

Drug Use Evaluation in Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovary syndrome also known as Stein- Lethal Syndrome is one of the most common endocrine disorder in women of reproductive age, in which level of sex hormones, oestrogen and progesterone are out of balance. Drug use evaluation has been helpful in determining the long-term evaluation of medication. Performing DUE in PCOS may integrate the best available evidence with clinical expertise and patient preference to provide the health professional with guidance on timely diagnosis, accurate assessment and optimal management of women in such complications.

Objective: To evaluate the drugs prescribed for polycystic ovary syndrome by reviewing, correlating and performing DUE thereby developing criteria and standard which describe optimal drug use.

Design: A prospective observational study was conducted over 6 months period (from October 2015 - March 2016) at SRM Medical College Hospital and Research Centre in 100 patients who had been chiefly diagnosed with PCOS condition.

Results: From the examined data it was determined that the effectiveness of drug therapy was more inclined in case of combination therapy compared to monotherapy.

Conclusion: Therefore, the results observed from the present study, it has been concluded that regularly prescribed first-line treatment of metformin/clomiphene citrate that is given in monotherapy has a long-term repeated cycle treatment.

Over an unsuccessful outcome, second-line treatment of combination therapy is preferred which improves some of the clinical features, biochemical makers and hormonal levels, hence improvement in the condition.

Metformin is one form of treatment that has been determined to be often used in combination with other drugs and has shown a better therapeutic effect in a short duration of time with less frequency compared to monotherapy form of prescription.

Keywords: *Drug Use Evaluation; Polycystic Ovary Syndrome; Therapeutic Outcome; Combination Therapy*

Abbreviations

PCOS: Polycystic Ovary Syndrome; DUE: Drug Use Evaluation

Introduction

Polycystic ovary syndrome also known as Stein-Leventhal syndrome is one of the most common endocrine disorder in women of reproductive age, in which levels of sex hormones, oestrogen and progesterone are out of balance. The prevalence of PCOS in women of reproductive age with a prevalence of approximately 5 - 10% worldwide [1].

Women with PCOS can present with a range of features including psychological (poor self-esteem, anxiety, depression), reproductive (menstrual irregularity, hirsutism, infertility and pregnancy complication) and metabolic features (insulin resistance, metabolic syndrome, pre-diabetes, type 2 DM and cardiovascular disease).

Not all women demonstrate all symptoms and there is no considered heterogeneity. The presentation can also vary across the life cycle. PCOS is a chronic condition manifestation that begins most commonly in the adolescence with menstrual irregularity and hyperandrogenism with transition overtime problems including infertility and metabolic complications [2-5].

Certain lifestyle changes such as diet and exercise are considered as first-line treatment for women with PCOS. Pharmacologic treatment is advised for conditions such as anovulation, hirsutism and menstrual irregularities. Medication for such conditions is given either in the form of monotherapy or combination therapy. Such treatment through drug therapy has brought about a better improvement in the condition [6].

Pathophysiology

The pathophysiology of the disorder is still fully not understood, which is the most common endocrinopathy of women in the child-bearing years. The heterogeneity of PCOS may very well reflect multiple pathophysiologic mechanisms, and the disorder itself can be initiated at any one for many entry points. Although the fundamental pathophysiologic defect in PCOS is unknown, these women have several interrelated characteristics, including insulin resistance, hyperandrogenism and altered gonadotrophin dynamics [7].

Based on the current understanding of PCOS, the underlying pathogenic mechanisms can be categorized as follows:

1. Insulin resistance and hyperinsulinemia
2. Deception of the hypothalamic pituitary- gonadal axis
3. Dysregulation of ovarian steroidogenesis
4. Abnormalities of adrenal steroidogenesis
5. Genetic factor

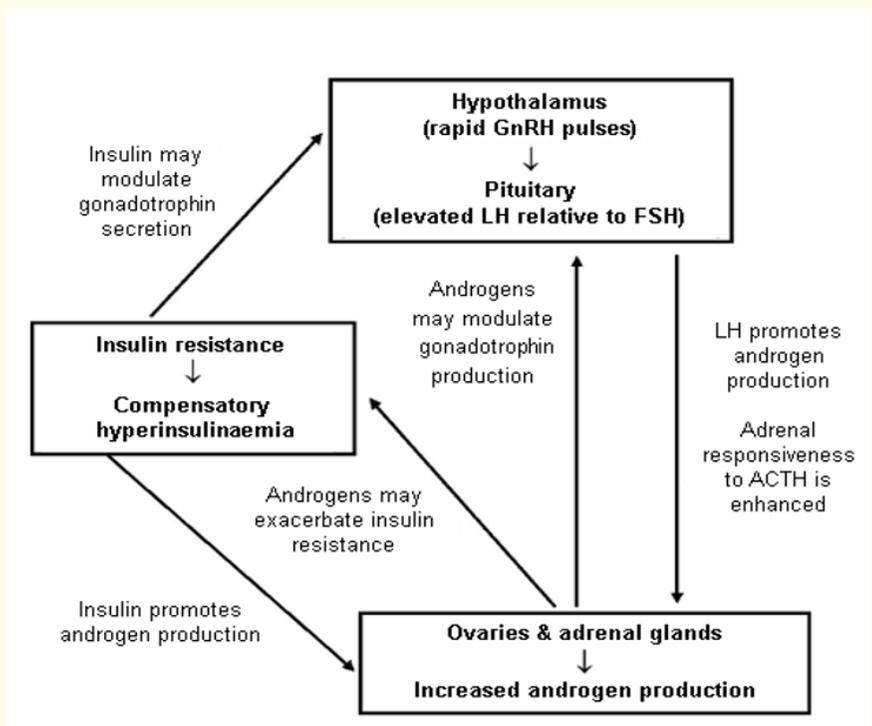


Figure A

Diagnosis of PCOS

A diagnosis of polycystic ovary syndrome can be made when at least two out of three of the following criteria are met:

1. The ovaries are 'polycystic' because:
 - 12 or more follicles are visible on one ovary, or
 - The size of one or both ovaries is increased.
2. There are:
 - High levels of 'male' hormones (androgens) in the blood (hyperandrogenism)
 - Symptoms suggesting an excess of androgens such as:
 - Excess facial or body hair growth
 - Scalp hair loss
 - Acne
3. There is menstrual dysfunction such as:
 - Lack of periods or menses (menstrual flow)
 - Menstrual irregularity
 - Lack of ovulation (where an egg is released).

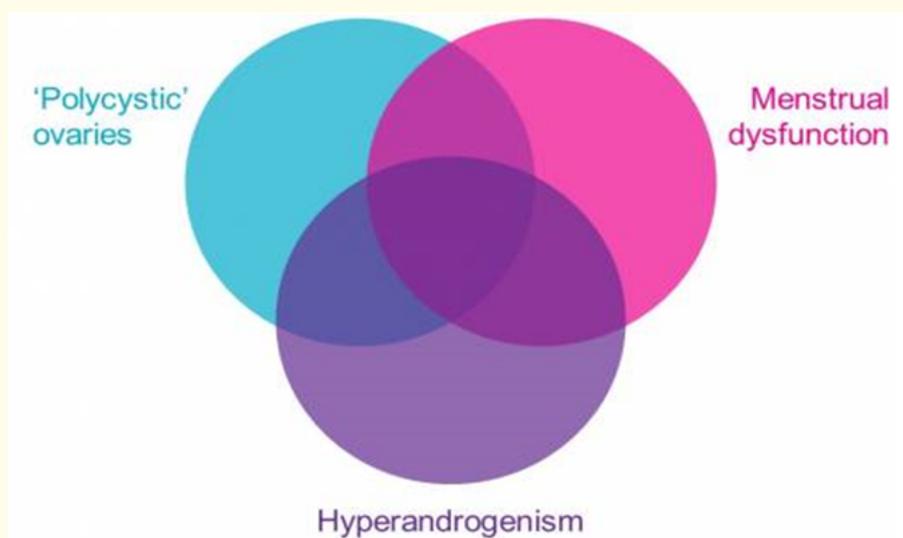


Figure B

With these criteria, a woman can be diagnosed with PCOS even if she has regular periods or normal androgen levels. This means women with PCOS can experience very different types of symptoms.

To make a correct diagnosis of PCOS, several other conditions that could cause similar symptoms of menstrual dysfunction to need to be ruled out [8,9].

In 2003, the Rotterdam European society of medicine (ESHRE/ASRM) sponsored PCOS consensus workshop group proposed that the diagnosis include clinical/ biochemical hyperandrogenism, and PCO on ultrasound, other aetiologies must be excluded. By adding of PCO criteria, the Rotterdam definition extended the diagnosis of PCOS to women with oligo-ovulation and PCOS (non-hyperandrogenic), as well as to women with hyperandrogenism and PCOS (ovulatory) [10].

Most recently, in 2009, the Androgen Excess and PCOS (AE-PCOS) society published a task force report emphasizing that PCOS is primary, hyperandrogenism (hirsutism) and ovarian dysfunction (oligo-anovulation/ PCO) thereby encompassing the Rotterdam ultrasound criteria but requiring hyperandrogenism for the diagnosis. None of the above groups has proposed different criteria for the diagnosis of PCOS in the adolescent state [11].

Definition of drug use evaluation

Drug use evaluation or drug utilization is defined as the “the prescribing, dispensing, administering, and ingesting of drugs”. The World Health Organization (WHO) expands on this definition by including outcome variables in their definition. Drug utilization is defined by the WHO as the “marketing, distribution, prescription, and use of drugs in society, with special emphasis on the result of medical, social, and economic consequences.

A drug utilization study is, therefore, a study designed to describe-quantitatively and the population of users of a given drug (or class of drugs) and/or the conditions of use (for example, indications, duration of treatment, dosage, previous or associated treatments and compliance) [12].

Types of drug use evaluation

Three broad categories of DUE are recognised, namely: The retrospective study, concurrent reviews and prospective reviews.

Retrospective studies

A retrospective drug use evaluation is an approved, systemic process that captures, reviews, analyses, and interprets aggregate medication use data within the specific health care environments. Data are archival in nature, in other words, collected and analysed after the events of major interest (the prescription, dispensing and the use of drugs) have occurred. The specific health care environment influences retrospective drug utilization because the quality and quantity of the data determine the scope, nature, and application of the review. These studies have little impact on immediate patient care but rather to serve to identify trends in prescribing practices that may lead to interventions aimed at enhancing prescribing behaviour. Their potential for preventing problems is limited, because the actual review may not take place for weeks after an error has been made or an inappropriate therapy has been administered. Retrospective studies are inexpensive, can be conducted rapidly and have easily accessible data.

Concurrent reviews

Concurrent reviews are conducted simultaneously with the dispensing process. If a potential problem is discovered, the dispensing function stops until authorization is received to continue as before or to initiate a modification or dosage correction. Concurrent reviews thus prevent therapeutic misadventures. They are more expensive and time-consuming than retrospective studies but have the potential for a much greater pay-off in preventing problems. The concurrent review requires a computer system or a well-organised drug profile system.

Prospective reviews

A prospective review is the option closest to the ideal and is more comprehensive than a concurrent review. Use of prospective review, based upon a complete drug and medical history obtained from an interview and from historical records, permits the practitioner to evaluate the patient’s pre-existing therapy on a retrospective basis, and then to prevent interactions by disallowing certain drugs for a patient based on a pre-existing review and by protocols already developed.

Retrospective and prospective DUE are not necessarily mutually exclusive. Their integration has the potential for the promotion of optimal prescribing practices. Retrospective DUE can detect new relationships and problems among modifications and disease. This information can then be programmed into a prospective DUE system to target patients who are at risk before drugs are dispensed.

Necessity of drug use evaluation

The principal objective of DUE is to facilitate rational drug use of drugs in populations. For the individual patient rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and an affordable price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate discussion on rational drug use and to suggest measures to change [9].

The role of clinical pharmacist in DUE

The role of the clinical pharmacist is to maximize the clinical effects of medicines by ensuring the selection of a most effective drug for each patient, minimizing adverse drug events by monitoring the drug therapy course of a patient and improving the patient's adherence with drugs. Clinical pharmacists also contribute to minimizing the cost of drug therapy and health care by providing cost-effective alternatives.

Clinical pharmacists ensure the correct use of drugs at three levels:

1. Before the drug is prescribed
2. During the time of drug prescription, and
3. After the drug is prescribed.

The role of the clinical pharmacist prior to the prescription of a drug can be explained in the context of conducting clinical trials and providing drug information. During the prescription stage, the clinical pharmacist detects and prevents drug interactions, adverse drug reactions and medication errors. The clinical pharmacist pays special attention to the dosage of drugs that require serum drug concentration monitoring. After the drug is prescribed, the clinical pharmacist must communicate with the patient. By conducting patient counselling, the clinical pharmacist can improve a patient's adherence with the drugs, monitor treatment response and improves the patient's awareness of their drugs. The clinical pharmacist also conducts outcomes research to evaluate the effectiveness of alternative drug therapy.

Purpose of DUE in PCOS

There is no consensus among different medical specialities as to the optimal management of PCOS. Diagnosis and treatment of PCOS can be therefore differ depending upon the health professionals consulted.

There are limited/no clinical data available for assessment of DUE in PCOS, rather PCOS is sometimes mentioned within the information given for the management of obesity, DM2.

The purpose is to integrate the best available evidence with clinical expertise and consumer preference to provide health professionals, consumer and policymakers with guidance on timely diagnosis, accurate assessment and optimal management of women with PCOS and to promote consistency of care and prevention of complication in tertiary care and speciality settings.

This is designed to:

- Review drug use and prescribing pattern.
- Provide feedback of results to clinicians.
- Develop criteria and standards which describe optimal drug use.
- Promote appropriate drug use through education and other interventions.
- Observe the pattern of drug use with current recommendations or guidelines for the treatment of the problems.

- Provide feedback on drug utilization data to prescribers.
- Relate the number of cases of adverse effects to the number of patients exposed certain conditions or to a special dose level, the information on the proper use of the drug can be improved such as indications, appropriate dose etc. So that withdrawal of the drug can be avoided.
- Evaluate drug use at the population level, according to age, sex, social class etc.
- Include a concept of appropriateness that is assessed relative to the indication for the treatment, thus they document the extent of inappropriate prescribing of the drugs and also the associated adverse, clinical, ecological and economic consequences.

Methodology:

Study design: Prospective observational study.

Study site: SRM Medical College Hospital and Research Centre.

Department: Gynaecology and Obstetrics (Infertility).

Study period: 6 months. October 2015 to March 2016.

Sample size: 100 patients.

Materials

- Patient's data entry format
- WHO guidelines
- Hospital formulary
- Access to drug information sources.

Inclusion criteria:

- Patients diagnosed with PCOS (age between 18 - 35 years).

Exclusion criteria

- Women above 35 years of age
- Patients with uterine fibroid
- Patients having endometrial cysts
- Adrenal/ ovarian tumours
- Acromegaly
- Patients with Cushing's syndrome.

Data collection

- A target of 100 patients having PCOS condition is selected and enrolled for the study.
- They will be analysed with necessary information regarding their complication and will be collected in a designed Performa.
- All these patients will be followed up for three months.

Data analysis

- The data gathered will be indexed by different parameters like age, sex, diagnosis, number of drugs, formulations prescribed.
- The deductive method will be carried out according to the study.

Results

Demographic results

Age categorization

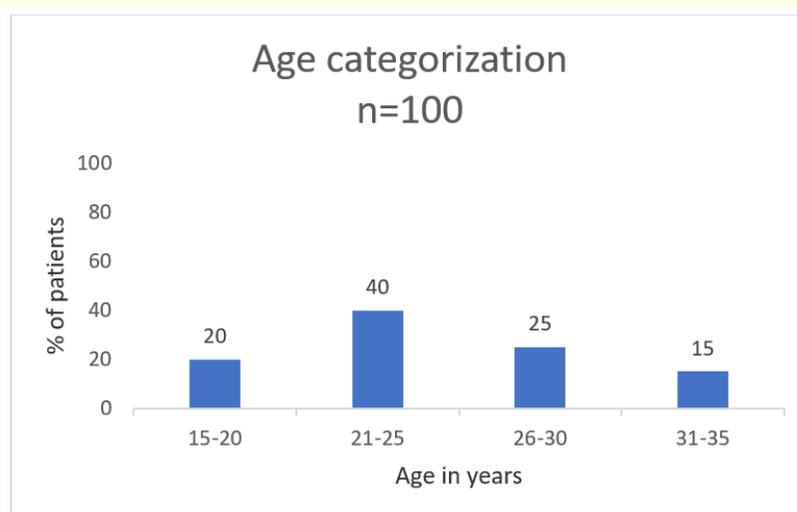


Figure 1: The graph represents age categorization in women with PCOS. Percentage of patients is given in y-axis (n = 100) and x-axis, age (years) = 15 - 35.

From the above figure, we could conclude that 40% of the patients affected by PCOS are under the age group of 15 - 35 when compared to the other age group.

BMI categorization

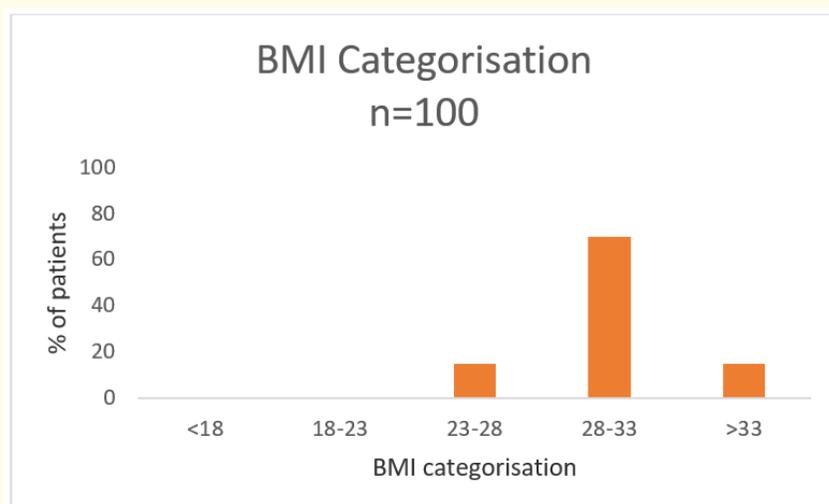


Figure 2: The graph represents the BMI categorization in subjects with PCOS. Percentage of patients is given in y-axis n = 10 and in x-axis BMI (kg/m²) = 18-35[1].

[1]: Normal BMI for the Asian population was obtained from NICE guideline(2014) in which the categories mentioned for Asians are: less than 18.5 kg/m² (underweight); 18.5 - 23 kg/m² (normal); 23 - 27.5 kg/m² (overweight) and 27.5 kg/m² or higher (obesity).

From the above data, it has been concluded that the patients with PCOS where 70% were classified in the obese category, so this can be considered as an important factor to identify PCOS condition in patients.

A literature review over obesity and PCOS (2010) had determined the same stating that, obesity is a common finding in PCOS and aggravates reproductive and metabolic features.

Categorization by Clinical presentation

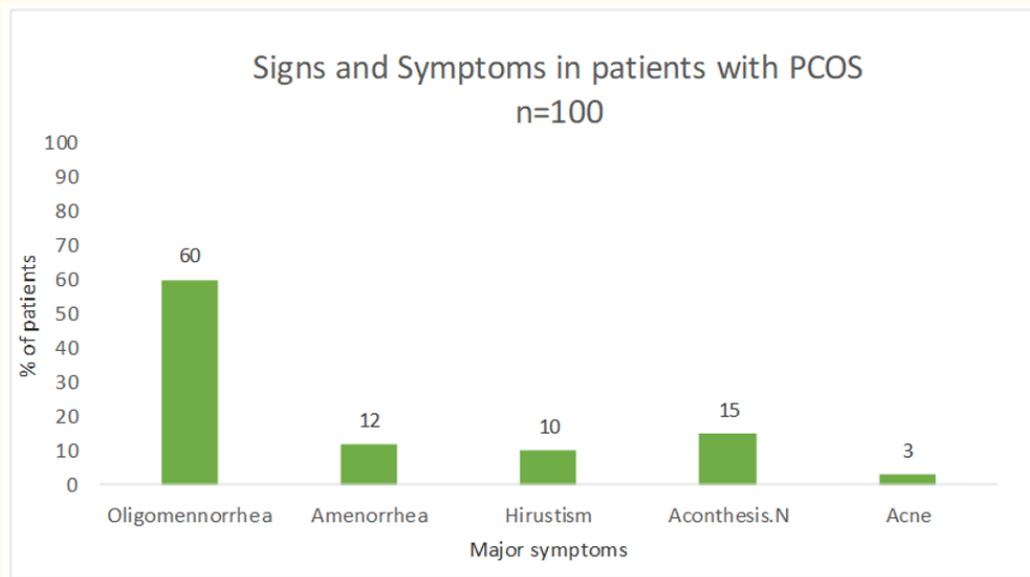


Figure 3: The histogram represents the categorization of clinical presentation in women having PCOS. Percentage of patients is given in y-axis and in x-axis common signs and symptoms in PCOS condition.

From the above chart, it was concluded that patients diagnosed with PCOS 60% were suffering from the irregular menstrual cycle as a major complication, compared to other signs and symptoms.

A review article from Androgen Excess and PCOS Society (2012) had made the same conclusion that one of the hallmark signs of PCOS, is irregular or even absent periods. Women with PCOS commonly have periods that are much further apart than the standard 28 days, and it is not uncommon for affected women to go several months between menstrual periods, or even have no periods at all.

Treatment for PCOS

The above chart given demonstrates the drug that was prescribed to the patients diagnosed with PCOS. Treatment options varied depending on the patient’s desire for contraception. Lifestyle modification is a central part of treatment for all manifestations of polycystic ovary syndrome.

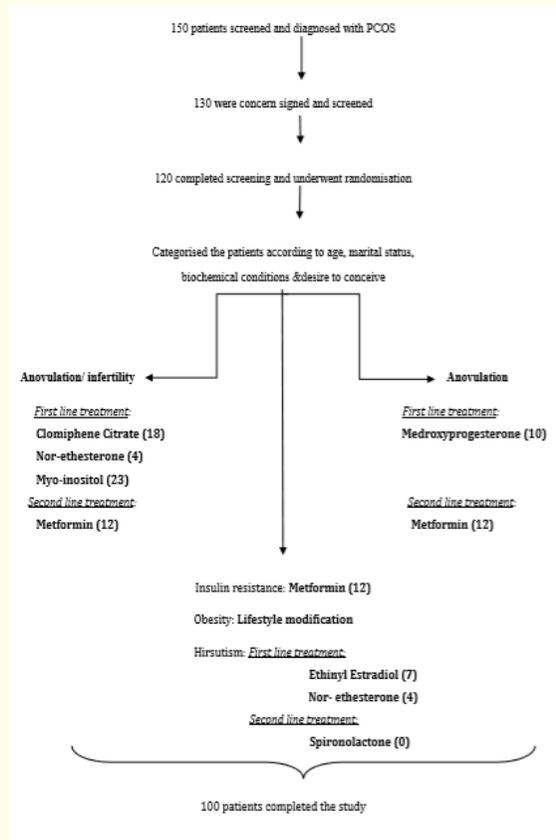


Figure 4: The flow chart represents the medication management that was done in women having PCOS.

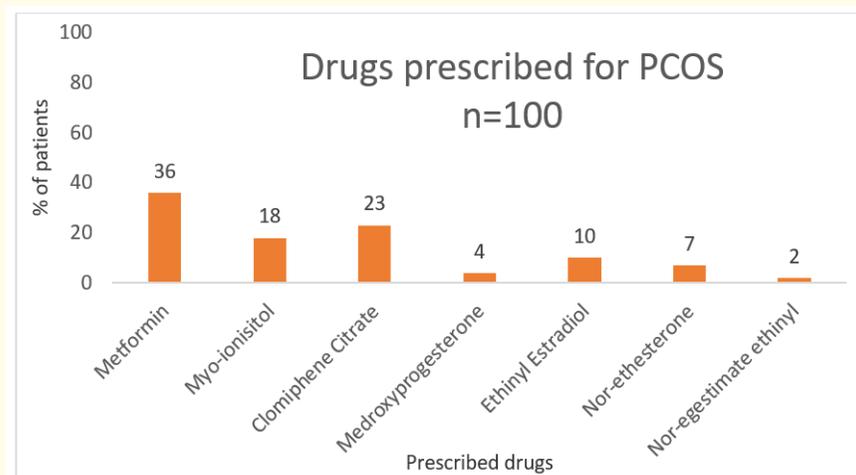


Figure 5: The given chart represents the drugs prescribed during treatment in women having PCOS.

Management of drug therapy for PCOS

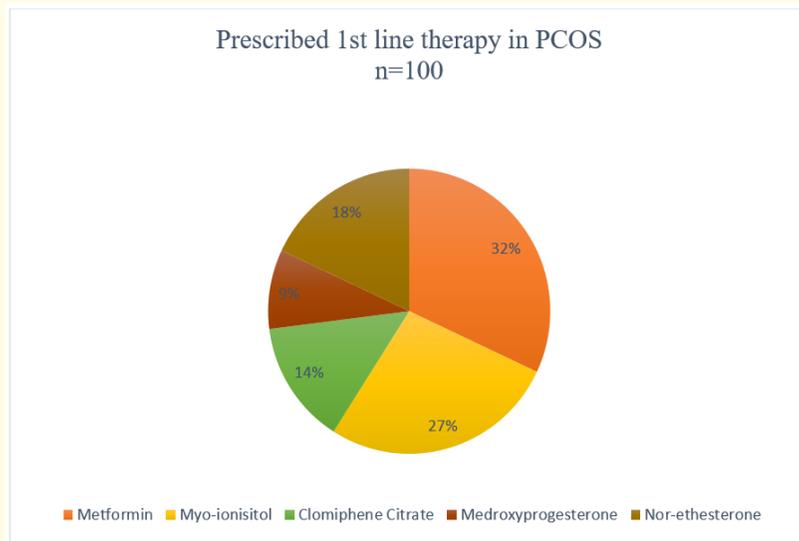


Figure 6: The Pi chart represents the frequency of drug prescribed to the patients with PCOS condition.

The above chart represents the medications prescribed which were individualized based on the patient’s clinical presentation and marital status, following with the condition of infertility or anovulation nature.

The effectiveness of drug therapy for PCOS

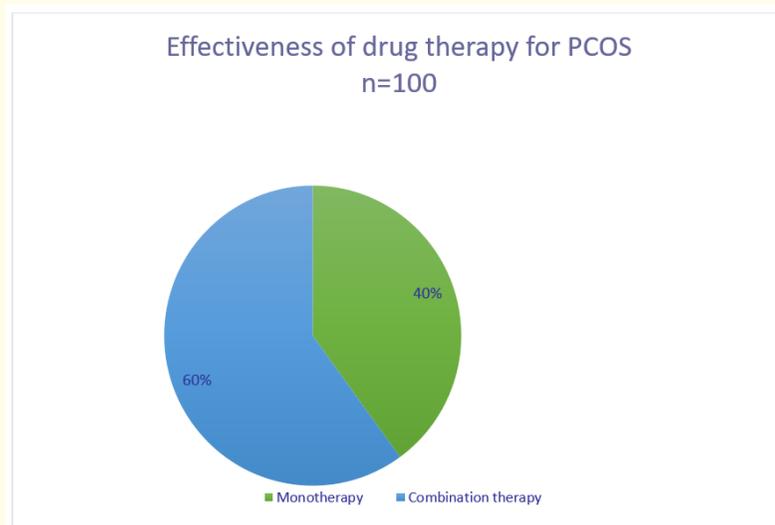


Figure 7: The Pi chart represents the effectiveness of the drug prescribed to the patients with PCOS condition.

The above chart represents the follow up done every 8 - 10 weeks for ≥ 6 months which was scheduled with interval history, review of menstrual status, assessment of drug-related side effects, brief physical examination and determination of their therapeutic effect, which showed that combination therapy was more effective than monotherapy in the patients.

The therapeutic outcome of drug therapy for PCOS

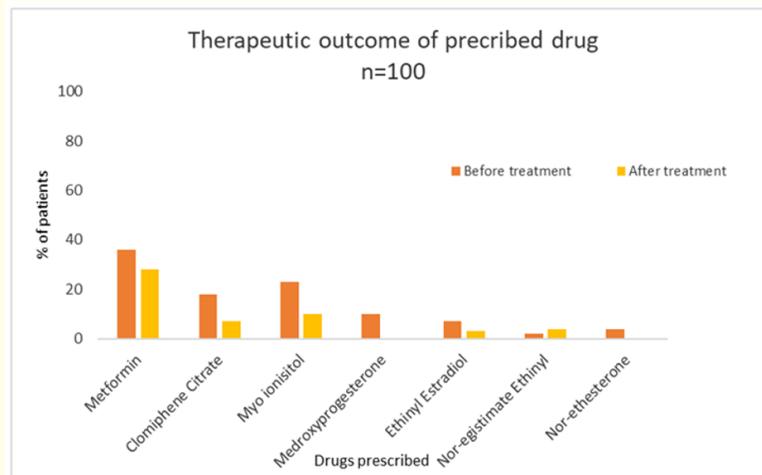


Figure 8: The graphical representation of the drug prescribed to the patients with PCOS condition.

The above chart represents the significant therapeutic outcome of the condition before and after the prescription of the drug through mono/combination treatment. However, metformin as monotherapy showed repeated cycles of long-term treatment in patients.

Discussion

In PCOS insulin resistance, disrupted folliculogenesis and hyperandrogenemia are distinct manifestations and are somehow correlated to each other and this condition increases the risk leading to long-term complications. The study has been conducted to evaluate the therapeutic effect of the drugs that are prescribed for PCOS condition on clinical, hormonal and fertility aspects.

The results determined below are for 100 patients’ data that were collected from the Department of Gynaecology and Obstetrics at SRM Medical College and Research Centre, Kattankulatur, Tamil Nadu, India.

The demographic profile in this study determines the age categorisation of the female patients affected by Polycystic Ovarian Syndrome that showed 33.8% of the subjects were ranging between 21 - 25 years of age group. Whereas in the study conducted by Lergo RS, *et al.* (2007), they have mentioned that patients affected by PCOS are from 25 - 30 years of age group.

In this current study, it has been observed that there was a significant decrease in weight gain and BMI after intervention through various combination treatments. Lyndal R, *et al.* (2016), have concluded the same.

In the clinical evaluation that was conducted for the drugs that are suggested for PCOS condition, the drugs have been prescribed in the treatment and analysed for which the reports have been discussed below.

As a first line treatment, metformin was predominantly prescribed as a single drug therapy, which resulted in repeated long-term cycle treatment in the patients.

Whereas there was a better positive incline in the combination therapy showing more therapeutic effect and a short cycle outcome in patients who had a will for conception. There had been a result of 42.4% of positivity in combination treatment followed by myoinositol with clomiphene citrate, and 31.2% for metformin with clomiphene citrate. Whereas a study conducted by Murizah Mohd Zain., *et al.* (2009) they have concluded by briefing that Clomiphene Citrate is superior to metformin in inducing ovulation in anovulatory women with PCOS. Addition of Metformin to Clomiphene Citrate does not significantly increase the ovulation, although there was a slight increase in the parameters when compared to the clomiphene Citrate or Metformin only treatment.

Considering the medications that were prescribed based on the patient's clinical data, marital status and condition of infertility or annovulation nature.

Medroxyprogesterone (18%) and Norethisterone (9%) was prescribed to the patients for the regulation of ovulation to the patients who were not desired to conceive.

Norgestimate Ethinyl was prescribed for patients affected by hyperandrogenism due to PCOS. This was in accordance with the study that was carried out by Johanna S Archer, *et al.* (2004), which subjects the same. Since the number of studies was limited for several drugs, the available evidence suggests that combination drug show more therapeutic effect compared to monotherapy resulting in a better therapeutic effect over a short period of treatment.

Conclusion

Medical treatment for PCOS is usually aimed at improving the clinical, endocrine and metabolic effects of this disease. The present study over drug use evaluation in polycystic ovary syndrome that was conducted in SRM Medical Hospital College and Research Centre in Kattankulathur, Tamil Nadu, India acts as an essential part of pharmacoepidemiology and it describes the extent nature and determinants of drug exposure.

Patients with a medical history of diabetes mellitus are prone to develop PCOS. Overweight and obese women are at higher risk of developing PCOS.

In this study out of 100 patient's data collected, it was determined that regularly prescribed first-line treatment was found to be metformin.

Over second-line therapy, combination treatment is preferred by prescribing Metformin with Clomiphene Citrate and Myoinositol with Clomiphene Citrate.

For the patients who do not desire to conceive they are prescribed with a mono treatment of Medroxyprogesterone/Ethinyl Estradiol.

Where excess androgenism is noticed Norgestimate Ethinyl is prescribed for the patients.

A combination of hormonal contraceptives, progestins, insulin-sensitizing agents and statins is effective and has metabolic and endocrine benefits.

Therefore, the results observed from the present study it has been concluded that combination treatment improves some of the clinical features, biochemical markers of insulin resistance and hormonal levels and hence long-term health status of women with PCOS. Metformin is one form of treatment that has been determined to often be used in combination with other drugs, which provide a better therapeutic effect in short duration of time with less frequency compared to monotherapy form of treatment.

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