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Research Article

Tamoxifen or Drospirenone and Ethinyl Estradiol: which is the first choice for infertile women with Polycystic Ovary Syndrome with Hirsutism

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Abstract

Objective: To evaluate the outcome of tamoxifen treatment in infertile hirsute women with PCOS and assessment of its effect on the hirsutism score. **Design:** Prospective non randomized study. **Setting:** Outpatients in Qena University Hospital. **Patients:** 96 infertile women with PCOS with hirsutism. **Interventions:** Fifty women received tamoxifen 40 mg daily which increased to 80 mg if ovulation did not occur. Forty six received 3 mg of drospirenone and 30µg of ethinyl estradiol. **Main Outcome Measures:** Ovulation and pregnancy rate. F-G scoring system and hormone levels were determined before and every 3 months during the treatment. **Results:** About 50% of women received tamoxifen got pregnant and there was significant decrease in hirsutism score with both drugs. No significant changes in FSH, LH, E_2 and DHEAS concentrations with EE/DRSP or tamoxifen. The free T an A levels decreased, whereas SHBG levels increased significantly with EE/DRSP in comparison to the basal and tamoxifen. **Conclusions:** Tamoxifen therapy in infertile hirsute women with PCOS is the first choice for treatment as it gives the chance for pregnancy and has a positive effect on hirsutism score without time consuming in treatment of the hirsutism before induction.

Keywords: Tamoxifen, yasmin, polycystic ovary syndrome, hirsutism

Introduction

The incidence of polycystic ovary syndrome (PCOS) in women of reproductive age ranging from 8.7% to 17.8% as it is the most common endocrine disorder (March et al., 2010) and accounts for 90% of the infertile women due to anovulation (Kousta et al., 1997). Diagnosis of PCOS is made by symptoms and signs of ovulatory dysfunction, androgen excess, and/or polycystic ovaries after the exclusion of other endocrine disorders (Norman et al., 2007) and the hirsutism is diagnosed by excessive male pattern of terminal hair growth in women (Rosenfield, 2005) and must be distinguished from hypertrichosis which is excessive growth of vellus hair in androgen independent areas (Hatch et al., 1981). Hirsutism scoring system according to Ferrimane Gallwey define hirsutism by a total score of 8 or more (Ferriman and Gallwey, 1961). The women having hirsutism without hyperandrogenemia and normal menstrual cycle are known as idiopathic hirsutism, the PCOS is the most common (80%) cause of hirsutism [Rosenfield, 2005; Ehrmann, 2005).

Oral contraceptive pills (OCPS) are the first line treatment for hirsutism with PCOS (Zouboulis et al., 2007) which decrease circulating androgens synergize the effect of anti androgens (Fitzgerald et al., 1999). The new progestin drospirenone (DRSP) is a spironolactone analogue that has antimineralocorticoid and antiandrogenic activity and is similar to endogenous progesterone. Further, it does not interfere with the increase in SHBG or it's binding to androgens (Krattenmacher, 2000) and has various favorable

metabolic effects, including the potential reduction of body weight. Despite the widespread use of EE/DRSP combination for contraception and recently for acne and seborrhea (van Vloten et al., 2002; Thorneycroft et al., 2004), its role in the treatment of patients with hirsutism has been limited to hirsute patients with polycystic ovary syndrome (Guido et al., 2004; Ibanez and de Zegher, 2004; Palep-Singh et al., 2004).

The aim of this study was to evaluate the outcome of induction of ovulation in infertile hirsute women with PCOS and assessment of its effect on the hirsutism score.

Materials and Methods

This prospective non randomized study was conducted on 96 women suffering from infertility due to PCOs with hirsutism were recruited in the study from outpatient clinic of Qena university hospital with written consent after approval by hospital ethics committee. A detailed evaluation of the infertile women was done by history taking, clinical examination and the modified Ferriman-Gallwey scoring system (Chen et al., 1996) was used to determine the degree of hisutism.

All patients had normal glucose tolerance and normal markers of thyroid, liver, kidney function, hysterosalpingography, semen analysis and laparoscopy if needed. PCOS diagnosed if two or more of the following parameters: oligomenorrhea/amenorrhea with positive progesterone withdrawal, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries by ultrasonography. None of them had been taking oral contraceptives or other long-term drugs in the last 6 months before the start of the study, nor were any of them on a regular diet. Body mass index (weight/height2, expressed as kg/m2) was recorded at the beginning of the study.

Fifty women received tamoxifen 40 mg (20 mg twice a daily) were given from day 5-9 of the menstrual cycle in the first cycle. The ovulation monitoring was done from day 11 onwards till the day of ovulation or day 20. At the same time endometrial thickness was also, measured. The dose of tamoxifen was increased to 80 mg (40 mg twice daily) if ovulation did not occur.The couples were allowed to practices natural sexual life and no intervention. The primary outcome was ovulation rate percycle and secondary outcome was pregnancy rate percycle. Forty six women received oral contraceptive Yasmin® (3 mg of drospirenone [DRSP] and 30µg of ethinyl estradiol [EE]; Schering AG, Berlin, Germany)**.**

The hirsutism was monitored clinically by a modified Ferriman-Gallwey scoring system to grade body hair growth, the degree of hirsutism was rated on a scale from 0 to 4 over 11body regions and the total score was obtained by summation the score for each body region and was determined before the study and again after 3 and 6 months of treatment. The score evaluation was performed by a single physician who was unaware of the treatment.

Hormone levels were determined before the study and every 3 months during the treatment. Blood samples were collected within the first 5 days of the menstrual cycle for measurement; Serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), Estradiol (E_2), free testosterone (T), androstenedione (A), dehydroepiandrosterone (DHEAS), and sex hormone binding globulin (SHBG) were measured by Chemiluminescent Microparticle Immunoassay (CMIA) (Abott, ARCHITECT system).

A self-evaluation of the clinical result was obtained from each women. The study was approved by the hospital ethics committee, and informed consent was obtained from all women.

Statistical Analysis

The outecome were evaluated by student's paired test and one-way analysis of variance for comparison within and between treatment groups, respectively. The chi-square test was employed to evaluate the statistical significance and the probability values less than 0.05 were considered. All analysis were performed using the statistical package for social science (Version 16.0 SPSS inc. Chicago, IL).

Results

A total of 96 patients were recruited for the study only 89 women completed the study, and their results are represented here. All women tolerated the treatment with no side effects leads to discontinuation of the drug intake.

The age of the women treated with tamoxifen (23 ± 5.7 years) was similar to those treated with EE/DRSP (22.9 ± 6.2 years). The women with primary and secondary infertility were similar in both groups (83%, 17% respectively) in tamoxifen treated women and (86%, 14% respectively) in women received EE/DRSP. The body mass index of the women treated with tamoxifen (24.3 ± 6.6 kg/m^2) was also similar to that treated with EE/DRSP (23.6 ± 7.8 kg/m^2). The duration of infertility in both groups varied and majority of the women with duration between 2 and 3 years.

Table 1 shows the ovulation rate with 80mg was higher than with 40 mg but not statistically different. About 50% got pregnant during the study but pregnancy rate per ovulatory cycle was significantly higher ($P < 0.001$) in 80 mg than the 40 mg group.
Clinical evaluation for hirsutism score are presented in table 2. With oral EE/DRSP there was improvement observed after 3 months of treatment while there was significant decrease in the hirsutism score after 6 months of therapy (*P<o.o5 vs. basal value).* While with tamoxifen a slower reduction in the hirsutism score was observed that reached statistical significance ($P < 0.05$) only after 6 months in comparison to the basal score and significant difference between both groups also, observed after 6 months.

Table 3 represents higher basal levels of free T, A and LH and lower basal levels of SHBG and FSH. No changes in FSH, LH and E_2 concentrations with EE/DRSP, while with tamoxifen their levels change toward the normal levels in comparison to the basal levels with no significant difference between both groups as regard to FSH and LH while this was significant as regard to E_2. Whereas the free T an A levels decreased significantly in both groups in comparison to basal levels with significant decrease with EE/DRSP in comparison to tamoxifen, the SHBG levels increased in both groups but were significantly with EE/DRSP in comparison to the basal and tamoxifen, whereas DHEAS levels did not change during therapy in both groups.

Patients' self-evaluation for improvement in hirsutism was presented in table 5 where the women in both groups see the results positively. Whereas 100% reported an excellent to good effect EE/DRSP therapy, only 89.5% of women who received tamoxifen expressed the same opinion and 10.5% of patients reported no beneficial effect at all with no changes found in the hematologic values, liver markers and kidney function throughout the study.

Discussion

PCOS with hirsutism is often treated with a combination of OCPs and antiandrogen (spironolactone) and some patients treated with induction of ovulation. Therapeutic choice in hirsute women with PCOS depends on; patient's age, fertility status, preferences for pregnancy or treating hirsutism or menstrual irregularity, the extent of hirsutism and accessibility and affordability.

Tamoxifen is antiestrogenic improving folliculogenesis by its direct action on the ovary as suggested by Fukushima et al., (1982). In spite of its equal effectiveness in inducing ovulation with clomiphene citrate, it also has a good effect on the endometrium and quality of cervical mucus (Steiner et al., 2005). Dhaliwal, et al., (2011) reported good pregnancy rates in women with PCOS and proves that tamoxifen is good first-line treatment for ovulation. Combined oral contraceptives have been widely investigated and are well-known as an effective treatment for hirsutism (Azziz, 2003). Although all achieve some reduction in serum androgen concentrations, their clinical benefit is blunted by variable androgenic activity of progestins within the formulations. The EE/DRSP combination exerts significant antiandrogenic activity and is especially effective in improving facial hirsutism also, it has a minor side effects (Batukan and Muderris, 2006).

This study was conducted to evaluate the outecome of the induction in hirsute women with PCOS as regard to the ovulation, pregnancy rates and hirsutism score. The ovulatory cycles was 66.4% and 77% (with 40mg and 80mg respectively) , Dhaliwal, et al., (2011) found that the ovulatory cycles at the dose of 40mg was 68% and at the 80mg was 86.6% which are comparable with our results. While Messinis et al., (1982) reported that the percentage ovulatory cycles was 56.2. The pregnancy rate in the present study at the dose of 40mg was 13% and at the dose of 80mg was 28% these results similar to that reported by Dhaliwal, et al., (2011) as the overall pregnancy rate was 48.8% and two-thirds of them were achieved with 80mg dose. Which were comparable with those reported by

Table1: Outcome of tamoxifen treatment.

Dose	No of treated cycles	Ovulatory cycles		Pregnancies per ovulatory cycle	
		No.	%	No.	%
40 mg	140	93	66.4	12	13
80 mg	74	57	77	16	28*

*Note: *P value <0.001*

Table 2: Clinical evaluation of hirsutism score before and during treatment

	Tamoxifen	Oral EE/DRSP	*P* value
Basal	15(8-28)	14(9-28)	>0.05
3 months	12(7-22)	11(6-20)	>0.05
6 months	9(4-15)*	5(1-11)*	<0.05

Note: Values are expressed as median (min-max).
* *P<o.o5 vs. basal value*
EE/DRSP _ ethinyl estradiol/drospirenone.

Table 3: Hormonal levels in both groups before and during treatment.

	Tamoxifen			Oral EE/DRSP		
	Basal	3 months	6 months	Basal	3 months	6 months
FSH (mIU/mL)	5.3 ± 2.3	5.9 ± 2.3	6.1 ± 2.8*	5.6 ± 2.2	5.5 ± 2.1	5.4 ± 2.2
LH (mIU/mL)	6.8 ± 3.4	5.8 ± 3.2	5.3 ± 2.1*	6.6 ± 3.2	6.4 ± 3.5	6.0 ± 3.3
E_2 (pg/mL)	68.6 ± 26.4	67.8 ± 29.2	64.4 ± 28.7*	69.2 ± 26.3	68.3 ± 30.6	68.8 ± 29.7†
Free T (pg/mL)	2.2 ± 1.4	2.0 ± 1.1	1.8 ± 0.8*	2.2 ± 1.5	1.7 ± 0.9*†	1.3 ± 0.7*†
A (ng/mL)	2.7 ± 0.8	2.5 ± 0.9	2.3 ± 0.8*	2.6 ± 0.9	2.1 ± 0.7*†	1.9 ± 0.5*†
SHBG (nmol/L)	35.9 ± 15.9	38.8 ± 16.1	41.4 ± 16.8	36. ± 16.8	47.4 ± 24.6	56.4 ±31.4*†
DHEAS (µg/mL)	2.8 ± 1.3	2.7 ± 1.2	2.6 ± 1.1	2.7 ± 1.3	2.6 ± 1.2	2.5 ± 1.3

Note: values are mean ± SD. EE/DRSP = ethinyl estradiol/drospirenone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E_2 = estradiol; T = testosterone; A = androstenidione; SHBG = sex hormone-binding globulin; DHEAS = dehydroepiandrosterne sulfate.
**P*<0.05 vs. basal value.
†*P*<0.05 vs. tamoxifen.

Table 4: Self-Evaluation of hirsutism at the end of the treatment**.**

	Tamoxifen		Oral EE/DRSP	
	No.	%	No.	%
Excellent effect	6	31.6	22	52.4
Good effect	11	57.9	20	47.6
No effect	2	10.5	0	0
worsening	0	0	0	0

Suginami et al., which was only 4.8% (Suginami et al., 1993).

DRSP, action explained by various mechanisms including a direct dose-dependent block of peripheral androgen receptors located on the dermis (Krattenmacher, 2000; Thorneycroft et al., 2004). The overall hirsutism score in our study in women treated with tamoxifen declined by 20% after 3 months to 40% after 6 months while with EE/DRSP the decline after 3 months was 21.4% and after 6 months was 64.3%, from these results significant differences between tamoxifen and EE/DRSP appears only after 6 months which means a time consuming and deprivation of the women from the chance of induction. Also, the aim of treatment is not complete removal of excessive hair, but instead to achieve a slower growth rate necessitating less need for cosmetic intervention and hair already transformed into terminal form is no longer receptive to medical therapy (Oláh, 2004). Our data with EE/DRSP are similar to those reported by Batukan and Muderris (2006) as the overall score declined by 67% to 78% after 6 to 12 months, respectively. Others have reported similar, but somewhat lower, improvement of hirsutism in PCOS patients who were treated with the EE/DRSP combination [van Vloten et al., 2002; Guido et al., 2004; Ibanez and de Zegher, 2004). Another study found that DRSP and cyproterone acetate containing COCs have similar efficacy on seborrhea and acne lesions as well as facial hair growth (van Vloten et al., 2002). Alternatively, Ibanez and de Zegher, (2004) compared a low-dose flutamide plus metformin combination with EE/DRSP in 32 hirsute patients with PCOS. They reported that both regimens were comparable in terms of reducing hirsutism score, with an approximately 30% decrease in both groups during the course of 9 months of therapy.

The tamoxifen has antiandrogenic effect by decreasing the LH level by improving folliculogenesis and ovulation so, the level of ovarian androgen decreased on the other hand the combination of EE and DRSP is capable of reducing ovarian androgen synthesis, both by direct inhibition of enzymatic pathways involved in their biosynthesis and indirectly through suppression of gonadotropin secretion (Krattenmacher, 2000).

Our investigation found a no significant decrease in gonadotropin in both groups the decline in LH was marked in patients as regard to the elevated basal level this more obvious with tamoxifen. Serum E_2 concentration did not changes significantly in both groups. The results were similar to the findings reported by Batukan and Muderris (2006). Depending on the fact that COCs inhibit the hypothalamus-pituitary-ovarian axis, many studies reported significant decrease in gonadotropin (Falsetti et al., 2001). In spite this, our results in agreement with the results of Guido et al., (2004), who evaluated the efficacy of EE/DRSP in hirsute women with PCOS and reported that serum FSH and E2 concentrations did not change significantlyafter therapy with EE/DRSP combination. On the other hand their patients had elevated pretreatment LH levels, decreased markedly after 3 months of treatment.

The levels of T and A in our study were decreased in both groups significantly as regard to the basal level. Also there were significant effects observed with EE/DRSP in comparison with those treated by tamoxifen. This might be due the different degree of inhibitory effect on LH secretion and it might also be due to the effect of ethinyl estradiol on the hepatic production of SHBG synthesis. These results are in concordance with these data reported by Batukan and Muderris (2006) also, similar changes reported by others (Guido et al., 2004; Ibanez and de Zegher, 2004).

Our investigation revealed no significant changes in SHBG with tamoxifen treatment in comparison with EE/DRSP were the resultant elevated SHBG concentrations are associated with decreased amount of active free T. The changes in SHBG which occur with EE/DRSP show significant rise during therapy (Batukan and Muderris, 2006). Other studies after 9 to 12 months of therapy indicated a three to four times increase of SHBG over baseline levels (Guido et al., 2004; Ibanez and de Zegher, 2004). There no changes in the serum DHEAS concentrations during therapy with tamoxifen or EE/DRSP in contrast to the results of Guido et al., (2004), who observed a significant decrease in serum DHEAS levels after 6 months of treatment with EE/DRSP. Others observed the same our results (Batukan and Muderris, 2006). In spite of the obvious antiandrogenic activity of EE/DRSP combination it should be kept in mind that an EE/DRSP has the same contraindications as other COC formulations (Thorneycroft et al., 2004).

The treatment did not seem to be has effect on liver, renal or haematological functions and no significant side effects in both groups.

Conclusion

In spite of significant antiandrogenic effect of EE/DRSP no significant difference in hirsutism score before 6 months and this effect is transient in addition to the possible systemic side effects. Also, about 50% of women got pregnant during the study and there was improvement in the hirsutism score, we conclude that tamoxifen therapy in infertile hirsute women with PCOS is the first choice for treatment as it gives the chance of pregnancy and has a positive effect on hirsutism score without time consuming.

Conflict of interest

The authors have no conflicts of interest.

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