



Altered Thyroid Function amongst the Infertile Insulin Resistant Women with Polycystic Ovarian Syndrome

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Authors' contribution

This work was carried out in collaboration among all authors. The study was designed by author UZ, who also wrote the protocol and the first draft of the manuscript, as well as the sampling and statistical analysis. The authors AIS and HAM were in charge of the literature searches and drafting of the manuscript. Author AF helped with the manuscript writing. Authors RR and MM completed all of the final settings and facilitated with the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a hormonal disorder common among women of the child-bearing age. Likewise, women with PCOS are more likely to be obese or overweight, which may be due to their higher Insulin resistance and TSH levels.

Aim: The study's objectives were to assess the prevalence of subclinical hypothyroidism in infertile PCOS, distribution of insulin resistant in PCOS women with subclinical hypothyroidism, and the efficacy of Metformin treatment in these women.

Methods: It was a single-center study which included all infertile patients who visited the

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Department of Obstetrics and Gynecology at a Karachi hospital between January 2019 and September 2019. The infertile PCOS patients were then divided into two groups: Group A (Insulin Resistant with Subclinical Hypothyroidism) and Group B. (Non-Insulin Resistant with Subclinical Hypothyroidism). Following the written consent, both the treatment groups received Metformin 500mg T.D. for three months.

Results: The infertile PCOS patients showed a higher prevalence of subclinical hypothyroidism. Insulin resistance was found to be 63.3% among subclinical hypothyroid PCOS women. Finally, three months of Metformin treatment resulted in a significant reduction in TSH levels in Insulin resistant PCOS women.

Conclusion: We identified a positive link between TSH levels and insulin resistance in PCOS women, both in terms of incidence and treatment.

Keywords: (PCOS) Polycystic ovarian syndrome; (TSH) thyroid stimulating hormone; (HOMAIR) homeostatic model assessment of insulin resistance.

1. INTRODUCTION

Polycystic ovary syndrome is the one of widely arising hormonal abnormality, affecting up to 10% women of childbearing year. It is distinguished by menstrual abnormalities, an excess of the androgen hormones and enlarged ovaries containing multiple small follicles (polycystic ovaries) [1]. In addition, a large number of women with PCOS also presents with signs of metabolic syndrome, comprising of insulin resistance, obesity, and dyslipidemia [2-4]. As a consequence of these metabolic abnormalities PCOS can harm a woman's health by increasing her chances of infertility, obstetrical complications, diabetes, and heart disease [5,6].

Numerous studies over the last decade have identified a clear link between PCOS and hypothyroidism [7,8]. The documented associations was seen between clinical and biochemical variables of the various PCOS phenotypic traits and thyroid dysfunction, but the association is still debatable [9].

TSH levels and Fasting insulin levels, as well as insulin resistance, were previously linked, with a higher prevalence of Subclinical hypothyroidism in women with metabolic syndrome. In view of the above outcome, hyperinsulinemia is found to play a key role following development of metabolic syndrome. This is again supported by the observation in hypothyroid patient, in which muscle and adipose tissue tend to reduce the uptake of glucose which leads to raised insulin levels in these patient [10,11].

Efforts to improve insulin resistance both through lifestyle changes and pharmacotherapeutic intervention has been proposed to alleviate the previously mentioned abnormalities, regain

ovulation, and improve reproductive health in women with PCOS. Furthermore, short-term Metformin administration in diabetes mellitus and obesity, reduces TSH levels significantly [12].

As a result of the afore-mentioned inferences, we aimed to assess:

- Frequency of Subclinical Hypothyroidism SCH (TSH levels) in infertile PCOS women
- Frequency of Insulin Resistant among Subclinical hypothyroid women with PCOS
- Efficacy of Metformin treatment on TSH Levels in insulin-resistant (IR) PCOS patients

2. MATERIALS AND METHODS

This is a single-centered study. The target population included all the infertile women who attended the Department of Obstetrics and Gynecology at a hospital of Karachi.

The participants were listed via convenient sampling technique between January 2019 to September 2019. The sample size was calculated by Sealed Envelope calculator version 201: (Significance level (alpha) 1%, 99% confidence interval Power (1-beta) 90, Percentage success in control group: 12%.

2.1 Control Group

- **Inclusion criteria:** Participants in the control group had normal menstruation and infertility.
- **Exclusion Criteria:** Diagnostic or metabolic hyperandrogenism,

galactorrhea, Diabetes mellitus, cardiovascular disease, history of cancer or any long-term illness, other pharmacotherapeutic therapy, smoking, or alcohol abuse.

2.2 PCOS Group

- **Inclusion criteria:** Infertility and PCOS

Patients with newly diagnosed PCOS were enrolled using the Rotterdam criteria. Two of the following three characteristics are required to detect PCOS cases, according to the criteria:

1. Oligo-ovulation or anovulation: Oligomenorrhea (more than 45 days or less than 8 cyclical per year) or Amenorrhea (more than 3 months in women with previous periodic menstruation) for six months
2. Hyperandrogenism: clinical (including signs such as hirsutism) or biological (including a raised free androgen index or free testosterone)
3. Polycystic ovaries on ultrasonography: >12 follicles in one or both ovaries, 2-9 mm in diameter and/or increased ovarian volume >10 m³

- **Exclusion Criteria:** Galactorrhea, Diabetes mellitus, cardiovascular disease, history of carcinoma or any long-term illness, other pharmacological therapy, smoking, or alcohol abuse.

The appearance of insulin resistance (IR) was assessed using the HOMA-IR (Homeostasis Model Assessment): fasting plasma glucose X Fasting insulin (mIU/l)/405 (mg/dl) Furthermore, as per clinical policy, all HOMA IR PCOS women were continually treated.

2.3 Study Procedure

The study protocol was carefully described to all the participants prior to obtaining consent. Following an agreement, PCOS patients were assigned to Group A (Insulin Resistant with Subclinical hypothyroidism) and Group B (Non-Insulin Resistant with Subclinical Hypothyroidism). After obtaining the written consent, both the treatment groups received Metformin 500mg T.D. for 3 months.

2.4 Statistical Analysis

SPSS version 20 was used to analyze the data. The numeric factor was represented as mean and standard deviation, while the categorical variable was represented as frequencies and percentages. The paired-t test was used to compare the pre and post result of all numerical parameter. The Independent Samples t Test was used to test the differences between the mean values of two groups. A *p*-value of 0.01 was considered statistically significant.

Upon admission and after 3 months of Metformin treatment, blood was drawn from the 30 PCOS women having subclinical hypothyroidism for analysis in the laboratory.

3. RESULTS

The total number of Controls with infertility consisted of 71 patients and PCOS with infertility consisted of 66 patients in our study. Out of the 71 controls 21 (29%) women presented with Subclinical Hypothyroidism (SCH) and from the 63 infertile women with PCOS, 30 (47%) had Subclinical Hypothyroidism (SCH). Considering TSH value > 2.5 as a cut-off point for detecting thyroid dysfunction (subclinical hypothyroidism), the infertile women with PCOS are more affected by SCH than infertile control women (Fig. 1).

After, dividing PCOS women into those with or without IR, as defined by HOMA-IR > 2.5 and >2.5, respectively, we witnessed a trend towards a higher frequency of thyroid dysfunction in IR-PCOS compared to those without PCOS. Out of 30 Subclinical Hypothyroidism with PCOS, 19 (63.3%) women presented with Insulin Resistance while 11 (36.6%) women were Non-Insulin Resistant (Fig. 2).

Lastly, IR PCOS women who were treated with Metformin for 3 months, showed a significant reduction in Insulin resistance (3.43 ± 0.58 to 2.08 ± 0.33 , $p= 0.000$) and TSH levels (3.47 ± 0.74 to 2.33 ± 0.39 $p=0.000$), as compared to baseline. However, there was no prominent reduction in TSH levels (3.78 ± 1.05 to 3.66 ± 0.82 , $p=0.022$) in Non-Insulin Resistant women with PCOS. When the TSH mean value (2.33 ± 0.39 vs. 3.66 ± 0.82 , $p= 0.001$) of both the group were compared it showed significant difference following 3 months of the treatment (Table 1).

4. DISCUSSION

PCOS is commonly exhibited through hyperinsulinemia and hyperandrogenism and is

considered most important endocrine disease in women of reproductive age. At present, this polygenic syndrome is also described as a disease with a combination of reproductive and metabolic characteristics due to various symptoms, including: raised adrenal and ovarian androgen levels, increased estrogen levels (especially estrone levels), low SHBG levels as well as high levels of Prolactin, TSH and Insulin [13-15]. Even though, cause of PCOS is still unidentified, it is assumed to be genetic due to the fact that PCOS has a genetic component [16].

Multiple studies have shown that insulin resistance and obesity are closely related to the occurrence and development of PCOS and its clinical characteristics [17,18]. And so, the role of

IR in the progression of PCOS led to the emergence of insulin-sensitizing drugs in an effort to regain ovulation and improve pregnancy outcomes.

It was the first time when Metformin was used to treat PCOS in 1994, when Velazquez and colleagues discovered it and observed a significant improvement in menstrual cycle irregularity, Body mass index, and circulating androgen production [19]. Since that day, Metformin has held a unique place in the treatment of PCOS because of its metabolic and gynecological benefits. Metformin not only reduces body weight, cardiovascular events, and dyslipidemia, but also reduces hyperinsulinemia and hyperandrogenemia, which lead to improved menstruation [20-23].

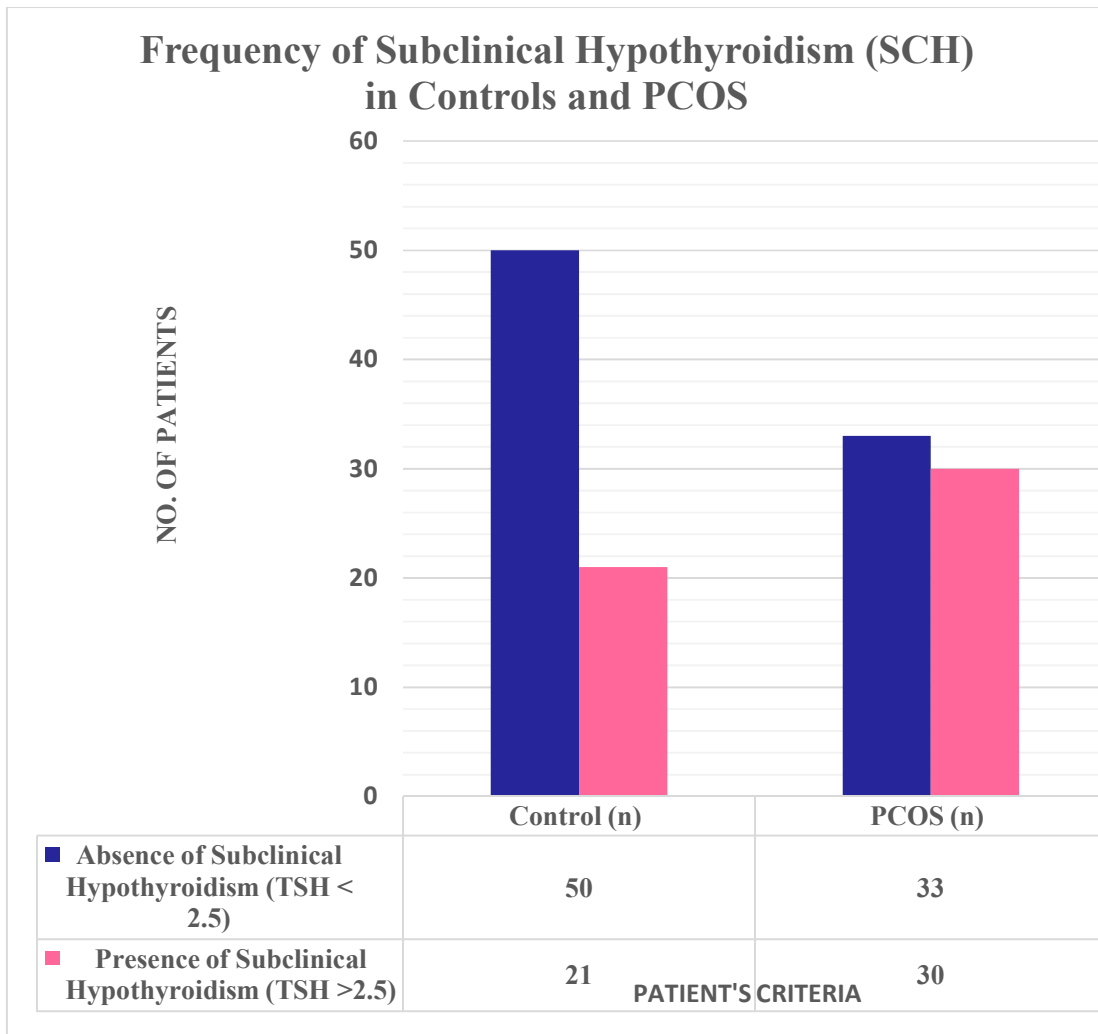


Fig. 1. Frequency of Subclinical Hypothyroidism in Controls and PCOS with Infertility

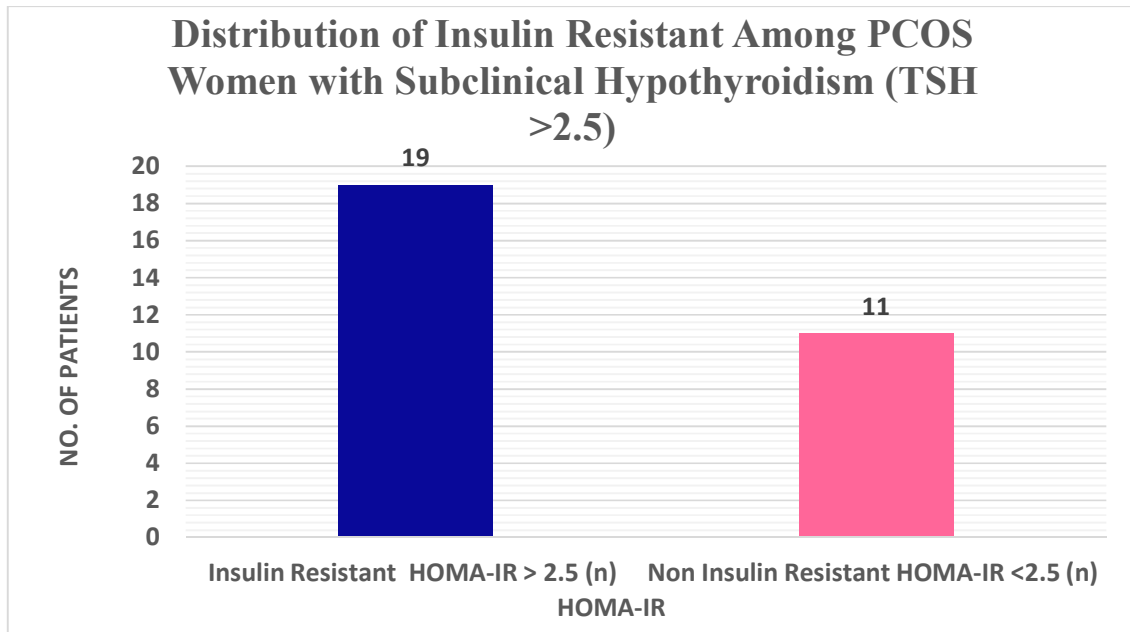


Fig. 2. Distribution of Insulin Resistance amongst PCOS Women with Subclinical Hypothyroidism

Table 1. TSH levels before and after 3 months of Metformin treatment amongst PCOS

Metformin	Homa IR	Non-homa IR	p-value
Before Treatment	3.43 ± 0.58	2.01 ± 0.27	0.000
After Treatment	2.08 ± 0.33	1.81 ± 0.36	0.076
p- value	0.000	0.067	
Metformin	TSH Levels (Homair)	TSH Levels (non homa IR)	p-value
Before Treatment	3.47 ± 0.74	3.78 ± 1.05	0.447
After Treatment	2.33 ± 0.39	3.66 ± 0.82	0.001
p- value	0.000	0.022	

In this research, we found that infertile PCOS patients had higher prevalence of subclinical hypothyroidism as compared to infertile control women. The verdicts of the current study are consistent with Nemati et al. who establish that PCOS women had a substantially higher prevalence of TSH with a significantly higher TSH levels above the maximum limit of normal when compared to the control group [24,25]. Similarly, another study also found the higher mean serum TSH level in PCOS women than in same-age controls which concluded higher proportion of PCOS had subclinical hypothyroidism [26]. On the other hand, the conflicting result were observed by Enzevaei et al. who witnessed no link between insulin resistance and subclinical hypothyroidism in PCOS patients [10].

The current data of PCOS patients with subclinical hypothyroidism have a significantly higher distribution of Insulin resistance (HOMA-IR > 2.5) 19 (63.3%). Mueller et al. have also observed, a higher prevalence of IR in patients with subclinical hypothyroidism in accordance with our observations [27]. Also, comparable findings were observed by researchers, who documented a higher insulin levels in subclinical hypothyroidism (TSH > 2.5) [28]. However, contrary results in an Indian study of Ganie et al. showed no clinical or hormonal association of insulin resistance with SCH among young PCOS women [29].

The study also demonstrated TSH-lowering effect in women with PCOS having insulin resistant after 3 months of Metformin therapy however, no substantial change was observed in

PCOS women without insulin resistance. Therefore, the relationship between TSH and insulin can be predicted. Consistent results were obtained by Mubarak et al, who demonstrated a significant reduction in TSH values along with reduction in insulin resistance. The researcher further added that TSH levels were significantly higher in patients with increased insulin resistance, regardless of whether the patients were obese or not, diabetic or non-diabetic and male or female [30]. Correspondingly, in a study of PCOS patients with hypothyroidism, a decrease in TSH values was seen after 4 months of Metformin treatment but they did not observe the TSH lowering effect in euthyroid women. Moreover, acceptance is required for PCOS women with SCH. Metformin can be a good option for PCOS women with SCH. Also, Metformin treatment led to a significant reduction in serum TSH levels in patients with SCH, and the effect was not dose dependent [31,32].

Fournier et al. [33] recently investigated the relationship between TSH levels and Metformin monotherapy and it was further hypothesized that Metformin monotherapy has been linked to a 55% reduction of TSH levels in participants with subclinical hypothyroidism. Furthermore, they also observed reduction in the TSH following 90–180 days [33].

5. CONCLUSION

PCOS is a multisystem disorder, and treating it necessitates a multidisciplinary approach. Metformin, an insulin-lowering agent, is thought to be a promising treatment for women with PCOS. The research findings of our study showed that infertile PCOS patients have a higher prevalence of Subclinical Hypothyroidism. Also, Metformin treatment significantly lowers TSH levels in IR PCOS patients. Therefore, we can say that Metformin's effect on TSH provides insight into its efficacy as a primary therapy or as an adjunctive treatment in patients with PCOS having insulin resistance and Subclinical Hypothyroidism.

6. STRENGTH OF THE STUDY

The study's strengths include:

- Strict criteria for interventional procedures' inclusion and exclusion
- Careful monitoring of treatment fidelity

7. LIMITATIONS

The study has certain limitations:

- Single centered study
- Small sample size
- Short duration of intervention

8. FUTURE RECOMMENDATIONS

Multi-center and durable clinical studies are needed to confirm the findings and different amounts of Metformin must be assessed for unsurpassed results.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

The authors obtained written informed consent from the patients and kept back.

ETHICAL APPROVAL

The Ziauddin University Ethics Review Committee approved the analysis. It was conducted in accordance with the Helsinki Declaration, and all participants provided the informed consent. The current clinical trial has been registered at clinicaltrials.gov in the United States National Library of Medicine (identifier: NCT04009603, Unique Protocol ID: 651118UZPHA).

Footnote: HOMA-IR >2.5 and TSH >2.5

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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