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Original Research

The Effect of Prednisolone Treatment on Pregnancy Rates in *in vitro* Fertilization Patients with Positive Thyroid Autoantibodies

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Abstract

Objective: This study aims to investigate the effect of prednisolone treatment on the pregnancy rates of *in vitro* fertilization (IVF) patients with positive thyroid autoantibodies.

Methods: This study was conducted in the IVF unit of Gazi University Faculty of Medicine. It included 158 patients who underwent intracytoplasmic sperm injection using the long-term protocol of a gonadotropin-releasing hormone (GnRH) agonist that was positive for thyroid autoantibodies. Each test's reference value was used as a positive measure of anti-thyroid peroxidase and anti-TG antibodies. On the day of oocyte intake, 44 of 158 patients were started on prednisolone, and the other 114 patients were followed up without medication.

Results: In the control group, pregnancy did not occur in 67.5% of the patients; it was determined that 21.1% were pregnant, 5.3% had biochemical pregnancies, 4.4% had twin pregnancies, 0.9% had triplet pregnancies, and 0.9% had ectopic pregnancies. In the extended prednisolone group, pregnancy did not occur in 56.8% of the patients; it was determined that 36.4% of them were pregnant, 4.5% had twin pregnancies, and 2.3% had biochemical pregnancies. An increase in pregnancy rate was observed in the extended prednisolone group, while a statistically significant difference was found between the groups in terms of the mean values of prednisolone according to pregnancy status ($p<0.05$). It was thus determined that the rate of conception increased in the extended prednisolone group compared to the controls.

Conclusion: There is a strong relationship between the presence of thyroid autoantibodies and poor IVF results. The coadministration of prednisolone can improve the clinical pregnancy rate in women affected by thyroid autoimmunity.

Keywords: Antithyroid autoantibodies, *in vitro* fertilization, prednisolone, pregnancy.

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Introduction

The prevalence of infertile couples varies between 10% and 25%. A total of 45% of the cases are associated with gynecological diseases, including endometriosis and tubal and ovarian dysfunction.[1] On the other hand, thyroid hormones affect reproduction in many ways. For example, it is known that hypothyroidism and hyperthyroidism cause impairment in ovarian functions and negatively affect pregnancy results. Although thyroid disorders have a higher prevalence in the reproductive period,[2,3] antithyroid autoimmunity is more common in infertile women compared to fertile women.[4,5] The prevalence of antithyroid antibodies (ATA) is estimated to be 15–20% in healthy pregnant women, 20–25% in women with recurrent miscarriages, and 20% in women with a history of *in vitro* fertilization (IVF).[6] Autoimmune thyroid disorders are caused by the production of ATA and the presence of an abnormal or damaged thyroid structure.[4] While thyroid dysfunction is known to affect normal ovarian function, its clinical importance in infertility is still controversial. Immunological factors such as autoimmune antibodies play an important role in implantation, placental development, and pregnancy outcomes.[7] Women with positive organ-specific autoantibodies, such as antithyroid and antiovarian antibodies, have a significantly lower pregnancy rate (10.8% vs. 25.0%) and lower rates of miscarriage (40.0% vs. 11.4%).[8,9] A number of retrospective studies have attempted to associate antithyroid autoimmunity with infertility. Although individual studies did not yield convincing results, a significant correlation was found between antithyroid autoimmunity and infertility when data were collected.[10,11] In the following studies, it was reported that there was a significant relationship between pregnancy loss and antithyroid autoimmunity.[12] Similarly, Negro *et al*.[4] showed that after administration of levothyroxine to euthyroid antibody-positive infertile women, the abortion rate decreased from 52% to 33% compared to untreated control patients. However, study results did not reach statistical significance, perhaps due to a small number of cases.

Failure to clarify the pathophysiology of ATA is one reason why adequate treatment strategies have not yet been determined.[4,12] The immunological dysfunction hypothesis on the basis of ATA production suggests that the use of glucocorticoids may be a therapeutic alternative.[13,14] In a study in which levothyroxine, acetylsalicylic acid, and prednisolone were given together, it was shown that ATA-positive women had a better ovarian response to gonadotropins compared to different adjuvant treatments, which resulted in higher rates of pregnancy and implantation.[15]

It has been reported that glucocorticoids can increase the effect of gonadotropins by suppressing androgen levels, thereby improving follicle development and increasing the production of growth factors such as insulin-like growth factor.[16] Glucocorticoids can also modulate cytokine levels involved in the response to ovarian stimulation. Concerning the use of corticosteroids before ovulation induction, there are very little data. In our study, we aimed to investigate the effect of prednisolone treatment on pregnancy rates in IVF patients with positive thyroid autoantibodies.

Methods

This study was conducted in the IVF unit of Gazi University Faculty of Medicine. It included 158 patients who underwent intracytoplasmic sperm injection (ICSI) using the long-term protocol of a gonadotropin-releasing hormone (GnRH) agonist that was positive for thyroid autoantibodies. Each test's reference value was used as a positive measure of anti-thyroid peroxidase and anti-TG antibodies. On the day of oocyte intake, 44 of the 158 patients were started on prednisolone, and the other 114 patients were followed up without medication. Inclusion criteria were (i) under 40 years of age, (ii) a body mass index between 18 and 29 kg/m^2, (iii) a follicle-stimulating hormone (FSH) value below 10 IU/L on the 3rd day of the menstrual cycle, (iv) infertile patients who had been treated for IVF-ET due to male factor, tubal factor or both, (v) patients without other autoimmune diseases, (vi) patients with three or more follicles of 18 mm after ovarian stimulation, and (vii) patients with no history of smoking.

Exclusion criteria were (i) the presence of polycystic ovary syndrome and endometriosis; (ii) a FSH value above 10 IU/L on the 3rd day of the menstrual cycle; (iii) two or less 18 mm follicles at the end of ovarian stimulation, (iv) patients with a concomitant autoimmune disease or patients with anticardiolipin, antinuclear antibodies, and lupus factor, (v) patients who had a total thyroidectomy and patients with a thyroid malignancy, or (vi) patients with a medical history of insulin-dependent diabetes mellitus or peptic ulcers. None of the patients received oral contraceptives during the menstrual cycle before ovarian stimulation. Patients receiving IVF treatment in our reproductive medicine center are routinely screened for their thyroid function and the presence of ATA on their first visit. Thyroid autoimmunity was defined as when the presence of TPO and/or TG antibody blood concentrations was higher than the upper limit of the reference range. Patients with different thyroid pathologies were excluded from the study protocol.

The reference values for thyroid gland function used in this study were as follows: TSH, 0.27–4.2 mIU/L; FT4, 12.0–22.0

pmol/L; and FT3, 2.8–7.1 pmol/L. Electrochemiluminescence immunoassay (Beckman DX1800) was used to test for antithyroid autoantibodies, and a positive result was defined as TG-Ab >115 IU/mL, TPO-Ab >34 IU/mL.

All selected antithyroid antibody-positive patients were randomized into treatment and control groups by a computer-generated list on the day the oocyte was taken. In the treatment group, prednisolone was started from the day the oocyte was taken and continued until the pregnancy test day. In the case of a positive test, this regimen was continued until the 8th week. After treatment, biochemical, ectopic, single, twin, and triplet pregnancies were determined. All patients were informed about any medical treatment, including the ICSI procedure and prednisolone application, and their consent was obtained.

IVF Protocol

Women who had ovarian stimulation based on the use of the GnRH agonist long-term protocol that was positive for the thyroid autoantibody in the IVF protocol received 0.2 mg of buserelin acetate twice a day for pituitary downregulation on the 21st day of their menstrual cycle. Insemination was performed with ICSI,[17] and fertilization was evaluated 16–18 h after ICSI. In these cases, the zygote morphology was evaluated according to criteria based on the evaluation of the number and distribution of nucleolar precursor bodies in the pronucleus. Embryos were observed on the second and 3rd days, and the embryo criteria used for transfer in the study were as follows: (i) Embryos containing 2PN and (ii) embryo class evaluation determined as ≥3.5 degrees/5 cells. Quality embryos had the following characteristics: (i) Containing 2PN and (ii) blastomere count ≥7 cells, (iii) symmetrical in shape and fracture monitored, and (iv) an embryo fragment ratio of 10%.[18]

Sperm-injected oocytes, zygotes, and embryos were incubated in G-FERT, equilibrating with 6% CO2 at 37°C. Embryos were transferred 3 days after ICSI using the embryo transfer (ET) kit. Supportive therapy was given with natural micronized progesterone administered intramuscularly.

Statistical Analysis

All statistical analyses in the study were done using SPSS 15.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as numbers and percentages. In terms of categorical variables, comparisons between the groups were made with Pearson's Chi-square test, and the differences between the groups in terms of continuous variables were analyzed using the Student's *t*-test. The results were evaluated within a 95% confidence interval, and $p<0.05$ was considered statistically significant.

Results

A total of 44 of the 158 patients participating in the study who were positive for thyroid autoantibodies were given prednisolone, and the treatment of the other 114 patients, the control group, was completed without IV prednisolone. The mean age of the control group was 31.10±5.61 years; it was 30.02±5.09 years in the extended group using prednisolone (Table 1).

In the control group, pregnancy did not occur in 67.5% of the patients, and it was determined that 21.1% were pregnant, 5.3% had biochemical pregnancies, 4.4% had twin pregnancies, 0.9% had triplet pregnancies, and 0.9% had ectopic pregnancies. In the extended prednisolone group, pregnancy did not occur in 56.8%, and it was determined that 36.4% of them were pregnant, 4.5% had twin pregnancies, and 2.3% had biochemical pregnancies. An increase in pregnancy rate was observed in the extended prednisolone group (Table 2).

When the cause of infertility was examined in the control group, it was determined that 53.5% had unexplained infertility and that 33.3% had male factor. In the extended prednisolone group, 33.2% had male factor and 44.1% had unexplained infertility (Table 3). When the anti-T and anti-TPO values after the transfer were examined in the groups participating in the study, the mean post-transfer anti-T value was found to be 246.83±467.11 in the control group and 86.85±88.24 in the extended prednisolone group (Table 1). The post-transfer anti-T value was determined to be significantly higher in the control group ($p=0.031$).

The mean post-transfer anti-TPO value was 797.00±1399.15 in the control group and 539.26±907.77 in the extended prednisolone group. The anti-TPO value was determined to be high in the control group, and no statistically significant difference was found between the groups in terms of post-transfer anti-TPO values ($P>0.05$). There was also no statistically significant difference between the groups in terms of basal hormonal values before ovarian stimulation, the amount of oocytes collected after stimulation, the number of killer embryos obtained from oocytes collected, the mean number of embryos transferred, and the quality distribution (Table 4). However, a statistically significant difference was found between the groups in terms of the mean values of prednisolone according to pregnancy status ($p<0.05$). It was determined that the rate of conception increased in the extended prednisolone group compared to the control group (Table 2).

Discussion

In the previous studies conducted on infertility, thyroid function disorders have not been adequately researched

Table 1. Distribution of laboratory values according to the groups

	Control	Prednisolone extended group	p-value
Anti-T before transfer	226.34±450.10	115.25±121.52	0.109
Anti-TPO before transfer	544.04±1137.69	658.95±1060.76	0.568
Anti-T after transfer	246.83±467.11	86.85±88.24	0.031*
Anti-TPO after transfer	797.00±1399.15	539.26±907.77	0.291
Female age	31.10±5.61	30.02±5.09	0.957
Male age	33.71±5.61	33.77±5.31	0.889
Duration of infertility	5.87±5.00	6.00±4.79	0.698
Number of IUI trials	1.92±1.81	1.79±1.83	0.698
Number of IVF trials	1.64±0.96	1.50±0.82	0.394

*p<0.05, anti-T: Anti-thyroglobulin; anti-TPO: Anti-thyroid peroxidase; IUI: Intrauterine insemination; IVF: In vitro fertilization.

Table 2. Distribution of the relationship between the groups in terms of pregnancy situations

	Control		Extended prednisolone group		Total	
	n	%	*n*	%	*n*	%
Biochemical pregnancy	6	5.3	1	2.3	7	4.4
Ectopic pregnancy	1	0.9	0	0	1	0.6
Pregnancy is not present	77	67.5	25	56.8	102	64.6
Single pregnancy	24	21.1	16	36.4	40	25.3
Twin pregnancy	5	4.4	2	4.5	7	4.4
Triplet pregnancy	1	0.9	0	0.0	1	0.6
Total	114	100.0	44	100.0	158	100.0

as a cause of infertility.[1,2] In a study conducted to evaluate whether the presence of antithyroid autoantibodies in the euthyroid female patients had negative results on IVF-ET, the mean serum TG concentrations were found to be significantly higher compared to the control group.[13]

In our study, when the control group's causes of infertility were examined, it was determined that 53.5% had unexplained infertility and that 33.3% had male factor. In the extended prednisolone group, 33.2% had male factor and 44.1% had unexplained infertility. There was no significant difference between the groups in terms of the causes of infertility. In a study conducted by Bussen *et al*.,[13] no evidence was found for a causally significant relationship between the participating groups in terms of infertility and thyroid antibodies. Similarly, in this study, the incidence of thyroid antibodies significantly increased in euthyroid women with recurrent IVF failure. Although this cause-effect relationship is an important issue and has not been fully elucidated, this finding shows that the presence of thyroid antibodies is associated with significantly poor IVF results, even in euthyroid female patients. Because these antibodies appear to be separate and independent markers for reproductive failure, their better explanation provides an opportunity to identify women at risk for an adverse outcome in the IVF-ET program. Therefore, it is emphasized that a determination of thyroid antibodies is important during the evaluation of women with recurrent IVF failure.[13]

The exact mechanism underlying the relationship between ATA and pregnancy development remains the subject of debate. Many studies have shown that a thyroid with a reduced functional reserve cannot compensate for the increased hormone requirement observed in early pregnancy.[14] A randomized study evaluating the effect of levothyroxine treatment on pregnancy outcomes in euthyroid women showed a significant (up to 52%) relative risk reduction in abortions. However, it remains to be confirmed whether thyroid hormone supplementation can be routinely recommended during ATA positive pregnancy[14] In addition, ATA can slow hCG increase and prevent its

Table 3. General characteristics of the groups

	Control group		Prednisolone extended group		*P*-value
	n	%	*n*	%	
Medicine history					
Levathron	30	26.3	14	31.8	0.201
None	84	73.7	29	65.9	
Methimazole	0	0.0	1	2.3	
Thyroid operation					
Nodule ap	1	.9	1	2.3	0.646
Thyroidectomy	1	.9	0	0.0	
None	112	98.2	43	97.7	
Cause of infertility					
Anovulation	2	1.8	2	4.5	0.149
Male factor	38	33.3	19	33.2	
Tubal factor	8	7.0	3	6.8	
Tubal factor + male factor	5	4.4	5	11.4	
Unexplained	61	53.5	15	44.1	
Male factor					
Azoospermia	5	4.4	0	0.0	0.028

Table 4. Clinical and biological results of ovarian stimulation for ICSI of the groups participating in the study

	Control	Prednisolone extended group	*P*-value
Basic E2 (pg/mL)	26.59±12.95	36.70±16.20	0.15
Basic FSH (mIU/mL)	6.06±1.40	6.57±1.48	0.19
Basic LH (mIU/mL)	6.97±5.64	6.14±3.54	0.52
TSH (mIU/L)	2.29±0.90	2.20±0.88	0.62
Antral follicle count	15.6±4.9	17.4±7.5	0.18
Obtain oocytes count	8.31±3.41	9.11±4.62	0.31
No. of high-quality embryos	6.4±3.8	5.5±4.7	0.547
Transferred embryos	2.3±0.7	2.1±0.5	0.37
Good quality embryos	0.8±0.5	1.0±0.7	0.47

*p<0.05, E2: Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone.

effect on the corpus luteum, which causes a decrease in progesterone and estrogen production.[15] It was assumed that ATA can bind to the surface of the oocyte and hence interfere with fertilization and embryo development.[16] Furthermore, thyroid hormones can directly affect trophoblast proliferation, survival and invasion, as well as angiogenic growth factor. The frequent presence of ATA in several non-thyroid autoimmune diseases supports an immune dysfunction hypothesis that these autoantibodies can be considered to be markers of unidentified autoimmune disorders.[13,17]

It has also been shown that thyroid antibodies can represent a marker for increased T-cell activation and that toxic cytokine production by active T-lymphocytes can modify cytokine networks in the local placental-decidual environment.[18] This study revealed consistent evidence for glucocorticoid therapy. It can correct autoimmune and inflammatory processes behind ATA production and reduce circulation levels that cause adverse effects on pregnancy development.[19] In fact, Taniguchi[20] reported a significant increase in the rate of implantations with glucocorticoids and clinical pregnancies in their study, even for women with antinuclear antibodies.

Kim *et al*.[9] showed that prednisolone and immunotherapy increased pregnancy rates in patients with unexplained infertility who underwent ovulation induction with intrauterine insemination. However, their study group patients were not tested for the presence of autoantibodies. Recently, intravenous immunoglobulin immunotherapy has been shown to have positive effects on IVF outcomes in patients with positive ATA. Given the possible side effects of these treatment programs, further research is needed to

understand the immunopathological mechanism of these organ-specific antibodies in relation to early implantation failure.[13]

A treatment that tries to modulate the immune system of patients with ATA, intravenous immunoglobulin, had a positive effect on IVF results, but concerns over possible side effects were raised. Revelli *et al*.[15] showed that ATA-positive patients who took a combination of levothyroxine, acetylsalicylic acid, and prednisolone had higher pregnancy and implantation rates than untreated patients. In this study, prednisolone was administered at a dose of 10 mg from the 1st day of ovarian stimulation to the hCG test day, except for 5 days following ET at 30 mg daily. Later, Turi *et al*.,[21] in their study evaluating the role of glucocorticoid prophylactic treatment, demonstrated a significantly higher pregnancy rate in the treated patients compared to the placebo group for 4 weeks before intrauterine fertilization. Similarly, Litwicka *et al*.[22] started glucocorticoid administration on the day of oocyte intake using a very low dose. While glucocorticoids may show a number of positive effects that improve early pregnancy formation in the first trimester of pregnancy, administration in late pregnancy was only until the 8th week as it may play a role in obstetric complications. Litwicka *et al*.[22] reported that general and clinical pregnancies and live birth rates were significantly higher in ATA-positive patients who received prednisolone supplements compared to ATA-positive untreated patients (60.0% vs. 30.0%, p=0.02; 46.6% vs. 16.6, p=0.03; and 46.6% vs. 20.0%, p=0.05). In another study, a significantly higher pregnancy rate (33.3%) was reported in the group treated with prednisolone in comparison to the placebo group (8.4%) as a result of steroid treatment in infertile women with ovarian stimulation and IUI antithyroid autoimmunity.[23] In our study, an increase in the rate of conception was observed in the prednisolone group compared to the control group ($p<0.05$).

The use of prophylactic steroids during pregnancy is still controversial. Some authors recommend using prednisolone throughout pregnancy to prevent complications of diseases such as systemic lupus erythematosus,[24] but others disagree.[25] Although high doses of corticosteroids have been shown to cause cleft palate and low birth weight in experimental animal models, there is no evidence that prednisolone or methylprednisolone is teratogenic in humans.[26] In a large retrospective study of women with asthma treated with corticosteroids during pregnancy, no increase in teratogenicity was reported compared to the general population.[27]

In the Turin's *et al*. series,[21] pregnancy was reported to be continued in two out of 24 women with antithyroid autoimmunity treated with prednisolone, in one out of 24 untreated women with antithyroid autoimmunity, and in one out of 50 women without antithyroid autoimmunity. In this regard, it has been observed that there is no long-term advantage to treatment with prednisolone in terms of good pregnancy outcomes, but we can consider that the autoimmune background of infertile women may continue to affect their pregnancy status.

Ovarian hyperstimulation may increase thyroid binding protein, which can lead to a decrease in the free thyroid hormones.[22] According to these results, it seems convincing enough to make it imperative to screen for thyroid function and thyroid autoimmunity before assisted reproductive techniques, especially in women with recurrent IVF failure, habitual abortion, and autoimmune disease. Although more research is required in larger study populations to draw a definitive conclusion, our preliminary experience suggests that prednisolone cotherapy may increase the pregnancy rate of IVF therapy in women affected by thyroid autoimmunity.

Conclusion

There is a strong relationship between the presence of thyroid autoantibodies and low IVF rates. Coadministration of prednisolone may improve the clinical pregnancy rate in women affected by thyroid autoimmunity.

Disclosures

Ethics Committee Approval: The Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital provided the ethics committee approval for this study (02.04.2019-2329).

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Conflicts of Interest: None declared.

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