Received: 4 Jun. 2008 **Accepted: 17 Feb. 2008**

Original Article

Effect of polycystic ovaries syndrome on outcome of assisted reproductive Technology in Isfahan Fertility-Infertility Center

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Abstract

Background: Polycystic ovaries syndrome (PCOS) is the most common disorder in infertile women with ovulation sterility. There are some instances of abnormal endocrine in the women stricken by this syndrome and so the clinical results of ovulating induction in them, because of severe response of ovary against ovulating induction, are very discussing and may lead to different results from those with normal ovary. In this research the effect of ovulating induction among this group of women was compared with the women with normal ovary and tubal sterility.

Methods: This prospective cohort study performed on 260 infertile pairs with PCOS and tubal factors under treatment using fertility assistance techniques in IFIC. The numbers of oocyte, concentration of testosterone and andrestandion, fertility rate and embryo quality were compared.

Results: The mean of oocyte retrieved, concentration of andrestandion in follicular and LH0 phases, and testosterone in LH0 phase were higher in PCOS patients ($p < 0.05$), but the fertilization rate indicated no difference between two groups. According to the results there was a significant association between the concentration of andrestandion and testosterone phase LH0 and the embryo quality.

Conclusion: The ovulation induction in PCOS by increasing the serum androgen concentration would lead to undesirable influence on oocyte, so that the achieved embryo has a lower quality and the ratio of good-quality embryo decrease, but because of the high number of oocyte and the number of achieved embryo in the women with PCOS the chance of growing more good-quality embryo is high

Key words: Polycystic ovary syndrome, ovulation induction, number of oocyte, androgen

IJNMR 2008; 13(2): 53-58

Polycystic ovary is a common syndrome among infertile women which is observed in an extended scope; so that on the one hand only the evidences of polycystic ovary in sonography (including the increase of ovary size more than 9 mm, the existence of 10 or more 2-8 mm cysts in one level and increase of stroma density) is observed and on the other hand clinical signs like oligomenorrhea, hirsotism, hyperandrogenism, and non-ovulation.[1]

The reason of non-ovulation in 83% of infertile pairs was PCOS and from 56% of pairs who had infertility with unknown reasons, 44% were reported PCOS with ovulations cycle.[2]

Environment endocrine system, which plays an important role during a completion period of follicular in oocyte growing before ovulation, is abnormal in women with PCOS and is along with vascular increase of follicular and abnormal act of granular cellules.[3]

There are also some reports from abnormal endocrine specifications in women with PCOS like high level of secondary insulin because of insulin resistance in cells, increasing LH concentration, and hyperandrogenism which may cause different reaction in ovary in women with PCOS against medical regimes of ovulation induction compare women with normal ovaries.[4-

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Research Article of Isfahan University of Medical Sciences, No: 80105.

[6] Okon et al showed that an increase in plasma androgen density has followed by a decrease in endometrial protein density like PP14 in secretory-phase endometerium and failure of implantation.[7] Also Horie et al have reported that androgens with harmful effects on endometrial function can increase abortion.[8] The study by Doi et al in 2005 showed that an increase in density of serum androgens in women with PCOS correlated positively with abnormal increase in LH.[9] Engmann et al reported that the increase of LH plasma density in follicular phase, in women with PCOS, was the reason of infertility history and increase of abortion.[2] But in the Okon et al and Rai et al studies, there was no difference of plasma LH in the women with recurrent abortion and normal.[7,10]

Ludwig et al study also showed that using GNRH agonists to treat LH, has a positive effect on embryo quality but no improvement of pregnancy outcome.[11] Clinical results of ovulation induction in women with PCOS had been very discussing due to the intensive response of ovary, and may be different with the results of women with normal ovary. Besides, the effect of ovulation induction drugs on ovary androgenic hormones and its side effects on embryo quality have been considered less. Recognizing the effect of ovulation induction on ovary androgen level in women with PCOS and also its probable effects on embryo quality is very essential as an important predictive factor of the result of fertility assistance techniques to make decision for treatment. So, in this research, determining the ovary reaction in women with PCOS against ovulation induction, the number of needed HMG ampoules for suitable induction of ovaries, the number of oocyte made from ovulation induction, the amount of serum androgens, fertilization ratio (the number of produced oocyte to the number of zygotes), embryo quality in primary levels and its relation to the amount of serum androgens in infertility group with PCOS under treatment with fertility assistance techniques were assessed and compared with the women with normal ovary which were under treatment because of tube infertility.

Methods

This research was a prospective cohort study and performed from September 2001 to March 2003 in Isfahan Fertility-Infertility Center (IFIC). 130 patients in fertile age with PCOS attended in this research. The recognition criteria in this group were high concentration of LH (the ratio of FSH to LH equal or more than 2), oligomenorrhea or hyperandrogenism (or any evidences of high androgen), and sonography evidences of PCOS based on the patient's file and the opinion of the physician.

The control group was consisted of 130 tube factor-resulted infertile patients with no evidences of PCOS. The recognition criterion for tube factor was closing one or two tubes based on laparoscopy findings or hysterosalpingography assessment. Sampling method was based on goal, so all the persons referred during the presence of the researcher, if had the criteria, involved in the study.

All patients with endometriosis, based on laparoscopic and cytological findings, or existence of abnormal parameters in the analysis of the spouse's sperm were exited from both groups (Exclusion criteria). All the studied women were under 40 years old and were the candidates for assisted reproductive technologies (IVF/ICSI). Ovulation induction (superovulation) was done by injection of HMG after control of Hypophyse, using GnRH agonist. Serial vaginal sonography was done to assess the growing of follicular and determining the dosage of ovulation induction drugs based on ovary response. When at least two follicles reached 17-20 mm, 10000 unit of HCG were injected and approximately 32 hours later taking ovum was done in general anesthesia condition. Using standard protocol of IVF and ICSI, artificial insemination was done and after 24 hours if the second prenucleus exists, insemination would consider positive and in the day two after insemination, assessing the embryo quality was done.

Scoring the embryo quality was as follows: score 3 for embryo with regular blastomers and without fragmentation (top-quality embryo); score 2 for embryo with irregular blastomers

and without fragmentation (mid-quality embryo); and score 1 for embryo with irregular blastomers and with fragmentation (low-quality embryo).[2] Cupping and separating serum for assessment of androgens were done after finishing ovulation induction in the first refer to sonography; examining the ovary follicular (follicular phase) was done between 1 to 8 hours before taking ovum from ovary (LH0 phase). The serum specimens were sent to Dr. Baghaei's lab to measure the andrestandion and serum testosterone using radio-immunoassay method. The amount of andrestandion and testosterone in follicular and LH0 phases, the number of oocyte, fertilization amount (the ratio of the number of zygote to the number of oocyte), the number of embryo, and the number of embryo with top, mid and low quality were assessed and compared in both groups. To statistical analyze of data, $\chi 2$ statistical test (to analyze qualitative variables) and t-test (to compare quantitative variables) were used via SPSS software. The significant level to accept of or reject the hypotheses was $p < 0.05$.

Results

In this research, 267 women between 18-40 years old were attended and 7 cases were excluded due to improper response of ovary to ovulation induction. The average age of women with PCOS and tube infertility was 31.27 and 29.45, respectively with no significant differences between two groups ($p > 0.05$).

Oocyte contributions to unsuccessful fertilization in women with PCOS and with tube factor were 3.1% and 4%, respectively. Statistical t-test showed that the average number of HMG ampoules needed induction in PCOS group was significantly less than the tube infertility group (23.93 ± 5.47 against 27.65 ± 11.01 and $p < 0.05$).

The average concentration of testosterone in follicular phase in women with PCOS was 1.04 ± 0.78 and in the women with tube infertility was 1.15 ± 0.83; No significant difference was shown by t-test ($p > 0.05$). Comparing the average concentration of testosterone in LH0 phase using t-test between two groups showed that the average concentration of testosterone in women with PCOS was significantly more than women with tube infertility (2.18 ± 1.98 against 1.24 ± 0.95, $p < 0.01$). The average concentration of andrestandion of follicular phase in women with PCOS and in tube infertility group was 4.18 ± 2.41 and 3.14 ± 1.87, respectively.

Also the average concentration of serum andrestandion in LH0 phase was 6.26 ± 2.62 in women with PCOS and 4.05 ± 1.82 in women with tube infertility. Statistical analysis using t-test showed that the average concentration of andrestandion in follicular phase and also the average concentration of andrestandion and testosterone in LH0 phase in women with PCOS was significantly more than group with normal ovary ($p < 0.01$, $p = 0.04$).

Comparing the average number of oocyte given from two groups (using t-test) showed that in women with PCOS it was significantly more than the second group (13.1 ± 9.39 against 8.04 ± 6.17, $p < 0.05$).

In this study, the fertilization amount (the ratio of fertilized oocyte to the total number of oocytes) was 64% in PCOS group and 67% in women with tube infertility. Comparing the amount of fertilization between two groups, considering the method of sperm insemination (IVF or ICSI) and ovary, showed no significant difference ($p > 0.05$). Results showed that the top-quality embryo in group with PCOS was 73.9% and in group with tube infertility was 77.5%. Also 8.5% of embryos in group with PCOS were in low-quality condition and 4.2% were seen in group with tube infertility. X^2 statistical test showed a significant relation between the kind of infertility and the quality of embryo ($p = 0.02$). The average number and standard deviation of the embryos produced by insemination was 7.79 ± 6.50 in PCOS group and 5.24 ± 3.92 in tube infertility group. T-test showed that the number of embryos in PCOS group was significantly more than other group ($p = 0.02$). Frequency distribution of embryo quality based on the amount of testosterone and andrestandion in follicular and LH0 phases is presented in tables 1 and 2.

Table 1. Embryo quality based on serum testosterone concentration in follicular and LH0 phases.

Embryo quality		top n(%)	mid n(%)	low n(%)	p value
Follicular Phase	0.1-1	396(63.7)	83(65.4)	41(85.4)	0.06
	1.1-2	147(23.6)	26(20.5)	3(6.3)	
	> 2	79(12.7)	18(14.2)	4(8.3)	
Total		622(100)	127(100)	48(100)	
LHO Phase	0.1-1	252(32.5)	33(23.6)	10(13.9)	0.006
	1.1-2	259(33.7)	60(42.9)	28(38.9)	
	> 2	258(33.6)	47(33.6)	34(47.2)	
Total		769(100)	140(100)	72(100)	

There was a close relationship between the amount of testosterone in follicular phase and embryo quality (p = 0.06). But no significant relation observed between the amount of serum andrestandion and embryo quality. Also a significant relation observed between testosterone and andrestandion in LH0 phase and embryo quality, so that 13.9% of low-quality embryos were in the group which in them the amount of testosterone in LH0 phase was between 0.1 and 1 nmol/l and 47.2% of low-quality embryos were observed in the group with more than 2 nmol/l testosterone (p = 0.006).

According to the results, 10.7% of top-quality and 7.6% of low-quality embryos were in the group which in them serum andrestandion was less than 3.1 ngr/ml (p < 0.01).

Discussion

This research showed that in women with PCOS, increasing the level of ovary androgens would lead to the decrease of ovum potential to produce top-quality embryo. The results also showed that the number of produced oocyte by ovulation induction in women with PCOS was more than women with tube infertility and normal ovary; also, the number of HMG ampoules needed to induct the ovary was less in PCOS group.

There is a belief that in women with PCOS, Struma blood flow in follicular phase is more than women with normal ovary.[7, 12] It has been also shown that the increase of Struma blood flow in this phase would lead to increase in receiving gonadotropin by ovary target cells which cause increase in ovary response to ovulation induction drugs and producing oocyte in the process of ovulation induction.[13, 14] Some studies have shown that the quality of oocyte is not suitable in the second phase of Meiosis

Table 2. Embryo quality based on serum andrestandion concentration in follicular and LH0 phases.

Embryo quality		top n(%)	mid n(%)	low n(%)	test result
Follicular Phase	< 3.1	223(35.4)	35(27.3)	17(35.4)	NS
	3.1-6	272(43.2)	60(46.9)	25(52.1)	
	> 6	135(21.4)	33(25.8)	6(12.5)	
Total		630(100)	128(100)	48(100)	
LHO Phase	< 3.1	84(10.7)	17(11.4)	6(7.6)	p = 0.006
	3.1-6	372(47.4)	68(45.6)	28(35.4)	
	> 6	329(41.9)	64(43)	45(57)	
Total		785(100)	149(100)	79(100)	

division (metaphase) in women with PCOS and this process lead to decrease of fertilization capability in oocyte[3]. In this study, although the amount of fertilization in women with PCOS was less than the group with normal ovary, but this difference was not statistically significant and there was no evidence in decrease of fertilization potential in produced oocytes by ovulation induction and hormone condition in women with PCOS. It is because not only the fertilization potential in oocyte, but also the condition of produced embryo are of the most important factors in successful infertility treatment in women, especially with PCOS;[15, 16] the reason is that besides the quality of produced oocyte by ovulation induction, their potential for growing and development is also very important and the researches showed that the successful fertilization is related to the number of top-quality embryos and also embryos placed into the uterus.[15] Frank et al (2003) reported that PCOS had no bad effect on embryo quality.[4] But the results of this research showed that in women with PCOS the amount of embryo cell development with good quality is less than women with normal ovary and this indicates the side effects of the syndrome on the next development of ovum cell. This study showed that the level of serum testosterone and andrestandion in LH0 phase is related to embryo quality; it meant that the increase of androgens level would lead to the increase of low-quality embryo.

Teissier et al found that increasing androgens inside ovary causes follicular production in ovulation induction in treatment regimes and increasing testosterone concentration in women with PCOS leads to decrease the quality of oocyte.[17] But this is very important that the response of ovary in most of the women with PCOS as produce more oocyte, caused to produce ovary androgens and the germ resulted from fertility assistance techniques faced these androgens. Cattral et al (2005) showed that women with PCOS, had faced with androgen in their intrauterine period on infancy; and this may cause increasing the potential of outbreak of PCOS in their germ.[18]

In women with PCOS, ovary response to ovulation induction would lead to more produced embryos by lab fertilization because of producing more oocyte compared to women with normal ovary. Since the chance of embryo development with good quality would increase due to more number of embryos and in fertility assistance techniques the probability of success in fertilization increase due to the ability of choosing embryo with good quality from all formed embryos. Ludwig et al (1999) showed that cumulative score of embryo quality in women with PCOS was more than control group.[11] But the high number of low-quality embryos in women with PCOS in conditions with no possibility to choose embryo for transferring into uterus cause to the failure of fertilization after ovulation induction in this group. In women with PCOS, if the ovulation induction had not been lead to the pregnancy and fertilization, another fertility assistance technique could be choose to produce an embryo with top-quality.

The researchers declare that have no conflict of interest in this study and they have surveyed under the research ethics.

Acknowledgement

The authors sincerely extend their thanks towards the financial department of Isfahan University of Medical Sciences who supported this research, all physicians of Isfahan Fertility and Infertility Center and Miss Leila Javaheri, Miss Mehrnoosh Motiei, Miss Hengameh Hajmomen and Parva Kohi for all their helps and cooperation.

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