International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Prevalence of Subclinical Hypothyroidism in Untreated PCOS Patients and PCOS Patients on Metformin at a Tertiary Care Hospital of Eastern India

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Abstract: ***Background: There is increasing evidence suggesting that PCOS is linked to the increased prevalence of thyroid diseases, especially subclinical hypothyroidism. This study aims to compare the prevalence of subclinical hypothyroidism in untreated PCOS patients with age - matched, diagnosed PCOS patients on metformin therapy for >6 months. The aim is to establish the effect of metformin on thyroid hormone status in patients with PCOS on metformin therapy for >6 months as compared to patients with PCOS without metformin therapy. Aims: To compare the prevalence of subclinical hypothyroidism in untreated PCOS patients with age - matched, diagnosed PCOS patients on metformin therapy for >6 months, in order to establish the effect of metformin on thyroid hormone status in patients with PCOS patients on metformin therapy for >6 months. Material and Methods: Serum TSH, FT4, and FT3 of all patients were measured. The study was conducted in the Department of Biochemistry and Department of Gynaecology in IPGME&R, Kolkata from February 2020 to July 2021 (18 months). Results: The mean TSH level of metformin - treated PCOS was 3.29±2.73 and among untreated was 4.15±3.28. There were no significant differences of FT4 and FT3 between the two groups. Conclusion: The metformin - treated PCOS group had a significantly lower mean TSH level than the untreated PCOS group (t198=2.02; p=0.022).***

Keywords: Polycystic Ovary Syndrome, Subclinical Hypothyroidism, Metformin

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders characterized by anovulation, hyperandrogenism, and polycystic ovaries, which affect up to 15–20% of women of reproductive age [1]. These patients are at risk of a range of metabolic and endocrinological disturbances that include infertility, obesity, insulin resistance, and metabolic syndrome [2–4]. In addition, there is also increasing evidence suggesting that PCOS is linked to the increased prevalence of thyroid diseases [5]. Primary hypothyroidism is a deficiency status in thyroid hormone production by the thyroid gland [6] causing several symptoms, such as the poor ability to tolerate colds, tiredness, constipation, depression, and weight gain. The severity of hypothyroidism varies significantly, from transient and subclinical forms to severe cases. Subclinical hypothyroidism (SCH), which is defined as an elevated TSH level in combination with normal T4 and free thyroxine (FT4) levels and lack of signs or symptoms of hypothyroidism, SCH is more common than overt hypothyroidism [7]. The prevalence of SCH is affected by geographic regions, ethnicity, and age in the general population [8–10].

Although SCH is a mild form, it also results in anovulatory cycles, sex hormone imbalances, subfertility, and adverse pregnancy outcomes [11–13], which are also features of women with PCOS. In addition, patients with SCH have increased metabolic risk of obesity, insulin resistance, and hyperlipidemia similar to those with PCOS [14, 15]. The prevalence of SCH in women with PCOS is variable, ranging from 11 to 36% [16]. Over the past decades, a large number of studies have investigated the prevalence of SCH in Since the prevalence of SCH differs from the geographic region, ethnicity, or age, the results of studies were inconsistent.

PCOS and hypothyroidism both together or individually add the risk for infertility and menstrual irregularities. it has been extensively demonstrated that thyroid hormones, and specifically T3, have insulin - antagonistic effects at the liver level that lead to an increased glucose hepatic output, via an enhanced rate of gluconeogenesis and glycogenolysis [17]. For this reason, all the existing criteria used for diagnosis of PCOS necessitate exclusion of hypothyroidism at first [18, 19]. Insulin resistance is more likely in women who had SCH than in women without SCH independent of age and BMI [20]. compromised immune system is likely to be a cause of the interaction between SCH and PCOS since SCH may result from autoimmune thyroiditis [21]. Normally, estrogen's immune stimulatory activity is neutralized by the anti - inflammatory actions of progesterone levels. However, progesterone level is near zero in PCOS because of anovulatory cycles [22]. As a result, estrogen overstimulates the immune system, that leads to high incidence of autoimmune diseases [23].

Metformin may be a beneficial choice for PCOS women with SCH. Metformin is considered one of the safest antihyperglycemic agents. This biguanide is an insulin sensitizer mainly in the liver, but also in the muscle, that activates AMP - activated protein kinase (AMPK), an intracellular sensor of nutrient availability and regulator of

energy homeostasis. A direct effect of AMPK modulation on thyroid function has been unraveled recently, and much of its function in the thyroid is currently unknown. The pharmacological activation of AMPK in normal thyrocytes results in decreased iodide uptake counterbalancing TSH action [24]. Activation of AMPK by metformin results in a strong reduction of iodide uptake through the thyroidal sodium iodide symporter.

The present hospital - based cross - sectional observational study aims to evaluate the prevalence of subclinical hypothyroidism in untreated PCOS patients and PCOS patients on metformin therapy.

2. Materials and Methods

The study was performed after obtaining approval from the Ethics committee of the Institute of Postgraduate Medical Education and Research.

Study Setting: A cross - sectional observational Study was conducted in the Department of Biochemistry &Department of Gynaecology, IPGME&R, Kolkata. Diagnosed untreated PCOS patients and PCOS patients on metformin therapy were selected from the Dept. of Gynaecology, IPGME&R, Kolkata, and biochemical parameters were analyzed in the Dept of Biochemistry of IPGME&R, Kolkata. The result was compared with age - matched controls and data were further analyzed for clinical correlation.

Timelines: February 2020 to July 2021 (18 months)

Definition of the population: 100 patients with diagnosed PCOS untreated and 100 PCOS patients on metformin therapy for >6 months, attending the Gynaecology OPD, IPGME&R, during the study period. Cases were taken as per inclusion and exclusion criteria.

Inclusion Criteria, Exclusion Criteria

Inclusion criteria for cases: Patients with diagnosed PCOS according to Rotterdam criteria, on metformin therapy >6 months, of age group 18 - 44 years, signed the informed consent form.

Inclusion criteria for controls: Patients with diagnosed PCOS according to Rotterdam criteria, untreated patients of age group 18 - 44 years, signed informed consent form.

Exclusion criteria:
1) Patients with diseases other than PCOS and taking any other kind of medicine could have influenced the test result.
2) Patients with a previous history of hypothyroidism.
3) PCOS patients on hormone therapy.
4) Patients on drugs affecting the thyroid profile [Lithium, Amiodarone], OCP, hormone replacement therapy using oral Estrogen, PPI, etc.

Sample Size: 100 patients clinically diagnosed with PCOS on metformin therapy>6 months and the same number of age - matched diagnosed PCOS patients according to Rotterdam criteria were selected as cases and controls respectively for the study.

Method of Data Collection (including sampling procedure): Patients' data were collected based on a predesigned datasheet. And findings of relevant clinical examination were recorded.10ml of venous blood sample was collected from large peripheral veins, taking aseptic precaution. Samples were collected in clot vial on day 3 of the patient's menstrual cycle. Serum was separated by centrifugation (3500 rpm for 5 minutes). And then the blood samples were analyzed for serum Insulin, serum TSH, FT3and FT4, serum LH, and FSH and FBS.

Laboratory Investigation Parameters –
Serum TSH, 2. Serum FT4, 3. Serum FT3, 4. Serum LH, 5. Serum FSH, 6. Serum FBS, 7. Serum Insulin

Control - 100 age - matched patients diagnosed with PCOS according to Rotterdam criteria attending the Gynaecology OPD, IPGME&R, were taken during the study period.

Schedule of Data Collection - From February 2020 to July 2021

100 patients with diagnosed PCOS untreated and 100 PCOS patients on metformin therapy for >6 months, attending the Gynaecology OPD, IPGME&R, during the study period, were selected as controls and cases respectively. Informed consent was taken. Relevant history was taken and clinical examination was performed. Venous blood was collected by taking aseptic precaution. After that biochemical analysis was performed in the Dept. of Biochemistry, IPGME&R.

Materials for Estimation of Study Variables
1) Refrigerators
2) Laboratory Centrifuge (Remi R - 8C)
3) Micropipettes
4) Reagents and Reagent kits
5) Autoanalyzer

Estimation of Thyroid Stimulating Hormone (TSH) –

Assay Principle:
The ADVIA Centaur TSH3 - Ultra assay is a third - generation assay that employs anti - FITC monoclonal antibody covalently bound to paramagnetic particles, an FITC - labeled anti - TSH capture monoclonal antibody, and a tracer consisting of a proprietary acridinium ester and an anti - TSH mAb antibody conjugated to bovine serum albumin (BSA) for chemiluminescent detection. A direct relationship exists between the amount of TSH present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Sample volume: This assay requires 100 µL of sample for a single determination

Estimation of serum free T4 (fT4)

Assay Principle:
The ADVIA Centaur CP FT4 assay is a competitive immunoassay using direct chemiluminescent technology. FT_4

in the patient sample competes with acridinium ester labeled T_4 in the Lite Reagent for a limited amount of biotinylated polyclonal rabbit anti - T antibody. Biotin - labeled anti - T4 is bound to avidin that is covalently coupled to paramagnetic particles in the Solid Phase. **Sample volume:** This assay requires 25 µL of sample for a single determination**.**

Estimation of serum free T3 (FT3) –

Assay Principle:
The ADVIA Centaur FT3 assay is a competitive immunoassay using direct chemiluminescent technology. FT3 in the sample competes with a T3 analog, which is covalently coupled to paramagnetic particles in the Solid Phase for a limited amount of a combination of acridinium ester - labeled monoclonal mouse anti - T3 antibodies in the Lite Reagent.
Sample Volume - This assay requires 50 µL of sample for a single determination.

Estimation of Luteinizing Hormone –
Principle: IMMULITE/IMMULITE 1000 LH is a solid - phase, two - site chemiluminescent immunometric assay. **Volume Required:** 50 µL serum. (Sample cup must contain at least 100 µL more than the total volume required.)

Estimation of Follicle Stimulating Hormone [FSH] –
Principle of the Procedure - IMMULITE/IMMULITE 1000 FSH is a solid - phase, two - site chemiluminescent immunometric assay. **Volume Required:** 50 µL serum. (Sample cup must contain at least 100 µL more than the total volume required.)

Estimation of Fasting Blood Sugar [FBS] –
GOD/PAP (glucose oxidase - phenol and 4 aminophenazone) method [Randox].

Estimation of Fasting Insulin –
Principle: IMMULITE/IMMULITE 1000 Insulin is a solid - phase, enzyme - labeled chemiluminescent immunometric assay.
Sample Volume: 100 µL serum or heparinized plasma. (Sample cup must contain at least 250 µL more than the total volume required.)

Interferences: Hemolysis, Lipemia, Jaundice, biotin supplementation show changes in results.

Statistical Analysis
Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2 EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC).

Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s. d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi - square (χ^2) test was performed to find the associations. Fisher Exact test was applied where Chi - square (χ^2) test was not applicable. t - test was used to compare the means of any parameters of the two groups. $p<0.05$ was taken to be statistically significant.

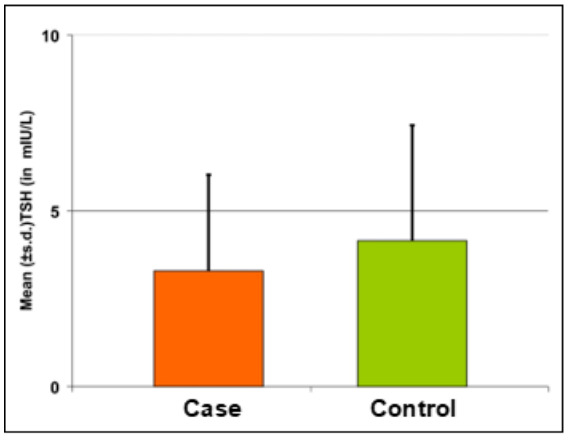
3. Result

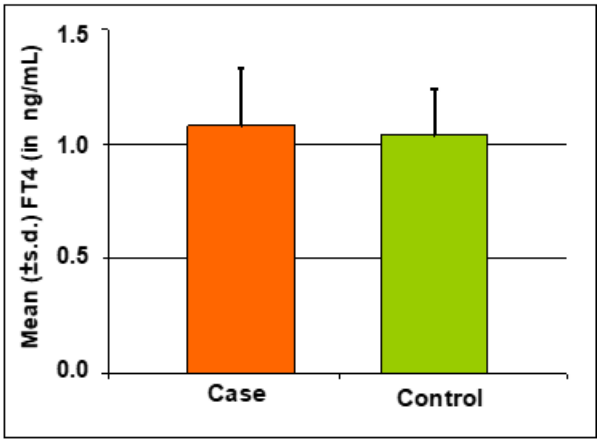
Mean ± SD	Case	Control	P Value
LH	6.29±1.91	9.81±1.48	p<0.0001
FSH	6.34±1.29	3.71±0.66	p<0.0001
TSH	3.29±2.73	4.15±3.28	p=0.022
FT4	1.08±0.25	1.04±0.20	p=0.35
FT3	2.15±0.55	2.11±0.52	p=0.12
FBS	79.06±6.02	85.37±9.14	p<0.0001
Fasting Insulin	10.56±1.32	11.44±2.80	p=0.005

Level of TSH and the patients of the two groups

TSH (in mIU/L)	Case	Control	TOTAL
High	16	20	36
Row %	44.4	55.6	100
Col %	16	20	18
Normal	84	80	164
Row %	51.2	48.8	100
Col %	84	80	82
TOTAL	100	100	200
Row %	50	50	100
Col %	100	100	100
Mean±s. d.	3.29±2.73	4.15±3.28	
Median	2.5	2.9	
Range	1.1 – 15.8	1.0 – 20.9	

t - test showed that the mean level of TSH of the patients of the controls was significantly higher than that of cases ($t_{198}=5.55$; $p<0.0001$).





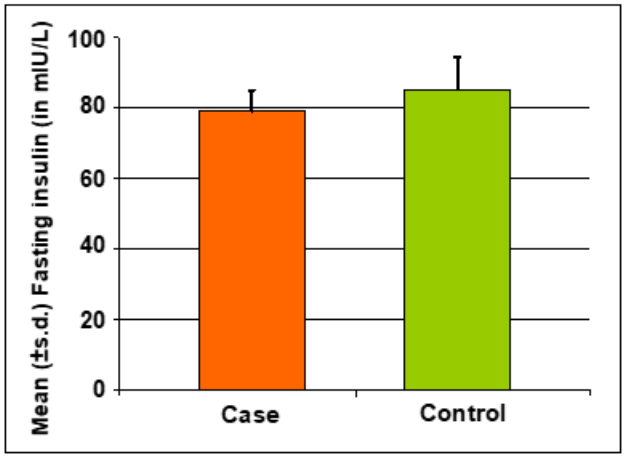
Level of FT4 and the patients of the two groups

FT4 (in ng/mL)	Case	Control	TOTAL
Low	16	15	31
Row %	51.6	48.4	100
Col %	16	15	15.5
Normal	82	85	167
Row %	49.1	50.9	100
Col %	82	85	83.5
High	2	0	2
Row %	100	0	100
Col %	2	0	1
TOTAL	100	100	200
Row %	50	50	100
Col %	100	100	100
Mean±s. d.	1.08±0.25	1.04±0.20	
Median	1.1	1.05	
Range	0.4 - 1.8	0.4 - 1.4	

t - test showed that there was no significant difference in mean FT4 of the patients of the two groups (t_{198}=1.24; p=0.21).

Level of fasting insulin and the patients of the two groups

Fasting insulin (in mIU/L)	Case	Control	Total
Low	0	0	0
Row %	0	0	0
Col %	0	0	0
Normal	100	100	200
Row %	50	50	100
Col %	100	100	100
TOTAL	100	100	200
Row %	50	50	100
Col %	100	100	100
Mean±s. d.	10.56±1.32	11.44±2.80	
Median	10.6	11.2	
Range	8.0 - 13.6	2.0 - 18.6	

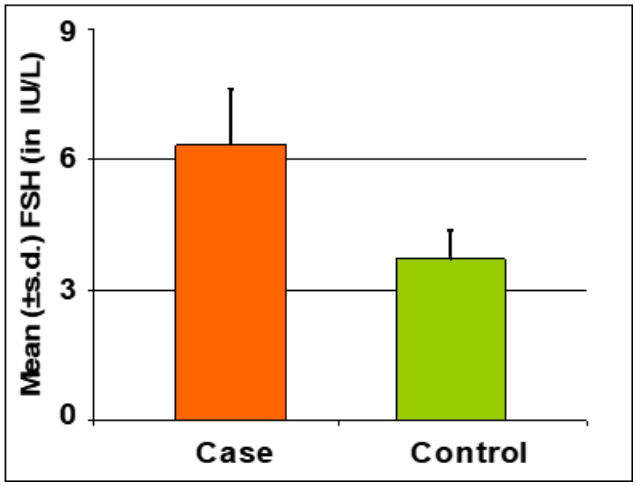


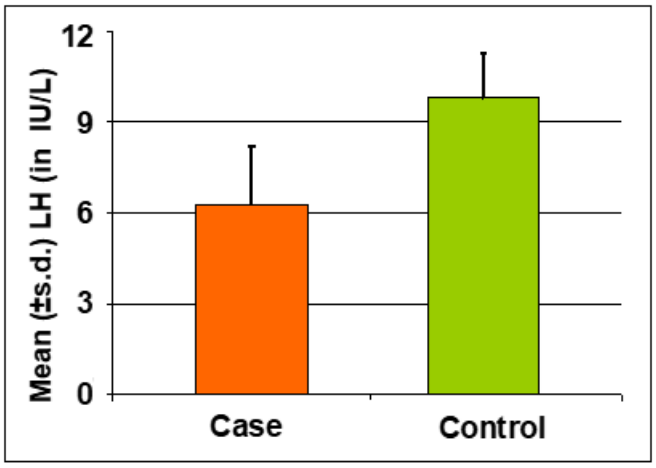
t - test showed that the mean level of fasting insulin of the controls was significantly higher than that of the cases (t_{198}=2.81; p=0.005).

t test showed that LH: FSH ratio of controls was higher than cases which was statistically significant (p<0.0001).

LH (in IU/L)	Case	Control	TOTAL
High	0	40	40
Row %	0	100	100
Col %	0	40	20
Normal	100	60	160
Row %	62.5	37.5	100
Col %	100	60	80
TOTAL	100	100	200
Row %	50	50	100
Col %	100	100	100
Mean±s. d.	6.29±1.91	9.81±1.48	
Median	5.8	9.8	
Range	3.7 - 10.0	6.8 - 11.8	

FSH (in IU/L)	Case	Control	TOTAL
High	100	20	120
Row %	83.3	16.7	100
Col %	100	20	60
Normal	0	80	80
Row %	0	100	100
Col %	0	80	40
TOTAL	100	100	200
Row %	50	50	100
Col %	100	100	100
Mean±s. d.	6.34±1.29	3.71±0.66	
Median	6.2	3.75	
Range	4.6 - 9.6	2.1 - 5.2	





4. Discussion

Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common (and perhaps overlooked) endocrine disorders in women of childbearing age. Genetic and environmental factors are believed to contribute to thyroid disorders in PCOS [1, 5]. Hypothyroidism is known to cause PCOS - like ovaries and overall worsening of PCOS and insulin resistance. Subclinical hypothyroidism (SCH), a mild form of hypothyroidism defined as elevated TSH with normal

free thyroxine levels, is a common diagnosis among women of reproductive age [25]. In some, but not all, studies, it has been associated with infertility, an increased risk of adverse pregnancy and neonatal outcomes, and possibly with an increased risk of neurocognitive deficits in offspring. Major contributing factors for irregular menstruation associated with infertility are from local (ovarian) cause like polycystic ovarian syndrome and /or systemic cause like Hypothyroidism, Hyperprolactinemia, Hyperinsulinemia [26, 27] All the above - said factors pose an individual risk for anovulation. Often, they present in combination. The compromised immune system is likely to be a cause of the interaction between SCH and PCOS.

Several of the early studies on metformin in PCOS were compiled in a meta- analysis by Lord and colleagues [Lord et al.2003]. They concluded accordingly that metformin was an effective treatment to induce ovulation in PCOS patients and that it was justifiable to use it as a first - line treatment. However, they emphasized that it should be used in conjunction with a change in lifestyle. Also, A significant reduction in serum TSH levels was observed in patients with SCH after treatment with metformin and the effect was not related to its dose. Several mechanisms have been hypothesized for explaining this effect: (a) a change in the affinity or number of TSH receptors; (b) an increase in the central dopaminergic tone; or (c) an interaction between metformin and TSH [28]. Meanwhile, metformin also plays a role in improving the ovulation rate and reproductive outcomes in women with PCOS [29]. In the last decade, several studies have reported a decrease in TSH levels following the administration of metformin in patients with polycystic ovary syndrome (PCOS).

A common finding in gynaecology outpatient department is that while treating individuals for PCOS for a period of a few months, in some patient menstruation and ovulation is restored while it remains uncorrected in some individuals. On further evaluation of these non - responding patients for the other causes of infertility / menstrual disorder, they were found to have co - existing Hypothyroidism which was mostly undiagnosed and /or untreated. These individuals were found to be mostly in subclinical status and some in overt hypothyroid state. Screening studies help to assess the prevalence of hypothyroidism and give insight into the epidemiology of this disorder in the population.

A cross - sectional study comprising two comparison groups was conducted among 100 newly diagnosed PCOS women of age group 18 - 44 years and 100 diagnosed PCOS women on metformin therapy of same age group; taken as case and control respectively, attending the Gynaecology outpatient department for menstrual irregularity and infertility. They were diagnosed based on revised Rotterdam criteria, 2003.

With serum TSH level of being >5μU/L μU/L but <10 μU/L, as a cutoff point with normal FT4 level to diagnose subclinical hypothyroidism we have identified the prevalence of subclinical hypothyroidism among 100 newly diagnosed PCOS women to be 14% and 100 diagnosed PCOS women on metformin therapy, to be 11%.

In a case - control study conducted by Maryam et al. a significant prevalence of autoimmune thyroiditis and goiter in PCOS [30] was reported. Sridhar et al reported a prevalence of 1.04% (2/13) of polycystic ovaries among hypothyroid patients.

In our study, 14% of newly diagnosed PCOS patients had subclinical hypothyroidism (SCH), 6% of newly diagnosed PCOS patients had overt hypothyroidism among case and among control 11% of PCOS patients on metformin therapy had SCH, 5% of PCOS patients on metformin had overt hypothyroidism.

Overall, 20% of newly diagnosed PCOS patients had thyroid disorders, 16% of PCOS patients on metformin therapy had thyroid disorders. This shows that there is a correlation between thyroid dysfunction and PCOS which is also supported by the findings of Maryam et al & Sridhar et al. [30] A similar finding of hypothyroidism among PCOS women was observed by Onno E Janssen et al study (20.6%) [31].

Again, thyroid disorders (SCH and overt hypothyroidism) are higher, 20% among newly diagnosed PCOS patients compared to PCOS patients on metformin, which is 16%; Recently it has been reported that metformin is able to interfere with thyroid hormone profile, as shown by a decrease in the serum levels of thyrotropin (TSH) to subnormal levels in hypothyroid patients in stable levothyroxine (L - T4) treatment [31, 32].

The most common cause of low insulin is type 1 diabetes, an autoimmune disease in which the pancreatic cells that normally produce insulin are destroyed, In PCOS low level of progesterone overstimulates the immune system that leads to the production of autoantibodies and therefore it can be labeled as an autoimmune disorder [33]. In our study, total 5 % of 100 newly diagnosed PCOS case had low fasting insulin levels which is 2 uIU/mL. Among 100 case total 3 patients with SCH had low fasting insulin and 2 patients with overt hypothyroidism had low fasting insulin which is as low as 2 uIU/mL. Among control, PCOS on metformin, all patients had a normal fasting insulin level.

5. Summary and Conclusion

The study found that the mean LH was significantly higher among controls than cases and mean FSH was significantly higher among cases than controls, thus LH: FSH ratio was higher among controls than cases.

It was found, the mean TSH level of controls was 4.15±3.28 and the mean TSH level of cases was 3.29±2.73, the mean TSH of controls was higher than cases which was statistically significant (t198=2.02; p=0.022).

We have identified the prevalence of subclinical hypothyroidism among controls was14% and among cases was 11%, where total hypothyroid (overt and subclinical) among controls was 20% and among cases was 16%.

The study concluded that the control group who were not on metformin had significantly higher BMI, mean FBS, mean fasting Insulin, mean LH and LH: FSH ratio than the case

group, thus the study concluded that metformin as one of the 1st line treatments for PCOS patients was significantly associated with long term better health outcome for treating PCOS patients.

As well as this study unveiled the mean TSH value significantly low among cases who were on metformin therapy for >6 months than the control group, the prevalence of subclinical hypothyroidism, as well as overt hypothyroidism, were more among controls, who were not on metformin therapy. These observations lend strong support to the hypothesis that metformin, one of 1st line treatments of PCOS, might have a lowering effect on serum TSH level without affecting the serum FT4, FT3 among patients with thyroid disorders. This study suggests that screening for hypothyroidism along with reproductive hormone profile should be evaluated in PCOS/infertile women for early diagnosis and management.

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