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Resistin levels of serum and follicular fluid in non-obese patients with polycystic ovary syndrome during IVF cycles

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Abstract: Objectives: To measure serum and follicular resistin, steroids hormone levels in women with PCOS (polycystic ovary syndrome) (*BMI* (body mass index)<25 kg/m^2), to assess possible correlations of resistin to hormonal and metabolic parameters and to analyze the clinical outcomes of in vitro fertilization-embryo transfer (IVF-ET) in women with PCOS and tubal infertility. Study design: We analyzed the clinical outcomes of IVF-ET in women with PCOS (*BMI*<25 kg/m^2) and tubal infertility during the years 2002 to 2004 and compared the serum and follicular fluid resistin levels, estradiol (E_2), progesterone (P), testosterone (T) levels in 20 PCOS and 20 healthy, age-matched women without PCOS during IVF-stimulated cycles. The correlations between the resistin levels and the outcomes of IVF-ET were evaluated. Results: No significant differences in resistin levels of either serum or follicular fluid between PCOS and control group were found. However, resistin levels in serum were higher than that in follicular fluid in both groups. Multiple regression analysis showed that resistin levels in serum did not correlate with BMI, estradiol, LH (luteinizing hormone) and insulin level in fasting blood. No significant correlations were found between follicular fluid reisistin levels and fertilization rate, implantation rate, clinical pregnancy rate or early miscarriage rate in both PCOS and control groups. Conclusion: Our results show that resistin does not have correlation with the hormonal and metabolic parameters as well as the outcomes of IVF. These data suggest that resistin is unlikely to be a local determinant factor in steroidogenesis and growth and maturation of oocytes during IVF-ET in lean women with PCOS.

Key words: Insulin resistance, Resistin, In vitro fertilization-embryo transfer, Polycystic ovary syndrome
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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility and affects 5%~10% of reproductive age women (Dunaif, 1997). It is characterized by hyperandrogenemia and chronic anovulation and is associated with insulin resistance, obesity and increased risk for type 2 diabetes (Knochenhauer *et al*., 1998). Insulin resistance is thought to play an important role in aetiology of PCOS (Chang *et al*., 1983; Shoupe *et al*., 1983). In vitro and in vivo studies showed that the sensitivity of insulin to glucose metabolism was subnormal and hyperinsulinaemia in women with PCOS. The administration of insulin sensitizing agents, such as metformin, may increase insulin sensitivity and thus induce ovulation (Nestler *et al*., 1998; Hasegawa *et al*., 1999; Vandermolen *et al*., 2001; Ghazeeri *et al*., 2003).

Obesity and insulin resistance affected the success of fertility treatment in PCOS patients. Ovulation induction with gonadotrophins in obese PCOS women required higher doses than in lean PCOS women, the rate of ovulatory cycles was lower and incidence of miscarriage was higher in obese women (Hamilton-Fairley *et al*., 1992; Fridstrom *et al*., 1997). However, insulin resistance was thought neither to be related to hormone levels nor to the IVF outcome. Obesity, independent of insulin resistance, is associated with relative gonadotropin resistance (Fedorcsak *et al*., 2001).

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The hormone resistin, a novel 12 500 cysteine-rich protein, is secreted by adipocytes. Resistin, a novel signaling molecule isolated in mice has been suggested to be the putative hormone thought to link obesity with type-2 diabetes (Steppan *et al*., 2001). Serum resistin levels are significantly increased in insulin-resistant mice and genetic (ob/ob, db/db) or diet-induced obese mice (Steppan *et al*., 2001). In addition, administration of resistin in mice impaired both glucose tolerance and insulin action, while administration of anti-resistin antibodies improved glucose and insulin action (Steppan *et al*., 2001). Their studies appeared to make a strong case for an adipose tissue secreted factor that links obesity to type-2 diabetes by producing insulin resistance.

Several reports discussed the association between PCOS and resistin. Seow *et al*.(2005) reported no difference in serum resistin levels between obese women with PCOS and normal-weight controls. In their study, no association of serum resistin levels with body mass index was observed. Variation in resistin gene promoter was not associated with PCOS (Urbanek *et al*., 2003). These findings suggest that resistin is unlikely to be a major determining factor in PCOS. However, Panidis *et al*.(2004) found significantly higher levels of resistin in the group of PCOS women with *BMI*>25 kg/m^2, compared with normal weight women with PCOS and *BMI*<25 kg/m^2 and control. A significant correlation between resistin and BMI had also been demonstrated. Resistin mRNA levels in adipocytes were increased 2-fold in PCOS patients (Seow *et al*., 2004), suggesting that the resistin gene may be a local determining factor in the pathogenesis of PCOS. Our study aims: (1) to measure serum and follicular resistin, steroids hormone levels in women with PCOS; (2) to assess possible correlations of resistin to the hormonal and metabolic parameters; (3) to analyze the clinical outcomes of in vitro fertilization-embryo transfer (IVF-ET) in women with PCOS and tubal infertility.

MATERIALS AND METHODS

Subjects

Fifty-three cycles of IVF in women with PCOS (*BMI*<25 kg/m^2) and 408 cycles of IVF in women with tubal infertility during the years 2002~2004 were analyzed. Women with PCOS were identified by clinical, laboratory and ultrasound criteria. The clinical criteria included oligomenorrhoea or amenorrhoea dating from menarche. The biochemical criteria were increased LH concentration, *LH*/*FSH* (luteinizing hormone/follicle stimulating hormone)≥2~3, and elevated T (testosterone) levels. The ultrasound criteria were enlarged ovaries with an increased stroma and >10 subcapsular follicles of 3~8 mm diameter, arranged peripherally around a dense core of stroma, as described by Adams *et al*.(1986). Control group included 408 women (*BMI*<25 kg/m^2) with regular cycles undergoing IVF-ET because of tubal infertility.

Stimulation protocol and IVF

1. GnRH Agonist–based protocol

Triptorelin (Decapeptyl CR, 0.1 mg; Ferring, Malmo, Sweden) was administered SC (subcutaneous) daily during the midluteal phase. In anovulatory patients, triptorelin was administered after 16 d of taking oral contraception (OC). Once pituitary down-regulation and ovarian suppression have been achieved, ovarian stimulation with exogenous gonadotropins is started while GnRH agonist administration is continuing concomitantly until the day of human chronic gonadotrophin (hCG) administration. Four ampoules of FSH (Gonal-F; Serono, Abonne, Switzerland) were given IM (intramuscular) daily for 2 d, followed by 2 ampoules of FSH given daily until the day of hCG (Sweden) administration as per the routine at our clinic.

2. Cycle monitoring

Transvaginal sonography every 2~3 d (or as required) together with test in serum LH, E_2 (estradiol) levels were used for cycle monitoring. Dose adjustments and monitoring frequency were based on patient response. hCG 10000 U was given when the leading follicles achieved a diameter of 16 mm; a transvaginal ultrasound–guided oocyte retrieval was scheduled 35 h later. Intracytoplasmic sperm injection was done in male infertility cases. Embryos were transferred 2~3 d after the oocyte retrieval. Luteal phase support was given by daily intramuscular injection of P in oil (80 mg).

3. Clinical pregnancy confirmation

A pregnancy test was administered 14 d after the embryo transfer. If the test was positive, a transvaginal ultrasound study was performed 2~3 weeks

later to confirm a clinical pregnancy.

Sample collection

Fasting blood samples were taken from 20 PCOS and 20 control group subjects. The collected FF (follicular fluid) ($\Phi \geq 1.8$ cm) was centrifuged at 1000 g for 10 min immediately. Blood samples were collected for thrice: basal, between 8:00~10:00 am on the day of hCG and 30 min before aspiration. All samples were kept at room temperature for at lease 30 min to allow the blood to clot and were then centrifuged at 2000 g for 15 min. Serum was collected and stored at −80 °C until assayed.

Hormonal profile

The concentrations of FSH, LH, oestradiol (E_2), testosterone (T) and progesterone (P) were measured by radioimmunoassay (RIA) (DEPU, Tianjing, China). For the above hormones, the intra- and inter-assay coefficients of variance (CV) were <10%.

Insulin assay

Insulin levels were assayed using CLIA (chemiluminescent immunoassay) (Beckman Coulter, USA). Assays were conducted according to the manufacturer's instructions. The sensitivity for the determination was 0.1 μU/ml.

Resistin assay

Resistin was determined by ELISA (R & D Systems Inc.; USA), and assays were conducted according to the manufacturer's instructions. The sensitivity for the determination was 0.26 ng/ml. The intra- and inter-assay CV were 5.0% and 8.2% respectively. The plasma sample was diluted 5-fold with ELISA buffer prior to assay.

Statistics

The Kolmogorov-Smirnov test was applied to both groups to test the normal distribution for each variable. Each variable was presented as mean±*SD*. Differences between the PCOS and control groups were compared, using the non-parametric Mann-Whitney U-test. Chi-square tests were used to compare the dichotomous data. Correlations between serum or follicular fluid resistin levels and steroid hormone levels and clinical parameters were calculated by Pearson's correlation coefficient using a two-tailed test. $P<0.05$ was considered significant.

RESULTS

Patient characteristics

The characteristics and hormonal profiles of the PCOS and control groups are shown in Table 1. There were no differences in age, BMI, or duration of infertility between the two groups. The levels of LH and the LH:FSH ratio were significantly higher in PCOS than in control group ($P<0.001$). PCOS women showed insulin resistance, with significantly higher insulin levels than the control group ($P=0.049$).

Outcomes of IVF-ET between PCOS and control group

Table 2 shows the clinical data for the IVF cycle characteristics and reproductive outcome in the women with PCOS for two years. There was no significant difference in the ampoules of gonadotrophin and duration of stimulation between two groups. The number of oocytes retrieved and the number of embryos were significantly higher in PCOS than that in control group ($P<0.001$ both). However, the fertili-

Table 1 Clinical and baseline hormone concentrations in PCOS and control groups

Variable	PCOS (n=53)	Controls (n=408)	P
Age (years)	29.68±3.74	30.81±2.76	0.326
BMI (kg/m^2)	22.67±3.74	20.68±2.31	0.071
Duration of infertility (years)	5.74±2.94	4.81±3.15	0.376
LH (U/L)	14.26±4.82	3.97±1.44	0.000
FSH (U/L)	6.73±1.40	5.89±1.94	0.435
LH/FSH	2.17±0.77	0.73±0.32	0.000
E_2 (pmol/L)	156.34±74.45	174.86±77.39	0.656
Prolactin (ng/ml)	19.26±7.61	24.06±6.80	0.280
Fasting insulin (μU/ml)	6.79±5.26	3.79±2.42	0.049

zation rate was significantly lower (P<0.001). The implantation rate, clinical pregnancy rate and miscarriage rate were not significantly different in both the control and PCOS groups. Because of the risk of ovarian hyperstimulation syndrome (OHSS) in women with PCOS, the ET cancelled rate was higher than in control group.

Resistin and steroids hormone levels in serum and follicular fluid

Table 3 shows the levels of serum on the day of oocytes retrieved and follicular resistin in both PCOS and control groups. There was no significant difference in the levels of serum or follicular resistin between the two groups. However, the follicular fluid resistin levels were significantly lower than the serum resistin levels in both the control and PCOS groups (P=0.0001).

Correlation of resistin and steroids hormone and outcomes of IVF-ET

No correlations were found between serum or follicular resistin levels and BMI, E_2, P, LH, T, fasting insulin, fertilization rate, implantation rate, clinical pregnancy rate, or early miscarriage rate in PCOS group and control groups. However, serum insulin concentrations showed significant positive correlation with BMI, amps of gonadotrophin, duration of stimulation (r=0.740, P<0.001; r=0.493, P=0.003; and r=0.547, P=0.001 respectively). The serum LH levels, the LH:FSH ratio showed significant negative correlation with ampoules of gonadotrophin, duration of stimulation (r=−0.591, P=0.013; r=−0.643, P=0.005; r=−0.400, P=0.011 and r=−0.486, P=0.048 respectively). Moreover, the P concentrations were significantly higher in control group than in PCOS group (P=0.001).

DISCUSSION

Our present study indicated that resistin concentrations in serum and follicular fluid and the correlation between the resistin and sex steroids in lean PCOS and healthy women. Our findings revealed that serum and follicular fluid resistin levels were comparable among PCOS and healthy women during IVF-cycles. Moreover, our study showed that serum resistin levels had no correlation with E_2, P, T, insulin levels in serum and BMI, and follicular fluid resistin

Table 2 Ovarian stimulation and IVF in PCOS and control groups

Variable	PCOS (n=53)	Controls (n=408)	P
Amps of gonadotrophin	29.42±10.45	30.92±3.32	0.106
Duration of stimulation (d)	11.43±2.53	11.60±2.22	0.625
No. of oocytes retrieved	21.57±9.86	13.86±7.15	0.000
No. of embryos	13.31±6.62	10.02±5.97	0.000
E_2 (pmol/L) before hCG injection	31700.12±24756.62	16788.75±16505.18	0.000
P (nmol/L) before hCG injection	3.06±2.50	2.31±1.98	0.023
Fertilization rate (%)	61.6	72.1	0.000
Implantation rate (%)	11.1	16.60	0.328
Clinical pregnancy rate (%)	38.5	42.0	0.798
Miscarriage rate (%)	40.0	14.38	0.116
OHSS rate (%)	22.9	4.7	0.000
ET cancelled rate (%)	54.3	4.2	0.000

Table 3 Serum and follicular fluid (FF) resistin and hormone levels in PCOS and control groups during IVF-cycles

Variable	PCOS (n=20)	Controls (n=20)	P
Serum E_2 (pmol/L)	31700.12±24756.62	16788.75±16505.18	0.000
Serum P (nmol/L)	3.06±2.50	2.31±1.98	0.023
Serum resistin (ng/ml)	15.83±10.06	12.96±11.27	0.445
FF E_2 (pmol/L)×10^4	55628.75±49289.13	51860.00±32787.52	0.805
FF P (nmol/L)	42626.25±27460.90	82193.33±33582.68	0.001
FF resistin (ng/ml)	9.52±7.44	8.83±6.93	0.793

levels had no correlation with sex steroids in follicular fluid. The resistin levels in serum were higher than that in follicular fluid during IVF-cycles, which accorded with those of Seow *et al*.(2005). Then statistical data in our study also showed that serum insulin concentrations have significant positive correlations with BMI, amps of gonadotrophin and duration of stimulation. Serum LH levels, the LH:FSH ratio had significant negative correlation with ampoules of gonadotrophin, and duration of stimulation. Moreover, the follicular fluid P concentrations were significantly higher in control group than in PCOS group.

Resistin is a signaling molecule induced during adipogenesis and is secreted by the adipocytes (Steppan *et al*., 2001). Several reports suggest that resistin plays a causative role in insulin resistance. Way *et al*.(2001) reported increased mRNA levels in adipose tissue from obese mice and rats treated with rosiglitazone and other PPARγ agonists. The administration of anti-resistin antibody to mice with diet-induced obesity, insulin resistance and hyperglycemia partially corrected the blood glucose levels and improved their sensitivity to exogenous insulin (Steppan *et al*., 2001). Yamauchi *et al*.(2001) reported reduced adipocyte resistin sensitivity in a mouse model of insulin resistance. Resistin blunted insulin-responsive glucose uptake in cultured 3T3-L 1adipocytes and pretreatment of resistin-secreting 3T3-L1 adipocytes with a neutralizing antibody augmented insulin-stimulated glucose transport (Steppan *et al*., 2001). Together, these dates suggest that resistin is a potential mediator of obesity-associated insulin resistance.

Women with PCOS are frequently insulin resistant, independent of obesity (Burghen *et al*., 1980). Several studies had reported that insulin resistance and compensatory insulinaemia in women with PCOS had direct effects on oocyte maturation and ovulation (Nestler *et al*., 1998; Vandermolen *et al*., 2001; Shepard *et al*., 1979; Lobo *et al*., 1982). However, Fedorcsak *et al*.(2001) reported insulin resistance did not affect the number of collected oocytes, the number of normal fertilized oocytes, implantation and pregnancy rates, the incidence of ovarian stimulation syndrome, and pregnancy outcome. Moreover, insulin resistance had no effect on hormone levels during ovarian stimulation. Insulin-resistant women tended to have lower SHBG (sex hormone binding globulin) and higher insulin concentrations and needed more FSH during stimulation. Our results showed that the ampoules of gonadotrophin were comparable among PCOS and controls during IVF-stimulation cycles. However, the results that serum insulin concentrations had a significant positive correlation with BMI, ampoules of gonadotrophin and duration of stimulation suggested the obesity and insulin resistance might affect the outcome of IVF or ICSI (intracytoplasmic sperm injection) in women with PCOS. In our studies we found that the follicular fluid progesterone levels were significantly lower in PCOS, but whether the lower progesterone levels are likely to be one of the factors of lower fertility rat in PCOS is not clear.

The role of resistin in PCOS had been investigated in several studies, which proved that variation in resistin gene promoter was not associated with polycystic ovary syndrome (Urbanek *et al*., 2003). Serum resistin levels were not elevated in PCOS women with insulin resistance (Panidis *et al*., 2004; Seow *et al*., 2004), and resistin was therefore not regarded as a major determining factor of PCOS-associated insulin resistance. However, Xita *et al*.(2004) reported resistin gene polymorphism was associated with body index in women. Seow *et al*.(2005) showed resistin mRNA levels in adipocytes were increased 2-fold in PCOS patients, suggesting that the resistin gene may be a local determining factor in pathogenesis of PCOS. Our study showed follicular fluid resistin levels were significantly lower than the serum resistin levels in both the control and PCOS groups and no difference in serum resistin levels between PCOS and control groups were found. Furthermore, there were no correlations between serum or follicular resistin levels and sex steroids or fertility rate, implantation rate, clinical pregnancy or miscarriage rate. These results suggest that resistin does not play a role in steroidogenesis, maturation, development of oocytes in women with PCOS and controls receiving IVF.

In our study, the PCOS patients and control group had normal weight (BMI<25 kg/m^2). We would collect subjects with BMI>25 kg/m^2 and compare the serum and follicular resistin level difference with that BMI<25 kg/m^2 for further study. Then we would study a polymorphism in the resistin gene in ovary

tissue and granulosa cell from PCOS patients during IVF-ET.

In conclusion, PCOS patients have lower fertility rate during IVF-stimulated cycles. The insulin resistance may affect the doses of gonadotrophin and the duration of stimulation during ovarian hyperstimulation. Resistin plays a role in neither steroidogenesis nor maturation and development of oocytes in women with PCOS and control group during IVF.

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