Polycystic Ovary Syndrome and Its Association with Immune Reproductive Disorders: A Retrospective Study

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Background: Polycystic ovary syndrome (PCOS) is usually present with reproductive dysfunction. Ovarian function of women with polycystic ovary syndrome might be disturbed, with resultant abnormal folliculogenesis and steroidogenesis. Although it is difficult to define the exact pathogenesis of anovulation, multiple other possible abnormalities have been postulated as contributory factors in the reproductive failure.
Objective: The study aimed to determine the association of polycystic ovary syndrome with immune reproductive disorder.
Materials and Methods: The study was carried out in a private institution from October 2017 to November 2017. A total of 192 patients were included in the study with ages ranging from 19-40 years old. Review of clinical charts and laboratory results were the primary mode of data gathering. The primary outcome of the study was the presence of immune reproductive disorders among women with and without polycystic ovary syndrome. The Rotterdam criteria were used for the diagnosis of polycystic ovary syndrome and positive results of immunoassays for the five categories were used for the basis for diagnosis of the immune reproductive disorder.
Results: A total of 102 patients were included in the first group and 90 were included in the second group. Out of 102 in Group A, 66 (64.71%) tested positive for immune reproductive disorder. On the other hand, out of 90 patients in Group B, 59 (65.56%) tested positive for immune reproductive disorder. The computed relative risk is almost 1, which means that there is no difference in the risk of having immune reproductive disorder for patients with or without polycystic ovary syndrome.
Conclusion: Current evidence does not support a central role of autoimmunity in the pathogenesis of PCOS.

Keywords: immune reproductive disorder, polycystic ovary syndrome, recurrent pregnancy loss, Rotterdam criteria.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic pathology affecting nearly 5-10% of reproductive-age women.[1] It is associated with menstrual disturbances, hirsutism, obesity and anovulatory infertility. Initially recognized as an endocrine disorder of reproductive age women, PCOS has now been expanded from a disorder that presents at menarche and ends at menopause to a disorder that may be present from birth to senescence.

In the Philippine setting, PCOS is best diagnosed by utilizing the 2003 Rotterdam criteria.[1] Based on these criteria, the diagnosis of PCOS requires the presence of any two of three criteria, namely oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries on ultrasound. This classification will lead to 4 phenotypes of PCOS.

Patients with PCOS have an increased rate of pregnancy loss (up to 50%).[2,3] In a local study, the prevalence of pregnancy loss among 377 women with polycystic ovarian morphology was 40.23%.[4] They are more likely to have a miscarriage for reasons other than aneuploidy.[3] Several factors are involved in recurrent pregnancy loss in patients with PCOS including elevated serum levels of luteinizing hormone, obesity, insulin resistance and hyperandrogenemia.[2] Recently, evidence shows inflammatory and immunological mechanisms may be involved in the pathogenesis of PCOS. It has been found that PCOS is associated with low grade systemic inflammation as evidenced by elevated levels of multiple markers of inflammation such as C-reactive protein, IL-18, IL-6, monocyte chemo attractant protein-1 and white blood cell count as well as endothelial dysfunction and increased oxidative stress.[5] Low-grade inflammation mainly from the adipose tissue is now considered an additional mechanism and a modulator in the formation of the various PCOS phenotypes. The resulting hypoxia, caused by hypoperfusion of the adipocytes, leads to the release of inflammatory mediators and the recruitment of macrophages. The continuous release of inflammatory cytokines associated with long-term metabolic and cardiovascular complications contributes to the maintenance of the syndrome.[6]

Recurrent pregnancy loss is defined by the American Society of Reproductive Medicine as two or more consecutive pregnancy losses prior to 20 weeks AOG.[7] There are five categories of immune reproductive disorders that can cause infertility, in vitro fertilization failure and pregnancy loss, with category 1 being the least severe and category 5 the most severe. A woman may test positive for one or more categories.

Category 1: HLA (human leukocyte antigen) compatibility - the couple's tissues are too similar genetically.

Category 2: Problems with blood clotting. Phospholipid adhesion molecules create an autoantibody response.

Category 3: An autoimmune response occurs to components in the embryo.

Category 4: Autoimmune response to sperm antigen.

Category 5: Certain types of immune cells increase in number and activity, including natural killer (NK) cells, antibodies to hormones, and antibodies to neurotransmitters

Materials and Methods

Study Design

This is a cross-sectional analytic study design.

Inclusion Criteria

The population consists of patients seeking fertility consult. Then it was narrowed down to patients seeking fertility consult who were evaluated for immune reproductive disorders and this group was further divided into 2 groups:

Group A - patients with PCOS seeking fertility consult and the population was grouped into those who have tested positive for one or more categories of the immune reproductive disorder and those tested negative for all the categories of immune reproductive disorder;

Group B - patients without PCOS seeking fertility consult and this population was grouped into those who have tested positive for one or more categories of the immune reproductive disorder and those tested negative for all the categories of immune reproductive disorder.

Exclusion Criteria

Patients with comorbidities such as hypertension, thyroid disease, diabetes mellitus, cardiovascular disease, pulmonary disease, vascular disease, history of smoking or use of illicit drugs were excluded in this study.

Study Procedures

This is a retrospective cross sectional study of women who consulted with polycystic ovary syndrome (PCOS) and matched women without PCOS from January 2012 to December 2016.

The primary outcome was the presence of immune reproductive disorders among the women with and without PCOS. Review of clinical charts and laboratory results were the primary mode of data gathering.

The target population were women seeking fertility consult. The Rotterdam criteria were used for the diagnosis of PCOS. Positive results of immune assays for the five categories (CATEGORY I-V) were the basis for the diagnosis of the immune reproductive disorders.

Characteristics such as age, gravidity, parity, duration of infertility, presence of Rotterdam phenotypes (oligo/anovulation, hyperandrogenism /hyperandrogenemia, polycystic ovaries on ultrasound) and category of immune reproductive disorders were tabulated.

Sample Size

The calculated sample size was based on an expert´s opinion that 70% of patients with PCOS also have associated one or more categories of the immune reproductive disorders. At 95% confidence interval, 80% power, the computed sample size was 58 per group.

Planned Analysis

The statistical data were processed using SPSS software, version 22.0. The demographic data (such as age, bmi, gravidity and parity) were presented through frequency and percentage distribution, mean average and standard deviation.

A contingency table was used to compute for the prevalence rate of IRD in patients with PCOS and prevalence rate of IRD in patients without PCOS. After getting the prevalence rate in both groups, relative risk was used to assess if there is a significant difference between the 2 groups. Chi-square was used to test if the prevalence rates/ proportion of the groups are equal.

Ethical Considerations

All patients' information included in this study was held anonymous and confidential. Patients' names were not included in the study, instead the charts and records were marked with numbers for identification. The data obtained were used only for the purpose of research and ample measure was taken to protect personal data/information.

Statistical Analysis

The statistical data processing was done using SPSS software, version 22.0. The demographic data were presented through frequency and percentage distribution. The demographics of the groups were observed by computing the average age, BMI and their standard deviations. The gravidity was assessed by determining which has the most number of patients (mode). Other studies such as Treatment for PCOS, Category of IRD, percentage of patients who are G0 with IRD etc. were presented using descriptive statistics.

The study used a contingency table to compute for the prevalence rate of IRD for patients with PCOS and prevalence rate of IRD of patients without PCOS. After getting the prevalence rate in both groups, relative risk was used to assess any significant difference between the 2 groups. A relative risk of 1 means that the prevalence rates of both groups are the same. Chi-square was also used to test if the prevalence rates/proportions of the groups are equal.

Results

A total of 192 patients aged 19-40 years old were included in the study. They were categorized into two groups. The first group (Group A) included patients who fulfilled the Rotterdam criteria of polycystic ovary syndrome with patients 26 - 40 years old, with an average age of 33.67 and average BMI of 22.61. The second group (Group B) included patients without polycystic ovary syndrome with patients 26 - 40 years old, with an

average age of 33.74 and average BMI of 21.48. Both groups were categorized into those who tested positive for one or more categories of the immune reproductive disorder and those who tested negative for all the categories of immune reproductive disorder.

A total of 102 patients were included in the first group and 90 were included in the second group. Out of 102 in Group A, 66 (64.71%) tested positive for IRD. On the other hand, out of 90 patients in Group B, 59 (65.56%) tested positive for immune reproductive disorder. The computed relative risk is almost 1, which means that there is no difference in the risk of having immune reproductive disorder for patient with or without polycystic ovary syndrome (Table 1).

Gravidity is the number of times a reproductive age women became pregnant. In patients who were diagnosed with PCOS, 62 (60%) belong to G0 or those who never became pregnant. While those without PCOS, 35 (39%) and 34 (38%) belong to G1 and G2 or those who had 1 to 2 previous pregnancies (Table 2).

Among patients with PCOS, the most frequent IRD Category is Category V with 36.43% distribution, followed in decreasing order by Category I (30%), Category III (20%), and Category II (13.57%) (Table 3).

Out of the 65 patients who underwent IRD treatment, 15 (23%) successfully became pregnant. There is a higher chance of pregnancy for those patients who undergo IRD treatment with PCOS than without PCOS (Table 4).

PCOS is best diagnosed by utilizing the 2003 Rotterdam criteria. Based on these criteria, the diagnosis of PCOS requires the presence of any two of three criteria, namely oligo and or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries on ultrasound. Table 5 shows that 58% of patients with IRD and 55% of patients without IRD have oligoanovulation and polycystic ovaries. Almost 30% (30/102) of the patients have all the phenotypic criteria.

Discussion

A substantial proportion of miscarriages are caused by chromosomal, anatomical and endocrinological abnormalities or infections. Still 40% of fetal losses remain a consequence of unexplained etiology. Fetal placental tissues were believed to be immunologically foreign to the maternal host, due to the presence of paternally inherited gene products and tissue-specific differentiation antigens. Thus pregnancy loss could

Table 1. Relationship of PCOS to gravidity.

Category	G0	G1	G2	G3	G4	G5	Grand Total
With PCOS	62	25	10	4		1	102
Without PCOS		35	34	19	2		90
Grand Total	62	60	44	23	2	1	192

Table 2. Prevalence rate of immune reproductive disorder (IRD) in patients with polycystic ovary syndrome versus those without polycystic ovary syndrome.

	With IRD	Without IRD	Total
With PCOS	66	36	102
No PCOS	59	31	90
Total	125	67	192

Table 3. Category of IRD in patients with PCOS

IRD Category	Count	Distribution
I	42	30.00%
II	19	13.57%
III	28	20.00%
IV		0.00%
V	51	36.43%
Total	140	100.00%

Table 4. Percentage of pregnancy after IRD treatment.

	PCOS	Without PCOS	Total
Number of IRD Treatment	46	19	65
Pregnant after IRD Treatment	12	3	15
Percentage of Pregnancy	26.09%	15.79%	23.08%

Table 5. PCOS phenotypes in patients with positive and negative IRD.

Phenotype	With IRD	Without IRD	Total
Oligoanovulation & Polycystic Ovaries	41	21	62
Hyperandrogenism & Polycystic Ovaries	7	3	10
Oligoanovulation, Hyperandrogenism & Polycystic Ovaries	18	12	30
Total	66	36	102

be caused by impaired maternal immune tolerance to a semi-allogenic conceptus. Other factors involved humoral and cellular immune responses that may also influence human reproductive failure. Several studies show that patients with PCOS have a 30-50% higher risk of miscarriage.[5,6,8] The state of estrogen excess has been linked to different autoimmune diseases. Estrogens increase the secretion of IL-4 in Th2 lymphocytes, IL-1 in monocytes, IL-6 in T-lymphocytes and interferone-γ in Th1 cells. During normal ovulatory menstrual cycle, the follicular phase is characterized by elevation of IL-6 whereas its levels are decreased in the luteal phase which is also characterized by negative correlation with progesterone. The stimulatory effect of estrogens on the immune system could be inhibited by progesterone. Patients with PCOS present low level of progesterone due to oligo/anovulation therefore the immune system could be over-stimulated leading to production of autoantibodies in these patients. This indicates a degree of immune dysregulation in PCOS and supports the possible link of immune reproductive disorders with PCOS.

Some studies, show results contradicting the aforementioned theory. In a study by Ogasawara, et al, there was no relation between the diagnosis of PCOS, PCO morphology, elevated luteinizing hormone, free testosterone or obesity and subsequent miscarriage rate.[9] So far, only studies on autoimmune thyroiditis have shown a clear link to PCOS while studies on other systemic and organ specific autoimmune diseases have conflicting or inadequate data.

In the study, the presence of hyperandrogenism/ hyperandrogenemia was less frequently noted in PCOS patients with IRD. This is supported by the theory that high levels of androgens seem to have a protective role against the development of autoimmune disease and it is estrogen that is involved in the stimulation of the immune system.

Elevated natural killer cell activity or Category V IRD was also the most common category noted in PCOS patients included in the study. It has been demonstrated that excessive numbers of strongly cytotoxic cells during early pregnancy may result in reproductive failure and decreased numbers of cytotoxic cells during late pregnancy may be required for fetal maintenance. Elevated NK-cell activity, reduced coagulation factor XII, elevated serum complement 3 and 4 and elevated cervical IL-6 and IL-8 may be predictors for further miscarriages in patients at high risk, however, further studies are needed to support this theory.

Another consideration of the study is the presence of high number of infertility patients who tested positive for immune reproductive disorders. A total of 192 patients seeking fertility consult were included in the study. Among these patients, 125 (65%) tested positive for IRD. This now questions the need for immunologic screening in infertility patients even if they do not present with recurrent pregnancy loss. It should be noted that 60% of the study population were nulliparous. There are several theories showing association of infertility and autoimmune disorders. First, serum autoantibodies such as anti-phospholipid, anti-thyroid, or antinuclear antibodies may be directly associated with infertility, regardless of the presence of a clinically-overt autoimmune disease. Second, autoimmunity may affect all stages of fertility, via ovarian failure, testicular failure, implantation failure, and pregnancy loss. Third, infertility may also be secondary to vasculitis associated with other conditions such as systemic lupus erythematosus and diabetes mellitus. This area of concern should be further investigated.

The failure of establish an association between PCOS and IRD may indicate that other maternal risk factors such as obesity, thrombophilia and insulin resistance and not PCOS alone might be major contributing factors to recurrent pregnancy loss.

Conclusion and Recommendation

To this date, there are no studies comparing the association of polycystic ovary syndrome with the complete immune reproductive disorder categories. This study shows no association of polycystic ovary syndrome in patients diagnosed with immune reproductive disorder. For some patients, some form of immune dysregulation may be the cause of recurrent pregnancy loss but evidence is not enough to suggest routine screening of PCOS patients for immune reproductive disorders. Current evidence does not support a central role of autoimmunity in the pathogenesis of PCOS. Other studies involving autoimmune and inflammatory processes such as thyroiditis, insulin resistance and obesity can be undertaken to further understand the physiology of immune reproductive disorders.

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