Cluster analysis of cardiovascular and metabolic risk factors in women of reproductive age

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Objective: To study the association between endocrine disturbances and metabolic complications in women seeking gynecologic care.
Design: Retrospective study, cluster analysis.
Setting: Outpatient clinic, university medical center.
Patient(s): 573 women, including 384 at low risk and 189 at high risk of cardiometabolic disease.
Intervention(s): None.
Main Outcome Measure(s): Cardiovascular and metabolic parameters and clinical and biochemical characteristics.
Result(s): Risk factors for metabolic disease are associated with a low age of menarche, high levels of high-sensitivity C-reactive protein and liver enzymes, and low levels of sex hormone-binding globulin. Overweight/obese status, polycystic ovary syndrome, oligo/amenorrhea, and hyperandrogenism were found to increase the risk of cardiometabolic disease. However, hyperprolactinemia and premature ovarian failure were not associated with the risk of cardiometabolic disease. In terms of androgens, the serum total testosterone level and free androgen index but not androstenedione or dehydroepiandrosterone sulfate (DHEAS) were associated with cardiometabolic risk.
Conclusion(s): Although polycystic ovary syndrome is associated with metabolic risk, obesity was the major determinant of cardiometabolic disturbances in reproductive-aged women. Hyperprolactinemia and premature ovarian failure were not associated with the risk of cardiovascular and metabolic diseases.
Clinical Trial Registration Number: NCT01826357. (Fertil Steril® 2014;101:1404–10. ©2014 by American Society for Reproductive Medicine.)
Key Words: Cardiovascular risk, cluster analysis, metabolic syndrome, PCOS

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A cluster of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus, which occur together more often than by chance, have become known as the metabolic syndrome (MetS) (1). The cardiovascular risk factors that comprise MetS have been recognized as a cluster since the 1920s (2). Although MetS and CVD are major causes of mortality for women of advanced age, the risks of MetS and CVD in reproductive-aged women are not well understood. Early detection of individuals at high risk for MetS by the use of accurate measures of insulin resistance (IR) could improve the detection and prevention of CVD and diabetes (3).

Recent studies have suggested that there are some clinically relevant differences between women and men in terms of the prevalence, presentation, management, and outcomes of the disease, but little is known about why CVD affects women and men differently (4). Over recent decades, mortality rates in men have steadily declined while those in women have remained stable. This knowledge gap may explain why cardiovascular health in women is not improving as fast as that of men (4). In particular, the risk of developing MetS and CVD for younger women has not been well studied.

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Although many aspects of CVD are similar in women and men, there is a growing body of evidence to support sex and gender dimorphism in the prevalence, presenting symptoms, management, and outcomes of CVD (4). For instance, Lee et al. (5) reported that women with diabetes have a significantly higher CVD mortality rate than men with diabetes. Women of reproductive age present with cyclic endocrine changes that might result in different MetS and CVD risk factors in comparison with men. Menstrual cycle irregularity may be a marker of metabolic abnormalities predisposing women to an increased risk for CVD (6). The most well-known correlation between metabolic syndrome and reproductive disorders is in women with polycystic ovary syndrome (PCOS), which is diagnosed by hyperandrogenism and chronic anovulation. Although studies of PCOS and metabolic complications have been widely reported, the understanding of the correlation between endocrine status and metabolic complications in reproductive-aged women remains limited and controversial (7–10).

Definitions of metabolic syndrome are usually problematic because they are based on arbitrary cutoff points for several quantitative variables, where each variable is related linearly to cardiovascular risk (11). Further, the risks of developing MetS and CVD vary depending on race and gender. To understand the risk factors of cardiovascular and metabolic disease in reproductive-aged women, the studied subjects should be specified. Cluster analysis is a statistical method based on algorithms that aims to minimize within-group variation and maximize between-group variation for the clustering variables (11). This technique is suitable for defining groups and reflecting the natural structure of data without relying on inappropriate arbitrary cutoffs (12). Cluster analysis can be used to identify groups of women sharing similar metabolic risk factor patterns. We conducted this retrospective study on reproductive-aged Taiwanese women, and we used cluster analysis to investigate the relationship between metabolic complications and biochemical/clinical characteristics of endocrinologic dysfunction in women of reproductive age.

MATERIALS AND METHODS

This study was approved by the institutional review board of Taipei Medical University, Wan Fang Hospital, Taipei, Taiwan, with the identifier Hsu2013-TMU-JIRB 201302002 and registered at ClinicalTrials.gov with the identifier NCT01826357. We retrospectively reviewed the medical records of female patients who visited our reproductive endocrinology clinic from January 1, 2009, to June 31, 2012.

Parameters of Cardiovascular Risk

Metabolic syndrome is a complex of interrelated risk factors for CVD and diabetes. These factors include dysglycemia, high blood pressure, elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels, and central adiposity (1). To evaluate the risk of MetS and CVD, the following 10 cardiometabolic parameters were used for initial cluster analysis in this study: systolic blood pressure, diastolic blood pressure, waist size, fasting insulin, fasting glucose, 2-hour glucose, total cholesterol, triglyceride, HDL, and low-density lipoprotein (LDL).

Study Data

Women who had a complete set of anthropometric measurements and clinical and biochemical data about endocrinologic and cardiovascular parameters were initially included. For comparison with the healthy volunteers, the chief complaints of the studied patients were menstrual irregularity, infertility, overweight status, acne/hirsutism, and other conditions (i.e., more than one complaint, transfer from other medical specialists, headache, abdomen pain, vaginal itching, etc.) (Supplemental Table 1). The patients' medical histories included a detailed menstrual and medical/surgical history, anthropometric measurements (weight, height, waist, and hip), and blood pressure.

The dates and assays performed for blood sampling have been previously described elsewhere (13). The following data were collected and calculated: [1] serum androgens, including total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), 17-α-OH progesterone, and free androgen index (FAI); [2] insulin sensitivity and glucose tolerance, including fasting insulin, fasting glucose, 2-hour glucose, and the homeostasis model assessment insulin resistance index (HOMA-IR); [3] lipid profiles, including total cholesterol, triglycerides, HDL, and LDL; [4] liver function and inflammatory markers, including glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and high sensitivity C-reactive protein (hs-CRP); and [5] sex hormone-binding globulin (SHBG), prolactin, and antimüllerian hormone (AMH).

The risks of MetS, impaired glucose tolerance, and diabetes were evaluated in every studied subject. The waist-to-hip ratio (WHR) was defined as waist circumference/hip circumference. Body mass index (BMI) was defined as the body weight in kilograms divided by the body height in meters squared (kg/m^2). Overweight/obese was defined as BMI ≥ 25 kg/m^2. All studied women received an ultrasonography examination. A vaginal ultrasound examination is preferred for young women without sexual experience, but we performed abdominal ultrasounds to detect polycystic ovaries.

Premature ovarian failure (POF) was defined as oligo/amenorrhea in women younger than 40 years with elevated serum FSH levels (FSH >16 mIU/mL). A diagnosis of POF was confirmed by serum examination of FSH 2 weeks later. Hyperprolactinemia was diagnosed when prolactin levels were above the upper limit of normal (24.20 ng/mL).

The following women were excluded from the study populations: [1] women who had been diagnosed with malignant tumors, Asherman syndrome, müllerian agenesis, or chromosomal anomalies; [2] women who had undergone menarche within the past 1 year or were older than 49 years; and [3] women who had received hormones and/or medicines for diabetes, hypertension, or dyslipidemia within the previous 3 months. A total of 713 women were included in the study for evaluation. To perform the cluster analysis, the above-mentioned 10 parameters were used to evaluate the risks of developing MetS and CVD (systolic pressure, diastolic pressure, waist size, fasting glucose, fasting insulin, 2-hour glucose, total cholesterol, triglyceride, HDL, and LDL).

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