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Research Article

THE POTENTIAL BENEFIT AND THE MECHANISM OF ACTION OF THYROXINE ON SERUM LIPIDS AND BLOOD FLOW INDEXES IN SUBCLINICAL HYPOTHYROIDISM WOMEN

SINAA ABDUL AMIR KADHIM[1]*, SHAIMAA ABDUL AMEER KADHUM[2], ALI JAWAD HAMZA[3]

[1]Department of Pharmacology and Therapeutics, College of Medicine, University of AL-Qadisiyah, AL-Diwaniyah Province, Iraq. [2]Department of Surgery, Radiology, College of Medicine, University of AL-Qadisiyah, AL-Diwaniyah Province, Iraq. [3]Department of Surgery, College of Medicine, University of AL-Qadisiyah, AL-Diwaniyah Province, Iraq. Email: Sinaa.kadhim@qu.edu.iq

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ABSTRACT

Objective: Even previous reports mentioned that thyroxine has beneficial effects on subclinical hypothyroidism (SCH); however, the mechanism by which thyroxine mediated such effect still unclear. Thus, we aim to find out the potential benefit of thyroxine administration in women with SCH through assessment of lipids profile with evaluation of uterine and ovarian blood flow indexes.

Patients and Methods: The current study included 80 women with SCH who had a history of recurrent intrauterine death. Those women were chosen from the cohort of pregnant ladies that routinely seek medical advice. For each woman, estimation of serum thyroid-stimulating hormone (TSH), serum lipids profile (low-density lipoprotein [LDL], total cholesterol [TC], and triglyceride [TG]), and also uterine and ovarian pulsatile index (PI) and resistance index (RI) using color Doppler ultrasound, was done at the beginning of study and then repeated following 2 months during which women were given oral thyroxine supplementation (50 μg/d). The study was carried out in Al-Diwaniyah Maternity and Child Teaching Hospital in Al-Diwaniyah province, Iraq and extended from September 2016 to January 2018.

Results: Mean serum TSH, LDL, TG, and TC were significantly reduced ($p<0.05$). Mean early follicular phase ovarian RI and PI and uterine RI were significantly reduced ($p<0.05$). In addition, mean late follicular phase ovarian RI and PI and uterine RI were significantly reduced ($p<0.05$).

Conclusion: Thyroxine administration to women with SCH significantly decreases serum lipids and increases uterine and ovarian blood flow by mechanism involving reduction in arterial RI and PI.

Key words: Subclinical hypothyroidism, Thyroxine, Uterine, Ovarian blood flow.

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INTRODUCTION

Thyroid disorders are seen frequently during pregnancy and briefly following labor. The second most frequent endocrine disorder affecting women throughout reproductive age is thyroid disease [1,2]. The chemical structure of human chorionic gonadotropin (HCG) is similar to that of thyroid-stimulating hormone (TSH), thus HCG is able to both stimulate the thyroid gland with subsequent increase in thyroxine hormone level [3]. The usual presentation of thyroid abnormality in women during pregnancy is high TSH and lower normal or sometimes even low thyroxine during the first trimester of pregnancy [4]. Women hypothyroidism has been accompanied by higher risk of reduced birth weight, altered neuropsychological maturation, fetal distress, and intrauterine death [5-7]. It has been suggested that women with clinical and subclinical hypothyroidism (SCH) must be given thyroxine throughout pregnancy to keep serum TSH within the desired reference range [4].

Uterine blood flow is increased up to 20-fold during normal pregnancy, and this has been regarded as a normal physiological response to maintain the growing fetus [8]. Nowadays, a color Doppler ultrasound technique is used to assess the uterine and ovarian blood flow depending on two indexes: The "pulsatile index (PI) and resistance index (RI)" that are negatively proportional to impedance to blood flow and this technique is regarded as an efficient way to evaluate both ovarian and uterine blood flow inadequacy [9-11].

Significant changes in serum lipids profile have accompanied SCH. Many published articles documented the high serum low-density lipoprotein (LDL), triglycerides (TGs), and total cholesterol (TC) in individuals suffering from hypothyroidism [12-14]. It has been shown that during pregnancy, TC, LDL, high-density lipoprotein (HDL), and TGs get rise [15]. Hypercholesterolemia that accompanies pregnancy is attributable also to alterations in liver metabolism, adipose metabolism, and sex steroid hormones [16]. Women with hyperlipidemia are associated with adverse fetal and maternal outcome and increased risk of premature labor and intrauterine death [17-19].

Hence, the aim of the present study was to evaluate the effect of thyroxine administration to women with SCH and who had a history of recurrent intrauterine fetal death through uterine and ovarian ultrasound blood flow estimation and serum lipids profile assessment before and after 2 months of treatment.

PATIENTS AND METHODS

The current study included 80 women with SCH who had a history of recurrent intrauterine death. Those women were chosen from the cohort of pregnant ladies that routinely seek medical advice. For each woman, estimation of serum TSH, serum lipids profile (LDL, TC, and TG), and also uterine and ovarian PI and RI using color Doppler ultrasound, was done at the beginning of study and then repeated following 2 months during which women were given oral thyroxine supplementation. The study was carried out in Al-Diwaniyah maternity and child teaching hospital in AL-Diwaniyah Province, Iraq and extended from September 2016 to January 2018.

Statistical analysis was carried out using SPSS version 23.0 and Microsoft Office Excel 2010. Nominal data were expressed as numbers and percentages while numeric data were expressed as mean and

standard deviation. Paired t-test was used to compare mean differences in serum TSH, LDL, TG, TC, ovarian, and uterine PI and RI. The level of statistical significance was considered at p≤0.05.

RESULTS

Mean serum TSH was significantly reduced from 7.35±0.97 to 3.81±0.52 mIU/L (p<0.05). Mean serum LDL was significantly reduced from 175.45±8.22 to 123.05±7.65 mg/dl (p<0.05). Mean serum TG was significantly reduced from 296.50±46.23 to 146.60±12.25 mg/dl (p<0.05). Mean serum TC was significantly reduced from 281.10±17.40 to 174.60±12.87 mg/dl (p<0.05), as shown in Fig. 1.

Mean early follicular phase ovarian RI was significantly reduced from 0.74±0.03 to 0.67±0.02 (p<0.05). Mean early follicular phase ovarian PI was significantly reduced from 2.51±0.17 to 2.10±0.18 (p<0.05). Mean early follicular phase uterine RI was significantly reduced from 2.31±0.14 to 1.84±0.15 (p<0.05), as shown in Fig. 2.

Mean late follicular phase ovarian RI was significantly reduced from 0.67±0.03 to 0.58±0.02 (p<0.05). Mean late follicular phase ovarian PI was significantly reduced from 16.55±1.36 to 12.45±0.89 (p<0.05). Mean late follicular phase uterine PI was significantly reduced from 2.63±0.13 to 2.02±0.08 (p<0.05), as shown in Fig. 2.

DISCUSSION

The present study showed that administration of thyroxine to women with SCH caused significant improvement in both ovarian and uterine blood flow as evident by significant lower mean PI and mean RI. In addition, the current study showed significant improvement in serum lipids profile of the women following thyroxin treatment.

The most frequent pathological hormone insufficiency is primary hypothyroidism, and the rate of subclinical and clinical disease is 4.3% and 0.3%, respectively [20]. Inadequacy of thyroid hormones results in a number of significant end-organ outcomes that also include reproductive system defects of the women. Prolonged hypothyroid status can alter gonadotropin production by raising serum prolactin (PRL) concentrations [21]. Clinical features, including impaired fertility and menstrual irregularities, are the consequence of "anovulation and/or luteal phase defect" [22].

Most women with hypothyroidism will develop amenorrhea. Reproductive disorders that accompany hypothyroidism include wide spectrum of abnormalities ranging from altered sexual maturation, irregular menstruation, and subfertility [23]. The effect of hypothyroidism on menstruation has been observed since the 1950s and is associated with alterations in cycle duration and blood amount [23]. SCH has been seen to be correlated with occult menorrhagia that becomes symptomatic later with the progression of thyroid illness [24]. Hypothyroidism causes an elevation in the levels of thyroid-releasing hormone which, in turn, stimulates secretion of TSH and PRL and PRL inhibits the synthesis and secretion of gonadotrophins [25]. It was observed that thyroid receptors are also found in ovarian surface epithelium and affect ovarian follicles, in addition to their existence in granulosa cells of ovarian follicles [26]. It has been seen that thyroxine controls a number of biological functions including cellular oxygen consumption, growth, embryonic development, cellular metabolism, and tissue maturation and differentiation [27].

Serum concentrations of LH and FSH are profoundly low in women with clinically symptomatic hypothyroidism when estimated between day 2 and 5 of the menstrual cycle [28]. Studies have demonstrated that serum estradiol was also reduced significantly in the hypothyroid state when compared to the control [29]. Studies have demonstrated a positive correlation in between TSH and PRL in hypothyroid women [30]. In many studies, it was shown that T4 administration in hypothyroidism normalizes PRL and LH levels, increases folliculogenesis and estradiol secretion, reverses menstrual abnormalities, and increases spontaneous fertility [31].

Uterine blood flow alternates along with alterations in the steroid levels throughout the length of the menstrual cycle and also during pregnancy. At time of follicular phase of the cycle that is typified by an elevated "estrogen-to-progesterone ratio," uterine blood flow becomes high. At time of the incoming luteal phase that is characterized by greater progesterone and less estrogen, uterine blood flow is low. On the other hand, at time of pregnancy that is characterized by greater estrogen and progesterone, uterine blood flow will increase and the increment is rising with advancing pregnancy. Because uterine blood flow patterns change along with the steroid hormone profile, many studies are focused on the ways by which these blood vascular responses are induced. Estradiol-17β (E2β) is a strong blood vessel dilator agent that has been utilized to evaluate ovarian steroid hormone actions on blood flow parameters [32].

Thyroid hormones play an important role in synthesis, mobilization, and metabolism of lipids [33]. Therefore, hypothyroidism is a major

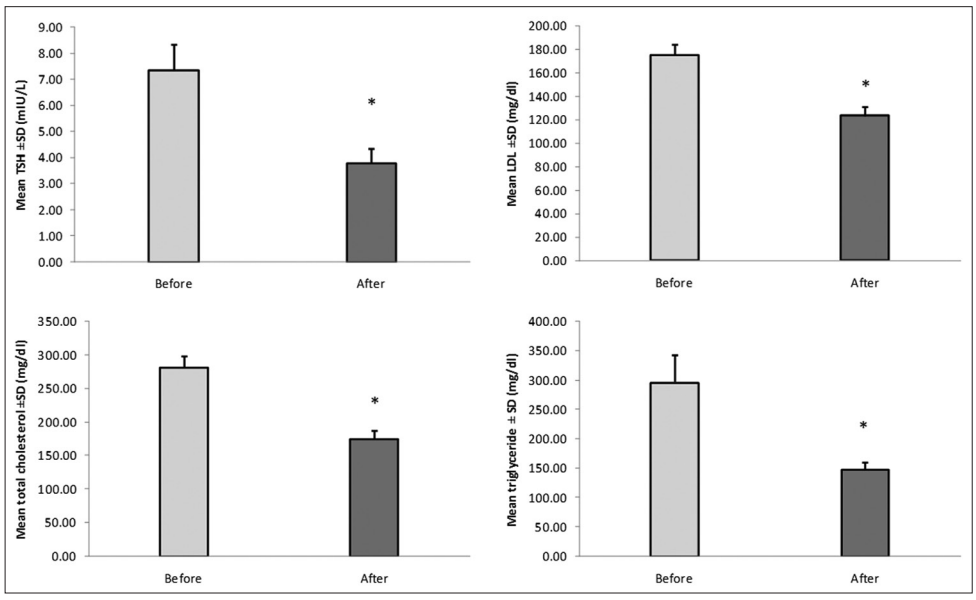

Fig. 1: Mean serum thyroid-stimulating hormone and lipids profile of pregnant women before and after thyroxin treatment

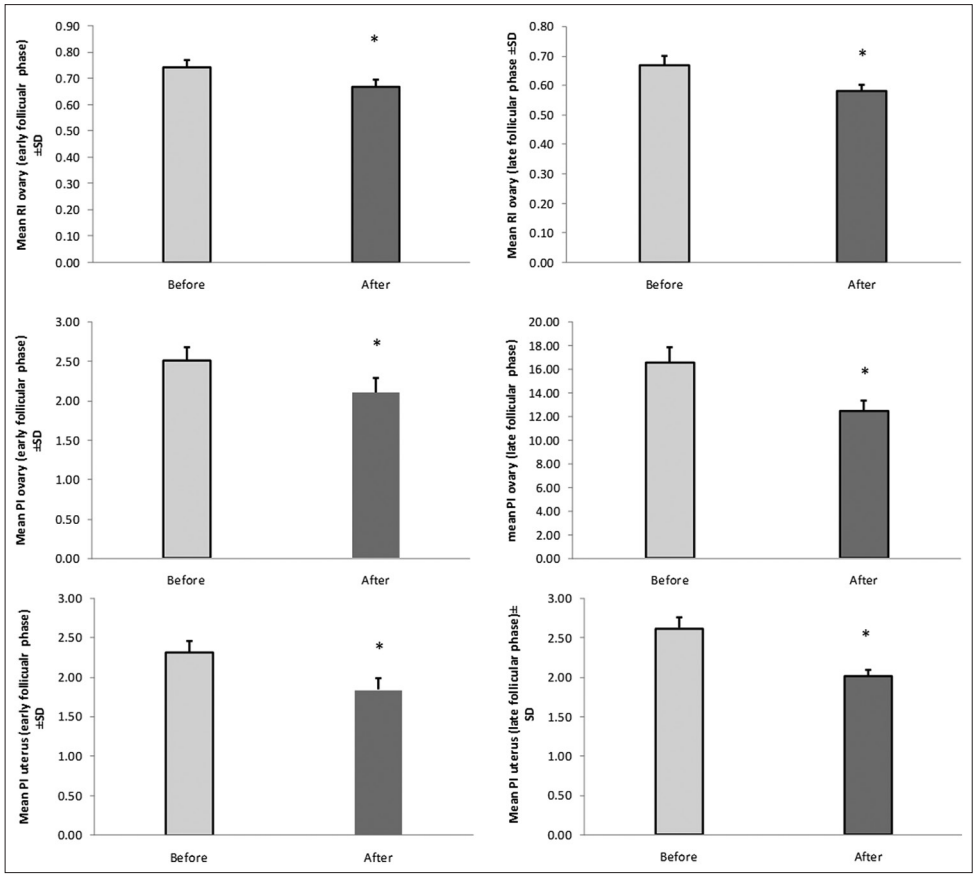

Fig. 2: Mean early and late ovarian resistance index, ovarian pulsatile index (PI), and uterine PI before and after thyroxin treatment

cause of secondary dyslipidemia. Investigations report elevated levels of TC and LDL in patients with overt hypothyroidism. Those patients may also present elevated to normal levels of TG and HDL [34,35]. In SCH, there is an elevation in TSH with normal levels of thyroxine (T4) and tri-iodothyronine (T3) [14,36].

In conclusion, thyroxine administration to women with SCH significantly increases uterine and ovarian blood flow and decreases serum lipids.

AUTHOR'S CONTRIBUTION

Sinaa Abdul Amir Kadhimwas provided the design, intellectual content, innovations, and protocol for conducting the study, majorly sample collection, and minor role in follow up of patients.

Shaimaa Abdul Ameer Kadhum has majorly performed ultrasound and Doppler study for the patients.

Ali Jawad Hamza has majorly follow-up of the patients during treatment, analysis of the data, and sincerely authored the article.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding publication of this article.

REFERENCES

1. Ramprasad M, Bhattacharyya SS, Bhattacharyya A. Thyroid disorders in pregnancy. Indian J Endocrinol Metab 2012;16:S167-70.
2. Kataria J, Gill GK, Kaur M. Interrelationship of thyroid hormones, obesity, and prolactin in infertile women. Asian J Pharm Clin Res 2018;11:136-7.
3. Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008;20:784-94.
4. Jaseem T, Hegdea A, Chakrapani M, Rao S, Manjrekar P, Rukmini MS. Lipids and ischemia-modified albumin in mild subclinical hypothyroidism response to levothyroxine replacement. Asian J Pharm Clin Res 2017;10:336-8.
5. Nazarpour S, Ramezani Tehrani F, Simbar M, Azizi F. Thyroid dysfunction and pregnancy outcomes. Iran J Reprod Med 2015;13:387-96.
6. Ezzeddine D, Ezzeddine D, Hamadi C, Abbas HA, Nassar A, Abiad M, *et al.* Prevalence and correlation of hypothyroidism with pregnancy outcomes among lebanese women. J Endocr Soc 2017;1:415-22.
7. Tudosa R, Vartej P, Horhoianu I, Ghica C, Mateescu S, Dumitrache I, *et al.* Maternal and fetal complications of the hypothyroidism-related pregnancy. Maedica (Buchar) 2010;5:116-23.
8. Browne VA, Julian CG, Toledo-Jaldin L, Cioffi-Ragan D, Vargas E, Moore LG. Uterine artery blood flow, fetal hypoxia and fetal growth. Philosophical transactions of the royal society B. Biol Sci 2015;370:20140068.
9. Adibi A, Khadem M, Mardanian F, Hovsepian S. Uterine and arcuate arteries blood flow for predicting of ongoing pregnancy in *in vitro* fertilization. J Res Med Sci 2015;20:879-84.
10. Shah D, Shah S, Parikh J, Bhatt CJ, Vaishnav K, Bala DV, *et al.* Doppler ultrasound: A good and reliable predictor of ovarian malignancy. J Obstet Gynaecol India 2013;63:186-9.
11. Wang L, Qiao J, Li R, Zhen X, Liu Z. Role of endometrial blood flow assessment with color doppler energy in predicting pregnancy outcome of IVF-ET cycles. Reprod Biol Endocrinol 2010;8:122.
12. Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM, *et al.* Alteration of lipid profile in subclinical hypothyroidism: A meta-analysis. Med Sci Monit 2014;20:1432-41.
13. Alamdari S, Amouzegar A, Tohidi M, Gharibzadeh S, Kheirkhah P, Kheirkhah P, *et al.* Hypothyroidism and lipid levels in a community based study (TTS). Int J Endocrinol Metab 2016;14:e22827.
14. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. Open Cardiovasc Med J 2011;5:76-84.
15. Bartels Ä, O'Donoghue K. Cholesterol in pregnancy: A review of knowns and unknowns. Obstet Med 2011;4:147-51.

16. Butte NF. Carbohydrate and lipid metabolism in pregnancy: Normal compared with gestational diabetes mellitus. Am J Clin Nutr 2000;71:1256S-61S.
17. Catov JM, Bodnar LM, Kip KE, Hubel C, Ness RB, Harger G, *et al.* Early pregnancy lipid concentrations and spontaneous preterm birth. Am J Obstet Gynecol 2007;197:610.e1-7.
18. Avis HJ, Hutten BA, Twickler MT, Kastelein JJ, van der Post JA, Stalenhoef AF, *et al.* Pregnancy in women suffering from familial hypercholesterolemia: A harmful period for both mother and newborn? Curr Opin Lipidol 2009;20:484-90.
19. Palinski W. Maternal-fetal cholesterol transport in the placenta: Good, bad, and target for modulation. Circ Res 2009;104:569-71.
20. Roberts CG, LadensonPW. Hypothyroidism. Lancet 2004;363:793-803.
21. Muderris II, Boztosun A, Oner G, Bayram F. Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism. Ann Saudi Med 2011;31:145-51.
22. Krassas GE. Thyroid disease and female reproduction. Fertil Steril 2000;74:1063-70.
23. Bals-Pratsch M, De Geyter C, Müller T, Frieling U, Lerchl A, Pirke KM, *et al.* Episodic variations of prolactin, thyroid-stimulating hormone, luteinizing hormone, melatonin and cortisol in infertile women with subclinical hypothyroidism. Hum Reprod 1997;12:896-904.
24. Sharma N, Sharma A. Thyroid profile in menstrual disorders. JK Science 2012;14:14-7.
25. Abraham R, Srinivasa Murugan V, Pukazhvanthen P, Sen SK. Thyroid disorders in women of puducherry. Indian J Clin Biochem 2009;24:52-9.
26. Saran S, Gupta BS, Philip R, Singh KS, Bende SA, Agroiya P, *et al.* Effect of hypothyroidism on female reproductive hormones. Indian J Endocrinol Metab 2016;20:108-13.
27. Aghajanova L, Lindeberg M, Carlsson IB, Stavreus-Evers A, Zhang P, Scott JE, *et al.* Receptors for thyroid-stimulating hormone and thyroid hormones in human ovarian tissue. Reprod Biomed Online 2009;18:337-47.
28. Wagner MS, Wajner SM, Maia AL. The role of thyroid hormone in testicular development and function. J Endocrinol 2008;199:351-65.
29. Acharya N, Acharya S, Shukla S, Inamdar SA, Khatri M, Mahajan SN, *et al.* Gonadotropin levels in hypothyroid women of reproductive age group. J Obstet Gynaecol India 2011;61:550-3.
30. Ajayi AF, Akhigbe RE, Ajayi LO. Hypothalamic-pituitary-ovarian axis in thyroid dysfunction. West Indian Med J 2013;62:835-8.
31. Binita G, Suprava P, Mainak C, Koner BC, Alpana S. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J Reprod Infertil 2009;10:207-12.
32. Atis G, Dalkilinc A, Altuntas Y, Atis A, Caskurlu T, Ergenekon E, *et al.* Sexual dysfunction in women with clinical hypothyroidism and subclinical hypothyroidism. J Sex Med 2010;7:2583-90.
33. Chang K, Lubo Zhang. Review article: Steroid hormones and uterine vascular adaptation to pregnancy. Reprod Sci 2008;15:336-48.
34. Velkoska Nakova V, Krstevska B, Bosevski M, Dimitrovski Ch, Serafimoski V. Dyslipidaemia and hypertension in patients with subclinical hypothyroidism. Prilozi 2009;30:93-102.
35. Pearce EN. Hypothyroidism and dyslipidemia: Modern concepts and approaches. Curr Cardiol Rep 2004;6:451-6.
36. Efstathiadou Z, Bitsis S, Milionis HJ, Kukuvitis A, Bairaktari ET, Elisaf MS, *et al.* Lipid profile in subclinical hypothyroidism: Is L-thyroxine substitution beneficial? Eur J Endocrinol 2001;145:705-10.