

## Review Article

# Thyroid disorders and fertility

Nilay Karaca<sup>1,\*</sup>, Yaşam Kemal Akpak<sup>2</sup>

<sup>1</sup>Bezmi Alem Vakif University, Medical Faculty, Department of Obstetrics and Gynecology, Istanbul, Turkey

<sup>2</sup>Ankara Mevki Military Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

**Received:** 14 April 2015

**Accepted:** 07 May 2015

### \*Correspondence:

Dr. Nilay Karaca,

E-mail: karacanilay@hotmail.com

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

Reproductive function is a vital process for continuation of life and requires an appropriate endocrine, molecular and cellular organization. In every stage starting from maturation of ovarian follicle up to implantation of the embryo, a convenient endocrine environment including normal thyroid hormone levels is of utmost importance. After the initial revelation of the correlation between reproductive health and thyroid functions in numerous studies have emphasized that both hyperthyroidism (OHT) and hypothyroidism (OH) are effective in female reproductive system, though varyingly. Our aim in this review is to evaluate effects of hyper- and hypothyroidism on fertility and also discuss relationship of infertility and assisted reproductive techniques (ART) regarding their effects over thyroid functions and auto-immunity under the guidance of current information.

**Keywords:** Adverse pregnancy outcome, Hyperthyroidism, Hypothyroidism, Levothyroxine, Thyroid autoimmunity

### INTRODUCTION

To be informed about some definitions and physiopathological mechanisms will be helpful in understanding the relationship between thyroid diseases and infertility-ART. Infertility is described as failure of a couple to conceive a pregnancy after regular sexual intercourse for 1 year. Its prevalence is estimated at 12-14% recently. Etiology of infertility includes male infertility (30%), female infertility (35%), combined infertility (20%) and unexplained infertility (15%).<sup>1,2</sup> In addition to these main causes other most significant factors having impact over fertilization, implantation and fetal development are immunological in origin. Anti-thyroid antibodies (ATA) are well studied part of immunological mechanisms having negative impact over fertility and also ART.<sup>3-6</sup>

In normal human, 0.03% of T4 and 0.3% of T3 in the circulation can be found as free hormones. 75% of T4 is transported as bound to thyroxin binding globuline (TBG), 20% to transtretine (TTR), 5% to albumin.<sup>7</sup> However, conditions of elevated estrogen (such as pregnancy or

ovarian stimulation) lead to increase in TBG level and decrease in TTR levels.<sup>8</sup> Concurrently, elevated estrogen levels lead to alterations in the dynamics of thyroid hormones by exerting effect over hypothalamo-pituitary-thyroid axis.<sup>9</sup> Rapid estrogen elevation during ovarian hyper stimulation leads to an increase in TBG and decrease in free T4 levels, consequently increase in TSH.<sup>7,8</sup> Poppe K. et al. have performed a study in 2004 in patients in their first IVF cycle with TSH values 0.4-2.5 mIU/L and they measured TSH at the day of HCG and repeated the TSH measurement in 16<sup>th</sup>-20<sup>th</sup> day of ovarian stimulation and have shown that TSH levels are higher relative to baseline values.<sup>10</sup>

Thyroid diseases are the most common endocrine disease in females at reproductive age.<sup>11</sup> Due to above mentioned features of thyroid hormones, evaluation of thyroid functions during both pregnancy and treatment of infertility and treating relevant pathologies become important. In early stage of pregnancy thyroid hormones are actively involved in the stage of placentation; because it was determined that T3 and epidermal growth factor have synergistic effect in the culture media.<sup>12</sup> Autoimmune mechanisms are involved

in the etiology of numerous thyroid diseases. Regardless of the fact that the patient has subclinical hypothyroidism or he/she is euthyroid, the distress experienced by the patient may stem from ATA. TSH levels are higher in ATA positive patients compared to ATA negative patients.<sup>13,14</sup> These antibodies may exert negative effects on fertility due to immune dysfunction, cellular damage and decrease in thyroid hormones.<sup>10,15</sup>

### **Hypothyroidism**

Hypothyroidism may lead to failure of sex steroids by disrupting the functioning of hypothalamo-pituitary-ovarian axis. Thus, a clinical picture in close relationship with menstrual irregularity, infertility, miscarriage and complications of unwanted pregnancy may occur.<sup>16,17</sup> The prevalence in the population is approximately 2-4%.<sup>18</sup> Even though there are several rare causes of hypothyroidism as post-iodine 131 treatment, post thyroiditis and drug induced hypothyroidism, the main reason of hypothyroidism is immunological.<sup>1</sup> Low levels of FT4 is the condition paving the way for symptoms of hypothyroidism and ovulatory dysfunction is the main clinical symptom of hypothyroidism. This condition leads to menstrual dysfunction 3 times more than the usual prevalence. The most common type of menstrual dysfunction is oligomenorrhea.<sup>19</sup>

As it's known, cells such as oocytes, cumulus cells and granulosa cells contain thyroid hormone receptors. In hypothyroidism, both the local effect of thyroid hormones on these receptors and prevention of release of pulsatile GnRH from hypothalamus lead to failure of healthy ovulation and prevent formation of high quality oocytes.<sup>15</sup> Concurrently, corpus luteum insufficiency due to disruption of LH release and hyperprolactinemia due to increased TRH release may also increase negative influences over normal menstrual cycle.<sup>10,14</sup>

In hypothyroidism, even though elevated TSH may reduce sex hormone binding protein (SHBP), increasing free testosterone and estradiol level, total serum level of these hormones are usually low.<sup>21</sup> Also, reduction in metabolic clearance of androstenedione and estron may increase aromatization of peripheral estrogens.<sup>22-23</sup> Both these mechanisms and decrease in hemostasis factors regardless of these mechanisms may lead to symptoms such as infertility, menorrhagia and polymenorrhea in hypothyroidism.<sup>4</sup>

There is no consensus over the TSH cut-off values which is a parameter that is used in diagnosis and classification. TSH normal range is a disputed subject among some authors. In a cohort study including 195 cycles in patients getting IVF therapy, when upper normal limit of TSH is considered 2.5, gestational age during delivery and birth weight of newborns were found to be significantly lower in patients having TSH values over this cut-off point. However, even though there's a tendency towards an increase in abortus the difference wasn't significant.<sup>24</sup>

Thyroid surveillance must be performed in patients presenting with infertility and replacement therapy should be done even in subclinical cases.<sup>25</sup> Even though scientific endocrine societies recommend surveillance in high risk patients,<sup>26</sup> routine surveillance before ART and surveillance of patients having history of abortus was recommended by many authors.<sup>6,27</sup> Various problems including fertility performance improves after using levothyroxine for treatment.<sup>19</sup> Since diagnosis of hypothyroidism is usually established before presentation of patients for infertility, prevalence of hypothyroidism in infertility is not clearly known. Similarly incidence of infertility in females with hypothyroidism is also not certain due to lack of studies about this subject.<sup>1</sup> In a study done in 299 female with infertility, TSH was found to be elevated in 4% and overt hypothyroidism was detected in 3.3%. Compared to other infertility cases, ovulatory dysfunction was found to be dominant in these cases.<sup>28</sup>

The changing body-mass index in pregnancy and particularly interaction of hCG with TSH receptors in the first trimester may lead to a pseudo reduction in thyroid hormones and this may delay the diagnosis of hypothyroidism.<sup>24,9</sup> Thus fluctuations in pregnancy should be monitored and treated appropriately. In some studies it was shown that in patients with hypothyroidism necessity of LT4 increases 30% in the first 5 weeks of pregnancy and this became stabilized in the 16<sup>th</sup>-20<sup>th</sup> week of pregnancy.<sup>29</sup> American Thyroid Association has recommended the proper range of value for TSH during pregnancy as 0.1-2.5 mIU/L in the first trimester; 0.2-3.0 mIU/L for the second and 0.3-3.0 mIU/L for the third. The same association has also emphasized that a single TSH measurement will not be enough but several measurements with some intervals will be more appropriate. In some studies it was shown that no treatment or inadequate treatment for hypothyroidism in pregnancy may lead to poor cognitive performance of the child and before that it may impair intrauterine placental glucose transport and thus may lead to some complications such as growth retardation and low birth weight.<sup>30</sup>

### **Subclinical Hypothyroidism**

Subclinical hypothyroidism (SCH) is described as absence of hypothyroidism symptoms with normal FT4 and elevated TSH values.<sup>31</sup> Although there's no consensus over upper normal limit of TSH, currently some authors suggest 2.5mIU/L.<sup>32</sup> Incidence of SCH in normal population is estimated at 4-8.5%, but it was determined that in patients with infertility and in advanced age the incidence increases.<sup>33</sup> According to the current literature treatment of SCH is not established yet. In a prospective randomized study 64 SCH patients with infertility was delivered 50 mcg levothyroxine (LT4) in the first day of controlled ovarian stimulation (COH) and it was shown that having grade 1 and embryo, implantation and live birth rates were higher in the

treatment group; but, no difference was found between groups regarding pregnancy rate per cycle. When pregnant groups were evaluated, treatment group with pregnancy experienced significantly less abortion than control group.<sup>34</sup> Also, in a study performed in IVF patients compared to euthyroid patients, woman with hypothyroidism even when treated had a significantly lower rate of implantation, clinical pregnancy and live birth.<sup>35</sup> In the study done by Cramer et al oocysts having problems in getting fertilized was found to be significantly higher in patients with higher TSH levels.<sup>36</sup> Even though ESHRE and RCOG have no definite recommendations for treating SCH, ESCP suggests treating SCH due to potential benefits of therapy.<sup>37</sup>

Feto-maternal effects of hypothyroidism such as abortus during pregnancy and mental retardation was clearly established.<sup>38</sup> Additionally, in recent times association of SCH with unwanted antenatal complications such as premature birth, placental detachment and intrauterine deaths was demonstrated.<sup>38-40</sup>

#### **Autoimmune thyroid diseases**

Autoimmune thyroid diseases (AITD); are the most common autoimmune conditions encountered in females in reproductive age characterized by presence of antibodies against to some structure of thyroid gland such as thyroglobulin (TG), thyroid peroxidase (TPO) and thyroid microsomal (TM).

Excessive immune response which is usually 5-10 times more in females stimulates organ specific or non-specific auto-immunity. Organ specific ATA occurring against TG damages thyroid follicle tissue, ATA occurring against TPO impedes iodination of tyrosine. Non-specific antibodies occur as a result of stimulation of T cells against specific thyroid molecules and subsequently effecting B cells. Abnormal immune response effects release of cytokines such as interferon- $\gamma$ , IL-4 and IL-10 and at the same time prevents successful implantation by altering profile of endometrial T-cells.<sup>41</sup>

It's known that ATA and some causes of infertility are related. In particular, there are studies reporting a significant and high correlation between ATA and endometriosis. Abalovich et al. have reported endometriosis was nearly 2 times more compared to control group (25% vs 14%) and Gerhard et al. reported endometriosis was nearly 5 times more (44% vs 9%).<sup>17,33</sup> Similarly, in patients with polycystic ovarian disease ATA positivity was significantly higher compared to control group.<sup>42,43</sup> Even association of this antibody positivity with premature ovarian insufficiency was also suggested.<sup>17</sup>

According to the hypothesis of a recent study, zona pellucida becomes a target for ATA since it has antigen groups similar to thyroid and thus fertility was negatively affected.<sup>44</sup> Similarly, according to the hypothesis in the

study of Monteleone et al. ATA within the follicle fluid damages oocyte maturation and thus success rate following ART decreases<sup>45</sup>. Even though above mentioned studies have demonstrated positive relation between AITD and low ART success rate, in 1999 Kutteh et al have shown that there is no significant difference between pregnancy positive and pregnancy negative patients after ART. In this study, similarly there was no difference between groups regarding TG and TPO antibody positivity and TSH concentration.<sup>46</sup> Also, in study performed by Reimad et al. there was no significant difference between and AITD and normal group regarding pregnancy rates.<sup>47</sup>

From the perspective of pregnancy outcomes in AITD, there is 3-5 times more abortus regardless of thyroid dysfunction.<sup>48,49</sup> Certainly, genetics, infection, hormones and environmental factors may have a role in etiology of abortus. However, correlation with thyroid autoantibodies was also studied. In a study performed by Negro et al. ATA positive ART patients treated by LT4 pregnancy rate wasn't different from ATA negative patients; however RR for abortus was 2.01 and birth rates was also lower in ATA positive patients.<sup>50</sup> Also in a prospectively designed randomized study anti-TPO and anti-TG antibodies were significantly higher in IVF patients with miscarriage compared to control group.<sup>34</sup> In 234 infertile patient with positive peroxidase antibody, in their first IVF cycle abortus was two times more frequent than control group.<sup>51</sup> Also in some studies, when thyroid antibodies are positive risk of abortus was found to be higher even if the patient are euthyroid.<sup>52,53</sup> In a meta-analysis carried out by Toulis et al. in 2010 abortus rate was found to be 2 times higher in euthyroid IVF patients with positive thyroid autoimmunity.<sup>54</sup> Revell et al. has emphasized in their study that during IVF, in order to increase pregnancy and implantation rates and reduce abortus rate ATA positive patients must be treated even if they are euthyroid.<sup>55</sup>

#### **Hyperthyroidism**

In women with hyperthyroidism hormonal changes effecting reproductive system may occur. Suthern et al. have reported that androstenedione and testosterone production increase in hyperthyroidism and subsequently this leads to elevation of estron and estradiol.<sup>56</sup> Both this mechanism and decrease in metabolic clearance of estrogen lead to higher plasma estrogen levels in women with hyperthyroidism.<sup>57</sup> Also some authors have stated that they detected elevation in serum LH, FSH and SHBG levels.<sup>58,59</sup>

Infertility incidence is about 5-8% in women with hyperthyroidism<sup>60</sup>. Even though in some studies endometrial biopsies proved that women were ovulating, it's still emphasized that hyperthyroidism is related with reduced fertility.<sup>61,62</sup> Additionally, Poppe et al. in a study performed in 2002 have reported that suppressed serum TSH levels are more frequent in ATA positive infertile

women compared to non-positive ones.<sup>63</sup> Previously menstrual disorders including particularly oligomenorrhea was reported as 50% in people with hyperthyroidism, but Krassas et al. found that the rate is around 21.5 % in thyrotoxicosis.<sup>4,64</sup>

Mean radioactive iodine (370 MBq) dose used in treating hyperthyroidism is curative and it doesn't affect gonadal performance. Still, because of teratogenic safety not to become pregnant for 6 months is recommended. Also, before planning a pregnancy to be sure that hypothyroidism is not present is essential.<sup>65</sup>

## CONCLUSION

Up to this time in numerous studies it has been emphasized that thyroid functions have effects over female infertility by both direct and indirect ways. Especially recently, widespread use of ART has revealed the fact that COH exerts considerable stress on thyroid functions and new information about relationship between female fertility and thyroid hormones have occurred.

In this review, we determined that hypo- and hyperthyroidism occur mostly in women with menstrual irregularity and AITD occur in women with infertility problem. At the same time, we have observed that ART success is considerably low in AITD. In both conditions treating malfunctioning thyroid alone corrects the symptoms and changes the outcome in ART. Thus, especially in women with poly- and hypomenorrhea thyrotoxicosis and in women with oligomenorrhea hypothyroidism should be investigated. Also, in anovulatory infertility and infertility due to endometriosis AITD should be kept in mind. Also in women with AITD, since effects of COH over thyroid function is more frequently observed, monitorization of TSH before or during stimulation in order to keep it below 2.5 mIU/L is important. We have observed in this review that numerous studies concentrated on treatment of subclinic hypothyroidism in women with menstrual problems during COH and ART.

As conclusion, since thyroid functions exert effect over fertility with various mechanisms; particularly in infertile pairs, especially if family history is positive thyroid dysfunction and autoimmunity should be investigated. In this review we have observed that further well designed clinical trials addressing various unclear issues regarding thyroid dysfunction and fertility are still needed.

*Funding: None*

*Conflict of interest: None declared*

*Ethical approval: Not required*

## REFERENCES

1. Poppe K, Velkeniers B and Glinoe D. Thyroid disease and female reproduction. *Clin Endocrinol (Oxf)* 2007;66:309-21.

2. Temel T, Akpak YK, Gün I, Oral S, Sofuoğlu K. Impact of paternal age on intracytoplasmic sperm injection cycle results. *Int J Reprod Contracept Obstet Gynecol* 2015;4:622-8.
3. Sahin H, Akpak YK, Berber U, Gün I, Demirel D, Ergür AR. Expression of P-cadherin (cadherin-3) and E-selectin in the villous trophoblast of first trimester human placenta. *J Turk Ger Gynecol Assoc* 2014;15:13-7.
4. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Batrinos M. Menstrual disturbances in thyrotoxicosis. *Clin Endocrinol (Oxf)* 1994;40:641-4.
5. Krassas GE. Thyroid disease and female reproduction. *Fertil Steril* 2000;74:1063-70.
6. Poppe K, Velkeniers B. Female infertility and the thyroid. *Best Pract Res Clin Endocrinol Metab* 2004;18:153-65.
7. Schussler GC. The thyroxine-binding proteins. *Thyroid* 2000;10:141-9.
8. Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997;18: 404-33.
9. Krassas GE, Poppe K, Glinoe D. Thyroid function and human reproductive health. *Endocr Rev* 2010; 31:702-55.
10. Poppe K, Glinoe D, Tournaye H, Schiettecatte J, Devroey P, van Steirteghem A, et al. Impact of ovarian hyperstimulation on thyroid function in women with and without thyroid autoimmunity. *Clin Endocrinol Metab* 2004;89:3808-12.
11. Davis LB, Lathi RB, Dahan MH The effect of infertility medication on thyroid function in hypothyroid women who conceive. *Thyroid* 2007; 17:773-7.
12. Kilby MD, Barber K, Hobbs E, Franklyn JA. Thyroid hormone action in the placenta. *Placenta* 2005;26:105-13.
13. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002;8:457-69.
14. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006;91:2587-91.
15. Poppe K, Glinoe D, Steirteghem AV, Tournaye H, Devroey P, Schiettecatte J, et al. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid* 2002;12:997-1001.
16. Poppe K, Glinoe D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. *Hum Reprod Update* 2003;9:149-61.
17. Gerhard I, Becker T, Eggert-Kruse W, Klinga K, Runnebaum B. Thyroid and ovarian function infertile women. *Hum Reprod* 1991;6:338-45.

18. Bjoro T, Holmen J, Krüger O, Midthjell K, Hunstad K, Schreiner T, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trøndelag (HUNT). *Eur J Endocrinol.* 2000;143:639-47.
19. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. *Clin Endocrinol (Oxf)* 1999;50:655-9.
20. Wakim AN, Polizzotto SL, Buffo MJ, Marrero MA, Burholt DR. Thyroid hormones in human follicular fluid and thyroid hormone receptors in human granulosa cells. *Fertil Steril* 1993;59:1187-90.
21. Gordon GG, Southren AL. Thyroid-hormone effects on steroid-hormone metabolism. *Bull NY Acad Med* 1977;53:241-59.
22. Longcope C, Abend S, Braverman LE, Emerson CH. Androstenedione and estrone dynamics in hypothyroid women. *J Clin Endocrinol Metab* 1990; 70:903-7.
23. Gallagher TF, Fukushima DK, Noguchi S, Fishman J, Bradlow HL, Cassouto J, et al. Recent studies in steroid hormone metabolism in man. *Recent Prog Horm Res* 1966;22:283-303.
24. Baker VL, Rone HM, Pasta DJ, Nelson HP, Gvakharia M, Adamson GD. Correlation of thyroid stimulating hormone (TSH) level with pregnancy outcome in women undergoing in vitro fertilization. *Am J Obstet Gynecol* 2006;194:1668-74.
25. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228-38.
26. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007;92:1-47.
27. Lazzarin N, Moretti C, De Felice G, Vaquero E, Manfellotto D. Further evidence on the Role of Thyroid autoimmunity in women with recurrent miscarriage. *Int J Endocrinol* 2012;2012:717185.
28. Arojoki M, Jokimaa V, Juuti A, Koskinen P, Irjala K, Anttila L. Hypothyroidism among infertile women in Finland. *Gynecol Endocrinol* 2000;14: 127-31.
29. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004;351:241-9.
30. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081-125.
31. Twigg G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. *J Autoimmun* 2012;38:275-81.
32. Brabant G, Beck-Peccoz P, Jarzab B, Laurberg P, Orgiazzi J, Szabolcs I, et al. Is there a need to redefine the upper normal limit of TSH? *Eur J Endocrinol* 2006;154:633-7.
33. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. *Gynecol Endocrinol* 2007; 23:279-83.
34. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2011;95:1650-4.
35. Scoccia B, Demir H, Kang Y, Fierro MA, Winston NJ. In vitro fertilization pregnancy rates in levothyroxine-treated women with hypothyroidism compared to women without thyroid dysfunction disorders. *Thyroid* 2012;22:631-6.
36. Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburgs ES, Hornstein MD, et al. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? *J Assist Reprod Genet* 2003;20:210-5.
37. Vissenberg R, Van den Boogaard E, Van Wely M, Van der Post JA, Fliers E, Bisschop PH et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2012;18:360-73.
38. Stagnaro-Green A, Chen X, Bogden JD, Davies TF, Scholl TO. The thyroid and pregnancy: a novel risk factor for very preterm delivery. *Thyroid* 2005;15: 351-7.
39. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;105:239-45.
40. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos JD, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 2000;7:127-30.
41. Artini PG, Uccelli A, Papini F, Simi G, Di Bernardino OM, Ruggiero M, et al. Infertility and pregnancy loss in euthyroid women with thyroid autoimmunity. *Gynecol Endocrinol* 2013;29:36-41.
42. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. *Eur J Endocrinol* 2004;150:363-9.
43. Kachuei M, Jafari F, Kachuei A, Keshтели AH. Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. *Arch Gynecol Obstet* 2012;285:853-6.
44. Kelkar RL, Meherji PK, Kadam SS, Gupta SK, Nandedkar TD. Circulating auto-antibodies against the zona pellucida and thyroid microsomal antigen

- in women with premature ovarian failure. *J Reprod Immunol* 2005;66:53-67.
45. Monteleone P, Parrini D, Faviana P, Carletti E, Casarosa E, Uccelli A, et al. Female infertility related to thyroid autoimmunity: the ovarian follicle hypothesis. *Am J Reprod Immunol* 2011;66:108-14.
  46. Kutteh WH, Schoolcraft WB, Scott RT Jr. Antithyroid antibodies do not affect pregnancy outcome in women undergoing assisted reproduction. *Hum Reprod* 1999;14:2886-90.
  47. Reimand K, Talja I, Metsküla K, Kadastik U, Matt K, Uibo R. Autoantibody studies of female patients with reproductive failure. *J Reprod Immunol* 2001; 51:167-76.
  48. Stagnaro-Green A, Glinoeer D. Thyroid autoimmunity and the risk of miscarriage. *Best Practice and Research. Best Pract Res Clin Endocrinol Metab* 2004;18:167-81.
  49. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol* 2004;150:751-5.
  50. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum Reprod* 2005;20:1529-33.
  51. Poppe K, Glinoeer D, Tournaye H, Devroey P, Van Steirteghem A, Kaufman L, et al. Assisted reproduction and thyroid autoimmunity: an unfortunate combination? *J Clin Endocrinol Metab* 2003;88:4149-52.
  52. Geva E, Amit A, Lerner-Geva L, Azem F, Yovel I, Lessing JB. Autoimmune disorders: another possible cause for in-vitro fertilization and embryo transfer failure. *Hum Reprod* 1995;10:2560-3.
  53. Bussen S, Steck T, Dietl J. Increased prevalence of thyroid antibodies in euthyroid women with a history of recurrent in-vitro fertilization failure. *Hum Reprod* 2000;15:545-8.
  54. Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. *Eur J Endocrinol* 2010;162:643-52.
  55. Revelli A, Casano S, Piane LD, Grassi G, Gennarelli G, Guidetti D, et al. A retrospective study on IVF outcome in euthyroid patients with anti-thyroid antibodies: effects of levothyroxine, acetyl-salicylic acid and prednisolone adjuvant treatments. *Reprod Biol Endocrinol* 2009;7:137.
  56. Southren AL, Olivo J, Gordon GG, Vittek J, Brenner J, Raffi F. The conversion of androgens to estrogens in hyperthyroidism. *J Clin Endocrinol Metab* 1974; 38:207-14.
  57. Ridgway EC, Longcope C, Maloof F. Metabolic clearance and blood production rates of estradiol in hyperthyroidism. *J Clin Endocrinol Metab* 1975; 41:491-7.
  58. Pontikides N, Kaltsas Th, Krassas GE. The hypothalamic-pituitary-gonadal axis in hyperthyroid female patients before and after treatment. *J Endocrinol Invest* 1990;13:203.
  59. Akande EO. The effect of oestrogen on plasma levels of luteinizing hormone in euthyroid and thyrotoxic postmenopausal women. *J Obstet Gynaecol Br Common* 1974;80:795-803.
  60. Joshi JV, Bhandarkar SD, Chadha M, Balaiah D, Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. *J Postgrad Med* 1993; 39:137-41.
  61. Goldsmith RE, Sturgis SH, Lerman J, Stanbury JB. The menstrual pattern in thyroid disease. *J Clin Endocrinol Metab* 1952;12:846-55.
  62. Pontikides N, Kaltsas TH, Krassas GE. The LH, FSH, PRL and progesterone levels in thyrotoxic female patients before and after treatment. *J Endocrinol Invest* 1990;13:164.
  63. Poppe K, Glinoeer D, Van Steirteghem A, Tournaye H, Devroey P, Schiettecatte J, et al. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid* 2002;12:997-1001.
  64. Tanaka T, Tamai H, Kuma K, Matsuzuka F, Hidaka H. Gonadotropin response to luteinizing hormone releasing hormone in hyperthyroid patients with menstrual disturbances. *Metabolism* 1981;30:323-6.
  65. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders & female infertility. *Best Pract Res Clin Endocrinol Metab* 2011;25:861-73.

DOI: 10.18203/2320-6012.ijrms20150135

**Cite this article as:** Karaca N, Akpak YK. Thyroid disorders and fertility. *Int J Res Med Sci* 2015;3:1299-304.