Analysis of the Prescription Patterns for Drugs Used in the Treatment of Polycystic Ovary Syndrome and the Distribution of Comorbidities Among Patients in Taiwan

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a complex disorder characterized by significant heterogeneity. While it is primarily marked by hyperandrogenism and ovarian dysfunction, its definition remains a subject of debate. Metformin, a well-established insulin sensitizer with a glucose-lowering effect, has been widely used for managing individuals with type 2 diabetes mellitus. Given that many women with PCOS exhibit insulin resistance, metformin has been incorporated into clinical practice as a viable treatment option for these patients. Furthermore, metformin exerts effects beyond its insulin-sensitizing action, targeting other facets of the condition as well.

Methods: Data were obtained from Taiwan's NHI database, which was maintained by the National Health Research Institutes (NHRI) and overseen by the state-run Bureau of NHI for research purposes. Patients with concurrent diagnoses of PCOS (ICD-9-CM 256.4) were included in the analyses from 1999 to 2006.

Results: A total of 634 patients with PCOS received treatment at regular clinics. Among them, 537 patients (89.5%) were treated solely for symptomatic control and fertility management. Among these patients, those using metformin (71 patients, 11.2%) were fewer than those using Clomiphene (212 patients, 33.4%) or hormonal therapy (338 patients, 53.8%).

Conclusion: In this study, we found that most women with PCOS received symptomatic control and fertility management in Taiwan and the using with metformin is in small group. It seems that physicians of Taiwan still need to establish a consensus on the treatment with metformin and the treatment of long-term comorbidities in patients with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) stands as the most prevalent endocrine disorder globally, with a recent increase in prevalence estimated at approximately 15-30%[1]. Clinical presentations of PCOS encompass chronic anovulation, hyperandrogenism, and the presence of polycystic ovaries detected through ultrasonography[2,3]. The signs of chronic anovulation included oligomenorrhoea and amenorrhoea. Hyperandrogenism can manifest as a biochemical abnormality, clinical features, or a combination of both. Clinical manifestations may include female-pattern alopecia, hirsutism, frank virilization, and acne.

Insulin resistance (IR) is a frequent characteristic of PCOS, stemming in part from adipose tissue dysfunction, leading to compensatory hyperinsulinemia. While this hyperinsulinemia helps maintain normal glucose levels, it adversely impacts ovarian androgen production[3,4]. Besides, metabolic dysfunction, characterized by IR and compensatory hyperinsulinemia, is prevalent in the vast majority of individuals affected by this condition and significantly raises the risk of developing type 2 diabetes mellitus (T2D) or gestational diabetes[5].

There are many health issues of PCOS, such as reproductive, metabolic and psychological concern[2,6]. Patients with PCOS have increasing risk of obesity, impaired glucose tolerance, IR, dyslipidemia, T2D and obstructive sleep apnea[2,6]. Luqian Zhao mention PCOS is associated with increased coronary heart disease risk from a meta-analysis[7].

Treatments of PCOS include lifestyle interventions, hormonal therapy, anti-androgen therapy and metformin[6]. Lifestyle interventions such as exercise, diet and behavior modification are the first step to improve IR and metabolic risk[8,9]. Oral hormone contraceptive agents containing estrogen are the main method for managing hyperandrogenism[6]. If hirsutism persisted, spironolactone is suggested to add for androgen block[6]. Metformin can improve insulin sensitivity, ovulation, and possibly hyperandrogenism[6].

To our knowledge, there have been few studies addressing the medication regimen for PCOS. This study was carried out to evaluate the treatment in patients with PCOS over a 8-year period from 1999 to 2006 in Taiwan, by using data of ambulatory care claims from Taiwan's National Health Insurance (NHI) program.

Methods

Study design and data source

Data were obtained from Taiwan's NHI database, which was maintained by the National Health Research Institutes (NHRI) and overseen by the state-run Bureau of NHI for research purposes[10]. The NHI program in Taiwan was started in 1995 and covered 23 million beneficiaries (almost 99.5% of the population) by the end of 2009[11]. The NHI claim datasets provide Taiwan-based information on diseases and prescription details to researchers. With ethical approval from the NHRI, we used data from ambulatory care claims (1999 – 2006) for the current study. The dataset was a representative sample of the national outpatient insurance claims. The NHRI employed a systemic random sampling method retrieving 1 in 500 records of outpatient visits in the NHI program, together with the related details of medical orders for those patients. The Bureau performed periodic reviews on a random sample of every 50 – 100 claims in each contracted hospital and clinic for quality assurance, and false diagnostic reports triggered a considerable penalty. The dataset we used in this study included information on patients' age, gender, diagnostic codes and prescription details over a period of 96 months (January 1999 to December 2006). Each patient's personal identification number was replaced by a dummy number, and the same patient kept the same dummy number in the dataset. All patients had to be 15-50 years of age to be included in the study. To avoid duplicated information, the data from the same patient was only allowed to be sampled once in the dataset. If a patient was sampled more than one time during the 96-month period, only the outpatient data of the earliest date was counted, and the repeated

sampled data (about 0.5% of the total information volume) were excluded from the analyses. (Figure 1)

The clinical diagnoses of the patients were coded by using the International Classification of Disease, ninth revision (ICD-9-CM) post-1995. Patients with concurrent diagnoses of PCOS (ICD-9-CM 256.4) were included in the analyses. The patients were further subdivided into those with symptoms control and fertility management or only treatment with concomitant disease in the analyses. Drug prescriptions were coded by using the National Drug Codes in the NHI program. Drug prescriptions for symptoms control and fertility management included clomiphene, metformin and hormonal therapy. Treatment for concomitant disease included anti-hypertensive medication, hemostatic drugs, pain-killer, anti-infective medication, gastrointestinal drug, lipid-lowering drug and antidiabetic agents.

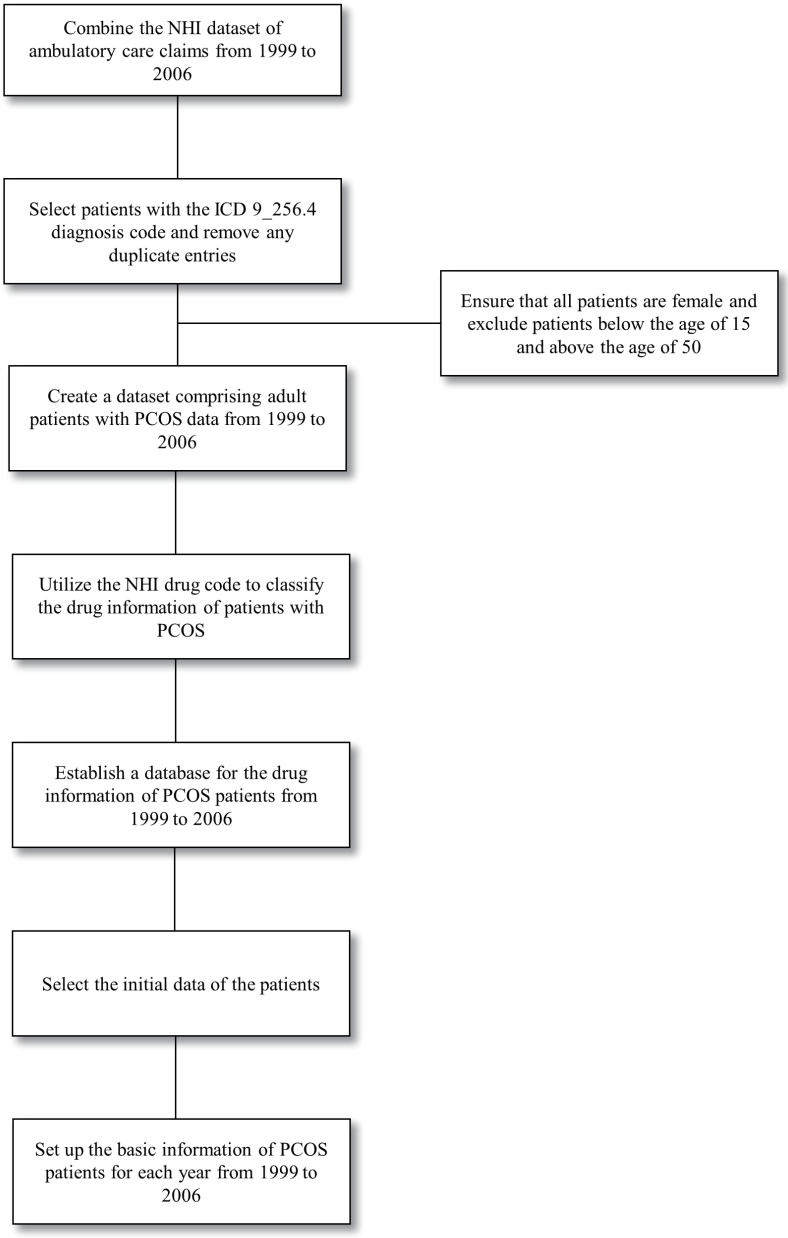

Figure 1. Study design and data source NHI, National Health Insurance; PCOS, Polycystic ovary syndrome; ICD, International Classification of Diseases

Statistical analysis

Data are expressed as mean (± standard deviation). Chi-square analyses were performed to compare the rate of different treatment with metformin. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, US). A p value of < 0.05 was considered statistically significant.

Results

We enrolled 822 patients diagnosed with PCOS between 1999 and 2006 (Table 1). Out of these, 634 patients received prescriptions and attended regular clinics. Among them, 537 patients (84.7%) focused on symptomatic management with fertility treatments, while 97 patients (15.3%) only received treatment for concurrent medical conditions. A subgroup of 36 patients (5.7%) exclusively used metformin, and 271 patients (42.7%) exclusively underwent hormonal therapy. In comparison, 146 patients (23%) used clomiphene alone, and 49 patients (7.7%) combined clomiphene with hormonal treatment. Additionally, 17 patients (2.7%) received both metformin and clomiphene treatment, and 18 patients received metformin in conjunction with hormonal therapy (Figure 2 and Table 2). The total number of patients using metformin (71 patients, 11.2%) was lower than those using clomiphene (212 patients, 33.4%, $p = 0.004$) and hormonal therapy (338 patients, 53.8%, $p < 0.001$). Furthermore, 97 patients received treatment for concurrent medical conditions, with only 6 women (0.9%) receiving anti-hypertensive medication. A mere 3 women (0.5%) used lipid-lowering drugs or antidiabetic agents (Table 2)

Discussion

The ages of diagnosis with PCOS in Taiwanese during 1999~2006 were about 27.7 – 30.2 year-old. Treatment for only symptomatic control is in larger group (84.7%). The group use hormonal therapy is more than metformin alone (53.3% and 11.2%, respectively). The most common treatment for concomitant disease were anti-infective medication. (6.3% respectively).

Women with PCOS may present with a variety of symptoms and the healthcare providers may treat them only for the presenting symptoms. The associated morbidities, including metabolic syndrome, increased risk for obesity, impaired glucose tolerance, diabetes and dyslipidemia may not be well-evaluated[12]. Dokras A and Witchel SF mentioned about the healthcare providers may miss an opportunity to identify PCOS associated health problems of women because there is no clear diagnosis for girls may transition into adulthood[12]. In our study, treatment for POCS related morbidities is lesser than symptomatic control group. It may due to the younger woman in our database and the associated health problems were in less evaluation.

The first-step for treatment of PCOS is lifestyle changes. Medical treatment is added if the effect of lifestyle modification is not enough. The medication include oral contraceptive pills, metformin, thiazolidinediones, and spironolactone[13] . Based on the 2023 International Evidence-Based Guidelines, lifestyle modification is deemed crucial for managing PCOS across the lifespan. For patients experiencing menstrual irregularities and hyperandrogenism, combined oral contraceptive

Table 1. Characteristics of patients with polycystic ovary syndrome in the study

Periods	1999	2000	2001	2002	2003	2004	2005	2006
Numbers of patients	33	57	76	93	118	140	144	161
Age(year)[a]	29.2±5.3	30.2±6.8	28.4±6.5	27.7±6.7	29.5±7.7	28.5±6.8	28.6±6.2	28.8±6.3

[a]Data are expressed as mean ±standard deviation or n (%)

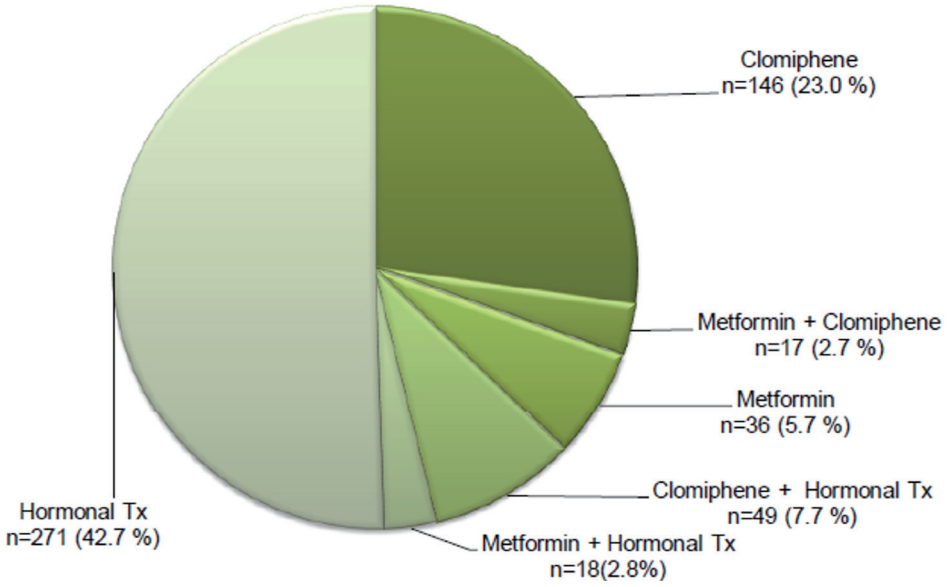

Figure 2. Symptomatic treatment of patients with polycystic ovary syndrome in the study Tx, Treatment

Table 2. Treatments of patients with polycystic ovary syndrome in the study

Treatment group (N=634)	Medication	Patient number (%)	p value
Symptomatic control and fertility management (N=537, 84.7%)	Patients with metformin use	71 (11.2%)	
	– Metformin alone	36 (5.7%)	
	– Metformin + Clomiphene[a]	17 (2.7%)	
	– Metformin + Hormonal treatment[b]	18 (2.8%)	
	Patients with clomiphene use	212 (33.4%)	0.004*
	– Clomiphene alone	146 (23.0%)	
	– Clomiphene + Hormonal treatment[c]	49 (7.7%)	
	– Metformin + Clomiphene[a]	17 (2.7%)	
	Patients with Hormonal therapy use	338 (53.3%)	<0.001*
	– Hormonal treatment alone	271 (42.7%)	
	– Metformin + Hormonal treatment[b]	18 (2.8%)	
	– Clomiphene + Hormonal treatment[c]	49(7.7%)	
Treatment with concomitant disease (N=97, 15.3%)	Anti-hypertensive medication	6 (0.9%)	
	Hemostatic drugs[#]	7 (1.1%)	
	Pain-killer	3 (0.5%)	
	Anti-infective medication	40 (6.3%)	
	Gastrointestinal drug	5 (0.8%)	
	Lipid-lowering drug and antidiabetic agents other than metformin	3 (0.5%)	
	Others	33 (5.2%)	

[a b c] = Each identical letter corresponds to the same set of data

* compared with the numbers of patients who used metformin, and a p-value less than 0.05 is statistically significant

[#] A hemostatic drug is defined as a substance that aids in the cessation of bleeding or hemorrhage

pills are still the preferred initial therapy. In cases of infertility, letrozole is considered the first-line therapy. Clomiphene combined with metformin, gonadotrophins, or ovarian surgery, is primarily reserved as a second-line treatment. Furthermore, metformin is primarily recommended for addressing metabolic concerns[14]. Current evidence also showed both lifestyle modification and metformin reduce fasting blood glucose and insulin levels in women with PCOS[8].

In adolescents aged 11 to 19 years with PCOS, both the oral contraceptive pill and metformin yielded comparable outcomes in terms of improving hirsutism scores, triglyceride levels, and high-density lipoprotein levels. Metformin, however, demonstrated a greater reduction in body mass index[15]. It proved to be superior in reducing the prevalence of dysglycemia and improving total cholesterol and low-density lipoprotein levels[15]. It is important to note that our study lacked data concerning the prevalence of lifestyle modifications, and we did not assess the effects of these medications

PCOS is characterized by its multifaceted features, which encompass ovulatory and menstrual dysfunction, hormonal imbalances, and insulin resistance. Conventional medications typically consist of single active ingredients targeting specific biological aspects. However, complementary and alternative medicine (CAM) may present an alternative approach to PCOS treatment. Previous studies have suggested that herbal remedies and acupuncture can offer varying degrees of relief from PCOS symptoms in affected women[16]. However, our study didn't assess the use of CAM within this population.

This study possesses several notable strengths, including a nationwide representative sample and a large sample size. However, it is important to acknowledge several factors that may have introduced bias into our results. First, our dataset lacked the capability to follow up with the same patients over time, which prevented us from gaining insights into their subsequent associated morbidities. Second, due to the cross-sectional nature of the data, we were unable to evaluate the effects of treatment. As a result, the impact of treatment on patients could not be assessed. Third, the data only included patients recruited from 1999 to 2006, so the results may not accurately represent the current situation.

In conclusion, our study reveals that the majority of women diagnosed with PCOS in Taiwan predominantly receive symptomatic control and fertility management through hormonal therapy, with metformin usage being relatively limited. Only 11.2% of patients opt for metformin treatment. Our findings suggest that healthcare providers should consider assessing comorbidities when diagnosing PCOS. It appears that, in Taiwan, doctors often view metformin treatment for PCOS patients as an adjuvant therapy rather than a primary medication. Given the significance of IR in PCOS, it is apparent that physicians in Taiwan may benefit from establishing a consensus regarding the use of metformin and the long-term management of comorbidities in PCOS patients.

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