Is gonadotropin-releasing hormone agonist usage really leading to thyroid dysfunction?

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(Received: April 11, 2018; Revised manuscript received: May 10, 2018; Accepted: May 22, 2018)

Abstract: *Objectives:* Gonadotropin-releasing hormone agonist (GnRHa) could influence the levels of sex hormones and thyroid hormones. The aim of this study was to investigate the effect of GnRHa on thyroid function. *Materials and methods:* The data of the patients were collected from the registrations of July 2014–October 2014. A total of 41 women who underwent one-time IVF cyclus were evaluated in this cross-sectional study. The patients were categorized into two groups according to the serum T_3, T_4, and TSH levels before and 2 weeks' after the administration of GnRHa. *Results:* Mean basal TSH and mean TSH levels on hCG day were 1.98 ± 0.77 and 1.75 ± 0.70, respectively. The difference between the two groups was statistically significant ($p < 0.05$). GnRHa did not lead to statistically significant difference on serum-free T_3 and T_4 levels. *Conclusions:* In conclusion, our results demonstrate that GnRHa led to a decrease on serum TSH level. Serum-free T_3 and T_4 levels were remained unchanged and this might be due to early measurement of the hormone levels (just 2 weeks later from GnRHa administration).

Keywords: GnRHa, IVF–ICSI, infertility, thyroid hormones, gonadotropin

Introduction

Gonadotropin-releasing hormone agonists (GnRHas) have been widely used during the practice of assisted reproduction techniques for more than four decades [1]. GnRHas are synthetic peptides exhibiting biologic reactions by connecting GnRH receptors. GnRHa has longer half time than GnRH and occupies its receptors. At first, GnRHa stimulates the pituitary to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH). However, after 10 days, LH and FSH secretions are decreased because of the downregulation of the GnRH receptors [2]. Thus, GnRHa-induced alteration in serum levels of the gonadotropins could lead to a thyroid dysfunction [3].

Moreover, previous studies have reported that there was an association between GnRHa and autoimmune thyroid disease [4, 5]. Although there are a lot of published studies about the influence of GnRHa on infertility, the association between GnRHa and thyroid dysfunction is still controversial. The estrogen reduction due to desensitization by downregulation of GnRH receptor could be responsible from thyroid disability [6]. The aim of this study was to evaluate the effect of GnRHa on thyroid function.

Materials and Methods

This trial was designed as retrospective cross-sectional study. The study protocol was reviewed and approved by the ethical committee of our clinic. The data of the patients were collected from the registrations of July 2014–October 2014. A total of 41 women who

underwent one-time *in vitro* fertilization (IVF) cyclus, due to infertility in Ankara Zekai Tahir Burak Women's Health Education and Research Hospital, were enrolled in the study. The patients were divided into two groups according to the serum T_3, T_4, and TSH levels before and 2 weeks after the administration of GnRHa. The patients in Group 1 had serum T_3, T_4, and TSH levels before GnRHa treatment. Group 2 contained the women who had serum T_3, T_4, and TSH levels after GnRHa.

The patient characteristics (basal hormone levels, duration of infertility, and ages of the patients) were analyzed. The groups were homogenous in terms of these parameters. The patients who underwent the testicular sperm extraction procedures were not included in the study.

Agonist and antagonist protocols were performed for controlled ovarian hyperstimulation (COH) individually. The choice of the protocol was performed according to the age, ovarian reserve, BMI, and clinician's preference. In microdose flare protocol patients, pituitary was downregulated with leuprolide acetate (Lucrin® daily 0.25 mg Abbott, USA). The first dose of leuprolide acetate of 0.1 mg/kg was given on day 2 of the menstrual cycle and given at the same dose until the human chorionic gonadotropin (hCG) day. The first dose of 150–225 U of daily rec-FSH (Gonal-F; Serono, Istanbul) and/or human menopausal gonadotropin (HMG) (Menogon, Ferring, Istanbul) were given on day 3 of the cycle and continued for the first 3 days of stimulation, after which daily dosing was determined individually. In antagonist regime, flexible daily GnRH antagonist protocol was preferred to induce pituitary downregulation (Cetrotide® 0.25 mcg; Merck Serono, Istanbul). GnRH antagonist was started when the leading follicle reached a diameter of 12–14 mm. Serial E2 levels and two-dimensional follicle measurements by transvaginal ultrasound imaging (Logic 200 Pro, General Electric, Korea) were performed until at least two dominant follicles reached dimensions of 18 mm or greater in diameter. hCG (Pregnyl®, 10,000 U, im; Organon, The Netherlands) was administered and followed by transvaginal oocyte retrieval 36 h later. Intracytoplasmic sperm injection (ICSI) was performed in all patients according to our clinical practice. Luteal phase support was routinely given as progesterone in the form of Crinone 8% gel (Serono) 90 mg daily for 14 days, when a pregnancy test was performed. Clinical pregnancy was diagnosed by the ultrasound demonstration of heartbeat in an intrauterine gestational sac.

Statistical analysis was performed using SPSS 17.00 (SPSS Inc., Chicago, IL). The χ^2 test was used for categorical variables and a paired sample *t*-test was used for continuous variables that were normally distributed. The p value of <0.05 was considered significant. The results were expressed as mean ± SD.

Results

A total of 41 women were included in the study. All the women were on their first cycle of IVF–ICSI. Mean age (years), duration of infertility (years), and body mass index (kg/m^2) were 28.7 ± 4.3, 5.1 ± 3.8, and 23.8 ± 2.7, respectively. Mean baseline FSH (IU/L), LH (IU/L), and E2 (pg/ml) were 7.6 ± 1.7, 5.9 ± 3.5, and 39.7 ± 15.1, respectively. Demographic and clinical characteristics of the patients were demonstrated in *Table I*. According to these data, the patients were distributed homogenously.

TSH level was significantly higher in Group 1 than in Group 2 ($p < 0.05$). Free T_3 levels were 3.0 ± 0.4 and 2.9 ± 0.3 in Groups 1 and 2, respectively and the difference was not statistically significant ($p = 0.68$). Free T_4 levels were distributed similarly between the two groups ($p = 0.60$) (*Table II*).

Discussion

In this retrospective cross-sectional study, the effect of GnRHa on thyroid function was assessed. The results of this study have shown that GnRHa led to a significant

Table I Characteristics of the patients

	Patients ($n = 41$)
Age (years)	28.7 ± 4.3
Duration of infertility (years)	5.1 ± 3.8
Baseline FSH (IU/L)	7.6 ± 1.7
Baseline LH (IU/L)	5.9 ± 3.5
Baseline E2 (pg/ml)	39.7 ± 15.1
BMI (kg/m^2)	23.8 ± 2.7

FSH: follicle stimulating hormone; LH: luteinizing hormone; BMI: body mass index

Table II Serum T_3, T_4, and TSH levels before and 2 weeks after the administration of GnRHa

	Before GnRHa ($n = 41$)	After GnRHa ($n = 41$)	p
T_3	3.0 ± 0.4	2.9 ± 0.3	0.68
T_4	0.8 ± 0.1	0.8 ± 0.1	0.60
TSH	1.9 ± 0.7	1.7 ± 0.7	<0.05*

TSH: thyroid stimulating hormone; GnRHa: gonadotropin-releasing hormone agonist.
*Statistically significant

decrease in serum TSH levels. However, serum-free T_3 and T_4 levels were not accompanied by TSH.

GnRHas are used for pituitary suppression in COH cycles. At first, these drugs cause an increase in serum FSH and LH levels. At the end of 2 weeks, FSH and LH decrease due to downregulation of GnRH receptors, paradoxically. The reason of this downregulation is the long half-life of GnRHa [7]. Jacobson [8] reported that GnRHa could be associated with autoimmune diseases, such as transient thyrotoxicosis. Recently, it was found that GnRHa exacerbates hyperthyroidism and leads to painless thyroiditis [9]. Massart et al. [10] retrospectively evaluated 73 patients who were treated with GnRHa. They found a significant reduction in free T_3 levels, but free T_4 and TSH levels remained unchanged. Finally, they claimed that GnRHa was not related with thyroid dysfunction and monitorization of thyroid activity during COH was not necessary.

More recently, a new study about the effect of COH on thyroid function was conducted by Busnelli et al. [11]. They measured serum TSH levels for four times and detected a significant increase in serum TSH levels. They concluded that COH could have an effect on TSH levels. On the contrary, in this study, we found a significant decline in serum TSH levels ($p < 0.05$).

The aim of this study was to demonstrate the effect of GnRHa on thyroid function. In this study, TSH levels were diminished but there were no change in serum-free T_3 and T_4 levels. These findings could be due to early measurement of the hormone levels. The limitations of this study were the restricted number of patients and lack of information about long-term impact. Large prospective and randomized trials are required to assess the influence of GnRHa on thyroid function.

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Funding sources: None.

Authors' contribution: NY and NH participated in project development and data collection. MK and YE-U participated in manuscipt writing and data analysis.

Conflict of interest: None.

Acknowledgements: None.

References

1. Maggi R, Cariboni AM, Montagnani MM, Moretti RM, Andrè V, Marzagalli M, Limonta P: GnRH and GnRH receptors in the pathophysiology of the human female reproductive system. Hum Reprod Update 22, 358–381 (2016)
2. Conn PM, Crowley WF Jr: Gonadotropin-releasing hormone and its analogues. N Engl J Med 324, 93–103 (1991)
3. Kasayama S, Miyake S, Samejima Y: Transient thyrotoxicosis and hypothyroidism following administration of the GnRH agonist leuprolide acetate. Endocr J 47, 783–785 (2000)
4. Amino N, Hidaka Y, Takano T, Tatsumi KI, Izumi Y, Nakata Y: Possible induction of Graves' disease and painless thyroiditis by gonadotropin-releasing hormone analogues. Thyroid 13, 815–818 (2003)
5. van Bon AC, Wiersinga WM: Goserelin-induced transient thyrotoxicosis in a hypothyroid woman on L-thyroxine replacement. Neth J Med 66, 256–258 (2008)
6. Han EJ, Song HD, Yang JH, Park SY, Kim SH, Yoon HK, Yim CH: Thyroid dysfunction associated with administration of the long-acting gonadotropin-releasing hormone agonist. Endocrinol Metab 28, 221–225 (2013)
7. Matsuda M, Morita S, Arima T, Inoue I, Miyamura K: Buserelin induced painless thyroiditis. Naika 75, 363–364 (1995)
8. Jacobson JD: Gonadotropin-releasing hormone: Potential role in autoimmunity. Int Immunopharmacol 1, 1077–1083 (2001)
9. Morita S, Ueda Y: Graves' disease associated with goserelin acetate. Acta Med Nagasaki 47, 79–80 (2002)
10. Massart F, Harrell JC, Federico G, Saggese G: Thyroid outcome during long-term gonadotropin-releasing hormone agonist treatments for idiopathic precocious puberty. J Adolesc Health 40, 252–257 (2007)
11. Busnelli A, Somigliana E, Ferrari S, Filippi F, Vannucchi G, Fugazzola L: The long-term impact of controlled ovarian hyperstimulation on thyroid function. Endocr Pract 22, 389–395 (2016)