行政院國家科學委員會專題研究計畫 期末報告

氧化壓力與環境荷爾蒙對多囊性卵巢婦女生殖荷爾蒙的影響

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 101-2629-B-038-001-
執 行 期 間 ：101 年 08 月 01 日至 102 年 07 月 31 日
執 行 單 位 ：臺北醫學大學婦產科

計 畫 主 持 人：徐明義
共 同 主 持 人：王靜瓊、許淳森、曾啟瑞、黃士懿、陳亦仁
計畫參與人員：此計畫無其他參與人員

報 告 附 件 ：出席國際會議研究心得報告及發表論文

公 開 資 訊 ：本計畫涉及專利或其他智慧財產權，1 年後可公開查詢

中 華 民 國 102 年 11 月 08 日

中 文 摘 要 ： 研究目的
探討血清鐵蛋白、胰島素抗性與代謝症候群在肥胖與非肥胖婦女之間之相關性。

研究方法
本研究為一回溯性研究，共納入 539 位女性受試者資料，其中 286 筆資料被診斷為多囊性卵巢症候群及 253 位非多囊性卵巢症候群婦女。

結果與討論
血清鐵蛋白與月經週期、性荷爾蒙結合球蛋白、睪固酮、雄二酮、三酸甘油脂及總膽固醇無論在肥胖及非肥胖婦女皆有關係。在肥胖的婦女(BMI>25)中，有高血清鐵蛋白(ferritin ≥45.5 ng/mL, n=270)者其胰島素抗性、葡萄糖耐受不良及肝臟功能酵素指數也會比低血清鐵蛋白(ferritin < 45.5 ng/mL, n=269)者來得高。然而，胰島素抗性及代謝分佈性並不具顯著差異在高血清鐵蛋白與低血清鐵蛋白兩組之間。若以血清鐵蛋白指數高低評估，在血清鐵蛋白指數表現較高的婦女有較高的風險會同時具有多囊性卵巢症候群及高雄性素血症。若以肥胖作為區分，高三酸甘油脂血症是婦女血清鐵蛋白異常最易被評估的代謝性疾病。

結論
我們發現在肥胖與非肥胖的育齡婦女其鐵離子增加與胰島素抗性及代謝症候群會有所不同，患有高三酸甘油脂血症的多囊性卵巢症候群婦女或許也與鐵的代謝異常有關。

中文關鍵詞： 多囊性卵巢症候群、鐵蛋白、肥胖、胰島素抗性、代謝症候群

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Results: Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride, and total cholesterol both in obese and non-obese women.

Obese women (BMI>25) with high ferritin (ferritin ≥45.5 ng/mL, n=270) levels had higher insulin resistance, impaired glucose tolerance, and liver enzymes than obese women with low ferritin levels (ferritin < 45.5 ng/mL, n=269). However, among non-obese women, insulin resistance and metabolic disturbances were not significantly different between high and low ferritin groups. Women with high ferritin levels had a greater risk of PCOS and hyperandrogenism than women with low ferritin levels. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance in women with elevated serum ferritin levels.

Conclusions: The pathogenesis of increased iron stores correlated with insulin resistance and metabolic syndrome among obese and non-obese premenopausal women was different. The hypertriglyceridemia in women with PCOS might be associated with iron metabolism.

英文關鍵詞： Polycystic ovary syndrome, ferritin, obesity, insulin resistance, metabolic syndrome.

行政院國家科學委員會補助專題研究計畫 **□期中進度報告**
■期末報告

環境荷爾蒙與氧化壓力對
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計畫參與人員：徐明義　曾啟瑞　陳亦仁　王靜瓊　黃士懿　許淳森

本計畫除繳交成果報告外，另含下列出國報告，共 1 份：
□移地研究心得報告
■出席國際學術會議心得報告
□國際合作研究計畫國外研究報告

處理方式：除列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

中　華　民　國　102　年　10　月　07　日

目錄

中文摘要

血清鐵蛋白在肥胖與非肥胖婦女的表現

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摘要

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關鍵字：多囊性卵巢症候群、鐵蛋白、肥胖、胰島素抗性、代謝症候群

英文摘要

Serum ferritin levels in obese and non-obese women

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Abstract

Object: To evaluate the association between serum ferritin levels and insulin resistance and metabolic syndrome in obese and non-obese women.

Methods: Retrospective study. Five hundred thirty-nine women, 286 of whom had PCOS and 253 of whom did not have PCOS, were included in the study.

Results: Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride, and total cholesterol both in obese and non-obese women. Obese women (BMI>25) with high ferritin (ferritin ≥ 45.5 ng/mL, n=270) levels had higher insulin resistance, impaired glucose tolerance, and liver enzymes than obese women with low ferritin levels (ferritin < 45.5 ng/mL, n=269). However, among non-obese women, insulin resistance and metabolic disturbances were not significantly different between high and low ferritin groups. Women with high ferritin levels had a greater risk of PCOS and hyperandrogenism than women with low ferritin levels. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance in women with elevated serum ferritin levels.

Conclusions: The pathogenesis of increased iron stores correlated with insulin resistance and metabolic syndrome among obese and non-obese premenopausal women was different. The hypertriglyceridemia in women with PCOS might be associated with iron metabolism.

Keywords: Polycystic ovary syndrome, ferritin, obesity, insulin resistance, metabolic syndrome.

報告內容

Introduction

Ferritin is a ubiquitous intracellular protein that is essential for the regulation of iron homeostasis. Serum ferritin level is a widely available clinical biomarker used to estimate body iron status. Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects 6-7% of premenopausal women (Azziz *et al.,* 2004). PCOS is clinically diagnosed by hyperandrogenism and chronic anovulation; however, its morbidity may include insulin resistance, type 2 diabetes mellitus, hypertension, cardiovascular disease and infertility (Lobo *et al.,* 2000). Increased serum ferritin levels have been found in women with PCOS (Escobar-Morreale *et al.,* 2005). Serum ferritin concentrations differ significantly according to sex, body status and ethnicity (Kim *et al.,* 2011; Cheng *et al.,* 2012). The correlation between serum ferritin levels and metabolic components in obese and non-obese women is not well understood. We therefore conducted this retrospective study to evaluate the relationship between ferritin levels, insulin resistance, metabolic disturbances, and PCOS-related syndrome among obese and non-obese women.

Materials and Methods

This study was approved by the Institutional Review Board of the Wan Fang Medical Center at Taipei Medical University, Taipei, Taiwan and was conducted at the Outpatient Clinic of the Wan Fang Medical Center at Taipei Medical University from 2010 Nov. 1 to 2012 Jul. 31. This study was registered at ClinicalTrail.gov (NCT01256970).

Study population

The participating women were recruited from among the patients who visited our Reproductive Endocrinology Clinics with chief complaints of infertility, menstrual disturbance, dysmenorrhea, and hirsutism. Each patient enrolled in this study signed an informed consent form The following patients were excluded when establishing the study populations: (1) women who had been diagnosed with congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome, disorders of the uterus, and chromosomal anomalies; (2) young women who had had menarche for less than 3 years, or women who were older than 45; and (3) women who received hormones or drugs for major medical diseases. The serum homocysteine level has been used for cardiac vascular risk evaluation beginning 2010 Nov.1. By 2012 Jul. 31, 400 women had been evaluated. Of these, 61 women were further excluded due to hyperprolactinemia (N=47) and ovarian failure (N=14). Finally, 339 women were included in this study.

Data collection

The subjects' medical history included a detailed menstrual and medical/surgical history, anthropometric measurements (weight, height, waist circumference, and hip circumference), and blood pressure. The number of menstrual cycles during the previous year was recorded. The waist-to-hip ratio (WHR) was defined as waist circumference/hip circumference. The dates and assays for blood sampling

have been previously described [14]. Total testosterone levels were measured by a commercial kit, TESTOSTERONE RIA DSL-4000 (Diagnostic Systems Laboratories, Inc. Webster, Texas 77598). The range of expected values is defined as the central 95% of the 168 female observations, corresponding to a range of 0.1 to 0.8 (ng/mL). Homocysteine levels were measured by a commercial kit (Abbott Laboratories, Abbott Park, IL 60064, USA). The range of expected values is defined as the central 95% of the 170 female observations, corresponding to a range of 4.6 to 12.4 μmol/L (Abbott AXSYS, Homocysteine, REF 5F51). Hyperhomocysteinemia was defined for women with serum homocysteine levels > 12.4 μmol/L.

The following components were measured and calculated: (1) total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), 17-α-OH progesterone, and the free androgen index; (2) fasting insulin, fasting glucose, 2-hour OGTT glucose level, and the homeostasis model assessment of the insulin resistance index (HOMA-IR); (3) serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin; (4) total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL); and (5) GOT (Glutamic Oxaloacetic Transaminase), GPT (Glutamic Pyruvic Transaminase), and high-sensitivity C-reactive protein (hs-CRP). The free androgen index (FAI) was calculated using the formula FAI=T (nmol/l) X100/SHBG (nmol).

PCOS was diagnosed according to the 2003 Rotterdam criteria, which required a minimum of 2 of the following 3 criteria for a diagnosis of PCOS: polycystic ovary morphology (PCOM), oligomenorrhea or amenorrhea (ANOV), and hyperandrogenism (HA). The definitions of ANOV and PCOM have previously been described in detail [15]. Hyperandrogenism (HA) was defined as hirsutism and/or biochemical hyperandrogenemia (BioHA). Hirsutism was evaluated using the modified Ferriman-Gallwey (mF-G) method, which was performed by a single technician. Hirsutism was defined as an mF-G score ≥ 6. BioHA was defined as a total serum testosterone ≥ 2.78 mmol/L.

Insulin sensitivity, impaired glucose tolerance, diabetes, and metabolic syndrome

The insulin sensitivity index was evaluated by the HOMA-IR using the following formulas:

HOMA-IR= (fasting insulin [μU/mL] × fasting glucose [mg/dL])/405.

WHO 2006 diagnostic criteria for diabetes were employed (fasting plasma glucose ≥ 7.0 mmol/L or 2–hour plasma glucose ≥ 11.1 mmol/L). Impaired glucose tolerance was defined as two-hour glucose levels of 7.8 to 11.1 mmol/L in the 75-g oral glucose tolerance test. In women with impaired glucose tolerance, the fasting plasma glucose level should be <7 mmol/L.

Metabolic syndrome (MBS) was defined (2005 National Cholesterol Education Program -Adult Treatment Panel III) as the presence of at least three of the following criteria: abdominal obesity (waist circumference > 80 cm in women), serum TG ≥ 1.7 mmol/L, serum HDL<1.3 mmol/L, systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, and fasting plasma glucose ≥7.0 mmol/L.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL). We evaluated the correlation between the serum homocysteine levels and PCOS-related parameters using Pearson's correlation coefficients with the two-tailed method. The data are presented as the mean ± standard deviation in table 2. We used the chi-squared and Fisher's exact tests to compare categorical variables and

ANOVA to compare continuous variables in table 2. Logistic regression analyses and an odds ratio with a 95% confidence interval were used to examine the relationship between hyperhomocysteinemia and the associated risk factors. Differences between groups were considered significant if the p-value was less than 0.05.

Results

The correlation analysis of homocysteine with the relative parameters are shown in Table 1. Serum homocysteine levels are correlated with the serum total testosterone level and the diastolic pressure.

There are 188 women with PCOS and 151 women without PCOS in all 339 studied cases. Serum homocysteine level are not different between women with PCOS and women without PCOS (homocysteine 11.1±3.0 vs. 10.8±2.7μmol/L, p=0.292).

Table 1: Correlation of ferritin with clinical and biochemical insulin resistance and metabolic syndrome (n=538)

	Total (n=538)		obese (n=233)		Non-obese (n=305)	
	Correlation	p-value	Correlation	p-value	Correlation	p-value
Age	-0.052	0.353	-0.076	0.251	-0.096	0.095
Body Mass Index	0.271	<0.001*	0.149	0.023*	0.044	0.442
Menstrual cycle length	0.320	<0.001*	0.378	<0.001*	0.124	0.031*
Sex Hormone-binding globulin	-0.249	<0.001*	-0.192	0.003*	-0.197	0.001*
high-sensitivity C-reactive protein	0.248	<0.001*	0.229	<0.001*	0.074	0.202
Total testosterone	0.221	<0.001*	0.151	0.021*	0.224	<0.001*
Androstenedione	0.181	<0.001*	0.164	0.012*	0.257	<0.001*
Dehydroepiandrosterone sulfate	0.065	0.132	0.059	0.373	0.056	0.333
17-α-OH progesterone	0.038	0.375	0.060	0.361	0.104	0.068
Fasting insulin	0.257	<0.001*	0.233	0.002*	0.009	0.872
Fasting glucose	0.270	<0.001*	0.258	<0.001*	0.092	0.115
HOMA-IR[a]	0.329	<0.001*	0.306	<0.001*	0.043	0.455
Haemoglobin A1c	0.284	<0.001*	0.258	0.001*	0.068	0.289
GOT[a]	0.561	<0.001*	0.621	<0.001*	0.048	0.411
Cholesterol	0.165	<0.001*	0.158	0.016*	0.129	0.026*
High-density lipoprotein	-0.196	<0.001*	-0.137	0.037*	-0.045	0.437
Low-density lipoprotein	0.158	<0.001*	0.091	0.168	0.094	0.107
Triglyceride	0.334	<0.001*	0.264	<0.001*	0.324	<0.001*
Systolic pressure	0.210	<0.001*	0.167	0.013*	-0.049	0.397
Diastolic pressure	0.220	<0.001*	0.175	0.009*	-0.040	0.497

According to the three diagnostic components of polycystic ovary syndrome, all 339 studied cases could be classified into eight subgroups: normal control (N=44; 10.7±2.9), polycystic ovary morphology (PCOM) only (N=33; 11.5±3.0), oligo/amenorrhea (Oligo/AN) only (N=49; 10.2±2.4), hyperandrogenism (HA) only (N=25; 11.0±2.4), PCOM and Oligo/AN (N=58; 10.4±2.2), PCOM and HA (N=22; 11.4±2.8), Oligo/AN and HA (N=28; 11.3±3.0), and PCOM+Oligo/AN+HA (N=80; 11.4±3.4). We found that the serum homocysteine levels were not different among women with these eight PCOS-related phenotypes (p=0.166).

However, the significantly elevated homocysteine could be found for women with biochemical

hyperandrogenemia (serum total testosterone ≥ 2.78 mmol/L). Women with hyperandrogenemia has significant higher serum homocysteine levels than women with normal serum total serum levels (11.9±3.4 vs. 10.7±2.6, p=0.001).

Table 2 presents the clinical and biochemical characteristics of women with hyperhomocysteinemia and euhomocysteinemia. Women with hyperhomocysteinemia had a significantly higher risk for biochemical hyperandrogenemia and higher serum levels of total testosterone than women with euhomocysteinemia. The prevalence of PCOS, PCOM, Oligo/AN, and metabolic disturbance were not different between the two groups. Furthermore, the parameters of insulin resistance and the lipid profiles were also similar between the two groups. The sign of clinical hyperandrogenism (hirsutism and the FG Score) were not different between women with and without hyperhomocysteinemia.

Table-2: A comparison of biochemical characteristics of obese and non-obese women with high and low ferritin

	Obese			Non-obese		
	Low	High		Low	High	
	Ferritin<45	Ferritin≧45	p-value	Ferritin<45	Ferritin≧45	p-value
Case number	88	145		178	127	
Ferritin (pmol/L)	24.9±12.4	116.9±99.1	<0.001*	25.4±12.0	81.4±38.8	<0.001*
Menstrual cycle length (days)	64.5±64.3	112.8±115.8	<0.001*	61.1±66.7	83.6±80.9	0.009*
PCOS	47%	63%	0.012*	38%	54%	0.006*
SHBG (nmol/L)*	32.0±17.2	23.1±12.9	<0.001*	58.7±28.4	47.8±27.6	0.001*
Total testosterone (nmol/L)	2.2±0.9	2.6±1.1	0.003*	1.8±0.8	2.1±1.0	<0.001*
Androstenedione (ng/dL)	2.5±1.3	2.9±1.3	0.022*	2.4±1.1	3.0±1.4	<0.001*
Insulin sensitivity and glucose tolerance						
Fasting Insulin (uIU/mL)	16.2±11.8	21.8±18.7	0.013*	8.9±10.9	8.4±4.6	0.689
Fasting glucose (mg/dL)	94.0±10.0	101.1±27.4	0.022*	87.7±7.3	89.4±16.2	0.243
2-hour glucose (mg/dL)	115.8±34.0	148.7±63.8	<0.001*	98.2±24.0	100.6±33.5	0.480
HOMA-IR*	3.9±3.0	5.7±5.5	0.005*	1.9±2.1	1.9±1.1	0.840
Diabetes mellitus %	3%	16%	0.003*	1%	2%	0.392
Liver function						
GOT* (IU/l)	24.1±10.1	32.0±20.9	0.001*	20.5±7.0	20.5±5.5	0.986
GPT* (IU/l)	24.1±13.9	41.3±34.4	<0.001*	16.7±9.7	17.8±9.2	0.300
Lipid profiles and blood pressure						
Cholesterol (mg/dL)	185.1±31.9	194.2±39.6	0.068	179.3±33.1	185.5±32.4	0.106
Triglycerides (mg/dL)	103.9±60.8	142.2±125.0	0.008*	60.8±28.0	78.0±70.6	0.004*
HDL* (mg/dL)	45.0±12.6	42.5±11.2	0.128	60.0±14.9	59.8±15.0	0.906
LDL* (mg/dL)	119.2±26.2	125.3±32.2	0.136	100.1±28.5	104.8±28.6	0.167

Logistic regression analyses were used to examine the relationship between hyperhomocysteinemia and the associated risk factors for all 339 subjects. The variables entered in this model included PCOM, Oligo/AN, biochemical hyperandrogenemia, and hirsutism. The results demonstrate that hyperandrogenemia is the only parameter that is significantly associated with hyperhomocysteinemia (Odds Ratio (OR) =2.24; 95% confidence interval (CI): 1.26-4.01). PCOM (1.21; 0.71-2.06), Oligo/AN (0.58, 0.34-1.01) and

hirsutism (0.95, 0.56-1.62) were not associated with the risk of hyperhomocysteinemia.

Comments

Women with polycystic ovary syndrome (PCOS) are often assumed, a priori, to be at an increased risk for cardiovascular disease (CVD). The underlying physiological mechanism of this increased vascular risk remains unexplained, but it may be related to worsening of endothelial dysfunction and/or structural vessel properties induced by oxidative stress [16]. An association between PCOS and CVD has not been established [4]. There is a possible association between PCOS and diabetes, lipid abnormalities, and other cardiovascular risk factors [17,18]. However, at long-term follow-up, the morbidity and mortality from of coronary heart disease among women with PCOS is not as high as previously predicted [19]. Menstrual cycle irregularity may be a marker of metabolic abnormalities predisposing women to increased risk for CVD [20]. However, there is little evidence for an association between hyperandrogenism per se and cardiovascular events [4].

Hyperhomocysteinemia is thought to be well-established risk factor for cardiovascular disease. Homocysteine, a sulfur-containing amino acid formed during the metabolism of methionine, exerts cytotoxic effects on the vascular endothelium [8]. Elevated total plasma homocysteine levels have been established as an independent risk factor for thrombosis and cardiovascular disease. A strong relationship between plasma homocysteine levels and mortality has been reported in patients with angiographically confirmed coronary artery disease [21]. The homocysteine level is correlated with the total testosterone level in this study. An association between homocysteine and insulin resistance has not been found in our study, and a previous report suggested that there is no correlation between the serum homocysteine concentration and insulin concentration, body mass, type of obesity, and diabetes status [16,22, 23].

Hyperandrogenism is usually defined as clinical and/or biochemical. However, hyperhomocysteinemia was associated with biochemical hyperandrogenemia, but not with hirsutism, in this study. The phenotypic variation in hyperandrogenic women might influence the findings of abnormal metabolic and cardiovascular risk parameters. Carmina found that homocysteine was elevated only in cases of classic hyperandrogenism with chronic anovulation PCOS, but not in cases of hyperandrogenism and polycystic ovaries in women with normal ovulatory cycles [13]. Our study demonstrated that hyperhomocysteinemia was associated with biochemical hyperandrogenism but not with clinical hyperandrogenism (Hirsutism). Although hirsutism was found more commonly in women with confirmed coronary artery disease [24], our results did not demonstrate abnormal serum homocysteine levels in women with hirsutism. This might imply the different pathways of metabolic disturbance between clinical and biochemical hyperandrogenism.

Several studies, including some population-based studies, have linked plasma homocysteine levels to blood pressure [25]. The association between homocysteine levels and diastolic pressure is also reported in this study. Mechanisms that could explain the relationship between homocysteine and blood pressure include increased arterial stiffness, endothelial dysfunction with decreased availability of nitric oxide, low folate status, and insulin resistance [25]. The correlation between homocysteine, total testosterone, and blood pressure might explain why hyperandrogenemic women with PCOS exhibited an elevated blood pressure independent of age, insulin resistance, obesity, or dyslipidemia [26]. The studied women evaluated

in the present study were recruited from the outpatient clinic of a tertiary care center and do not reflect the true distribution of the general population. Therefore, the results should be applied to the general population with caution. The study populations consisted entirely of Chinese Taiwanese. We previously published findings indicating that the prevalence of hirsutism was less common in our population [27]. The study should be verified in different ethnic populations.

We concluded: For women with PCOS, elevated serum total testosterone level should be the major factor that associated with increased serum homocysteine levels. The association between biochemical hyperandrogenism and hyperhomocysteinemia might contribute to the cardiovascular risk for women with PCOS.

Acknowledge

This work was supported by the National Science Council Grant NSC 101-2629-B-038-001 and Taipei Medical University – Wan Fang Hospital Grant 99TMU-WFH-03-2

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國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   - ■ 達成目標
   - □ 未達成目標（請說明，以 100 字為限）
     - □ 實驗失敗
     - □ 因故實驗中斷
     - □ 其他原因

   說明：

2. 研究成果在學術期刊發表或申請專利等情形：

   論文：□已發表 ■未發表之文稿 □撰寫中 □無

   專利：□已獲得 □申請中 ■無

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3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

   本研究為探討肥胖與非肥胖婦女血清中鐵蛋白的表現，我們發現在肥胖與非肥胖的育齡婦女其鐵離子增加與胰島素抗性及代謝症候群會有所不同，患有高三酸甘油脂血症的多囊性卵巢症候群婦女或許也與鐵的代謝異常有關。相關疾病對國人的健康影響大而深遠，國內應該可以結合不同領域學者探討相關問題。

國科會補助專題研究計畫出席國際學術會議心得報告

日期：102 年 10 月 07 日

計畫編號	NSC－101－2629－B－038－001		
計畫名稱	環境荷爾蒙與氧化壓力對多囊性卵巢婦女生殖荷爾蒙的影響		
出國人員 姓名	徐明義	服務機構 及職稱	臺北醫學大學醫學系
會議時間	102 年 04 月 17 日至 102 年 04 月 23 日	會議地點	Vienna, Austria.
會議名稱	（中文）第五屆國際糖尿病前期及代謝症候群大會 （英文）5th International Congress on PREDIABETES and the METABOLIC SYNDROME.		
發表題目	（中文）肥胖與非肥胖婦女血清中鐵蛋白指標 （英文）Serum ferritin levels in obese and non-obese women.		

一、參加會議經過

前往奧地利首都維也納參加第五屆 International Congress on PREDIABETES and the METABOLIC SYNDROME 並發表研究成果報告。

二、與會心得

除了參與大會學術研討外，並於 4 月 20 日以北醫名義發表 Serum ferritin levels in obese and non-obese women 壁報論文。本次大會的研討主軸在於糖尿病前趨症狀與代謝症候群的相關研究，肥胖問題也是大會研討的主要問題之一，這是跨領域的研究，相關疾病對國人的健康影響大而深遠，國內應該可以結合不同領域學者探討相關問題。

三、發表論文全文或摘要

Serum ferritin levels in obese and non-obese women.

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Abstract

Object: To evaluate the association between serum ferritin levels and insulin resistance and metabolic syndrome in obese and non-obese women.
Methods: Retrospective study. Five hundred thirty-nine women, 286 of whom had PCOS and 253 of whom did not have PCOS, were included in the study.
Results: Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride, and total cholesterol both in obese and non-obese women. Obese women (BMI>25) with high ferritin (ferritin ≥ 45.5 ng/mL, n=270) levels had higher insulin resistance, impaired glucose tolerance, and liver enzymes than obese women with low ferritin levels (ferritin < 45.5 ng/mL, n=269). However, among non-obese women, insulin resistance and metabolic disturbances were not significantly different between high and low ferritin groups. Women with high ferritin levels had a greater risk of PCOS and hyperandrogenism than women with low ferritin levels. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance in women with elevated serum ferritin levels.
Conclusions: The pathogenesis of increased iron stores correlated with insulin resistance and metabolic syndrome among obese and non-obese premenopausal women was different. The hypertriglyceridemia in women with PCOS might be associated with iron metabolism.
Funding : This work was supported by the National Science Council Grant NSC 101-2629-B-038-001

Keywords: Polycystic ovary syndrome, ferritin, obesity, insulin resistance, metabolic syndrome.

四、建議

無特別

五、攜回資料名稱及內容

會議手冊封面及主持人報告論文目錄頁。

Poster Session 2: Metabolic Syndrome: Various aspects

Poster No

97 THE LINK BETWEEN INTESTINAL DYSBIOSIS AND METABOLIC SYNDROME IN OVERWEIGHT/OBESITY: ROLE OF HYDROGEN BREATH TEST
L. Vigna, P. Marraccini, A.S. Tirelli, R. De Giuseppe, E. Grossi, F. Bamonti, *Milano, Italy*

98 THYROID DYSFUNCTIONS INFLUENCE PATIENTS' ANTHROPOMETRIC PARAMETERS, LIPID METABOLISM AND OXIDATIVE STRESS - A CLINICAL TRIAL PILOT FOLLOW-UP STUDY
C. Ragginer, C. Bernecker, P. Kieslinger, S. Pailer, B. Rehberger, M. Labacher, M. Truschnig-Wilders, H.-J. Gruber, *Graz, Austria*

99 LIPIDS PROFILE IN METABOLIC SYNDROME PATIENTS SUFFERING SLEEP DISORDERS
M.A. Sierra-Beltrán, J.L. Romero-Flores, R. Rodriguez, M.H. Ramos-Ostos, *Mexico City, Mexico*

100 HYPERSENSITIVE C REACTIVE PROTEIN LEVELS AMONG METABOLIC SYNDROME PATIENTS WHO HAVE MEMORY RECALL DEFICITS
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101 METABOLIC IMPACT ON CENTRAL OR ABDOMINAL ADIPOSITY IN PATIENTS WITH A NORMAL BODY MASS INDEX
R. Vega-Zapata, M.A. Sierra-Beltrán, M.H. Ramos-Ostos, *Mexico City, Mexico*

102 SERUM FERRITIN LEVELS IN OBESE AND NON-OBESE WOMEN
M.-I. Hsu, P.-C. Ko, S.-Y. Huang, C.-S. Hsu, *Taipei, Taiwan R.O.C.*

103 IMPACT OF ORAL 1&25DIHYDROXY VITAMIN D3 REPLACEMENT THERAPY ON COMPONENTS OF METABOLIC SYNDROME IN TYPE 2 DIABETIC

六、其他

無

其它資料

檢附相關論文：

1. 「Endometrial thickness in women with ovulatory dysfunction」，於 2013 年 04 月發表於 Gynecological Endocrinology 期刊。
2. 「Changes in the PCOS phenotype with age」，於 2013 年 08 月發表於 Steroids 期刊。

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ORIGINAL ARTICLE

Endometrial thickness in women with ovulatory dysfunction†‡

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Abstract

This study is designed to evaluate the relationship between endometrial thickness and clinical/biochemical parameters in women with chronic anovulation. One hundred and twenty women with ovulatory dysfunction were prospective included, endometrial thickness and endocrine and metabolic parameters were measured. The interval between the examination day and the day of the most recent menstrual bleeding (the anovulatory interval) for the studied subject was an average of 145 ± 186 days. The endometrial thickness averaged 7.1 ± 3.2 mm. Correlation analyses revealed that the endometrial thickness was positively correlated with body mass index but was not correlated with age, serum androgens, or estradiol (E_2) levels. We further classified the subjects into two groups based on endometrial thickness: Group A, endometrial thickness <7 mm and Group B, endometrial thickness $\geq$7 mm. The anovulatory interval, follicle-stimulating hormone, luteinizing hormone, E_2 and androgen levels were not significantly different between Groups A and B. Group B had higher body weight and more risk for metabolic syndrome. We concluded that endometrial thickness in women with ovulatory dysfunction is positively correlated with body weight status but is not correlated with serum androgens or E_2 levels.

Keywords

Amenorrhea, body mass index, endometrium, polycystic ovary syndrome

History

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Introduction

Endometrial thickness is the primary parameter used to screen for endometrial hyperplasia and/or endometrial cancer [1]. Endometrial thickness is positively correlated with endometrial hyperplasia [1]. The long-term risk of endometrial hyperplasia and endometrial carcinoma is thought to be due to chronic anovulation and unopposed estrogen [2]. Women with chronic anovulation have an increased risk for developing endometrial cancer, and endometrial hyperplasia may be a precursor to adenocarcinoma [2]. The relative risk of developing endometrial carcinoma increases by more than three-fold following a diagnosis of chronic anovulation [3]. The correlation between chronic anovulation and endometrial cancer is thought to be related to prolonged estrogen stimulation that results in endometrial hyperplasia, which is the major cause of endometrial cancer. In the presence of documented anovulation, an endometrial thickness of more than 7 mm can be associated with endometrial hyperplasia, and in this case, an endometrial biopsy is recommended [1]. Transvaginal ultrasound measurement of endometrial thickness was thought to be a biomarker of estrogen exposure in a study of postmenopausal women [4]. However, the risk of increased endometrial thickness in women of reproductive age with ovulatory dysfunction has not been studied. Because endometrial thickness is the key parameter for evaluating endometrial hyperplasia in women with chronic anovulation, we conducted this prospective study to evaluate the relationship of endocrine and metabolic parameters with endometrial thickness in women with ovulatory dysfunction.

Materials and methods

This study was approved by the Institutional Review Board of Wan Fang Medical Center at Taipei Medical University in Taipei, Taiwan, and was conducted at the Reproductive Endocrinology Clinic of Wan Fang Medical Center at Taipei Medical University between 1 June 2009 and 31 July 2012.

The number of menstrual cycles during the previous year was recorded. Ovulatory dysfunction was defined as oligomenorrhea/amenorrhea in this study. Average menstrual interval was defined as 365 divided the number of menstrual cycles in the previous year. Oligomenorrhea was defined as an average menstrual interval >35 days per year. [5]. The subjects included oligomenorrheic women of reproductive age who presented to our outpatient clinic with more than 45 days after their most recent menstrual bleeding. All of the subjects provided informed consent. The following subjects were excluded from the study populations: (1) women who had been diagnosed with hyperprolactinemia, hypogonadotropic hypogonadism, ovarian failure, uterine disorders (e.g. Asherman's syndrome, Müllerian agenesis, myoma, adenomyosis, endometrial polyps or a congenital uterine abnormality) or chromosomal anomalies; (2) women with a serum progesterone level of $\geq$1.4 ng/mL; (3) women who had experienced menarche less than three years prior to the start of the study; (4) women who underwent abdominal but not vaginal

†The abstract of this work was submitted to the American Society for Reproductive Medicine 67th Annual Meeting 15–19 October 2011.
‡Capsule: Endometrial thickness in women with ovulatory dysfunction is correlated with BMI but not with serum hormone levels.
*These authors contributed equally to this work.

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Table 1. Clinical and biochemical presentations of anovulatory women classified as having an endometrial thickness of <7 mm (Group A) or an endometrial thickness of ≥7 mm (Group B).

	Total	Range	Group A Endometrial thickness <7 mm	Group B Endometrial thickness ≥7 mm	A versus B *p* Value
Case number	120		64	56	
Endometrial thickness (mm)	7.1 ± 3.2	1.0–23.6	5.0 ± 1.4	9.5 ± 2.9	
Age (y/o)	29.9 ± 4.8	20–41	29.5 ± 5.0	30.4 ± 4.7	0.288
Number of cycle per year	5.2 ± 3.3	1–18	4.6 ± 3.2	5.8 ± 3.3	0.062
Anovulatory interval (days)†	144.8 ± 186.3	45–1556	170.3 ± 241.4	115.7 ± 82.1	0.110
PCOS	77%(85/120)		74% (43/64)	79% (42/56)	0.530
Hyperandrogenemia	47% (56/120)		39% (25/64)	55% (31/56)	0.075
metabolic syndrome	37%(85/120)		25% (16/64)*	50% (28/56)*	0.004*
Hypertension	30%(36/120)		22% (14/64)*	39% (22/56)*	0.038*
HDL<1.3 mmol/L	56%(67/120)		48% (31/64)	64% (36/56)	0.082
Triglycerides >1.7 mmol/L	19%(23/120)		16% (10/64)	23% (13/56)	0.296
Waist >80 cm	59%(71/120)		50% (32/64)*	70% (39/56)*	0.029*
FPG ≥7.0 mmol/L	25%(30/120)		16% (10/64)*	36% (20/56)*	0.013*
Height (cm)	159.3 ± 4.5	148–170	159.0 ± 4.4	159.8 ± 4.6	0.341
Weight (kg)	65.5 ± 18.1	42–128	61.3 ± 15.8*	70.3 ± 19.4*	0.006*
BMI (kg/m^2)	25.8 ± 7.0	16.0–47.6	24.3 ± 6.2*	27.5 ± 7.5*	0.011*
Waist (cm)	86.0 ± 15.9	57–134	82.5 ± 17.4*	90.0 ± 16.4*	0.009*
Hip (cm)	99.9 ± 12.0	81–128	97.4 ± 11.2*	102.7 ± 12.2*	0.014*
Waist to hip ratio	0.86 ± 0.08	0.7–1.1	0.84 ± 0.09	0.87 ± 0.08	0.065
Total testosterone (nmol/L)	2.4 ± 1.0	0.5–5.2	2.3 ± 0.9	2.6 ± 1.1	0.123
Androstenedione (ng/dL)	10.7 ± 5.0	0.4–35.3	10.9 ± 5.4	10.6 ± 4.7	0.739
DHEAS (ng/dL)‡	5024 ± 2838	244–12423	4657 ± 2494	5443 ± 3157	0.131
SHBG (nmol/L)‡	36.7 ± 22.9	5.0–135.2	42.0 ± 25.8	30.6 ± 17.2*	0.006*
17-OH PRG (ng/dL)	3.0 ± 1.8	0.2–13.3	2.9 ± 1.6	3.0 ± 2.0	0.820
LH (mIU/mL)	11.2 ± 7.5	0.2–34.0	12.2 ± 8.2	10.1 ± 6.4	0.118
FSH (mIU/mL)	6.6 ± 1.7	2.8–11.2	6.8 ± 1.7	6.5 ± 1.6	0.347
E_2 (ng/mL)	58.9 ± 93.4	10.0–876.0	56.2 ± 72.9	62.1 ± 113.0	0.729
TSH (mIU/mL)	2.0 ± 1.2	0.3–5.8	2.0 ± 1.1	2.1 ± 1.2	0.870
Prolactin (ng/mL)	14.0 ± 7.6	2.8–40.5	13.6 ± 7.5	14.5 ± 7.7	0.497
Progesterone (ng/mL)	0.7 ± 0.3	0.2–1.5	0.7 ± 0.3	0.7 ± 0.3	0.957
Fasting insulin (uIU/mL)	107.9 ± 104.1	3.6–582.6	96.8 ± 85.4	120.6 ± 121.6	0.214
Fasting glucose (mg/dL)	5.3 ± 1.2	4.1–12.4	5.1 ± 0.9*	5.5 ± 1.4*	0.040*
HOMA-IR‡	3.8 ± 3.7	0.1–35.4	3.2 ± 3.4	4.5 ± 5.8	0.128
Cholesterol(mg/dL)	5.2 ± 1.0	3.4–8.2	5.2 ± 0.9	5.2 ± 1.0	0.732
Triglyceride (mg/dL)	1.2 ± 1.1	0.3–6.4	1.1 ± 0.8	1.4 ± 1.3	0.138
HDL(mg/dL)‡	1.4 ± 0.5	0.7–3.2	1.5 ± 0.6	1.3 ± 0.5	0.064
LDL(mg/dL)‡	3.2 ± 0.9	1.5–6.1	3.2 ± 0.8	3.2 ± 0.9	0.732
hsCRP (mg/dL)‡	2.7 ± 4.0	0.2–21.1	2.6 ± 4.5	2.9 ± 3.4	0.708
GOT(IU/L)‡	26.3 ± 16.2	9.0–157.9	27.2 ± 18.9	25.3 ± 12.6	0.531
GPT(IU/L)‡	27.4 ± 23.6	9.4–161.8	27.6 ± 22.9	27.2 ± 24.6	0.930

Data are either mean ± SD or are percentage; *$p < 0.05$.

†Anovulatory interval is the days between examination and the first day of last menstrual bleeding in studied subject.

‡DHEAS: dehydroepiandrosterone sulfate, GOT: Glutamic Oxaloacetic Transaminase, GPT: Glutamic Pyruvic Transaminase, and FPG: fasting plasma glucose

ultrasonography and (5) women who had received hormones or drugs for major medical diseases, such as diabetes or cardiovascular disease. A total of 120 women were prospectively recruited for the study (Figure 1). The subjects' medical histories, including their menstrual, medical, and surgical histories, were recorded. Anthropometric parameters were measured in all of the subjects when informed consent was provided.

This study was designed to evaluate endometrial thickness during prolonged anovulation. Blood samples were collected from the subjects more than 45 days after their most recent menstrual bleeding. Progesterone levels were measured in every subject using a commercial kit (DPC Coat-A-Count Progesterone, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Anovulation was confirmed by determining that the progesterone level was ≤1.4 ng/mL. The following parameters were measured or calculated: (1) serum androgens, including total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), sex hormone-binding globulin (SHBG), and 17-α-OH progesterone; (2) insulin sensitivity and glucose tolerance, including fasting insulin and glucose levels and the homeostasis model assessment of the insulin resistance index (HOMA-IR); (3) hormonal parameters, including serum thyroid-stimulation hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), serum estradiol (E_2) and prolactin levels; (4) lipid profiles, including total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) and (5) liver function and inflammatory markers, including GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transaminase) and high-sensitivity C-reactive protein (hsCRP). The measurement of the aforementioned biomarkers has been previously described [6]. Hyperandrogenemia was defined as total serum testosterone of ≥2.98 mmol/L (0.86 ng/mL, where 1 ng/mL = 3.47 mmol/L).

Polycystic ovary syndrome (PCOS) was diagnosed using the 2003 Rotterdam criteria, which require a minimum of two of the following three criteria for a diagnosis of PCOS: polycystic

Table 2. Correlation analysis between the endometrial thickness and related parameters.

	Pearson's correlation	*p* Value
Age (y/o)	0.115	0.212
Menarche (y/o)	−0.112	0.223
Number of cycle per year	0.262	0.004*
Anovulatory interval†	−0.224	0.014*
Height (cm)	0.065	0.483
Weight (kg)	0.240*	0.009*
BMI (Kg/m^2)	0.229*	0.012*
Waist (cm)	0.195*	0.033*
Hip (cm)	0.242*	0.008*
Waist to hip ratio	0.086	0.348
Total testosterone (nmol/L)	0.080	0.386
Androstenedione (ng/dL)	−0.074	0.423
DHEAS (ng/dL)‡	0.134	0.145
17-OH PRG (ng/dL)	0.031	0.737
LH (mIU/mL)	−0.128	0.163
FSH (mIU/mL)	−0.154	0.092
E_2 (ng/mL)	0.009	0.923
TSH (mIU/mL)	−0.041	0.655
Prolactin (ng/mL)	0.044	0.634
SHBG (nmol/L)‡	−0.182*	0.047*
Fasting Insulin (uIU/mL)	0.050	0.590
Fasting Glucose (mg/dL)	0.158	0.086
HOMA-IR‡	0.086	0.350
Cholesterol (mg/dL)	−0.199	0.030*
Triglyceride (mg/dL)	0.096	0.295
HDL(mg/dL)	−0.213*	0.020*
LDL(mg/dL)	−0.088	0.340
hsCRP (mg/dL)‡	0.142	0.121
systolic pressure	0.235*	0.011*
Diastolic pressure	0.320*	<0.001*

*$p < 0.05$

†Anovulatory interval is the days between examination and the first day of last menstrual bleeding in studied subject.

‡DHEAS: dehydroepiandrosterone sulfate

ovarian morphology, oligomenorrhea or amenorrhea, and biochemical hyperandrogenism. The insulin sensitivity index was evaluated using the HOMA-IR and the following formula:

$$\text{HOMA} - \text{IR} = (\text{fasting insulin}[\mu\text{U/mL}] \times \text{fasting glucose}[\text{mg/dL}])/405.$$

Ultrasonography

Real-time ultrasonography was performed with a 5-MHz vaginal transducer. A single ultrasound machine was used to evaluate endometrial thickness in all patients (Medison SA-8000 Live, Seoul, Korea). The vaginal probe was covered with a coupling gel and inserted into a condom, which was then inserted into the vaginal fornix, with the subject in the lithotomy position. With the uterus imaged in the longitudinal plane, the endometrial thickness was measured at the thickest point between the two basal layers of the anterior and posterior uterine walls. Two ultrasound technicians performed all of the examinations. One board-certified obstetrics-gynecology physician reviewed all of the printed images from each transvaginal ultrasound examination.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). The data are presented as the mean ± standard deviation. We used χ^2 and Fisher's exact tests to compare the categorical variables and ANOVA to compare the continuous variables (Table 1). The means of more than two groups were compared using one-way ANOVA with *post hoc* Dunnett's tests. Equal variances were not assumed. Differences between groups were considered to be significant when $p < 0.05$. We evaluated the correlations between the endometrial thickness and the examined parameters using two-tailed Pearson's correlation coefficients (Table 2).

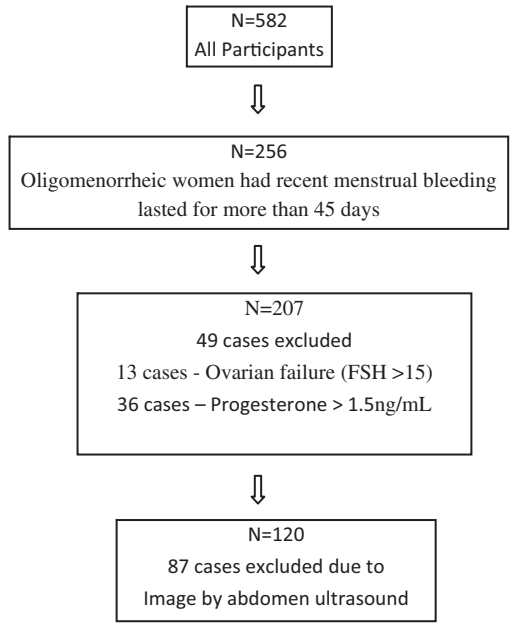

Figure 1. Flow chart of samples used in analyses.

Results

One hundred and twenty anovulatory women aged 20–41 years old (mean ± SD, 29.9 ± 4.8 years) were enrolled in this study. Of these, 85 (77%) were diagnosed with PCOS, and 35 (23%) were diagnosed with idiopathic ovulatory dysfunction. The clinical and biochemical characteristics of the subjects are presented in Table 1. Transvaginal sonography and a laboratory examination were performed during prolonged anovulation. The average interval between the examination day and the day of the most recent menstrual bleeding for the subjects (the anovulatory interval) was 144.8 ± 186.3 days (range, 45–1556 days). The endometrial thickness in the subjects ranged from 1.0 to 23.6 mm with an average of 7.1 ± 3.2 mm.

Table 2 shows a positive correlation of endometrial thickness with body weight, body mass index (BMI), blood pressure and anovulatory interval. In contrast, endometrial thickness was negatively correlated with HDL and SHBG levels. However, endometrial thickness was not correlated with age, serum total testosterone, androstenedione, DHEAS, FSH, LH or E_2 levels. Specifically, the average endometrial thickness was greater in the overweight/obese (BMI ≥ 25) women than in the lean (BMI < 25) women (7.7 ± 3.8 versus. 6.6 ± 2.3 mm, $p = 0.046$). We further classified all of the subjects into two groups based on endometrial thickness (Table 1): Group A, endometrial thickness <7 mm ($n = 64$); Group B; endometrial thickness ≥7 mm ($n = 56$). Group B showed a significantly greater body weight and BMI compared to Group A. The number of cycles per year, anovulatory interval, serum total testosterone, androstenedione, DHEAS, TSH, E_2, LH, FSH and prolactin levels were not significantly different between Group A and Group B. Group B had significantly higher BMI and more prevalence of hypertension, glucose intolerance and metabolic syndrome than Group A.

Stepwise linear regression analysis was applied to the aforementioned parameters (age, the number of cycles per year,

the anovulatory interval, BMI, fasting insulin and glucose levels, the HOMA-IR, cholesterol, triglycerides, HDL, LDL, GPT, LH, FSH, E_2, PRL, total testosterone, SHBG and DHEAS). The number of cycles per year and BMI were significant predictors of endometrial thickness.

Discussion

Endometrial thickness is an important predictor of endometrial hyperplasia [1]. In women with chronic anovulation, the endometrium is exposed to the prolonged stimulatory effects of estrogens, which are unopposed by the inhibitory effects of progesterone that is produced during an ovulatory menstrual cycle. The prevalence of endometrial hyperplasia is similarly high in women with PCOS and in women with chronic anovulation [7]. However, in our study, endometrial thickness in women with prolonged anovulation was variable (1.0–23.6 mm).

Both the endometrial volume and thickness significantly increase in the follicular phase of the menstrual cycle, reaching a plateau around the time of ovulation and remaining relatively stable throughout the luteal phase [8]. Endometrial thickness during a prolonged follicular phase has not been well studied. A state of relative hypoestrogenemia after GnRH-analogue administration can be predicted with a high degree of accuracy via ultrasonographic measurement of endometrial thickness [9]. Endometrial thickness and hormonal status are thought to be highly correlated, an assumption that is not supported by our results. The intermenstrual interval and the duration of anovulation are also independent of endometrial thickness. In contrast, body weight and the BMI have a strong positive correlation with endometrial thickness.

In our study, overweight/obesity was a major risk factor for increased endometrial thickness in women with ovulatory dysfunction. Overweight/obese women with prolonged anovulation had a significantly increased endometrial thickness compared to lean women. Furthermore, women with thicker endometrium had higher risk of hypertension and metabolic syndrome than women with thinner endometrium. Iatrakis et al. [10] reported that women with PCOS and insulin resistance had a thicker endometrium compared to normal control women. Andolf et al.'s [11] study of postmenopausal women revealed a high prevalence of thick endometrium in asymptomatic women, while endometrial thickness was correlated with BMI. It is possible that obesity and insulin resistance expose the endometrium to the trophic effects of hyperinsulinemia, combined with the increased peripheral conversion of circulating estrogens [10]. It is also possible that lower serum SHBG levels in overweight/obese women may combine with increased free estrogen levels to increase the estrogenic effect on the endometrium.

Although endometrial thickness may not be the only predictor of endometrial hyperplasia, it is still an important marker for the clinical screening of endometrial abnormalities. We did not perform an endometrial biopsy on every subject; therefore, a correlation between endometrial thickness and endometrial hyperplasia could not be identified. Chronic anovulation, obesity, and hyperinsulinemia are all associated with PCOS and endometrial carcinoma. It has been assumed that PCOS predisposes women to endometrial cancer [12]. Cheung [1] performed endometrial biopsies on 56 women with PCOS and suggested that average intermenstrual interval and endometrial thickness are significant predictors of endometrial hyperplasia [1]. Our study demonstrates that endometrial thickness correlate with the duration of anovulation negatively, which might be explained by the fact that the average intermenstrual interval and endometrial thickness were independent risk factors for endometrial hyperplasia.

Conclusion

Endometrial thickness in women with ovulatory dysfunction was positively correlated with BMI but uncorrelated with the serum E_2 and androgens levels. Endometrial thickness in obesity and hypertension women with ovulatory dysfunction should be closely monitored.

Declaration of interest

Authors declare they do not have any potential conflict of interest.

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Changes in the PCOS phenotype with age

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of reproductive-age women. The diagnosis of PCOS is mainly based on the following three components: (1) hyperandrogenism, (2) oligo-amenorrhea, and (3) the observation of polycystic ovaries on a sonogram. The comorbidities may include insulin resistance, type II diabetes mellitus, hypertension and cardiovascular disease. Importantly, the diagnostic criteria and complications related to PCOS are age-dependent. Androgen production in women may decrease because of ovarian aging or decreased production by the adrenal glands over time. The prevalence of hirsutism and acne decreases with age. Ovarian volume and follicle number also decrease with age, with the age-related decrease in follicle number seemingly greater than that of ovarian volume. Aging may also be associated with increased risk of insulin resistance and metabolic disturbances. Therefore, these age-related changes may affect the observed incidence and complications of PCOS. In adolescent patients, the criteria described above pose particular diagnostic problems because the characteristics of normal puberty often overlap with the signs and symptoms of PCOS. Hyperandrogenism and chronic anovulation are the primary disturbances in younger women with PCOS; whereas, obesity, insulin resistance, and metabolic disturbances are predominant in older women with PCOS. The deterioration of insulin resistance during the reproductive life of women with PCOS appears to be mainly attributable to the increase in obesity. Therefore, if body weight could be controlled properly, younger hyperandrogenic PCOS women might reduce their risk of insulin resistance and metabolic disturbances later in life.

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of reproductive-age women, affecting an estimated 6–8% [1] of such individuals depending on the diagnostic criteria applied [2]. PCOS is a complex and heterogeneous disorder presenting a challenge for clinical investigators. It is a multifaceted reproductive, cosmetic, and metabolic problem, with an enigmatic pathophysiological and molecular basis [3]. Although PCOS may have a genetic component, the clinical features of this disorder change with age, from adolescence to menopause and beyond [4]. PCOS has potentially profound implications for women regarding anovulatory infertility and other symptoms related to elevated androgen levels in reproductive-aged women. In addition, older women are prone to significant health problems related to hyperinsulinemia, with a high risk for diabetes and cardiovascular risk factors [5]. The comorbidities of PCOS over the lifespan of an affected woman may require individual therapeutic strategies, which could prevent long-term chronic metabolic diseases [4].

2. Diagnostic criteria

Three diagnostic classification systems are currently in use for PCOS: the National Institutes of Health (NIH) criteria, the Rotterdam criteria, and the Androgen Excess and PCOS Society criteria. All of these criteria require the exclusion of other disorders, such congenital adrenal hyperplasia and tumors. According to the NIH criteria, PCOS is diagnosed by the combination of chronic oligo- or anovulation and clinical or biochemical signs of hyperandrogenism [6]. According to the Rotterdam criteria, PCOS is diagnosed in the presence of two of the following three symptoms: (1) oligomenorrhea, anovulation; (2) hyperandrogenism; and (3) the observation of polycystic ovaries by sonography [7]. Most recently, the Androgen Excess Society published a task force report emphasizing that androgen excess is a central feature of the disease and that PCOS should be defined by the presence of hyperandrogenism in

Abbreviations: PCOS, polycystic ovarian syndrome; NIH, National Institutes of Health; HPO, hypothalamic–pituitary–ovarian; AMH, anti-Müllerian hormone; PCO, polycystic ovary morphology; AFC, antral follicle count; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding Globulin; mF-G score, modified Ferriman–Gallwey score; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OR, odd ratio.

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combination with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) [1]. Regardless of the set of criteria used, the diagnosis of PCOS is determined by the three following components: (1) hyperandrogenism (HA), (2) oligo-amenorrhea (OA), and (3) the observation of polycystic ovaries (PCOs) on a sonogram.

3. PCOS diagnostic criteria change with age

The clinical and biochemical presentations of PCOS change with age [4]. The clinical presentation of chronic anovulation varies by age, with amenorrhea and oligomenorrhea being common among adolescents [8]. The menstrual cycles may become regular with age in women with PCOS [9,10]. The production of androgens in women may decrease because of ovarian aging or decreased production by the adrenal glands over time [11]. Hyperandrogenism partially resolves before menopause in women with PCOS [12]. Ovarian volume and follicle number decrease with age in women both with and without PCOS [13]. Furthermore, aging may also be associated with a defect in insulin action [14]. Therefore, the clinical features and metabolic consequences of PCOS may vary with age [15], and these age-related changes may affect the observed incidence of PCOS [16]. To understand the age-related changes in the diagnostic criteria of PCOS, it is crucial to determine the complications of the related syndromes.

4. Adolescence

Common features of normal puberty, namely, menstrual irregularities and insulin resistance, obscure the diagnosis of adolescent PCOS [17]. Adolescents have a high prevalence of oligo-anovulation with prolonged menstrual intervals. Menstrual irregularity is common in the early years after menarche, and oligo-anovulation may be normal [18]. Menstrual disturbances in adolescents are often explained by the immaturity of the hypothalamic–pituitary–ovarian (HPO) axis. Disordered regulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release has been implicated in the pathogenesis of PCOS. The serum concentrations of sex hormones increase with age, from premenarchal to postmenarchal [19]. In a study of postmenarchal women, approximately 80% of the cycles were anovulatory in the first year after menarche, 50% in the third, and 10% in the sixth, and it is generally accepted that it may take up to 5 years after menarche for the HPO axis to reach maturation [19]. Furthermore, concomitant eating disorders are frequent, and secondary amenorrhea can be associated with anorectic behavior in adolescents [20].

Ovarian appearance in the early postmenarchal years may differ from that in adulthood. In a sonographic study of healthy girls, uterine growth continued several years after menarche; furthermore, the average ovarian volume increased from early childhood until the age of approximately 16 [21]. The difference between a multifollicular appearance and polycystic ovarian morphology in adolescents is poorly defined [21]. In adolescent patients, the criteria described above pose particular diagnostic problems because the characteristics of normal puberty often overlap with the signs and symptoms of PCOS [22].

Mild hair growth and chronic anovulation are also regarded as normal components of the late stages of puberty and early adolescence and may persist for several years; therefore, the diagnosis is often not made until later in life, when endocrine and metabolic dysfunctions have been firmly established [23]. Hyperandrogenism, defined as clinical and or biochemical hyperandrogenism, might present differently for adolescents. Although most diagnostic criteria include hirsutism, acne, or androgenic alopecia as markers of clinical hyperandrogenism, acne and alopecia were not suggested as clinical markers for the diagnosis of PCOS in adolescents [24]. The most important finding for clinical hyperandrogenism in female adolescents is progressive hirsutism [23].

Adolescent hyperandrogenemia is associated with a reduction in peripheral tissue insulin sensitivity and compensatory hyperinsulinemia, which implies an increase in the risk of type II diabetes [25]. The increase in the prevalence of obesity, particularly among younger age groups, is likely to have long-term implications for cardiovascular disease (CVD) at relatively young ages. Applying adult criteria for PCOS diagnosis to adolescent girls did not reliably identify girls at risk for metabolic syndrome; indeed, an elevated BMI was the strongest indicator of metabolic syndrome risk factors [26]. Therefore, consideration should be given to the management of girls and young women with polycystic ovaries and PCOS as this group may have different needs and health risks than older women [27].

To diagnose PCOS in adolescents, guidelines have recently been purposed [24]. Hyperandrogenism was diagnosed by elevated blood androgens (hyperandrogenemia) or documented progressive hirsutism and discounting clinical finding such as acne and alopecia [24]. A definitive diagnosis of PCOS in adolescents should require all three Rotterdam elements (not just 2 out of 3) [24].

5. Anti-Müllerian hormone (AMH)

Anti-Müllerian hormone (AMH) is produced by the granulosa cells of preantral and small antral follicles, and its levels can be assessed in serum. As AMH is largely expressed during folliculogenesis, from the primary follicular stage to the small antral stage, serum levels of AMH represent both the quantity and quality of the ovarian follicle pool and may be an useful marker of ovarian reserves [28,29]. The serum AMH level was strongly and positively related to the number of antral follicles assessed by ultrasound at baseline [30]; furthermore, AMH levels were also positively associated with testosterone levels and ovarian volume [31]. We demonstrated that AMH is a good predictor of PCOS and that the prevalence of PCOS increased with an increase in AMH concentration [32]. AMH is reported to be independent of menstrual cycle in most studies [33], which underlines its robustness as a biological marker of ovarian aging [33]. AMH levels decreased with an increase in age in both the PCOS cases and normo-ovulatory controls [33]. AMH measurement could be useful in the prediction of the menopausal transition [29,34]. Using AMH as a predicative marker, the reproductive lifespan of PCOS women is an average of 2 years longer than that of normo-ovulatory women [33]. Carmina conducted a longitudinal study of 54 women with PCOS aged 35–39 years (mean 37 ± 1 year) and 20 age- and weight-matched control women. The results indicated that the AMH levels decreased by approximately 40% in PCOS (6.7–3.9 ng/mL, 40% decrease) and control (1.7–1.0 ng/mL, 41% decrease) subjects during 5-year average intervals [35].

6. Polycystic ovarian morphology

Polycystic ovarian morphology (PCO) is defined by ovarian volume (>10 cm^3) and/or increased antral follicle count (AFC $\geqslant$ 12 per ovary) by ultrasonographic examination. PCO is a common, age-dependent finding among ovulatory women [36]. Ovarian volume and follicle number decrease with age in both healthy women and women with PCOS [13]. In a study using data obtained from 58,673 observations of ovarian volume, there is a statistically significant decrease in ovarian volume with each decade of life from age 30 to age 70 [37]. Pavlik's study demonstrated a stable ovarian volume up to age 35, a rapid decline between ages 35 and 55, and a very minor decline after age 55 [37]. The ovarian volume in women aged 25–51 years was reported to reflect the number of primordial

follicles remaining and ovarian volume measurement by transvaginal sonography may determine the ovarian reserve and reproductive age [38]. Menopause and ovarian failure occur as a consequence of the continuous utilization of a fixed store of primordial follicles, leading to almost total depletion at midlife.

The number of growing follicles at a given age is correlated with those of the primordial stages [39]. The great majority of follicles that disappear are lost by atresia, and the rate of loss accelerates in the last decade of menstrual life [39]. After the numbers had fallen to the critical figure at 37.5 years of age, the loss rate increases, corresponding to a faster rate of ovarian aging at approximately 51 years of age [40]. Alsamarai suggested that the decrease in ovarian volume was less pronounced in women with PCOS than in control subjects [13]. In normal ovulatory women, ovarian volume was significantly lower in all age groups over 40 years compared with the 35-to-39 age group, with measurable decreases across each decade of reproductive life starting at age 40 [41]. We performed a cross-sectional study in 781 cases between the ages of 20 and 40 (453 PCOS and 328 non-PCOS) and found that the ovarian volume was not significantly correlated with age in either PCOS or non-PCOS women [42].

In a community-based study of 262 ovulatory women ages 25–45, Johnstone reported that the prevalence of PCO was 32% and decreased with age but that the percentage of women with AFC $\geqslant$ 12 decreased from 62% 25–30 years old to 7% at 41–45 years old [36]. The age-related decrease in follicle number seems more dominant than the age-related decrease in ovarian volume [36].

7. Ovarian aging

Ovarian aging results in the diminution of the follicular cohort in both normal and PCOS women, associated with decreased inhibin B and AMH levels [43]. Similarly, the decreasing capacity of the ovaries to release androgens in response to hCG stimulation was observed in both healthy and PCOS women [44]. In a study on the effect of age on the ovarian response to gonadotropin in women with PCOS, although there were no significant age-related differences in the ovulation rate, the pregnancy rate was significantly lower in the older PCOS patients than younger PCOS patients [45]. In terms of age-related decline in adrenal androgen production, the adrenal capacity to secrete androgens (except for DHEA) remains more stable during the menopausal transition in women with PCOS than in the normal control women [46]. Advanced age in normogonadotrophic anovulatory infertile women is associated with lower LH and androgen levels and with a decreased number of ovarian follicles. Although the observed differences are relatively small during reproductive years, these age-related changes may affect the observed incidences of PCOS [16].

8. Oligo-amenorrhea

Oligo-amenorrhea is one of the key components for the diagnosis of PCOS. Several studies suggest that a gradual normalization of menstrual cycle abnormalities occurs in PCOS with increasing age [10,16]. AMH levels indicate the quantity of the ovarian follicle pool and may be a useful marker of ovarian reserves [28]. We demonstrated that serum AMH levels were strongly correlated to the number of menstrual cycles per year [32], which could explain the tendency of women with PCOS achieve cycle regularly as they grow older [12]. In a study of oligo-amenorrheic infertile women, advanced age in normogonadotrophic anovulatory infertile women is associated with lower LH and a decreased number of ovarian follicles [16]. Decreases in serum AMH levels with age could be explained by ovarian follicle loss with increasing age. In Carmina's study of 54 anovulatory hyperandrogenic women with PCOS, after a 5-year follow-up, 10 anovulatory patients out of 54 (approximately 20%) became ovulatory at a mean age of 42 years [47]. Elting studied 205 women with PCOS using a telephone questionnaire, revealing a highly significant linear trend for a shorter menstrual cycle length with increasing age; the proportion of women with regular menstrual cycles increased from 41% for women ages 30–35 to 100% in the oldest group, ages 51–55 [10].

Women with PCOS achieve regular menstrual cycles with age, and the development of a new balance in the polycystic ovary, caused solely by follicle loss through ovarian aging, can explain the occurrence of regular cycles in older patients with PCOS [10]. In a study of aging women with PCOS comparing those who became regular with those still menstruating irregularly, a lower follicle count for women with PCOS was predictive of the achievement of regular menstrual cycles with age [48], confirming that a decrease in the size of the follicle cohort from ovarian aging is largely responsible for the regular menstrual cycles in aging PCOS women [48]. Although the observed differences are relatively small during reproductive years, these age-related changes in women with oligo-amenorrhea may affect the observed incidence of PCOS [16].

9. Hyperandrogenism

Clinical and biochemical androgen excesses were the major characteristics of women with PCOS; however, the elevated serum concentrations of androgens are the most consistent biochemical abnormalities and may be considered the hallmark of the syndrome [49]. An age-related decrease in androgen secretion, as in normal women, also occurs in women with PCOS. Ovarian steroid secretion capacity starts to decline as early as approximately 30 years of age [44]; hyperandrogenism partly resolves before menopause in women with PCOS [12]. Acne and hirsutism were thought to be the major clinical markers of clinical hyperandrogenism. We studied 781 women and found that the prevalence of acne and hirsutism were both negatively correlated with age in women with and without PCOS [42]. Bili studied 472 oligo-amenorrheic infertile patients and found that age was inversely correlated with testosterone, androstenedione and dehydroepiandrosterone [16]. Moran studied 145 hyperandrogenic women and reported a negative association between DHEAS levels and age [50]. Winters studied 84 women with PCOS and found that the levels of total testosterone and non-SHBG–bound testosterone were lower in older women with PCOS [12].

Although the decreasing ovarian capacity to release androgens in response to hCG stimulation observed in healthy women also occurs in women with PCOS, PCOS basal serum levels of androgens and ovarian androgen secretion capacity are markedly increased and remain high throughout the reproductive years [44]. In a longitudinal study of 193 women who were followed from a mean age of 22 years to a mean age of 43 years, an approximately 25% decrease in testosterone levels and an approximately 30% decrease in DHEAS were observed [35]. We demonstrated that all serum androgen markers (total testosterone, androstenedione, and DHEAS) were significantly negatively correlated with age. Furthermore, the prevalence of acne and hirsutism decreased with advanced age, modified FG score, and serum DHEAS levels, and there was a significant negative association with age in women with and without PCOS [42]. Accordingly, the prevalence of both clinical hyperandrogenism and biochemical hyperandrogenemia should decrease in women of advanced age.

10. Metabolic syndrome and insulin resistance

Metabolic syndrome and insulin resistance were the major concerns among the long-term complications in women with PCOS. Metabolic syndrome is a cluster of adverse cardiovascular features,

Table 1
PCOS phenotype changes with age in cross-sectional and longitudinal studies.

Authors	Study	Patients	Results
Liang et al. (2011) [42]	Cross-sectional	453 PCOS and 328 non-PCOS	Younger PCOS had significantly higher androgens levels, but lower BMI and lower insulin resistance than older PCOS.
Panidis et al. (2012) [61]	Cross-sectional	1212 PCOS and 254 healthy women	A progressive decline in hyperandrogenic phenotype and increased insulin resistance with advancing age.
Carmina et al. (2012) [47]	Longitudinal	193 women with PCOS, aged 20–25 years, and followed at 5-year intervals for 20 years	After 20 years of follow-up in women with PCOS. After 10 years, androgens decreased; at 15 years, waist circumference increased; at 20 years, there were more ovulatory cycles, suggesting a milder disorder, whereas the persisting metabolic abnormalities increased.

including central obesity, atherogenic dyslipidemia, insulin resistance, a prothrombotic state, elevated blood pressure, and increased circulation proinflammatory markers [26]. Age is also an important risk factor for developing metabolic disorders and insulin resistance. Aging may also be associated with a defect in insulin action that is manifested by decreased whole-body tissue sensitivity to insulin without a change in tissue responsiveness [14]. The glucose intolerance may reflect part of the aging process. In elderly subjects, the severity of carbohydrate intolerance is directly correlated with the degree of peripheral insulin resistance [51].

We reported that advanced age was associated with increased cholesterol, triglyceride, and low-density lipoprotein (LDL) levels; furthermore, fasting glucose and 2-h glucose were both significantly correlated with age [42]. The National Cholesterol Education Program Adult Treatment Panel (ATPIII; third report of the National Cholesterol Education Program) guidelines define metabolic syndrome according to the following five parameters: waist circumference, fasting serum glucose, fasting serum triglycerides, serum high-density lipoprotein (HDL) cholesterol and blood pressure. Most of these parameters worsen with age. Therefore, it is logical that metabolic syndrome and insulin resistance are also age-dependent.

11. Obesity

Obesity is a prominent feature of PCOS, occurring in 40–50% of patients [52,53]. Lipid abnormalities, including elevated LDL and triglyceride levels and decreased HDL, are often found in women with both PCOS and obesity [54]. Obesity appears to exert an additive, synergistic impact on the manifestations of PCOS, independently and negatively affecting insulin sensitivity, diabetes risk and cardiovascular profile [55,56]. Obesity unmasks or amplifies symptoms and endocrine and metabolic abnormalities. We studied 273 women and found that obesity (Odd Ratio (OR) = 14.0, 95% CI, 7.5–26.5) results in a higher risk for developing insulin resistance than hyperandrogenemia (OR = 2.1, 1.3–3.6) or oligo-amenorrhea (OR = 1.8, 1.0–3.3) [57]. Furthermore, body weight status was the major factor determining the risk of impaired glucose tolerance and metabolic syndrome in women with PCOS [58].

Obesity is not only a major determinant of long-term complications in PCOS but also an important factor in the diagnosis of PCOS [59]. In one study, the prevalence of PCOS was greater in overweight and obese women than in lean women [60]. Obesity worsens both biochemical hyperandrogenemia and chronic anovulation, which are the two most important diagnostic criteria of PCOS [60]. We found that obese subjects with PCOS had a higher risk of developing oligomenorrhea (OR = 2.2, 1.3–3.7) and biochemical hyperandrogenemia (OR = 2.6, 1.6–4.2) than non-obese women with PCOS [59]. Therefore, when assessing the diagnosis and complications, obesity should be thoroughly taken into account.

12. Phenotypes change with age

The best way to study the aging process in women with PCOS is to perform a longitudinal study with same subject; however, it is difficult to include a large sample size with a long-time follow up. Therefore, large-sample-size cross-sectional studies might also provide some useful information (Table 1).

13. Case studies

As described above, the age of subjects could influence the status of diagnosed PCOS. Subjects with PCOS, as diagnosed by 2003 Rotterdam criteria, might have different phenotypes according to age group. We reported a cross-sectional study that included 453 women with PCOS and found that for women who fulfilled diagnostic criteria for PCOS, younger women had a significantly higher percentage of acne and hirsutism, higher mF-G score, and lower cholesterol and triglycerides than older women. In contrast, older women had higher levels of obesity, lower levels of androgens, and higher levels of insulin resistance and metabolic disturbances than younger women [42]. Our results were confirmed by Panidis, who studied 1,212 women with PCOS and found a progressive decline in circulating androgens with advancing age [61]. Furthermore, patients 21–30 years old had lower plasma glucose and insulin levels, lower homeostasis model assessment of insulin resistance index, and lower BMI than patients 31–39 years old [61]. From cross-sectional studies, among patients with diagnosed PCOS, chronic anovulation and hyperandrogenism were the predominant characteristics in adolescents. Because the prevalence of clinical and/or biochemical hyperandrogenism significantly decreased with age and the severity of menstrual disturbance may improve after the age of 20, ovarian volume and morphology seem to be relatively stable with age for women younger than 35 [37,42]. Therefore, polycystic ovary morphology became the prevalent inclusion criterion used by some investigators for the diagnosis of PCOS in women over 20 years of age.

Both our study and that of Panidis found that the prevalence of PCOS phenotypes changed with age, with younger women with PCOS having more severe hyperandrogenism but lower insulin resistance and BMI than older women with PCOS [61]. Interestingly, serum testosterone levels were positively correlated with BMI [42], and the prevalence of hyperandrogenism was twice as high for obese women as for non-obese women [59]. To fulfill the diagnostic criteria, older women with PCOS had a higher prevalence of obesity than younger women [42,61]; therefore, the deterioration of insulin resistance during the reproductive life of women with PCOS appears to be mainly attributable to the increase in obesity [61].

However, the question is whether younger hyperandrogenic PCOS women will become older obese women with insulin resistance? This question could not be answered by a cross-sectional study. Recently, Carmina published a large longitudinal study that included 193 women with PCOS, aged 20–25 years, who were diagnosed according to Rotterdam criteria and followed at 5-year intervals for 20 years [47]. After 10 years, androgens decreased; at 15 years, waist circumference increased; and at 20 years, ovarian volume decreased. Serum luteinizing hormone and follicle-stimulating hormone decreased non-significantly, and fasting

insulin and quantitative insulin-sensitivity check index was unchanged. Eighty-five women (44%) were ovulatory at 20 years, and 18 women (8%) could no longer be diagnosed as having PCOS [47]. After 20 years of follow-up in women with PCOS, androgens and ovarian volume decreased and there were more ovulatory cycles, suggesting a milder disorder, whereas metabolic abnormalities persisted and waist circumference increased [47].

14. Conclusion

Most available data suggest that the prevalence of cardiovascular diseases in women with polycystic ovary syndrome (PCOS) is lower than expected based on risk calculations during fertile years. Advanced age is associated with decreased hyperandrogenism and increased metabolic disturbances in women with and without PCOS. Hyperandrogenism and chronic anovulation may be the major disturbances in younger women with PCOS, however, increases in body weight might contribute to insulin resistance and metabolic disturbances in later life. If body weight could be controlled properly, young hyperandrogenic PCOS women might not necessarily become older obese insulin-resistant PCOS women.

Acknowledgments

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國科會補助專題研究計畫出席國際學術會議心得報告

日期：102 年 10 月 07 日

計畫編號	NSC－101－2629－B－038－001		
計畫名稱	環境荷爾蒙與氧化壓力對多囊性卵巢婦女生殖荷爾蒙的影響		
出國人員 姓名	徐明義	服務機構 及職稱	臺北醫學大學醫學系
會議時間	102 年 04 月 17 日至 102 年 04 月 23 日	會議地點	Vienna, Austria.
會議名稱	（中文）第五屆國際糖尿病前期及代謝症候群大會 （英文）5th International Congress on PREDIABETES and the METABOLIC　SYNDROME.		
發表題目	（中文）肥胖與非肥胖婦女血清中鐵蛋白指標 （英文）Serum ferritin levels in obese and non-obese women.		

一、參加會議經過

前往奧地利首都維也納參加第五屆 International Congress on PREDIABETES and the METABOLIC　SYNDROME 並發表研究成果報告。

二、與會心得

除了參與大會學術研討外，並於 4 月 20 日以北醫名義發表 Serum ferritin levels in obese and non-obese women 壁報論文。本次大會的研討主軸在於糖尿病前趨症狀與代謝症候群的相關研究，肥胖問題也是大會研討的主要問題之一，這是跨領域的研究，相關疾病對國人的健康影響大而深遠，國內應該可以結合不同領域學者探討相關問題。

三、發表論文全文或摘要

Serum ferritin levels in obese and non-obese women.

Ming-I Hsu MD[1], Chun-Sen Hsu MD[1], Chii-Ruey Tzeng[2], MD.[1]

Department of Obstetrics and Gynaecology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [2]Department of Obstetrics and Gynaecology, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan

Abstract

Object: To evaluate the association between serum ferritin levels and insulin resistance and metabolic syndrome in obese and non-obese women.

Methods: Retrospective study. Five hundred thirty-nine women, 286 of whom had PCOS and 253 of whom did not have PCOS, were included in the study.

Results: Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride, and total cholesterol both in obese and non-obese women. Obese women (BMI>25) with high ferritin (ferritin ≥ 45.5 ng/mL, n=270) levels had higher insulin resistance, impaired glucose tolerance, and liver enzymes than obese women with low ferritin levels (ferritin < 45.5 ng/mL, n=269). However, among non-obese women, insulin resistance and metabolic disturbances were not significantly different between high and low ferritin groups. Women with high ferritin levels had a greater risk of PCOS and hyperandrogenism than women with low ferritin levels. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance in women with elevated serum ferritin levels.

Conclusions: The pathogenesis of increased iron stores correlated with insulin resistance and metabolic syndrome among obese and non-obese premenopausal women was different. The hypertriglyceridemia in women with PCOS might be associated with iron metabolism.

Funding : This work was supported by the National Science Council Grant NSC 101-2629-B-038-001

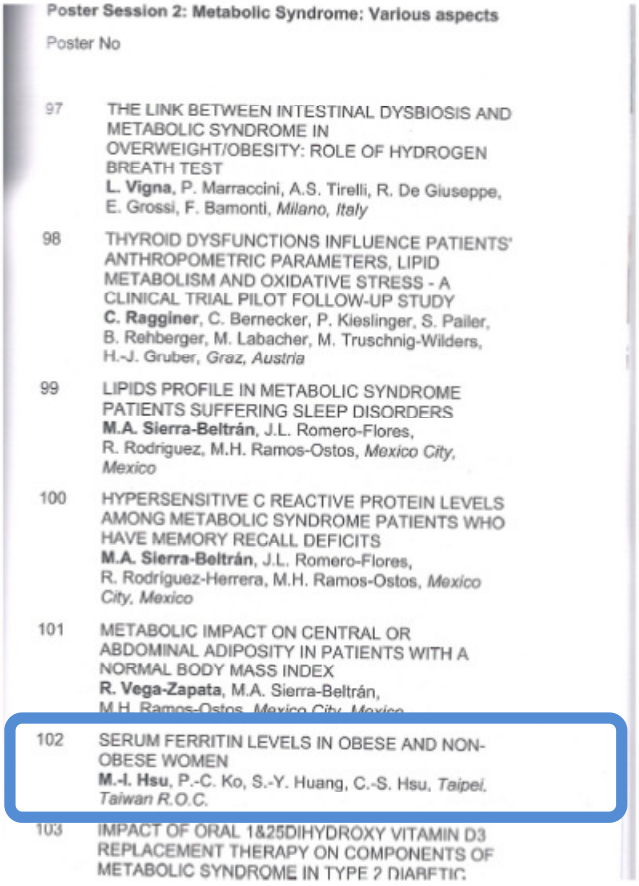
Keywords: Polycystic ovary syndrome, ferritin, obesity, insulin resistance, metabolic syndrome.

四、建議

無特別

五、攜回資料名稱及內容

會議手冊封面及主持人報告論文目錄頁。



Poster Session 2: Metabolic Syndrome: Various aspects

Poster No

97 THE LINK BETWEEN INTESTINAL DYSBIOSIS AND METABOLIC SYNDROME IN OVERWEIGHT/OBESITY: ROLE OF HYDROGEN BREATH TEST
L. Vigna, P. Marraccini, A.S. Tirelli, R. De Giuseppe, E. Grossi, F. Bamonti, *Milano, Italy*

98 THYROID DYSFUNCTIONS INFLUENCE PATIENTS' ANTHROPOMETRIC PARAMETERS, LIPID METABOLISM AND OXIDATIVE STRESS - A CLINICAL TRIAL PILOT FOLLOW-UP STUDY
C. Ragginer, C. Bernecker, P. Kieslinger, S. Pailer, B. Rehberger, M. Labacher, M. Truschnig-Wilders, H.-J. Gruber, *Graz, Austria*

99 LIPIDS PROFILE IN METABOLIC SYNDROME PATIENTS SUFFERING SLEEP DISORDERS
M.A. Sierra-Beltrán, J.L. Romero-Flores, R. Rodriguez, M.H. Ramos-Ostos, *Mexico City, Mexico*

100 HYPERSENSITIVE C REACTIVE PROTEIN LEVELS AMONG METABOLIC SYNDROME PATIENTS WHO HAVE MEMORY RECALL DEFICITS
M.A. Sierra-Beltrán, J.L. Romero-Flores, R. Rodriguez-Herrera, M.H. Ramos-Ostos, *Mexico City, Mexico*

101 METABOLIC IMPACT ON CENTRAL OR ABDOMINAL ADIPOSITY IN PATIENTS WITH A NORMAL BODY MASS INDEX
R. Vega-Zapata, M.A. Sierra-Beltrán, M.H. Ramos-Ostos, *Mexico City, Mexico*

102 SERUM FERRITIN LEVELS IN OBESE AND NON-OBESE WOMEN
M.-I. Hsu, P.-C. Ko, S.-Y. Huang, C.-S. Hsu, *Taipei, Taiwan R.O.C.*

103 IMPACT OF ORAL 1&25DIHYDROXY VITAMIN D3 REPLACEMENT THERAPY ON COMPONENTS OF METABOLIC SYNDROME IN TYPE 2 DIABETIC

六、其他

無

國科會補助計畫衍生研發成果推廣資料表

日期:2013/09/24

國科會補助計畫	計畫名稱: 氧化壓力與環境荷爾蒙對多囊性卵巢婦女生殖荷爾蒙的影響
	計畫主持人: 徐明義
	計畫編號: 101-2629-B-038-001- 學門領域: 性別主流科技計畫

無研發成果推廣資料

101 年度專題研究計畫研究成果彙整表

計畫主持人：徐明義	計畫編號：101-2629-B-038-001-
計畫名稱：氧化壓力與環境荷爾蒙對多囊性卵巢婦女生殖荷爾蒙的影響	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	1	1	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	2	1	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	無

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估 ■達成目標 □未達成目標（請說明，以 100 字為限） □實驗失敗 □因故實驗中斷 □其他原因 說明：
2. 研究成果在學術期刊發表或申請專利等情形： 論文：□已發表 ■未發表之文稿 □撰寫中 □無 專利：□已獲得 □申請中 ■無 技轉：□已技轉 □洽談中 ■無 其他：(以 100 字為限)
3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)