



VOLUME 02 ISSUE 02 (2023)

AMERICAN JOURNAL OF
**MEDICAL SCIENCE
AND INNOVATION**
(AJMSI)



PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

Serum Levels of Thyroid Hormones in Infertile and Fertile Women Attending a Tertiary Care Hospital in North-Central Nigeria: A Comparative Reproductive Medicine Study

Halima Inya Aliu-Ayo¹, Kikelomo Temilola Adesina², Abiodun Akanbi Gafar Jimoh², Aloysius Obinna Ikwuka^{3*}Francis Chigozie Udeh³, Sikiru Abayomi Biliaminu⁴, Olayinka Waheed Ayo⁵

Article Information

Received: August 28, 2023**Accepted:** September 30, 2023**Published:** October 14, 2023

Keywords

Thyroid Hormones, Thyroid Disorders, Female Infertility, Female Fertility, Reproductive Medicine, Comparative Study, Reproductive Endocrinology, Reproductive Gynecology

ABSTRACT

Thyroid hormones have profound effects on reproduction. Normal thyroid function is necessary to maintain reproductive physiology, but its functional abnormalities may cause infertility manifesting as menstrual cycle irregularities. Aim of this research was to determine the serum levels of thyroid hormones in infertile and fertile women attending a tertiary care hospital in North-Central Nigeria. This comparative, reproductive medicine, cross-sectional study was carried out among one hundred and six (106) women attending the Gynecology Clinic of the Department of Obstetrics and Gynecology and the Family Planning Clinic of a tertiary care hospital in North-Central Nigeria. Women with a history suggestive of either primary or secondary infertility and the control women with no history of infertility were evenly grouped. Venous blood samples were collected and analyzed using Enzyme-Linked Immunosorbent Assay (ELISA) technique to determine fT₃, fT₄ and TSH levels. Data obtained were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23, and the level of statistical significance was set at p<0.05 and at a confidence interval of 95% for all inferential statistics. Majority (90.6%) of the 106 participants were euthyroid. However, most of the thyroid disorders (80%) were noticed in the infertile women, as 15.1% of them had one form of thyroid disorder. The mean TSH, fT₃ and fT₄ levels were higher in the infertile patients than in the control group, but the values were still within normal reference range. Mean values of TSH, fT₃ and fT₄ for the patients and controls were 1.35±1.65 versus 0.85±1.08 mIU/mL, 2.79±1.51 versus 2.19±1.15 pg/mL, and 1.15±0.33 versus 0.99 ± 0.29 ng/dL respectively. Median for TSH, fT₃ and fT₄ in the patients and controls were as follows: 0.80 (0.40–1.55) versus 0.60 (0.40–0.85) mIU/mL, 2.40 (1.45–4.20) versus 1.70 (1.35–2.95) pg/mL, and 1.10 (1.00–1.30) versus 1.00 (0.90–1.10) ng/dL respectively. The differences in the median between the patients and controls were statistically significant for fT₃ and fT₄ with p-values of 0.031 and 0.002 respectively. Subclinical hypothyroidism was the most prevalent (7.5%) thyroid disorder identified in the infertile women. Serum levels of thyroid hormones and prevalence of thyroid disorders were significantly higher in the infertile patients compared to the fertile women, although the overall prevalence of thyroid disorders was quite low.

INTRODUCTION

Gametes are ova and sperm cells that are haploid and have one copy of each type of chromosome i.e. 1–22 X or 1–22 Y (Ikwuka, 2023a). The sperm cell must fertilize an ovum in vivo or in vitro for conception (pregnancy) to occur. Infertility is a global health problem, a social demoralizing condition for couples and it is an important cause of marital disharmony (Panti, 2014). It is defined as failure to achieve clinical pregnancy after 12 months (1 year) of regular unprotected sexual intercourse – regular sexual intercourse is 2-3 times sexual intercourse per week (World Health Organization, 2010). Infertility can be further classified into primary infertility, in which no previous pregnancies have occurred and secondary infertility in which a prior pregnancy, although not necessarily a live birth, has occurred (Yao, 2002). The incidence of infertility suggests that 10-15% couples experience infertility (Bhattacharya, 20007), constituting

the major cause of gynecological consultations in Nigeria (Jimoh, 2011; Obuna, 2012; Okonofua, 2005). One of the greatest desires of couples is successful reproduction, especially in Africa, where a high premium is placed on childbearing. Infertility therefore causes severe emotional and social distress for the couple especially the social stigma attached to it in Africa (Gerias, 1992).

The endocrine system is the second key regulator of organ system function after the nervous system. The endocrine system uses hormones as chemical messengers in signaling, once stimulated. Upon stimulation, the thyroid gland secretes thyroid hormones (THs) which include tri-iodothyronine (T₃) and thyroxine (T₄). These hormones have a role in controlling basal metabolic rate (BMR), growth, and the development and differentiation of many cells in the body (Habibu, 2016). Normal thyroid gland function is described as euthyroidism, below normal as hypothyroidism, and above normal as hyperthyroidism.

¹ Department of Obstetrics and Gynaecology, R-Jolad Hospital, Lagos, Nigeria

² Department of Obstetrics and Gynaecology, University of Ilorin & University of Ilorin Teaching Hospital, Ilorin, Nigeria

³ College of Medicine and Health Sciences, American International University West Africa, Banjul, The Gambia

⁴ Department of Chemical Pathology and Immunology, University of Ilorin & University of Ilorin Teaching Hospital, Ilorin, Nigeria

⁵ The Bridge Clinic, Lagos, Nigeria

* Corresponding author's e-mail: aloyssiussweet@yahoo.com

Hyperthyroidism has been linked with oxidative stress and various systemic immune inflammatory processes. In inducing oxidative stress, major free radicals that are of physiological significance are superoxide anion, hydroxyl radical, and hydroperoxyl radical, while non-radical is hydrogen peroxide (Ikwuka, 2023b). In addition, the interplay, role and effects of metabolic syndrome diseases on female fertility are still being investigated by different researchers. Metabolic syndrome diseases, MSD (Hypertension, etc) are interrelated diseases with very high morbidity and mortality rates (Ikwuka, 2015; Ikwuka, 2017a; Ikwuka, 2017c; Ikwuka, 2023c; Virstyuk, 2016). Results from different studies have shown that high levels of blood pressure, glucose and lipid metabolic disorders, asymptomatic hyperuricemia, activation of systemic immune inflammation and fibrogenesis, contribute to kidney damage (Ikwuka, 2017d; Ikwuka, 2017e; Ikwuka, 2018a; Ikwuka, 2018c; Ikwuka, 2018d; Ikwuka, 2019a; Ikwuka, 2019c; Ikwuka, 2022; Ikwuka, 2023d; Virstyuk, 2017a; Virstyuk, 2018a; Virstyuk, 2019; Virstyuk, 2021a; Virstyuk, 2021b). Adiposity, diabetes mellitus and dyslipidemia have also been linked with erectile dysfunction (Baysah, 2023).

Other than hormonal imbalance, several factors including hazards linked to certain occupations (long distance driving, military, etc); previous history of genital infections (e.g. gonorrhea, orchitis, etc); previous history of surgery in the genital tract or inguinal region; lifestyle choices (sedentary lifestyle, lack of exercise, sleep deprivation, etc); environmental factors (e.g. exposure to ionizing radiation, pesticides, heat from tight underwears and hot baths) can adversely affect semen parameters and lead to male infertility (Baysah, 2023). In addition, lifestyles such as alcohol and tobacco consumption have been reported to cause infertility in men (Baysah, 2023). The effects of alcohol intake on semen quality have been reported to be caused by oxidative stress caused by an imbalance between Reactive Oxygen Species (ROS) produced by the alcohol consumed in the form of free radicals that contain one or more unpaired electrons and antioxidants (Ekechi, 2023). Nicotiana tabacum (local snuff) has been reported to have adverse effects on fertility and pregnancy in female wistar rats (Udeh, 2023a; Udeh, 2023b).

An established association between thyroid dysfunctions and infertility exists. These dysfunctions in the form of hyper- or hypothyroidism can adversely affect fertility by the presence of anovulatory cycles, luteal phase defects, high prolactin (PRL) levels, sex hormone imbalances, delayed onset of puberty, menstrual abnormalities, and miscarriages (Doufas, 2000; Poppe, 2003; Poppe, 2007; Rijal, 2011). However, the relative frequency and the chronology of the onset of reproductive dysfunction concerning the onset and type of thyroid disorder have not been well defined (Deshmukh, 2015).

Increasing evidence derived from experimental and clinical studies suggests that the hypothalamic-pituitary-thyroid axis and hypothalamic-pituitary-ovarian axis are physiologically related. Thyroid hormones (THs) receptors and their mRNA have been detected in

human granulosa cells and direct effects of iodine and THs on ovarian function have been proposed recently (Poppe, 2003). TH scan directly affects granulosa cells, corpus luteum and oocytes (Biswas, 1993), and they regulate follicle-stimulating hormone (FSH) stimulation in follicles and prevent their apoptosis (Kabodmehri, 2021). Thyroid-stimulating hormone (TSH) working in synergy with FSH can proliferate the granulosa cells (Kabodmehri, 2021). Therefore, an increase in TSH and thyrotropin-releasing hormone (TRH) can cause ovulatory dysfunction or corpus luteum dysfunction. In addition, the underperformance of the thyroid gland can affect ovarian function indirectly by decreasing the binding activity of sex hormone binding globulin (SHBG), increasing prolactin (PRL) levels and delaying luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH) (Lee, 2014).

The prevalence of thyroid dysfunction in infertile women is quite high. In a study done at Aminu Kano Teaching Hospital, Kano, Nigeria; thyroid disorders were observed in 23.4% of the subjects (Emokpae, 2011). The prevalence of thyroid dysfunction in infertile women was found to be 33.3% in a study by (Rahman, 2008) in India and 23% by (Sharma, 2012) while (Shivaleela, 2012) found a prevalence of 42%. However, a study done in Port-Harcourt, Nigeria by (Orazulike, 2018) showed a much lower prevalence of thyroid disorders in infertile women, which was 4.6%.

Subclinical thyroid dysfunctions (i.e. subclinical hyperthyroidism or subclinical hypothyroidism) may go unnoticed by unwary clinicians because these patients do not exhibit clinically overt physical symptoms and signs. This may lead to avoidable surgical interferences and related complications. With the advent of modern techniques, the estimation of various hormones can be done rapidly and reliably. The diagnosis of thyroid disorders can easily be made and appropriate treatment instituted with the results usually very gratifying.

Metabolic Syndrome Diseases require new and effective treatment regimens. Dapagliflozin which is a Sodium-Glucose Linked Transporter 2 (SGLT-2) inhibitor and Liraglutide which is a Glucagon-like Peptide 1 Receptor Agonist (GLP-1 RA) have been found to increase the effectiveness of treatment and improve the clinical course of type 2 diabetes mellitus and hypertension in patients with such comorbidities (Ikwuka, 2017b; Ikwuka, 2018b; Ikwuka, 2019b; Ikwuka, 2021; Virstyuk, 2017b; Virstyuk, 2018b; Virstyuk, 2018c). Rauwolfia vomitoria has a neuroprotective ability at it elevates antioxidants and suppresses lipid peroxidation (Ekechi, 2023). Proper management of thyroid dysfunction results in improvement in health status, normalization of menstrual abnormalities and restoration of normal fertility (Miciński, 2006). Therefore, it is very important to screen thyroid abnormalities in women with infertility, particularly in countries considered as areas with endemic goitre since female infertility associated with thyroid dysfunction in these areas is common (Zimmermann, 2008).

MATERIALS AND METHODS

Study Setting

This study was conducted at the Gynecology Clinics of the Department of Obstetrics and Gynecology of the University of Ilorin Teaching Hospital (UTH), Ilorin, Kwara State, North-Central Nigeria. UTH is located at Oke-Oyi, Old Jebba Road in Ilorin. The hospital serves as a major referral centre for Kwara State and parts of the nearby states of Oyo, Osun, Ekiti, Kogi and Niger. UTH is a tertiary care hospital, although it also offers primary and secondary healthcare services, and it is approved to undertake undergraduate and postgraduate medical training. The Gynecology Clinic is open to all, and an average of 144 women access healthcare at the clinics weekly, with 25% of them being for infertility cases (follow-up and new cases).

Study Population

The study population consisted of reproductive age women (18-45 years) attending the Gynecology Clinic of UTH, and with a history of inability to conceive of more than one year duration. This included those with previous pregnancies irrespective of outcome (secondary infertility) and those with no previous pregnancy (primary infertility). The control group consisted of consenting fertile women, who had carried pregnancy to term within two years prior to this study, and who were new patients at the Family Planning Clinic of UTH.

Sample Size and Sampling Technique

The formula for sample size calculation for a comparative, cross-sectional study was used (Charan, 2013). The parameter, proportion of thyroid disorders in women, was extracted from a previous study by (Fatima, 2014).

$$N = \frac{2(Z_{(\alpha/2)} + Z_{\beta})^2 \times P(1-P)}{(P_1 - P_2)^2}$$

N = Sample size

$Z_{(\alpha/2)} = 1.96$ at type 1 error of 5%

$Z_{\beta} = 1.28$ at 90% power

P_1 = Proportion of thyroid disorder in infertile women (47%)

P_2 = Proportion of thyroid disorder in fertile women (16%). P_1 and P_2 were extracted from a previous study by (Fatima, 2014).

P = Pooled prevalence = [prevalence in one group (P_1) + prevalence in another group (P_2)] / 2

$$P = [(0.47 + 0.16) / 2] = 0.32$$

$$N = \frac{2(1.96 + 1.28)^2 \times 0.32(1-0.32)}{(0.47-0.16)^2}$$

$$N = \frac{2(10.497)(0.2176)}{(0.31)^2}$$

$$N = \frac{2(10.497)(0.2176)}{0.0961}$$

$$N = 47.5$$

$N \sim 48$ patients

To make provision for attrition, 10% of the sample size was added. Thus 53 women in each arm of the study, and a total sample size of one hundred and six (106) women were recruited for the study. Respondents (patients and controls) were recruited consecutively till the sample size was complete.

Inclusion Criteria

Study participants were consenting women of reproductive age group (18-45 years) with primary or secondary infertility. Control group consisted of consenting fertile women matched for age. The control group members were new clients at the Family Planning Clinic, apparently healthy, with no history of infertility, have carried a pregnancy to term, and had no record of contraceptive use two years prior to this study.

Exclusion Criteria

Female patients outside the age group of 18-45 years; with previous or present thyroid disorders; women on steroids, hormonal contraceptives, or intrauterine contraceptive devices; women with a history of bleeding disorders; women with co-existing uterine fibroids (leiomyoma uteri).

Data Collection Method

The study spanned 6 months. Patients who presented with infertility were selected based on the inclusion criteria. Eligible women were informed and counseled about the study in a simple language that they understood. The study proforma was designed to obtain respondents' socio-demographic status, history of infertility, history of anterior neck swelling and other symptoms suggestive of thyroid disorder, medical conditions and past surgical procedures.

Sample Collection

Four milliliters (4ml) of whole blood sample was collected from a peripheral vein from each participant after an overnight fast of 8-10 hours into a labeled plain sample bottle. Food affects TSH levels, TSH decreases postprandial and a possible explanation for this is food-induced elevation of circulating somatostatin and consequent suppression of TSH (Takano, 1995). Patients who had coincidentally fasted for 8-10 hours at the first contact with the researcher were recruited while those who had already eaten were recruited at their next visit after they had been informed. Blood samples were allowed to stand for about 1-2 hours to allow clotting and retraction. The sera was drained from the clot and later centrifuged at 1,000 revolutions per minute (rpm) for 10 minutes. The whole sera obtained was transferred into labeled plain containers and kept frozen at -20°C before analysis.

Laboratory Procedures

Serum concentrations of TSH, fT3 and fT4 were determined by using Enzyme-linked immunosorbent assay (ELISA) kits manufactured by Monobind Ltd using Rayto microplate well reader. All reagents, calibrators/ standards and patients' specimens were brought to room temperature (20-27°C). The microplate wells for each calibrator/ standard and patient specimen were formatted, and the following steps described by (Winter, 2012) were taken:

1. 50µl of the calibrator and the patient specimen were dropped into the assigned well with a pipette.

2. 100µl of TSH, fT3, and fT4 enzyme reagent was added to each well.

3. The microplate was swirled gently for 20-30 seconds and then incubated for 60 minutes at room temperature.

4. The contents of the microplate were discarded by decantation, and the plate was tapped and blotted dry with absorbent paper.

5. 350µl of wash buffer was added followed by decantation, a process that was repeated 2 additional times.

6. 100µl of working substrate solution was added to all wells without shaking the plates. This was incubated for 15 minutes at room temperature.

7. 50µl of stop solution was added to each well and mixed for 15-20 seconds.

8. The absorbance/optical density was read in each well at 450nm. The results were read within 30 minutes of adding the stop solution.

9. Calibration curves were plotted for each analyte to determine the corresponding concentration of these analytes in the patients' samples.

Criteria for Diagnosis of Thyroid Dysfunction

The reference range of values for THs that was used for this study is the range of normal values on the kit used (TSH: 0.39-6.16 mIU/mL; fT3: 1.4-4.2 pg/mL; and fT4: 0.7-2.0 ng/dL) (Monobindinc, 2012a; Monobindinc, 2012b; Monobindinc, 2012c). Abnormal thyroid function can be categorized as hyperthyroidism (elevated fT3, fT4, and decreased TSH), hypothyroidism (decreased fT3, fT4, and elevated TSH), subclinical hyperthyroidism (normal fT3, fT4, but low TSH), and subclinical hypothyroidism (normal fT3, fT4, but elevated TSH) (Habibu, 2016).

Data Analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 23. Categorical variables (thyroid disorders) were presented as proportions and analyzed using the Chi-square test with Fisher's exact correction

used in cases where more than 20% of expected counts were less than 5. The continuous variable that is normally distributed (like age) was presented as mean and analyzed using the T-test while those that were not normally distributed (the THs levels) were presented as median and interquartile range and analyzed using the Mann-Whitney U test. The test of normality was done using the Shapiro-Wilk test. The level of statistical significance was set at $p < 0.05$ at a confidence interval of 95% for all inferential statistics.

Ethical Considerations

Ethical approval for this study was obtained from the Ethical Review Committee of UITH. Informed written consent was obtained from each participant after adequate counseling and all data from the study were treated with confidentiality and used solely for the study. Patients with thyroid abnormalities were referred for further evaluation, treatment, and were co-managed with endocrinologists.

RESULTS AND DISCUSSION

The findings in the one hundred and six (106) study participants are as shown below.

Socio-Demographic Variables of Participants

Table 1 shows the socio-demographic variables of the infertile women and control group. Women in the age group 25-28 years had the highest frequency of 30.2%, while women below 25 years of age had the lowest frequency of 13.2%. The mean age for the infertile and control group was 32.18 ± 6.47 years and 31.4 ± 5.74 years respectively. The majority of the patients and control (79.2% and 81.1%) respectively were employed. The majority of the study participants had a tertiary level of education (69.8%) and were Yorubas (83%). There were no significant differences in the age, occupation, educational status and ethnicity of the study participants in the two groups.

Table 1: Socio-demographic variables of the infertile women (patients) and fertile (control) group

Socio-demographic variable	Patient n (%)	Control n (%)	Total n (%)	χ^2 / t	p-value
Age (years)					
< 25	9 (17.0)	5 (9.4)	14 (13.2)	2.932	0.569
25 – 29	14 (26.4)	18 (34.0)	32 (30.2)		
30 – 34	7 (13.2)	11 (20.8)	18 (17.0)		
35 – 39	15 (28.3)	12 (22.6)	27 (25.5)		
40 – 45	8 (15.1)	7 (13.2)	15 (14.2)		
Total (n)	53	53	106		
Age (Mean $\pm$ SD)*	32.18$\pm$6.47	31.40$\pm$5.74		0.651ⁱ	0.516
Occupational status					
Employed	42 (79.2)	43 (81.1)	85 (44.3)	0.509	0.808
Unemployed	11 (20.8)	10 (18.9)	21 (19.8)		
Total (n)	53	53	106		
Educational status					
None	1 (1.9)	1 (1.9)	2 (1.9)	1.784 ^f	0.759

Primary	1 (1.9)	2 (3.8)	3 (2.8)		
Secondary	16 (30.2)	11 (20.8)	27 (25.5)		
Tertiary	35 (66.0)	39 (73.6)	74 (69.8)		
Total (n)	53	53	106		
Ethnicity					
Yoruba	45 (84.9)	43 (81.1)	88 (83.0)	1.137 ^f	0.822
Hausa	2 (3.8)	1 (1.9)	3 (2.8)		
Igbo	2 (3.8)	3 (5.7)	5 (4.8)		
Others	4 (7.5)	6 (11.3)	10 (9.4)		
Total (n)	53	53	106		

χ^2 : Chi square; t: Independent Samples T test; f: Fisher's exact test

Gynecological Variables and Symptoms Found among the Infertile and the Fertile Groups

Figure 1 illustrates the types of infertility found among the infertile patients. Secondary infertility was identified in 75.5% of the infertile women while 24.5% had primary infertility.

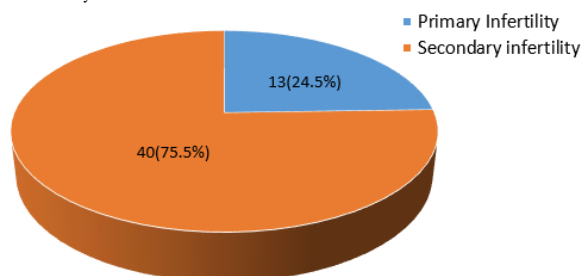


Figure 1: Types of infertility among the participants

Table 2 illustrates the symptoms present in the infertile patients and the control (fertile) group. None of the participants presented with anterior neck swelling. Two (3.8%) of the infertile patients experienced palpitations compared to three (5.7%) in the control group. Only one (1.9%) patient lost weight as against none in the control. Four (7.5%) patients had a history of abnormal weight gain as against two (3.8%) in the control group. Previous history of miscarriages was more prominent in infertile women (30.2%) than in fertile women (7.5%). Heat or cold intolerance was only evident among the infertile women (3.8%), and this group had more members (7.5%) with decreased libido than 1.9% seen in the control group. Of all these symptoms, only previous miscarriages presented a significant difference (p-value = 0.003) between the two groups.

Table 2: Symptoms found in women with infertility (patients) and the control (fertile) group

Variables	Patient n (%)	Control n (%)	Total n (%)	χ^2	p-value
Anterior neck swelling					
No	53 (100.0)	53 (100.0)	106(100.0)		
Palpitations					
Yes	2 (3.8)	3 (5.7)	5 (4.7)	0.210 ^f	1.000
No	51 (96.2)	50 (94.3)	101 (95.3)		
Weight loss					
Yes	1 (1.9)	0 (0.0)	1 (0.9)	1.010 ^f	1.000
No	52 (98.1)	53 (100.0)	105 (99.1)		
History of abnormal weight gain					
Yes	4 (7.5)	2 (3.8)	6 (5.7)	0.707 ^f	
No	49 (92.5)	51 (96.2)	100 (94.3)		0.678
Previous miscarriage					
Yes	16 (30.2)	4 (7.5)	20 (18.9)	8.874	
No	37 (69.8)	49 (92.5)	86 (81.1)		0.003*
Heat or cold intolerance					
Yes	2 (3.8)	0 (0.0)	2 (1.9)	2.038 ^f	
No	51 (96.2)	53 (100.0)	104 (98.1)		0.495
Decreased libido					
Yes	4 (7.5)	1 (1.9)	5 (4.7)	1.889 ^f	
No	49 (92.5)	52 (98.1)	101 (95.3)		0.363

χ^2 : Chi square test; f: Fisher's exact test; *: p-value <0.05

Comparison of the Serum Levels of Thyroid Hormones and Thyroid Dysfunctions in the Infertile Patients and the Control (Fertile) Group

Table 3 compares the serum levels of thyroid hormones of infertile and fertile women. The mean TSH, fT3 and fT4 levels were higher in the infertile women than in the fertile women with mean values of 1.35 ± 1.65 versus 0.85 ± 1.08 mIU/mL for TSH, 2.79 ± 1.51 versus 2.19 ± 1.15

pg/mL for fT3, and 1.15 ± 0.33 versus 0.99 ± 0.29 ng/dL for fT4. A significant difference was only in fT3 (p-value = 0.023) and fT4 (p-value = 0.009). The median for TSH, fT3 and fT4 was higher in the infertile group than in the fertile group, although only significant in fT3 (p-value = 0.031) and fT4 (p-value = 0.002). The lower and upper limits of the three parameters were within the normal reference range.

Table 3: Comparison of thyroid hormone levels of patients with infertility and the control (fertile) group

Variables	Patients	Control	U	p-value
TSH (mIU/mL)				
Mean ± SD	1.35±1.65	0.85±1.08	1149.000	0.064
Median (IQR)	0.80 (0.40-1.55)	0.60 (0.40-0.85)		0.105
fT3 (pg/mL)				
Mean ± SD	2.79±1.51	2.19±1.15	1062.500	0.023*
Median (IQR)	2.40 (1.45-4.20)	1.70 (1.35-2.95)		0.031*
fT4 (ng/dL)				
Mean ± SD	1.15±0.33	0.99±0.29	924.000	0.009*
Median (IQR)	1.10 (1.00-1.30)	1.00 (0.90-1.10)		0.002*

U: Mann-Whitney U test; *: p-value <0.05

Table 4: Prevalence of thyroid disorders among the infertile women (patients) and the control (fertile) group

Variable	Patient n (%)	Control n (%)	Total n (%)	χ^2	p-value	OR (95% CI)
Thyroid disorders						
Present	8 (15.1)	2 (3.8)	10 (9.4)	3.975f	0.046*	4.533 (0.915 – 22.465)
Absent	45 (84.9)	51 (96.2)	96 (90.6)			

χ^2 : Chi square; OR: Odds ratio; 95% CI: 95% Confidence interval; *: p-value <0.05

Table 4 demonstrates the prevalence of thyroid disorders among the infertile women (patients) and the control (fertile) group. Eight (15.1%) patients had thyroid disorders compared to two (3.8%) in the control group, a difference statistically significant (p-value = 0.046). Forty-five (84.9%) infertile and 51 (96.2%) fertile women were euthyroid.

Table 5 compares the pattern of thyroid disorders among infertile and fertile women. Four (7.5%) of the infertile women had subclinical hypothyroidism while one (1.9%) of the fertile women had subclinical hypothyroidism, and the difference was not significant (p-value = 0.37). Overt i.e. clinical hypothyroidism was present in two of the infertile patients but was absent in the fertile women. Overt i.e. clinical hyperthyroidism was present in two of the infertile women while only one of the fertile women

had it, and the difference was not significant (p-value = 1.000). Majority of the study participants were euthyroid – as observed in 45 (84.9%) of the infertile women as against 51 (96.2%) in the fertile women.

Table 6 shows the association between thyroid dysfunction and menstrual cycle abnormality. Five (62.5%) out of eight infertile women with thyroid dysfunction had menstrual irregularities, and others (37.5%) had normal menses. Thirteen (28.9%) out of forty-five euthyroid infertile women had menstrual irregularities, and others (71.1%) had normal menses. Of the two fertile women with a thyroid disorder, one had a menstrual anomaly and the others did not. Six (11.8%) of the fifty-one euthyroid fertile women had menstrual irregularities, while others (45) did not. These differences were not statistically significant (p-value >0.05).

Table 5: Pattern of thyroid dysfunction among infertile women and control (fertile) women

Thyroid disorder	Patients n (%)	Control n (%)	Total n (%)	χ^2 / t	p-value
Subclinical hypothyroidism	4 (7.5)	1 (1.9)	5 (4.7)	0.800	0.371
Overt (clinical) hypothyroidism	2 (3.8)	0 (0.0)	2 (1.9)	NA	
Overt (clinical) hyperthyroidism	2 (3.8)	1 (1.9)	3 (2.8)	0.000	1.000
None	45 (84.9)	51 (96.2)	96 (90.6)	0.260	0.610
Total	53	53	106		

χ^2 : Chi-square; NA: Chi-square not available because of zero '0' value

Table 6: Association between thyroid dysfunction and menstrual cycle abnormality

Thyroid disorder	Menstrual abnormality					
	Present	Absent	Total	χ^2	p-value	OR (95% CI)
	n (%)	n (%)	n (%)			
Patient						
Present	5 (62.5)	3 (37.5)	8	3.421 ^f	0.104	4.103 (0.854 – 19.716)
Absent	13 (28.9)	32 (71.1)	45			
Total	18	35	53			
Control						
Present	1 (50.0)	1 (50.0)	2	2.454	0.249 ^f	7.500 (0.413 - 136.271)
Absent	6 (11.8)	45 (88.2)	51			
Total	7	46	53			

χ^2 : Chi square; OR: Odds ratio; 95% CI: 95% Confidence interval

Undiagnosed and untreated thyroid disease can be a cause of infertility as well as sub-fertility which have important medical, economic, and psychological implications in our society (Verma, 2012). Aside from infertility, thyroid dysfunction could cause other reproductive disorders such as abnormal sexual development or menstrual irregularities. Even in fertility, pregnancy can be complicated by anemia due to SCD and despite the significant need for effective treatment options for SCD patients, current treatments both traditional and newly developed, only ameliorate acute and chronic SCD manifestations without addressing the underlying cause (Musa, 2023).

Of the infertile women, 75.5% had secondary infertility and 24.5% primary infertility. This is consistent with the findings of (Panti, 2014) which reported that 67.2% infertile female patients had secondary infertility and 32.8% had primary infertility. This dominance of secondary infertility in this study agrees with previous studies in Africa (Bala, 2003; Ekanem, 2006; Obuna, 2012; Okonofua, 2003), but contrasts the finding in most Western societies where primary infertility dominate with 63.1-80.0% (Habbu, 2016; Nasir, 2016).

In this study, 30.2% of infertile patients had previous miscarriages, a value close to the 37% reported by (Orazulike, 2018). Previous miscarriage was the only pregnancy outcome reported in their study by its design. It was also reported by the patient with some possible recall bias. Notwithstanding, this suggests that subfertility and pregnancy wastage are associated with thyroid disorders in women. Other symptoms presented by the subjects were palpitation (3.8%), weight loss (1.9%), abnormal weight gain (7.5%), heat/cold intolerance (3.8%), and decreased libido (7.5%). None of the 106 participants had anterior neck swelling.

The mean serum levels of thyroid hormones (TSH, fT3 and fT4) in this study were within the normal reference range although higher in the infertile women. The overall prevalence of thyroid disorders was 15.1% and 3.8% in the infertile and fertile women respectively. A similar study done in Port-Harcourt, Nigeria by (Orazulike, 2018)

found a much lower prevalence of thyroid disorders of 4.6% in infertile women. Similar studies done in India by (Rahman, 2008) and another by (Rijal, 2011) reported a prevalence of 25.6% and 33.0% respectively. Similarly, (Habbu, 2016), (Sharma, 2012), and (Shivaleela, 2012) reported higher prevalence rates (between 23.0- 42.3%) of thyroid disorders in infertile women. Thyroid hormone synthesis is influenced by iodine and it varies from clime to clime depending on water, soil, diet and fortification (Utiger, 2006). With this knowledge, the difference in the prevalence of thyroid disorders in these studies can therefore be related to the variation in the study participants' consumption of iodine-containing meals (Elahi, 2007).

TSH was higher, but fT3 and fT4 levels were significantly higher when serum levels of thyroid hormones of the patients are compared with that of the control group. (Habbu, 2016) and (Shivaleela, 2012) also reported findings of elevated mean serum fT3 and fT4 but low TSH in the infertile patients. (Orazulike, 2018) found no significant difference in the mean serum fT3, fT4, TSH, and TPOAb between patients and controls. These findings were different from the findings of (Fatima, 2014) where serum fT3 and fT4 were significantly decreased and serum TSH was significantly increased in infertile females when compared with fertile females. Serum fT3 and fT4 may be higher where a large proportion of the patients are hyperthyroid and the reverse may be the case when a large proportion of the patients are hypothyroid.

On types of thyroid dysfunction in this study, 9.4% had one type of thyroid dysfunction and 90.6% were euthyroid. In agreement with this, (Elahi, 2007) reported that 89.3% infertile patients and 93.4% fertile control were euthyroid. This finding is consistent with that of (Goswami, 2009), (Orazulike, 2018), and (Rijal, 2011). With infertile women being euthyroid, this suggests that other cause(s) of infertility aside from thyroid disorders should be evaluated during infertility examination as there can be significant single or multiple causes of infertility. Subclinical hypothyroidism was the most predominant thyroid disorder in this study. A study done in Kano

Nigeria by (Emokpae, 2011) got a higher prevalence (14.9%) for subclinical hypothyroidism as against the 9.4% in this present study. This may be because Emokpae's study assessed only TSH in hyperprolactinemic women focusing only on subclinical thyroid diseases while overt (clinical) thyroid diseases were not considered at all. Hypothyroidism is associated with increased production of TRH, which stimulates the anterior pituitary to secrete TSH and prolactin. Hyperprolactinemia adversely affects fertility potential by impairing GnRH pulsatility and thereby affecting ovarian function (Poppe, 2003). Therefore, it is advisable to check TSH and PRL levels in every infertile female, regardless of their menstrual rhythm (Abdul, 2015). Moreover, concerning subclinical hypothyroidism (Poppe, 2003) reported a prevalence of 0.9% and (Bohnet, 1981) reported a prevalence of 11%. The prevalence of subclinical hypothyroidism in subfertile women has been reported to vary from 0.7% to 43% (Poppe, 2007). This wide range is due to the differences in the sensitivity of serum TSH measurement. The revised clinical practice guidelines of the Endocrine Society recommend the measurement of serum TSH in women over the age of 30 years with infertility or a prior history of miscarriage, to screen for thyroid dysfunction (De Groot, 2012). In clinical practice guidelines for hypothyroidism in adults, the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) have recommended that treatment with L-thyroxine should be considered in women of childbearing age with subclinical hypothyroidism when they are planning a pregnancy (Garber, 2012). If infertile women planning pregnancy are diagnosed with subclinical hypothyroidism as well as overt (clinical) hypothyroidism, they are recommended to be treated to reduce risks of miscarriage and fetal developmental impairment or to improve the in vitro fertilization outcome (Lee, 2014). Evidence suggests that treating thyroid disorders and keeping TSH levels below 2.5 mIU/L may improve conception rates in infertile women and reduce early pregnancy loss (Garber, 2012). In the study by (Bohnet, 1981), subclinical hypothyroidism was considered an infertility factor by itself because treatment with L-thyroxine 50 mg/day normalized the mid-progesterone secretion and two out of the eleven treated women became pregnant.

Thyroid disorders have a known association with menstrual irregularities which may lead to infertility (Krassas, 1990). In this study, menstrual irregularities were significantly more predominant in the infertile patients than in the fertile control and 62.5% of the infertile patients with thyroid disorders had menstrual irregularities. (Orazulike, 2018) reported menstrual irregularities in 50% of the patients. (Nasir, 2016) also reported menstrual irregularities in 19.6% of the patients. (Goswami, 2009) similarly reported menstrual irregularities in 61.2% of the infertile patients and that 50% infertile patients with hypothyroidism had menstrual irregularities.

The impact of hypothyroidism on ovulation and menstrual function is related to numerous interactions of thyroid hormones with the female reproductive system, in turn causing infertility. In hypothyroidism, increased TRH production leads to hyperprolactinemia and altered gonadotropin-releasing hormone (GnRH) pulsatile secretion. This leads to a delay in luteinizing hormone (LH) response and inadequate corpus luteum leading to abnormal follicular development and ovulation. At the cellular level, thyroid hormone receptors are expressed in human oocytes and granulosa cells, and the hormones synergize with the follicle-stimulating hormone-mediated luteinizing hormone/human chorionic gonadotropin (hCG) receptor to exert direct stimulatory effects on granulosa cell function of progesterone production (Poppe, 2004). Altering the peripheral metabolism of estrogen and decreasing sex hormone-binding globulin (SHBG) production is another pathway by which hypothyroidism may impact on fertility. These pathways may result in abnormal feedback at the pituitary level and consequently infertility (Bassey, 2015).

Several aspects of the reproductive axis influenced by hyperthyroidism are comparable with the situation in hypothyroid women. In hyperthyroidism, the SHBG production, the conversion of androgens to estrogens, and the gonadotrophin response to GnRH are increased. The decrease in menstrual flow may also be related to effects on hemostatic factors, including the synthesis of factor VIII (Krassas, 2000). Women with hyperthyroidism and fertility problems should be treated with antithyroid drugs and/or surgery according to the cause of hyperthyroidism (Krassas, 2000).

CONCLUSION

Serum levels of thyroid hormones and the prevalence of thyroid disorders were significantly higher in the infertile patients when compared with the fertile women. Although the overall prevalence was quite low, thyroid abnormalities could still be implicated as a cause of female infertility. It is recommended that all infertile women should have thyroid function tests as part of their infertility work-up as many patients with thyroid diseases can easily be missed if they are not screened. Direction for future research on this topic would be to evaluate the menstrual pattern and irregularities and relate these to thyroid disorder patterns among women within this study setting. This will give a clearer picture of the relationship between symptoms of menstrual irregularities and thyroid dysfunction which varies from region to region.

Acknowledgments

Special thanks to all the infertile and fertile women who voluntarily participated in this study after making an informed decision.

Authors' Contribution

All authors contributed in different aspects of the research.

Conflict of Interest

The authors guarantee responsibility for everything published in this manuscript, as well as the absence of a conflict of interest and the absence of their financial interest in performing this research and writing this manuscript.

REFERENCES

- Abdul, R. & Seema, M. (2015). Effect of clinical/sub-clinical hypothyroidism on fertility in infertility case and the response of treatment for hypothyroidism on fertility in cases of infertility. *Journal of Dental and Medical Sciences*, 14(2), 5–8.
- Bala, M., Alfred, A. & Mohammed, B. (2003). Clinical presentation of infertility in Gombe, North-Eastern Nigeria. *Tropical Journal of Obstetrics and Gynaecology*, 20(2), 93–96.
- Bassey, I. E., Udoh, A. E., Essien, O. E., Kokoabasi, I., Isong, P., Gali, R. M. & Archibong, E. E. (2015). Thyroid hormones and prolactin levels in infertile women in South-South Nigeria. *Journal of Clinical and Diagnostic Research*, 9(3), 13–15.
- Baysah, P. V., Ikwuka, A. O., Udeh, F. C., Bleh, D. P. & Vilorio, T. (2023). Pathophysiological Effects of Alcohol and Tobacco Consumption on Semen Parameters of Men Attending a Fertility Clinic in West Africa. *American Journal of Biomedical and Life Sciences*, 11(4), 73–81. <https://doi.org/10.11648/j.ajbls.20231104.13>.
- Bhattacharya, S. (2007). *Infertility*. In: D. K. Edmonds (Ed.), *Dewhurst's Textbook of Obstetrics and Gynaecology*. Blackwell Publishers: Oxford, 440–460.
- Biswas, R., Bandyopadhyay, A., Guin, S. & Bhattacharya, S. (1993). Binding of thyroid hormone to mouse granulosa cell nuclei and its biological relevance. *Journal of Biosciences*, 18(3), 327–335.
- Bohnet, H., Fiedler, K. & Leidenberger, F. (1981). Subclinical hypothyroidism and infertility. *Lancet*, 5, 1287.
- Charan, J. & Biswas, T. (2013). How to calculate sample size for different study designs in medical research. *Indian Journal of Psychological Medicine*, 35(2), 121–126.
- De Groot, L., Abalovich, M., Alexander, E., Amino, N., Barbour, L. & Co-Bin, R. (2012). Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, 97(8), 2543–2565.
- Deshmukh, P., Boricha, B. G. & Pandey, A. (2015). The association of thyroid disorders with abnormal uterine bleeding. *International Journal of Reproduction, Contraception, Obstetrics and Gynaecology*, 4(3), 701–708.
- Doufas, A. & Mastorakos, G. (2000). The hypothalamic-pituitary-thyroid axis and the female reproductive system. *Annals of the New York Academy of Sciences*, 900, 65–76.
- Ekanem, I. & Ekanem, A. (2006). Endometrial pathology associated with infertility among Nigerian women. *Nigerian Postgraduate Medical Journal*, 13(4), 344–347.
- Ekechi, H. O., Ikwuka, A. O., Udeh, F. C. & Abraham, J. C. (2023). Effects of Ethanol Extract of *Rauwolfia vomitoria* Leaf on Lipid Profile and Cerebellar Histology in Cisplatin-induced Oxidative Stress. *British Journal of Medical and Health Research*, 10(5), 16–39. <https://doi.org/10.5281/zenodo.8042521>.
- Elahi, S., Tasneem, A., Nazir, I., Nagra, S. & Hyder, S. (2007). Thyroid dysfunction in infertile women. *Journal of the College of Physicians and Surgeons Pakistan*, 17(4), 191–194.
- Emokpae, M., Osadolor, H. & Omole, O. (2011). Sub-clinical hypothyroidism in infertile Nigerian women with hyperprolactinaemia. *Nigerian Journal of Physiological Sciences*, 26(1), 35–38.
- Fatima, A., Hooja, N., Mital, P., Singh, N. & Gothwal, S. (2014). Correlation of menstrual pattern with thyroid hormone level in infertile women. *International Journal of Sciences & Applied Research*, 1(2), 10–12.
- Garber, J., Cobin, R., Gharib, H., Hennessey, J., Klein, I. & Mechanick, J. (2012). Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocrinology Practice*, 18(6), 988–1028.
- Gerias, A. & Rushwan, H. (1992). Infertility in Africa. *Population Sciences*, 12, 25–46.
- Goswami, B., Patel, S., Chatterjee, M., Koner, B. & Saxena, A. (2009). Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. *Journal of Reproduction and Infertility*, 10(3), 207–212.
- Habbu, P. P. & Shaikh, A. K. (2016). Study of thyroid dysfunction in association with infertility. *International Journal of Biochemistry Research Review*, 11(2), 1–6.
- Ikwuka, A. O. (2015). Risk factors for the pathogenesis of diabetes mellitus type 2. *Materials of 84th Scientific and Practical Conference of Students and Young Scientists with International Participation "Innovations in medicine"*, p. 19. Available online: http://www.ifnm.edu.ua/images/snt/files/konferenciya/Tezu_2015.pdf
- Ikwuka, A. O. (2017)a. Dyslipidemia risk severity in patients with diabetes mellitus type 2 and essential hypertension. *Journal of the 21st International Medical Congress of Students and Young Scientists*, p. 59.
- Ikwuka, A. O. (2017)b. Effectiveness of dapagliflozin in patients with diabetes mellitus type 2 and essential hypertension. *Book of abstracts of the 7th International Students' Scientific Conference of Young Medical Researchers*, p. 102. Available online: http://www.stn.umed.wroc.pl/files/lm/Accepted_papers.16113.pdf
- Ikwuka, A. O. (2017)c. Influence of dyslipidemia in patients with diabetes mellitus type 2 and essential hypertension. *The Pharma Innovation Journal*, 6(3), 101–103. Available online: <http://www.thepharmajournal.com/archives/?year=2017&vol=6&issue=3&part=B>
- Ikwuka, A. O. & Haman, I. O. (2017)d. Features of kidney damage in patients with diabetes mellitus type

- 2 and essential hypertension. *Journal of 86th Scientific and Practical Conference of Students and Young Scientists with International Participation "Innovations in medicine"*, p. 144. Available online: [http://www.ifnmu.edu.ua/images/snt/86-konf-tezi%20\(1\).pdf](http://www.ifnmu.edu.ua/images/snt/86-konf-tezi%20(1).pdf)
- Ikwuka, A. O., Virstyuk, N. G. & Luchko, O. R. (2017)e. Features of the functional state of kidneys in patients with diabetes mellitus type 2 and essential arterial hypertension. *Materials of scientific-practical conference with international participation "Babenkivski reading"*, p. 48.
- Ikwuka, A. O. (2018)a. Clinical dynamics in patients with diabetes mellitus type 2 and concomitant essential hypertensive disease treated with dapagliflozin. *Journal of the 22nd International Medical Congress of Students and Young Scientists*, p. 32.
- Ikwuka, A. O. (2018)b. Clinical effectiveness of SGLT-2 inhibitors in patients with diabetes mellitus type 2 and essential hypertensive disease. *Endocrine Practice*, 24(1), 74. [https://doi.org/10.1016/S1530-891X\(20\)47129-0](https://doi.org/10.1016/S1530-891X(20)47129-0).
- Ikwuka, A. O. (2018)c. Features of kidney damage in patients with arterial hypertension and type 2 diabetes mellitus and optimization of treatment. Specialized Academic Council IFNMMU, Available online: http://www.ifnmu.edu.ua/images/zagalna_informacia/spec_vcheni_radi/2017-2019/%D0%9420.601.01/Ikwuka/Avtoreferat.pdf
- Ikwuka, A. O. & Paliy, Yu. (2018)d. Structural changes of the left ventricular myocardium in patients with essential arterial hypertension and diabetes mellitus type 2. *Abstracts of the 87th Scientific Conference of Students and Young Scientists with International Participation "Innovations in medicine"*, p. 25-26. Available online: https://www.ifnmu.edu.ua/images/snt/zaproshennia_eng.pdf
- Ikwuka, A. O. (2019)a. Clinical dynamics of nephropathy in patients with diabetes mellitus type 2 and concomitant essential hypertensive disease. *Clinical Medicine*, 19(2), s39. <https://doi.org/10.7861/clinmedicine.19-2-s39>.
- Ikwuka, A. O. (2019)b. Clinical effectiveness of GLP-1 RAs in patients with metabolic syndrome diseases. *Endocrine Practice*, 25(1), 104-105. [https://doi.org/10.1016/S1530-891X\(20\)46611-X](https://doi.org/10.1016/S1530-891X(20)46611-X).
- Ikwuka, A. O. & Virstyuk, N. G. (2019)c. Pattern of cardiac remodelling of the left ventricle in patients with essential hypertensive disease and concomitant type 2 diabetes mellitus. *Clinical Medicine*, 19(3), s92. <https://doi.org/10.7861/clinmedicine.19-3-s92>.
- Ikwuka, A. O. & Virstyuk, N. G. (2021). Influence of SGLT2 inhibitor and A2RB (AT1) on fibrogenesis and heart failure in patients with essential hypertensive disease combined with diabetes mellitus type 2. E-Poster No. 143 of the 44th & 45th Annual General and Scientific Meeting of the West African College of Physicians (WACP), 1 - 3 November, 2021. <https://doi.org/10.13140/RG.2.2.26912.87047>.
- Ikwuka, A. O. & Virstyuk, N. (2022). Prognostic markers of nephropathy in patients with dual metabolic syndrome diseases (essential hypertensive disease and concomitant type 2 diabetes mellitus). *Endocrine Practice*, 28(5), S65-S66. <https://doi.org/10.1016/j.eprac.2022.03.164>.
- Ikwuka, A. O. (2023)a. *Dr. Aloy's Core Essential Series (DACES) Medical Genetics*. 1st Edition. Science and Education Publishing, USA, p. 9. ISBN: 978-1-958293-02-7
- Ikwuka, A. O. (2023)b. *Dr. Aloy's Core Essential Series (DACES) Immunology*. 1st Edition. Science and Education Publishing, USA, p. 30. ISBN: 978-978-795-866-7
- Ikwuka, A. O. & Virstyuk, N. (2023)c. Patterns and Influence of Cardio-Metabolic Insufficiency in Patients with Essential Hypertensive Disease and Concomitant Type 2 Diabetes Mellitus. *Endocrine Practice*, 29(5), S32-S33. <https://doi.org/10.1016/j.eprac.2023.03.076>.
- Ikwuka, A. O., Virstyuk, N. G., Luchko, O. R. & Kobitovych, I. (2023)d. Heterogeneity Of Renal Pathogenicity On The Background Of Asymptomatic Hyperuricemia In Patients With Dual Metabolic Syndrome Diseases (Essential Hypertensive Disease and Type 2 Diabetes Mellitus). *British Journal of Medical and Health Research*, 10(2), 1-9. <https://doi.org/10.5281/zenodo.7690636>.
- Jimoh, A., Saka, M., Saidu, R., Salaudeen, G., Saka, A. & Raji, H. (2011). Sperm bank scheme and surrogacy institution; willingness and utilization of assisted reproductive technology among women of reproductive age group in Ilorin, Nigeria. *West African Journal of Assisted Reproduction*, 2(1), 33-39.
- Kabodmehri, R., Sharami, S. H., Sorouri, Z. Z., Ghashti, G. G., Milani, F., Chaypaz Z. & Ghalandari, M. (2021). The relationship between thyroid function and ovarian reserve: a prospective cross-sectional study. *Thyroid Research*, 14(1), 22.
- Krassas, G. E., Pontikides, N., Kaltsas, T., Papadopoulou, P., Paunkovic, J. & Paunkovic, N. (1990). *Disturbances of menstruation in hypothyroidism*. *Clinical Endocrinology*, 50(5), 655-659.
- Krassas, G. E. (2000). Thyroid disease and female reproduction. *Fertility and Sterility*, 74(6), 1063-1070.
- Lee, Y., Kim, C., Kwack, J., Ahn, J., Kim, S., Chae, H. & Kang, B. (2014). Subclinical hypothyroidism diagnosed by thyrotropin-releasing hormone stimulation test in infertile women with basal thyroid-stimulating hormone levels of 2.5 to 5.0 mIU /L. *Obstetrics and Gynaecology Sciences*, 57(6), 507-512.
- Miciński, P., Wielgus, E., Wojcieszyn, M. & Pawlicki, K. (2006). Abnormal ovarian reserve test reflects thyroid dysfunction. *Polish Journal of Gynaecological Investigations*, 9(1), 30-34.
- Monobindinc. (2012)a. Thyrotropin (TSH) Test System. Product code: 325-300. Lake Forest.
- Monobindinc. (2012)b. Free Triiodothyronine(fT3) Test System. Product code: 1325-300. Lake Forest.

- Monobindinc. (2012)c. Free Thyroxine (fT4) Test System. Product code: 1225-300. Lake Forest.
- Musa, S., Ikwuka, A. O., Udeh, F. C., Musa, A. A., & Chukwuezie, U. C. (2023). CRISPR-Cas9 Genomic Editing as an Innovation in the Management of Sickle Cell Disease: A Systematic Review. *American Journal of Medical Science and Innovation*, 2(2), 36-48. <https://doi.org/10.54536/ajmsi.v2i2.1760>.
- Nasir, S., Khan, M. M., Ahmed, S., Alam, S. & Ziaullah, S. (2016). Role of thyroid dysfunction in infertile women with menstrual disturbances. *Gomal Journal of Medical Sciences*, 14(1), 20-24.
- Obuna, J., Ndukwe, E., Ugboma, H., Ejikeme, B. & Ugboma, E. (2012). Clinical presentation of infertility in an outpatient clinic of a resource poor setting, South-East Nigeria. *International Journal of Tropical Diseases and Health*, 2(2), 123-131.
- Okonofua, F. E. (2005). Female and male infertility in Nigeria: Studies on epidemiology of infertility in Nigeria with special references to the role of genital tract infections and sexual reproductive risk factors. Sweden: Department of Public Health Sciences Divisions of International Health, 9-19.
- Okonofua, F. E. (2003). *Infertility in Sub-Saharan Africa*. In: F. E. Okonofua & K. Odunsi (Eds.), *Contemporary Obstetrics and Gynaecology for Developing Countries*, 128-156. Women's Health and Action Research Center.
- Orazulike, N. & Odum, E. (2018). Evaluation of thyroid function in infertile female patients in Port-Harcourt, Nigeria. *Tropical Journal of Obstetrics and Gynaecology*, 35(1), 38-42.
- Panti, A. & Sununu, Y. (2014). The profile of infertility in a teaching hospital in North-West Nigeria. *Sabel Medical Journal*, 17(1), 7-11.
- Poppe, K., Glinier, D. & Velkeniers, B. (2007). Thyroid autoimmunity and female infertility. *Clinical Endocrinology*, 66(5-6), 309-321.
- Poppe, K. & Velkeniers, B. (2004). Female infertility and the thyroid: Best Practice & Research. *Clinical Endocrinology & Metabolism*, 18(2), 153-165.
- Poppe, K. & Velkeniers, B. (2003). Thyroid disorders in infertile women. *Annals of Endocrinology*, 64(1), 45-50.
- Rahman, D., Fatima, P. & Banu, J. (2008). Thyroid disorders in female subfertility. *Journal of Chittagong Medical College Teachers Association*, 19, 46-50.
- Rijal, B., Shrestha, R. & Jha, B. (2011). Association of thyroid dysfunction among infertile women visiting infertility center of Om Hospital, Kathmandu, Nepal. *Nepal Medical College Journal*, 13(4), 247-249.
- Sharma, B., Kumar, A., Singh, C. & Kansal, R. (2012). Significance of thyroid profile (serum T3, T4 and TSH) in infertile women. *Indian Journal of Community Health*, 24(2), 148-152.
- Shivaleela, M., Poornima, R., Amit, D. & Jayaprakash, D. (2012). Thyroid dysfunction in infertile women. *Research Articles of Biological Sciences*, 2, 53-58.
- Takano, K., Ajima, M., Teramoto, A., Hata, K. & Yamashita, N. (1995). Mechanisms of action of somatostatin on human TSH-secreting adenoma cells. *American Journal of Physiology*, 268(4 Pt 1), E558-E564.
- Udeh, F. C., Ikwuka, A. O., Epete, M. A., & Igwe, E. C. (2023)a. Effects of Oral Consumption of Nicotiana Tabacum During Pregnancy on the Liver and Prolactin Levels of Adult Female Wistar Rats. *European Journal of Veterinary Medicine*, 3(2), 1-5. <https://doi.org/10.24018/ejvetmed.2023.3.2.93>.
- Udeh, F. C., Ikwuka, A. O., Epete, M. A., & Igwe, E. C. (2023)b. Effects of Local Tobacco Snuff Ingestion during Pregnancy on Renal Functions and Histology Architecture of Female Wistar Rats and on the Birth Weight of Their Pups. *American Journal of Medical Sciences and Medicine*, 11(1), 1-5. <https://doi.org/10.12691/ajmsm-11-1-1>.
- Utiger, R. (2006). Iodine nutrition - more is better. *New England Journal of Medicine*, 354, 2819-2821.
- Verma, I., Sood, R., Juneja, S. & Kaur, S. (2012). Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism on infertility. *International Journal of Applied & Basic Medical Research*, 2(1), 17-20.
- Virstyuk, N. G., Ikwuka, A. O., Haman, I. O. & Adebomi, M. S. (2016). Diabetes mellitus type 2, arterial hypertension and dyslipidemia. *Materials of 2nd International Scientific and Practical Conference "Therapeutic readings: modern aspects of diagnosis and treatment of diseases of internal organs"*, p. 46-47.
- Virstyuk, N. G. & Ikwuka, A. O. (2017)a. Diagnostic and prognostic markers of the diabetes mellitus type 2 course in connection with essential arterial hypertension taking into account the kidney function. *Precarpathian Journal Pulse*, 8(44), 53-62.
- Virstyuk, N. H., Ikwuka, A. O., Losyuk, L. V., Kobrynska, O. Ya. & Markiv, H. D. (2017)b. Dapagliflozin utility in patients with diabetes mellitus type 2 and essential hypertensive disease. *Actual Problems of Modern Medicine*, 4(60)1, 76-79. Available online: http://www.umsa.edu.ua/journal2stat4_2017_eng.html
- Virstyuk, N. G. & Ikwuka, A. O. (2018)a. Features of asymptomatic hyperuricemia in patients with diabetes mellitus type 2 and concomitant essential arterial hypertension. *Clinical and Experimental Pathology*, 1(63), 22-26. <https://doi.org/10.24061/1727-4338.XVII.1.63.2018.5>.
- Virstyuk, N. G., Ikwuka, A. O. & Didushko, O. M. (2018) b. Effect of dapagliflozin on the level of uric acid during asymptomatic hyperuricemia in patients with diabetes mellitus type 2 and concomitant arterial hypertension. *Art of Medicine*, 1(5), 21-26. Available online: <https://art-of-medicine.ifnm.edu.ua/index.php/aom/article/view/179/150>
- Virstyuk, N. H. & Ikwuka, A. O. (2018)c. Dapagliflozin influence on the clinical course of diabetes mellitus type 2 and essential hypertension in patients. Recent Advances in Environmental Science from the Euro-Mediterranean and Surrounding Regions, 2007-2008.

- https://doi.org/10.1007/978-3-319-70548-4_582.
- Virstyuk, N. G. & Ikwuka, A. O. (2019). Nephropathic characteristics in patients with diabetes mellitus type 2 and essential hypertensive disease. *Art of Medicine*, 1(5), 44-47. <https://doi.org/10.21802/artm.2019.1.9.44>.
- Virstyuk, N. G. & Ikwuka, A. O. (2021)a. Asymptomatic hyperuricemia and functional state of the kidneys in patients with essential arterial hypertension and concomitant diabetes mellitus type 2. *European Journal of Clinical Medicine*, 2(3), 100-104. <https://doi.org/10.24018/clinicmed.2021.2.3.65>.
- Virstyuk, N. H., Ikwuka, A. O., Luchko, O. R. & Kocherzhat, O. I. (2021)b. Peculiarities of renal insufficiency in patients with diabetes mellitus type 2 and arterial hypertension. Materials of scientific-practical conference with international participation “Achievements and prospects of experimental and clinical endocrinology” Twentieth Danilevsky readings, 86-87.
- Winter, W., Schatz, D. & Bertholf, R. (2012). The Thyroid: Pathophysiology and Thyroid Function Testing. In: C. Burtis, E. Ashwood & D. Burns (Eds), *Teitz Textbook of Clinical Chemistry and Molecular Diagnostics*, Saunders, 1905–1944.
- World Health Organization (2010). Mother or nothing: The agony of infertility. World Health Organization Bulletin, 877–953.
- Yao, M. & Schust, D. (2002). Infertility. In: J. Berek (Ed.). *Novak's Gynaecology, Lippincott Williams and Wilkins*, p. 973–1066.
- Zimmermann, M., Jooste, P. & Pandav, C. (2008). Iodine-deficiency disorders. *Lancet*, 372 (9645), 1251–1262.