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# Metabolic complications associated with oral contraceptive mode of treatment in women with polycystic ovary syndrome

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## ABSTRACT

*Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder of reproductive aged women. It is characterized by menstrual irregularity, hyperandrogenism and polycystic ovaries. Clinical features of hyperandrogenism include acne, alopecia and hirsutism. Currently various approaches like oral contraceptive pills (OCPs), insulin sensitizers, anti androgens etc are in use to treat PCOS. OCPs which are considered as the first line of treatment in women with PCOS is still a matter of debate regarding its effect on the metabolic aspect. The present study aimed to assess the effect of OCP's mode of treatment on the metabolic status of women with PCOS by evaluating anthropometric, biochemical, hormonal & insulin parameters. The present study regarding metabolic assessment clearly gives an indication regarding the safety use of OCPs mode of treatment in women with PCOS. Statistically significant decreased levels of hormonal profile (LH, FSH and testosterone) and FG-score were found in OCP treated PCOS group as compared to drug naive PCOS group, indicating efficacy of OCP treatment. However, OCP treated PCOS subjects show rise in various parameters like weight, waist-hip ratio, BMI and basic biochemical parameters. Moreover, statistically significant increase was found in fasting insulin level and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) with significant reduction in QUICKI (Quantitative Sensitivity Insulin Check Index) in OCP treated PCOS group as compared to drug naive PCOS group. Our finding suggests that although OCPs help in regularizing menstrual cycles and reduces the various clinical features associated with hyperandrogenism by improving hormonal levels, it increases the risk of various metabolic disorders like Insulin resistance, Type2DiabetesMellitus(T2DM) and dyslipidemia etc.*

***Keywords:*** *Insulin Resistance, Metabolic Syndrome, Oral Contraceptive Pills, Polycystic Ovary Syndrome.*

## I. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a most common endocrine and reproductive disorder found in women of reproductive age. Its prevalence has been found to be 6-10 % in the female population [1].PCOS is characterized by the presence of three main phenotypic features like hyperandrogenism, ovulatory dysfunctions and polycystic ovaries on ultrasonography (USG).The most common phenotype seen among PCOS women is anovulation and

upto 95% of women with PCOS experiences some type of anovulation [2,3]. Anovulation may be displayed as oligomenorrhea (< 8 menstrual periods in one year) or amenorrhea (absence of menstrual periods > 3months) [4]. Hyperandrogenism is one of the persistent phenotype feature of PCOS. It can be assessed either clinically or biochemically. Clinical manifestation of hyperandrogenism includes hirsutism, acne and alopecia. Biochemical hyperandrogenism can be assessed by measuring circulating androgen level. Almost 60% of women with PCOS are known to experience hyperandrogenism [5]. One of the diagnostic features is presence of polycystic ovaries on USG. Ultrasonographic description for establishment of PCOS must fulfill the criteria like the presence of 12 or more follicles in each ovary measuring 2-9mm in diameter, and/or increased ovarian volume (>10ml)[6]. There are various diagnostic criteria regarding PCOS which are in use like National Institute of Health (NIH), Rotterdam and Androgen Excess Society (AES). Rotterdam criteria, is considered to be more inclusive than the other two criteria, of NIH and AES. Rotterdam criteria, involves presence of two out of three diagnostic features required to establish PCOS.

It is hypothesized that the majority of women with PCOS have a genetic predisposition exacerbated by adverse lifestyle and obesity, causing IR (insulin resistance). IR is a condition where inspite of having normal insulin concentrations in the body, it does not produce normal insulin response in various target tissues. IR results the impaired stimulation of glycogen formation in the skeletal muscles, liver, kidney and adipose tissues and is further exacerbated by obesity [7,8]. As a result, IR causes compensatory hyperinsulinemia which further contributes to hyperandrogenism and gonadotropin aberrations. High insulin level causes LH stimulation of the theca cells of the ovaries and results in the increased production of androgens [9, 10]. IR causes effect on adrenal glands as well to produce ACTH-mediated androgen production [11]. Circulating SHBG are also reduced by high insulin levels which results in the increased free bioavailability of testosterone [12, 13]. Hyperinsulinemia also affects granulosa cells in small follicles (follicular arrest of about 4mm in diameter). The follicular arrest may be caused by premature activation of LH-mediated terminal differentiation of granulosa cells [14]. It results in the induction of early response to LH on granulosa cells of small follicles. The premature activation of granulosa cells to LH induces terminal differentiation causing the arrest of follicular growth which eventually results in Anovulation [15] .

Oral Contraceptive Pills (OCPs) are considered as the first line treatment for PCOS. OCP's play a great role in the reduction of LH levels without surges. OCP's are the combination of estrogen and progestin component. Estrogen part helps to stimulate the hepatic production of SHBG [16].Thus, estrogen part helps to reduce bioavailability of free androgen. So, the various symptoms associated with androgen excess like hirsutism, acne and alopecia are reduced. While as, the progestin component acts as an antagonistic to androgen at its receptors. Thus, reducing the action of male steroid hormone namely testosterone at the target organ. The progestin component protects endometrium from hyperplasia and can reduce the risk of endometrial cancer [17]. Effective treatment for about 3- 6 months results in decreased production of free androgens. Thus, the growth of new hair and growth of terminal hair is reduced [18]. OCP's are also beneficial in the reduction of ovarian volume and ovarian cysts. Higher estrogen doses are required in the preparation of OCP's so as to attain significant protection against ovarian cysts [19]. There are overall clinical benefits of OCP treatment. But, all the mentioned beneficial effects of OCP treatment, there are various adverse effects of OCP treatment on metabolic,

cardio vascular, BMI and HOMA IR of patients [21-23]. There is an intensive use of OCP's for treatment of PCOS women but less data is available to evaluate the relationship between the use of oral contraceptives and metabolic profile in these women.

The main aim of this study was to evaluate effects of OCP treatment on anthropometric, bio-chemical and hormonal parameters in PCOS women.

## II. MATERIALS AND METHODS

### 2.1 Subjects

Although 200 subjects were screened who attended the Endocrinology and Gynaecology Clinics, those who presented with menstrual disturbances (oligo-/ amenorrhea), hyperandrogenism (alopecia, acne and acanthosis), infertility or polycystic ovaries on USG. But only 100 out of 200 were found eligible to be taken further in this study design and the diagnosis was done on the basis of Rotterdam criteria. Subjects who were newly diagnosed as PCOS and were not taking any kind of drug treatment served as controls(n=50) and those subjects who received OCP's (Ethinyl estradiol 0.03mg, levonorgestrel 0.15mg) as mode of treatment for at least 6 months served as cases(n=50) .

### 2.2 Clinical and Anthropometric measures

All the PCOS subjects underwent a clinical and biochemical examination. Clinical examination includes establishment of quantitation of hyperandrogenism by assessing: acne, hirsutism and Acanthosis nigricans. FG-score provides the quantitation of hirsuitism and a score of >8 out of 36 on 9 different body parts has been taken significant. Various anthropometric measures like weight in (Kg), Height in (cm), waist –hip in (cm), W/H ratio and BMI ($Kg/m^2$) were done prior to biochemical investigations. All the participants were informed about study and the written informed consent was obtained from all the subjects. Ultrasonographic examination for establishment of PCOS was considered as the presence of 12 or more follicles, measuring 2–9 mm in diameter, in each ovary and/or increased ovarian volume (>10 ml).

### 2.3 Biochemical and Hormonal Investigations

Blood serum was obtained in clot- activator vials for the investigations of basic biochemical, insulin and hormonal profile. Blood Sugar Fasting (BSF) was performed after 10-14 hour fasting. OGTT was performed with 75 grams of oral anhydrous glucose load dissolved in 300ml of water. Blood samples were drawn after every one hour for Oral glucose tolerance test (OGTT). All basic biochemical parameters (OGTT, KFT, LFT and LIPID PROFILE) were estimated on semi automated analyzer (TRANSASIA ERBA CHEM-7) by using ERBA diagnostic Mannheim Gmbh kits. Insulin was measured by ELISA on BIORAD analyzer using Raybiotech kits. HOMA-IR Homeostasis Model Assessment of Insulin Resistance to estimate insulin resistance and QUICKI –Quantitative Insulin Sensitivity Check Index to estimate insulin sensitivity [24]. Hormonal analysis (17-OHP, T4, TSH, Testosterone and PRL) was done by using Chemiluminescence Immunoassay.

The sampling for hormonal analysis was done on $2^{nd}$ to $7^{th}$ day of the follicular phase of menstrual cycle. Hormonal analysis which was done to rule out various other diseases include:

- 17-hydroxy progesterone (17-OHP) excludes NCAH
- Testosterone excludes androgen-secreting neoplasms

- Thyroid stimulating hormone (TSH) excludes thyroid dysfunction
- Prolactin excludes hyper/hypo prolactinaemia.

## III. STATISTICAL ANALYSIS

Various statistical softwares were employed for data analysis like: SPSS 16.0 version and Minitab. Data was expressed as mean± SD and a P value of <0.05 was used as a criterion for statistical significance.

## IV. RESULTS

Comparison of Anthropometric parameters between the two study groups is summarized in Table1.The mean age of OCP treated PCOS group and drug naive PCOS group was comparable (25.16±4.86 Vs 22.82±4.83, p=0.018). The mean BMI ($Kg/m^2$) for OCP treated group and drug naive group was (24.61±3.53vs23.11±3.71, p=0.041) respectively. Mean FG score of OCP treated PCOS group and drug naive PCOS group was found to be (7.70±1.25 Vs 10.12±2.36, p=<0.0001) respectively.

Comparative analysis of Hormonal profile between the two study groups i.e., OCP treated PCOS and drug naive PCOS groups is summarized in Table 2.A significant difference was observed in LH, FSH and Testosterone levels between the two respective groups. The values for LH (3.98±3.18 Vs8.99±5.44, p =0.000), FSH (6.37±2.88 Vs 6.50±2.83, p= 0.82) and testosterone (39.34±13.91 vs50.52±17.03, p=0.0005) in OCP users Vs non-users.

Comparative evaluation of basic Biochemical parameters like OGTT, LFT, KFT and Lipid Profile between the two study groups is shown in Table 3.All the parameters were found to be slightly increased in OCP treated PCOS group as compared to drug naive PCOS group .Out of all biochemical parameters only cholesterol and SGOT was found significantly increased in OCP treated PCOS group as compared to drug naive PCOS group. The values for cholesterol being (179.24±19.05 Vs167.40±13.60, p=0.0005) and SGOT (27.56±2.43 Vs26.09±3.54, p=0.018).

Insulin profile between drug naive PCOS group and a comparative OCP treated PCOS group is shown in Table 4. Statistically significant difference was observed in OCP treated group as compared to drug naive group. The levels of insulin (15.94±5.05 vs13.31±3.28, p= 0.014), HOMA-IR (3.49±1.10 vs2.94±1.03, p=0.031) and QUICKI (0.32±0.01 vs0.33±0.02, p= 0.019) in OCP treated and drug naive PCOS subjects respectively.

**Table 1: Anthropometric parameters of Controls (PCOS drug naive) and Cases (OCP treated PCOS).**

| Parameters | Mean ±SD(Controls) n=50 | Mean ± SD(Cases) n=50 | p-value |
|---|---|---|---|
| Menarche | 13.10±1.11 | 12.94±1.11 | 0.47 |
| Age | 22.82±4.83 | 25.16±4.86 | 0.018 |
| BMI($kg/m^2$) | 23.11±3.71 | 24.61±3.53 | 0.041 |
| Weight(kg) | 57.44±10.43 | 60.92±9.34 | 0.083 |

| | | | |
|---|---|---|---|
| Height(cm) | 157.53±5.83 | 157.38±7.34 | 0.91 |
| Waist(cm) | 88.26±9.51 | 93.46±9.00 | 0.0060 |
| Hip (cm) | 93.22±6.86 | 97.26±7.07 | 0.0047 |
| Waist hip ratio | 0.95±0.06 | 0.96±0.06 | 0.24 |
| FG score | 10.12±2.36 | 7.70±1.25 | <0.0001 |

**Table 2: Hormonal profile of Controls (drug naive PCOS) and Cases (OCP treated PCOS).**

| **Parameters** | **Mean ± SD(Controls) n=50** | **Mean ±SD(Cases) n=50** | **p-Value** |
|---|---|---|---|
| LH (IU/L) | 8.99±5.44 | 3.98±3.18 | 0.0000 |
| FSH (IU/L) | 6.50±2.83 | 6.37±2.88 | 0.82 |
| LH-FSH Ratio | 1.63±1.22 | 0.74±0.56 | 0.000 |
| Serum total testosterone (ng/ml) | 50.52±17.03 | 39.34±13.91 | 0.0005 |

**Table 3: Biochemical parameters of Controls (PCOS drug naive) and Cases (OCP treated PCOS) .**

| **Parameters** | **Mean ±SD(Controls) n=50** | **Mean ±SD(Cases) n=50** | **p- Value** |
|---|---|---|---|
| Blood glucose fasting( mg/dl) | 87.50±10.98 | 89.92±7.84 | 0.21 |
| Blood glucose-1hr( mg/dl) | 120.96±10.70 | 121.91±7.53 | 0.61 |
| Blood glucose-2hr ( mg/dl) | 101.56±9.80 | 103.06±7.00 | 0.38 |
| Cholesterol( mg/dl) | 167.40±13.60 | 179.24±19.05 | 0.0005 |
| Triglycerides(mg/dl) | 111.32±16.68 | 113.58±14.89 | 0.48 |
| S. Creatinine(mg/dl) | 0.88±0.15 | 0.92±0.20 | 0.20 |
| S. Uric Acid(mg/dl) | 4.37±0.82 | 4.49±1.06 | 0.52 |
| Blood Urea(mg/dl) | 26.32±4.60 | 27.71±5.95 | 0.19 |
| SGPT(IU/L) | 20.92±4.06 | 21.15±3.21 | 0.76 |
| SGOT(IU/L) | 26.09±3.54 | 27.56±2.43 | 0.018 |

**Table 4: Comparison of means of Insulin, QUICKI and HOMA-IR between Controls (drug naive PCOS) and Cases (OCP treated PCOS) .**

| Parameters | Mean±SD(Controls) n=50 | Mean±SD(Cases) n=30 | p-Value |
|---|---|---|---|
| Fasting Insulin (µIU/ml) | 13.31±3.28 | 15.94±5.05 | 0.014 |
| HOMA IR | 2.94±1.03 | 3.49±1.10 | 0.031 |
| QUICKI | 0.33±0.02 | 0.32±0.01 | 0.019 |

## V. DISCUSSION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorder. It is characterized by chronic anovulation, hyperandrogenemia and/or polycystic ovarian morphology. Clinical hyperandrogenism is one of the most noticeable features of PCOS. Clinical androgen excess in women with PCOS manifests in the form of acne, hirsutism, and/or alopecia. Insulin resistance and compensatory hyperinsulinemia have been recognized as the intrinsic features of PCOS. For most of clinicians Oral contraceptive pills (estrogen + progestron) are considered the first-line treatment for PCOS women. There are some controversial issues concerning OCs. Treatment with OCP's has shown decrease in free androgens, reduces new hair growth and the growth of terminal hair [17]. It also reduces inflammatory acne count by 30-60% with improvement in 50-90% of patients [25]. Estrogen component of OCP'S have shown to suppress LH secretion and thus reducing the ovarian androgen production. It has also been shown to increase sex hormone binding globulin (SHBG) and helps to reduce free testosterone.

Our results are in agreement with various other studies as the present study also showed a significant decrease in LH (table 2), testosterone (table 2) and FG-score (table 1) in OCP treated PCOS women as compared to drug naive PCOS women. Thus, it is evident from our study that OCP treatment helps to decrease free androgen levels and reduce its clinical manifestations. But, the use of OCPs for longer duration of time puts the OCP users at various health risks. This was evaluated in terms of various parameters like anthropometry (Weight, BMI, Waist, Hip), OGTT, insulin and lipid profile. The assessed parameters were found to be deranged in OCP treated PCOS women.

Present study showed weight gain (table1) in OCP treatment PCOS women as compared to drug naive PCOS women. Our data also showed statistically significant increase in waist circumference (table1), hip circumference (table1) and BMI (table1) in OCP users as compared to non-users. Our finding is in agreement with the study of Vrbikova J et al., observed weight gain in 19 OCP treated PCOS women [26].

Dyslipidaemia has been commonly detected with the use of oral contraceptives in PCOS women [27]. COC (Combined Oral Contraceptive) treatment of PCOS also has been shown to cause an increase in total cholesterol, triglycerides, HDL and LDL cholesterol [28, 29]. Our data showed significant increase in total cholesterol (table3) and insignificant increase in TG (table3) in OCP treated PCOS women when compared to drug naive PCOS women.

The first ever study which was conducted regarding the impact of OCPs on the glucose tolerance dates back to 1960s and was reported to have deleterious effect on glucose metabolism with the use of high dose COCs [30, 31]. While as the other study carried by Gaspard et al did not report any harmful effect of using low dose COCs when were administered for a period of 13 months to almost 27 OCP users. According to the recommendations in the eligibility criteria of the World Health Organization (WHO), COCs can be used by PCOS and diabetes subjects but progesterone only contraceptives are to be recommended to be used in the presence of associated vasculopathy. Almost 60-80 % of all women with PCOS are known to have IR and about 95% of obese PCOS women are known to have IR [32, 33]. Our results show insignificant increase in glucose 0 hour (table3), 1hour (table3) and 2 hour (table3) in OCP treated PCOS women as compared drug naive PCOS women. Significant difference has been observed in fasting insulin (table4), HOMA IR (table4) and QUICKI (table4) in OCP treated PCOS women as compared to drug naive PCOS women. Thus, our data is suggestive of negative metabolic effects of oral contraceptive in PCOS women.

## VI. CONCLUSION

It is clear from our study that OCP treatment helps to regularize the menstrual cyclicity. It also helps to improve hyperandrogenism. Thus the various clinical symptoms like hirsutism and acne were found to be reduced. The hormonal profile of OCP treated PCOS patients was also found to be improved. But at the same time, use of OCPs does contribute to the worsening of disease process. We observed a worsening of biochemical parameters like OGTT and lipid profile. Increased lipid profile can increase the risk of various metabolic and cardiovascular diseases. Increased insulin levels confer an increased risk for glucose intolerance that may enhance the risk for type 2 Diabetes. The conventional treatment with OCPs causes worsened consequences in these women. Thus OCP treatment increases the risk of dyslipidemia and type 2 Diabetes Mellitus. Although this was a pilot study with limited number of cases and controls but all this taken together suggests that the OCPs may affect already existing metabolic derangements in PCOS women .The deranged metabolic parameters give a clear indication of various risks associated with the use of OCPs in PCOS women.

## VII. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## VIII. ACKNOWLEDGEMENTS

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