Chapter-I

1.1 Introduction

The thyroid gland is a vital hormone gland in human body. It plays a major role in the metabolism, growth and development of the body. It also regulate many body functions by constantly releasing a steady amount of thyroid hormones into the bloodstream. If the body needs more energy in certain situations – for instance, during pregnancy, thyroid gland is altered to produces more hormones. Thyroid disorders during pregnancy are associated with serious maternal and fetal outcomes (Khakurel, *et al.* 2021).

The thyroid gland secretes 2 thyroid hormones (THs), 3,5,3′-triiodothyronine (T3) and 3,5,3′,5′−tetraiodothyronine (T4 also known as thyroxine). THs are synthesized using iodine, influence metabolism, and biosynthesize proteins in the body. These THs are regulated by thyroid stimulating hormone (TSH), which is secreted by the anterior pituitary gland. In turn, TSH is regulated by the hypothalamus via thyrotropin-releasing hormone (TRH). Thyroid hormones exhibit a variety of effects on the heart and peripheral vascular system. It is well known that they raise the heart rate and cardiac contractility, improve the systolic and diastolic function of the heart, and decrease the systemic vascular resistance (SVR) in resting condition (Klein and Ojamaa, 2001).

The thyroid hormone is well known for controlling metabolism, growth, and many other bodily functions. The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain proper feedback mechanism and homeostasis (Singh and Sandhu, 2019).

Thyroid hormones are vital for the proper functioning of the female reproductive system, since they modulate the metabolism and development of ovarian, uterine, and placental tissues. Therefore, hypo- and hyperthyroidism may result in subfertility or infertility or both in women.

Other well-documented sequelae of maternal thyroid dysfunctions include menstrual/estral irregularity, anovulation, abortion, preterm delivery, preeclampsia, intrauterine growth restriction, postpartum thyroiditis, and mental retardation in children (Silva, *et al.* 2018).

It is believed that around 10% of the Bangladeshi people suffer from clinically evident thyroid disorders. Subclinical hypo and hyperthyroidisms are included as thyroid disorders adding another 10% population to be dysthyroid totalling 20% of the population suffering from any type of thyroid disorders (Ansari, 2014).

Thyroid dysfunction is usually acquired and can occur at any time in life. The prevalence of clinical and subclinical hypothyroidism in women of reproductive age and during pregnancy is 0.3% and 4.3% respectively (Hollowell, *et al.* 2002; Idris, *et al.* 2005).

Hypothyroidism usually results from autoimmune thyroiditis, in which the body's own antibodies react against key thyroid proteins, such as thyroperoxidase (TPO) and/or thyroglobulin (Tg) resulting in destruction and the loss of gland function (Thangaratinam, *et al.* 2011). The occurrence of hypothyroidism in women is associated with reproductive disorders, such as delayed onset of puberty, anovulation, ovarian cysts, menstrual/estral irregularity, infertility, increased frequency of spontaneous abortions, and the birth of preterm infants with low birth weight and congenital anomalies (Panciera, *et al.* 2012; Krassas, *et al.* 2010; Silva *et al.* 2012). In addition, research has recently shown that, these gestational changes also result from compromised placental development with reduced proliferation and increased apoptosis of trophoblastic cells and a failure of intrauterine migration associated with alterations in the endocrine, immune, and angiogenic profiles at the maternal–fetal interface (Silva, *et al.* 2015; Souza, *et al*. 2017).

Thyroid disorders are the second most common endocrine dysfunction seen in pregnancy (Zhou *et al.* 2019). Various changes occur in thyroid function during pregnancy, and poor adjustments to these physiological changes result in thyroid dysfunction (Pahwa and Mangat 2018; Mannisto *et al.* 2010). These changes occur due to increased thyroid hormone-binding globulin (TBG) concentration, increased iodine clearance in the kidneys, and thyrotrophic

effect of human chorionic gonadotropin (HCG) (Saki *et al.* 2014; Korde *et al.* 2018). During pregnancy, optimum maternal thyroid function is essential for both the mother and the fetus (Joshi *et al*. 2015). Thyroid dysfunction can have an immense impact on pregnancy outcomes and fetal development. Various adverse effects such as miscarriage, preeclampsia, anemia, low birth weight, preterm birth, increased maternal and fetal morbidity, and mortality is reported (Sreelatha *et al.* 2017; Reid *et al.* 2010).

Thyroid dysfunction is one of the most common endocrine disorders of women in Bangladesh. It affects the female reproductive system and can be manifested by menstrual irregularities, pregnancy loss and infertility. The imbalance in the thyroid system in women with unexplained infertility highlights the importance of thyroid hormone for female fertility. The improvement of blastocyst development by adding thyroid hormone in early embryo cultures and the presence of proteins related to thyroid in fallopian tubes suggest involvement of thyroid hormone in early embryo development.

It is well known that, thyroid dysfunction have negative influence on female fertility and there is growing evidence of a correlation between untreated thyroid dysfunction during pregnancy and adverse pregnancy outcome for the pregnant woman and the growing fetus. Even the association between subclinical hypothyroidism (SCH) with infertility and adverse pregnancy outcomes is discussed, it's clear that untreated hypothyroidism and hyperthyroidism are associated with pregnancy complication. This highlights the importance of proper screening model for detection of thyroid dysfunction in early pregnancy. The aim of the study to survey on the pattern of thyroid hormone status among the reproductive age of women.

1.2 Research Objective

1.2.1 General Objective

To study on the pattern of thyroid hormone status and its complications among the reproductive age group of women.

1.2.2 Specific Objectives

- To study the prevalence of thyroid disorder and its complications among the reproductive age group of women in Chattogram.
- To evaluate the thyroid hormone level and its complications in reproductive age group of women in Chattogram.

Chapter-II

Review of literature

2. THYROID

2.1.1 Thyroid hormones

Thyroid hormones (TH), thyroxine (T4) and 3,3', 5-trijod-L-tyronin (T3), are secreted from and stored in the thyroid gland. Thyroid hormones regulate energy homeostasis, cell proliferation, and carbohydrate-, fat- and protein metabolism (Akram, 2019).

2.1.2 The hypothalamic and the pituitary regulation of thyroid hormone secretion

The production of THs is mainly regulated by hypothalamic – pituitary – thyroid axis (Werner *et al.* 1968). Thyroid stimulating hormone (TSH) stimulates the production of TH in response to thyroid releasing hormone, produced by the hypothalamus. Thyroid releasing hormone (TRH) is transported to the pituitary via the hypothalamic hypophyseal portal system. TSH and TRH are regulated by negative feedback by T3 and T4. Furthermore, thyroid hormone levels are under influence of other hormones such as glucocorticoids, somatostatin, dopamine, prolactin, estrogen and growth hormones.

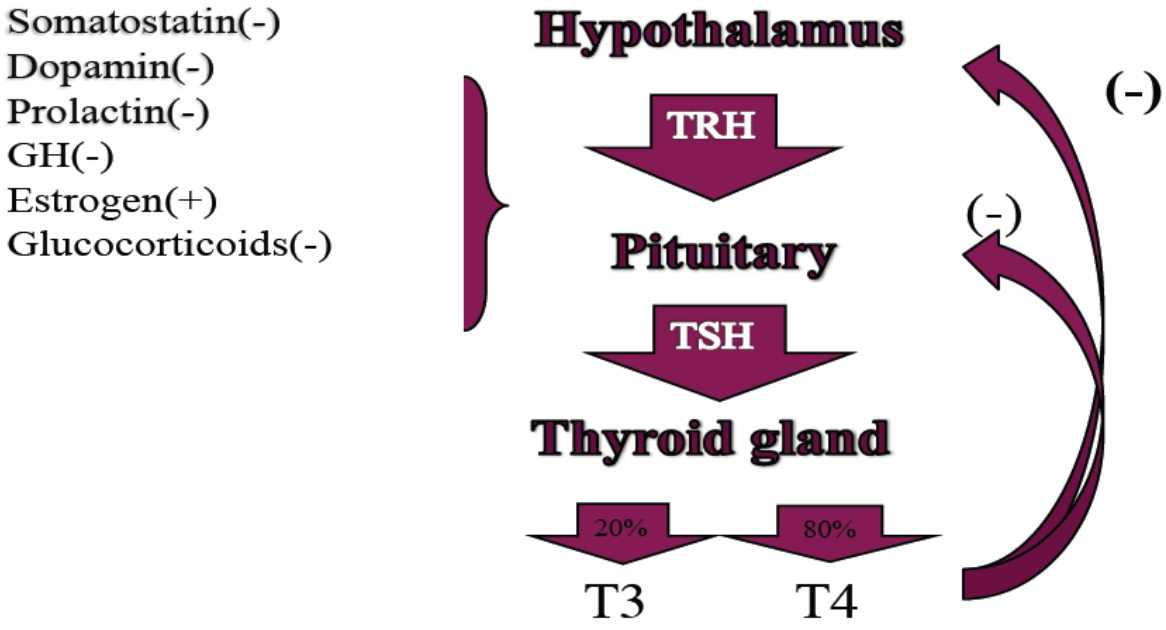

Figure 1. The hypothalamic--pituitary--thyroid axis.

2.1.3 Thyroid stimulating hormone, TSH and TSH receptor

TSH is a heterodimeric glycoprotein hormone that shares the α-subunit with other glycoprotein hormones, such as human chorionic gonadotrophin (hCG), follicle stimulating hormone (FSH) and luteinizing hormone (LH) but it has an unique β-subunit. TSH exerts its effect by binding to the TSH-receptor (TSH R), which is located in the cell membrane of thyroid follicular cells. TSH R is a member of the G-protein associated receptor family, similar to the hCG and LH receptors (Vassart *et al.* 2004). TSH R expression has been shown in thyroidal tissue and also in extra-thyroidal tissues such as adipose tissue, testes, ovaries and endometrium (Aghajanova *et al.* 2011).

2.2 THYROID DYSFUNCTION

Changes in serum concentration levels of TSH are the most commonly used indicator of thyroid dysfunction such as autoimmune thyroid dysfunction, hypothyroidism, subclinical hypothyroidism and hyperthyroidism.

2.2.1 Hypothyroidism

Hypothyroidism is defined as low levels of thyroid hormone combined with elevated levels of TSH. Hypothyroidism can be due to low secretion of hormone from the thyroid gland, primary hypothyroidism, or due to low levels of TSH, that is central hypothyroidism. The worldwide prevalence of hypothyroidism is between 0.6 to 12 per 1000 women and 1.3 to 4 per 1000 men (Vanderpump *et al.* 1995).

Iodine deficiency is the most common cause of hypothyroidism worldwide (Andersson *et al.* 2012; Zimmermann *et al.* 2012). In iodine sufficient countries like Sweden, the most common thyroid disorder is chronic autoimmune thyroiditis, usually known as Hashimoto's thyroiditis. The diagnosis of Hashimoto's thyroiditis is confirmed by the presence of anti-thyroid peroxidase antibodies (TPO-Ab) (McLeod and Cooper 2012). Hypothyroidism can also be caused by earlier treatment of Graves´ disease such as antithyroid drugs, thyroidectomy or radioiodine treatment. Symptoms of hypothyroidism are nonspecific and vary due to the severity of the disorder. Dry brittle hair and nails are common in these patients who may also have symptoms of chilliness, fatigue, weight gain and slowing of higher mental function. Treatment of hypothyroidism is thyroid hormone (L-T4) substitution.

2.2.2 Subclinical hypothyroidism

Subclinical hypothyroidism (SCH), defined as elevated serum levels of TSH combined with normal thyroid hormone levels (Poppe *et al.* 2003). Studies performed in the United States have shown a prevalence of 3 to 15 % of SCH. Women with SCH may have vague or nonspecific symptoms or have symptoms similar to those with hypothyroidism. Women with TPO-Ab and elevated TSH levels are at higher risk of progressing from SCH to hypothyroidism (Huber *et al.* 2002). Women with TPO-Ab are at higher risk to development postpartum thyroiditis (Premawardhana *et al.* 2004).

2.2.3 Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism is defined as elevated thyroid hormone levels combined with almost undetectable levels of TSH. It affects approximately 2.0 % of women and 0.2 % of men worldwide. The most common type of hyperthyroidism is Graves´ disease. This condition is due to stimulation of thyroid gland by TRAb on the thyroid follicular cells (Jacobson *et al.* 1997). Common symptoms of hyperthyroidism are weight loss, palpitations, tremulousness, heat intolerance, and anxiety. Physical findings such as tachycardia, thyroid enlargement and tremor are also seen. Treatment options are: anti-thyroid drugs, surgery and radioiodine treatment.

2.3 THYROID DYSFUNCTION AND FEMALE REPRODUCTION

2.3.1 Hypothyroidism

Women with hypothyroidism have low levels of sex hormone binding globulin (SHBG) and low levels of estrogen and testosterone. Menstrual disturbances such as oligomenorrhea, amenorrhea and menorrhagia are common in hypothyroid women. These 12 disturbances can partly be due to TRH-induced hyperprolactinemia and thus altered pulsatile GnRH secretion and partly due to defect hemostasis with low levels of coagulation factors (Akinci *et al.* 2011).

2.3.2 Hyperthyroidism (thyrotoxicosis)

Thyrotoxicosis may lead to different symptoms ranging from normal menstrual cycles to menstrual irregularities such as menorrhagia, oligomenorrhea, amenorrhea, anovulation and

reduced fertility (Poppe *et al.* 2002). Women with Graves´ Disease have 2 to 3 times higher serum levels of estrogen and LH during all phases of the menstrual cycle, probably due to high levels of SHBG. The production of testosterone and androstenedione is also increased in these women (Redmond, 2004).

2.4 Related previous study

Unuane et al. (2020) observed thyroid autoimmunity (TAI) and/or thyroid dysfunction are prevalent in women of reproductive age and have independently been associated with adverse fertility and pregnancy outcomes, in the case of spontaneous conception or after assisted reproductive technology (ART). Thus, it seems reasonable to screen for thyrotropin (TSH) and thyroid peroxidase autoantibodies (TPO-abs) in infertile women attempting pregnancy. However, even if the relationship between fertility and thyroid dysfunction and/or TAI persists when properly controlled for other variables, it remains challenging to claim causation. Several studies with different designs (cross sectional, case control, prospective and retrospective cohort studies) have looked at the association between thyroid autoimmunity, thyroid function and fertility. Heterogeneity among study results are related to small numbers of included patients, poor study design, selection of causes of infertility and different assays used to measure TAI, thyroid hormones and TSH reference values. Indeed, there is no consensus regarding the upper limit of normal for TSH to define thyroid dysfunction and the cut-off levels for intervention. Furthermore, data from interventional trials looking at the impact of levothyroxine treatment on fertility outcome in randomised controlled studies are scarce. Despite the recent update of the guidelines by the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease during Pregnancy and the postpartum, many questions remain unsettled in ART

Guo et al. (2018) observed serum levels of thyroid hormones including free triiodothyronine (FT3), total triiodothyronine (TT3), free thyroxine (FT4), total thyroxine (TT4) and thyroid-stimulating hormone (TSH) were abstracted from the medical records. Relationships between tertiles of metal levels (setting the lowest tertile as the reference) and percent changes in thyroid hormones were estimated by multivariable adjusted linear regression models. Few

epidemiological studies have investigated associations of exposure to multiple metals with thyroid hormone homeostasis, especially for the pregnant women. Five metals [arsenic (As), selenium (Se), manganese (Mn), nickel (Ni), antimony (Sb)] were significantly linked to decreased levels of one or more thyroid hormones based on trend tests in the single-metal models. Percent changes [95% confidence intervals (CIs)] in thyroid hormones for the third tertiles of metals remained significant between FT3 and As [−3.53% (−5.48%, −1.54%)]; and between TT3 and As [−4.19% (−7.00%, −1.31%)]; and between FT4 and Mn [−2.05% (−3.49%, −0.58%)], Sb [−1.99% (−3.44%, −0.52%)] in the multiple-metal models. Thyroid hormone concentrations were reversely related to the levels of blood metals of As, Mn and Sb among Chinese pregnant women. Additional prospective studies are warranted to confirm the causality. Paper capsule: Exposure to multiple metals was reversely associated with one or more thyroid hormones in the Chinese pregnant women.

Tasnim and Begum (2017) assessed thyroid hormone status in female infertility. Infertility is a global health issue causing great personal sufferings and distress. It is also matter of social injustice and inequality. Both hyperthyroidism and hypothyroidism causes menstrual disturbances secondary to anovulation. The degree of disturbances varies from abnormal sexual development through menstrual irregularity to infertility. Serum T3 and T4 were significantly lower in group B than that of group A ($P<0.001$). The results of the their study, it may be concluded that lower level of serum T3,T4 may be related with infertility.

Unnikrishnan et al. (2013) reported that the prevalence of self reported and undetected hypothyroidism, and anti-thyroid peroxidase (anti-TPO) antibody positivity was assessed. Hypothyroidism is believed to be a common health issue in India, as it is worldwide. A total of 5376 adult male or non-pregnant female participants ≥18 years of age were enrolled, of which 5360 (mean age: 46±14.68 years; 53.70% females) were evaluated. The overall prevalence of hypothyroidism was 10.95% (n=587, 95% CI, 10.11-11.78) of which 7.48% (n = 401) patients self reported the condition, whereas 3.47% (n=186) were previously undetected. Inland cities showed a higher prevalence of hypothyroidism as compared to coastal cities. A significantly higher (P <0.05) proportion of females vs. males (15.86% vs 5.02%) and older vs. younger (13.11% vs 7.53%), adults were diagnosed with hypothyroidism. Additionally, 8.02% (n = 430)

patients were diagnosed to have subclinical hypothyroidism (normal serum free T4 and TSH >5.50 µIU/ml) Anti – TPO antibodies suggesting autoimmunity were detected in 21.85% (n = 1171) patients. The prevalence of hypothyroidism was high, affecting approximately one in 10 adults in the study population. Female gender and older age were found to have significant association with hypothyroidism. Subclinical hypothyroidism and anti-TPO antibody positivity were the other common observations.

Silva et al. (2018) summarized and update the available information related to the role of thyroid hormones in the morphophysiology of the ovary, uterus, and placenta in women and animals and the effects of hypo- and hyperthyroidism on the female reproductive system. Thyroid hormones are vital for the proper functioning of the female reproductive system, since they modulate the metabolism and development of ovarian, uterine, and placental tissues. Therefore, hypo- and hyperthyroidism may result in subfertility or infertility in both women and animals. Other well-documented sequelae of maternal thyroid dysfunctions include menstrual/estral irregularity, anovulation, abortion, preterm delivery, preeclampsia, intrauterine growth restriction, postpartum thyroiditis, and mental retardation in children. Several studies have been carried out involving prospective and retrospective studies of women with thyroid dysfunction, as well as in vivo and in vitro assays of hypo- and hyperthyroidism using experimental animal models and/or ovarian, uterine, and placental cell culture. These studies have sought to elucidate the mechanisms by which thyroid hormones influence reproduction to better understand the physiology of the reproductive system and to provide better therapeutic tools for reproductive dysfunctions that originate from thyroid dysfunctions.

Hema et al. (2020) observed abnormal uterine bleeding (AUB) is one of the commonest presentations encountered in gynecological outpatient department. Menstruation is also regulated by many mechanisms, including thyroid hormone. So, for definitive management of AUB, it becomes imperative to assess thyroid status in those with abnormal uterine bleeding. Total of 522 presented with AUB. AUB was most common among woman age >40 years at 49.23% (257 of total 522 cases). AUB was more common in Multipara at 61.49% (321 of 522 cases). Menorrhagia was commonest pattern in AUB accounting for 51.34% (268 of 522cases). Thyroid dysfunction was present in 12.27% (64 of 522) of cases with AUB. Among them

hypothyroid was most common accounting for 8.81% (46 of 522 cases). Hyperthyroidism was present in 3.44% (18 of 522 cases). Menorrhagia was most common pattern in Hypothyroidism at 65.21% (30 of 46 cases, followed by polymenorrhea at 17.39% (8 of 46 cases). Oligomenorrhea was most common in hyperthyroid group at 55.54% (10 of 18 cases) closely followed by hypomenorrhea at 44.44% (8 of 18 cases). Abnormal uterine bleeding (AUB) is one of the commonest gynecological complaints at gynecological OPD. Thyroid dysfunction is noted consistently in cases of AUB. So, evaluation of thyroid profile should be part of evaluation of AUB, especially during perimenopause.

Nargis et al. (2018) carried out to see the prevalence of thyroid disorders among infertile women with menstrual irregularities. It was a cross sectional study conducted at the Department of Obstetrics and Gynecology, IbnSina Medical College, Dhaka from January to December 2016. They studied total 160 infertile women and 100 normal fertile women volunteers were selected on OPD basis between age group of 18-45 years. Out of 160 infertile women, 100 were of primary infertility and 60 of secondary infertility. There was a higher prevalence of hypothyroidism in the infertile women as compared to the fertile one in the study group, particularly in secondary infertility. Oligomenorrhoea was most common in infertile women. Hypothyroidism is commonly associated with ovulatory failure. Hence, assessment of serum TSH is mandatory in the work up of all infertile women, especially those presenting with menstrual irregularities. So the basic approach should be to identify those hypothyroid individuals who have greatest risk for the development of infertility. Long standing hypothyroidism may develop ovulatory dysfunction. So identifying and treating hypothyroidism at an earlier stage before the appearance of ovulatory dysfunction can have potentially great preventive value.

Ganie et al. (2020) estimated the prevalence of thyroid disorders and evaluated urinary iodine concentration (UIC) and thyroid autoantibody status among Gujjar and Bakerwal tribes of Kashmir valley. A total of 763 subjects (56.4% women and 43.6% men) with a mean(±SD) age of 39.46 (±17.51) ranging from 10 to 85 years and mean(±SD) body mass index (BMI) of 21.28 (±4.16) kg/m2 were studied. Goiter was detected in 6.8%, while 33.2% subjects had some form of thyroid dysfunction (including 24.1% subclinical and 6.8% overt hypothyroidism). Subclinical and overt hyperthyroidism was observed in 1.3 and 0.9% of

cases, respectively. Anti-TPO Ab was elevated in 13.6%, while the median [interquartile range (IQR)] for UIC was 154.50 (135) μg/L [156.13 (134) μg/L in men and 147.26 (136) μg/L in women]. A negative correlation was observed between UIC and anti-TPO Ab ($r = -0.087$, $P = <0.05$). These novel data on iodine and thyroid status among a tribal population of India generally inhabiting in remote sub-Himalayan belts demonstrate high prevalence of subclinical hypothyroidism (SCH) with persistent iodine deficiency. These preliminary data may warrant large well-designed studies to carry out comprehensive assessment of the problem in this high-risk and marginalized population.

Fupare et al. (2015) carried out to correlate thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women. The prevalence of infertility is estimated to be between 12 and 14%. It thus represents a common condition, with important medical, economic and psychological implications. Prolactin and TSH were positively correlated with each other. They were also negatively correlated with LH, FSH & T3 in infertile groups. Therefore we can say that hyperprolactinemia& hypothyroidism plays key role in etiopathogenesis of infertility. Long standing hypothyroidism may develop ovulatory dysfunction, and hyperprolactinemia. So identifying and treating hypothyroidism at an earlier stage before the appearance of ovulatory dysfunction and hyperprolactinemia, can have potentially great preventive value. So TSH screening of all females of early reproductive age group should be done so as to detect subclinical thyroid problem and to prevent infertility risk.

Goswami et al. (2009) reviewed the impact of thyroid status on the menstrual function and fertility of the subjects. The increased prevalence of upper normal limit of TSH and raised antithyroperoxidase antibody titer indicate, relatively more frequent occurrence of compensated thyroid function in infertile women. This finding necessitates considering such cases for a thorough investigation of pituitary-thyroid axis. The majority of the infertile and fertile women were euthyroid. In infertile group, the crude prevalence of hypothyroidism was slightly higher in the infertile group in comparison with that of the general population. There was a positive correlation between serum TSH and prolactin levels in the infertile subjects. Menstrual disorders (mainly oligomenorrhea), were reported by about 60% of the infertile women. Hyperprolactinemia was depicted in 41% of the infertile women while it was only 15% in the control group. The infertile women with hypothyroidism had significantly higher prolactin

levels when compared to the subjects with hyper- or euthyroidism. There was a significant association between abnormal menstrual patterns and anovulatory cycles, as observed on endometrial examination of infertile subjects with raised serum prolactin levels. There is a greater propensity for thyroid disorder in infertile women than the fertile ones. There is also a higher prevalence of hyperprolactinemia in infertile patients.

Dittrich et al. (2011) reviewed presents an overview of the impact of thyroid disorders on reproduction. Thyroid disorders have a great impact on fertility in both sexes. Hyperthyroidism and hypothyroidism cause changes in sex hormone-binding globulin (SHBG), prolactin, gonadotropin-releasing hormone, and sex steroid serum levels. In females, thyroid hormones may also have a direct effect on oocytes, because it is known that specific binding sites for thyroxin are found on mouse and human oocytes. There is also an association between thyroid dysfunction in women and morbidity and outcome in pregnancy. In males, hyperthyroidism causes a reduction in sperm motility. The numbers of morphologically abnormal sperm are increased by hypothyroidism. When euthyroidism is restored, both abnormalities improve or normalize. In women, the alterations in fertility caused by thyroid disorders are more complex. Hyper- and hypothyroidism are the main thyroid diseases that have an adverse effect on female reproduction and cause menstrual disturbances—mainly hypomenorrhea and polymenorrhea in hyperthyroidism, and oligomenorrhea in hypothyroidism. In recent studies, it has become evident that it is not only changes in serum levels of SHBG and sex steroids that are responsible for these disorders, but also alterations in the metabolic pathway. Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function.

Verma et al. (2012) studied the prevalence of clinical/sub-clinical hypothyroidism in infertile women and the response of treatment for hypothyroidism on infertility. Of 394 infertile women, 23.9% were hypothyroid (TSH > 4.2 μIU/ml). After treatment for hypothyroidism, 76.6% of infertile women conceived within 6 weeks to 1 year. Infertile women with both hypothyroidism and hyperprolactinemia also responded to treatment and their PRL levels returned to normal. Measurement of TSH and PRL should be done at early stage of infertility check up rather than straight away going for more costly tests or invasive procedures. Simple, oral hypothyroidism treatment for 3 months to 1 year can be of great benefit to conceive in otherwise asymptomatic infertile women.

Chapter-III

Materials and methods

3.1 Study design: Descriptive type of Cross-sectional study.

3.2 Study place: Institute of Nuclear Medicine and Allied Sciences, Chittagong and Southern Medical College, Chittagong Metropolitan city.

3.3 Study duration: From April 2020 to March 2021

3.4 Study population: Patients with thyroid disorder women were included in this study

3.5 Selection Criteria

Inclusion criteria:

- Patients having different thyroid problem
- Female sex
- Age 15-45 years

Exclusion criteria:

- Age <15 years and > 45 years,
- postmenopausal women,
- subjects using contraceptive pill,
- Patients with history of systemic disease
- Participants who were unwilling to participate

3.6 Sampling method: Non probability type of purposive sampling

3.7 Sample size

Sample size determination depends on time and resources. As prevalence of thyroid hormone disorder in Bangladesh was not known we expected prevalence were 50% of thyroid hormone disorder. So estimated population was calculated by using the following statistical formula:

$n=z^2p\ (1-p)/d^2$

Where n= the desired sample size

Z=the standard normal deviate, usually set at 1.96 at 5 % level which corresponds to 95% confidence level.

P means prevalence = 0.5 (50%)

The degree of accuracy or precision level is d which is considered at 5%.

The higher value of d will yield lower sample size and smaller value of d will yield higher sample size.

Suppose 50% (p=0.05) of the thyroid hormone disorder.

Z statistic is 1.96, which corresponds to the 95% confidence level.

d is the level of accuracy that is considered 0.05 (5%).

$$= \frac{Z^2 p(1-p)}{(d)^2}$$

$$= \frac{(1.96)^2 x0.5(1-0.5)}{(0.05)^2}$$

$$= \frac{3.8416x0.5x0.5}{(0.05)^2}$$

$$= \frac{0.9604}{0.0025}$$

$$= 384.16$$

Using the above formula the expected sample size were taken n=385 cases among them 15 patients were dropout.

3.8 Data collection Methods

A structured questionnaire was developed to note down the demographic and risk factors data related to the occurrence of thyroid problem. The data were collected from the laboratory and direct interviewing.

3.9 Data Management & Analysis Plan

After collecting data and following data cleaning, database preparation, statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A descriptive analysis was performed for all data. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies. Chi-Square/Fisher exact test was used to analyze the categorical variables, shown with cross tabulation. A "p" value <0.05 was considered as statistically significant. The results were presented in tables, figures & diagrams.

3.10 Quality Control & Quality Assurance

In order to ensure quality control and assurance of the study-

- Before being used in real data collection, the crafted questionnaire was pre-tested, analyzed, and updated.
- Data collectors were get special instruction.
- The study was performed the data analysis and write the final report.

3.11 Ethical consideration

In this study, keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects 1964, the nature and purpose of the study was informed in detail to all participants. Voluntary participations were encouraged. There were no physical, psychological and social risks to the subjects. Informed and understood written consent was taken from every patient before enrollment. Privacy, anonymity and confidentiality of data information identifying any patient were maintained strictly. Each patient was enjoyed every right to participate or refuse or even withdrawn from the study at any point of time. Before starting this study ethical clearance was taken from Institutional Review Board (IRB). Data taken from the participants were coded and regarded as confidential and kept locked under investigator for purposeful use only. No experimental new drug was administered and no placebo was used here.

Chapter-IV

Results

Table 1: Distribution of the study patients by age (n=370)

Age (years)	Number of patients	Percentage
≤25	82	22.2
26-35	186	50.3
>35	102	27.6
Mean ±SD	30.8±6.6	
Range (min-max)	20-42	

The distribution of study participants by age is shown in Table I, which reveals that, more half (49.4%) of the participants were between the ages of 26-35, followed by older than (27.6%) and younger than 25 years old (22.2%) were affected with thyroid problem in this area. With a range of 20 to 42 years old patient were found with thyroid problem and the average age was determined to be 30.8±6.6 years.

Table 2: Distribution of the study patients according to parity (n=370)

Parity	Number of patients	Percentage
Nulli (No child)	34	9.2
Primi (One child)	192	51.9
Multi (≥2 child)	144	38.9

Among 370 thyroid patients, more than half 192(51.9) of the patient were primipara, 144 (38.9%) were multipara, and 34 (9.2%) were nullipara (table 2). This result indicates that, the primipara women are more prone to thyroid problem than multipara and nullipara.

Table 3: Distribution of the study patients according to abnormal uterine bleeding (n=370)

Abnormal uterine bleeding	Number of patients	Percentage
Hypomenorrhea	34	9.2
Menorrhagia	193	52.2
Oligomenorrhea	45	12.2
Polymenorrhea	98	26.5

According to Table 3, which depicts the distribution of abnormal uterine bleeding among study participants, more than half (52.2%) of patients had menorrhagia, 98(26.5%) had polymenorrhea, 45(12.2%) had oligomenorrhea, and 34(9.2%) had hypomenorrhea.

Table 4: Distribution of the study patients according to body mass index (n=370)

BMI (kg/m^2)	Number of patients	Percentage
Normal (<25.0)	27	7.3
Overweight (25.0-29.9)	338	91.4
Obese (≥30.0)	5	1.4
Mean ±SD	26.6±1.7	
Range (min-max)	21.0-30.3	

Table 4 depicts the distribution of body mass index among research participants. The majority of patients (91.4%) had a BMI of 25.0-29.9 kg/m^2, 27(7.3%). The BMI ranged from 21.0 to 30.3 kg/m^2, with a mean of 26.6±1.7 kg/m^2.

Table 5: Distribution of the study patients according to blood pressure and urine iodine (n=370)

Variable	Number of patients	Percentage
SBP (mmHg)		
Normal	309	83.5
Abnormal	61	16.5
Mean±SD	137.8±12.9	
DBP (mmHg)		
Normal	259	70.0
Abnormal	111	30.0
Mean±SD	85.0±6.7	
Urine iodine (µg/L)		
Normal	19	5.0
Abnormal	366	95.0
Mean±SD	155.3±11.2	

The distribution of blood pressure and urine iodine among research participants is shown in Table 5. The mean SBP was determined to be 137.8±12.9 mmHg, DBP was 85.0±6.7 mmHg, and urine iodine was 155.3±11.2 µg/L.

Table 6: Distribution of the study patients according to thyroid profile (n=370)

Variable	Number of patients	Percentage
FT3 (pg/ml)		
Low	91	24.6
Normal	269	72.7
Abnormal	10	2.7
Mean±SD	2.97±0.77	
FT4 (ng/ml)		
Low	51	13.8
Normal	298	80.5
Abnormal	21	5.7
Mean±SD	1.27±0.35	
TSH (µlU/ml)		
Hyperthyroidism	19	5.1
Euthyroidism	256	69.2
Hypothyroidism	95	25.7
Mean±SD	3.31±1.81	

Table 6 reveals that the mean FT3 was 2.97±0.77 pg/ml, the FT4 was 1.27±0.35 ng/ml, and the TSH was 3.31±1.81 µlU/ml.

Table 7: Association between abnormal uterine bleeding and thyroid hormone status (n=370)

Abnormal uterine bleeding	Thyroid hormone status					
	Hyperthyroidism (n=19)		Euthyroidism (n=256)		Hypothyroidism (n=95)	
	n	%	n	%	n	%
Hypomenorrhea	8	42.1	21	8.2	5	5.3
Menorrhagia	2	10.5	128	50.0	63	66.3
Oligomenorrhea	8	42.1	30	11.7	7	7.4
Polymenorrhea	1	5.3	77	30.1	20	21.0

Abnormal uterine bleeding	P value
Hypomenorrhea vs Menorrhagia	0.055^{ns}
Hypomenorrhea vs Oligomenorrhea	1.000^{ns}
Hypomenorrhea vs Polymenorrhea	0.418^{ns}
Menorrhagia vs Oligomenorrhea	0.021^{s}
Menorrhagia vs Polymenorrhea	0.531^{ns}
Oligomenorrhea vs Polymenorrhea	0.312^{ns}

s= significant, ns= not significant

p value reached from Turkey test

Table 7 shows that 8(42.1%) patients were found hypomenorrhea in hyperthyroidism, 21(8.2%) in euthyroidism and 5(5.3%) in hypothyroidism. Eight (42.1%) patients were found oligomenorrhea in hyperthyroidism, 30(11.7%) in euthyroidism and 7(7.4%) in hypothyroidism. The difference was statistically significant ($p<0.05$) between Menorrhagia and Oligomenorrhea groups.

Table 8: Association between age and thyroid hormone status (n=370)

Age (years)	Thyroid hormone status					
	Hyperthyroidism (n=19)		Euthyroidism (n=256)		Hypothyroidism (n=95)	
	n	%	n	%	n	%
≤25	3	15.8	66	25.8	13	13.7
26-35	13	68.4	137	53.5	36	37.9
>35	3	15.8	53	20.7	46	48.4

Age (years)	P value
≤25 vs 26-35	0.960^{ns}
≤25 vs >35	0.005^{s}
26-35 vs >35	0.002^{s}

s= significant, ns= not significant

p value reached from Turkey test

Table 8 shows that 13(68.4%) patients belonged to age 26-35 years in hyperthyroidism, 1372(53.5%) in euthyroidism and 36(37.9%) in hypothyroidism. The difference were statistically significant ≤25 vs >35 years and 26-35 vs >35 years age groups.

Table 9: Association between socioeconomic status and thyroid hormone status (n=370)

Socioeconomic status	Thyroid hormone status					
	Hyperthyroidism (n=19)		Euthyroidism (n=256)		Hypothyroidism (n=95)	
	n	%	n	%	n	%
Lower	10	52.6	82	32.0	35	36.84
Lower-middle	8	42.1	105	41.0	45	47.36
Upper-middle	1	5.3	69	27.0	15	15.78

Age (years)	P value
Lower vs Lower-middle	0.657^{ns}
Lower vs Upper-middle	0.734^{ns}
Lower-middle vs Upper-middle	0.260^{ns}

ns= not significant

p value reached from Turkey test

Table 9 shows that 1(5.3%) of the patients come from upper middle class family in hyperthyroidism, 69(27.0%) in euthyroidism and 17(15.78%) in hypothyroidism. The difference was not statistically significant ($p>0.05$).

Table 10: Association between iodine intake and thyroid hormone status (n=370)

Iodine intake	Thyroid hormone status						P value
	Hyperthyroidism (n=19)		Euthyroidism (n=256)		Hypothyroidism (n=95)		
	n	%	n	%	n	%	
Yes	1	5.3	5	2.0	14	14.73	0.001[s]
No	18	94.7	251	98.0	81	85.26	

s= significant

p value reached from Turkey test

Table 10 shows that 1(5.3%) patients iodine intake in hyperthyroidism, 5(2.0%) in euthyroidism and 14(14.73%) in hypothyroidism. The difference was statistically significant ($p<0.05$).

Table 11: Association between infertility and thyroid hormone status (n=370)

Infertility	Thyroid hormone status						p value
	Hyperthyroidism (n=19)		Euthyroidism (n=256)		Hypothyroidism (n=95)		
	n	%	n	%	n	%	
Yes	7	36.8	2	0.8	48	50.5	0.001[s]
No	12	63.2	254	99.2	47	49.5	

s= significant

p value reached from chi square test

Table 11 shows that 7(36.8%) patients were found infertile in hyperthyroidism, 2(0.8%) in euthyroidism and 48(50.5%) in hypothyroidism. The difference was statistically significant ($p<0.05$) among three groups. Some women develop infertility after having their first child.

Chapter-V

Discussion

The distribution of study participants by age is shown in Table I, which reveals that, more half (49.4%) of the participants were between the ages of 26-35, followed by older than (27.6%) and younger than 25 years old (22.2%) were affected with thyroid problem in this area. With a range of 20 to 42 years old patient were found with thyroid problem and the average age was determined to be 30.8±6.6 years. This result is supported by another study conducted by Hema et al. (2020) reported that, the disorder was more common in 40 years old and older women accounting for 49.28%. Our observation is also an agreement of the studies of Guo et al. (2018), Unnikrishnan et al. (2013), Nargis et al. (2018) and Ganie et al. (2020), they were reported mean age was 30.19±4.09 years, 45.85 years, 26.52±3.12 years and 39.46±17.51 years.

In this study we have found that, more than half 192(51.9) of the patient were primipara, 144 (38.9%) were multipara, and 34 (9.2%) were nullipara. Similar observation was found by Guo et al. (2018), reported as 547 (59.78%) patients were nulliparous and 368(40.22%) were multipara. However, different observation was reported by Hema et al. (2020), they reported the thyroid problem is more common amongst multiparous woman contributing to 61.49%.

According to Table 3, which depicts the distribution of abnormal uterine bleeding among study participants, more than half (52.2%) of patients had menorrhagia, 98(26.5%) had polymenorrhea, 45(12.2%) had oligomenorrhea, and 34(9.2%) had hypomenorrhea. This result is supported by another study conducted by Hema et al. (2020) they reported the most common menstrual disorder pattern seen in Abnormal uterine bleeding (AUB) was menorrhagia which was 51.34%. Next commonest was polymenorrhea 21.26%. In another study, Laxmiand Kaur (2018) noted 55.3% presented with menorrhagia among all cases of AUB. In similar study done by Ajamani et al. (2016) and found that, menorrhagia accounted for 50% of all AUB. Jinger et al. (2017) had also observed oligomenorrhea as the most common menstrual disorder in hyperthyroidism (75%). Authors found hypomenorrhea as the next common finding in hyperthyroidism. Jinger et al. (2017) and Koutrass (1997) also found hypomenorrhea as the

next common disorder. Nargis et al. (2018) also observed 42% patients was found oligomenorrhoea in primary infertile and 51.7% in secondary infertile.

Table 4 depicts the distribution of body mass index among research participants. The majority of patients (91.4%) had a BMI of 25.0-29.9 kg/m^2, 27(7.3%). The BMI ranged from 21.0 to 30.3 kg/m^2, with a mean of 26.6±1.7 kg/m^2. A study conducted by Guo et al. (2018) also reported normal BMI was found before pregnancy 68.2%. Ganie et al. (2020) observed the mean BMI was found 21.28±4.16 kg/m^2.

In this study that mean SBP was determined to be 137.8±12.9 mmHg, DBP was 85.0±6.7 mmHg, and urine iodine was 155.3±11.2 μg/L. Ganie et al. (2020) reported the mean SBP was found 121.73±17.88 mmHg, DBP was 79.82±12.07 mmHg and median urine iodine was 154.50 μg/L.

In current study showed that mean FT3 was 2.97±0.77 pg/ml, the FT4 was 1.27±0.35 ng/ml, and the TSH was 3.31±1.81 μlU/ml. Similar observation was found by Tasnim and Begum (2017) they observed the mean serum T3 was found 2.34±0.56 nmol/L in group A (healthy women) and 2.09±0.55 nmol/L in group B (infertile women). The mean serum T4 was found 139.83±23.83 nmol/L in group A and 120.36±38.29 nmol/L in group B. Mean serum T3 and T4 level were significantly lower ($P<0.001$) in group B that of group A. Another study by Nargis et al. (2018) also agreement with our observation they reported mean FT3 was found 2.36±1.74 pg/ml in primary infertile and 2.17±0.98 in pg/ml in secondary infertile. The mean FT4 was found 1.47±0.62 ng/ml in primary infertile and 1.43±0.54 in ng/ml in secondary infertile. The mean TSH was found 4.59±2.53 μlU/ml in primary infertile and 4.74±2.59 in μlU/ml in secondary infertile. Ganie et al. (2020) reported the mean FT3 was found 1.29±1.10 ng/ml, FT4 was 7.25±1.91 and TSH was 4.62±5.02 μlU/ml.

In this study observed that majority (69.2%) patients were found in euthyroidism, 95(25.7%) in hypothyroidism and 19(5.1%) in hyperthyroidism. Among hypothyroidism patients, 93(84.5%) patients had subclinical hypothyroidism and 17(15.5%) had overt hypothyroidism. Another study observation was found by Nargis et al. (2018), 16.9% of infertile patients and 7.0% of the control group were hypothyroid. Hema et al. (2020) discovered that 87.73% of people were euthyroid, 8.81% were hypothyroid, and 3.44% were hyperthyroid. According to Guo et al.

(2018), thyroid hormone production increased to respond to the higher metabolic demands of pregnancy (Soldin et al., 2007). Deficiencies in maternal thyroid hormones are related with the pregnancy complications (e.g. spontaneous abortion, preterm delivery, gestational diabetes and placental abruption) and adverse outcomes in neonates and offspring (e.g. fetal distress, low birth weight and impaired neuropsychological development) (Nathan and Sullivan, 2014). Unnikrishnan et al. (2013) reported the prevalence of hypothyroidism in the overall study population was 10.95%. Goswami et al. (2009) reported significantly higher serum TSH levels were noted in the infertile cases with euthyroidism ($p<0.01$) and hypothyroidism ($p<0.001$) when their distributions were compared to their respective control groups. The rise in serum FT4 and FT3 in the infertile group with hyperthyroidism was found to be significantly higher as compared to the control group with hyperthyroidism ($p<0.001$). Serum FT4 value was significantly lower ($p<0.01$) in the infertile group with hypothyroidism when compared to the control group with hypothyroidism. Verma et al. (2012) also observed the 94 infertile women diagnosed with hypothyroidism (alone or with hyperprolactinemia), 72 (76.6%) infertile women conceived after treatment with drugs for hypothyroidism (dose depending upon severity of hypothyroidism, i.e. TSH levels).

In current study showed that 98(42.1%) patients were found hypomenorrhea in hyperthyroidism, 21(8.2%) in euthyroidism and 5(5.3%) in hypothyroidism. Eight (42.1%) patients were found oligomenorrhea in hyperthyroidism, 30(11.7%) in euthyroidism and 7(7.4%) in hypothyroidism. The difference was statistically significant ($p<0.05$) between Menorrhagia and Oligomenorrhea groups. A similar observation was made by Hema et al. (2020) they observed in hypothyroidism, menorrhagia was the commonest menstrual disorder pattern, accounting 65.21% of all menstrual pattern abnormality. Next commonest was polymenorrhea at 17.39%. In hyperthyroid group, oligomenorrhea was commonest type of menstrual disorder pattern, which was 55.54%. However, hypomenorrhea was close second at 44.44%. There is high association observed between types of menstrual disturbances and thyroid type and it is found statistically significant ($p<0.001$). Krasses et al. (1999) the prevalence of menstrual irregularities (mainly oligomenorrhoea) reached 23% among 171 hypothyroid patients, while being only 8% in 214 controls ($p<0.05$).

In this study showed that 13(68.4%) patients belonged to age 26-35 years in hyperthyroidism, 1372(53.5%) in euthyroidism and 36(37.9%) in hypothyroidism. The difference were statistically significant ≤25 vs >35 years and 26-35 vs >35 years age groups. This result is supported by previous studies conducted Hema et al. (2020) observed Majority of the hypothyroid cases were in age group >40 years accounting to 60.86%. The highest number of hyperthyroid cases were in age group of 21-30 years, 50%. More number of hypothyroid cases were in >40 years age group and a smaller number of cases in <20 years age group. There is high association observed between age groups and thyroid type and it is found statistically significant ($p<0.001$). Unnikrishnan et al. (2013) reported Subclinical hypothyroidism (SCH) was observed in 430 (8.02%, 95% CI: 7.29-8.74) participants. Frequency of SCH was highest (8.93%) in the age group of above 55 years and lowest in the age group of 18-35 years (6.91%), though no statistically significant association was found with age ($P=0.1534$). However, in a comparable geographical area of Gangetic basin in West Bengal, the prevalence of hypothyroidism in 3814 subjects from all age groups was even higher (29%) (Chandra et al., 2003). There was a predominance of thyroid dysfunction in women in their study, and is consistent with worldwide reports, especially those in midlife (46-54 years). Given the association between thyroid disorders and cardiovascular risk factors such as hypertension and dyslipidemia (Luboshitzky and Herer, 2004). The prevalence of hypothyroidism in women of reproductive age (20-40 years) varies between 2% to 4% (Cramer et al., 2003). Ganie et al. (2020) reported age, gender, or UIC did not significantly affect TSH or thyroid dysfunction.

In this current study showed that 1(5.3%) of the patients come from upper middle class family in hyperthyroidism, 69(27.0%) in euthyroidism and 17(15.5%) in hypothyroidism. Olmos et al. reported that frequency of hypothyroidism treatment was higher in women, browns, highly educated participants and those with high net family incomes.

In this study showed that 1(5.3%) patient iodine intake in hyperthyroidism, 5(2.0%) in euthyroidism and 14(14.73%) in hypothyroidism. The difference was statistically significant ($p<0.05$). Abraham et al. (2009) in their studies showed that the incidence of thyroidism is more in coastal area which might be due to the increase intake of iodine containing foods. Hypothyroidism also is prevalent in this area which may be associated to higher intake of iodine rich foods causing negative feedback mechanism.

Chapter-VI

Conclusion

- The present study revealed that the relative risk of female infertility significantly increased in thyroid disorder women.
- Some women develop infertility after having their first child.
- So systematic screening of thyroid hormone should be considered in all women with female cause of infertility.
- It can be suggested that a general screening for thyroid dysfunction during early pregnancy, by use of TSH levels, is optimal.
- Furthermore, the imbalance in the thyroid system in women with unexplained infertility highlights the importance of thyroid hormone for female fertility.

Chapter-VII

Strength and Weakness

- The study was conducted in a selected hospital. So the study population might not Represents the whole country.
- During the corona epidemic, there was a problem in taking data

Chapter-VIII

Recommendations and future perspective

Further studies can be undertaken by including large number of patients.

Chapter-IX

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