The Relationship between Antithyroid Antibody and Pregnancy Outcome in Invitro Fertilization and Embryo Transfer

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Abstract

Background of the study: One type of assisted reproductive technique is intracytoplasmic sperm injection (ICSI) Despite use ofintracytoplasmic sperm injectionICSI it remain has low birth rate due to failure rate there are many markers associated with poor predict the outcome one of these factor effect outcome inintracytoplasmic sperm injection ICSI presence of antithyroid antibody ineuthyroid patient

Aim of study: To examine the effect of antithyroid antibody on pregnancy results following the in vitro fertilization and fetus transmit

Methods and patients : Cross section study conducted at AL-Sader infertility center atotal of eighty one Iraqi women were enrolled in this study of them 22positive antithyroid antibody,59 negative antithyroid antibody were undergone intra-cytoplasmic sperm injection ICSI in Al-Sader infertility center. The group of the study involved onlyeuthyroid women outwardly any clinically showed autoimmune illness.

Result:there was higher significant difference p value<0.004 in fertilization rate number of available embryos p value<0.003 and number of transfer embryos p value< 0.001among study group which was higher in group of women with antithyroid negative followed by,group with antithyroid positive in infertile euthyroid women **Conclusion**:patients with antithyroid antibody associated with poor pregnancy outcome in infertile euthyroid women undergoingintracytoplasmic sperm injection ICSI

Keywords*: antithyroid antibody , pregnancy outcome , invitro fertilization , embryo transfer*

Introduction

The definition of Subfertility when the husband and the wife couldn't conceive following one year of unprotected sex affair (and there is no other cause, such as breastfeeding or postnatal amenorrhea) [(1)]. It affects 12 –15% of all couples[(2)]. Subfertility developed due to many factors and casues including both male and female factors. It classified to primary subfertility and Secondary subfertility [(3).] It has been estimated that subfertility affects 12-15 percent of all couples [(4)], where seventy percent struggle with intial subfertility, i.e. with no conception in the past and theirt percent secondary subfertility when the couple had conceived previously and whatever the outcome [(5)]**.** The couple suffering infertile are advised to be tested for the elements that might be impairing fertility. The results of these measurments could be used as this information by the specialists of infertility to advise the husband and the wife regarding the possibilities of subfertility etiologies and to provide special plan for treatment for the special treatment of the couple. Its crucial to notice that the

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husband and the wife can have many influences that contribute to subfertility; thus, a full primary diagnostic test must be be taken to find the main subfertility's causes, the coupls evaluations is performed on the same time, [6]the treatment, evaluation, and recognition of subfertility makes the partners stressed and worried[7]. The emotional state of the couple should not be ignored by the clinicians which may include marital discord, anxiety, anger, and depression. Information must be informative supportive.

Treatment of subfertility included both male and femal and include medical and surgical approaches [8]. The conception of Assisting is the advice of normal conception through various forms of science research. The advancement of the enghanced approaches, specifically in forms of stimulations of controlled ovarian and ovulation induction, enabled the success process of anovulatory female treatment[9]. Assisted conception includes three primary types; injection of intracytoplasmic sperm, insemination of intrauterine, and in vitro fertilisation. Previous studies showed some links between Female infertility and the thyroid dysfunction, therefore we tried in this work to examine the influence of antithyroid antibody on pregnancy results utilizing the technique of embryo transmit and in vitro fertilization among Iraqi women with subfertility.

Methods and patients

This study was planned as a prospective study performed in Al-Sadder Teaching Hospital/fertility center, Najaf, Iraq during period from 20th March till 31st December 2019.These patients were eightyone subfertile couples who were underwent Intracytoplasmic sperm injection

Inclusion criteria:

1. Age ranged from eighteen to forty-five years

2. The female has not been through treatment of adjuvant like glucocorticoids and thyroid hormones at the the research is being taken.

3. Normal TSH

4. Negative for LAC "lupus anticoagulant" and ACA "anticardiolipin antibody" before the start of the induction of ovulation

5. Exist of morphologically normal spematozoa within sperm (male factor)

6. Normal utrine cavity

Exclusion criteria

1. Female partner with thyriod dysfunction

2. Female partner with hyperprolactinemia

3. Azoospermia

4. Confirmed endometriosis.

All women were asked to be seen at cycle day 2 (CD2) to evaluate if she was suitable for ICSI program, the history was taken from the patients included name, age, menstrual history, type of subfertility whether primary or secondary, duration and causes of subfertility, history of previous IVF and its outcome, family history, drug history. Examination had been done to each patient including body weight and height. The Body mass index (BMI) measured as individual body weight in Kg divided by square of her height in meters. Trans-vaginal ultrasound (TVUS) scan was performed to all patients using vaginal probe (5-7 MHZ). The baseline scan done to measure the endometrialthickness(mm), number of antral follicles (AFC), check the uterus and ovaries for any pathologies like fibroid, polyp, or ovarian cysts. All women sent for hormonal assay include FSH, LH, estradiol, Thyroid stimulating hormone (TSH), prolactin, anticardiolipin antibody, lupus anticoagulant and antithyroid antibody. Also routine screening blood tests of both partners for human immune deficiency virus (HIV), hepatitis B virus, (HBV) and hepatitis C virus (HCV). Before treatment, all women partners sent for seminal fluid analysis

Controlled ovarian hyperstimulation protocol

Using of one of following protocols in study.

1.Agonist GnRH protocol (short protocol)

GnRH agonist has been initiated by giving 0.1mg/day of triptoreline (decapeptyl) from the cycle day two .The gonadotropins are started from the cycle day three with one of the following drugs: Recombinant FSH or HMG and doses according to patient till the follicle maturation monitoring by transvaginal ultrasound once

the follicles(dominant follicle) were reached diameter 18 or more,trigger was given to the patient. Ovum pickup was done using transvaginal ultrasound at 34 hours after trigger was given in dosing differed, depending on the age of patient and the response to stimulation.

2. Agonist GnRH protocol (Long protocol)

The agonist GnRH is given in late luteal section at cycle day 21 of preceding cycle. When the pituitary is down regulate. Transvaginal ultrasound was done to follow the maturation of follicles then added HCG, a minimum 3 follicles turned to be diameter 18 or more then ovum picked up after 34 hours.

3. Antagonist protocol:

On antagonist protocol gonadotrophin (human menopausal gonadotropin, recombinant FSH) started at day 3 of cycle, antagonist regime by used cetrotide (0.25 mg) starting after a week or at the time the dominant follicles reach the with a diameter of 14 mm. Once the follicles were have reached diameter 18 or more, trigger was given to the patient. Ovum pickup was done using transvaginal ultrasound at 34 hours after trigger was given in dosing differed, depending on the age of patient and the response to stimulation.

Ova pick up (OPU): Oocyte collection was performed 34 to 36 hours after trigger given; the procedure of oocyte retrieval was performed under general anesthesia. Under ultrasound guidance, aspiration of follicles done by using thin needle (REPRO Line, Germany) the researchers aspirated the fluid of follicular using gentle suction. The aspirated fluid then sent immediately to laboratory to be tested using a microscopy by embryologisty to detect the oocytes and then the collected oocytes were transferred into culture medium in incubator. After that denudation process was performed by phenol red, the embryologist scored the oocytes using the inverted microscope, also he noted the maturation phases of the oocytes. Meanwhile sperm preparation was done; semenspecimen was obtained after 3-5 days of the sexual abstinence in labeled standard sterile disposable plastic container at the day of pickup. Semen analysis was evaluated using the criteria of WHO pre and post the preparation process of semen. The preparation of semen included rinsing from seminal plasma, leukocytes, and bacteria. this approach can remove prostaglandins that cause uterinecontraction

ICSI: Intracytoplasmic semen injection was done on the whole oocytes which are morphologically intact that thrusted out the polar body number one (metaphase II). The procedure ICSI was as follow, a spermatozoon with single motile was chosen and immobilized thru pushing tail among dish's bottom and the 33 microneedle. After that, the tail-first was aspirated by the cell of the sperm into the pipette injection, a mature an oocyte which was matured was installed thru grabbing the pipette with the body of first polar at the position of six o'clock. The plan of oocyte at 3 o‟‟clock position, the pipette of injection was introduce at 3 o'clock and oolemma rupture was achieved by small suction. The cell of sperm was given into the oocyte accompanied with thee minimal volume of medium and the pipette could be withdrawn cautiously, the procedure conducted in a dish of plastic microinjection including 10-µl droplets of (ferticult TM-HEPES, Belgium) buffered medium covered with mineral oil. After injection steps, oocytes were cultured and washed in micro-droplets wrapped with oil which was light paraffin. They are incubated at 37□C in an wnvironment of PH of 7.2-7.4 5%CO2, and 5%O2. Next is embryo cleavage and fertilization, the oocytes were examined for fertilization next day after ICSI. Oocytes were deemed to be natural fertilized as 2 polar bodies were presented simultaneously accompanied with 2 clear observable pronuclei (two PN).

Intracytoplasmic sperm injection was carried out on all morphologically intact oocytes that have extruded the first polar body (metaphase II). In Intracytoplasmic sperm injection (ICSI) procedure, a single motile spermatozoon is selected and immobilized by pressing its tail between the 33 microneedle and the bottom of the dish. The sperm cell is then aspirated tail-first into the injection pipette, a mature oocyte is fixed by holding pipette with the first polar body at the 6 o‟‟clock position. The plan of oocyte at 3 o‟‟clock position, the injection pipette is introduce at 3 o‟‟clock and rupture of the oolemma is ascertained by slight suction. the oocyte is delivered into the semen cell with minimal volume of medium and the pipette can be outgoing accurately, the steps executed in a plastic microinjection dish involving 10-µl droplets of (ferticult TM-HEPES, Belgium) buffered medium covered with mineral oil. in accordance with injection steps , oocytes cultured and rinsed in micro-droplets

envelopped with paraffin oil. they sprem are brood at 37□C in an weather of 5% O2, 5% CO2 and PH of 7.2-7.4. subsequent is embryo cleavage and fertiliaztion , the oocytes were investigated f next day for fertiliaztion after ICSI. in addation , they are deemed oocytes to be normally fertilized when two polar bodies are presented together with two clearly visible pronuclei (two PN).

Fertilization is assessed sixten–eighteen hours post the ICSI and the cleavage rate was teested two–three days after the retrieval of oocyte. transformation of embryo was conducted after the retrieval of oocyte process on the fifth day at thephase of blastocyst. The subjects of the study were scheduled for embryotransfer (embryos were transferred by using trans-cervical catheter either fresh or freezed embryos (Cook catheter Ob/Gyn, USA) to the uterus under abdominal ultrasound guidance). The pregnancy was assured by measuring the serum HCG concentration 12 days after the transfer proess of embryo. The phase of Luteal was supplied by 50mg progesterone in oily injection IMand lasted till the detection of fetal heartbeat.

Main outcomes measures: In this study were duration of stimulation (days), numbers of (75 IU) gonadotropin ampules , estradiol levels on day of hCG, mature follicles numbers, endometrial thickness, numbers of oocytes retrieved, numbers of total embryos number of embryo transfer, +ve pregnancy test,then u/s to confirm pregnancy and follow up until12 weeksAlso measure Women's serum samples for antithyroid antibodies.

Regarding the thyroid peroxidase antibody, as being <9 IU/ml and for thyroglobulin antibody as being<4IU/ml, the normal values were accepted. The samples of Blood taken from venous blood from your arm IU/ml after collection of the whole blood allow the blood to clot by leaved itundisturb at room temperature this usually taken15-30 minute removed the clot by centrifuged at1000-2000 x g for 10 minute in arefrigerated centrifuge the result supernatant is a serum then send to laboratory to measure value of antithyroid antibody

Results

A total of 81 patients were enrolled in the study. The parameters were summarized in the table (1): -

Table (1): the means of the parameters included in the study.

Parameters	Statistical N=81	
Age(year)	Mean±SD Min-Max	30.22±6.24 19-45
BMI (kg/m2)	Mean±SD Min-Max	27.72±2.49 22-33
Duration of infertility (year)	Mean±SD Min-Max	8.37±3.87 2-19
Basal FSH(IU\L)	Mean±SD Min-Max	4.87±1.83 1.3-9.8
Basal LH(IU\L)	Mean±SD Min-Max	3.40±1.70 0.6-9.1
TSH (u IU\L)	Mean±SD Min-Max	1.93±.86 0.13-3.60
E2(pg\ml)	Mean±SD Min-Max	32.48±11.19 5.8-66.0
Prolactin(ng\ml)	Mean±SD Min-Max	26.94±8.19 11.2-54.0
Total Gn. Dose (IU)	Mean±SD Median Min-Max	2206.48±766.83 1800.00 900-3900

E2 at day of HCG trigger(pg\ml)	Mean±SD Median Min-Max	2457.63±3185.96 2258.00 495-29950.0
Duration of Stimulation (days)	Mean±SD Min-Max	11.01±1.10 9-14
No. of retrieval oocytes	Mean±SD Min-Max	8.43±4.39 1-20
No. of available embryos	Mean±SD Min-Max	3.26±1.00 1-6
No. of transfer embryos	Mean±SD Min-Max	3.07±1.03 1-6
Antithyoglobulin antibody	Mean±SD Median Min-Max	3.36±7.64 0.40 0.10-42.40
Antithyroid peroxidase antibody	Mean±SD Median Min-Max	7.03±13.03 0.90 0.20-44.30

The number and percentage for each subgroup as the following: -

Table (2): Demographic characteristic of studied wamen(The number and percentage)

Variables	Categories	N=81	Percent
Type of infertility	primary. Infertility	65	80.2%
	secondary. Infertility	16	19.8%
Etiology of infertility	Male Factor	37	45.7%
	Female Factor	12	14.8%
	Unexplained	32	39.5%
Protocol	Agonist	69	85.2%
	Antagonist	12	14.8%
Outcome Groups (pregnancy test)	Positive	47	58%
	Negative	34	42%
Fate of Pregnancy N=47	continue pregnancy until12weeks	14	29.7%
	Abortion	33	70.3%
Antithyroid	Positive	22	27.2%
	Negative	59	72.8%

The number and percentage of the patients included in the study. according type of infertility, etiology of infertility, protocol, outcome, fate of pregnancy and state of antithyroid

The patients were divided into two subgroupsantithyroid positive groups(n=22) and antithyroid negative groups(n=59) (table 3): There is no significance difference between duration of infertility, BMI, and age between two groups (antithyroid positive and antithyroid negative group) (P-value >0.05)

There is significant difference in the days of stimulation (P-value 0.047) Fertilization rate (P-value 0.0047), No.of available embryos(P-value >0.003),No. of transfer embryos(P-value >0.05) between two groups.

Table (3): The general characteristic in antithyroid positive and antithyroid negative groups.

Antithyroid groups / Parameters	POSITIVE N=22	NEGATIVE N=59	Sig. P-value
Age (years) (Mean±SD)	31.86±6.49	29.61±6.09	0.150
BMI (kg\m2) (Mean±SD)	28.36±2.08	27.47±2.60	0.153
Duration of infertility (years) (Mean±SD)	8.91±4.29	8.17±3.72	0.448
Duration of Stimulation (days)	11.41±1.26	10.86±1.01	0.047
No. of retrieval oocytes	7.36±3.22	8.83±4.71	0.182
Fertilization rate	42.95±22.38	47.11±20.04	0.0042
No. of available embryos	2.73±1.03	3.46±0.92	0.003
No. of transfer embryos	2.36±1.05	3.34±0.90	<0.001

There were no significant difference in basal hormones level (s.FSH, s.LH, s.TSH, s.prolactin andE2 at day of trigger) between antithyroid positive and antithyroid negative groups (table 4). and there was significant difference in total gonadotrophin dose and basal E2

Statistical analysis appeared there were no essential difference regarding duration of stimulation, number of retrieval oocytes between two groups

In the antithyroid positive group, the fertilization rate, the number of available embryo and the number of transfer embryo were dramatically lower than antithyroid negative group.

Table (4): The basal hormones levels in antithyroid positive and antithyroid negative groups.

Antithyroid groups / Parameters	POSITIVE N=22		NEGATIVE N=59		Sig.
	Mean±SD	MEDAIN	Mean±SD	MEDAIN	
Basal FSH(IU\ML)	5.28±2.16	5.1	4.72±1.69	4.8	0.218
Basal LH(IU\ML)	3.58±1.71	3.0	3.33±1.70	3.1	0.558
TSH(uIU\L)	1.87±1.01	1.7	1.96±0.80	2.0	0.678
E2	28.55±7.03 *	27.0	33.95±12.11	32.0	0.016
Prolactin(ng\ml)	24.75±8.30	25.0	27.75±8.07	25.0	0.143
Total Gn. Dose(IU)	2636.36±827.53 *	2700.0	2046.19±683.30	1800.0	0.002
E2 at day of HCG trigger(pg\ml)	1964.64±779.11	1999.0	2641.46±3695.15	2363.0	0.188

Regarding the outcome in patients in antithyroid positive groups and antithyroid negative groups, the antithyroid negative groups had higher rate of abortion compared to antithyroid positive groups (P value <0.001) while the continuity of pregnancy was higher in the antithyroid negative groups compared to antithyroid positive groups (P value <0.001)(figure 1).

In contrast to that there was no essential difference in the failure to get pregnancy between antithyroid positive groups and antithyroid negative groups (figure 1).

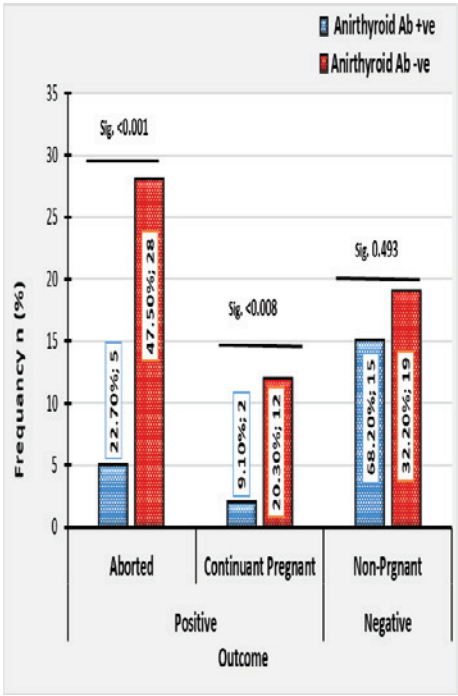

Figure (1): The outcome in patients in antithyroid positive groups and antithyroid negative groups.

Discussion

The present cross section study assessed the relationship between antithyroid antibody and pregnancy outcome inintracytoplasmic sperm insemination (ICSI),hence atotal of eighty one Iraqi women were enrolled in this study of them 22positive antithyroid antibody,59 negative antithyroid antibody were undergone ICSI in Al-sader infertility center the group of the study contained onlyeuthyroid female with no clinical manifested autoimmune illness

It seems unlikely that antithyroid antibody (ATA) decreases the rate of pregnancy (no significant difference regarding failure to get pregnant among antithyroid positive groups and antithyroid negative groups). (p-value 0.493).

Hypothyroidism (subclinical define as upper normal level of TSH with elevated level of free T4) may be associated with negative results such as failure to conceive, pre-eclampsia, perinatal mortality, preterm birth, and miscarriage. Moreover, normal TSH, subclinical hypothyroidism, were reported until two prevent of pregnancies.(10)(11)

The limitations of the current research is the assessment of results of pregnancy after ICSI–embryo transmit cycle and moderately low quantity of patient because narrow time of fallow up.

Confoundingthyroid dysfunction was excluded in this study by including only women with normal TSH concentrations.Relationships between thyroid autoimmunity and unexplainedinfertility, miscarriage, recurrent miscarriage, pretermbirth and maternal post-partu thyroiditis were reported independently from thyroid hormone concentrations(12).

In the our study antithyroid positive group, the rate of fertilization, the available number of embryo and the quantity of transfer embryo were dramatically lower than antithyroid negative group. The receptors thyroid hormone were labelled in human oocyte and can help in the trophoblastic differentiation and stimulation in the function of granulosacell (13). It was recommended that antithyroid antibodies have the responsibility for reducing fertility possible thru restricting the receptors(12). Therefore, the effect of the antibodies on the IVF cycles results were examined. despite the ATA existing is related with low result of IVF.

The antithyroid negative groups had higher rate of abortion compared to antithyroid positive groups (P value <0.001).

ATA presence is connected with the high risk of miscarriage in spontaneous pregnancy (14). Anyway, the rate of miscarriage is not higher in pregnancy of IVF attained in ATA-positive women compared with ATA-negative women in another metaanalysis

Studies found that the stimulation of ovarian might have suppressive impact on the immunity of humoral during the transfer of embryo despite the fact that the number is limited, the study have not negative effect of antithyroid antibodies on the rate of miscarriage in females considered by transfer of ICSI–embryo (15)

Alexander EK et al (2017) in infertile female, preconceptional TSH2.5 mIU/L is not connected with contrary reproductive results; anyway, anti-TPO are connected with miscarriage high risk and reduced possibility of live-birth. This study is disagree with our study. (16)

K. Łukaszuk et al (2015) individuals diagnosed of anti-TPO antibodies regarding the rates of live birth, rates of pregnancy, implantation, fertilization revealed there was no significant differences also, no high danger regarding miscarriage after IVF-ET comparing with the negative for anti-thyroid antibodies compare with our result disagree(17)

Benaglia L et al(2013) the research showed that sick female diagnosed with anti-TPO antibodies regarding rates of live birth, rates of pregnancy implantation, fertilization there was no significant differences, moreover, regarding miscarriage, no high danger was found following IVF-ET comparing with the adverse for anti-thyroid antibodies this study disagree with our study.(18)

R. C. Smallridge et al (2013). Due to the unclear evidence, the study can't suggest screening for the euthyroid treatment or thyroid autoantibodies for patients with positive thyroid autoantibodies at the pregnancy time.(19)

Prummel MF et al (2012) the antithyroid antibody existing is harmful for the results of pregnant after IVF-ET, therefore, duture research to examine suitable treatments to control function of the immune of ATA positive individuals to diagnosed enhance the result of IVF agree with our research.[20]

Grtner,et al(1)(2009) Anti-thyroid antibodies, although it is not connected with thyroid dysfunction, are supposed to lead to a poor results of in vitro fertilization this agree with our study[21]

Limitations of the current research could be described as the pregnancies results assessment of using ICSI–embryo transfer cycles and relatively low number of patient because narrow time of fallow up.

Conclusions

The antithyroid antibody's presence is harmful for the results of pregnancy using ICSI-ET in euthyroid infertile women in the abscence of other autoimmune disease. Hence we recommended further studies with estimated freeT4 in addition toTSH and large sample size and prolong time for follow up further studies should investigate suitable treatments to design immune function of ATA positivepatients to improve IVF result.

No **conflicts of Interest**

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References

1. Marbut M., Hadri D. and Hadi D. The effect of oxidative stress on semen parameters of normal and infertile man in Tikrit city. Tikrit medical journal. 2011; 17 (1): 1-10.
2. American Urological Association Male Subfertility Best Practice Policy Panel. The optimal evaluation of the infertile male: AUA best practice statement 2010. Retrieved January 7, 2016
3. Olooto W E; Adetola A A ;and Abayomi T B. A review of Female Infertility; important etiological factors and management. J. Microbiol. Biotech. Res.,2012;2(3):379-385.
4. American Urological Association Male Subfertility Best Practice Policy Panel. The optimal evaluation of the infertile male: AUA best practice statement 2010. Available from: http://www.auanet.org/guidelines/. accessed on 14th October 2020.
5. YakoubKhalaf. Female infertility. David M. Luesly, Philip N. Baker, Linda Cardozo et al in Obstetrics and Gynaecology an evidence-based text for MRCOG. 3rd edition, 2016; 8 (2): 624-42
6. .Practice Committee of American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. FertilSteril 2012; 98:302.
7. Cousineau TM, Domar AD. Psychological impact of infertility. Best Pract Res ClinObstetGynaecol 2007; 21:293.
8. National Institute for Health and Care Excellence, Fertility: assessment and treatment for people with fertility problems. 2013. Available at: https://pubmed.ncbi.nlm.nih.gov/25340218/. Accessed on 12 Jan 2020
9. Surrey ES, Minjarez DA, Stevens JM, Schoolcraft WB. Effect of myomectomy on the outcome of assisted reproductive technologies. FertilSteril 2005;83:1473–1479.
10. Krassas, G.E., Poppe, K., Glinoer, D., 2010. Thyroid function and human reproductive health. Endocr. Rev. 31, 702–755.
11. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. The Journal of Clinical Endocrinology & Metabolism. 2010 Sep 1;95(9):4227-34.
12. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. The Journal of Clinical Endocrinology & Metabolism. 2011 Jun 1;96(6):E920-4.
13. Zhong YP, Ying Y, Wu HT, Zhou CQ, Xu YW, Wang Q, Li J, Shen XT, Li J. Relationship between antithyroid antibody and pregnancy outcome following in vitro fertilization and embryo transfer. International journal of medical sciences. 2012;9(2):121
14. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH.

Significance of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human reproduction update. 2011 Sep 1;17(5):605-19.

15. Haller K, Sarapik A, Talja I, Salumets A, Uibo R. Controlled ovarian hyperstimulation changes the prevalence of serum autoantibodies in in vitro fertilization patients. American Journal of Reproductive Immunology. 2006 Nov;56(5□6):364-70.
16. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315–89
17. Łukaszuk K, Kunicki M, Kulwikowska P, Liss J, Pastuszek E, Jaszczołt M, et al. The impact of the presence of antithyroid antibodies on pregnancy outcome following intracytoplasmatic sperm injection-ICSI and embryo transfer in women with normal thyreotropine levels. Journal of endocrinological investigation. 2015 Dec 1;38(12):1335-43.
18. Benaglia L, Busnelli A, Somigliana E, Leonardi M, Vannucchi G, De Leo S, et al. Incidence of elevation of serum thyroid-stimulating hormone during controlled ovarian hyperstimulation for in vitro fertilization. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014 Feb 1;173:53-7.
19. Smallridge RC, Glinoer D, Hollowell JG, Brent G. Thyroid function inside and outside of pregnancy: what do we know and what don't we know?. Thyroid. 2005 Jan 1;15(1):54-9.
20. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. Eur J Endocrinol. 2012; 150:751–755
21. Gärtner R. Thyroid disorders during pregnancy. Deutsche medizinische Wochenschrift (1946). 2009 Jan;134(3):83.