台灣 PCOS 多囊性卵巢症候群影響因子之探討

Prevalence of Insulin Resistance and Determination of Risk Factors for Glucose Intolerance in Polycystic Ovary Syndrome

中文摘要

本研究目的在探討多囊性卵巢症候群(polycystic ovary syndrome; PCOS)患者之危險因子，如：年齡、雄性素、BMI、胰島素抗性指標等。本研究採 cross section design，從台安醫院生殖醫學中心之不孕症病人群中，鑑定是否爲多囊性卵巢病人，所有病人均收集其血液檢體，並利用結構式問卷調查方式，研究對象的月經週期史、過去病史及家族疾病史等人口學資料。研究結果顯示，不孕症病患中屬於多囊性卵巢症候群患者較一般不孕症病患年紀輕且體重也較重；體內胰島素抗性指標經 BMI 調整後仍較對照組高(fasting insulin 5.6 vs. 4.1 μU/ml, $p=0.001$; 2h insulin 38 vs. 27 μU/ml, $p=0.001$; fasting glucose 97.2 vs. 94.4 mg/dl, $p=0.001$; 2h glucose 108 vs. 96 mg/dl, $p=0.001$; testosterone 0.4 vs. 0.3 ng/ml, $p=0.001$; homeostasis model assessment, HOMA：1.3 vs. 1.0, $p<0.001$)。以 multiple linear regression 模式分析，發現年齡、飯前血糖、飯前胰島素及刺激後之胰島素等，對刺激後的血糖呈現統計上有意義的影響，但 BMI 及腰臀比則不呈統計上的意義性，本研究結果也發現，台灣多囊性卵巢病患同時具備較高的胰島素抗性，而這些特性也是心血管疾病的危險因子，因此，預防多囊性卵巢的發生或惡化應該與預防心血管疾病類似，即低油飲食、規律運動、均衡飲食等生活習慣的培養是很重要的，而控制體重對於台灣的不孕症病人可能並不是最重要的要務。

研究結果也發現，在台灣的不孕症的病人中屬於排卵障礙者，其血糖不正常比率遠較低於白種人，多囊性卵巢病患血糖不正常比例爲 14%，而白種人幾乎達 30~40%；然而，台灣糖尿病患併發洗腎的比率位居全世界第一已有七年，而在英國許多的洗腎中心，也發現在同樣的糖尿病控制過程當中，黃種人比較容易導致腎臟的病變，所以相信不同人種的胰島素抗性之表現也不同，因此在不孕症的研究中，應儘量找出中國人自己的判讀指標。本研究另外收集了尚未進行試管嬰兒療程病人的血糖指數，經追蹤其生產狀況後，發現流產者比順產者有較高之 BMI、飯前血糖、飯前胰島素、飯後胰島素及 HOMA 值；進一步使用 ROC curve 分析流產與順產者的特性時，顯示飯前血糖值是最好的鑑別指標，其切點爲 98.5 mg/dl，敏感度 73%及精確度 73%，而刺激後血糖值則次之，其切點爲 106.5 mg/dl，敏感度 54%及精確度 72%，其切點均低於世界衛生組織飯前血糖值≧110 mg/dl 及刺激後血糖≧140 mg/dl 之標準；意即血糖較高的病人有較高的流產機會，但其血糖值僅介於白種人所謂的正常血糖值範圍中，所以相信中國人的血糖值及胰島素抗性，於判讀上與白種人應該是不同的。

在男性賀爾蒙接受器基因(androgen receptor gene)的甲基化(methylation) 研究中顯示，通常多囊性卵巢病人體內雄性素(androgen)之濃度都較正常女性爲高。雄

性素與雄性素受器(Androgen Receptor, AR) 結合之後，形成雄性素-AR 複合體，會一起進入細胞核內，活化下游基因的轉錄，因此，AR 被視爲一轉錄因子(transcription factor)。已有許多報告指出，AR 其 exon 1 上的 CAG 重複片段與 AR 基因的活性相關，因此想藉由分析多囊性卵巢病人與 AR 基因 CAG 重複片段數目與疾病的相關性。在隨機取樣抽取病人 115 例與正常人 125 例的檢體 DNA 後，使用 PCR 放大此 CAG 片段，以基因型分析其 CAG 重複片段數目之差異；並以酵素 Hpa II 檢測其甲基化程度，最後以 independent t-test 進行統計分析。從研究中發現國人多囊性卵巢病患的甲基化表現跟外國人多囊性卵巢症者的甲基化表現不同，外國人有甲基化的 CAG repeat 較長，而台灣的多囊性卵巢病患並無此發現。
綜合以上研究，台灣人必須要有自己的判讀指標。基本上，以種族性而言，黃種人的祖先均吃較多的纖維且生活於較不富裕的環境情況下，相信中國人的血糖以及胰島素抗性的判讀上，皆有必要比白種人控制地更加嚴格，才能避免日後代謝疾病症候群的發生。

英文摘要

In order to explore the risk factors, such as android obesity, insulin resistance, homocysteine, lipid profile of polycystic ovary syndrome (PCOS) in women. A cross-sectional study was performed. Two groups with and without PCOS women were included at the center for reproductive medicine and infertility in Taiwan Adventist Hospital. The demographic characteristics were collected by structural questionnaire that included the life habits, history of menstration, past history and family history etc. The blood samples were also collected for biochemical examination and identification of genetic polymorphysium.
Our results showed that PCOS patients are younger (32.7y vs. 35.3y) with a higher BMI (22.4 vs. 20.6 kg/m2) than the controls. Even after BMI adjustment, PCOS patients still had significantly higher fasting glucose (97.2 vs. 94.4 mg/dl), fasting insulin (5.6 vs. 4.1 μIU/ml), 2h glucose (108.1 vs. 96.0 mg/dl) and 2h insulin levels (38.0 vs. 27.0μIU/ml), and higher HOMA-IR values (1.3 vs. 1.0) than control patients. The prevalence of IGT and DM in PCOS patients was 7.6 and 3.1% ($p<0.05$), respectively, compared to 2.9 and 0.2% ($p<0.05$) in the control group, respectively. Only fasting glucose and insulin, 2h insulin, HOMA IR, age androstenedione and status (PCOS vs. control) had significant impact on 2h glucose. However, BMI and waist-to-hip ratio did not show significant impact on 2h glucose.
Chinese women with PCOS are at increased risk for insulin resistance and glucose intolerance than controls. BMI failed to show significant impact on 2h glucose in our infertility patients.Because the risk factors of PCOS is identical to cardiovascular risk factors, therefore, low oil diet, exercise regularly, control the body weight that maybe

the most important lifestyles for prevention.
We also would like to determine the association between a 75 gm oral glucose tolerance test and its possible relationship to pregnancy outcome and tried to find the glucose level with the risk by ROC curve. Between January, 2004 and April, 2006, we included two hundred and eighty first IVF cycle patients in Taiwan Adventist Hospital in this prospective study. Before the IVF cycle every patient underwent hormone assay testing and a 2 hour 75 gm oral glucose tolerance test. Subjects were followed until the result of the IVF cycle was known and stratified by outcomes.
We analyzed the relationship between glycemic parameters and insulin resistance by OGTT and IVF pregnancy outcome. We also did the linear regression between birth weight and preconception fasting insulin, 2h glucose and 2h insulin. We did the ROC curve of glycemic parameters between preterm birth and full term birth to identify the risk factors of preterm birth. There were 120 out of 280 patients who conceived after their initial IVF cycle. (The pregnancy rate was 42.9%.) 23 out of 120 (19.0%) pregnant patients had a pregnancy loss. For ongoing pregnancy patients, 25 of 89 (28%) had complication. The most common pregnancy complication was preterm birth (N=11). Preterm birth had higher BMI (23.46 vs. 20.97; P=0.017), higher fasting glucose 107.36 vs. 95.14; P= 0.000) and higher fasting insulin (10.55 vs. 6.20; P=0.039), higher 2h glucose (120.55 vs. 99.97; P=0.015) and higher HOMA IR (3.43 vs. 1.45; P= 0.009) than the normal full term patients. Linear regression between birth weight and fasting glucose for the normal full term patients (R2=0.1187; P=0.02), and HOMA IR (R2=0.1297; P=0.02) showed positively related. So we suggested that oral glucose tolerance testing (especially in patients with higher body mass index) before proceeding with IVF may help to identify groups at higher risk and may help to target an intervention to prevent preterm labor in these patients. And we do think we need to collect more our data base and to define our own criteria for glucose intolerance.
As the" thrifty gene theory" we postulated Chinese people may have different insulin gene espression cascade. So we study androgen receptor gene (AR gene). It is known PCOS patients have hyperandrogenemia from hyperexpression of androgen receptor binding cascade. And it was reported in Caucasian PCOS patients the longer CAG repeat in andogen receptor gene are preferentially metylated. And the shorter CAG repeat gene was preferentially activated and expressed and casued hyperandrogenemia. We would like to determine whether Chinese PCOS patients also had shorter CAG repeat androgen receptor gene preferentially activated and the longer CAG repeat androgen receptor gene is methylated. When compared with Caucasion, androgen receptor gene expressed differently in Chinese PCOS patients who have not the longer CAG repeat androgen receptor gene is methylated.
In conclusion, Chinese women with PCOS are at increased risk for insulin resistance

and glucose intolerance than controls. BMI failed to show significant impact on 2h glucose in our infertility patients. And before proceeding with IVF, preconception oral glucose tolerance testing is suggested, especially in patients with higher body mass index, to help identify groups at higher risk for preterm birth. Androgen receptor gene in Chinese PCOS patients expressed differently when compared with Caucasion. We stongly suggest that several risk factor clusters together in Chinese PCOS women and its contribution to the development of cardiovascular disease need more evidence to confirm in the future.