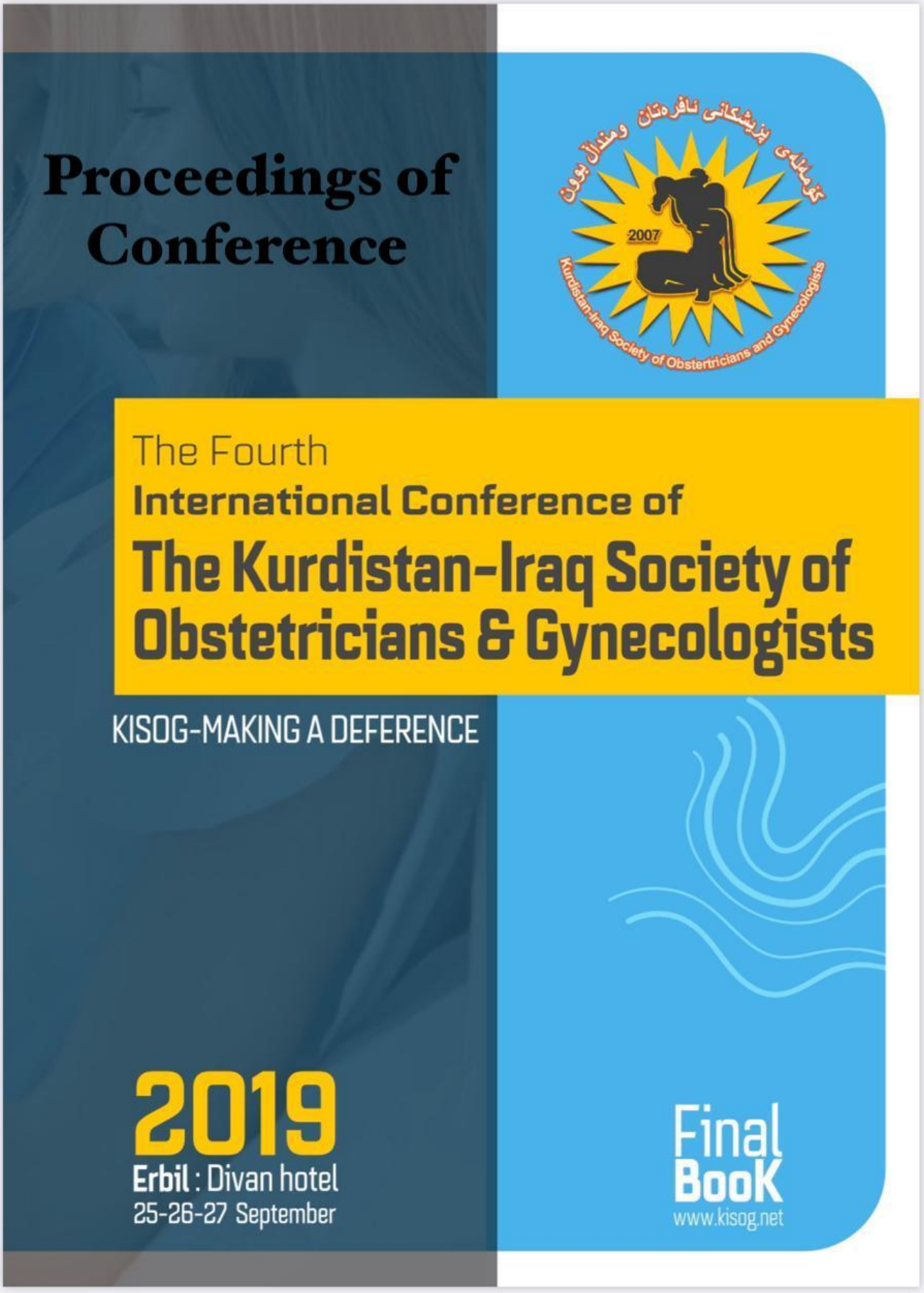
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Prevalence of subclinical hypothyroidism in women with unexplained infertility and the effect of thyroxin on pregnancy rate

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Abstract

In this study, we assessed the prevalence of subclinical hypothyroidism in women with unexplained infertility and evaluated the effect of thyroxine treatment on their ability to conceive. A cross-sectional study screened 400 women at an infertility center in Iraq for subclinical hypothyroidism. A single-arm clinical trial was conducted; women with subclinical hypothyroidism were given 25–50 µg thyroxine daily and were followed up to determine pregnancy rates. Two-thirds of participants conceived 10 weeks to 2 years after starting thyroxine. Mean time to conception was 14.56 ± 4.83 months, and 1.8% of conceiving women had miscarriages. Low parity (OR = 0.56, 95% CI: 0.36–0.86, p-value = 0.009) and longer duration of infertility (OR = 2.65, 95% CI: 1.13–6.19, p-value = 0.024) were associated with conception. In this setting, there was a high rate of SCH in women with unexplained infertility (> 40%) and a high conception rate after these women received thyroxine treatment. A thyroid profile should be included in infertility management, and women with subclinical hypothyroidism should be treated with thyroxine.

Keywords: Thyroxine; Subclinical hypothyroidism; Miscarriage; Infertility; Conception.

Introduction

Subclinical hypothyroidism (SCH) indicates an elevated thyroid-stimulating hormone (TSH) level with normal free thyroxine levels; SCH is considered a mild or compensated form of primary hypothyroidism[1] .Subclinical hypothyroidism is found in 0.7%–10.2% of infertile women (especially those with ovulatory disorders)[2]

However, controversies persists in the definition of SCH and the decision of when to treat, especially for women attempting pregnancy[3]and because the reference range of TSH changes during pregnant, some defend using pregnancy thresholds for the treatment of women attempting to become pregnant in order to decrease the potential risks associated with SCH in pregnancy[4].

Previous studies have suggested that elevated TSH can affect fertility, but there is disagreement about at which level TSH begins to affect fertility. Data from the National Health and Nutrition Examination Survey showed that a TSH of 6.10 mIU/L affected fertility, whereas the national Academy of Clinical Biochemistry's data suggested that the limit was 2.5 mIU/L. Current guidelines from the American Thyroid Association set the upper limit for normal TSH at 4 mIU/L. All previous data have concerned women trying to conceive generally, without specifying unexplained infertility. One study revealed that nearly twice as many women with unexplained infertility had TSH levels of 2.5 mIU/L or higher, compared with the control group (26.9% versus 13.5%)[5].

During pregnancy, SCH can cause adverse maternal and perinatal outcomes; these may be prevented by suitable drug treatment[6]. However, despite the well-established recommendations for the screening and treatment of overt hypothyroidism in infertile women, the treatment for SCH in this group remains controversial[6]. Guidelines from the American Endocrine Society, the American Association of Clinical Endocrinologists, and the American Thyroid Association recommend thyroxine (T4) treatment for infertile women with SCH who want to conceive[7]. However, excluding studies conducted during in vitro fertilization (IVF) cycles, few published reports exist on the prevalence of SCH and its treatment outcomes among infertile women. Moreover, findings are inconsistent, with some advocating pre-IVF SCH treatment

and others reporting no benefit of thyroxine treatment for SCH [8-12]. Therefore, there is a need to determine the prevalence of SCH and assess its treatment outcomes among infertile women. Research on the epidemiology and treatment of SCH would generate data allowing medical professionals to provide appropriate treatment for women with SCH and unexplained infertility. The current study aimed to determine the prevalence of SCH among women with unexplained infertility and to evaluate the pregnancy rate after thyroxine treatment.

Materials and methods

This cross-sectional, single-arm, non-randomized clinical trial was conducted at the Infertility Centre in the Maternity Teaching Hospital in Erbil city, Kurdistan, Iraq, from September 1, 2016, to July 1, 2018, to determine the SCH prevalence and the efficacy of thyroxine for managing women with unexplained infertility. Infertile couples were investigated thoroughly to identify the causes of the infertility, including assessments of their histories, clinical examination, gynecological examination, trans-vaginal ultrasonography, hematological profile, and hormonal profile. All women were negative for thyroid-specific antibodies (antithyroid peroxidase antibodies, ATO-Abs). Salpingography and hysteroscopy were performed where indicated.

The inclusion criteria were as follows: unexplained infertility, TSH $\geq$ 2.5 mIU/L, normal T3 and T4 levels, and negative for ATO-Abs. The exclusion criteria were current history of overt hypothyroidism or hyperthyroidism, recurrent pregnancy loss, obvious cause of female infertility (e.g., tubal blockage, pelvic inflammatory disease), ovarian dysfunction, and abnormal seminal fluid analysis or other male-related infertility factor. These investigations and procedures were conducted to avoid any confound variable that may indirectly cause conception.

Infertility was defined as the failure to become pregnant after 12 months of regular, unprotected sexual intercourse [13]. Male-specific infertility was measured by two semen analyses 3 months apart assessed using World Health Organization criteria [14]. Secondary infertility was defined as the inability to become pregnant again among women who had previously been pregnant[15].

Unexplained infertility was defined in couples where the woman had apparently normal ovarian function, fallopian tubes, uterus, cervix, and pelvis; the couple had adequate coital frequency; and the man had apparently normal testicular function, genitourinary anatomy, and ejaculate[13]. Subclinical hypothyroidism in pregnancy was defined as a TSH level higher than the pregnancy-related reference range, with a normal serum thyroxine concentration[16]. The TSH reference range in pregnancy is trimester-dependent; 2.5 mIU/L is the recommended normal value upper limit in the first trimester[17].

The study was approved by the Ethics and Scientific Committee of the Kurdistan Board of Medical Specialty on 22nd of July, 2016.The clinicalTrial.gov Registration Number NCT03712683 was approved on line. After participants provided written informed consent, face-to-face interviews were conducted to administer a questionnaire which was prepared by the researches containing participants demographic characters, obstetrical history, types of infertility, BMI in kg/m^2 .The dose of thyroxin the participant will use, follow up of participant before and during first trimester .Participant with unexplained infertility and SCH (TSH > 2.5 mIU/L) were enrolled in the study.

Weight and height were measured using standard methods to calculate body mass index. BMI participants were categorized in to normal weight and overweight/obese groups based on a special criteria of (normal weight, BMI=18.5-24.9kg/m^2);overweight/obese,BMI≥25 kg/m^2)[18].Thyroid function was evaluated in all the patients using the basal serum level of TSH and thyroxine (T4) to differentiate overt hypothyroidism (low T4) from SCH. TSH, T3, and T4 were measured using Elecsys and Cobase analyzers (Roche diagnostics, Mannheim, Germany).

Daily thyroxine treatment with levothyroxine sodium tablets (Euthyrox 50µg and 25 µg, Merck Serono, Switzerland) was initiated, and subjects were followed up in a combined endocrinological/gynecological clinic.

The treatment aimed to reduce TSH levels to < 2.5 mIU/L. Women with TSH levels > 2.5 and ≤ 4 mIU/L were prescribed 25 µg tablets, while women with TSH levels > 4 mIU/L were given 50 µg.(Figure 1)

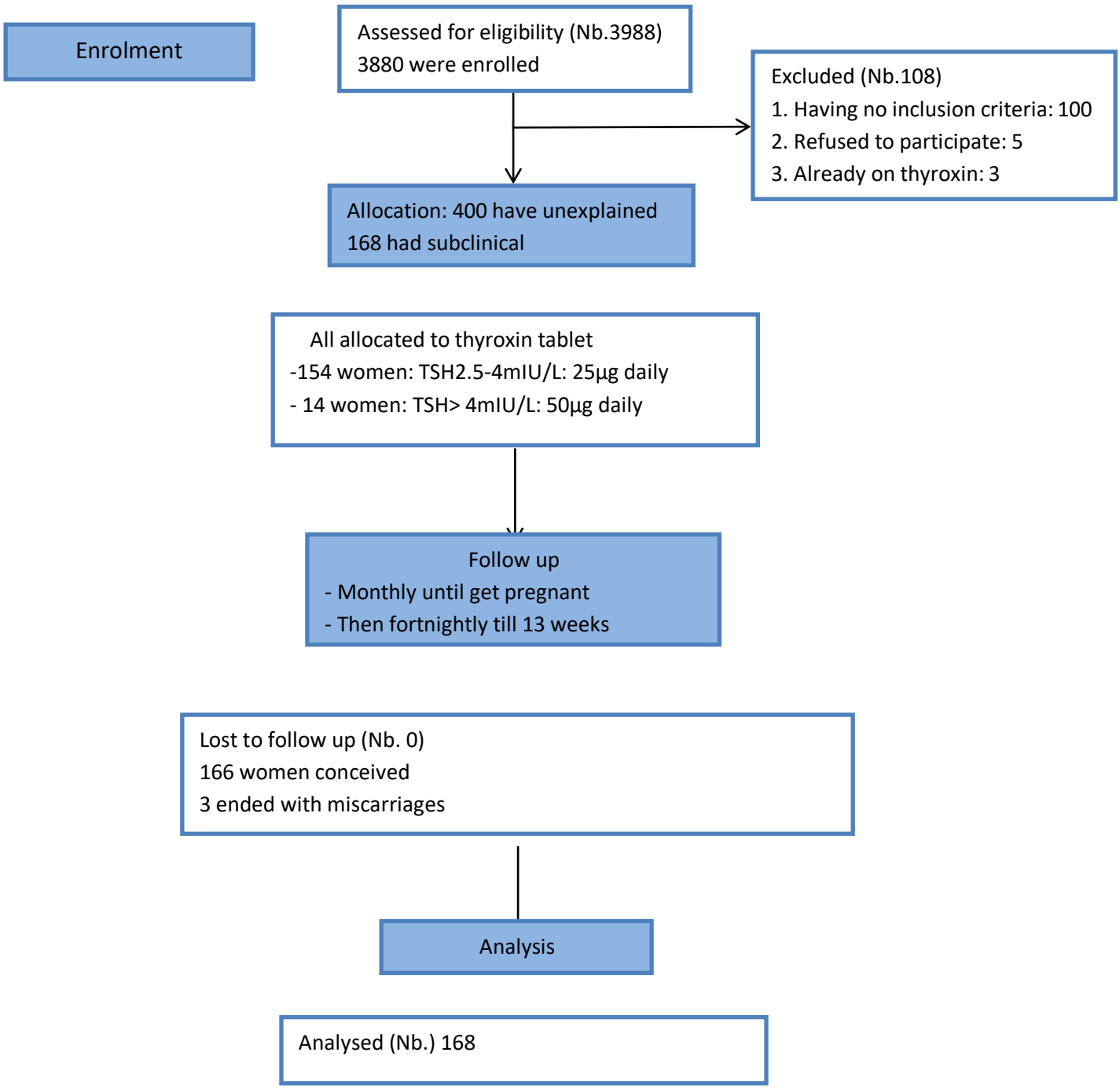

Figure (1): Sample flow chart

Women were followed up on TSH and T4 levels. Serum TSH levels were measured 4–6 weeks after beginning the therapy, adapting the thyroxine dosage if these levels increased or decreased. When pregnancy was confirmed, the treatment was continued until 13 weeks gestation.

Sample size estimation

Epi-info software[19] was used to perform a sample size calculation, assuming a 19.29% prevalence of raised TSH and normal T4[20]. A sample size of 166 infertile women was sufficient to estimate a 95% confidence interval of ± 6% for the prevalence rate.

Statistical analysis

Statistical Package for Social Sciences (Version 22, IBM) was used for the analysis. Categorical variables were presented as proportions. Continuous data checked for normality using the Shapiro–Wilk test were expressed as means (standard deviation, SD) when normally distributed and medians (interquartile range, IQR) when not normally distributed. Proportions and medians (IQR) were compared by post-treatment conception status using Chi-squared tests and non-parametric Mann–Whitney U tests, respectively. Logistic regression was performed with conception or pregnancy as the dependent variable and sociodemographic, clinical and biochemical factors as the independent variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. P-value ≤ 0.05 was considered statistically significant.

Results

General characteristics

Of the 400 women with unexplained infertility, 168 (42.0%) had SCH and received thyroxine (**Figure 1**). The follow-up duration was 13 (10.0–24.0) months (Table 1). The mean (± SD) thyroxine dose was 47.3 ± 12.2 µg before pregnancy and 58.4 ± 3.2 µg during pregnancy (Table 2).

Table (1): Clinical and biochemical characteristics of infertile women with subclinical hypothyroidism

Variable	Median	Interquartile range
Age, year	29.0	25–34
Parity	0	0–2
Duration of infertility, years	3.0	2–4
Body mass index, kg/m^2	25.2	23.8-26.6
Thyroxine, nmol/L	14	12.5–19.6
Duration of follow-up, months	13.0	10–24.0

Table (2): history of miscarriage and type of infertility in women with subclinical hypothyroidism

Variable	Number	Percentage
History of miscarriage		
No	135	80.4
Yes	33	19.6
Type of infertility		
Primary	90	53.6
Secondary	78	46.4

Most (122, 72.6%) of the women receiving thyroxine treatment conceived within 10 weeks to 2 years. The mean time to conception was 14.56 ± 4.83 months. Three (1.8%) women had miscarriages (Figure 1). Parity was significantly lower and infertility duration was significantly longer in the women who conceived, but there was no significant difference in post-treatment conception status by age, BMI, TSH, T4, history of miscarriage, or infertility type (Table 3).

Table (3): Clinical and biochemical characteristics of infertile women with subclinical hypothyroidism who conceived compared with those who did not.

Variable	**Women who conceived (122)**	**Women who did not conceive (46)**	**p-value**
Median (interquartile range)			
Age, year	28.5 (24.7–33.2)	30.0(25.0–37.2)	0.214
Parity	0 (0–2)	1(0–3)	0.003
Duration of infertility, years	3.0(3.0–4.0)	3.0(2.0–3.0)	0.005
Body mass index, kg/m^2	25.4(23.8–26.7)	24.9(23.8–26.6)	0.380
Thyroid stimulating hormone, mIU/L	4.5(3.8–5.4)	4.4(3.9−4.8)	0.427
Thyroxine, nmol/L	14.0(12.2–16.1)	14.4(12.9–15.9)	0.206
Number (%)			
History of miscarriage			
No	101(82.2)	34(73.9)	0.200
Yes	21(17.2)	12(26.1)	
Type of infertility			
Primary	71(58.2)	19(41.3)	0.058
Secondary	51(41.8)	27(58.7)	

In the logistic regression, low parity (OR = 0.56, 95% CI: 0.36–0.86, p-value = 0.009) and longer duration of infertility (OR = 2.65, 95% CI: 1.13–6.19, p-value = 0.024) were associated with conception and pregnancy (Table 4).

Table (4): Factors associated with pregnancy based on logic regression analysis.

Variable	OR	95% CI	p-value
Age, year	0.99	0.92–1.07	0.963
Parity	0.56	0.36–0.86	0.009
Duration of infertility, years	2.65	1.13–6.19	0.024
Body mass index, kg/m^2	1.00	0.88-1.14	0.380
Thyroid stimulating hormone, mIU/L	1.31	0.91−1.88	0.143
Thyroxine, nmol/L	0.95	0.83–1.10	0.548
History of miscarriage			
No	Reference		
Yes	1.68	0.53–5.31	0.378
Type of infertility			
Primary	1.17	0.38–3.61	0.782
Secondary	Reference		

Discussion

We assessed the prevalence of SCH in women with unexplained infertility and evaluated the impact of thyroxine treatment on their ability to conceive. We found a high prevalence (42.0%) of SCH among women with unexplained infertility and a high (72.6%) pregnancy rate following thyroxine treatment. Varying rates (0.9%–40%) of SCH have been reported for infertile women in different populations[2, 21.]

These differences may be explained by differing causes of infertility and criteria used to define SCH[21, 8, 22.]

We have found a higher pregnancy rate (72.6%) following thyroxine treatment compared with previously reported pregnancy rates for infertile women (37% and 44.1%) [23,8] . A wide range of pregnancy rates (0%–96%) have been reported for infertile women after thyroxine treatment[4,9]. Although a study conducted by Yoshioka et al. showed a high rate (84.1%) of pregnancy for infertile women with SCH treated with thyroxine, 29.3% experienced miscarriage[24]. There is insufficient evidence to support routine thyroxine treatment for infertile women with SCH not planning to undergo artificial reproductive techniques [1]. Although this may be a valid treatment for infertile women without thyroid antibodies, thyroxine treatment may be useful for preventing progression to overt hypothyroidism after conception [1]. Thyroxine treatment reportedly offers better maternal and fetal outcomes for women who do undergo artificial reproductive techniques[6]. Indeed, thyroxine treatment can improve embryo quality and pregnancy outcomes in women with SCH who have undergone IVF and intracytoplasmic sperm injections[11]. Guidelines from the American Endocrine Society, the American Association of Clinical Endocrinologists, and the American Thyroid Association recommend thyroxine (T4) treatment for patients with SCH who want to have children [7].
Three (1.8%) women in our study had miscarriages. This rate was lower than that reported in a previous study of infertile women with SCH who were treated with thyroxine (7.4%) [10]. Yoshioka et al. also reported a higher rate of miscarriage (29.3%) among women with SCH who received thyroxine[22] .

One of the strengths of our study is the strict inclusion and exclusion criteria, which allowed us to confirm subfertility to control for other possible factors contributing to infertility. Our comparison group comprised women with a similar fertility evaluation compared with the unexplained infertility group, differing only on serum TSH level.
A second strength of the study is using TSH > 2.5 mIU/L to confirm SCH. This was below the required level according to most guidelines. Because of the high rate of pregnancy observed in women with unexplained infertility, this level is assumed to be ideal. Finally, this study was a prospective study.

Although ATO-Abs are not used to diagnose SCH, elevated levels have been associated with increased pregnancy complications. High ATO-Abs levels are associated with thyroid dysfunction and miscarriage [24].Because women with high ATO-Abs require thyroxine therapy even when TSH level is normal, we excluded these women from the present study.

One limitation of our study is the lack of reference values for TSH and T4 in Iraq, therefore, we used international cut-off values. Second, we did not follow up through delivery because our objective was to follow up participants until the end of first trimester. Future studies should prolong their follow up.

We observed a high rate of SCH in women with unexplained infertility. There was a high conception rate among women with SCH following thyroxine treatment. Thyroid profiles should be included in infertility work ups, and women with unexplained infertility and SCH may benefit from thyroxine treatment.

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Disclosure of interest

Both authors declare that they have no conflict of interest

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