improve ovarian follicular growth and ovulation in PCOS women who did not respond to previous stimulation with gonadotropin alone.

Among the 39 patients who were treated with finasteride (5 mg daily for 2 months), the development of mature

follicles \geq 17 mm occurred in only 14 (35.89%) patients and 3 pregnancies (21.43%) had occurred among these 14 patients.

Results of the present study including number of responded patients (35.89%), percentages of patients who developed mono-follicle (78.57%) and those who developed 2 mature follicles (21.42%), ET measured at day 12 of the third menstrual cycle after two months of treatment with finasteride (7.3 \pm 1.1mm) and pregnancy rate per patient (21.43%) could not compared to other studies.

Up to knowledge role of finasteride in the treatment of PCOS related infertility had been investigated only by one study done by Tartagni *et al.*(2010) [33] who found that the addition of finasteride to conventional protocol of ovarian stimulation with gonadotropin can improve ovarian follicular growth in PCOS women who did not respond to previous stimulation with gonadotropin alone.

Result of the present study confirms what had been found by Tartagni *et al.* (2010) [33] study in which the

administration of finasteride during ovarian stimulation with rFSH improves ovulation rate in selected hyperandrogenic anovulatory women.

The high loss rate experienced by women with PCOS is partly due to compromised oocyte quality, but may also be due to the compromised uterine perfusion that occurs as a result of elevated androgen levels. [29] No occurrence of any miscarriage among the pregnancies that were achieved by treatment with finasteride-OCP combination goes with Ajoss *et al.* (2002) who found that the correction of androgen status clearly results in a decrease in the spontaneous abortion rate in these individuals. [29]

Conclusion

Treatment with finasteride combined with an OCP for 2 months had a good promising effect in PCOS related infertility.

Recommendation

1. Use Finasteride for longer term of therapy.
2. Investigate the role of other antiandrogens for the treatment of PCOS related infertility.
3. Use a combination of Finasteride and other medication such as metformin.

Aknowledgment

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Rreferences

1. Polson DW, Wads Worth J, Adams J, Franks S. (1988). Polycystic ovarian

a common finding in normal woman, Lancet,; 1: 870-872.

2. Franks S. (1995). Polycystic ovarian syndrome. N Engl J Med,; 333: 853-861.

3. Goldenberg N, Glueck C (2008). Medical therapy in women with polycystic ovarian syndrome before and during pregnancy and lactation. Minerva Ginecol 60 (1): 63-75.

4. Boomsma CM, Fauser BC, Macklon NS. (2008). Pregnancy complications in women with polycystic ovary syndrome. Semin. Reprod. Med. 26 (1): 72-84.

5. Dunaif A. (1992). Insulin resistance and ovarian dysfunction The Endocrinologist ; 2: 248-260.

6. Dunaif A, Graf M. (1989). Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with polycystic ovary syndrome. J Clin Invest.; 83 : 23- 29.

7. Barbieri RI, Smith S, Ryan KJ. (1988). The role of hyperinsulinemia In the pathogenesis of ovarian hyperandrogenism. Fertil Steril,; 50: 197-212.

8. Plymate Sr, Matej La, Jones Re. (1988). Inhibition of sex hormone-binding globulin production in human hepatoma (Hep G2) cell line by insulin and prolactin. J Clin Endocrinol Metab.; 67: 460-464.

9. Paquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi V, Colitta D, Fiorini S, Cognigni GE, Filicori M, Morselli-Labate AM. (2000). Effect of long term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab,; 85: 2767-2774.

10. Mishell DR, Stenchever MA, Droegemueller W, Herbst AL. (1997). Chapter 39. Comprehensive

- Gynecology, Third Edition. St. Louis, Mo: Mosby;:1087-1112.
11. Poretsky L, Piper B.(1994).Insulin resistance, hypersensitivity of LH, and dual defect hypothesis for the pathogenesis of polycystic ovary syndrome. *Obstet Gynecol.*; 84:613-621.
 12. Berga SL. (1998). The obstetrician-gynecologist's role in the practical management of polycystic ovary syndrome. *American Journal of Obstetrics and Gynecology.* 179: 6 Suppl. S Part 2 (DEC):S109-S113.
 13. Legro RS. (1998). Polycystic ovary syndrome: Current and future treatment paradigms. *American Journal of Obstetrics and Gynecology.* 179: 6 Suppl. S Part 2 (DEC):S101-S108.
 14. Taylor AE. (1998). Understanding the underlying metabolic abnormalities of polycystic ovary syndrome and their implications. *American Journal of Obstetrics and Gynecology* 179: 6 Suppl. S Part 2 (DEC):S94-S100.
 15. Diamantikandarakis E, Mitrakou A, S Raptis, Tolis G, Duleba AJ. (1998) .The effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in the polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 83: 8(AUG):2699-2705.
 16. Falsetti L, Defusco D, Eleftheriou G, Rosina B. (1997). Finasteride (5 mg daily) or flutamide (259 mg twice daily) for 6 consecutive months. Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. *Gynecological Endocrinology* 11: 4 (AUG):251-257.
 17. Deleo V, Lanzetta D, Dantona D, Lamarca A, Morgante G. (1998). Hormonal effects of flutamide in young women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 83: 1(JAN):99-102.
 18. Sinclair R: Male pattern androgenic alopecia. *BMJ* 1998, 317:865-869.
 19. Cilotti A, Danza G, Serio M. (2001). Clinical application of 5 alpha reductase inhibitors. *J Endocrinol Invest*, 24:199-203.
 20. US Physician Package Insert.
 21. Liang T, Rasmusson G, Brooks J. (1983). Biochemical and biological studies with 4-aza-steroidal 5 α -reductase inhibitors. *J Steroid Biochem*; 19: 385–390
 22. Sudduth SL, Koronkowski MJ. (1993). Finasteride: the first 5 alpha-reductase inhibitor. *Pharmacotherapy*; 13: 309-25.
 23. Tartagni M, Schonauer LM, De Salvia MA, Cicinelli E, De Pergola G, D'Addario V.(2000).Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertil Steril*; 73:718–23.
 24. FDA guidance on blood donors and medications" (pdf). U.S. Food and Drug Administration. Archived from the original on October 31,2005.<http://web.archive.org/web/20051031172818/http://www.fda.gov/Cber/bldmem/72893.pdf>. Retrieved 01-02-2009.
 25. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 19:41.
 26. Speroff L, Glass RH, Kase NG. (1999). Hormone biosynthesis, metabolism, and mechanism of action. In: *Clinical gynecologic endocrinology and infertility*. Baltimore, Lippincott, Williams & Wilkins, 6th Ed, 31-105; 488-521; 1097-1132.
 27. Nandi Nupur, Bhattacharya Mahua, Tolasaria Amit and Bhadra Banasree. (2011). Experience of Using Letrozole as a First-Line Ovulation Induction Agent in Polycystic Ovary

- Syndrome (PCOS). Al Ameen J Med Sci (AJMS) 4(1):75-79.
28. Ganesh A, Goswami S.K, Chattopadhyay R, Chaudhury K, Chakravarty B. (2009). Comparison of letrozole with continuous gonadotropins and clomphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomphene citrate failure: a randomized prospective clinical trial. J Assist Reprod Genet.; 26(1):19-24.
29. Ajoss S, Guerriero S, Paoletti AM, Orrù M, Melis, GB. (2002). The antiandrogenic effect of flutamide improves uterine perfusion in women with polycystic ovary syndrome. Fertil Steril; 77:1136-40.
30. George P.Chrousos (2009) The Gonadal Hormones And Inhibitors. In Basic And Clinical Pharmacology by Bertram G.Katzung, Susan B.Masters and Anthony J. Trevor.11th edition (40):699-726. McGraw -Hill.
31. Peter J. Snyder (2006) Androgens. In Goodman and Gilman's The Pharmacological Basis of Therapeutics by Laurence L. Brunton, John S.Lazo, Keith L. Parker. 11th edition; (58):1573 -1585. McGraw-Hill Companies, Inc.USA.
32. Robaire, B; Henderson, N. (2006) Actions of 5 α -reductase inhibitors on the epididymis. Molecular and Cellular Endocrinology 250 (1-2): 190–5.
33. Tartagni M, Cicinelli E, De Pergola G, Lavopa C, Di Naro E, De Salvia MA, Loverro G. (2010) Effect of finasteride on ovulation induction in nonresponder (hyperandrogenic) polycystic ovary syndrome (PCOS) women. Fertility and Sterility Volume 94, Issue 1 , Pages 247-249.
34. Medicines and Healthcare products Regulatory Authority (2006-04-11)Cyproterone Acetate (PDF). <http://www.mhra.gov.uk/home/groups/lunit1/documents/websiteresources/con2023735.pdf>.
35. Diamanti-Kandarakis E, Baillargeon J-P, Iuorno M, Jakubowicz D, Nestler J. (2003) A Modern Medical Quandary: Polycystic Ovary Syndrome, Insulin Resistance and Oral Contraceptive Pills. J Clin Endoc Metab 88(5):1927-1932.
36. Vrbikova, J. and Cibula, D. (2005) Combined oral contraceptives in the treatment of polycystic ovary syndrome. Hum. Reprod. Update, 11:277–291.
37. George P.Chrousos (2009) The Gonadal Hormones and Inhibitors. In Basic and Clinical Pharmacology by Bertram G.Katzung, Susan B.Masters and Anthony J. Trevor.11th edition, McGraw-Hill. (40): pp.699-726.