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Hypothyroidism among subfertile women

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Summary

Introduction: Association between hypothyroidism and infertility has been demonstrated, but its prevalence in subfertile women is not well documented. *Objective:* To estimate the prevalence of hypothyroidism in a cohort of subfertile women. *Materials and Methods*: Retrospective chart of 200 women aged 17 to 40 years with infertility attending the Reproductive Endocrine and Infertility Medicine Department between April 2008 and October 2010 was reviewed. Rate of established or newly diagnosed hypothyroidism was measured, as well as the associations between TSH > 4.2 mIU/L and patient characteristics, causes of infertility, and laboratory parameters. *Results*: Fourteen percent had established and 14.5% had newly diagnosed hypothyroidism. Subclinical hypothyroidism was determined for 42 (21%) women. Hypothyroidism associated significantly with both increased LH and anovulatory related infertility: LH (8.49 IU/L *vs*. 6.86 IU/L; $p = 0.036$) and anovulation in 47.8% *vs*. 27.3% ($p = 0.009$) of women with TSH > 4.2 mIU/L and TSH ≤ 4.2 mIU/L, respectively. *Conclusion*: This study confirms an association between hypothyroidism and infertility and highlights the need to check thyroid hormone levels prior to infertility treatment.

Key words: Hypothyroidism; Infertility; Retrospective; Prevalence.

Introduction

The clinical definition of infertility is the inability to conceive after one year of regular intercourse without contraception [1]. Infertility affects an estimated 12–14% of women [2]. Causes of infertility include male factors (30% of cases) and female factors such as endometriosis, tubal disorders, and ovulatory dysfunction (35% of cases) [2, 3]. Thyroid dysfunction in women of reproductive age can lead to a variety of gynecological disorders ranging from menstrual irregularities to infertility [3].

The feedback loop responsible for increased thyrotrophic-releasing hormone (TRH) secretion and excess release of prolactin has been postulated as an underlying cause of hypothyroidism. Physiological consequences of hypothyroidism include ovulation dysfunction, luteal phase defects,oligomenorrhea, and amenorrhea [4-6]. Other manifestations of this condition include reductions in sex hormone-binding globulin (SHBG) and total estradiol levels, a rise in unbound fraction of testosterone and estradiol, and compromised metabolic clearance of estrone and androstenedione [7-10]. Furthermore, through a direct leutotropic effect, thyroid stimulating hormone (TSH) and TRH may aggravate corpus luteum dysfunction [9, 10]. Thus it becomes essential to screen for hypothyroidism in the presence of ovulatory deficiencies [3, 10]. The typical workup for diagnosing menstrual disorders and infertility includes investigation of triiodothyronine (T3), prohormone thyroxine (T4), TSH, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin [2, 4, 9].

Thyroid autoimmunity (TAI) is the most common autoimmune disorder, affecting 5–20% of women of childbearing age and can be associated with both hypo- and hyperthyroidism [2, 4, 5, 9-11]. The prevalence of isolated TAI along with normal thyroid function is higher in some infertility-related disorders, such as endometriosis and polycystic ovary syndrome [2, 3, 7, 8].

Menstrual abnormalities can improve following treatment of thyroid dysfunction; however, a similar treatment effect toward improving fertility has yet to be determined. The present authors sought to estimate the prevalence of hypothyroidism in subfertile women attending clinics at a tertiary care hospital.

Materials and Methods

This retrospective study reviewed the charts of 200 women who presented with infertility at the Reproductive Endocrine and Infertility Medicine Department (REIMD), Women's Specialized Hospital, King Fahad Medical City (KFMC), Riyadh, Saudi Arabia, from April 2008 to October 2010. Eligible subjects were women aged 17–40 years with parity < four.

After obtaining IRB approval, the files of infertile women who attended the clinics during the study period were reviewed. Examination of the data identified patient characteristics and cause of infertility. Patient data including history, examination, laboratory investigations, and ultrasound findings were entered into an excel worksheet for statistical evaluation. The laboratory tests relevant to this study were all performed during the follicular phase of the subjects. A power calculation performed at the design stage assumed a 5% precision, 7.5% prevalence of hypothyroidism (95% confidence interval (CI) limits specified as 2.3–12.3%), and population

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Table 1. — *Patient demographics and clinical characteristics.*

Statistic	Mean ± SEM	(Min, max)
Age (years)	29.58 ± 0.34	(18, 40)
BMI (kg/m^2)	30.69 ±0.50	(14.2, 62.5)
Infertility duration (years)	5.41 ±0.27	(1.0, 19.0)
E2 (pmol/L)	241.14 ±42.73	(20, 1044)
Prolactin (mIU/L)	587.72 ±64.83	(4, 7215)
FT4 (pmol/L)	15.83 ±0.72	(2.5, 137.0)
TSH (mIU/L)	3.70 ±0.29	(0.3, 36.2)
FSH (IU/L)	7.64 ±0.58	(1.5, 75.0)
LH (IU/L)	7.23 ±0.33	(0.4, 36.8)

Table 2. — *Causes of infertility among 200 Saudi subfertile women.*

Causes of infertility	Total number of patients	Percentage (%)
Male factor	79	39.5
Anovulation	64	32.0
Unexplained	33	16.5
PCOS	21	10.5
Tubal factor	20	10.0
Other	13	6.5

of n = 4000, which estimated a sample size of n=102.

Results

The study analyzed patient charts for 200 infertile women seen at the REIMD from April 2008 to October 2010. General characteristics of the study patients are shown in Table 1. Women in this study had an average age of 29.58 ± 0.34 (18–40) years and mean duration of infertility of 5.44 years (± 0.27, range 1 to 19). Parity ranged from 0 to 3 (mean 0.49 ± 0.78). Six patients (3.0%) had a medical history of hyperprolactinemia while 145 (72.5%) had no prior medical history. Approximately one-third (30.5%) of patients had a history of hyperprolactinemia or prolactin level > 550 mIU/L; normal range of prolactin levels was considered 72-511 mIU/L. Twenty-eight (14%) subjects had a previous history of hypothyroidism. Male factor was the most common cause of infertility (39.5%) followed by anovulation, which affected 32% of women (Table 2).

Out of the 57 patients, 28 (14%) had a history of hypothyroidism and the remaining 29 (14.5%) were newly diagnosed. Therefore, a total of 57 patients (28.5%) were diagnosed with hypothyroidism. TSH levels were within normal range for 151 (75.5%) patients while 42 (21%) patients had subclinical hypothyroidism (SH) characterized by a high TSH reading (> 4.2 mIU/L) and FT4 in normal range (12-22 pmol/L). Six (3%) patients had increased TSH with low FT4 levels (< 12 pmol/L). Simultaneous low TSH (0.053 mIU/L) and low FT4 (10.4 pmol/L) levels occurred for one (0.5%) patient. Of the 200 women evaluated, 143 (72.4%) had no drug use history while 25 (12.5%) used thyroxin and 11 (5.5%) used metformin. The majority of patients (72.5%) had normal ultrasound findings. Frequent menstrual irregularities occurred for 65 (32.5%) women and primary infertility was diagnosed in 108 (54%) patients.

Table 3. — *Causes of infertility stratified according to TSH levels.*

Causes of infertility	TSH (mIU/L)				*p*-value
	≤ 4.2 (n=154)		> 4.2 (n=46)		
	n	%	n	%	
Parity					
0	102	66.2	32	69.6	0.698
1	31	20.1	9	19.6	
2	20	13.0	4	8.7	
3	1	0.6	1	2.2	
Infertility					
Primary	83	53.9	25	54.3	0.957
Secondary	71	46.1	21	45.7	
Male factor					
No	90	58.4	31	67.4	0.276
Yes	64	41.6	15	32.6	
Anovulation					
No	112	72.7	24	52.2	0.009
Yes	42	27.3	22	47.8	
Unexplained					
No	130	84.4	37	80.4	0.523
Yes	24	15.6	9	19.6	
PCOS					
No	141	91.6	38	82.6	0.082
Yes	13	8.4	8	17.4	
Tubal factor					
No	140	90.9	40	87.0	0.433
Yes	14	9.1	6	13.0	
Other					
No	143	92.9	44	95.7	0.500
Yes	11	7.1	2	4.3	
Menstrual history					
Regular	104	68.0	29	64.4	0.658
Irregular	49	32.0	16	35.6	
Associated symptoms					
No	88	85.4	25	83.3	0.777
Yes	15	14.6	5	16.7	
USS abnormality					
No	102	69.9	24	53.3	0.041
Yes	44	30.1	21	46.7	
Medical history					
No	105	72.4	30	66.7	0.458
Yes	40	27.6	15	33.3	
Drug history					
No	88	68.8	21	55.3	0.124
Yes	40	31.3	17	44.7	
Pregnancy					
No	93	61.6	30	71.4	0.241
Yes	58	38.4	12	28.6	
Miscarriage					
No	140	90.9	44	95.7	0.298
Yes	14	9.1	2	4.3	

Table 4. — *Patient characteristics and laboratory parametersstratified by TSH levels.*

	TSH (mIU/L)		*p*-value
	≤ 4.2 (n=154)	> 4.2 (n=46)	
Age (years)	29.92 ± 0.39 (20, 40)	28.43 ± 0.67 (18, 38)	0.067
BMI (kg/m^2)	30.75 ± 0.61 (14.2, 62.5)	30.50 ± 0.69 (19.0, 41.7)	0.830
Infertility duration (years)	5.50 ± 0.32 (1.0, 19.0)	5.13 ± 0.52 (1.0, 14.5)	0.570
E2 (pmol/L)	255.25 ± 60.97 (20, 1044)	215.49 ± 49.96 (78, 650)	0.664
Prolactin (µg/L)	552.28 ± 65.33 (4, 7215)	704.29 ± 177.06 (14, 6342)	0.323
FT4 (pmol/L)	16.17 ± 0.95 (10.1, 137.0)	14.87 ± 0.54 (2.5, 23.0)	0.429
TSH (mIU/L	2.44 ± 0.08 (0.3, 4.2)	7.92 ± 1.04 (4.3, 36.2)	< 0.001
FSH (IU/L)	7.86 ± 0.74 (1.5, 75.0)	6.91 ± 0.43 (3.6, 21.0)	0.485
LH (IU/L)	6.85 ± 0.38 (0.4, 36.8)	8.49 ± 0.66 (1.9, 17.4)	0.036

Table 3 shows the prevalence of infertility causes stratified according to TSH > 4.2 mIU/L and ≤ 4.2 mIU/L while the data in Table 4 summarizes patients' demographics and laboratory parameters stratified using the same TSH criteria. Women in the hypothyroid group had a significantly higher mean LH compared to those with TSH ≤ 4.2 mIU/L: 8.49IU/L *vs*. 6.86IU/L for high and low TSH groups, respectively, $p = 0.036$. Subjects in the hypothyroid group were also more likely to have anovulatory related infertility; 22 (47.8%) *vs*. (42 (27.3%), for those with TSH > 4.2 mIU/L and TSH ≤ 4.2 mIU/L, respectively; $p = 0.009$. There was no statistical difference in BMI between the two groups; body mass index (BMI = 30.50 (± 0.69) kg/m^2) *vs*. 30.75 ± 0.61 for hypothyroid compared non-hypothyroid subjects, respectively. There was a notable 9.8% decrease in pregnancy rate in the group of women with hypothyroidism, accompanied by a 4.8% decrease in the miscarriage rate in the same group, although both were not statistically significant ($p = 0.241$ and $p = 0.298$, respectively) (Table 3).

Discussion

This retrospective chart review identified preexisting, or newly diagnosed hypothyroidism in 28.5% of subfertile women, a finding that supports an association between hypothyroidism and infertility reported previously [3, 12]. Adequate thyroxin replacement can help restore fertility and allow the return of prolactin levels to the normal range [13, 14]. In one prospective study (n = 394) simple oral treatment for hypothyroidism enabled 76.6% of infertile women to conceive within six weeks to one year [3]. Yoshioka *et al.* likewise demonstrated an enhanced pregnancy rate following treatment with levothyroxine (L-T4) for SH in a subfertile Japanese population (n = 69) [15].

The reported prevalence of hypothyroidism varies by geographic region, being more common in women than men, and tends to increase with age [16]. Cross-sectional studies in Europe, USA, Japan, and India have determined a prevalence between 1% and 8% [16, 17]. In one of the largest, Northern European epidemiology studies to date (n = 94,009), the prevalence of hypothyroidism in women of reproductive age varied between 2% and 4% [18]. Studies both prospective and retrospective in infertile women have shown a wide distribution of SH prevalence ranging from 0.7–43% [19]. Data reported here agree with the upper limit of this SH window as SH was determined for 21% of subjects (42/200).

A recent analysis of blood samples collected during routine check-ups from 600 Saudi women 18–45 years with no history of menstrual or reproductive disorders identified hypothyroidism in 18% of cases [20]. The population in this study resembles the one reported here; however, the present patients had a higher incidence of hypothyroidism suggesting underlying thyroid dysfunction as a plausible cause of their infertility. Why a higher prevalence of hypothyroidism has been reported in selected populations of Saudi women of reproductive age compared to the accepted range of 2–4% is an interesting question. Vitamin D deficiency offers one explanation. Alsuwaida *et al.* showed that vitamin D deficiency is a common problem in healthy Saudi adults, especially among young females [21]. Lack of vitamin D significantly associated with AITD in a large cohort of Korean patients (n = 6,685) [22]. Likewise, Mackawy *et al.* demonstrated a correlation between hypothyroidism and hypovitaminosis D with hypocalcemia in a small cohort of Saudi adults [23]. Body mass index may also play a role. In a cross-sectional study, Saudi patients with documented subclinical hypothyroidism had a significantly higher BMI ($p < 0.001$) as well as elevated triglycerides ($p = 0.001$) compared to controls [24]. The data reported here did not follow a similar trend with respect to BMI.

Hypothyroidism has been linked to menstrual disturbances, infertility, an increased risk of miscarriage, and long term health problems [25]. Interestingly, in our population, a decrease in pregnancy rate has been found along with a decrease in miscarriage rate in women with hypothyroidism. Furthermore, women with infertility originating from anovulatory causes, in particular, seem to have an increased risk for SH. A single center study of 89 infertile women reported a significantly higher prevalence of SH in women with ovulation disorders (20.5%) compared to those with normal ovulation (8.3%) [4]. In agreement with these findings, anovulatory women in the present study were more likely to have hypothyroidism than not and the result reached statistical significance. Other studies have reported high levels of TSH (range 6.3% to 69%) in

women with ovulatory disorders, and lower levels for other causes of infertility (male and tubal: 1.5–2.6%). These investigations have concluded a need for repeat testing among subfertile women because SH can progress rapidly [26, 27].

Approximately one-third of the present subjects had documented hyperprolactinemia or prolactin levels above the normal range. While hyperprolactinemia is a well-established cause of infertility, the underlying mechanism is not well understood [28]. A rise in prolactin may contribute to infertility through inhibitory effects on hypothalamic gonadotropin-releasing hormone (GnRH) neurons and/or on the pituitary gland [28, 29]. The immediate impact regardless of mechanism is a disturbance in GnRH secretion and consequent reduction in circulating LH levels required for normal follicular development [9, 28]. Hypothyroid, compared to non-hypothyroid women in this study had significantly higher levels of LH suggesting that factors other than GnRH inhibition are contributing to their infertility. Studies have shown that T3 exerts some control over FSH and LH on steroid biosynthesis. T3 receptors have been identified in both human and mouse oocytes [30-34]. Cramer *et al.* determined high TSH levels as a predictor of in-vitro fertilization (IVF) failure, mainly due to the failure of oocytes to achieve fertilization [35]. Thus, problems with oocytes fertilization or impaired steroid production as a result of hypothyroidism may have impacted fertility in the present subjects with hypothyroidism.

The main limitation of the present study is the small number of patients and retrospective nature of the study. However, the current study is relevant considering the lack of data from the region regarding the role of hypothyroidism in subfertile women. One may argue that women with a history of hypothyroidism may have already received treatment for their condition that could have biased the results. This would likely represent a small minority of patients and add little bearing on the main conclusions of the study.

In conclusion, this study confirms previous reports of the association between hypothyroidism and infertility. The prevalence of which is 28.5 % in the present study population. The association between anovulation and hypothyroidism emphasizes the need to screen for hypothyroidism and perhaps control thyroid hormone levels prior to initiating infertility treatment.

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