A Comparative Study of Oocyte Quality Between Hypothyroid and Non-Hypothyroid Patients Undergoing Fertility Treatment

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KEYWORDS

Infertility, ICSI,IVF, unexplained infertility, endometriosis, polycystic ovary disease (PCOD) decreased ovarian reserve (DOR), oocyte quality, hypothyroidism

ABSTRACT

Background:

Oocyte quality can be influenced by various factors, including hypothyroidism. This study aimed to compare the oocyte quality between hypothyroid and non-hypothyroid patients undergoing fertility treatments. The study was conducted as a retrospective analytical investigation at DPU in vitro fertilization (IVF) & Endoscopy Centre, Pimpri, Pune.

Method:

This retrospective cohort study assessed the oocyte quality of hypothyroid and non-hypothyroid women with diminished ovarian reserve (diminished ovarian reserve (DOR)), polycystic ovarian disease (polycystic ovarian disease (PCOD)), endometriosis, and unexplained infertility who were undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment. Clinical data from 400 patients were analyzed, with 182 selected for evaluation. Among these, 50% (n=91) had hypothyroidism, and the other 50% (n=91) did not.

Results:

The comparative study of oocyte quality showed no statistically significant differences between hypothyroid and non-hypothyroid groups in terms of total retrieved oocytes or quality categories (A: Good, B: Fair, C: Poor). Subgroup analyses of unexplained infertility (p=0.346), diminished ovarian reserve (DOR) (p=0.718), endometriosis (p=0.167), and polycystic ovarian disease (PCOD) (p=0.68) also showed no significant differences in oocyte quality between the groups.

Conclusion:

Women with hypothyroidism who underwent in vitro fertilization (IVF) were more likely to produce fewer oocytes and exhibit greater oocyte dysmorphism compared to non-hypothyroid women. However, these differences were not statistically significant

Categories: Obstetrics/Gynaecology, Infertility, Public health,

Introduction

Women of reproductive potential are highly susceptible to thyroid dysfunction, which can adversely affect their reproductive system [1]. According to a study by the National Institutes of Health, patients undergoing fertility treatment with high thyroid-stimulating hormone (TSH) levels are more likely to require in vitro fertilization (IVF) treatment compared to the general population [2]. The exact proportion remains unclear due to differences in study design, patient selection, and demographics [2]. Changes in thyroid function, particularly hypothyroidism, can lead to several dysfunctions, including metabolic alterations, inflammation, irregular menstrual patterns, anovulation, ovarian failure, and a higher incidence of miscarriage [3-4]. Studies have demonstrated that hypothyroidism can disrupt gonadotropin secretion by elevating serum prolactin levels [3-4]. Since the introduction of ultrasonography, cases of primary hypothyroidism have shown an increase in ovarian volume and a bilateral multicystic appearance of ovaries, which can sometimes resemble polycystic ovaries [5]. In summary, thyroid hormones significantly influence the female reproductive axis, with the hypothalamus-pituitary- ovarian and thyroid axes intricately interconnected and mutually influential.

Materials And Methods

Aims and objectives of the study

This study aimed to compare the quality of oocytes between hypothyroid and non-hypothyroid women.

Participants

A retrospective cohort study analyzed clinical data from 400 patients who underwent fertility treatment at DPU in vitro fertilization (IVF) & Endoscopy Center, Pune, Maharashtra.
Out of 400 cases, 182 patients were included in the study, comprising 50% hypothyroid (n=91) and 50% non- hypothyroid (n=91) women who received infertility treatment at the center from September 2021 to February 2024.

Inclusion criteria

Age >25 years and <45 years, Hypothyroidism with
thyroid-stimulating hormone (TSH) ≥2.5,
Patients with other risk factors such as diminished ovarian reserve (DOR), Endometriosis, and polycystic ovarian disease (PCOD). EXCLUSION CRITERIA
Age <25 years and >45 years,
Patients with underlying diseases incompatible with pregnancy, Patients
with empty follicular syndrome,
Hyperthyroidism.

Methodology

A retrospective comparative study was conducted between September 2021 and February 2024 on 182 women who underwent fertility treatment at DPU in vitro fertilization (IVF) & Endoscopy Center, Pune, Maharashtra. Of these, 91 women with hypothyroidism and 91 without hypothyroidism, meeting both inclusion and exclusion criteria, were included in the study. The study collected in vitro fertilization (IVF) cycle results, peak E2 levels, demographic data, and infertility history.

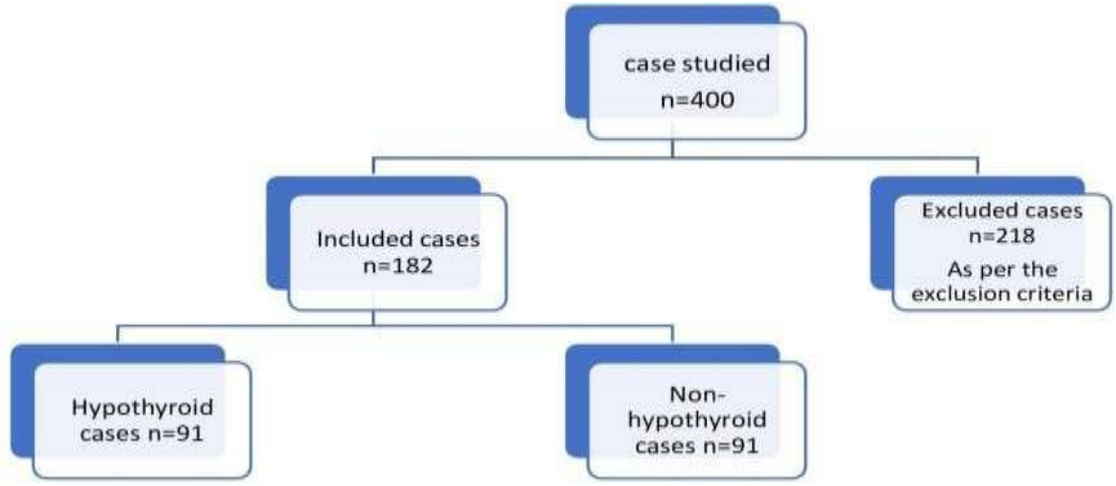
All patients had their thyroid-stimulating hormone (TSH) levels measured before commencing in vitro fertilization (IVF) treatment. Hypothyroid women had been previously diagnosed by their primary care physician and had received treatment with levothyroxine (12.5-75 μg/day) for at least 3 months, adjusted to maintain a thyroid-stimulating hormone (TSH) level of ≥2.5 μU/mL (normal range in our hospital). Non-hypothyroid women had thyroid-stimulating hormone (TSH) levels <2.5. No patients included in the study were diagnosed with hyperthyroidism based on thyroid-stimulating hormone (TSH) levels, and none had visible goiter or palpable thyroid nodules.

Controlled ovarian hyperstimulation (COH) was performed using either a standard gonadotropin-releasing hormone agonist or a progesterone-primed ovarian stimulation protocol (PPOS) for all participants. Human menopausal gonadotropin (hMG, 300-600 IU daily) was administered until at

least three follicles ≥18 mm in diameter were present. Subsequently, recombinant human chorionic gonadotropin (hCG, 375 mg) or agonist trigger decapeptide (0.2 mg) was administered subcutaneously. Oocyte retrieval was performed 35 hours post-hCG trigger, and cumulus-oocyte complexes (COCs) were graded after incubation in fertilization media for 2-3 hours.

Morphological assessments of oocytes were conducted based on cumulus corona cell presentation. Granulosa cells differentiate into mural GCs lining the follicular wall and cumulus cells surrounding the oocyte. Cumulus corona cells in close contact with the oocyte develop cytoplasmic projections that cross the zona pellucida and form gap junctions with the oolemma, forming a cumulus-oocyte complex. Hyaluronic acid secretion indicates nuclear maturity, and denudation using hyaluronidase allows precise determination of oocyte nuclear status, typically indicated by the presence of a first polar body (PBI).

FIGURE 1: Statistical Analysis



Data analysis

Data was collected using a preformed validated questionnaire. Data entry was done in Microsoft Excel and analysis was done using RStudio version 2023.03.1+446 Categorical variables were expressed in terms of frequency and percentage, and continuous variables in terms of mean and standard deviation. The association between two categorical variables was analyzed using a chi-square test with $p<0.05$ as a statistically significant value at 95% Confidence Interval.

Results

Baseline characteristics, number, and oocyte quality of both hypothyroid (50%) and non-hypothyroid groups (50%) are presented in
table *1*.

The mean age of the patient in the hypothyroid group was 35±10 and the non-hypothyroid group was 32.5±8.5.

A common indication for in vitro fertilization (IVF) treatment was Unexplained infertility (53), diminished ovarian reserve (DOR) (27), Endometriosis (8), and polycystic ovarian disease (PCOD) (3) in both groups.

Out of 91 hypothyroid patients, 79.1% of patients underwent LA protocol and 67.1% of patients underwent progesterone-primed ovarian stimulation protocol (PPOS).

After oocyte retrieval, we found that hypothyroid patients had fewer (581) oocytes than those in non- hypothyroid groups (772) but it was not statistically significant.

The quality of the oocytes was compromised in the hypothyroid group, but it was not statistically significant.

Characteristics	TSH≥2.5 (Hypothyroid =91)	TSH<2.5 (Non-hypothyroid=91)
Age(yrs)	35±10	32.5±8.5
Indication to IVF		
PCOS	3	3
Endometriosis	8	8
DOR	27	27
Unexplained infertility	53	53
PPOS	19(20.8%)	30(32.9%)
LA Protocol	72(79.1%)	61(67.1%)
Total no. of oocyte	581(42.9%)	772(57.0%)
Good quality of oocyte(A)	323(55.6%)	407(52.7%)
Fair quality of oocyte(B)	118(20.3%)	176(22.8%)
Poor quality of oocyte(C)	140(24.1%)	189(24.5%)

TABLE 1: Baseline characteristics, number, and oocyte quality of both hypothyroid and non-hypothyroid groups

Indication	Hypothyroid	Non-Hypothyroid	P-value
Number of oocytes retrieved	581 (42.9%)	772 (57.1%)	
Good quality oocytes (A)	323 (55.6%)	407 (52.7%)	
Fair quality oocytes (B)	118 (20.3%)	176 (22.8%)	0.479
Poor quality oocytes(C)	140 (24.1%)	189 (24.5%)	

TABLE 2: Comparative analysis of the total number and oocyte quality of both Hypothyroid and Non-hypothyroid groups.

Table *2* shows the comparative study of total retrieved oocytes and good (A), fair (B), and poor (C) quality of oocytes from both hypothyroid and non-hypothyroid groups, and the p-value is 0.479 which is not statistically significant.

Figure *2* shows the Comparative analysis of the total number and oocyte quality of both Hypothyroid and Non-hypothyroid groups

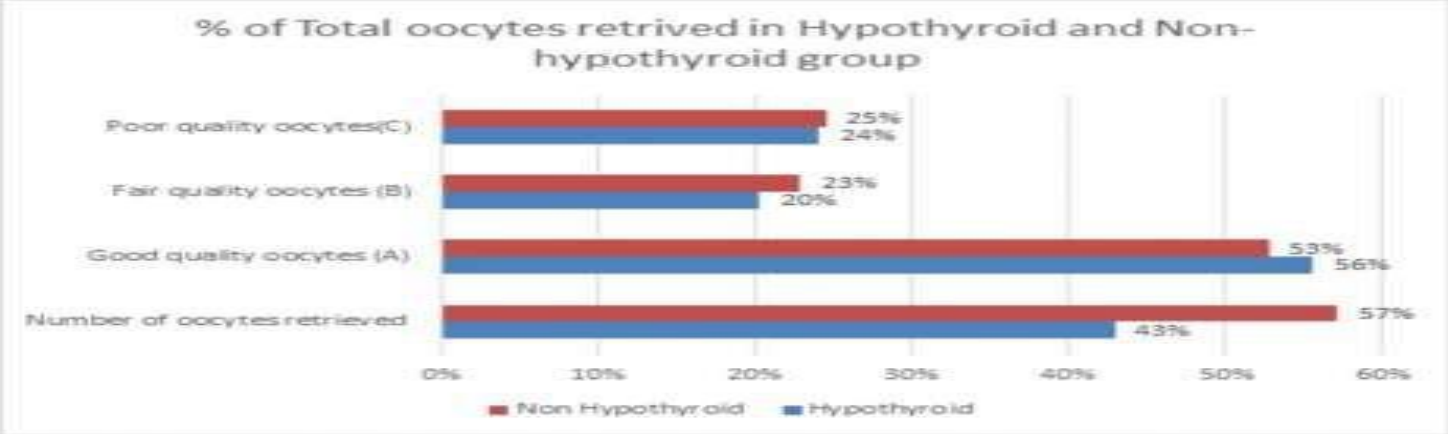


FIGURE 2: % of Total oocytes retrieved in Hypothyroid and Non-hypothyroid group

Indication	Sub Groups	Number of oocytes retrieved	Good quality oocytes (A)	Fair quality oocytes (B)	Poor quality oocytes (C)	P-value
DOR	Hypothyroid	99 (44.2%)	57 (57.6%)	19 (19.2%)	23 (23.2%)	0.718
	Non-Hypothyroid	125 (55.8%)	67 (53.6%)	23 (18.4%)	35 (28.0%)	
Endometriosis	Hypothyroid	31 (31.6%)	18 (58.1%)	9 (29.0%)	4 (12.9%)	0.167
	Non-Hypothyroid	67 (68.4%)	34 (50.7%)	13 (19.4%)	20 (29.9%)	
PCOS	Hypothyroid	41 (36.6%)	24 (58.5%)	7 (17.1%)	10 (24.4%)	0.68
	Non-Hypothyroid	71 (63.4%)	37 (52.1%)	17 (23.9%)	17 (23.9%)	
Unexplained infertility	Hypothyroid	410 (44.6%)	224 (54.6%)	83 (20.2%)	103 (25.1%)	0.346
	Non-Hypothyroid	509 (55.4%)	269 (52.8%)	123 (24.2%)	117 (23.0%)	

TABLE 3: Comparative analysis of the total number and oocyte quality of hypothyroid and non-hypothyroid

Table 3 shows the comparative study of total retrieved oocytes and good (A), fair (B), and poor (C) quality of oocytes in both hypothyroid and non-hypothyroid groups with all subgroups like Decreased ovarian reserve (diminished ovarian reserve (DOR)), Endometriosis, PCOS, and Unexplained Infertility and the p-value is not statistically significant in each group

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Indication	Sub Groups	Number of oocytes retrieved	Good quality oocytes (A)	Fair quality oocytes (B)	Poor quality oocytes (C)	P-value
DOR	Hypothyroid	99 (44.2%)	57 (57.6%)	19 (19.2%)	23 (23.2%)	0.718
	Non-Hypothyroid	125 (55.8%)	67 (53.6%)	23 (18.4%)	35 (28.0%)	
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	Non-Hypothyroid	71 (63.4%)	37 (52.1%)	17 (23.9%)	17 (23.9%)	
Unexplained infertility	Hypothyroid	410 (44.6%)	224 (54.6%)	83 (20.2%)	103 (25.1%)	0.346
	Non-Hypothyroid	509 (55.4%)	269 (52.8%)	123 (24.2%)	117 (23.0%)	

Table 4 shows the comparative study of total retrieved oocytes and good (A), fair (B), and poor (C) quality of oocytes in both hypothyroid and non-hypothyroid groups with all subgroups like Decreased ovarian reserve (diminished ovarian reserve (DOR)), Endometriosis, PCOS, and Unexplained Infertility and the p-value is not statistically significant in each

Discussion :

Thyroid hormones have been reported to influence oocyte maturation, with their receptors present in granulosa, cumulus cells, and the mature oocyte of the human ovarian follicle. Data reported in the literature support the concept that thyroid hormones play an important direct role in ovulation, early follicular development, differentiation, and stimulation of steroidogenic capacity in granulosa cells. Hypothyroidism in women can cause menstrual irregularities, primarily oligomenorrhea, and is associated with hyperprolactinemia, which decreases levels of E2, T, and Gn in the blood. After achieving euthyroidism, the levels of these hormones increase [6].

Based on studies, hypothyroidism (with or without polycystic ovaries) significantly increases the basal ovarian size compared to control patients. Therefore, hypothyroidism profoundly impacts ovarian size, in addition to causing ovarian cysts. Cyst formation may also lead to ovarian enlargement. Findings indicate that ovarian cysts resembling those seen in polycystic ovary syndrome may form due to hypothyroidism. Since serum-free T levels may be indirectly affected by hypothyroidism, these patients may exhibit signs of hirsutism. We did not evaluate hirsutism scores for our patients as it was not a prominent finding [3].

The molecular link between thyroid dysfunction and ovarian dysfunction is still largely unknown, but thyroid dysfunction can affect both the ovarian cycle and ovulation. Hypothyroidism decreases metabolic clearance of androstenedione and estrone in women and increases peripheral aromatization [5].

As a consequence of hypothyroidism, there was also low aromatase expression in the ovarian follicular fluid (FF), resulting in a reduced number of oocytes retrieved during assisted fertilization procedures. Thus, it is concluded that the low expression of aromatase in the ovary likely results from the small size of large tertiary follicles (antral follicles). Similarly, this low aromatase expression in antral follicles of hypothyroid animals might be associated with changes in the corpus luteum rather than changes in folliculogenesis. It has been demonstrated that hypothyroidism influences rat corpus luteum proliferation, angiogenesis, and apoptosis [4].

In this retrospective study, we focused on the impact of hypothyroidism on oocyte quality and number. The study results demonstrate that oocyte quality is comparable between women with hypothyroidism and those without. This assessment is based on the total number of oocytes and the quality categories of good, fair, and poor oocytes in both groups. It was observed that among hypothyroid patients, fewer oocytes were retrieved, and more displayed dysmorphisms such as granulation and dark cytoplasm. We also investigated the quality of oocytes in different groups, which had not been previously studied extensively due to the various factors that can affect oocyte quality, such as diminished ovarian reserve (DOR), endometriosis, and polycystic ovarian disease (PCOD).

However, due to the small sample size, the statistical power of this study was limited.

Conclusions

Our study demonstrated that women with hypothyroidism who underwent in vitro fertilization (IVF) were much more likely to produce fewer oocytes and a greater number of dysmorphic oocytes when compared to women with non- hypothyroidism who underwent the treatment. However, due to the small sample size, the statistical power of this study was limited. Consequently, further studies with larger sample sizes might be needed to confirm the relationship between Hypothyroidism and the quality and number of oocytes retrieved.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Instituational ethics sub committe, Dr.D.Y.Patil Medical College, Hospital & Research Centre,Pimpri,Pune issued approval I.E.S.C./W/133/2024 dated 15/07/2024. The Committee did not find anything ethically objectionable towards publication of the original research. Hence, waiver is granted for this original research.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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