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## Decoding Infertility: The Interplay of Hypothyroidism, PCOS, and Reproductive Challenges

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### Abstract:

#### Objective:

The primary objectives of this study are to find the incidence ratio and percentage of hypothyroidism and PCOS in infertile females, the impact of these endocrine conditions on reproductive health, and explore the interrelation between hypothyroidism and PCOS with each other and with infertility.

#### Methods:

A prospective study of 4 months was conducted at Central Park Teaching Hospital in which 43 women aged 18-45 presenting with PCOS, hypothyroidism, or both were enrolled. These females underwent diagnostic evaluation for PCOS and examination of TSH levels based on the Rotterdam criteria, 2003. Males, women outside of the reproductive age window, women undergoing fertility treatments, chronically ill patients, and those having thyroid disorders other than hypothyroidism were among the exclusion criteria. The data was analyzed statistically to understand the prevalence and relationship between PCOS, hypothyroidism, and infertility. Ethical approval and informed consent were obtained.

#### Results:

5-7% of the infertile females suffered from subclinical hypothyroidism whereas the prevalence of PCOS was greater than 70-80% of the females. 11-36% of the females diagnosed with PCOS were also found to have hypothyroidism causing infertility. The data suggested that women suffering from these conditions exhibit a greater risk of infertility, along with menstrual irregularities, hormonal imbalances, and metabolic dysfunctions.

#### Conclusion:

These findings highlight the importance of the coexistence of the intricately interlinked pathologies: PCOS, hypothyroidism, and infertility and how they aggravate reproductive difficulties, suggesting the need for appropriate diagnostic and therapeutic approaches.

#### Importance:

This study signifies the need for a holistic diagnostic approach, improved reproductive health outcomes, and early detection and treatment of PCOS and hypothyroidism to maintain a balance of hormones and improve fertility. It also provides valuable insights for future research and public health strategies.

## **Introduction**

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.<sup>1</sup> It poses various noteworthy emotional, physical, and social difficulties to individuals, affecting almost 17.5% of adults worldwide (or every 1 in 6 individuals)<sup>1</sup> according to WHO. It reportedly affects 22% of the Pakistani population.<sup>2</sup> The etiology of this condition is multifactorial, the most common causes being ovulatory disorders, tubal factors, and male factor infertility. This disease may also be a result of conditions such as endometriosis, leiomyoma, thyroid dysfunction, decreased ovarian reserve, PCOS, etc. with unexplained infertility also being a major factor. Reproductive health is also affected by age-related factors, lifestyle, and environmental factors.<sup>3</sup> Infectious diseases such as genital TB or historically prominent sexually transmitted diseases also contribute to infertility.<sup>4</sup> This research focuses on the two highlighted determinants of ovarian dysfunction, the duodenal disorders: PCOS and Hypothyroidism.

## **PCOS**

Polycystic ovarian syndrome is the most commonly occurring hormonal disorder in females of reproductive age. Polycystic ovarian morphology, oligomenorrhea/amenorrhea, chronic anovulation, hirsutism, and eventually infertility are its distinguishing features.<sup>5</sup> It is also marked by hyperestrogenism and hyperandrogenism,<sup>6</sup> increased levels of LH, and decreased levels of FSH as well as insulin resistance.<sup>7</sup>

## **PCOS about Infertility**

LH and FSH collaborate to stimulate the normal growth of follicles and ovulation. Androgen production and release during folliculogenesis is dependent upon theca cells of LH and FSH. Hyperandrogenism may be caused by hyperinsulinemia, again a symptom of PCOS, as theca cells are extremely sensitive to insulin.<sup>8</sup> Abnormal levels of these hormones as seen in PCOS may be disastrous for the developing follicles thus leading to infertility.<sup>9</sup>

## **Hypothyroidism**

Hypothyroidism is the deficiency of thyroid activity (vii) characterized by low levels of free T3 and T4 levels and increased levels of TSH.<sup>10</sup> Its symptoms include lethargy, tiredness, dry skin,

constipation, weight gain, and cold intolerance.<sup>11</sup> It may be diagnosed by measuring the TSH levels and free T4 levels in the blood. An elevated level of TSH and the normal free T4 level may indicate the presence of *subclinical hypothyroidism*.<sup>12</sup>

### **Hypothyroidism and Infertility**

Females with increased TSH levels show a lower rate of pregnancy than females with normal TSH levels.<sup>13</sup> Hypothyroidism may cause elevated prolactin levels, anovulation, and luteal phase defects.<sup>14</sup> Increased prolactin has inhibitory effects on GnRH secretion that in turn reduces the secretion of LH and FSH from the pituitary gland, thus influencing fertility.<sup>15</sup>

### **PCOS and hypothyroidism**

These closely related endocrine disorders despite having distinctive disease processes, lead to the same disease: infertility. The prevalence of thyroid dysfunction is 2.5 times higher in females affected with PCOS than in normal females.<sup>16</sup> Some of the pathophysiological mechanisms could potentially link hypothyroidism and PCOS such as hyperinsulinemia, unbalanced hormones, and a disturbed hypothalamic-pituitary-ovarian axis. They also show a similar metabolic profile representing dyslipidemia, obesity, and a potential risk of cardiovascular diseases along with low quality of life.<sup>17</sup> Both these diseases challenge normal conception with irregular menstrual period defects, folliculogenesis, and pregnancy complications. Due to the similar and overlapping symptoms of both diseases, diagnostic challenges are faced such that thyroid disorders are marked as exclusion criteria for PCOS diagnosis.<sup>18</sup> Hypothyroidism may exhibit a cystic morphology of ovaries due to increased prolactin and anovulation due to an imbalance in LH and FSH levels. (i) The similar phenotype and metabolic symptoms make the diagnosis of these fertility-affecting diseases complicated<sup>19</sup>. This makes the treatment of infertility a multi-disciplinary approach requiring the help of endocrinologists, gynecologists, dietitians, and many more.

### **Reproductive challenges**

Many females despite having healthy oögonia and follicles, undergo the stress of infertility due to various reproductive challenges such as tubal blockages which may be caused by endometriosis, obstruction, infection, or inflammatory diseases.<sup>20</sup> Several uterine factors may be a reason for infertility such as fibroids, polyps, uterine malformation, Asherman's syndrome, etc. Male factor infertility and idiopathic infertility are also one of the common types of infertility.

## **Methodology**

This prospective cohort study was conducted in Central Park Medical College and Teaching Hospital Lahore from May 2024 to September 2024 on 43 subjects after non-random collection following the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB# CPMC/IRB-No/ \*1415\* ) of Central Park Medical College and Teaching Hospital. Verbal informed consent was obtained from all participants before inclusion in the study, and patient confidentiality was maintained throughout the study. The sample size was calculated using open epi software based on subjects diagnosed with PCOS and subjects diagnosed with hypothyroidism with a normal range at 95% significance level. Using a prospective cohort design and stringent diagnostic criteria. Women attending obstetrics/gynecology or endocrinology clinics for routine checkups were screened for eligibility using their medical reports. Inclusion Criteria were women with an age ranging from 18-45, diagnosed with either PCOS or hypothyroidism. Males, women outside of the reproductive age window, women undergoing fertility treatments, chronically ill patients or those with genetic disorders affecting fertility, and those having thyroid disorders other than hypothyroidism were among the exclusion criteria. Clinical and demographic data were collected from eligible participants, including age, parity, gestational age, blood pressure measurements, and laboratory results. Laboratory tests were conducted in credible medical labs to measure the level of TSH (normal: 0.4-42 uIU/L), free T3 (3.3-6.8 pmol/L), free T4 (12-22 pmol/L), and androgen levels (testosterone=249- 836 ng/dl) (AMH=1-10ng/ml) in the blood. The diagnostic tool for the identification of PCOS and hypothyroidism was the Rotterdam criteria and checking the levels of TSH, T3, and T4 hormones respectively. According to the study depictions, anovulation, clinical symptoms of elevated androgens, and polycystic ovarian morphology on ultrasound were the characteristics of a PCOS patient, and increased TSH or decreased free T4 levels were the characteristics of hypothyroidism. Pearson and Spearman correlation coefficients were calculated to assess the continuous variables (TSH/T4 levels, androgen levels, positive pregnancy rate) of this investigation. The correlation between TSH levels and successful pregnancy rates was analyzed specifically. Pearson correlation was used for normally distributed variables whereas Spearman correlation was used to assess the monotonic relationship between non-distributed variables. Multiple regression analysis was done to understand the effects of hypothyroidism and PCOS on reproductive outcomes individually and collectively. Binary outcomes such as the presence or absence of infertility were calculated using

logistic regression analysis. The data of participants was secured in an electric database. All collected data was entered into the SPSS software version 27. T-tests were used to compare the mean values of continuous variables between groups whereas the chi-square test was used to compare categorical variables.

Variables	N=43	%	Mean Standard deviation +/-
<b>Age in years</b>			
18-20	1	2.3%	
21-25	4	9.3%	
26-30	14	32.5%	
31-35	11	25.5%	
36-40	9	20.9%	
41-45	4	9%	7.1667 ±3.966
<b>Marital status</b>			
Married	43	100%	
<b>Duration of infertility</b>			
>5 years	12	27%	
5-10 years	18	41%	
>10 years	13	30%	14.3333 ±3.638
<b>Education</b>			
No formal education	0	0%	
Matriculation	3	6.97%	
Intermediate	8	18.6%	
Bachelors	18	41.86%	
Masters	11	25.58%	
PhD	3	6.97%	7.1667 ±5.294
<b>Employment</b>			

Employed	26	60.4%	
Unemployed	17	39.53%	21.5 ±8.82
<b>BMI</b>			
<18.5	4	9.30%	
18.5-24.9	10	23.2%	
25.0-29.9	24	55.8%	
>30	5	11.6%	10.75 ±9.031
<b>Age at menarche</b>			
<13 years	17	39.53%	
13-18 years	25	58.13%	
>18 years	1	2%	14.3333 ±13.828
<b>Duration of menstrual cycle</b>			
≤3 days	9	20.9%	
4-6 days	19	44.1%	
7-9 days	7	16.2%	
≥10 days	8	18.60%	10.75 ±5.449

### Results:

43 females with their age ranging from 25 to 45 years old were recruited for this investigation. 41.8% of these females (n=18) were diagnosed with PCOS based on Rotterdam criteria 2003 whereas 20.9% of the females (n=9) were diagnosed with hypothyroidism based on elevated levels of TSH (>4mU/L). 16.2% of the recruited females (n 7) were diagnosed with both PCOS and hypothyroidism and the rest of the 20.9% (n = 9) faced infertility due to other reproductive challenges (infantile uterus, fibroids, polyps, male factor, oligomenorrhea, testicular injury during road traffic accident and tubal blockage). The correlation analysis results according to the topic of the investigation revealed a positive correlation between free T4 levels and successful pregnancy rates whereas higher TSH levels were responsible for fewer ovulatory cycles and thus infertility. Increased levels of TSH and the diagnosis of PCOS both were unfavorable for normal conception

according to multiple regression analysis. Therefore the logistic regression analysis revealed that both hypothyroidism and PCOS were directly proportional to the incidence of infertility. The females in which both PCOS and hypothyroidism were recognized show a higher rate of infertility rather than the females having either one or none of these diseases. The average number of ovulatory cycles per year was also significantly lower in females of this group. Therefore, successful pregnancy outcomes were the least in this subgroup (n=1) as compared to those with only PCOS (n=7) or hypothyroidism (n=4). These findings highlight the significance of proper screening and monitoring of thyroid dysfunction in women with PCOS and the clinical protocols to have them investigated separately for improved fertility outcomes with early treatment and management.

### **Discussion:**

The target of this investigation was to signify the correlation between PCOS and hypothyroidism and their association with infertility. Our results reveal a noticeable link between these endocrine disorders and decreased fertility. PCOS has been ruled out as a leading and frequently occurring cause of infertility around the globe by WHO classified by chronic anovulation, insulin insensitivity, and increased androgens, interfering with normal ovulation and conception<sup>21</sup>. Hypothyroidism, due to similar features caused by abnormal GnRH levels, leading to unsuccessful folliculogenesis and luteal phase dysfunction, further worsens hormones and thus, ovulation.<sup>22</sup> The TSH levels and ovulation are found to be indirectly related to each other i.e. higher TSH levels or low free T3 and free T4 levels disrupt normal conception whereas the positive link between free T4 levels and fertilization implies that normal thyroid function is directly proportional to reproductive health.<sup>23</sup> The multiple regression analysis signifies that both hypothyroidism and PCOS have a detrimental effect on reproductive health, both individually and in combination, as they adversely affect the number of ovulatory cycles and notably increase the rate of infertility by the logistic regression analysis. This is due to hormonal and metabolic disturbances making it difficult to accomplish normal conception.

Several shortcomings affect the findings of this study despite the obvious association between the conditions. The primary limitation was the small sample size being recruited from a single hospital and recruitment bias as all the female subjects belonged to an urban area with a stronger

socioeconomic status. Due to this, we may not be able to generalize the results over a wider population of women, both in terms of area and status, especially those underprivileged. Another drawback of this research is the self-reported clinical data which may not be cent per cent reliable. This data includes information about menstrual irregularities, detailed dietary habits, and lifestyle factors. Insulin insensitivity could have enhanced the metabolic dysfunction associated with PCOS and hypothyroidism, a thing poorly caught in this investigation. This underreporting or exaggerated reporting may cause bias making it difficult to understand the true extent of the reproductive dysfunction.

Future researchers are recommended to expand the area of investigation and reproduce these results in large-scale, diverse cohorts with authentic data in community-based settings to increase generalizability. The possibility of identifying the genetic underpinnings of this triad is also foreseen in the future and maybe availed by future investigators.

The results of this research emphasize the importance of comprehensive assessment and early and customized intervention in females presenting with the targeted endocrine disorders discussed, to depress the chances of infertility in the future. Routine screening of thyroid in patients is crucial along with keeping a check on the hormonal changes in the body. What's even more essential is the screening of thyroid dysfunction in women with PCOS as both occurring together potentially exacerbate the fertility outcomes. Addressing metabolic disturbances such as BMI, insulin insensitivity, dyslipidemia, and hypertension benefits both reproductive health and the overall fitness and well-being of an individual.

Given the increasing incidence of hypothyroidism and PCOS in women of reproductive age, our investigation sheds some light on the importance of an integrated approach which may have significant implications for improving fertility outcomes on a wider scale.

Our research foregrounds the correlation of PCOS and hypothyroidism with compromised reproductive outcomes, both individually and together, forming a triad of infertility. It points up the significance of early intervention and fertility treatments to improve the normal mechanism of conception. It represents a crucial area of research in reproductive health that deserves ongoing attention, considering the increased ratio of infertility in the females of this era.

## Conclusion:

This study highlights the impact of PCOS and hypothyroidism on normal conception, individually and together, thus forming a triad. This underscores the urge for routine checkups for thyroid function alongside an extensive treatment plan for PCOS to optimize positive results of fertilization and the overall well-being of the women. Continuous research is essential to have a better understanding of the topic and its management for the betterment of female reproductive health.

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