FOLLICULAR GROWTH AFTER METFORMIN TREATMENT WITH CLOMIPHENE CITRATE, OR LOW DOSE RECOMBINANT FSH IN INSULIN RESISTANT POLYCYSTIC OVARY

Abd El Samie A. A.., M. D.
Faculty of Medicine, El Fayoum University

ABSTRACT

Objective: To study the effect of insulin sensitizer metformin on follicular growth and pregnancy outcome with clomiphene citrate or minimal stimulation by recombinant FSH inductions that are monitored by transvaginal ultrasound in patients with resistant polycystic ovary syndrome (PCOS).

Methods: The study included 60 patients with insulin resistant PCOs randomly allocated into two groups: Study group: (Group I) included 30 patients. They were pretreated with Metformin in a dose of 500 mg tablets tds and were monitored till their serum insulin and testosterone levels become normalized then ovulation induction was done by clomiphene citrate in a dose of 50-100 mg daily starting from the fifth day of the menstrual cycle for 5 days in 15 patients [group IA]. In the other 15 patients of the study group induction of ovulation was done by recombinant FSH in a dose of 50 to 75 m iu per day strating from the 5th day of the menstrual cycle for a maximum of 5 days [group IB]. The follicular growth was monitored by T.V, US from day 10-14 of the menstrual cycle. The control group [group II] included 30 patients who did not receive Metformin. Subgroup IIA: Included 15 patients in which induction of ovulation was done by clomiphene citrate, and group IIB included 15 patients where ovulation induction was done by recombinant FSH as in the study group, and were also monitored in the same way.

Results: Monofollicular ovulation occurred in 5% of the studied clomiphene group compared to 6.66% in the control clomiphene group; 13.33% in the studied rFSH group and 46.66% in the control rFSH group had a monofollicular ovulation. Two or more mature follicles occurred in 44.3% in the control clomiphene group, while 86.66% in the studied rFSH group and 33.3% in the control rFSH showed a similar response. The rate of pregnancy was 33.32% in the studied clomiphene group compared to 13.33 in the control group, while the pregnancy rate was 53.32% in the studied rFSH group compared to 33.33% in the control rFSH group.

Conclusion: The insulin sensitizer Metformin should be used as a pretreatment adjuvant therapy in the management of infertile patients with resistant polycystic ovary syndrome. This can improve the ovarian response as well as occurrence of pregnancy.

INTRODUCTION

The primary abnormality in PCOS resides within the ovaries or the ovarian abnormality could be secondary to extra ovarian disturbances [1]. The primary defect in PCOS could also reside at the level of the hypothalamic - pituitary axis. Here, a defect in the normal mechanisms controlling gonadotrophin secretion could result in a primary derangement giving rise to the typical changes of polycystic ovaries [2].

In addition to an intrinsic ovarian abnormality, other potential initiating abnormalities include excess adrenal androgen secretion, obesity and hyperinsulinemia usually associated with insulin resistance [1]. Insulin resistance and hyperinsulinemia might be the initiator of a vicious circle of endocrine deregulation found in PCOs; therefore, correction of

this background metabolic derangement might restore normal reproductive endocrine regulation, and this is the rational of using insulin sensitizers in PCOs. The suggested links between insulin resistance, FSH responsiveness and PCOS [3] could be an altered serum leptin level [4], abnormal androgen metabolism and or upregulated expression of IGF-1 in the ovarian stroma [5].

Recombinant derived FSH and LH have been developed by transfixing the human gonadotrophin genes into Chinese hamster ovary cell lines and are now available for therapeutic use. Because the polycystic ovary is usually very sensitive to stimulation by hormones, it is important to start with low doses of gonadotrophins and follicular development must be very carefully monitored by ultrasound scans. Close monitoring should enable treatment to be suspended if three or more follicles develop to avoid the risk of multiple pregnancy or ovarian hyperstimulation syndrome [6].

According to a study done in 2002, nearly 30% of obese women with PCOS had amenorrhea [The rate was lower in women with normal weight]. In PCOS, increased androgen production produces high LH levels and low FSH levels, so that follicles are prevented from producing mature ova. Without ovulation, progesterone is no longer produced, whereas estrogen levels remain normal. A low starting dose [50-75 iu] for ovulation induction by gonadotrophins is usually recommended [7], and the dose is adjusted according to ovarian response [8]. The ovarian response and follicular count and size are monitored with serial ultrasound and serum E_2 measurements [9].

MATERIALS & METHODS

The study included 60 patients (60 cycles) with insulin resistant PCOS (1-2 cycles per patient). Confirmed polycystic ovary syndrome evidenced by endocrine parameters of chronic anovultion (mid-luteal progesterone) and elevated serum testosterone levels, and monographic visulization of polycystic ovarian morphology (increased ovarian volume > 9 cm^3, more than ten follicles of 308 mm diameter, and increase in stromal density). Insulin resistance was documented by fasting insulin to glucose ratio and timed postprandial serum insulin levels. The patients were included into 2 groups; the study group (1) composed of 30 patients pretreated with metformin (Amophage® 500 mg tablet / Amoun/ Egypt) three times daily which was continued till serum fasting insulin level was normal (< 28 mcu/ml and 112 mcu/ml for 30 minutes postprandial and or 79 mcu/ml for 120 minutes postprandial). Insulin resistance was evaluated by dividing fasting gloucose over fasting insulin, (value: 24.5 was considered insulin resistance). Also, normal total serum testosterone < 0.8 mg/ml. This is usually required 12 ± 4 weeks pretreatment with metformin before ovulation induction.

Group I:

The study group : was subdivided into group IA composed of 15 patients in which ovulation induction was done by clomiphene citrate 50-100 mg/daily from day 3 of the cycle. Group IB consisted of 15 patients from the study group with ovulation induction done by low dose recombinant FSH (50IU "puregon"® daily for 4 days starting from day 5) till 2-3 follicles with 12 mm diameter are detected. After 4 days of stimulation, folliculometry was done for the 30 patients of the study group using trans-vaginal ultrasonography (5-7 MHZ) starting from day nine of the cycle and continued daily till one or more follicles reached a dimension of 18-20 mm.

Group II:

The control group: composed of 30 patients who did not receive metformin. Also, subdivided into 2

sub groups: II A and II B. In group IIA, ovulation induction was done by clomiphene citrate as in group I A; in group II B ovulation induction was done by low dose recombinant FSH as in group I B. Folliculometry was done in the same way as in the study group and human chorionic gonadotrophin (HCG) (Profasi® 5000 IU) was given by I M injection when the leading follicle was ≥ 17 mm. Empirical luteal phase support was done by oral dydrogesterone 10 mg twice daily (Duphaston® solvay) and was continued till menstruation, or positive pregnancy test (urinary) and positive cardiac pulsations of pregnancy. Main outcome measures: incidence of monovulation, or more, and recording singleton, twin and triplet pregnancies.

RESULTS

The study involved 60 patients (60 cycles and 60 inductions of ovulation) included into two groups: Study group that consisted of 30 patients with PCOS pretreated with the insulin sensitizer merformin and a control group that included 30 patients who did not receive metformin. Induction of ovulation was done by clomiphene citrate in 30 patients and by low dose recombinant FSH in another 30 patients. Patient characteristics showed that the mean age + S.D. was 26.2 ± 2 years; parity: All the cases were nulliparae with primary infertility duration of 4.5±2.1 years. Monoovulation was detected in 5% of the clomiphene study group compared to 6.66% in the control clomiphene group, while in the study of rFSH it was 13.33% and 46.66% in the control rFSH group Two or more mature follicles occurred in 44.#% in the study clomiphene group compared to only 13.33% in the control clomiphene group while it was 86.66% in the study rFSH group and 33.33% in the control rFSH group. The rate of pregnancy was 33.32% in the study clomiphene group compared to 13.33% in the control comiphene group. In the low dose FSH, the pregnancy rate was 53.32% in the study group compared to 33.33% in the control grooup.

Table I : The numbers of mature follicles (t-test).

	Study group	t	p	Control group
	Mean ± SD			Mean ± SD
Clomiphene	8 ± 2.30	0.41	> 0.05	3 ± 0
r FSH	8.25 ± 2.87	0.04	< 0.05	8 ± 2.30

Table II : Z-test for the numbers of mature follicles.

Induction		Study		Z-test		Control	
F		No	%	Z	P	No	%
Clomiphene n = 18	1	9	50%	0.3	> 0.05	1	6.66 %
	2	4	22.2%	0.2	> 0.05	2	13.33 %
	3	3	16.6%	0.53	> 0.05	-	-
	4	1	5.5%	0.62	> 0.05	-	-
rFSH	1	2	13.33%	- 0.4	> 0.05	9	46.66 %
	2	9	60%	0.45	> 0.05	3	20 %
	3	4	26.66%	0.3	> 0.05	2	13.33 %
	4	0	0	0	0	0	0

Table III : The pregnancy rate in clomiphene inductions.

Pregnancy	Study n = 15		Z-test		Control n = 15	
	No	%	Z	P	No	%
Singleton	4	26.66	0.64	> 0.05	2	13.33
Twins	1	6.66	2.97	> 0.05	-	-
Triplets	-	0	-	-	-	-

Table IV : The pregnancy rate in low dose r FSH inductions.

Pregnancy	Study n = 15		Z-test		Control n = 15	
	No	%	Z	P	No	%
Singleton	5	33.33	0.69	> 0.05	3	20
Twins	2	13.33	0	0	2	13.33
Triplets	1	6.66	2.97	> 0.05	-	-

DİSCUSSION

Insulin resistance is a heterogenous condition resulting from a variety of insulin receptor and post receptor disorders [10]. Burghen et al, showed that serum insulin concentrations were proportional to serum concentrations of testosterone, and speculated that insulin resistance in women with PCOS was a direct result of their hyperandrogenism [11]. Using of insulin sensitizers in PCOS for correction of metabolic derangement might restore normal reproductive endocien regulation, and this is the rational of using insulin sensitizers in PCOS[3].

In this study, metformin was used as an insulin sensitizer in PCOS patients, before ovarian induction for spontaneous conception in the absence of other infertility factors in order to increase ovarian response to the used methods for induction. This was confirmed by the increased rate of follicular growth during monitoring of induction. Our findings show that there is an increase in the ovarian response to clomiphene citrate induction of ovulation after adequate metformin pretreatment compared to clomiphene citrate induction alone without metformin with significant differences between the two groups. This is in agreement with Imani et al (2000)[3] study who found that a significant positive correlation of ovarian response in clomiphene citrate induction of ovulation in PCOS patients with metformin pretreatment which was 94.4% with positive ovarian response in the study group and only 20% in he control group. The present findings show that there is an increase of ovarian response to low dose recombinatn FSH induction after adequate metformin pretreatment comapred to recombinant FSH induction without metformin (99.9% with the study group and 79.9% with the control group). This is in agreeement with fulghesu et al., (1997), who found a significant positive correlation of ovarian response in PCOS with low dose rFSH after pretreatment with the insulin sensitize metformin[12].

The present findings show that there is an increase in pregnancy rate after metformin pretreatment in the clomiphene citrate induction group to 27.7% compared to non metformin clomiphene induction group which was 13.3% only. Also, there was an increase in pregnancy rate after metformin low dose recombinant FSH induction group to 53.3% comapred to 33.3% in non-metformin low dose recombinant FSH induction group. This is in agreement with Hassan et al., (2002) study who found an increased pregnancy rate to 45% after metformin pretreatment with low dose recombinant FSH in PCOS patients[13].

CONCLUSION

Correction of the metabolic syndrome by metformin as an insulin sensitizer before stimulation, could improve ovarian response to low dose gonadotropin induction and to a lesser extent to clomiphene citrate induction, which when used together with monitoring the patients with serum FSH could increase the incidence of ovulation and increase the spontaneous conception rate in insulin resistant PCOS.

REFERENCES

1. Poretskyl piper B: Insulin resistance, hypersecretion of LH and a dual defect hypothesis for the pathogenesis of polycystic ovary syndrome. Obstet Gynecol (1994) 64: 613-621.
2. Guzick D S, wing R, smith D et al: Endocrine consequences of weight loss in obese hyperrandogenic anovulatory women. Fertil Steril (1994) 61: 598-604.

3. Imani B, Ekjkmans MJ, Dejong FH, payne NN,: Free androgen index and leptin are the most prominent endocrine predictors of ovarian response in clomiphene citrate induction of ovulation in PCOS. J. Clin endocrinol metab, 2000, 85(2): 676.

4. Carmina E, Ferin M, Gonzalez F, Lobo RA,: Evidence that insulin of and rogens may participate in the regulation of serum leptin levels in women. Fertil-Sterial (1991) 72(5): 926-31.

5. Thierry Van Dessel HJ, Lee PD, Faessen G, Faouser BC, Guidic LC: Elevated serum levels of free IGF-1 in PCOS. J Clin Endocrinol. Meta.

6. Levene MI, Wild J, Steer P (1992) Higher Multiple Births and Modern Management of Infertility in Britain. Br J Obstet: Gynaecol 99: 607-613.

7. Goverde AJ, Medonell J, Vermeiden JPW, Schats R, Rutten FFH, Schoemaker J. Intrauterine insemination or in-vitro fertilization and male sub fertility; a randomized trial cost effectiveness analysis. Lacet 2000; 355: 13-18.

8. Salah O, Balen AH. New concepts in super ovulation startegies for assisted conception treatments. Curr. Opion. Obstet. Gynecol., 2000; 12: 201-206.

9. Nachetigall MJ, Schwartz LB: The application of transvaginal ultrasound for ovulation induction and in-vitro fertilization. Clin Obstet Gynecol. 1996; 231-247.

10. Rahillys O. Moller DE: Mutant insulin receptors in syndromes of insulin resistance. Clin Endocrinol (1992); 36: 605-632.

11. Burghen G A, Givens Jr, Kitabachi AE.,: Correlation of hyperandrogenism with hyperinsulinism in polycystic ovaryt disease. J Clin. Endocrinol. Metab (1980) 53: 905-508.

12. Fulghesu AM, Villa P, pavone V, Guido M, Apa R, Caruso A, Lanzone A, mancusos: The impact of insulin secretion on the ovarian response to exogenous gonadotropin in polycystic ovary syndrome J. Clin Endocrinol Metab 1997; 136(5): 488-492.

13. Hassan H. A; El-Gezeiry D, baghday I, Sheikh M, Tamer M.: Severe ovarian hyperstimulation syndrome in insulin resistant polycystic ovarian syndrome: Improved results after metformin treatment, with low dose recombinatn FSH monitoring. Mid. East Fertil. Soc. J 2002; 31: 36 (7).