ORIGINAL ARTICLE

Clinical analysis of Chinese infertility women with premature ovarian failure

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Submitted: June 8, 2007 *Accepted: July 8, 2007*

Key words: **premature ovarian failure; infertility; clinical analysis; karyotype; estrogen**

Neuroendocrinol Lett 2007; **28**(5):580–584 **PMID:** 17984952 NEL280507A32

Abstract

OBJECTIVE: Infertility is one of important issues in patients with premature ovarian failure (POF) during their reproductive life. This study would analyze the features of infertility women with POF. Patients: 138 Chinese infertility women with POF were accrued from the women who visited the Reproductive Medical Center in Shandong Provincal Hospital of Shandong University between May 2003 and November 2006.

METHOD: This study analyzed the clinical, etiology features and karyotype of 138 patients, then evaluate the effect of the therapy.

RESULTS: It showed that most patients physical situation were suitable for assisted reproductive therapy. The infertility women with POF had high rate of abnormal karyotype (11/65, 16.92%) and lower severe autoimmune disorders rate (2/138,1.45%). And some of them demonstrated family aggregation. FSH was dropped apparently after estrogen-progesterone therapy ($p<0.05$). The spontaneous pregnancy incidence of the women was 2.17% (3/138).

CONCLUSION: The infertility women with POF were suitable for assisted reproductive therapy and donor oocyte could be an alternate way. Their high chromosomal abnormality rate showed the importance of genetic screening. And estrogen-progesterone therapy was benefit for improving their endocrine environment.

Abbreviations

ANOVA	- analysis of variance
ART	- assisted reproductive therapy
E2	- estradiol
FSH	- follicle-stimulating hormone
HRT	- hormone replacement therapy
LH	- luteotrophic hormone
POF	- premature ovarian failure
PRL	- prolactin
To	- testosterone

INTRODUCTION

Premature ovarian failure (POF) is characterized by amenorrhea with constant estrogen deficiency and elevated gonadotropin levels in the post-menopausal range (especially FSH≥40IU/L) before the age of 40 (Gandar, 1988), represents the end stage of a variety of disorders that result in the loss of ovarian follicles. Previous researches

have documented that POF is a heterogeneous disease that affects 1–2% in women during their theoretically reproductive life (Letur e*t al.*, 2004). The affects rate reaches 4–18% in women with secondary amenorrhea (Coulam *et al.*, 1986). Heterogeneity of POF means, in particular, that the POF can be caused by a wide variety of the possible etiology. The possible reasons now known could be chromosomal abnormalities, autoimmune disorders, familial genetic origin and other permanent damage to ovaries. The left about 50% women suffered idiopathic POF without known reasons (Woad *et al.*, 2006). Although progresses have been made in the study on the etiology, the cause of POF remains elusive in the majority of patients.

POF is an endocrine disturbance that hurts women in both physical and spiritual sides (Nelson e*t al.*, 2005). Besides estrogen deficiency symptom, the women with POF always accompanied significant psychosocial sequelae and major health implications. However, premature ovarian failure should not be considered as a premature menopause for about 5% to 10% POF patients could be conceive spontaneously after diagnosis (van Kasteren, Schoemaker, 1999). And follicular activity is found in majority of women with POF (Conway e*t al.*, 1996). But up to dates any attempts to increase induced ovulation rate in POF failed, oocyte donation is the most possible method for women desiring fertility (Kalantaridou e*t al.*, 1998). So female infertility is an obvious consequence of POF and most POF cases would suffer infertility.

Clinically, we found premature ovarian failure is one of the important reasons causing infertility. These cohorts women with POF who have the desire for fertility are different with some special features from the whole patients with POF. Up to now, no report has been appeared about this side. To fill this blank, we analyzed some clinical features of these cohort infertility patients with POF in the present study. With the addition of this part POF we may understand the pathogenesis of POF further, and it is also benefit to classification, more suitable treatment and more effective prevention of POF.

MATERIALS AND METHODS

Patients' samples

In present study, 138 Chinese infertility women with POF were accrued from the women who visited the Reproductive Medical Center in Shandong Provincal Hospital of Shandong University between May 2003 and November 2006. The diagnosis of POF was confirmed by case history, serum sex hormone level and the ultrasound image. Infertility is defined as a couple does not pregnant after 1 year of normal sexual activity without contraceptives. Patients with other diseases and the male partner reasons causing infertility were excluded in this study. No patients took hormone medicine within 3 months prior to attending our study.

This is a retrospective study based on the usual clinical practice. Informed consent for the study was obtained from all subjects. The study was approved by the Ethics Committees of Shandong University.

Clinical detection

All patients answered a standard questionnaire by personal interview regarding general characteristics (age, bore place, occupation and nation, education), lifestyle history (operation, poison, radiation contact and smoking, drinking, narcotics habits), disease history, reproductive history (obstetric and abortion history, duration of infertility), menstrual characteristics (age at menarche, average duration of bleeding and average cycle length, algomenorrhea), menstrual disorder (duration of amenorrhea, hormone replacement therapy history) , presence and intensity of estrogen deficiency symptomatology (hectic fever, hidrosis, emotional lability, lassitude, and cardiovascular system, osteoporosis, etc) and family history with reproductive outcomes.

Transvaginal ultrasound was done to record each patient size of uterus, ovaries, endomembrane and lesions if existed, and pelvic examination was also done.

Serum sex hormone analysis

All patients were taken fasting blood for serum sex hormone examination twice for diagnosis. For the patients had menstrual disorder, random blood was taken before any treatment. Serum sex hormone including follicle-stimulating hormone (FSH), luteotrophic hormone (LH), prolactin (PRL), testosterone (To), estradiol (E_2) was detected by chemiluminescence immunization (Beckman Access Health company, USA). Another serum hormone was examined after hormone replacement therapy at their menstrual cycles 3rd day.

Karyotype analysis

We persuaded all patients with POF after diagnosis to take karyotype examination, but only parts of them accepted it. Peripheral blood was taken to cultivate the leukocyte for karyotype analysis by G-binding technology. In our study, there were 65 cases do the examination.

Treatment strategy

All patients received hormone replacement therapy (HRT) after dianosis, here's the detail: the dose of estrogens is 1–2 mg one times a day, which continued for 21 days in a treatment menstrual cycle. Progesterone luteohormone, 20 mg/d, intramuscular, added for the last 5 days. Usually, after 3 treatment cycles, serum sex hormone was rechecked. Corticosteroids could add in the treatment cycles. Ovulation stimulation could be attempt only when the patient's FSH dropped below 40 IU/L after HRT.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, version 10.0. (SPSS Inc, Chicago, IL, USA.), and statistical sig-

nificance was taken at the two-tailed 0.05 p-level. The clinical features of the patients and their serum sex hormone were described by analysis of variance (ANOVA). The HRT effect to the serum sex hormone was analyzed by Friedman M and Newman-Keuls test.

RESULTS

The main medical history characteristics and their menstrual and childbearing history were detailed in Table 1.

All patients had estrogen deficiency symptoms in some extent and the severity was correlated with age, duration of POF, therapy and duration of therapy. They complained about vegetative dystonie symptom such as hectic fever, hidrosis, emotional lability, and lassitude. And some had depauperate and dry urogenital tract and mastoptosis. Transvaginal ultrasound showed depauperate uterine (means 3.67 cm×2.91 cm), ovaries and endometria in the POF patients, 66 of whose ovaries could not be identified by ultrasound. No patient had cardiovascular system disorders and osteoporosis symptom in the study.

The karyotypes results were shown in Figure 1 and the distributions were shown in Table 3. The chromosomal abnormalities rate was 16.92% (11/65). Gonadal hormone results were shown in Table 2. FSH dropped significantly after HRT ($p<0.05$). LH and E_2 showed no difference after HRT ($p>0.05$). All patients estrogen deficiency symptoms were alleviated during hormone replacement therapy. 2 patients got pregnant during HRT and 1 woman got pregnant by ovarian stimulation after HRT.

DISCUSSION

In the 138 POF patients, the number of secondary amenorrhea (131/138, 94.93%) was obviously prior to that of primary amenorrhea (7/138, 5.07%), which means better ovarian developing in these cohort women. Besides, except for their menstrual disorder, their physical situations were relatively normal. Few patients had cardiovascular system disease or other severe disease, and most patients BMI were in normal range, which means that the physical situations of these women in the study were competent to assisted reproductive therapy and further pregnancy.

Analysis of etiology in figure 1 shows two etiology features in the infertility patients with POF. One important feature is chromosomal abnormalities rate (16.92%, 11/65) high, apparently higher than the 5% in the long-term review of POF, also higher than 8.8% Portnoi *et al.* (2006) reached in his study. X-chromosome is the main chromosomal abnormalities concentration. Besides 6 Turner cases, there were 4 POF patients with X-chromosome structural abnormalities. The break and rearrange point mainly span from Xq22 to Xq25, just the area proved to be correlated with ovarian dysfunction.

Table 1. Results of the univariate analysis of the infertility patients with POF.

Age (years) (SD)	30.36 (4.05)
Duration of infertility (per month; SD)	50.93 (37.01)
Primary infertility	110 (110/138, 79.71%)
Secondary infertility	28 (28/138, 20.29%)
Amenorrhea	
Primary amenorrhea	7 (7/138, 5.07%)
Secondary amenorrhea	131 (131/138, 94.93%)
Age at menarche (SD)	14.69 (1.81)
BMI (missing)	
BMI <20kg/m^2	27 (27/138, 19.57%)
BMI 20–25kg/m^2	94 (94/138, 68.12%)
BMI 25–30kg/m^2	10 (10/138, 7.25%)
BMI >30kg/m^2	7 (7/138, 5.07%)
Previous pregnancies	
None (primary infertility)	110 (110/138, 79.71%)
1	21 (21/138, 15.22%)
2	5 (5/138, 3.62%)
≥3	2(2/138, 1.45%)
Previous delivery	
Never pregnant	110
Induced abortion (man-time)	15
Spontaneous abortion (man-time)	3
Removal of hydatidiform mole (man-time)	1
Ectopic pregnancy	1
Live birth (man-time)	14
Family history	
Parents consanguineous marriage	4
Menstrual disorder family history	9

Furthermore, four patients' parents were consanguineous marriage, and nine patients had POF family history. From the above, we could conclude that genetic abnormalities were more important in these infertility patients with POF than other POF patients. So genetic screening including karyotype analysis in these patients is necessary.

Table 2. Gonadal hormone results.

	FSH (IU/L)	LH (IU/L)	PRL (ng/ml)	To (ng/ml)	E_2 (pg/ml)	TSH
Initial	74.42±27.67*	32.90±16.62	12.43±10.10	29.21±24.85	28.60±35.44	1.89±1.51
Sec.	75.07±27.67*	33.06±18.04	---	---	26.36±43.75	---
Thr.	65.07±25.58	30.27±19.32	---	---	33.43±32.71	---
F	5.93	1.04			1.27	
P	0.0029	0.3536			0.2806	

p-value of 0.5 was used as entry criterion

Table 3. Karyotpye distribution.

GROUP	NORMAL KARYOTYPE	CHROMOSOMAL ABNORMALITIES		
		X-chromosomal abnormalities		Autosomal abnormalities
		Numerical aberration	Structural abnormalities	
Sample size (n)	54	6	4	1
Percentage (%)	83.03	9.23	6.15	1.54
Karyotype	46,XX	45,XO/47,XXX	Long &/ short arm	13,14

Another feature is low incidence in severe autoimmune disorders in these patients. Only 2 cases (1.45%) had immunological diseases, one with nephrotic syndrome and the other with rheumatoid disease. Though autoimmune disorders were proved in POF patients (Kelkar e*t al.*, 2005; Pires *et al.*, 2006) and many autoantibodies were found. However,owing to the variety origin of autoantibodies, no consensus on the ovarian antigenic determinants had been reached till now. So it's difficult for us to diagnose autoimmune disorders in POF patients in clinical work. Meanwhile, POF patients with severe autoimmune diseases were not suitable for pregnancy, so few of them ask for assisted reproductive therapy.

Although the etiology of POF is heterogenic, hormone replacement therapy (HRT) is still the cornerstone of treatment. HRT could well improve estrogen deficiency syndrome, and lower the risk of angiocardiopathy (CD) and cerebrovascular disease (CVD). Furthermore, HRT could maintain bone density of patients with POF to avoid osteoporosis. In this study, FSH dropped apparently after estrogen-progesterone therapy. There were 2 patients ovulation recovered and gained pregnancy during HRT. And one patient got pregnant by ovarian stimulation when the serum FSH dropped below 40IU/L level after HRT. Tartagni *et al.* (2007) once concluded that exogenous estrogen could lower FSH level in patients with POF and benefit to improve the success of rate of ovulation induction with exogenous gonadotropins. Zargar *et al.* (2000) once speculated this situation maybe because exogenous estrogen down regulate gonadotrophin receptors and restore the sensitivity of the few remaining ovarian follicles . Meanwhile, the follow exogenous progesterone is useful in creating secretory endometrium and could lower LH and FSH in the cycle reported before (Fatemi e*t al.*, 2007). So we choose estrogen-progesterone to substitute simple estrogen replacement therapy in present study. However, the pregnancy rate (3/138, 2.17%) in the study was lower than the spontaneous 5–10% pregnancy rate after diagnosis in the literature (van Kasteren, Schoemaker. 1999). So most infertility patients with POF might need assisted reproductive therapy, donor oocyte maybe a choice.

In conclusion, the infertility women with POF were suitable for assisted reproductive therapy and donor oocyte could be an alternate way. Their high chromosomal abnormality rate showed the importance of genetic screening. And estrogen-progesterone therapy was benefit for improving their endocrine environment.

ACKNOWLEDGEMENTS

We gratefully thank for the members of the study for their assay expertise. We also thank the subjects in this protocol for their patience and persistence. This study was financially supported by the National Basic Research Program "973" of China to Zi-Jiang Chen (2006CB944004) and the National Natural Science Foundation of China to Zi-Jiang Chen (30670777).

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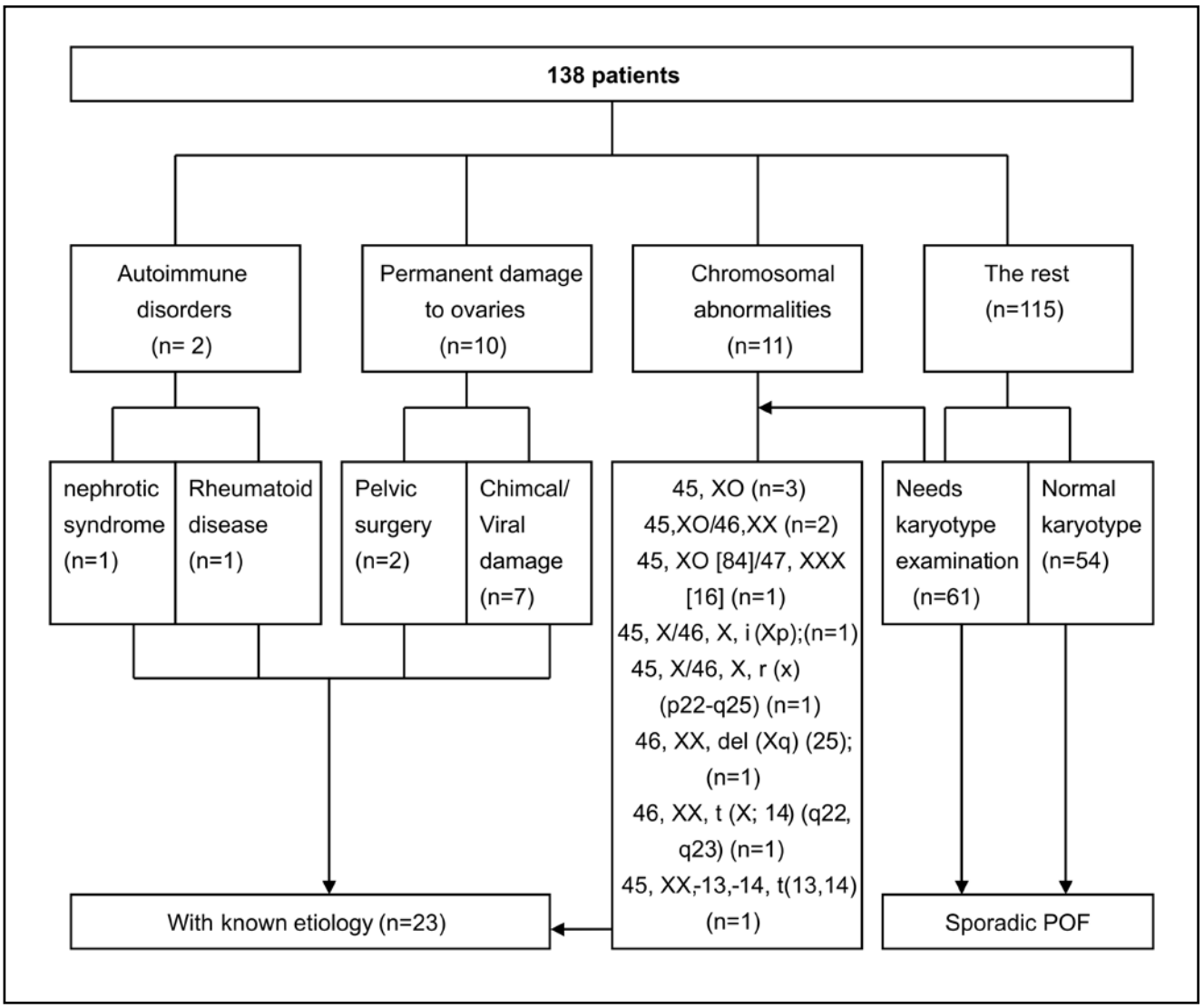

Figure 1. Analysis of etiology in the infertility patients with POF .

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