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Human Reproductive Health in Relation to Thyroid Alterations

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Abstract

Background: Thyroid alterations have adverse effects on other health systems in the body, and reproductive system is one of the most affected organs. Here, we perform a comprehensive analysis on the effects of different thyroid abnormalities on sexual and reproductive-related hormones in both men and women in different age groups. **Method:** A comprehensive analysis was performed on 15,043 subjects within the reproductive age (15 - 49 years). They were tested for thyroid markers (TSH, FT4, anti-TPO, anti-Tg) and 13 reproductive hormones in Vibrant America Clinical Laboratory between March 2016 to July 2018. The alterations of each reproductive hormone in hypothyroidism, hyperthyroidism, anti-TPO+ anti-Tg+ groups were evaluated. **Results:** A total of 10,626 women was tested. Women with hypothyroidism had elevated cortisol and low SHBG and DHEA-S. Women with hyperthyroidism showed elevated total testosterone and SHBG. Women seropositive for anti-TPO had elevated total testosterone and low cortisol. Women seropositive for anti-Tg had low parathyroid hormones. Similarly, a total of 4417 men was tested. Men with hypothyroidism had low IGF-I. Similarly, men with hyperthyroidism had low DHEA-S, but elevated estradiol, FSH, LH and prolactin. Men seropositive for anti-TPO had elevated SHBG and low progesterone. Men seropositive for anti-Tg had elevated progesterone. The reproductive and related hormone levels of age group 36 - 49 showed the most variations. **Conclusion:** Our results clearly show that individuals with different thyroid alterations have different effects on reproductive health, especially in the age group 36 - 49. Hence, routine testing and follow-up checkups on reproductive system would be beneficial for individuals in the age group 36 - 49 with thyroid disorders.

Keywords

Reproductive Hormones, Hypothyroidism, Hyperthyroidism, Thyroid Disease,

Thyroid Autoantibodies

1. Introduction

Reproductive hormones are responsible for several aspects of human sexual behaviors. Imbalances in steroid hormones may lead to impaired sexual function and decreased fertility in both men and women [1] [2]. Particularly, women suffer from menstrual irregularities, miscarriages, adverse pregnancy and neonatal outcomes while men suffer from abnormal sperm morphology, changes in sperm motility, etc. Thyroid disease is considered one of the main endocrine conditions responsible for hormone imbalances in both men and women affecting their reproductive system. These endocrine systems have been linked since the functions of both thyroid gland and gonadal system are under the control of the hypothalamus-pituitary-gonadal axis.

Thyroid disease is mainly categorized as hypothyroidism and hyperthyroidism and both these conditions can have adverse effects on reproductive health. In women, hypothyroidism is responsible for subfertility in approximately 2.3% compared to the 1.5% incidence rate of women in the general population [3]. Hypothyroidism is commonly observed in pregnancy with a 0.5% overt disease and a 2.5% subclinical disease in pregnant women [3]. Graves' disease, which is the common form of hyperthyroidism in pregnancy has been observed in 1% of pregnant women [3]. In men, hypothyroidism causes abnormal sperm morphology, reduced sperm motility, impaired sexual behaviors, including hypoactive sexual desire (HSD), erectile dysfunction (ED) and ejaculatory disorders [4]. Hyperthyroid men were reported with significant reduction in semen volume, sperm count, sperm motility, number of morphologically normal sperm, gynecomastia as well as impaired sexual behaviors similar to hypothyroid men [4].

Anti-TPO and anti-Tg are commonly observed in autoimmune thyroid disease (AITD) has gained increased attention over the past years. Women with AITD have been associated with lower fertilization rates, poorer embryo quality, and lower pregnancy rates [5]. The presence of thyroid autoantibodies, in euthyroid subjects was reported to have a threefold increase in the odds ratio of miscarriages compared to healthy women [6]. Women with AITD have been suggested to have a 5% - 10% risk of developing hypothyroidism in pregnancy with a 2 - 4-fold increased risk of preterm labor [3]. Unfortunately, the association of reproductive health in male subjects with thyroid antibodies has been poorly studied. Some studies reported that the presence of elevated levels of anti-TPO may be associated with pathozoospermia or asthenozoospermia [7].

It is crucial to study the effects of different thyroid dysfunctions on reproductive health in both genders. Numerous studies have shown the effect of thyroid disease on reproductive hormones, but each study only focused on one subcategory of thyroid disorder. None of the studies compared these common subcate-

gories of thyroid disease in relation to sexual and reproductive-related hormones in both genders in one study. Since the upper limit of the TSH reference range is currently debatable, and typically based on the laboratory reference levels, a comprehensive study between these common subcategories of thyroid disorder would provide considerably meaningful comparative results.

In this study, we performed a comprehensive analysis including the common thyroid subcategories (subclinical/overt hypothyroidism and subclinical/overt hyperthyroidism) and autoantibodies related to AITD separately for 13 sexual and reproductive-related hormones for a large population size of 15,043 including 10,626 women and 4417 men in different reproductive age groups. Their serology was used to evaluate the association of sexual and reproductive-related hormones with thyroid disorders in both genders in different ages. Our results showed different alterations in sexual and reproductive related-hormone levels in different thyroid subcategories thus evidencing that different thyroid dysfunctions could complicate the regular functions of the reproductive system in different ways.

2. Material and Methods

2.1. Patient Selection and Study Design

A total of 10,626 women and 4417 men between age 15 - 49 were tested in the Vibrant America Clinical Laboratory for thyroid markers (TSH, FT4, anti-TPO, anti-Tg) between March 2016 to July 2018. Same cohort was simultaneously tested for 13 reproductive and other related hormones. Estradiol, FSH, LH and Progesterone were not included in the analysis for women since the reference ranges were depending on women hormonal phases. This retrospective analysis was completed using de-identified laboratory test results. Demographics of subjects in each group is listed in Table 1. Inclusion and exclusion criteria are listed below.

Inclusion Criteria:

- Subjects between age 15 - 49.
- Subjects who tested both TSH and FT4 or anti-TPO or anti-Tg at each visit.

Exclusion Criteria:

- Subjects age < 15 years and 49 < years.
- Subjects who did not test for both TSH and FT4 together or anti-TPO or anti-Tg at each visit.

The physician reported ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) codes were used to provide clinical information on these subjects. Subjects were divided into subgroups depending on the presence of thyroid hormones and autoantibody.

Hypothyroidism—Subjects with either subclinical or Overt hypothyroidism.

Hyperthyroidism—Subjects with either subclinical or Overt hyperthyroidism.

Thyroid negative (thyroid)—Subjects with normal levels of TSH and FT4 (control group for hypothyroidism and hyperthyroidism).

Anti-TPO positive (anti-TPO+)—Subjects with increased levels of anti-TPO antibodies.

Anti-TPO negative (anti-TPO-)—Subjects with normal levels of anti-TPO antibodies (control group for anti-TPO+ group).

Anti-Tg positive (anti-Tg+)—Subjects with increased levels of anti-Tg antibodies.

Anti-Tg positive (anti-Tg-)—Subjects with normal levels of anti-Tg antibodies (control group for anti-Tg+ group).

These subcategories were evaluated for sexual and reproductive-related hormone levels in different age groups (15 - 49, 15 - 25, 26 - 35, 36 - 49 years).

2.2. TSH, FT4, Anti-TPO and Anti-Tg Tests

TSH, FT4, anti-TPO and anti-Tg were measured using the commercial Roche e601 Analyzer, (Roche Diagnostics, Indianapolis, IN, USA) according to the manufacturer's recommendations. All reagents were purchased from Roche Diagnostics (Indianapolis, IN, USA). Human serum specimens were used on Elecsys immunoassay analyzers (Roche Diagnostics, Indianapolis, IN, USA).

Table 1. Demographics of subjects in each group.

	Hypothyroidism	Hyperthyroidism	Thyroid-	Anti-TPO+	Anti-TPO-	Anti-Tg+	Anti-Tg-
Age 15 - 49							
Female							
Age (X ± SD)	37 ± 9	39 ± 8	36 ± 9	37 ± 9	37 ± 9	37 ± 9	36 ± 9
Male							
Age (X ± SD)	36 ± 9	40 ± 8	36 ± 9	37 ± 9	36 ± 9	37 ± 9	36 ± 9
Age 15 - 25							
Female							
Age (X ± SD)	21 ± 3	21 ± 3	21 ± 3	21 ± 3	21 ± 3	21 ± 3	21 ± 3
Male							
Age (X ± SD)	21 ± 3	21 ± 2	20 ± 3	21 ± 3	20 ± 3	21 ± 3	20 ± 3
Age 26 - 35							
Female							
Age (X ± SD)	31 ± 3	31 ± 3	31 ± 3	31 ± 3	31 ± 3	31 ± 3	31 ± 3
Male							
Age (X ± SD)	30 ± 3	32 ± 3	31 ± 3	31 ± 3	31 ± 3	31 ± 3	31 ± 3
Age 36 - 49							
Female							
Age (X ± SD)	43 ± 4	44 ± 4	43 ± 4	43 ± 4	43 ± 4	43 ± 4	43 ± 4
Male							
Age (X ± SD)	43 ± 4	44 ± 4	43 ± 4	43 ± 4	43 ± 4	43 ± 4	43 ± 4

X—Average; SD—Standard Deviation.

Specific TSH monoclonal antibodies Specifically directed against human TSH were employed in the Elecsys TSH assay (Roche Diagnostics, Indianapolis, IN, USA). The antibodies labeled with a ruthenium complex consist of a chimeric construct from human and mouse-specific components. As a result, interfering effects due to HAMA (human anti-mouse antibodies) were largely eliminated.

The Elecsys FT4 test employed a specific anti-T4 antibody labeled with a ruthenium complex to determine the free thyroxine. The quantity of antibody used was so small (equivalent to approx. 1% - 2% of the total T4 content of a normal serum sample) that the equilibrium between bound and unbound T4 remained virtually unaffected.

Elecsys anti-TPO assay employed recombinant antigens and polyclonal anti-TPO antibodies whereas Elecsys anti-Tg assay employed monoclonal human anti-Tg antibodies.

2.3. Reference Ranges for Thyroid Markers

Thyroid hormone reference ranges are subject to the lab where the test is performed. In this study, we used the reference ranges that majority of the commercial test labs and hospital labs use. The reference range of thyroid markers in a healthy control used in this study is shown in Table 2.

The categorization of serologic thyroid positivity by evaluating TSH and FT4 levels used in this study is shown in Table 3.

2.4. Hormone Tests

The vibrant reproductive hormone test includes 13 different reproductive and other related hormones. They are cortisol, parathyroid hormone, estradiol, FSH, LH, progesterone, total testosterone, SHBG, DHEA-S, IGF-I, estriol, estrone,

Table 2. Reference ranges for thyroid markers studied [8].

Marker	Reference Range
TSH	0.3 - 4.2 mIU/L
FT4	0.9 - 1.7 ng/dL
Anti- TPO	<9.0 IU/mL
Anti-Tg	<4.0 IU/mL

Table 3. Thyroid disease categorization.

Disease Condition	TSH	FT4
Hypothyroidism		
Subclinical hypothyroidism	>4.2 mIU/L	0.9 - 1.7 ng/dL
Overt hypothyroidism	>4.2 mIU/L	<0.9 ng/dL
Hyperthyroidism		
Subclinical hyperthyroidism	<0.3 mIU/L	0.9 - 1.7 ng/dL
Overt hyperthyroidism	<0.3 mIU/L	>1.7 ng/dL

prolactin. The Elecsys Cortisol II immunoassay (Roche Diagnostics, Indianapolis, IN, USA) is used to measure serum cortisol levels. The Elecsys assay (Roche Diagnostics, Indianapolis, IN, USA) for determining intact Parathyroid hormone employs a sandwich test principle in which a biotinylated monoclonal antibody reacts with the N-terminal fragment and a monoclonal antibody labeled with a ruthenium complex reacts with the C-terminal fragment. The Elecsys Estradiol III assay (Roche Diagnostics, Indianapolis, IN, USA) employs a competitive test principle using two monoclonal antibodies specifically directed against 17β-estradiol. The Elecsys FSH assay (Roche Diagnostics, Indianapolis, IN, USA) employs two different monoclonal antibodies specifically directed against human FSH. Similarly, the Elecsys LH assay (Roche Diagnostics, Indianapolis, IN, USA) employs two monoclonal antibodies specifically directed against human LH. The Elecsys Testosterone II assay (Roche Diagnostics, Indianapolis, IN, USA) is based on a monoclonal antibody specifically directed against testosterone. The Elecsys SHBG assay (Roche Diagnostics, Indianapolis, IN, USA) employs two monoclonal antibodies specifically directed against human SHBG. The Elecsys DHEA-S assay (Roche Diagnostics, Indianapolis, IN, USA) is based on a monoclonal antibody specifically directed against DHEA-S. An enzyme-labeled chemiluminescent immunometric assay is used to detect human IGF-I. The Elecsys Prolactin II assay (Roche Diagnostics, Indianapolis, IN, USA) employs two monoclonal antibodies specifically directed against human prolactin.

2.5. Patient and Public Involvement

This study does not include any patient or public involvement and is based on retrospective analysis of de-identified laboratory data. IRB exemption (work order #1-1098539-1, July 2018) was determined by the Western Institutional Review Board (WIRB) for Vibrant America Biorepository to use de-linked and de-identified remnant human specimen and medical data for research purposes.

2.6. Statistical Analysis

The retrospective analysis on clinical data from de-identified subjects was performed via Java for Windows version 1.8.161 and R for Windows version 3.5.0. Data were expressed as mean ± standard deviation (SD) when the distribution was Gaussian. Pearson's Chi-squared test was used when the observed count is <5 to evaluate the association between the presence of clinical variables evaluated. P value < 0.05 was considered statistically significant.

3. Results

3.1. Reproductive and Other Related Hormones in Women with Thyroid Alterations

A total of 10,626 women between age 15 - 49 were tested for thyroid hormones and antibodies. The clinical information on majority of these patients were provided by physicians as ICD-10-CM (International Classification of Diseases,

Tenth Revision, Clinical Modification) codes. The percentage distribution of the top 20 ICD-10-CM codes reported is listed in Table 4. The top two ICD codes were fatigue and Vitamin D deficiency respectively.

Next, the hormone levels of 13 reproductive and other related hormones were simultaneously measured to evaluate any abnormalities in the same cohort. A detailed analysis of the total 13 hormones and their hormonal and antibody level fluctuations are reported in Tables S1-S4 in supplementary material. Details on hormones, which were significantly altered in women with hypothyroidism and hyperthyroidism are shown in Table 5 while Table 6 provides information on elevated/reduced hormones in subjects with elevated anti-TPO and anti-Tg (The total subjects that performed each test was different in each group which is reflected by different denominators).

As shown in Figure 1, cortisol hormone was elevated in women with hypothyroidism while SHBG and DHEA.S levels were significantly reduced compared to the controls (euthyroid subjects). Hyperthyroid women showed elevated levels of total testosterone and SHBG. Women seropositive for anti-TPO had elevated levels of total testosterone and reduced levels of cortisol while women

Table 4. Top 20 physician-reported ICD-10-CM codes distribution for women with thyroid alterations.

ICD-10-CM	Description	Hypothyroidism (%)	Hyperthyroidism (%)	Anti-TPO (%)	Anti-Tg (%)
R5383	Other fatigue	55.8	55.2	58.4	59.9
E559	Vitamin D deficiency, unspecified	32.2	26.2	26.9	28.2
E039	Hypothyroidism, unspecified	24	39.3	15.6	15.8
M2550	Pain in unspecified joint	17.4	8.3	12.9	13.8
E349	Endocrine disorder, unspecified	12.6	19.3	13.7	12.3
K5900	Constipation, unspecified	7.9	9	8.2	9.4
E782	Mixed hyperlipidemia	5.7	4.8	4.3	4.7
E785	Hyperlipidemia, unspecified	4.7	6.2	4.3	4.7
R638	Other symptoms and signs concerning food and fluid intake	6.3	2.8	6.8	7
R5382	Chronic fatigue, unspecified	7.3	6.2	8.2	7.1
Z0000	Encounter for general adult medical examination without abnormal findings	5.7	5.5	6.7	6.2
E079	Disorder of thyroid, unspecified	6.6	9	6.2	5.9
F419	Anxiety disorder, unspecified	8.2	6.2	7.1	7.4
I10	Essential (primary) hypertension	4.1	2.1	2.1	2.4
K909	Intestinal malabsorption, unspecified	6	4.1	5.3	5.8
G4700	Insomnia, unspecified	8.5	2.8	6.3	6
D539	Nutritional anemia, unspecified	3.2	6.2	4.7	4.7
N926	Irregular menstruation, unspecified	4.7	1.4	7.1	7
R7989	Other specified abnormal findings of blood chemistry	4.4	5.5	4.6	4.5
Z79899	Other long term (current) drug therapy	3.8	9	4.5	4.8

Table 5. Reproductive hormonal changes in women with hypothyroidism and hyperthyroidism.

	Hypothyroidism		Hyperthyroidism	
	%	Range	%	Range
Cortisol	↑103/578 (17.8%)	17.5 - 46.0	→	-
Total Testosterone	→	-	↑49/279 (17.6%)	49.0 - 460.1
SHBG	↓32/573 (5.6%)	6.5 - 24.2	↑95/266 (35.7%)	122.1 - 643
DHEA-S	↓63/579 (10.9%)	0.1 - 145.9	→	-

↑-Increased; ↓-Reduced; → -No Change; Units: Cortisol-μg/dL; Parathyroid Hormone-pg/mL; Total Testosterone-ng/dL; SHBG-nmol/L; DHEA-S-μg/dL; IGF-I-ng/mL.

Table 6. Reproductive hormonal changes in women with elevated anti-TPO and anti-Tg.

	Anti-TPO+		Anti-Tg+	
	%	Range	%	Range
Cortisol	↓980/7618 (12.9%)	0.4 - 6.14	→	-
Parathyroid Hormone	→	-	↓68/5331 (1.3%)	0 - 14.48
Testosterone	↑1460/7873 (11.3%)	40.87 - 1478.0	→	-

↑-Increased; ↓-Reduced; → -No Change; Units: Cortisol-μg/dL; Parathyroid Hormone-pg/mL; Total Testosterone-ng/dL.

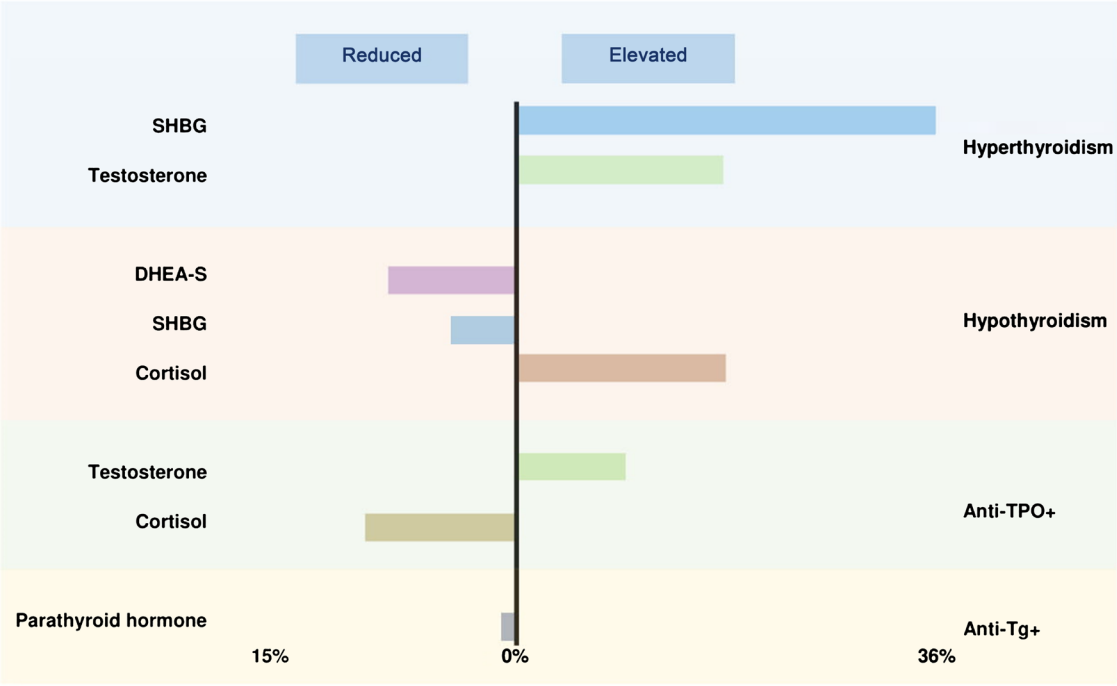

Figure 1. Hormonal changes in female with different thyroid disparities. Significantly altered hormones are only shown in the figure. The percentage of reduction (on the left) or increase (on the right) are shown in comparison to the control groups in each thyroid disorder.

seropositive for anti-Tg reduced levels of parathyroid hormone.

Next, we sought to evaluate the effect of age on reproductive and other related

hormones in women with thyroid disorder. Table 7 provides the details of the hormones that showed a significant alteration in each age category (refer Tables S5-S16 for full analysis including all 13 hormones).

Age 15 - 25 group only had elevated levels of cortisol and total testosterone respectively in women with hypothyroidism and anti-TPO seropositivity. Age 26 - 35 group only had reduced levels of total testosterone in women with hyperthyroidism. The age group 36 - 49 is the most affected group. Hypothyroid women in that age group had elevated levels of cortisol hormone with reduced levels of SHBG, DHEA-S and IGF-I. In contrast, hyperthyroid women in that age group showed elevated levels of total testosterone and SHBG. In addition, women seropositive for anti-TPO had elevated levels of DHEA-S.

3.2. Reproductive and Other Related Hormones in Men with Thyroid Alterations

A total of 4417 men between age 15 - 49 were tested for thyroid hormones and autoantibodies. Similarly, The clinical information on majority of these patients were provided by physicians as ICD-10-CM codes. The percentage distribution of the top 20 ICD-10-CM codes reported is listed in Table 8. The top two ICD codes were fatigue and Vitamin D deficiency respectively.

Table 7. The effect of age on reproductive and other related hormones in women with thyroid disparity.

	Cortisol	Parathyroid hormone	Testosterone	SHBG	DHEA-S	IGF-I
15 - 25						
Hypothyroidism	↑33/88 (37.5%)	→	→	→	→	→
Hyperthyroidism	→	→	→	→	→	→
Anti-TPO+	→	→	↑143/1043 (13.7%)	→	→	→
Anti-Tg+	→	→	→	→	→	→
26 - 35						
Hypothyroidism	→	→	→	→	→	→
Hyperthyroidism	→	→	↓4/52 (7.7%)	→	→	→
Anti-TPO+	→	→	→	→	→	→
Anti-Tg+	→	→	→	→	→	→
36 - 49						
Hypothyroidism	↑44/347 (12.7%)	→	→	↓20/347 (5.8%)	↓35/347 (10.1%)	↓10/122 (7.7%)
Hyperthyroidism	→	→	↑40/205 (19.5%)	↑70/194 (36.1%)	→	→
Anti-TPO+	→	→	→	→	↑247/4504 (5.5%)	→
Anti-Tg+	→	→	→	→	→	→

↑-Increased; ↓-Reduced; → -No Change; Units: Cortisol-μg/dL; Parathyroid Hormone-pg/mL; Total Testosterone-ng/dL; SHBG-nmol/L; DHEA-S-μg/dL; IGF-I-ng/mL.

Table 8. Top 20 physician-reported ICD-10-CM codes distribution for men with thyroid alterations.

ICD-10-CM	Description	Hypothyroidism (%)	Hyperthyroidism (%)	Anti-TPO (%)	Anti-Tg (%)
R5383	Other fatigue	60.8	65	60.5	61.1
E559	Vitamin D deficiency, unspecified	34.2	45	33.4	35.5
E039	Hypothyroidism, unspecified	22.5	25	13.4	13.7
E291	Testicular hypofunction	16.7	15	17.1	18.1
M2550	Pain in unspecified joint	11.7	20	17.8	18.3
E349	Endocrine disorder, unspecified	11.7	10	10.4	10.3
E785	Hyperlipidemia, unspecified	10.8	15	8.2	8.2
R638	Other symptoms and signs concerning food and fluid intake	10.8	5	9	9.8
R6882	Decreased libido	10	5	9.8	9.4
R5381	Other malaise	9.2	5	4.7	4.8
E663	Overweight	6.7	0	4.1	3.8
R5382	Chronic fatigue, unspecified	5.8	5	5.6	5.7
I10	Essential (primary) hypertension	5	0	6.9	6.7
D539	Nutritional anemia, unspecified	5	10	4.9	5.2
G4700	Insomnia, unspecified	5	0	6.1	6.3
K909	Intestinal malabsorption, unspecified	5	20	3.8	4.3
E782	Mixed hyperlipidemia	4.2	5	6.9	7
Z79899	Other long term (current) drug therapy	4.2	10	4.9	5.2
R7989	Other specified abnormal findings of blood chemistry	4.2	5	4.6	4.8
E119	Type 2 diabetes mellitus without complications	3.3	0	3.3	3

The hormone levels of 13 reproductive hormones were simultaneously measured to evaluate any abnormalities in the same cohort. A detailed analysis of the total 13 hormones and their hormonal and antibody level fluctuations are reported in Tables S17-S20 in supplementary material. Details on hormones, which were significantly altered in men with hypothyroidism and hyperthyroidism are shown in Table 9 while Table 10 provides information on altered hormones in subjects with elevated anti-TPO and anti-Tg (The total subjects that performed each test was different in each group which is reflected by different denominators).

As shown in Figure 2, IGF-I was elevated in men with hypothyroidism compared to the controls (euthyroid subjects). Hyperthyroid men showed elevated levels of estradiol, FSH, LH and DHEA-S. Men seropositive for anti-TPO had elevated levels of SHBG while men seropositive for anti-Tg had reduced levels of progesterone.

Next, we evaluated the effect of age on reproductive and other related hormones in men with thyroid disorders. Table 11 provides the details of the hormones that showed a significant alteration in each age category (refer Tables S21-S32 for full analysis including all 13 hormones).

Table 9. Reproductive hormonal changes in men with hypothyroidism and hyperthyroidism.

	Hypothyroidism		Hyperthyroidism	
	%	Range	%	Range
SHBG	→	-	↑14/37 (37.8%)	56.6 - 189.5
DHEA-S	→	-	↓6/35 (17.1%)	23.8 - 153.7
IGF-I	↓8/98 (8.2%)	15.5 - 145.0	→	-
Estradiol	→	-	↑3/34 (8.8%)	61.6 - 113.9
FSH	→	-	↑3/30 (10.0%)	12.9 - 121.9
LH	→	-	↑6/30 (20.0%)	8.7 - 61.2

↑-Increased; ↓-Reduced; → -No Change; Units: Cortisol-μg/dL; Estradiol-pg/mL; FSH-mIU/mL; LH-mIU/mL; Total Testosterone-ng/dL; SHBG-nmol/L; DHEA-S-μg/dL; IGF-I-ng/mL, Prolactin-ng/mL.

Table 10. Reproductive hormonal changes in men with elevated anti-TPO and anti-Tg.

	Anti-TPO+		Anti-Tg+	
	%	Range	%	Range
SHBG	↑518/3102 (16.7%)	3.6 - 16.4	→	-
Progesterone	↓657/2539 (25.9%)	0.2 - 6.3	↓ 392/1965 (19.9%)	0.2 - 17.0

↑-Increased; ↓-Reduced; → -No Change; Units: Cortisol-μg/dL; Parathyroid Hormone-pg/mL; Estradiol-pg/mL; FSH-mIU/mL; Progesterone-ng/mL.

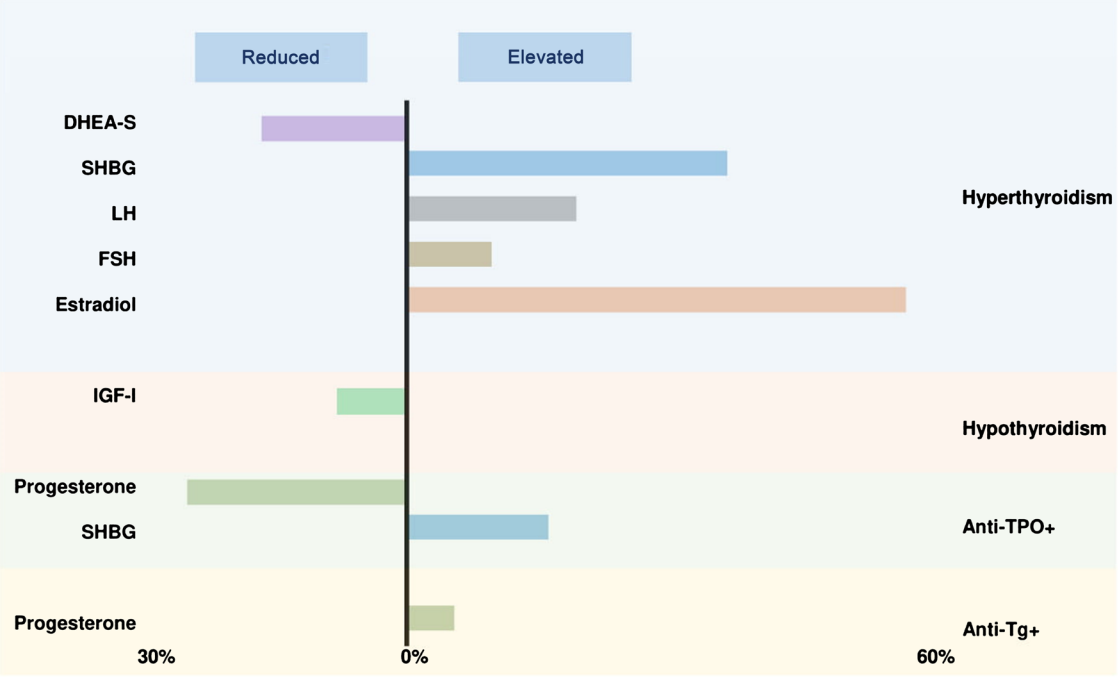

Figure 2. Hormonal changes in male with different thyroid disparities. Significantly altered hormones are only shown in the figure. The percentage of reduction (on the left) or increase (on the right) are shown in comparison to the control groups in each thyroid disorder.

Table 11. The effect of age on reproductive and other related hormones in men with thyroid disparity.

	Testosterone	SHBG	DHEA-S	IGF-I	Estradiol	Progesterone
15 - 25						
Hypothyroidism	↓10/43 (23.3%)	→	→	↓3/20 (15.0%)	→	→
Hyperthyroidism	→	→	→	→	→	→
Anti-TPO+	→	→	→	→	→	↑37/351 (10.5%)
Anti-Tg+	→	→	→	→	→	→
26 - 35						
Hypothyroidism	→	→	→	→	→	→
Hyperthyroidism	→	→	→	→	→	→
Anti-TPO+	→	→	→	→	→	↓ 172/699 (24.6%)
Anti-Tg+	→	→	→	→	→	→
36 - 49						
Hypothyroidism	→	→	→	→	→	→
Hyperthyroidism	→	↑13/28 (46.4)	↓4/25 (16.0%)	→	↑3/25 (12.0%)	→
Anti-TPO+	→	↑323/1860 (17.4%)	→	→	→	↓436/1489 (29.3%)
Anti-Tg+	→	→	→	→	→	↑55/1146 (4.8%)

↑-Increased; ↓-Reduced; → -No Change; Units: Total Testosterone-ng/dL; SHBG-nmol/L; DHEA-S-μg/dL; IGF-I-ng/mL; Estradiol-pg/mL; Progesterone-ng/mL.

Age 15 - 25 group only had reduced levels of total testosterone and IGF-1 in hypothyroid subjects and elevated levels of progesterone in seropositive anti-TPO subjects. Age 26 - 35 group only had reduced levels of progesterone in men seropositive for anti-TPO. The age group 36 - 49 is the most affected group. Hyperthyroid men in that age group had elevated levels of SHBG and estradiol hormones with reduced levels of DHEA-S. Men seropositive for anti-TPO had elevated levels of SHBG and reduced levels of progesterone hormone. Men seropositive for anti-Tg had elevated levels of progesterone.

4. Discussion

Thyroid alterations are associated with other disorders and closely linked to the diseases that are under the control of the hypothalamus-pituitary-gonadal axis. Sexual and reproductive-related hormones are controlled by the hypothalamus-pituitary-gonadal axis and affect the individuals with derailed thyroid functions. Our study is a comprehensive analysis including the common thyroid subcategories (subclinical/overt hypothyroidism and subclinical/overt hyperthyroidism) and autoantibodies related to AITD separately for 13 sexual and reproductive-related hormones for a large population size of 15,043 including 10,626 women and 4417 men in different reproductive age groups.

In this study, we used the physician reported ICD-10-CM codes to provide the clinical information about the subjects. The ICD-10-CM an internationally rec-

ognized alphanumeric code, created by the World Health Organization (WHO) for physicians and other healthcare providers to report their diagnosis, symptoms, and procedures specific for each disease, disorder, injury, infection, and symptom. The percentage distribution of the ICD-10-CM could provide clinical information on subjects used in this study. The top ranked ICD-10-CM codes were nonspecific symptoms representing fatigue (ICD-10-CM-R5383) and vitamin D deficiency (ICD-10-CM-E559). Thyroid disease usually contains nonspecific symptoms such as fatigue, hair loss, etc. which are also symptoms of vitamin D deficiency.

Our analysis between thyroid dysfunction and sexual and reproductive-related hormones showed that different thyroid alterations could affect sexual and reproductive-related hormones in different ways. Hyperthyroid women showed elevated levels of SHBG and total testosterone, while hypothyroid women showed reduced levels of SHBG and DHEA-S but elevated levels of cortisol. Hyperthyroid men had significantly elevated levels of SHBG, LH, FSH, estradiol and reduced levels of DHEA-S, while hypothyroid men had reduced levels of IGF-I. An interesting finding is that SHBG levels were in opposite directions in hyperthyroidism and hypothyroidism in women. SHBG is a protein that binds and transports sex hormones such as testosterone, estrogen to target cells. Studies showed that the levels of SHBG could be increased in hyperthyroidism due to the effects of elevated thyroid hormones on its production by the liver, [9] which was also reflected by our results. Several studies also showed a positive correlation between SHBG binding capacity and FT4 and FT3 levels in hyperthyroid patients. [10] The increase in the affinity of SHBG to testosterone in hyperthyroid subjects could reduce the metabolic clearance rate of testosterone thus, increasing the total serum testosterone levels that were agreeing with our results for hyperthyroid women. However, the underlying mechanism of the effect of hypothyroidism on SHBG is still under review, but our results show that the effect is opposite to that in hyperthyroidism in women [11]. Some studies have shown subnormal to normal levels of SHBG in hypothyroidism [12]. Our data followed the same pattern for men, where hyperthyroidism showed elevated levels of SHBG while hypothyroidism showed normal levels [13]. Since the SHBG level has least effect on reducing the testosterone levels in hypothyroidism, as suggested by other studies, the primary reason for the reduction may be due to hypogonadotropic hypogonadism, where hypothyroidism impairs the ability of pituitary to respond to GnRH, thus, ultimately reducing the testosterone secretion [14]. Apart from these major hormones Cortisol, DHEA-S and IGF-I have shown significantly different levels in subjects with thyroid disease compared to control subjects. Cortisol is a steroid hormone, produced in the adrenal gland and releases in response to any kind of stress in the body. The elevated levels of cortisol in hypothyroidism in women could be mainly due to the decreased metabolic clearance of cortisol and decrease in the negative feedback of cortisol on the hypothalamic-pituitary-adrenal axis [15]. DHEA-S is an an-

drostane steroid that is produced by sulfation of DHEA in the adrenal cortex. DHEA-S is one of the precursors of male hormones androstenedione, testosterone and dihydrotestosterone and female hormone estrogens [16]. We found that serum DHEA-S levels were significantly reduced in hypothyroid women. As Tagawa *et al.* suggested, the reduction in DHEA-S in hypothyroidism may be due to the significant reduction in the activity of the enzyme, cytochrome P-450$_{SCC}$ involved in the biosynthesis of all steroidal hormones, including DHEA-S [17]. Our results with DHEA-S in hyperthyroid men showed opposite results compared to previous studies done by other researchers. They suggest that steroidogenesis could be activated by thyroid hormones in hyperthyroidism leading to elevated levels of DHEA-S [17] [18]. However, we found reduced levels of DHEA-S in hyperthyroid men. Estradiol, FSH, LH and Progesterone were not included in the analysis for women since the reference ranges were depending on women hormonal phases. Even though estradiol is predominant in female sex hormone estrogen, it also plays an essential role in male sexual functions [19]. Studies have shown that elevated levels of SHBG in hyperthyroidism could indirectly increase the levels of LH and estradiol [20]. Our results followed the same trend as hyperthyroid men in our study had elevated levels of SHBG, LH and estradiol.

Next, we focused on assessing the sexual and reproductive-related hormone levels in subjects with seropositive thyroid autoantibodies, anti-TPO and anti-Tg. Our results showed that women with anti-TPO positivity had reduced levels of cortisol and elevated levels of total testosterone. Reduced cortisol levels could be attributed to the primary adrenal insufficiency (PAI) or failure to produce adequate levels of cortisol in autoimmune thyroid disease that has been reported in variable occurrences in different countries [21]. In our results, we observed high levels of testosterone in women seropositive for anti-TPO. The prevalence of thyroid autoimmunity has been found to be consistently increased in polycystic ovary syndrome (PCOS) that could lead to increase testosterone levels in women. It is suspected that PCOS and autoimmune thyroid disease may have a pathogenic link since they share similar factors, such as genetic susceptibility and sub inflammation/autoimmunity to the development of the disease [22]. In addition, we found higher levels of SHBG and low levels of progesterone in anti-TPO positive men, while reduced levels of parathyroid hormone and elevated levels of progesterone in women and men with anti-Tg positivity respectively.

Finally, we grouped the thyroid subcategories of men and women into smaller sub-groups based on their age to evaluate the effect of age on their reproductive and other related hormones. In both genders, age groups 15 - 25 and 26 - 35 did not show any major effect on reproductive and other related hormones. However, the age group 36 - 49 showed the most significant effect confirming that age has a significant effect on reproductive hormonal changes in thyroid diseased subjects.

One of the limitations in our study was the inability to account for subjects with other thyroid diseases such as central hypothyroidism. We did not account

for these secondary thyroid diseases since these disorders are very rare compared to primary thyroid disease. In addition, our study did not account for the smoking history and ethnicity because this information was not available in the data source.

5. Conclusion

In conclusion, our comprehensive study showed that different thyroid alterations affect differently on both male and female reproductive health, especially in the age group 36 - 49. Hence, frequent testing and follow-up routines should be considered on reproductive and other related hormones specially, if an individual in the age group 36 - 49 is susceptible to thyroid disease.

Ethics Approval and Consent to Participate

This study is based on retrospective analysis of de-identified laboratory data, hence was exempted from formal ethical reviews by WIRB (#1-1098539-1). The data and materials in this manuscript have not been published elsewhere and are not under consideration by another journal.

Availability of Data and Material

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

TS, HK, KK, and TW performed the research. TS, HK, JJ, and VJ designed the study. TS, HK, KB, QS and VR analyzed the data. TS and HK wrote the article.

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Competing Interests

Siriwardhane is an employee of Vibrant America LLC. Krishna, Ranganathan, Song, Jayaraman, Wang, Bei, Rajasekaran, Krishnamurthy, are employees of Vibrant Sciences LLC, CA, USA.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sarrel, P.M. (1990) Ovarian Hormones and the Circulation. *Maturitas*, **12**, 287-298. https://doi.org/10.1016/0378-5122(90)90008-T

[2] Katib, A. (2015) Mechanisms Linking Obesity to Male Infertility. *Central European Journal of Urology*, **68**, 79-85. https://doi.org/10.5173/ceju.2015.01.435

[3] Jefferys, A., Vanderpump, M. and Yasmin, E. (2015) Thyroid Dysfunction and Re-

productive Health. *The Obstetrician & Gynaecologist*, **17**, 39-45. https://doi.org/10.1111/tog.12161

[4] Kumar, A., Shekhar, S. and Dhole, B. (2014) Thyroid and Male Reproduction. *Indian Journal of Endocrinology and Metabolism*, **18**, 23-31. https://doi.org/10.4103/2230-8210.126523

[5] Seungdamrong, A., *et al.* (2017) Preconceptional Antithyroid Peroxidase Antibodies, But Not Thyroid-Stimulating Hormone, Are Associated with Decreased Live Birth Rates in Infertile Women. *Fertility and Sterility*, **108**, 843-850. https://doi.org/10.1016/j.fertnstert.2017.08.026

[6] Mehran, L., *et al.* (2013) Management of Thyroid Peroxidase Antibody Euthyroid Women in Pregnancy: Comparison of the American Thyroid Association and the Endocrine Society Guidelines. *Journal of Thyroid Research*, **2013**, Article ID: 542692. https://doi.org/10.1155/2013/542692

[7] Trummer, H., *et al.* (2001) Thyroid Hormones and Thyroid Antibodies in Infertile Males. *Fertility and Sterility*, **76**, 254-257. https://doi.org/10.1016/S0015-0282(01)01875-1

[8] Mayo Clinic Laboratories. 1995-2019. http://mayocliniclabs.com/test-catalog

[9] Selva, D.M. and Hammond, G.L. (2009) Thyroid Hormones Act Indirectly to Increase Sex Hormone-Binding Globulin Production by Liver via Hepatocyte Nuclear Factor-4α. *Journal of Molecular Endocrinology*, **43**, 19-27. https://doi.org/10.1677/JME-09-0025

[10] Pugeat, M., *et al.* (1996) Clinical Utility of Sex Hormone-Binding Globulin Measurement. *Hormone Research*, **45**, 148-155. https://doi.org/10.1159/000184778

[11] Brenta, G., *et al.* (1999) Variations of Sex Hormone-Binding Globulin in Thyroid Dysfunction. *Thyroid*, **9**, 273-277. https://doi.org/10.1089/thy.1999.9.273

[12] Hampl, R., *et al.* (2003) Interpretation of Sex Hormone-Binding Globulin Levels in Thyroid Disorders. *Thyroid*, **13**, 755-760. https://doi.org/10.1089/105072503768499644

[13] Foldes, J., *et al.* (1990) The Measurement of the Serum Sex-Hormone Binding Globulin in Various Thyroid Diseases. *Acta Medica Hungarica*, **47**, 81-90.

[14] Meikle, A.W. (2004) The Interrelationships between Thyroid Dysfunction and Hypogonadism in Men and Boys. *Thyroid*, **14**, S17-S25. https://doi.org/10.1089/105072504323024552

[15] Iranmanesh, A., *et al.* (1990) Dynamics of 24-Hour Endogenous Cortisol Secretion and Clearance in Primary Hypothyroidism Assessed before and after Partial Thyroid Hormone Replacement. *The Journal of Clinical Endocrinology & Metabolism*, **70**, 155-161. https://doi.org/10.1210/jcem-70-1-155

[16] Longcope, C. (1996) Dehydroepiandrosterone Metabolism. *Journal of Endocrinology*, **150**, S125-S127.

[17] Tagawa, N., *et al.* (2000) Serum Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate, and Pregnenolone Sulfate Concentrations in Patients with Hyperthyroidism and Hypothyroidism. *Clinical Chemistry*, **46**, 523-528.

[18] Yamakita, N., *et al.* (2001) Dehydroepiandrosterone Sulphate Is Increased and Dehydroepiandrosterone-Response to Corticotrophin-Releasing Hormone Is Decreased in the Hyperthyroid State Compared with the Euthyroid State. *Clinical Endocrinology*, **55**, 797-803. https://doi.org/10.1046/j.1365-2265.2001.01420.x

[19] Schulster, M., Bernie, A.M. and Ramasamy, R. (2016) The Role of Estradiol in Male

Reproductive Function. *Asian Journal of Andrology*, **18**, 435-440.
https://doi.org/10.4103/1008-682X.173932

[20] Sanyal, T., *et al.* (2012) Gynaecomastia as the Initial Presentation of Thyrotoxicosis. *Indian Journal of Endocrinology and Metabolism*, **16**, S352-S353.

[21] Yamamoto, T. (2015) Comorbid Latent Adrenal Insufficiency with Autoimmune Thyroid Disease. *European Thyroid Journal*, **4**, 201-206.
https://doi.org/10.1159/000433532

[22] Arduc, A., *et al.* (2015) High Prevalence of Hashimoto's Thyroiditis in Patients with Polycystic Ovary Syndrome: Does the Imbalance between Estradiol and Progesterone Play a Role? *Endocrine Research*, **40**, 204-210.
https://doi.org/10.3109/07435800.2015.1015730

Supplementary Material

Table S1. Age group 15 - 49. Reproductive hormonal changes in women with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 641)				Thyroid Negative (n = 9217)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	60/578 (10.4%)	0.558 - 6.12	103/578 (17.8%)	17.04 - 46	1036/8256 (12.5%)	0.365 - 6.14	0.1434	983/8256 (11.9%)	12.1 - 55.37	0
Parathyroid Hormone	2/495 (0.4%)	13.74 - 14.43	32/495 (6.5%)	65.5 - 498.9	74/7056 (1%)	5.5 - 14.48	0.2397	357/7056 (5.1%)	65.5 - 200.1	0.207
Estradiol	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
FSH	N/A	N/A	N/A	N/A	0/3 (0%)	N/A	1	1/3 (33.3%)	61.09 - 61.09	1
LH	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
Progesterone	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
Total Testosterone	124/582 (21.3%)	2.5 - 59.5	40/582 (6.9%)	48.6 - 523.1	1762/8503 (20.7%)	2.5 - 159.2	0.7771	730/8503 (8.6%)	48.18 - 1010	0.1745
SHBG	32/573 (5.6%)	6.5 - 24.2	122/573 (21.3%)	123.1 - 844.9	239/8270 (2.9%)	5.14 - 24.5	0.0005	2117/8270 (25.6%)	122.1 - 732.3	0.0249
DHEA-S	63/579 (10.9%)	0.1 - 145.9	34/579 (5.9%)	256.4 - 641.5	678/8249 (8.2%)	3.34 - 159.3	0.0312	634/8249 (7.7%)	256.6 - 881.1	0.1301
IGF-I	12/189 (6.3%)	35.51 - 141	9/189 (4.8%)	246,413.83	120/3237 (3.7%)	16.78 - 203	0.101	182/3237 (5.6%)	198,585.18	0.7352
Estriol	0/91 (0%)	N/A	3/91 (3.3%)	300.7 - 635.3	0/1327 (0%)	N/A	1	27/1327 (2%)	351.3 - 851.8	0.4357
Estrone	15/120 (12.5%)	9.3 - 16.2	0/120 (0%)	N/A	278/1860 (14.9%)	9 - 16.5	0.5493	43/1860 (2.3%)	186.4 - 859.52	0.1081
Prolactin	0/10 (0%)	N/A	3/10 (30%)	33.46 - 35.84	4/150 (2.7%)	3.92 - 4.78	1	28/150 (18.7%)	23.51 - 75.58	0.409

Table S2. Age group 15 - 49. Reproductive hormonal changes in women with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 301)				Thyroid Negative (n = 9217)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	29/253 (11.5%)	0.801 - 6.13	26/253 (10.3%)	12.43 - 36.47	1036/8256 (12.5%)	0.365 - 6.14	0.6761	983/8256 (11.9%)	12.1 - 55.37	0.4895
Parathyroid Hormone	5/212 (2.4%)	12.44 - 13.8	7/212 (3.3%)	66.14 - 203.7	74/7056 (1%)	5.5 - 14.48	0.1399	357/7056 (5.1%)	65.5 - 200.1	0.3191
Estradiol	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
FSH	N/A	N/A	N/A	N/A	0/3 (0%)	N/A	1	1/3 (33.3%)	61.09 - 61.09	1
LH	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
Progesterone	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1

Continued

Total Testosterone	51/279 (18.3%)	2.62 - 134.9	49/279 (17.6%)	49,460.10	1762/8503 (20.7%)	2.5 - 159.2	0.3593	730/8503 (8.6%)	48.18 - 1010	0
SHBG	2/266 (0.8%)	12.3 - 22.5	95/266 (35.7%)	122.1 - 643	239/8270 (2.9%)	5.14 - 24.5	0.0361	2117/8270 (25.6%)	122.1 - 732.3	0.0003
DHEA-S	22/267 (8.2%)	11.9 - 135.5	23/267 (8.6%)	269.1 - 579.1	678/8249 (8.2%)	3.34 - 159.3	1	634/8249 (7.7%)	256.6 - 881.1	0.6577
IGF-I	4/101 (4%)	55.56 - 96.63	8/101 (7.9%)	210,554.80	120/3237 (3.7%)	16.78 - 203	0.7888	182/3237 (5.6%)	198,585	0.4451
Estriol	0/26 (0%)	N/A	0/26 (0%)	N/A	0/1327 (0%)	N/A	1	27/1327 (2%)	351.3 - 851.8	1
Estrone	8/59 (13.6%)	11.1 - 16.2	1/59 (1.7%)	493.4 - 493.4	278/1860 (14.9%)	9 - 16.5	0.9133	43/1860 (2.3%)	186.4 - 859.52	1
Prolactin	0/4 (0%)	N/A	0/4 (0%)	N/A	4/150 (2.7%)	3.92 - 4.78	1	28/150 (18.7%)	23.51 - 75.58	1

Table S3. Age group 15 - 49. Reproductive hormonal changes in women with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 8592)				Anti-TPO- (n = 1950)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	980/7618 (12.9%)	0.365 - 6.14	936/7618 (12.3%)	12.1 - 55.37	191/1792 (10.7%)	0.7 - 6.1	0.0122	208/1792 (11.6%)	12.5 - 47.1	0.4521
Parathyroid Hormone	68/6436 (1.1%)	7 - 14.48	312/6436 (4.8%)	65.5 - 268.6	17/1597 (1.1%)	5.5 - 14.3	1	104/1597 (6.5%)	65.5 - 498.9	0.0087
Estradiol	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
FSH	0/3 (0%)	N/A	1/3 (33.3%)	61.09 - 61.09	N/A	N/A	1	N/A	N/A	1
LH	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
Total Testosterone	1460/7873 (18.5%)	2.5 - 134.9	729/7873 (9.3%)	48.18 - 1010	528/1830 (28.9%)	2.56 - 159.2	0	130/1830 (7.1%)	48.2 - 624.3	0.004
SHBG	215/7657 (2.8%)	6.5 - 24.4	1949/7657 (25.5%)	122.1 - 844.9	79/1798 (4.4%)	5.14 - 24.5	0.0006	470/1798 (26.1%)	122.1 - 562.2	0.5686
DHEA-S	649/7673 (8.5%)	0.1 - 159.3	586/7673 (7.6%)	256.4 - 881.1	152/1779 (8.5%)	5.9 - 147.9	0.9442	127/1779 (7.1%)	261.6 - 762.4	0.5046
IGF-I	101/2826 (3.6%)	16.78 - 203	151/2826 (5.3%)	198 - 572	39/845 (4.6%)	21.06 - 106	0.199	61/845 (7.2%)	221,585.18	0.0492
Estriol	0/1335 (0%)	N/A	27/1335 (2%)	300.7 - 880.9	0/163 (0%)	N/A	1	7/163 (4.3%)	305.8 - 677.4	0.1187
Estrone	287/1907 (15%)	9 - 16.5	36/1907 (1.9%)	189.6 - 859.52	26/211 (12.3%)	9.3 - 16.44	0.3385	9/211 (4.3%)	186.4 - 374.4	0.0433
Prolactin	3/152 (2%)	3.92 - 4.78	28/152 (18.4%)	23.51 - 112.9	1/18 (5.6%)	4.62 - 4.62	0.3636	4/18 (22.2%)	25.46 - 52.03	0.7501

Table S4. Age group 15 - 49. Reproductive hormonal changes in women with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 7019)				Anti-Tg- (n = 3524)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	773/6235 (12.4%)	0.365 - 6.14	760/6235 (12.2%)	12.1 - 53.53	398/3175 (12.5%)	0.681 - 6.13	0.8742	384/3175 (12.1%)	12.1 - 55.37	0.9206
Parathyroid Hormone	68/5331 (1.3%)	5.5 - 14.48	276/5331 (5.2%)	65.5 - 268.6	17/2702 (0.6%)	8.9 - 14.37	0.0105	140/2702 (5.2%)	65.59 - 498.9	1
Estradiol	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
FSH	0/2 (0%)	N/A	1/2 (50%)	61.09 - 61.09	0/1 (0%)	N/A	1	0/1 (0%)	N/A	1
LH	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	0/1 (0%)	N/A	0/1 (0%)	N/A	N/A	N/A	1	N/A	N/A	1
Total Testosterone	1303/6471 (20.1%)	2.5 - 159.2	562/6471 (8.7%)	48.18 - 912.2	684/3231 (21.2%)	2.5 - 153.9	0.245	296/3231 (9.2%)	48.2 - 1010	0.4588
SHBG	189/6314 (3%)	6.5 - 24.29	1604/6314 (25.4%)	122.1 - 844.9	104/3140 (3.3%)	5.14 - 24.5	0.4358	815/3140 (26%)	122.1 - 585	0.5797
DHEA-S	525/6299 (8.3%)	0.1 - 159.3	494/6299 (7.8%)	256.4 - 881.1	276/3153 (8.8%)	0.109 - 147.9	0.5155	218/3153 (6.9%)	258.4 - 703.4	0.1161
IGF-I	90/2461 (3.7%)	21.06 - 203	142/2461 (5.8%)	198,572	50/1209 (4.1%)	16.78 - 106	0.5354	69/1209 (5.7%)	198,585.18	0.9989
Estriol	0/962 (0%)	N/A	20/962 (2.1%)	300.7 - 851.8	0/537 (0%)	N/A	1	14/537 (2.6%)	305.8 - 880.9	0.633
Estrone	188/1381 (13.6%)	9.1 - 16.2	25/1381 (1.8%)	188.95 - 859.52	126/739 (17.1%)	9 - 16.5	0.0395	20/739 (2.7%)	186.4 - 625.31	0.2279
Prolactin	2/101 (2%)	4.78 - 4.78	20/101 (19.8%)	23.51 - 112.9	2/69 (2.9%)	3.92 - 4.62	1	12/69 (17.4%)	23.67 - 52.03	0.8453

Table S5. Age group 15 - 25. Reproductive hormonal changes in women with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 97)				Thyroid Negative (n = 1264)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	5/88 (5.7%)	0.558 - 5.95	33/88 (37.5%)	19.46 - 46	156/1167 (13.4%)	0.81 - 6.1	0.0556	245/1167 (21%)	12.59 - 50.64	0.0005
Parathyroid Hormone	1/77 (1.3%)	13.74 - 13.74	1/77 (1.3%)	66.48 - 66.48	23/1009 (2.3%)	5.5 - 14.48	1	10/1009 (1%)	66.24 - 84.55	0.5564
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Continued

Total Testosterone	7/87 (8%)	4.55 - 42.8	11/87 (12.6%)	48.84 - 80.34	131/1145 (11.4%)	2.53 - 72.9	0.4286	146/1145 (12.8%)	48.3 - 537.1	1
SHBG	6/85 (7.1%)	6.97 - 23.62	23/85 (27.1%)	123.3 - 555.3	55/1125 (4.9%)	5.14 - 24.1	0.5322	274/1125 (24.4%)	122.1 - 562.1	0.6689
DHEA-S	9/89 (10.1%)	55.12 - 145.9	7/89 (7.9%)	285.5 - 574.8	118/1134 (10.4%)	31.19 - 147.9	1	143/1134 (12.6%)	300.7 - 761	0.2517
IGF-I	1/27 (3.7%)	141 - 141	4/27 (14.8%)	267 - 413.83	14/428 (3.3%)	59.1 - 203	0.6064	71/428 (16.6%)	306.08 - 572	1
Estriol	0/24 (0%)	N/A	0/24 (0%)	N/A	0/227 (0%)	N/A	N/A	2/227 (0.9%)	351.3 - 509	1
Estrone	6/24 (25%)	12.5 - 14.8	0/24 (0%)	N/A	59/274 (21.5%)	9.3 - 15.9	0.8913	3/274 (1.1%)	186.4 - 345.4	1
Prolactin	0/7 (0%)	N/A	2/7 (28.6%)	33.46 - 34.02	0/22 (0%)	N/A	N/A	4/22 (18.2%)	26.54 - 75.58	0.6119

Table S6. Age group 15 - 25. Reproductive hormonal changes in women with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 17)				Thyroid Negative (n = 1264)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	3/17 (17.6%)	4.12 - 5.8	2/17 (11.8%)	19.94 - 20.2	156/1167 (13.4%)	0.81 - 6.1	0.4896	245/1167 (21%)	12.59 - 50.64	0.5485
Parathyroid Hormone	0/12 (0%)	N/A	0/12 (0%)	N/A	23/1009 (2.3%)	5.5 - 14.48	1	10/1009 (1%)	66.24 - 84.55	1
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Testosterone	1/14 (7.1%)	34.9 - 34.9	1/14 (7.1%)	78 - 78	131/1145 (11.4%)	2.53 - 72.9	1	146/1145 (12.8%)	48.3 - 537.1	1
SHBG	0/15 (0%)	N/A	6/15 (40%)	122.2 - 177.7	55/1125 (4.9%)	5.14 - 24.1	1	274/1125 (24.4%)	122.1 - 562.1	0.2729
DHEA-S	2/15 (13.3%)	109.4 - 135.5	2/15 (13.3%)	340.9 - 416.4	118/1134 (10.4%)	31.19 - 147.9	0.6646	143/1134 (12.6%)	300.7 - 761	1
IGF-I	0/9 (0%)	N/A	4/9 (44.4%)	421.511 - 554.8	14/428 (3.3%)	59.1 - 203	1	71/428 (16.6%)	306.08 - 572	0.0509
Estriol	0/1 (0%)	N/A	0/1 (0%)	N/A	0/227 (0%)	N/A	1	2/227 (0.9%)	351.3 - 509	1
Estrone	1/1 (100%)	16.2 - 16.2	0/1 (0%)	N/A	59/274 (21.5%)	9.3 - 15.9	0.2182	3/274 (1.1%)	186.4 - 345.4	1
Prolactin	N/A	N/A	N/A	N/A	0/22 (0%)	N/A	1	4/22 (18.2%)	26.54 - 75.58	1

Table S7. Age group 15 - 25. Reproductive hormonal changes in women with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 1166)				Anti-TPO- (n = 253)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	142/1058 (13.4%)	0.558 - 6.1	242/1058 (22.9%)	12.59 - 50.64	28/243 (11.5%)	1.36 - 6.1	0.4924	43/243 (17.7%)	15.5 - 45.5	0.0942
Parathyroid Hormone	17/908 (1.9%)	7.8 - 14.48	13/908 (1.4%)	66.24 - 268.6	7/218 (3.2%)	5.5 - 13.8	0.3331	0/218 (0%)	N/A	0.0851
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Testosterone	88/1043 (8.4%)	2.53 - 72.9	143/1043 (13.7%)	48.3 - 537.1	54/238 (22.7%)	2.88 - 60.1	0	20/238 (8.4%)	49.39 - 79.6	0.0349
SHBG	42/1024 (4.1%)	6.97 - 23.62	261/1024 (25.5%)	122.1 - 562.1	22/235 (9.4%)	5.14 - 24.1	0.0017	45/235 (19.1%)	122.9 - 350.8	0.0501
DHEA-S	113/1040 (10.9%)	31.19 - 146	122/1040 (11.7%)	322.7 - 658.4	20/237 (8.4%)	62.4 - 147.9	0.3242	33/237 (13.9%)	285.5 - 761	0.4106
IGF-I	15/359 (4.2%)	59.1 - 203	48/359 (13.4%)	267 - 572	1/117 (0.9%)	106 - 106	0.135	33/117 (28.2%)	312.01 - 536.42	0.0004
Estriol	0/237 (0%)	N/A	2/237 (0.8%)	351.3 - 509	0/23 (0%)	N/A	N/A	0/23 (0%)	N/A	N/A
Estrone	65/280 (23.2%)	9.3 - 16.2	2/280 (0.7%)	345.4 - 345.4	5/29 (17.2%)	12.1 - 13.6	0.6182	1/29 (3.4%)	186.4 - 186.4	0.2567
Prolactin	0/28 (0%)	N/A	5/28 (17.9%)	26.54 - 112.9	0/3 (0%)	N/A	N/A	2/3 (66.7%)	33.46 - 52.03	0.1199

Table S8. Age group 15-25. Reproductive hormonal changes in women with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 898)				Anti-Tg- (n = 520)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	99/823 (12%)	0.558 - 6.1	185/823 (22.5%)	12.7 - 46.82	71/477 (14.9%)	1.77 - 6.1	0.1656	100/477 (21%)	12.59 - 50.64	0.571
Parathyroid Hormone	18/700 (2.6%)	5.5 - 14.48	9/700 (1.3%)	66.24 - 268.6	6/425 (1.4%)	10 - 12.43	0.2747	4/425 (0.9%)	66.48 - 75.95	0.7762
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Continued

Total Testosterone	88/805 (10.9%)	2.65 - 60.1	105/805 (13%)	48.3 - 537.1	54/475 (11.4%)	2.53 - 72.9	0.8821	57/475 (12%)	48.4 - 103	0.6488
SHBG	38/797 (4.8%)	6.97 - 24.1	195/797 (24.5%)	122.1 - 555.3	25/461 (5.4%)	5.14 - 23.3	0.7046	111/461 (24.1%)	123.9 - 562.1	0.931
DHEA-S	77/800 (9.6%)	37.49 - 146	97/800 (12.1%)	285.5 - 645.4	56/476 (11.8%)	31.19 - 147.9	0.2649	57/476 (12%)	301.6 - 658.4	1
IGF-I	11/320 (3.4%)	75.4 - 203	51/320 (15.9%)	306.08 - 572	5/155 (3.2%)	59.1 - 106	1	29/155 (18.7%)	267 - 536.42	0.5312
Estriol	0/169 (0%)	N/A	1/169 (0.6%)	351.3 - 351.3	0/91 (0%)	N/A	N/A	1/91 (1.1%)	509 - 509	1
Estrone	47/203 (23.2%)	9.3 - 16.2	0/203 (0%)	N/A	23/106 (21.7%)	9.7 - 15.9	0.8833	3/106 (2.8%)	186.4 - 345.4	0.0396
Prolactin	0/17 (0%)	N/A	5/17 (29.4%)	26.54 - 112.9	N/A	N/A	N/A	2/14 (14.3%)	29.68 - 52.03	0.4117

Table S9. Age group 26 - 35. Reproductive hormonal changes in women with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 157)				Thyroid Negative (n = 2633)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	20/143 (14%)	1.78 - 6.12	26/143 (18.2%)	18.5 - 42.23	243/2371 (10.2%)	0.611 - 6.13	0.2015	377/2371 (15.9%)	12.31 - 55.37	0.5453
Parathyroid Hormone	0/125 (0%)	N/A	9/125 (7.2%)	65.6 - 498.9	27/2035 (1.3%)	7 - 14.37	0.4007	83/2035 (4.1%)	65.6 - 149.5	0.1473
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Testosterone	17/144 (11.8%)	4.23 - 51.6	12/144 (8.3%)	48.61 - 141.9	374/2414 (15.5%)	2.52 - 121.6	0.2822	214/2414 (8.9%)	48.2 - 695.6	0.9464
SHBG	6/141 (4.3%)	15.81 - 23.26	32/141 (22.7%)	123.1 - 844.9	64/2339 (2.7%)	7.72 - 24.23	0.4261	671/2339 (28.7%)	122.2 - 732.3	0.1507
DHEA-S	19/143 (13.3%)	10.92 - 142.7	14/143 (9.8%)	343.2 - 530.8	264/2354 (11.2%)	3.52 - 159.3	0.5333	247/2354 (10.5%)	340.2 - 762.4	0.8998
IGF-I	1/40 (2.5%)	41.15 - 41.15	3/40 (7.5%)	288 - 377	35/861 (4.1%)	16.78 - 96.01	1	47/861 (5.5%)	235 - 585.18	0.4819
Estriol	0/17 (0%)	N/A	1/17 (5.9%)	635.3 - 635.3	0/387 (0%)	N/A	1	13/387 (3.4%)	392.6 - 851.8	0.4577
Estrone	2/25 (8%)	11.4 - 11.4	0/25 (0%)	N/A	69/502 (13.7%)	9 - 16.4	0.5575	18/502 (3.6%)	191.02 - 859.52	1
Prolactin	N/A	N/A	N/A	N/A	1/39 (2.6%)	4.78 - 4.78	1	11/39 (28.2%)	23.51 - 42.19	1

Table S10. Age group 26 - 35. Reproductive hormonal changes in women with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 66)				Thyroid Negative (n = 2633)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	4/60 (6.7%)	0.801 - 6	7/60 (11.7%)	13.9 - 30.6	243/2371 (10.2%)	0.611 - 6.13	0.515	377/2371 (15.9%)	12.31 - 55.37	0.4784
Parathyroid Hormone	4/52 (7.7%)	13.1 - 13.8	2/52 (3.8%)	66.14 - 79.2	27/2035 (1.3%)	7 - 14.37	0.0066	83/2035 (4.1%)	65.6 - 149.5	1
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Testosterone	7/60 (11.7%)	2.62 - 49.8	8/60 (13.3%)	49 - 111.7	374/2414 (15.5%)	2.52 - 121.6	0.5287	214/2414 (8.9%)	48.2 - 695.6	0.3332
SHBG	0/57 (0%)	N/A	19/57 (33.3%)	124.3 - 643	64/2339 (2.7%)	7.72 - 24.23	0.4034	671/2339 (28.7%)	122.2 - 732.3	0.537
DHEA-S	8/57 (14%)	11.9 - 89.93	7/57 (12.3%)	354.6 - 460	264/2354 (11.2%)	3.52 - 159.3	0.6504	247/2354 (10.5%)	340.2 - 762.4	0.8289
IGF-I	2/24 (8.3%)	58.2 - 92.36	1/24 (4.2%)	355.16 - 355.16	35/861 (4.1%)	16.78 - 96.01	0.2652	47/861 (5.5%)	235 - 585.18	1
Estriol	0/9 (0%)	N/A	0/9 (0%)	N/A	0/387 (0%)	N/A	1	13/387 (3.4%)	392.6 - 851.8	1
Estrone	2/12 (16.7%)	11.1 - 11.1	0/12 (0%)	N/A	69/502 (13.7%)	9 - 16.4	0.6755	18/502 (3.6%)	191.02 - 859.52	1
Prolactin	0/1 (0%)	N/A	0/1 (0%)	N/A	1/39 (2.6%)	4.78 - 4.78	1	11/39 (28.2%)	23.51 - 42.19	1

Table S11. Age group 26 - 35. Reproductive hormonal changes in women with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 2376)				Anti-TPO- (n = 552)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	234/2130 (11%)	0.444 - 6.13	343/2130 (16.1%)	12.31 - 55.37	43/502 (8.6%)	1.1 - 6.1	0.1314	76/502 (15.1%)	13.4 - 38.38	0.6432
Parathyroid Hormone	30/1810 (1.7%)	7 - 14.37	70/1810 (3.9%)	65.6 - 149.5	3/449 (0.7%)	7.5 - 13.7	0.1835	26/449 (5.8%)	65.6 - 498.9	0.0934
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Continued

Total Testosterone	279/2164 (12.9%)	2.52 - 121.6	203/2164 (9.4%)	48.21 - 695.6	128/517 (24.8%)	3.3 - 73.7	0	38/517 (7.4%)	48.2 - 596.5	0.1723
SHBG	45/2095 (2.1%)	7.8 - 23.8	597/2095 (28.5%)	122.2 - 844.9	29/506 (5.7%)	7.72 - 24.5	0	140/506 (27.7%)	122.3 - 562.2	0.7519
DHEA-S	238/2129 (11.2%)	3.52 - 159.3	217/2129 (10.2%)	340.5 - 702.8	63/498 (12.7%)	16.01 - 141.5	0.3953	58/498 (11.6%)	340.2 - 762.4	0.3827
IGF-I	33/707 (4.7%)	16.78 - 96.01	45/707 (6.4%)	235 - 483.824	6/246 (2.4%)	40.58 - 80.5	0.1826	13/246 (5.3%)	274 - 585.18	0.6486
Estriol	0/372 (0%)	N/A	13/372 (3.5%)	392.6 - 880.9	0/49 (0%)	N/A	N/A	2/49 (4.1%)	677.4 - 677.4	0.6898
Estrone	66/490 (13.5%)	9 - 16.4	15/490 (3.1%)	191.02 - 859.52	8/59 (13.6%)	11.7 - 15.9	1	3/59 (5.1%)	228.7 - 228.7	0.4282
Prolactin	1/35 (2.9%)	4.78 - 4.78	9/35 (25.7%)	23.51 - 42.19	0/5 (0%)	N/A	N/A	2/5 (40%)	25.46 - 26.78	0.603

Table S12. Age group 26-35. Reproductive hormonal changes in women with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 1964)				Anti-Tg- (n = 964)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	182/1757 (10.4%)	0.444 - 6.13	279/1757 (15.9%)	12.47 - 53.53	95/875 (10.9%)	1.78 - 6.1	0.745	140/875 (16%)	12.31 - 55.37	0.9815
Parathyroid Hormone	27/1508 (1.8%)	7 - 14.1	65/1508 (4.3%)	65.6 - 108.9	6/751 (0.8%)	10.19 - 14.37	0.0961	31/751 (4.1%)	66 - 498.9	0.9268
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Testosterone	270/1810 (14.9%)	2.52 - 121.6	155/1810 (8.6%)	48.2 - 695.6	137/871 (15.7%)	2.62 - 94.9	0.6233	86/871 (9.9%)	48.62 - 596.5	0.299
SHBG	46/1754 (2.6%)	7.8 - 24.23	495/1754 (28.2%)	122.3 - 844.9	28/847 (3.3%)	7.72 - 24.5	0.3918	242/847 (28.6%)	122.2 - 585	0.8892
DHEA-S	195/1773 (11%)	3.52 - 159.3	196/1773 (11.1%)	340.2 - 762.4	106/854 (12.4%)	16.01 - 128	0.3172	79/854 (9.3%)	340.5 - 638.3	0.1781
IGF-I	23/631 (3.6%)	38.6 - 96.01	43/631 (6.8%)	235 - 518.51	16/322 (5%)	16.78 - 89.71	0.422	15/322 (4.7%)	242 - 585.18	0.2405
Estriol	0/272 (0%)	N/A	8/272 (2.9%)	392.6 - 851.8	0/149 (0%)	N/A	N/A	7/149 (4.7%)	465.2 - 880.9	0.5125
Estrone	43/360 (11.9%)	9.5 - 15.8	13/360 (3.6%)	191.02 - 859.52	31/189 (16.4%)	9 - 16.4	0.1863	5/189 (2.6%)	227.3 - 300.2	0.7253
Prolactin	1/24 (4.2%)	4.78 - 4.78	7/24 (29.2%)	23.51 - 42.19	0/16 (0%)	N/A	N/A	4/16 (25%)	23.67 - 26.78	1

Table S13. Age group 36 - 49. Reproductive hormonal changes in women with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 387)				Thyroid Negative (n = 5320)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	35/347 (10.1%)	0.9 - 6.1	44/347 (12.7%)	17.04 - 39.08	637/4718 (13.5%)	0.365 - 6.14	0.084	361/4718 (7.7%)	12.1 - 47.1	0.0012
Parathyroid Hormone	1/293 (0.3%)	14.43 - 14.43	22/293 (7.5%)	65.5 - 142.5	24/4012 (0.6%)	8.6 - 14.3	1	264/4012 (6.6%)	65.5 - 200.1	0.621
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
FSH	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	1/1 (100%)	61.09 - 61.09	1
LH	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Total Testosterone	100/351 (28.5%)	2.5 - 59.5	17/351 (4.8%)	48.6 - 523.1	1257/4944 (25.4%)	2.5 - 159.2	0.2271	370/4944 (7.5%)	48.18 - 1010	0.0835
SHBG	20/347 (5.8%)	6.5 - 24.2	67/347 (19.3%)	123.1 - 476	120/4806 (2.5%)	7 - 24.5	0.0006	1172/4806 (24.4%)	122.1 - 637.8	0.0382
DHEA-S	35/347 (10.1%)	0.1 - 79.3	13/347 (3.7%)	256.4 - 641.5	296/4761 (6.2%)	3.34 - 94.4	0.0067	244/4761 (5.1%)	256.6 - 881.1	0.3139
IGF-I	10/122 (8.2%)	35.51 - 70.2	2/122 (1.6%)	246 - 387.08	71/1948 (3.6%)	21.06 - 97.02	0.0229	64/1948 (3.3%)	198 - 467	0.4309
Estriol	0/50 (0%)	N/A	2/50 (4%)	300.7 - 305.8	0/713 (0%)	N/A	1	12/713 (1.7%)	390.3 - 813.5	0.2322
Estrone	7/71 (9.9%)	9.3 - 16.2	0/71 (0%)	N/A	150/1084 (13.8%)	9.1 - 16.5	0.442	22/1084 (2%)	188.95 - 734.5	0.3928
Prolactin	0/3 (0%)	N/A	1/3 (33.3%)	35.84 - 35.84	3/89 (3.4%)	3.92 - 4.78	1	13/89 (14.6%)	24.28 - 61.24	0.3942

Table S14. Age group 36 - 49. Reproductive hormonal changes in women with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 218)				Thyroid Negative (n = 5320)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	22/176 (12.5%)	0.837 - 6.13	17/176 (9.7%)	12.43 - 36.47	637/4718 (13.5%)	0.365 - 6.14	0.7874	361/4718 (7.7%)	12.1 - 47.1	0.4033
Parathyroid Hormone	1/148 (0.7%)	12.44 - 12.44	5/148 (3.4%)	71.49 - 203.7	24/4012 (0.6%)	8.6 - 14.3	0.5968	264/4012 (6.6%)	65.5 - 200.1	0.166
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
FSH	N/A	N/A	N/A	N/A	0/1 (0%)	N/A	1	1/1 (100%)	61.09 - 61.09	1
LH	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1

Continued

Total Testosterone	43/205 (21%)	2.68 - 134.9	40/205 (19.5%)	52.23 - 460.1	1257/4944 (25.4%)	2.5 - 159.2	0.1755	370/4944 (7.5%)	48.18 - 1010	0
SHBG	2/194 (1%)	12.3 - 22.5	70/194 (36.1%)	122.1 - 432.1	120/4806 (2.5%)	7 - 24.5	0.3347	1172/4806 (24.4%)	122.1 - 637.8	0.0003
DHEA-S	12/195 (6.2%)	15.74 - 58.19	14/195 (7.2%)	269.1 - 579.1	296/4761 (6.2%)	3.34 - 94.4	1	244/4761 (5.1%)	256.6 - 881.1	0.2707
IGF-I	2/68 (2.9%)	55.56 - 96.63	3/68 (4.4%)	210 - 352.22	71/1948 (3.6%)	21.06 - 97.02	1	64/1948 (3.3%)	198 - 467	0.492
Estriol	0/16 (0%)	N/A	0/16 (0%)	N/A	0/713 (0%)	N/A	1	12/713 (1.7%)	390.3 - 813.5	1
Estrone	5/46 (10.9%)	11.2 - 14.5	1/46 (2.2%)	493.4 - 493.4	150/1084 (13.8%)	9.1 - 16.5	0.7231	22/1084 (2%)	188.95 - 734.5	0.6192
Prolactin	0/3 (0%)	N/A	0/3 (0%)	N/A	3/89 (3.4%)	3.92 - 4.78	1	13/89 (14.6%)	24.28 - 61.24	1

Table S15. Age group 36 - 49. Reproductive hormonal changes in women with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 5050)				Anti-TPO- (n = 1145)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	604/4430 (13.6%)	0.365 - 6.14	351/4430 (7.9%)	12.1 - 45.3	120/1047 (11.5%)	0.7 - 6.1	0.0693	89/1047 (8.5%)	12.5 - 47.1	0.579
Parathyroid Hormone	21/3718 (0.6%)	8.6 - 14.43	229/3718 (6.2%)	65.5 - 185.7	7/930 (0.8%)	12.6 - 14.3	0.6706	78/930 (8.4%)	65.5 - 203.7	0.0177
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
FSH	0/1 (0%)	N/A	1/1 (100%)	61.09 - 61.09	N/A	N/A	1	N/A	N/A	1
LH	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Total Testosterone	1093/4666 (23.4%)	2.5 - 134.9	383/4666 (8.2%)	48.18 - 1010	346/1075 (32.2%)	2.56 - 159.2	0	72/1075 (6.7%)	48.2 - 624.3	0.1118
SHBG	128/4538 (2.8%)	6.5 - 24.4	1091/4538 (24%)	122.1 - 637.8	28/1057 (2.6%)	7.5 - 24.5	0.8403	285/1057 (27%)	122.1 - 552.5	0.0516
DHEA-S	298/4504 (6.6%)	0.1 - 90.3	247/4504 (5.5%)	256.4 - 881.1	69/1044 (6.6%)	5.9 - 94.4	1	36/1044 (3.4%)	261.6 - 536.5	0.0089
IGF-I	53/1760 (3%)	31.53 - 97.02	58/1760 (3.3%)	198 - 467	32/482 (6.6%)	21.06 - 96.63	0.0004	15/482 (3.1%)	221 - 432.18	0.9552
Estriol	0/726 (0%)	N/A	12/726 (1.7%)	300.7 - 813.5	0/91 (0%)	N/A	1	5/91 (5.5%)	305.8 - 438.8	0.0423
Estrone	156/1137 (13.7%)	9.1 - 16.5	19/1137 (1.7%)	189.6 - 734.5	13/123 (10.6%)	9.3 - 16.44	0.4038	5/123 (4.1%)	188.95 - 374.4	0.1342
Prolactin	2/89 (2.2%)	3.92 - 4.78	14/89 (15.7%)	24.28 - 61.24	1/10 (10%)	4.62 - 4.62	0.276	0/10 (0%)	N/A	0.3489

Table S16. Age group 36 - 49. Reproductive hormonal changes in women with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 4157)				Anti-Tg- (n = 2040)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	492/3655 (13.5%)	0.365 - 6.14	296/3655 (8.1%)	12.1 - 47.1	232/1823 (12.7%)	0.681 - 6.13	0.475	144/1823 (7.9%)	12.1 - 42.15	0.839
Parathyroid Hormone	23/3123 (0.7%)	8.6 - 14.43	202/3123 (6.5%)	65.5 - 203.7	5/1526 (0.3%)	8.9 - 14.17	0.1363	105/1526 (6.9%)	65.59 - 200.1	0.639
Estradiol	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
FSH	0/1 (0%)	N/A	1/1 (100%)	61.09 - 61.09	N/A	N/A	1	N/A	N/A	1
LH	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Progesterone	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1
Total Testosterone	945/3856 (24.5%)	2.5 - 159.2	302/3856 (7.8%)	48.18 - 912.2	493/1885 (26.2%)	2.5 - 153.9	0.1869	153/1885 (8.1%)	48.2 - 1010	0.7466
SHBG	105/3763 (2.8%)	6.5 - 24.29	914/3763 (24.3%)	122.1 - 637.8	51/1832 (2.8%)	9.4 - 24.5	1	462/1832 (25.2%)	122.1 - 552.5	0.4689
DHEA-S	253/3726 (6.8%)	0.1 - 90.3	201/3726 (5.4%)	256.4 - 881.1	114/1823 (6.3%)	0.109 - 94.4	0.4851	82/1823 (4.5%)	258.4 - 703.4	0.1736
IGF-I	56/1510 (3.7%)	21.06 - 97.02	48/1510 (3.2%)	198 - 467	29/732 (4%)	36.3 - 96.63	0.86	25/732 (3.4%)	198 - 432.18	0.8658
Estriol	0/521 (0%)	N/A	11/521 (2.1%)	300.7 - 813.5	0/297 (0%)	N/A	1	6/297 (2%)	305.8 - 669.8	1
Estrone	98/818 (12%)	9.1 - 16.2	12/818 (1.5%)	188.95 - 734.5	72/444 (16.2%)	9.1 - 16.5	0.0436	12/444 (2.7%)	190.99 - 625.31	0.1872
Prolactin	1/60 (1.7%)	4.78 - 4.78	8/60 (13.3%)	24.64 - 61.24	2/39 (5.1%)	3.92 - 4.62	0.5599	6/39 (15.4%)	24.28 - 49.21	1

Table S17. Age group 15 - 49. Reproductive hormonal changes in men with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 255)				Thyroid Negative (n = 3982)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	26/222 (11.7%)	1.06 - 6.09	20/222 (9%)	15 - 32.5	390/3504 (11.1%)	0.61 - 6.13	0.8753	245/3504 (7%)	11.98 - 40.8	0.3177
Parathyroid Hormone	3/192 (1.6%)	8.8 - 13.53	6/192 (3.1%)	65.84 - 101.5	37/3004 (1.2%)	8.36 - 14.3	0.7314	113/3004 (3.8%)	65.64 - 465.4	0.7986
Estradiol	152/222 (68.5%)	5.2 - 25.52	7/222 (3.2%)	62.4 - 90.1	2392/3540 (67.6%)	5.02 - 25.74	0.8388	72/3540 (2%)	61.22 - 247.4	0.3751
FSH	29/206 (14.1%)	0.1 - 1.42	6/206 (2.9%)	12.7 - 34.04	451/3291 (13.7%)	0.1 - 1.44	0.9627	58/3291 (1.8%)	12.47 - 63.9	0.354
LH	33/207 (15.9%)	0.1 - 1.59	13/207 (6.3%)	8.75 - 21.3	425/3325 (12.8%)	0.1 - 1.64	0.2276	186/3325 (5.6%)	8.68 - 53.67	0.7948
Progesterone	59/198 (29.8%)	0.059 - 0.191	9/198 (4.5%)	0.176 - 3.01	742/3124 (23.8%)	0.052 - 0.194	0.0653	146/3124 (4.7%)	0.15 - 17.43	1

Continued

Total Testosterone	46/249 (18.5%)	16.75 - 334.6	18/249 (7.2%)	876.6 - 1488	573/3885 (14.7%)	5.5 - 347.3	0.1322	320/3885 (8.2%)	837.7 - 1499	0.6575
SHBG	22/239 (9.2%)	3.9 - 16.3	31/239 (13%)	56.24 - 118.4	247/3762 (6.6%)	3.6 - 16.44	0.148	607/3762 (16.1%)	56 - 226.6	0.2284
DHEA-S	13/228 (5.7%)	21.94 - 187.1	21/228 (9.2%)	375.2 - 693.2	154/3572 (4.3%)	8 - 205.6	0.4086	423/3572 (11.8%)	261.6 - 972	0.2744
IGF-I	8/98 (8.2%)	15.52 - 145	7/98 (7.1%)	235 - 401.05	59/1759 (3.4%)	11.99 - 99.36	0.0274	105/1759 (6%)	200 - 599	0.7972
Estriol	0/26 (0%)	N/A	0/26 (0%)	N/A	0/364 (0%)	N/A	1	7/364 (1.9%)	208.4 - 426.5	1
Estrone	4/37 (10.8%)	N/A	3/37 (8.1%)	54.4 - 62.43	89/537 (16.6%)	9 - 10.1	0.4899	17/537 (3.2%)	51.2 - 88.6	0.1316
Prolactin	0/11 (0%)	N/A	4/11 (36.4%)	20.38 - 24.09	4/151 (2.6%)	1.91 - 4.01	1	23/151 (15.2%)	15.26 - 35.85	0.0882

Table S18. Age group 15 - 49. Reproductive hormonal changes in men with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 38)				Thyroid Negative (n = 3982)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	4/30 (13.3%)	3.7 - 5.32	4/30 (13.3%)	20.7 - 24.79	390/3504 (11.1%)	0.61 - 6.13	0.5704	245/3504 (7%)	11.98 - 40.8	0.1568
Parathyroid Hormone	1/27 (3.7%)	10.2 - 10.2	1/27 (3.7%)	78.32 - 78.32	37/3004 (1.2%)	8.36 - 14.3	0.2897	113/3004 (3.8%)	65.64 - 465.4	1
Estradiol	20/34 (58.8%)	5.9 - 23.92	3/34 (8.8%)	61.58 - 113.9	2392/3540 (67.6%)	5.02 - 25.74	0.3683	72/3540 (2%)	61.22 - 247.4	0.0333
FSH	5/30 (16.7%)	0.129 - 1	3/30 (10%)	12.93 - 121.9	451/3291 (13.7%)	0.1 - 1.44	0.8392	58/3291 (1.8%)	12.47 - 63.9	0.0168
LH	6/30 (20%)	0.3 - 1.38	6/30 (20%)	8.7 - 61.24	425/3325 (12.8%)	0.1 - 1.64	0.367	186/3325 (5.6%)	8.68 - 53.67	0.0028
Progesterone	8/28 (28.6%)	0.065 - 0.182	3/28 (10.7%)	0.19 - 5.07	742/3124 (23.8%)	0.052 - 0.194	0.7089	146/3124 (4.7%)	0.15 - 17.43	0.1437
Total Testosterone	9/37 (24.3%)	22.9 - 204.1	5/37 (13.5%)	865.7 - 1400	573/3885 (14.7%)	5.5 - 347.3	0.162	320/3885 (8.2%)	837.7 - 1499	0.3902
SHBG	3/37 (8.1%)	8.5 - 13.7	14/37 (37.8%)	56.6 - 189.5	247/3762 (6.6%)	3.6 - 16.44	0.7328	607/3762 (16.1%)	56 - 226.6	0.0009
DHEA-S	6/35 (17.1%)	23.79 - 153.7	5/35 (14.3%)	364.2 - 486.2	154/3572 (4.3%)	8 - 205.6	0.0011	423/3572 (11.8%)	261.6 - 972	0.8554
IGF-I	1/17 (5.9%)	110 - 110	1/17 (5.9%)	297 - 297	59/1759 (3.4%)	11.99 - 99.36	0.444	105/1759 (6%)	200 - 599	1
Estriol	0/4 (0%)	N/A	0/4 (0%)	N/A	0/364 (0%)	N/A	1	7/364 (1.9%)	208.4 - 426.5	1
Estrone	1/5 (20%)	N/A	0/5 (0%)	N/A	89/537 (16.6%)	9 - 10.1	1	17/537 (3.2%)	51.2 - 88.6	1
Prolactin	0/2 (0%)	N/A	2/2 (100%)	20.28 - 21.01	4/151 (2.6%)	1.91 - 4.01	1	23/151 (15.2%)	15.26 - 35.85	0.0258

Table S19. Age group 15 - 49. Reproductive hormonal changes in men with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 3284)				Anti-TPO- (n = 1087)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	336/2870 (11.7%)	0.61 - 6.13	160/2870 (5.6%)	12.21 - 30.97	90/954 (9.4%)	0.7 - 6.12	0.0609	113/954 (11.8%)	20.7 - 24.4	0
Parathyroid Hormone	28/2435 (1.1%)	8.36 - 14.29	87/2435 (3.6%)	65.64 - 465.4	15/852 (1.8%)	8.8 - 14.3	0.24	35/852 (4.1%)	78.32 - 78.32	0.5446
Estradiol	1930/2919 (66.1%)	5.02 - 25.74	71/2919 (2.4%)	61.22 - 247.4	689/964 (71.5%)	5.2 - 25.7	0.0024	22/964 (2.3%)	61.58 - 113.9	0.8863
FSH	363/2666 (13.6%)	0.1 - 1.44	54/2666 (2%)	12.47 - 121.9	141/915 (15.4%)	0.1 - 1.4	0.1966	13/915 (1.4%)	52.2 - 52.2	0.3061
LH	339/2687 (12.6%)	0.1 - 1.64	158/2687 (5.9%)	8.68 - 61.24	143/929 (15.4%)	0.1 - 1.6	0.0366	50/929 (5.4%)	8.7 - 27.1	0.631
Progesterone	657/2539 (25.9%)	0.052 - 0.194	138/2539 (5.4%)	0.15 - 6.29	160/868 (18.4%)	0.053 - 0.192	0	32/868 (3.7%)	0.212 - 0.212	0.0509
Total Testosterone	425/3204 (13.3%)	10.3 - 347.3	275/3204 (8.6%)	837.7 - 1499	212/1057 (20.1%)	5.5 - 345	0	81/1057 (7.7%)	1013 - 1400	0.3826
SHBG	191/3102 (6.2%)	3.6 - 16.44	518/3102 (16.7%)	56 - 189.5	89/1037 (8.6%)	3.9 - 16.4	0.0088	144/1037 (13.9%)	56.6 - 189.5	0.0366
DHEA-S	138/2930 (4.7%)	8 - 203.5	338/2930 (11.5%)	304.2 - 955.3	42/990 (4.2%)	24.9 - 205.6	0.6033	124/990 (12.5%)	364.2 - 486.2	0.4367
IGF-I	47/1374 (3.4%)	15.4 - 145	72/1374 (5.2%)	200 - 599	25/534 (4.7%)	11.99 - 99.36	0.2445	44/534 (8.2%)	N/A	0.0185
Estriol	0/344 (0%)	N/A	6/344 (1.7%)	208.4 - 426.5	0/58 (0%)	N/A	1	1/58 (1.7%)	N/A	1
Estrone	74/518 (14.3%)	9 - 10.1	18/518 (3.5%)	51.3 - 88.6	23/77 (29.9%)	9.1 - 10	0.001	4/77 (5.2%)	N/A	0.5114
Prolactin	3/145 (2.1%)	1.91 - 4.01	23/145 (15.9%)	15.26 - 35.85	1/23 (4.3%)	3.6 - 3.6	0.4483	6/23 (26.1%)	21.01 - 21.01	0.3636

Table S20. Age group 15 - 49. Reproductive hormonal changes in men with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 2530)				Anti-Tg- (n = 1846)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	238/2204 (10.8%)	0.7 - 6.11	152/2204 (6.9%)	11.98 - 40.8	189/1622 (11.7%)	0.61 - 6.13	0.4373	121/1622 (7.5%)	13.07 - 35.2	0.5449
Parathyroid Hormone	29/1882 (1.5%)	8.36 - 14.29	68/1882 (3.6%)	65.64 - 465.4	14/1407 (1%)	8.8 - 14.3	0.2269	54/1407 (3.8%)	65.66 - 138.4	0.8071
Estradiol	1518/2256 (67.3%)	5.02 - 25.74	49/2256 (2.2%)	61.22 - 316.7	1103/1629 (67.7%)	5.25 - 25.7	0.808	44/1629 (2.7%)	61.58 - 189.8	0.338
FSH	309/2074 (14.9%)	0.1 - 1.43	40/2074 (1.9%)	12.5 - 121.9	195/1512 (12.9%)	0.1 - 1.44	0.098	27/1512 (1.8%)	12.47 - 63.9	0.8514
LH	296/2088 (14.2%)	0.1 - 1.62	119/2088 (5.7%)	8.68 - 61.24	186/1533 (12.1%)	0.1 - 1.64	0.0821	89/1533 (5.8%)	8.7 - 53.49	0.9492

Continued

Progesterone	392/1965 (19.9%)	0.052 - 0.194	111/1965 (5.6%)	0.15 - 17.02	425/1445 (29.4%)	0.052 - 0.194	0	59/1445 (4.1%)	0.15 - 17.43	0.0459
Total Testosterone	373/2476 (15.1%)	5.5 - 345	208/2476 (8.4%)	843.5 - 1499	265/1789 (14.8%)	10 - 347.3	0.8539	148/1789 (8.3%)	837.7 - 1496	0.926
SHBG	160/2402 (6.7%)	3.6 - 16.37	387/2402 (16.1%)	56.04 - 226.6	120/1740 (6.9%)	4.2 - 16.44	0.8141	277/1740 (15.9%)	56 - 189.5	0.9018
DHEA-S	105/2280 (4.6%)	20.63 - 192.8	278/2280 (12.2%)	331.6 - 972	75/1643 (4.6%)	8 - 205.6	1	185/1643 (11.3%)	261.6 - 922.3	0.3989
IGF-I	35/1142 (3.1%)	11.99 - 110	60/1142 (5.3%)	200 - 599	37/768 (4.8%)	15.4 - 145	0.0644	56/768 (7.3%)	205 - 597	0.0835
Estriol	0/235 (0%)	N/A	4/235 (1.7%)	208.4 - 426.5	0/167 (0%)	N/A	1	3/167 (1.8%)	210.5 - 236.8	1
Estrone	57/356 (16%)	9 - 10.1	14/356 (3.9%)	51.2 - 88.6	40/239 (16.7%)	9.1 - 10	0.9032	8/239 (3.3%)	51.3 - 87.4	0.8813
Prolactin	2/96 (2.1%)	3.69 - 4.01	17/96 (17.7%)	15.65 - 35.85	2/72 (2.8%)	1.91 - 3.6	1	12/72 (16.7%)	15.26 - 33.95	1

Table S21. Age group 15 - 25. Reproductive hormonal changes in men with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 47)				Thyroid Negative (n = 559)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	6/43 (14%)	3.54 - 5.81	4/43 (9.3%)	20.11 - 32.5	58/508 (11.4%)	0.61 - 6.1	0.8022	51/508 (10%)	12.79 - 40.8	1
Parathyroid Hormone	2/36 (5.6%)	8.8 - 13.53	0/36 (0%)	N/A	11/448 (2.5%)	10.5 - 14.3	0.2508	6/448 (1.3%)	66.33 - 80.19	1
Estradiol	25/38 (65.8%)	5.5 - 25.4	0/38 (0%)	N/A	359/489 (73.4%)	5.25 - 25.7	0.4071	0/489 (0%)	N/A	1
FSH	2/35 (5.7%)	0.905 - 1.1	0/35 (0%)	N/A	38/456 (8.3%)	0.117 - 1.43	1	2/456 (0.4%)	14.24 - 20.3	1
LH	1/36 (2.8%)	1.4 - 1.4	1/36 (2.8%)	9.9 - 9.9	18/459 (3.9%)	0.116 - 1.6	1	24/459 (5.2%)	8.69 - 13.53	1
Progesterone	7/35 (20%)	0.059 - 0.19	3/35 (8.6%)	0.307 - 0.571	56/454 (12.3%)	0.058 - 0.194	0.2972	35/454 (7.7%)	0.15 - 1.69	0.7461
Total Testosterone	10/43 (23.3%)	48 - 332.2	0/43 (0%)	N/A	60/533 (11.3%)	10,344.30	0.0381	24/533 (4.5%)	837.7 - 1210	0.2447
SHBG	6/40 (15%)	5.57 - 14.46	3/40 (7.5%)	59.85 - 73.8	37/510 (7.3%)	6.4 - 16.4	0.1467	92/510 (18%)	56.04 - 226.6	0.1255
DHEA-S	4/40 (10%)	68.57 - 187.1	6/40 (15%)	495.2 - 693.2	21/505 (4.2%)	34.6 - 203.5	0.1021	74/505 (14.7%)	261.6 - 955.3	1
IGF-I	3/20 (15%)	39.7 - 145	4/20 (20%)	332.5 - 401.05	8/240 (3.3%)	56.23 - 97.6	0.0433	42/240 (17.5%)	303.55 - 599	0.7622
Estriol	0/4 (0%)	N/A	0/4 (0%)	N/A	0/70 (0%)	N/A	1	1/70 (1.4%)	210.5 - 210.5	1
Estrone	1/4 (25%)	N/A	0/4 (0%)	N/A	22/79 (27.8%)	10 - Sep	1	0/79 (0%)	N/A	1
Prolactin	N/A	N/A	N/A	N/A	1/15 (6.7%)	3.69 - 3.69	1	4/15 (26.7%)	15.26 - 21.96	1

Table S22. Age group 15 - 25. Reproductive hormonal changes in men with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 3)				Thyroid Negative (n = 559)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	0/3 (0%)	N/A	1/3 (33.3%)	24.79 - 24.79	58/508 (11.4%)	0.61 - 6.1	1	51/508 (10%)	12.79 - 40.8	0.2758
Parathyroid Hormone	0/2 (0%)	N/A	0/2 (0%)	N/A	11/448 (2.5%)	10.5 - 14.3	1	6/448 (1.3%)	66.33 - 80.19	1
Estradiol	0/2 (0%)	N/A	0/2 (0%)	N/A	359/489 (73.4%)	5.25 - 25.7	0.0719	0/489 (0%)	N/A	1
FSH	0/2 (0%)	N/A	0/2 (0%)	N/A	38/456 (8.3%)	0.117 - 1.43	1	2/456 (0.4%)	14.24 - 20.3	1
LH	0/2 (0%)	N/A	1/2 (50%)	10 - 10	18/459 (3.9%)	0.116 - 1.6	1	24/459 (5.2%)	8.69 - 13.53	0.1056
Progesterone	0/2 (0%)	N/A	1/2 (50%)	0.19 - 0.19	56/454 (12.3%)	0.058 - 0.194	1	35/454 (7.7%)	0.15 - 1.69	0.1518
Total Testosterone	1/3 (33.3%)	N/A	0/3 (0%)	N/A	60/533 (11.3%)	10 - 344.3	0.3045	24/533 (4.5%)	837.7 - 1210	1
SHBG	0/3 (0%)	N/A	0/3 (0%)	N/A	37/510 (7.3%)	6.4 - 16.4	1	92/510 (18%)	56.04 - 226.6	1
DHEA-S	0/3 (0%)	N/A	0/3 (0%)	N/A	21/505 (4.2%)	34.6 - 203.5	1	74/505 (14.7%)	261.6 - 955.3	1
IGF-I	1/1 (100%)	110 - 110	0/1 (0%)	N/A	8/240 (3.3%)	56.23 - 97.6	0.0373	42/240 (17.5%)	303.55 - 599	1
Estriol	0/1 (0%)	N/A	0/1 (0%)	N/A	0/70 (0%)	N/A	1	1/70 (1.4%)	210.5 - 210.5	1
Estrone	0/1 (0%)	N/A	0/1 (0%)	N/A	22/79 (27.8%)	9 - 10	1	0/79 (0%)	N/A	1
Prolactin	N/A	N/A	N/A	N/A	1/15 (6.7%)	3.69 - 3.69	1	4/15 (26.7%)	15.26 - 21.96	1

Table S23. Age group 15 - 25. Reproductive hormonal changes in men with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 447)				Anti-TPO- (n = 184)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	45/400 (11.3%)	0.61 - 6.1	35/400 (8.8%)	12.79 - 30.97	21/172 (12.2%)	1.94 - 5.99	0.852	22/172 (12.8%)	12.8 - 40.8	0.1844
Parathyroid Hormone	9/342 (2.6%)	10.5 - 14.16	5/342 (1.5%)	66.33 - 80.19	5/157 (3.2%)	8.8 - 14.3	0.9557	2/157 (1.3%)	75.11 - 75.2	1
Estradiol	271/380 (71.3%)	5.25 - 25.7	0/380 (0%)	N/A	127/167 (76%)	5.3 - 25.5	0.2981	0/167 (0%)	N/A	1
FSH	32/347 (9.2%)	0.117 - 1.44	0/347 (0%)	N/A	11/159 (6.9%)	0.179 - 1.4	0.4896	2/159 (1.3%)	14.24 - 20.3	0.0983
LH	11/351 (3.1%)	0.1 - 1.4	21/351 (6%)	8.69 - 13.53	10/159 (6.3%)	0.116 - 1.6	0.1554	6/159 (3.8%)	9.4 - 10.1	0.413

Continued

Progesterone	49/351 (14%)	0.058 - 0.194	37/351 (10.5%)	0.15 - 1.85	15/155 (9.7%)	0.066 - 0.192	0.2337	6/155 (3.9%)	0.183 - 1.69	0.021
Total Testosterone	43/421 (10.2%)	10.3 - 332.2	21/421 (5%)	837.7 - 1210	29/179 (16.2%)	10 - 344.3	0.0539	6/179 (3.4%)	851.7 - 1069	0.5033
SHBG	34/395 (8.6%)	5.57 - 16.4	65/395 (16.5%)	56.04 - 179.8	10/175 (5.7%)	9.9 - 14.88	0.306	31/175 (17.7%)	56.25 - 226.6	0.8033
DHEA-S	21/393 (5.3%)	34.6 - 203.5	53/393 (13.5%)	304.2 - 955.3	6/173 (3.5%)	43.4 - 186.8	0.4531	30/173 (17.3%)	261.6 - 763.4	0.2867
IGF-I	11/177 (6.2%)	39.7 - 145	24/177 (13.6%)	303.55 - 599	3/91 (3.3%)	56.23 - 97.6	0.3944	23/91 (25.3%)	317.29 - 597	0.0265
Estriol	0/61 (0%)	N/A	1/61 (1.6%)	210.5 - 210.5	0/14 (0%)	N/A	1	0/14 (0%)	N/A	1
Estrone	15/71 (21.1%)	9 - 9.3	0/71 (0%)	N/A	8/14 (57.1%)	10 - Oct	0.0146	0/14 (0%)	N/A	1
Prolactin	1/12 (8.3%)	3.69 - 3.69	3/12 (25%)	15.26 - 19.61	0/4 (0%)	N/A	1	1/4 (25%)	21.96 - 21.96	1

Table S24. Age group 15 - 25. Reproductive hormonal changes in men with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 350)				Anti-Tg- (n = 281)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	34/314 (10.8%)	1.8 - 6.06	27/314 (8.6%)	12.79 - 40.8	32/258 (12.4%)	0.61 - 6.1	0.649	30/258 (11.6%)	13.38 - 32.5	0.2877
Parathyroid Hormone	11/271 (4.1%)	8.8 - 14.16	3/271 (1.1%)	66.33 - 80.19	3/228 (1.3%)	13.94 - 14.3	0.0999	4/228 (1.8%)	71.31 - 75.2	0.7076
Estradiol	220/304 (72.4%)	5.5 - 25.63	0/304 (0%)	N/A	178/243 (73.3%)	5.25 - 25.7	0.8936	0/243 (0%)	N/A	1
FSH	23/278 (8.3%)	0.117 - 1.43	1/278 (0.4%)	14.24 - 14.24	20/228 (8.8%)	0.179 - 1.44	0.9682	1/228 (0.4%)	20.3 - 20.3	1
LH	13/282 (4.6%)	0.1 - 1.6	14/282 (5%)	8.69 - 13.53	8/228 (3.5%)	0.116 - 1.4	0.6905	13/228 (5.7%)	9.02 - 12.85	0.8644
Progesterone	28/276 (10.1%)	0.059 - 0.193	29/276 (10.5%)	0.15 - 1.85	36/230 (15.7%)	0.058 - 0.194	0.0852	14/230 (6.1%)	0.15 - 0.588	0.1062
Total Testosterone	40/334 (12%)	21.82 - 344.3	15/334 (4.5%)	848.5 - 1210	32/266 (12%)	10 - 332.2	1	12/266 (4.5%)	837.7 - 1069	1
SHBG	25/316 (7.9%)	5.57 - 16.22	47/316 (14.9%)	56.04 - 226.6	19/254 (7.5%)	6.4 - 16.4	0.973	49/254 (19.3%)	56.25 - 179.8	0.1977
DHEA-S	17/315 (5.4%)	34.6 - 186.2	44/315 (14%)	369.5 - 955.3	10/251 (4%)	43.4 - 203.5	0.5586	39/251 (15.5%)	261.6 - 845.4	0.6856
IGF-I	8/138 (5.8%)	39.7 - 110	21/138 (15.2%)	303.55 - 599	6/130 (4.6%)	79.9 - 145	0.873	26/130 (20%)	323.92 - 597	0.3853
Estriol	0/43 (0%)	N/A	0/43 (0%)	N/A	0/32 (0%)	N/A	1	1/32 (3.1%)	210.5 - 210.5	0.4267
Estrone	11/49 (22.4%)	9 - 9	0/49 (0%)	N/A	12/36 (33.3%)	9.3 - 10	0.3848	0/36 (0%)	N/A	1
Prolactin	1/5 (20%)	3.69 - 3.69	1/5 (20%)	19.61 - 19.61	0/11 (0%)	N/A	0.3125	3/11 (27.3%)	15.26 - 21.96	1

Table S25. Age group 26 - 35. Reproductive hormonal changes in men with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 62)				Thyroid Negative (n = 1090)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	6/52 (11.5%)	2.9 - 6.09	7/52 (13.5%)	19.8 - 31.6	99/986 (10%)	1.26 - 6.12	0.9099	83/986 (8.4%)	11.98 - 31	0.314
Parathyroid Hormone	0/46 (0%)	N/A	2/46 (4.3%)	66.37 - 200.5	12/847 (1.4%)	8.36 - 14.29	1	23/847 (2.7%)	65.66 - 115.2	0.3727
Estradiol	43/56 (76.8%)	7.6 - 25.33	1/56 (1.8%)	61.05 - 183	668/980 (68.2%)	5.3 - 25.74	0.2284	12/980 (1.2%)	65.8 - 189.8	0.5165
FSH	6/50 (12%)	1.13 - 1.42	2/50 (4%)	12.85 - 48.77	90/922 (9.8%)	0.1 - 1.43	0.7846	13/922 (1.4%)	12.47 - 40.77	0.178
LH	5/50 (10%)	0.878 - 1.59	5/50 (10%)	8.9 - 36.21	66/930 (7.1%)	0.1 - 1.63	0.6231	50/930 (5.4%)	8.78 - 34.71	0.2853
Progesterone	16/49 (32.7%)	0.063 - 0.191	2/49 (4.1%)	0.156 - 6.98	192/869 (22.1%)	0.052 - 0.194	0.123	45/869 (5.2%)	0.151 - 17.43	1
Total Testosterone	7/62 (11.3%)	16.75 - 242.6	3/62 (4.8%)	772.6 - 1425	150/1066 (14.1%)	11.44 - 345.3	0.6699	57/1066 (5.3%)	838.4 - 1437	1
SHBG	5/59 (8.5%)	10.9 - 16.3	10/59 (16.9%)	58.2 - 167.9	72/1035 (7%)	3.6 - 16.31	0.8558	151/1035 (14.6%)	56 - 186.7	0.7575
DHEA-S	4/56 (7.1%)	21.94 - 157	7/56 (12.5%)	296 - 855.9	69/983 (7%)	37.6 - 205.6	1	173/983 (17.6%)	436.8 - 922.3	0.4242
IGF-I	1/20 (5%)	30.41 - 30.41	2/20 (10%)	283 - 319.03	14/477 (2.9%)	18.09 - 96.15	0.4648	21/477 (4.4%)	241 - 487.33	0.2352
Estriol	0/6 (0%)	N/A	0/6 (0%)	N/A	0/113 (0%)	N/A	1	2/113 (1.8%)	344 - 426.5	1
Estrone	0/6 (0%)	N/A	0/6 (0%)	N/A	28/150 (18.7%)	9.4 - 9.9	0.5921	0/150 (0%)	N/A	1
Prolactin	0/2 (0%)	N/A	0/2 (0%)	N/A	0/39 (0%)	N/A	1	9/39 (23.1%)	15.65 - 33.95	1

Table S26. Age group 26 - 35. Reproductive hormonal changes in men with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 7)				Thyroid Negative (n = 1090)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	1/5 (20%)	4.3 - 4.3	0/5 (0%)	N/A	99/986 (10%)	1.26 - 6.12	0.4132	83/986 (8.4%)	11.98 - 31	1
Parathyroid Hormone	0/4 (0%)	N/A	0/4 (0%)	N/A	12/847 (1.4%)	8.36 - 14.29	1	23/847 (2.7%)	65.66 - 115.2	1
Estradiol	3/7 (42.9%)	9.6 - 21.1	0/7 (0%)	N/A	668/980 (68.2%)	5.3 - 25.74	0.2193	12/980 (1.2%)	65.8 - 189.8	1
FSH	0/6 (0%)	N/A	2/6 (33.3%)	13.8 - 52.8	90/922 (9.8%)	0.1 - 1.43	1	13/922 (1.4%)	12.47 - 40.77	0.0035
LH	0/5 (0%)	N/A	2/5 (40%)	9.15 - 28.38	66/930 (7.1%)	0.1 - 1.63	1	50/930 (5.4%)	8.78 - 34.71	0.0272

Continued

Progesterone	0/4 (0%)	N/A	1/4 (25%)	0.184 - 0.184	192/869 (22.1%)	0.052 - 0.194	0.5814	45/869 (5.2%)	0.151 - 17.43	0.195
Total Testosterone	4/6 (66.7%)	30.7 - 110.2	1/6 (16.7%)	744.6 - 1433	150/1066 (14.1%)	11.44 - 345.3	0.0049	57/1066 (5.3%)	838.4 - 1437	0.2843
SHBG	1/6 (16.7%)	9.04 - 9.04	1/6 (16.7%)	63.9 - 179.6	72/1035 (7%)	3.6 - 16.31	0.3542	151/1035 (14.6%)	56 - 186.7	1
DHEA-S	2/7 (28.6%)	23.79 - 104.7	1/7 (14.3%)	359.8 - 773.8	69/983 (7%)	37.6 - 205.6	0.0842	173/983 (17.6%)	436.8 - 922.3	1
IGF-I	0/4 (0%)	N/A	1/4 (25%)	347.91 - 347.91	14/477 (2.9%)	18.09 - 96.15	1	21/477 (4.4%)	241 - 487.33	0.1713
Estriol	N/A	N/A	N/A	N/A	0/113 (0%)	N/A	1	2/113 (1.8%)	344 - 426.5	1
Estrone	0/1 (0%)	N/A	0/1 (0%)	N/A	28/150 (18.7%)	9.4 - 9.9	1	0/150 (0%)	N/A	1
Prolactin	0/1 (0%)	N/A	1/1 (100%)	20.28	0/39 (0%)	N/A	1	9/39 (23.1%)	15.65 - 33.95	0.25

Table S27. Age group 26 - 35. Reproductive hormonal changes in men with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 888)				Anti-TPO- (n = 293)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	85/794 (10.7%)	1.26 - 6.09	51/794 (6.4%)	12.06 - 31.6	22/264 (8.3%)	1.64 - 6.12	0.3224	41/264 (15.5%)	11.98 - 31	0
Parathyroid Hormone	8/681 (1.2%)	8.36 - 14.29	18/681 (2.6%)	65.5 - 172	4/236 (1.7%)	8.8 - 13.9	0.5173	8/236 (3.4%)	66.7 - 81.73	0.7129
Estradiol	545/808 (67.5%)	5.3 - 25.74	12/808 (1.5%)	61.03 - 313	182/257 (70.8%)	5.8 - 25.61	0.3508	5/257 (1.9%)	65.9 - 189.8	0.8203
FSH	76/740 (10.3%)	0.1 - 1.43	16/740 (2.2%)	12.48 - 117.5	27/252 (10.7%)	0.15 - 1.4	0.9362	1/252 (0.4%)	13.58 - 13.58	0.0878
LH	51/745 (6.8%)	0.1 - 1.63	44/745 (5.9%)	8.7 - 46.2	26/254 (10.2%)	0.3 - 1.6	0.1067	14/254 (5.5%)	8.78 - 16.5	0.9389
Progesterone	172/699 (24.6%)	0.052 - 0.194	38/699 (5.4%)	0.15 - 6.98	38/239 (15.9%)	0.064 - 0.19	0.007	13/239 (5.4%)	0.191 - 17.43	1
Total Testosterone	107/871 (12.3%)	11.44 - 345.3	49/871 (5.6%)	375.5 - 1498	55/283 (19.4%)	15.3 - 345	0.0036	14/283 (4.9%)	858.9 - 1440	0.7748
SHBG	52/847 (6.1%)	3.6 - 16.31	130/847 (15.3%)	56.5 - 180.2	30/281 (10.7%)	16 - May	0.0161	37/281 (13.2%)	56.1 - 125.1	0.4265
DHEA-S	58/799 (7.3%)	21.94 - 160.2	136/799 (17%)	248.9 - 971.8	21/268 (7.8%)	59.05 - 205.6	0.8593	50/268 (18.7%)	453.6 - 917.2	0.6047
IGF-I	11/367 (3%)	30.41 - 96.15	17/367 (4.6%)	189 - 354.09	4/141 (2.8%)	18.09 - 93.4	1	7/141 (5%)	302 - 487.33	1
Estriol	0/98 (0%)	N/A	1/98 (1%)	227.9 - 664.4	0/25 (0%)	N/A	1	1/25 (4%)	344 - 344	0.3665
Estrone	20/135 (14.8%)	9.6 - 9.9	0/135 (0%)	N/A	9/27 (33.3%)	9.4 - 9.4	0.0438	1/27 (3.7%)	68.7 - 68.7	0.1667
Prolactin	0/37 (0%)	N/A	7/37 (18.9%)	15.49 - 127.8	0/5 (0%)	N/A	1	3/5 (60%)	17.14 - 33.95	0.0782

Table S28. Age group 26 - 35. Reproductive hormonal changes in men with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 681)				Anti-Tg- (n = 504)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	56/613 (9.1%)	1.26 - 6.09	54/613 (8.8%)	12.06 - 31.6	52/448 (11.6%)	1.64 - 6.12	0.2254	38/448 (8.5%)	15.73 - 27.9	0.939
Parathyroid Hormone	8/524 (1.5%)	8.36 - 14.29	15/524 (2.9%)	65.5 - 174.4	4/396 (1%)	8.8 - 13	0.5693	11/396 (2.8%)	65.66 - 83.96	1
Estradiol	417/619 (67.4%)	5.3 - 25.74	11/619 (1.8%)	61.03 - 141.5	312/448 (69.6%)	5.58 - 25.68	0.4702	6/448 (1.3%)	65.2 - 189.8	0.752
FSH	63/574 (11%)	0.1 - 1.43	12/574 (2.1%)	12.48 - 117.5	40/421 (9.5%)	0.103 - 1.4	0.5164	5/421 (1.2%)	12.47 - 24.08	0.4019
LH	42/574 (7.3%)	0.1 - 1.59	37/574 (6.4%)	8.7 - 44.6	35/428 (8.2%)	0.3 - 1.63	0.6995	21/428 (4.9%)	8.71 - 21.3	0.3705
Progesterone	108/543 (19.9%)	0.052 - 0.194	27/543 (5%)	0.15 - 6.98	102/397 (25.7%)	0.056 - 0.193	0.0423	24/397 (6%)	0.152 - 17.43	0.5676
Total Testosterone	100/671 (14.9%)	16.75 - 345	36/671 (5.4%)	375.5 - 1498	63/487 (12.9%)	11.44 - 345.3	0.3874	27/487 (5.5%)	838.4 - 1437	0.9989
SHBG	44/658 (6.7%)	3.6 - 16.31	99/658 (15%)	59.19 - 180.2	38/473 (8%)	4.2 - 16.31	0.456	69/473 (14.6%)	56 - 186.7	0.8975
DHEA-S	46/618 (7.4%)	21.94 - 192.8	108/618 (17.5%)	248.9 - 971.8	33/452 (7.3%)	37.6 - 205.6	1	79/452 (17.5%)	436.8 - 922.3	1
IGF-I	7/309 (2.3%)	30.41 - 96.15	12/309 (3.9%)	189 - 392.6	8/201 (4%)	18.09 - 93.4	0.3943	12/201 (6%)	241 - 487.33	0.3824
Estriol	0/69 (0%)	N/A	2/69 (2.9%)	233.4 - 664.4	0/54 (0%)	N/A	1	0/54 (0%)	N/A	0.5034
Estrone	19/91 (20.9%)	9.6 - 9.8	0/91 (0%)	N/A	10/71 (14.1%)	9.4 - 9.9	0.3614	1/71 (1.4%)	68.7 - 68.7	0.4383
Prolactin	0/23 (0%)	N/A	6/23 (26.1%)	15.49 - 127.8	0/19 (0%)	N/A	1	4/19 (21.1%)	18.94 - 33.95	1

Table S29. Age group 36 - 49. Reproductive hormonal changes in men with hypothyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hypothyroidism (n = 146)				Thyroid Negative (n = 2333)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	14/127 (11%)	1.06 - 6.07	9/127 (7.1%)	15 - 27.7	233/2010 (11.6%)	0.652 - 6.13	0.9591	111/2010 (5.5%)	12.2 - 35.2	0.5865
Parathyroid Hormone	1/110 (0.9%)	11.6 - 11.6	4/110 (3.6%)	67.05 - 101.5	14/1709 (0.8%)	9 - 14	0.6091	84/1709 (4.9%)	65.64 - 465.4	0.8171
Estradiol	84/128 (65.6%)	5.2 - 25.52	6/128 (4.7%)	62.4 - 90.1	1365/2071 (65.9%)	5.02 - 25.74	1	60/2071 (2.9%)	61.22 - 247.4	0.3761
FSH	21/121 (17.4%)	0.1 - 0.765	4/121 (3.3%)	15.97 - 23	323/1913 (16.9%)	0.1 - 1.44	0.9928	43/1913 (2.2%)	12.5 - 63.9	0.3591
LH	27/121 (22.3%)	0.1 - 1.58	7/121 (5.8%)	8.75 - 12.6	341/1936 (17.6%)	0.1 - 1.64	0.2354	112/1936 (5.8%)	8.68 - 53.67	1

Continued

Progesterone	36/114 (31.6%)	0.059 - 0.19	4/114 (3.5%)	0.214 - 3.01	494/1801 (27.4%)	0.052 - 0.194	0.394	66/1801 (3.7%)	0.152 - 17.02	1
Total Testosterone	29/144 (20.1%)	85.81 - 334.6	15/144 (10.4%)	876.6 - 1488	363/2286 (15.9%)	5.5 - 347.3	0.2183	239/2286 (10.5%)	839.6 - 1499	1
SHBG	11/140 (7.9%)	3.9 - 15.91	18/140 (12.9%)	56.24 - 118.4	138/2217 (6.2%)	3.9 - 16.44	0.5547	364/2217 (16.4%)	56.05 - 181.7	0.3218
DHEA-S	5/132 (3.8%)	35.68 - 79.45	8/132 (6.1%)	375.2 - 545.5	64/2084 (3.1%)	8 - 159.3	0.8403	176/2084 (8.4%)	331.6 - 972	0.4236
IGF-I	4/58 (6.9%)	15.52 - 90.15	1/58 (1.7%)	235 - 235	37/1042 (3.6%)	11.99 - 99.36	0.2693	42/1042 (4%)	200 - 474.84	0.7229
Estriol	0/16 (0%)	N/A	0/16 (0%)	N/A	0/181 (0%)	N/A	1	4/181 (2.2%)	208.4 - 420.49	1
Estrone	3/27 (11.1%)	N/A	3/27 (11.1%)	54.4 - 62.43	39/308 (12.7%)	9.1 - 10.1	1	17/308 (5.5%)	51.2 - 88.6	0.2112
Prolactin	0/9 (0%)	N/A	4/9 (44.4%)	20.38 - 24.09	3/97 (3.1%)	1.91 - 4.01	1	10/97 (10.3%)	15.69 - 35.85	0.0168

Table S30. Age group 36 - 49. Reproductive hormonal changes in men with hyperthyroidism. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Hyperthyroidism (n = 28)				Thyroid Negative (n = 2333)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	3/22 (13.6%)	3.7 - 5.32	3/22 (13.6%)	20.7 - 24.4	233/2010 (11.6%)	0.652 - 6.13	0.7353	111/2010 (5.5%)	12.2 - 35.2	0.122
Parathyroid Hormone	1/21 (4.8%)	10.2 - 10.2	1/21 (4.8%)	78.32 - 78.32	14/1709 (0.8%)	9 - 14	0.168	84/1709 (4.9%)	65.64 - 465.4	1
Estradiol	17/25 (68%)	5.9 - 23.92	3/25 (12%)	61.58 - 113.9	1365/2071 (65.9%)	5.02 - 25.74	0.9945	60/2071 (2.9%)	61.22 - 247.4	0.0372
FSH	5/22 (22.7%)	0.129 - 1	1/22 (4.5%)	52.2 - 52.2	323/1913 (16.9%)	0.1 - 1.44	0.6596	43/1913 (2.2%)	12.5 - 63.9	0.3988
LH	6/23 (26.1%)	0.3 - 1.38	3/23 (13%)	8.7 - 27.1	341/1936 (17.6%)	0.1 - 1.64	0.4334	112/1936 (5.8%)	8.68 - 53.67	0.1488
Progesterone	8/22 (36.4%)	0.065 - 0.182	1/22 (4.5%)	0.212 - 0.212	494/1801 (27.4%)	0.052 - 0.194	0.4887	66/1801 (3.7%)	0.152 - 17.02	0.5634
Total Testosterone	4/28 (14.3%)	22.9 - 204.1	4/28 (14.3%)	1013 - 1400	363/2286 (15.9%)	5.5 - 347.3	1	239/2286 (10.5%)	839.6 - 1499	0.5282
SHBG	2/28 (7.1%)	8.5 - 13.7	13/28 (46.4%)	56.6 - 189.5	138/2217 (6.2%)	3.9 - 16.44	0.6926	364/2217 (16.4%)	56.05 - 181.7	0.0001
DHEA-S	4/25 (16%)	24.9 - 153.7	4/25 (16%)	364.2 - 486.2	64/2084 (3.1%)	8 - 159.3	0.0075	176/2084 (8.4%)	331.6 - 972	0.159
IGF-I	0/12 (0%)	N/A	0/12 (0%)	N/A	37/1042 (3.6%)	11.99 - 99.36	1	42/1042 (4%)	200 - 474.84	1
Estriol	0/3 (0%)	N/A	0/3 (0%)	N/A	0/181 (0%)	N/A	1	4/181 (2.2%)	208.4 - 420.49	1
Estrone	1/3 (33.3%)	N/A	0/3 (0%)	N/A	39/308 (12.7%)	9.1 - 10.1	0.3393	17/308 (5.5%)	51.2 - 88.6	1
Prolactin	0/1 (0%)	N/A	1/1 (100%)	21.01 - 21.01	3/97 (3.1%)	1.91 - 4.01	1	10/97 (10.3%)	15.69 - 35.85	0.1122

Table S31. Age group 36 - 49. Reproductive hormonal changes in men with positive anti-TPO. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-TPO+ (n = 1949)				Anti-TPO- (n = 610)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	206/1676 (12.3%)	0.652 - 6.13	74/1676 (4.4%)	12.21 - 29.27	47/518 (9.1%)	0.7 - 6.12	0.0542	50/518 (9.7%)	12.2 - 35.2	0
Parathyroid Hormone	11/1412 (0.8%)	43357	64/1412 (4.5%)	65.64 - 465.4	6/459 (1.3%)	10.2 - 13.3	0.4516	25/459 (5.4%)	65.72 - 158.4	0.5009
Estradiol	1114/1731 (64.4%)	5.02 - 25.74	59/1731 (3.4%)	61.22 - 247.4	380/540 (70.4%)	5.2 - 25.7	0.0117	17/540 (3.1%)	61.57 - 316.7	0.8756
FSH	255/1579 (16.1%)	0.1 - 1.44	38/1579 (2.4%)	12.5 - 63.9	103/504 (20.4%)	0.1 - 1.3	0.0313	10/504 (2%)	12.5 - 25.45	0.7041
LH	277/1591 (17.4%)	0.1 - 1.64	93/1591 (5.8%)	8.68 - 53.67	107/516 (20.7%)	0.1 - 1.56	0.102	30/516 (5.8%)	8.7 - 17	1
Progesterone	436/1489 (29.3%)	0.052 - 0.194	63/1489 (4.2%)	0.152 - 6.29	107/474 (22.6%)	0.053 - 0.19	0.0054	13/474 (2.7%)	0.175 - 17.02	0.1848
Total Testosterone	275/1912 (14.4%)	10.95 - 347.3	205/1912 (10.7%)	839.6 - 1499	128/595 (21.5%)	5.5 - 342.9	0	61/595 (10.3%)	841.7 - 1491	0.8036
SHBG	105/1860 (5.6%)	4.23 - 16.44	323/1860 (17.4%)	56.05 - 189.5	49/581 (8.4%)	3.9 - 16.4	0.0206	76/581 (13.1%)	56.2 - 187.2	0.0176
DHEA-S	59/1738 (3.4%)	8 - 159.3	149/1738 (8.6%)	331.6 - 884.6	15/549 (2.7%)	24.9 - 153.7	0.5311	44/549 (8%)	338.6 - 972	0.7472
IGF-I	25/830 (3%)	15.4 - 94.47	31/830 (3.7%)	200 - 386.53	18/302 (6%)	11.99 - 99.36	0.0341	14/302 (4.6%)	203 - 474.84	0.6072
Estriol	0/185 (0%)	N/A	4/185 (2.2%)	208.4 - 420.49	0/19 (0%)	N/A	1	0/19 (0%)	N/A	1
Estrone	39/312 (12.5%)	9.5 - 10.1	18/312 (5.8%)	51.3 - 88.6	6/36 (16.7%)	9.1 - 9.1	0.6576	3/36 (8.3%)	51.2 - 60.46	0.4667
Prolactin	2/96 (2.1%)	1.91 - 4.01	13/96 (13.5%)	15.69 - 35.85	1/14 (7.1%)	3.6 - 3.6	0.338	2/14 (14.3%)	19.15 - 24.09	1

Table S32. Age group 36 - 49. Reproductive hormonal changes in men with positive anti-Tg. The significance was not considered when the total number of subjects tested for each hormonal group is ≤10.

	Anti-Tg+ (n = 1499)				Anti-Tg- (n = 1061)					
	Reduced	Range (reduced)	Elevated	Range (elevated)	Reduced	Range (reduced)	P value (reduced)	Elevated	Range (elevated)	P value (elevated)
Cortisol	148/1277 (11.6%)	0.7 - 6.11	71/1277 (5.6%)	12.2 - 35	105/916 (11.5%)	0.652 - 6.13	0.9809	53/916 (5.8%)	13.07 - 35.2	0.8947
Parathyroid Hormone	10/1087 (0.9%)	10.9 - 14	50/1087 (4.6%)	65.64 - 465.4	7/783 (0.9%)	9 - 13.84	1	39/783 (5%)	65.72 - 138.4	0.7858
Estradiol	881/1333 (66.1%)	5.02 - 25.74	38/1333 (2.9%)	61.22 - 316.7	613/938 (65.4%)	5.3 - 25.7	0.7483	38/938 (4.1%)	61.58 - 171.8	0.1477
FSH	223/1222 (18.2%)	0.1 - 1.37	27/1222 (2.2%)	12.5 - 52.2	135/863 (15.6%)	0.1 - 1.44	0.1349	21/863 (2.4%)	12.86 - 63.9	0.8513

Continued

LH	241/1232 (19.6%)	0.1 - 1.62	68/1232 (5.5%)	8.68 - 53.67	143/877 (16.3%)	0.1 - 1.64	0.064	55/877 (6.3%)	8.7 - 53.49	0.5274
Progesterone	256/1146 (22.3%)	0.054 - 0.194	55/1146 (4.8%)	0.152 - 17.02	287/818 (35.1%)	0.052 - 0.193	0	21/818 (2.6%)	0.159 - 1.95	0.016
Total Testosterone	233/1471 (15.8%)	5.5 - 344.2	157/1471 (10.7%)	843.5 - 1499	170/1036 (16.4%)	10.95 - 347.3	0.7435	109/1036 (10.5%)	839.6 - 1496	0.9556
SHBG	91/1428 (6.4%)	3.9 - 16.37	241/1428 (16.9%)	56.05 - 181.7	63/1013 (6.2%)	4.23 - 16.44	0.9449	159/1013 (15.7%)	56.05 - 189.5	0.4709
DHEA-S	42/1347 (3.1%)	20.63 - 159.3	126/1347 (9.4%)	331.6 - 972	32/940 (3.4%)	8 - 140.9	0.7945	67/940 (7.1%)	333 - 863.8	0.0706
IGF-I	20/695 (2.9%)	11.99 - 99.36	27/695 (3.9%)	200 - 474.84	23/437 (5.3%)	15.4 - 94.47	0.0595	18/437 (4.1%)	205 - 471.83	0.9681
Estriol	0/123 (0%)	N/A	2/123 (1.6%)	208.4 - 420.49	0/81 (0%)	N/A	1	2/81 (2.5%)	217.7 - 236.8	0.6501
Estrone	27/216 (12.5%)	9.5 - 10.1	14/216 (6.5%)	51.2 - 88.6	18/132 (13.6%)	9.1 - 9.1	0.8871	7/132 (5.3%)	51.3 - 87.4	0.829
Prolactin	1/68 (1.5%)	4.01 - 4.01	10/68 (14.7%)	15.69 - 35.85	2/42 (4.8%)	1.91 - 3.6	0.5567	5/42 (11.9%)	16.6 - 23.77	0.8966