RBM ONLINE

ELSEVIER

Article

Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome

Zewu Li [a,b], ***Yueting Zhu*** [c], ***Hongchang Li*** [c], ***Wenjie Jiang*** [c], ***Hongbin Liu*** [c], ***Junhao Yan*** [c], ***Zi-Jiang Chen*** [a,b,c,*], ***Weiping Li*** [a,b,*]

[a] *Centre for Reproductive Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200135, China*

[b] *Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Shanghai 200135, China*

[c] *Centre for Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University; National Research Centre for Assisted Reproductive Technology and Reproductive Genetics; The Key laboratory of Reproductive Endocrinology (Shandong University), Ministry of Education Shandong Provincial Key Laboratory of Reproductive Medicine, China*

Zewu Li received his doctorate from Qilu Hospital, Shandong University, China, in 2015. He undertook postdoctoral research at the Center for Reproductive Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China. His research has focused on finding new diagnostic markers for ovulation disorder illness and embryo selection.

KEY MESSAGE

Serum and follicular fluid LIF concentrations were found to be lower in PCOS women compared with non-PCOS controls, suggesting that reduced LIF concentrations could be related to the disordered folliculogenesis seen in PCOS patients. LIF concentrations in embryo culture medium may be useful to predict pregnancy outcome following IVF.

A B S T R A C T

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology. Leukaemia inhibitory factor (LIF) affects many reproductive activities, including follicular development, embryo implantation and growth. The aim of this study was to evaluate LIF concentrations in serum and follicular fluid of women with PCOS and controls who underwent IVF with embryo transfer (IVF–ET). Serum and follicular fluid LIF concentrations were lower in women with PCOS compared with controls. Oestradiol concentrations in follicular fluid were higher in PCOS subjects compared with controls. LIF concentrations in serum ($r = 0.6263$, $P < 0.05$) and follicular fluid ($r = 0.7093$, $P < 0.05$) were negatively correlated with oestradiol concentration in the PCOS group. LIF concentrations in follicular fluid showed no difference between women who conceived and women who did not in both PCOS and control groups. However, LIF concentrations in embryo culture medium were higher in women who conceived following IVF compared with women who did not, in combined PCOS and control groups. The findings indicate that low LIF concentrations in serum and follicular fluid may contribute to disordered folliculogenesis in PCOS. LIF concentrations in embryo culture medium may predict the outcome of IVF treatment.

© 2018 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

* Corresponding author.
E-mail address: chenzijiang@hotmail.com (ZJ Chen); liweiping@renji.com (W Li).

https://doi.org/10.1016/j.rbmo.2017.12.020
1472-6483/© 2018 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology (Lebkowska et al., 2016). It is the most common hormonal disorder in young women, estimated to affect 5.0–13.9% of women during their reproductive years (Melo et al., 2010; Yu and Wang, 2016). The aetiology of PCOS is multifactorial and involves endocrine and metabolic components, as well as imbalance of local ovarian regulatory factors. The pathologic changes in PCOS are characterized by hyperandrogenism and endocrine disorders due to ovulatory dysfunction, which is one cause of female infertility. PCOS is not only a reproductive disorder, but also a syndrome with metabolic consequences that could affect a woman's health during different stages of reproductive and post-reproductive life (Dunaif and Fauser, 2013; Orio and Palomba, 2014). The prevalence of PCOS is related to both genetic and environmental factors (Crosignani and Nicolosi, 2001). However, the pathogenesis of PCOS has not been fully elucidated.

It has been demonstrated that PCOS is related to local regulatory factors (Sahin et al., 2014). Leukaemia inhibitory factor (LIF) is a local regulatory factor in the ovary (Hsieh et al., 2005; Ozörnek et al., 1999) belonging to the interleukin (IL)-6 family, and is a highly glycosylated, secreted protein composed of 180 amino acid residues. It has different biological activities in different tissues and cells. LIF can regulate the growth and differentiation of many kinds of cells, including embryonic stem cells, archaeocytes, liver cells and endothelial cells (Salleh and Giribabu, 2014). In recent years, it has been reported that LIF may affect reproductive processes including follicle growth, embryo growth and differentiation (Aghajanova, 2010; Dozio et al., 2009). Previous studies have demonstrated that LIF concentrations in the follicular fluid increase before ovulation, and that there is a positive correlation between LIF concentrations and quality of oocytes (Lédée-Bataille et al., 2001; Paiva et al., 2009). However, the concentrations of LIF in the serum of PCOS patients, and whether LIF can act as a biomarker for predicting the outcomes of IVF with embryo transfer (IVF–ET), remain unknown.

In the present study, the concentrations of LIF and oestradiol were examined in women with PCOS and controls, and the relationship between LIF and oestradiol concentrations in serum and follicular fluid was explored, with the aim of further investigating the pathogenesis of PCOS-related infertility. The correlation of LIF concentrations in embryo culture medium with IVF–ET outcomes was also investigated to evaluate the potential of LIF as a biomarker for predicting clinical pregnancy.

Materials and methods

Subjects

A total of 94 patients who underwent IVF–ET between August 2016 and January 2017 in the Centre for Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University, were recruited for this study. Forty women with PCOS and 40 weight-matched control subjects participated in the study because 14 patients were lost to follow-up. Diagnosis of PCOS was carried out according to the revised Rotterdam consensus (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). The women with PCOS were diagnosed based on olio-amenorrhoea and hyperandrogenaemia after excluding non-classic congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinaemia and thyroid disease. Polycystic ovaries were verified by ultrasound in all subjects with PCOS. The control group consisted of women who had regular menstrual cycles (28 ± 2 days, blood progesterone concentrations measured between the 18th and 21st days of the menstrual cycle, >10 ng/ml in two consecutive cycles) without clinical or biochemical hyperandrogenism or polycystic ovary and with no history of any drug intake for at least 3 months. Women in the control group had either Fallopian tube obstruction, or normal reproductive health but an infertile male partner. Sex hormone concentrations and routine biochemical examinations of control subjects were normal, and patients had no history of genitourinary diseases, or severe cardiovascular, liver or kidney disease. Additional exclusion criteria for both groups were smoking and alcohol consumption. All patients in the PCOS and control groups underwent IVF–ET. The data for all subjects were obtained from clinical and pathologic records including age and history of menstruation. Routine measurements of body weight and height, hair growth and distribution were recorded. All subjects provided written informed consent in accordance with Institutional Review Board guidelines for the protection of human subjects. The study received ethical approval from the Institutional Review Board on 6 January 2017 (reference number 16).

Ovarian stimulation and follicular fluid and embryo culture supernatant collection

All patients were stimulated by the long protocol. Ovarian follicular development was stimulated with recombinant human FSH (Merck Serono, Switzerland) at doses of 225–450 IU/day. Ovulation was triggered by human chorionic gonadotrophin (HCG 4000–10000 IU) (Livzon Pharmaceutical, China) when at least two follicles were 18 mm and half of the remainder were >15 mm. Oocytes were recovered transvaginally under ultrasound guidance approximately 34.5 h later. All monitoring of controlled ovarian hyperstimulation (COH) as well as egg retrievals and embryo transfers were performed by one of five physicians. Follicular fluid was preserved at oocyte retrieval, by collecting the liquid aspirated from the follicle into the suction tube, to avoid contamination by blood. Follicular fluid samples from each follicle were pooled for each patient for measurement of LIF concentrations. Pooled follicular fluid was centrifuged at 1500*g* for 10 min and the supernatant was stored at –20°C.

Collected oocytes were cultured in a four-well multi-dish with 600 ml of culture medium added with serum substitute supplement. Each well contained from one to four oocytes. An IVF technique was used for insemination. Oocyte fertilization was observed 16–18 h after insemination under an inverted microscope. Fertilized eggs were cultured to blastocysts. The same culture methodology and media were used for embryos in both groups. All embryo transfers were performed using a Wallace catheter under direct ultrasound guidance 120 h after egg retrieval. Embryos were cultured individually and LIF concentration in culture medium was only measured for the embryos that were transferred when comparing pregnant and non-pregnant groups. The original droplets of embryo culture supernatants collected for each embryo were centrifuged at 1000*g* for 10 min and stored at –20°C, then were tested for LIF concentration.

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020

LIF and hormone assays

Venous blood (2 ml) was collected on the third day of the menstrual cycle after fasting. If subjects had oligomenorrhoea or amenorrhoea, fasting venous blood could be collected at any time. Serum, follicular fluid and embryo culture supernatant LIF concentrations were measured by enzyme-linked immunosorbent assay (R and D Systems, USA). Both inter-assay and intra-assay coefficients of variation for LIF assays were less than 10%. The lower limit of detection for LIF was 8 pg/ml. The concentrations of serum oestradiol, FSH, LH, progesterone, testosterone and prolactin (PRL), and follicular fluid oestradiol and progesterone, were measured by chemiluminescence (Roche, Switzerland). The lower limit of detection for oestradiol, FSH, LH, progesterone, testosterone and PRL were 18.4 pmol/l, 0.1 IU/l, 0.1 IU/l, 0.095 nmol/l, 0.087 nmol/l and 0.996 mIU/l, respectively.

Luteal support and judgement of pregnancy outcome

After fertilization, progesterone (Abbott, the Netherlands) was administered by intramuscular injection at a dose of 60 mg per day and continued for 14 days for corpus luteum support. If pregnancy was confirmed, progesterone administration was continued until the 10th week of pregnancy. Biochemical pregnancy was defined as blood HCG >10 IU/l on the 14th day of transplantation. Clinical pregnancy was confirmed with ultrasound examination of the number of gestational sacs and fetal heartbeat on approximately the 64th day after embryo transfer.

Statistical analysis

The data were expressed as mean ± standard deviation (SD). The data between two samples were compared by Mann–Whitney *U*-test, and the counting and grading data were analysed by chi-squared test. The relationship between the parameters was analysed by Pearson correlation analysis. All calculated *P*-values were two-sided, and $P < 0.05$ was used to determine statistical significance. Statistical analyses were performed using GraphPad Prism software (GraphPad Software, USA) and SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The average age in the PCOS group was 28.37 ± 3.67 years (range: 20–37 years), and 30.17 ± 4.24 years (range: 25–41 years) in the control group. There was no significant difference in age between the two groups. The PCOS group included 20 cases of oligomenorrhoea (50%), six cases of amenorrhoea (15%), 35 cases of irregular menstruation (87.5%), nine cases of hirsutism (pubic hair) (22.5%), 10 cases of acne (25%), 20 cases of primary infertility (50%) and 20 cases of secondary infertility (50%). The subjects in the control group had normal menstrual cycles and no evidence of hirsutism or acne, but there were 10 cases of primary infertility (25%) and 30 cases of secondary infertility (75%). In the control group, there were 29 patients with infertility due to Fallopian tube obstruction (72.5%), while the remaining women were normal and the infertility was caused by male factors (11 cases, 27.5%) (**Table 1**).

Table 1 – Clinical–pathological characteristics of PCOS and control subjects.

	PCOS (n = 40)	*Control (n = 40)*
Age (years)	28.37 ± 3.67	30.17 ± 4.24
Body mass index (kg/m^2)	26.72 ± 3.04	25.15 ± 2.25
Oligomenorrhoea	20 (50%)	0
Amenorrhoea	6 (15%)	0
Irregular menstruation	35 (87.5%)	0
Hirsutism	9 (22.5%)	0
Acne	10 (25%)	0
Primary infertility	20 (50%)	10 (25%)
Secondary infertility	20 (50%)	30 (75%)
Fallopian tube obstruction	0	29 (72.5%)
Male factor	0	11 (27.5%)

Values are expressed as mean ± SD or number (%).
PCOS = polycystic ovary syndrome.

Table 2 – Sex hormone and LIF concentrations in PCOS and control subjects.

	PCOS	*Control*	*P-value*
Oestradiol (pmol/l)	149.04 ± 61.91	138.25 ± 79.35	NS
LH (IU/l)	12.87 ± 7.82	7.59 ± 4.47	0.031
FSH (IU/l)	5.82 ± 1.33	7.12 ± 0.75	NS
LH/FSH	1.78 ± 1.01	1.82 ± 1.27	NS
Progesterone (nmol/l)	2.19 ± 0.86	2.07 ± 0.58	NS
Testosterone (nmol/l)	1.38 ± 0.71	0.71 ± 0.31	0.014
PRL (mIU/l)	367.39 ± 184.86	292.56 ± 112.78	NS
LIF (pg/ml)	44.27 ± 5.57	74.85 ± 2.44	0.0231

Values are expressed as mean ± SD or number (%).
LIF = leukaemia inhibitory factor; PCOS = polycystic ovary syndrome; PRL = prolactin.

Serum concentrations of LH, testosterone, FSH, oestradiol, PRL and LIF

Serum concentrations of LH and testosterone were significantly elevated in women with PCOS compared with control subjects ($P < 0.05$). The serum LH concentrations in the PCOS patients were 12.87 ± 7.82 IU/l and higher than those in the control group (7.59 ± 4.47 IU/l) ($P < 0.05$). The serum testosterone concentrations in the PCOS group (1.38 ± 0.71 nmol/l) were higher than those in the control group (0.71 ± 0.31 nmol/l; $P < 0.05$; **Table 2**). Moreover, the concentrations of serum LIF in the PCOS group (44.27 ± 5.57 pg/ml) were lower than those in the control group (74.85 ± 2.44 pg/ml; $P < 0.05$; **Figure 1A**). There were no significant differences in the serum concentrations of FSH, oestradiol and PRL between the PCOS and control groups (**Table 2**).

Correlation between serum LIF and other serum hormone concentrations in PCOS patients

In the PCOS group, serum LIF concentrations were negatively correlated with oestradiol concentrations (**Figure 2A**). However, there were no significant correlations between serum LIF concentrations and LH/FSH ratio (**Figure 2B**), testosterone concentrations (**Figure 2C**) and progesterone (**Figure 2D**). In the control subjects, serum LIF concentrations were not correlated with serum concentrations of

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020

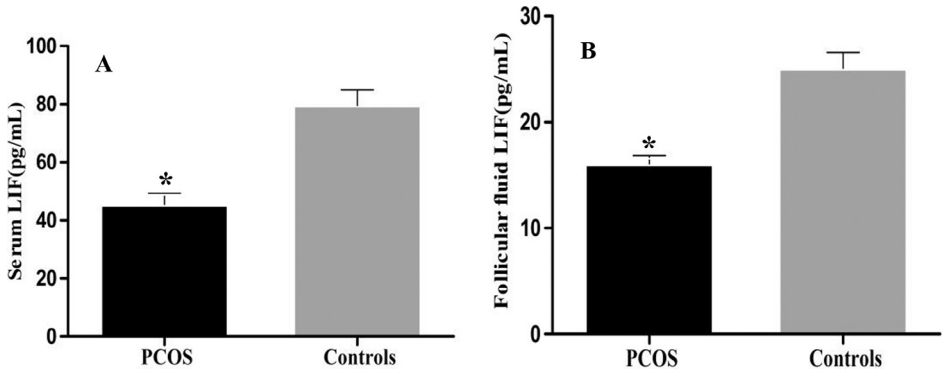

Figure 1 – Leukaemia inhibitory factor (LIF) measured in serum (A) and follicular fluid (B) of polycystic ovary syndrome (PCOS) and control subjects (*$P < 0.05$).

oestradiol, progesterone and testosterone, and LH/FSH ratio (data not shown).

Concentrations of LIF and oestradiol, progesterone in follicular fluid and the correlations between LIF and oestradiol, progesterone in follicular fluid

The LIF concentrations in the follicular fluid in the PCOS group (16.08 ± 4.17 pg/ml; **Table 3**) were lower than those in the control group (25.07 ± 9.2 pg/ml; $P < 0.05$; **Figure 1B**). In the PCOS group, the LIF concentrations in follicular fluid were negatively correlated with oestradiol concentrations (**Figure 3A**). However, there was no significant correlation between follicular fluid progesterone concentrations and LIF concentrations (**Figure 3B**).

LIF concentrations in follicular fluid and embryo culture medium from subjects with different pregnancy outcomes

The clinical pregnancy rate in the PCOS group was 22.5%, which was significantly lower than that in the control group (52.5%). In both the PCOS and control groups, the LIF concentrations in the follicular fluid of women who conceived consequent to the treatment were not significantly different to those in women who did not (**Figure 4A and B**). The LIF concentrations in embryo culture medium from women who

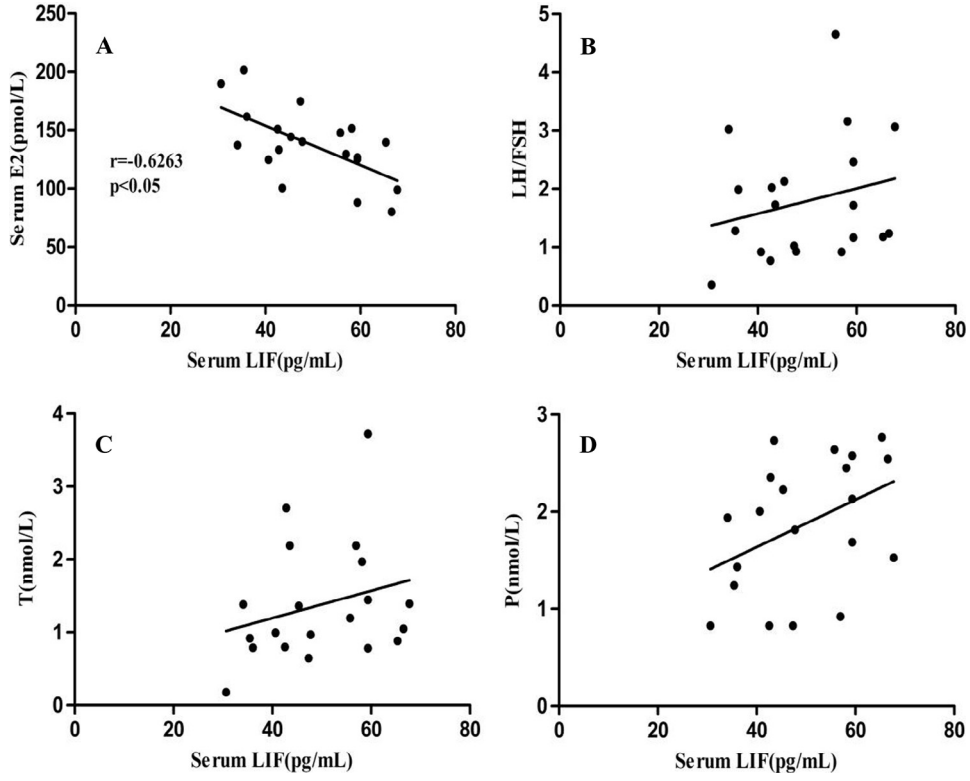

Figure 2 – Correlation between LIF expression and serum hormone concentrations in PCOS patients. (A) Inverse correlation between LIF expression and oestradiol concentrations. (B, C, D) No correlation between LIF expression and LH/FSH ratio, testosterone and progesterone concentrations.

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020

Table 3 – Sex hormone and LIF concentrations in follicular fluid between PCOS and control subjects.

	PCOS	Control
Oestradiol (×10^2 pmol/l)	23.74 ± 4.14	19.22 ± 5.17
Progesterone (×10^4 nmol/l)	11.26 ± 4.39	10.78 ± 3.4
LIF (pg/ml)	16.08 ± 4.17[a]	25.07 ± 9.2

[a] Significantly different to the control group, $P < 0.05$.
Values are expressed as mean ± SD or number (%).
LIF = leukaemia inhibitory factor; PCOS = polycystic ovary syndrome.

conceived consequent to the treatment were significantly higher than those from women who did not in the combined PCOS and control groups ($P < 0.05$; **Figure 4C**). To evaluate the potential of LIF concentrations in the embryo culture medium for predicting clinical pregnancy, receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) values were determined with the highest specificity and sensitivity set as the optimal prediction point (**Figure 4D**). Optimal prediction point, sensitivities, specificities and AUC values were 35.79 pg/ml, 82.6%, 72.4% and 0.762 (95% confidence interval [CI]: 0.632–0.891), respectively. The present results

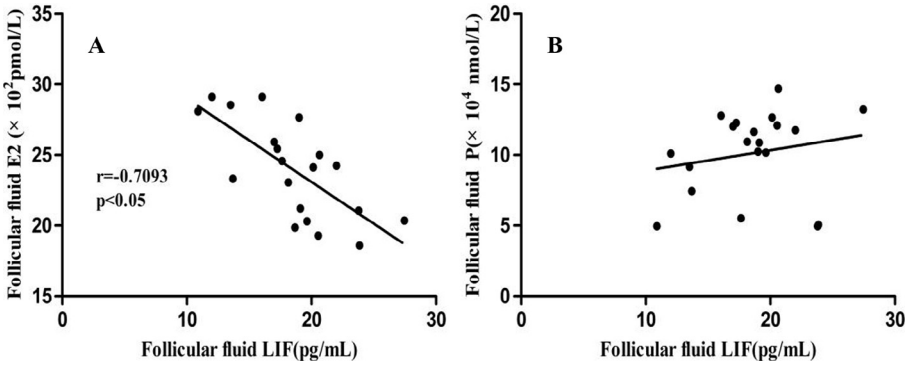

Figure 3 – Correlation between LIF and hormone concentrations in follicular fluid with PCOS patients. (A) Inverse correlation between LIF and oestradiol concentrations. (B) No correlation between LIF and progesterone concentrations.

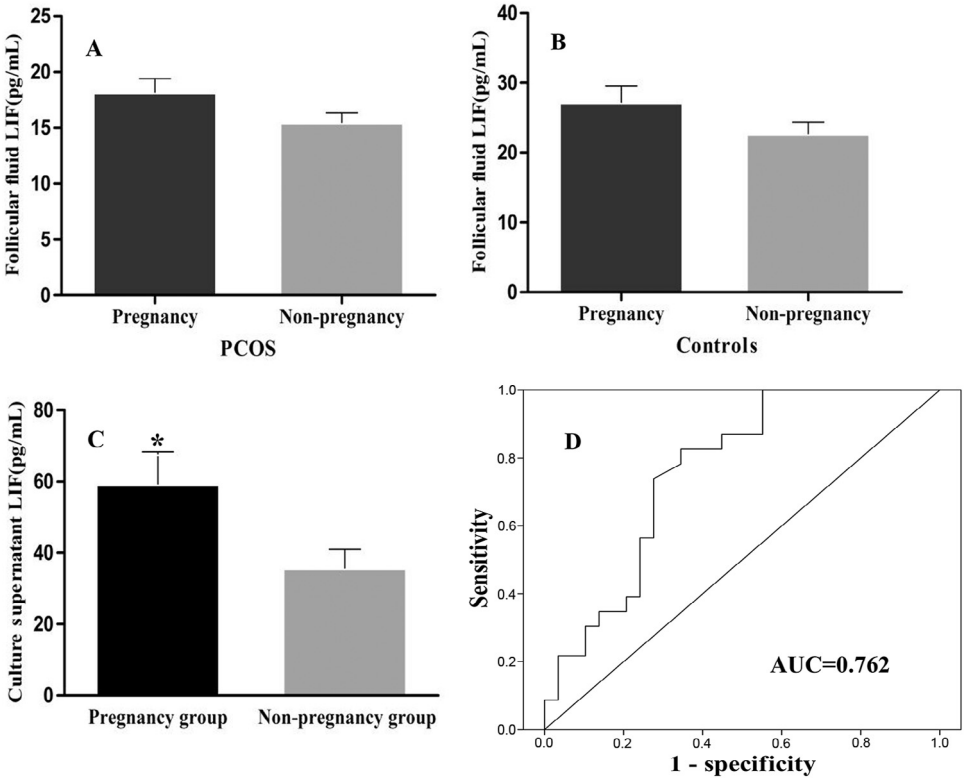

Figure 4 – LIF concentrations in women who conceived consequent to the treatment (Pregnancy) and women who did not (Non-pregnancy). (A) LIF concentrations in follicular fluid of PCOS patients in women who conceived consequent to the treatment and those who did not. (B) LIF concentrations in follicular fluid of control women who conceived consequent to the treatment and those who did not. (C) LIF concentrations in embryo culture supernatant of all women who conceived consequent to the treatment and women who did not. (*$P < 0.05$). (D) ROC curve analysis to assess the predictive powers of clinical pregnancy.

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020

indicate that the LIF concentration in embryo culture medium could be used as a predictor for IVF–ET outcomes.

Discussion

PCOS is the most common endocrine disorder in women of reproductive age and is the main cause of non-ovulatory infertility. Data clearly show that the LIF concentrations in serum and follicular fluid were decreased in PCOS patients compared with control women without PCOS, and its concentrations were negatively correlated with oestradiol concentrations. Low LIF concentrations in the serum and follicular fluid of PCOS patients may be an important factor for folliculogenesis disorder.

LIF is a secretory glycoprotein, which is a member of the IL-6 family. Since 1988, researchers have confirmed that LIF can inhibit the differentiation and maintain the proliferation of embryonic stem cells. It has been demonstrated that LIF affects all aspects of reproductive activities including follicular development, embryo implantation, growth, development and differentiation, among others. LIF has been found to be associated with infertility, recurrent abortion and other diseases (Aghajanova, 2010).

This study found that LIF concentrations were lower in the serum of PCOS patients compared with the controls and were negatively associated with oestradiol concentrations. Presumably the mechanism by which oestradiol mediates LIF expression is disrupted in PCOS patients (Laszlo and Nathanson, 2003). Sawai et al. (1997) reported that oestradiol can stimulate LIF secretion, and the increased concentrations of LIF are consistent with the increased oestradiol in a dose-dependent manner (Aloisi et al., 1994; Elias et al., 1994). Oestradiol mediates its actions via protein kinase C, which catalyses serine phosphorylation of target proteins. The secretion of LIF mediated by oestradiol is blocked by H7, a PKC inhibitor, and genistein, indicating that the oestradiol-mediated LIF transduction pathway is regulated by PKC activity. LIF is also derived from the macrophages and granulosa cells in follicular fluid. Follicular fluid provides the microenvironment for oocyte maturation and contains growth factors and cytokines that regulate the growth and development of oocytes. Follicular fluid from PCOS patients can affect the function of granulosa cells and follicular cells. Haidari et al. (2008) found that LIF alone or in combination with a co-culture system increases the growth of cultured mouse pre-antral follicles; however, LIF had no effect on the maturation rates of the mouse follicle. The abnormal effects of steroid hormones on the function of granulocytes are complex, and they may have a certain impact on LIF production. De Matos and other researchers have confirmed that the recombinant FSH and LIF can significantly improve the quality of mouse oocytes, the cleavage rate of embryos, blastocyst formation rate and delivery rate in mice (De Matos et al., 2008).

In this study, the causes of infertility in the control group were tubal obstruction and male factor, and patients had normal hormone concentrations. LIF was detected in the follicular fluid of PCOS and control patients, suggesting that LIF is produced locally in the ovary and plays a role in autocrine and/or paracrine secretion to promote the development and maturation of oocytes. LIF concentrations were lower in both serum and follicular fluid compared with the controls and in PCOS patients were negatively associated with oestradiol concentrations, indicating that abnormal LIF concentrations may be one of the reasons for ovarian dysfunction in PCOS patients.

The ability to select the most competent embryos for transfer is essential to the success of assisted reproductive technologies. Because LIF can significantly improve the quality of mouse oocytes, the cleavage rate of embryos, blastocyst formation rate and delivery rate in mice, the concentrations of LIF in the follicular fluid and embryo culture medium were tested from women who conceived consequent to the treatment and women who did not. It was found that the concentrations of follicular fluid LIF were not statistically significantly different in the women who conceived consequent to the treatment compared with women who did not in the PCOS and control groups; however, the LIF concentrations in embryo culture medium were higher in the women who conceived consequent to the treatment than in the women who did not in the combined PCOS and control groups, indicating that the concentrations of LIF in embryo culture medium may predict IVF–ET outcomes.

This study had some limitations worth noting. First, blood samples were not taken during ovarian stimulation. This is important because the use of ovulation-inducing agents may affect serum LIF concentrations. Second, LIF concentrations were analysed in the pooled follicular fluid rather than in the follicular fluid derived from the dominant follicle, and this may not have accurately reflected the dynamic changes in LIF concentrations that occur during follicle development. In future studies, it is intended to collect serum samples throughout the process of ovarian stimulation as well as to adequately sample the dominant follicle, in order to further confirm the role of LIF in the pathogenesis of PCOS.

In conclusion, the LIF concentrations in serum and follicular fluid are decreased in the PCOS patients compared with infertile controls without PCOS, and negatively correlated with oestradiol concentrations. This may be one of the reasons for ovarian dysfunction in PCOS patients. This evidence may help to clarify the aetiology of PCOS and seek new treatments for PCOS patients. Meanwhile, LIF concentrations in embryo culture medium may act as a non-invasive biomarker for predicting IVF–ET outcomes. However, the results in this study should be validated in a large sample in the future.

Acknowledgement

This work was supported in part by grants from the National Natural Science Foundation (81490743, 81370692, 81370687 and 81701526).

ARTICLE INFO

Article history:
Received 17 March 2017
Received in revised form 15 December 2017
Accepted 20 December 2017

Keywords:
Follicular fluid
Leukaemia inhibitory factor
Oestradiol
Polycystic ovary syndrome
Pregnancy outcomes

REFERENCES

Aghajanova, L., 2010. Update on the role of leukaemia inhibitory factor in assisted reproduction. Curr. Opin. Obstet. Gynecol. 22, 213–219.

Aloisi, F., Rosa, S., Testa, U., Bonsi, P., Russo, G., Peschle, C., Levi, G., 1994. Regulation of leukaemia inhibitory factor synthesis in cultured human astrocytes. J. Immunol. 152, 5022–5031.

Crosignani, P.G., Nicolosi, A.E., 2001. Polycystic ovarian disease: heritability and heterogeneity. Hum. Reprod. Update 7, 3–7.

De Matos, D.G., Miller, K., Scott, R., Tran, C.A., Kagan, D., Nataraja, S.G., Clark, A., Palmer, S., 2008. Leukaemia inhibitory factor induces cumulus expansion in immature human and mouse oocytes and improves mouse two-cell rate and delivery rates when it is present during mouse in vitro oocyte maturation. Fertil. Steril. 90, 2367–2375.

Dozio, E., Ruscica, M., Galliera, E., Corsi, M.M., Magni, P., 2009. Leptin, ciliary neurotrophic factor, leukaemia inhibitory factor and interleukin-6: class-I cytokines involved in the neuroendocrine regulation of the reproductive function. Curr. Protein Pept. Sci. 10, 577–584.

Dunaif, A., Fauser, B.C., 2013. Renaming PCOS–a two-state solution. J. Clin. Endocrinol. Metab. 98, 4325–4328.

Elias, J.A., Zheng, T., Whiting, N.L., Marcovici, A., Trow, T.K., 1994. Cytokine-cytokine synergy and protein kinase C in the regulation of lung fibroblast leukaemia inhibitory factor. Am. J. Physiol. 266, L426–L435.

Haidari, K., Salehnia, M., Rezazadeh Valojerdi, M., 2008. The effect of leukaemia inhibitory factor and coculture on the in vitro maturation and ultrastructure of vitrified and nonvitrified isolated mouse preantral follicles. Fertil. Steril. 90, 2389–2397.

Hsieh, Y.Y., Chang, C.C., Tsai, H.D., Lin, C.S., 2005. Leukaemia inhibitory factor in follicular fluid is not related to the number and quality of embryos as well as implantation and pregnancy rates. Biochem. Genet. 43, 501–506.

Laszlo, G.S., Nathanson, N.M., 2003. Src family kinase-independent signal transduction and gene induction by leukaemia inhibitory factor. J. Biol. Chem. 25, 7750–7757.

Lebkowska, A., Adamska, A., Karczewska-Kupczewska, M., Nikołajuk, A., Otziomek, E., Milewski, R., Górska, M., Wołczyński, S., Kowalska, I., 2016. Serum anti-Müllerian hormone concentration in women with polycystic ovary syndrome and type 1 diabetes mellitus. Metabolism 5, 804–811.

Lédée-Bataille, N., Laprée-Delage, G., Taupin, J.L., Dubanchet, S., Taieb, J., Moreau, J.F., Chaouat, G., 2001. Follicular fluid concentration of leukaemia inhibitory factor is decreased among women with polycystic ovarian syndrome during assisted reproduction cycles. Hum. Reprod. 16, 2073–2078.

Melo, A.S., Vieira, C.S., Barbieri, M.A., Rosa-E-Silva, A.C., Silva, A.A., Cardoso, V.C., Reis, R.M., Ferriani, R.A., Silva-de-Sá, M.F., Bettiol, H., 2010. High prevalence of polycystic ovary syndrome in women born small for gestational age. Hum. Reprod. 25, 2124–2131.

Orio, F., Palomba, S., 2014. Reproductive endocrinology: New guidelines for the diagnosis and treatment of PCOS. Nat. Rev. Endocrinol. 10, 130–132.

Ozörnek, M.H., Bielfeld, P., Krüssel, J.S., Hirchenhain, J., Jeyendran, R.S., Koldovsky, U., 1999. Epidermal growth factor and leukaemia inhibitory factor levels in follicular fluid. Association with in vitro fertilization outcome. J. Reprod. Med. 44, 367–369.

Paiva, P., Menkhorst, E., Salamonsen, L., Dimitriadis, E., 2009. Leukaemia inhibitory factor and interleukin-11: critical regulators in the establishment of pregnancy. Cytokine Growth Factor Rev. 20, 319–328.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum. Reprod. 19, 41–47.

Sahin, S.B., Ayaz, T., Cure, M.C., Sezgin, H., Ural, U.M., Balik, G., Sahin, F.K., 2014. Fibroblast growth factor 21 and its relation to metabolic parameters in women with polycystic ovary syndrome. Scand. J. Clin. Lab. Invest. 74, 465–469.

Salleh, N., Giribabu, N., 2014. Leukaemia inhibitory factor: roles in embryo implantation and in nonhormonal contraception. Sci. World J. 2014, 201514.

Sawai, K., Matsuzaki, N., Okada, T., Shimoya, K., Koyama, M., Azuma, C., Saji, F., Murata, Y., 1997. Human decidual cell biosynthesis of leukaemia inhibitory factor: regulation by decidual cytokines and steroid hormones. Biol. Reprod. 56, 1274–1280.

Yu, Q., Wang, J.B., 2016. Subclinical Hypothyroidism in PCOS: Impact on Presentation, Insulin Resistance, and Cardiovascular Risk. Biomed Res. Int. 2016, 2067087.

Please cite this article in press as: Zewu Li, et al., Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2017.12.020