SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

(PhD)

Impact of endocrine disorders on IVF outcomes

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The PhD Defense takes place at the Lecture Hall of Department of Obstetrics and Gynecology, University of Debrecen
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1.Introduction

The rate of infertility is increasing worldwide. Healthcare providers must manage difficulties in reproduction caused by endocrinological changes or disorders, delayed childbearing, negative environmental effects, as well as changes in lifestyle and nutrition. The prevalence of infertility has significantly increased over the past decades, affecting 8–12% of couples of reproductive ages. The primary indications for in vitro fertilization (IVF) were anatomical disorders of the female reproductive tract (occlusion of the fallopian tubes and endometriosis). Poor semen quality is the sole cause of infertility in 20% of couples and contributes to fertility issues in another 20%. With the development of the intracytoplasmic sperm injection effective treatment for male infertility has become widely available. Diminished ovarian reserve (DOR) and increased genetic damage of the oocyte pool are also significant indications for in vitro fertilization (IVF) resulting from delayed childbearing. As for the females, DOR and chronic anovulation can be the most frequent indications for IVF. Increasing incidence of endocrine diseases with age may have further negative effects on fertilization rate. In the case of ovulatory dysfunction, ovulation induction treatment usually restores fertility. Among the endocrine disorders causing ovulatory dysfunction in patients enrolled to assisted reproduction programs, marked prevalence of thyroid disease, polycystic ovarian syndrome (PCOS), diminished ovarian reserve (DOR) and hyperprolactinaemia have been observed. Except for DOR, endocrine disorders are not the leading indications for ART, but their treatment prior to ART is necessary to achieve optimal results.

2. Aims of the study

1. We examined the incidence of different endocrinological abnormalities and their distribution in association with the primary indications of IVF in women participating in the IVF program.

2. The subjects were divided into two groups: patients with symptoms of an endocrinological abnormality (study group) and patients without endocrinological changes (control group). The groups were then compared. IVF treatment was started after the necessary therapeutic endocrinological corrections. The following pathologies were detected in the study group: PCOS, hypothyroidism without TAI, TAI, DOR and hyperprolactinaemia. We also examined the patients' age, BMI, laboratory parameters: anti-Mullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), thyroid stimulating hormone (TSH), fT3, fT4, thyroid peroxidase antibody (TPOAb),), thyroglobulin antibody (TGAb), antisperm antibody, total testosterone (TT), dehydroepiandrostendione-sulfat (DHEAS), androstendione, 17-hydroxi-progesterone (17- OHP), sexual hormone binding globulin (SHBG), and glucose and insulin levels at 0, 60, 120 minutes, retrieved oocyte count, the number of cycles required for achieving pregnancy and the clinical pregnancy rate. We examined the efficiency of IVF treatment in the individual endocrinological groups and we repeated it after data correction for age. We examined what effect the endocrinological diseases, optimized as possible, had on IVF treatment after therapy.

3. Further examinations were conducted on the effect of antithyroid antibodies on reproduction. We analyzed the fertility parameters of infertile women enrolled in the study who had been suffering from Hashimoto's thyroiditis, subclinical or clinical hypothyroidism and receiving thyroxine replacement. Patients in the study group received thyroxine replacement and were euthyreoid at IVF treatment. Before the IVF cycles endocrinological parameters were uniformly assessed: thyroid function and antibodies, reproductive hormones (AMH, FSH, LH, E2, PRL, testosterone, DHEAS, 17-OHP, AD) and OGTT (0-60-120 min glucose and insulin). Following descriptive comparison of laboratory parameters, age adjusted analyses of retrived oocytas, fertilization rate (FR), clinical pregnancy rate (CPR), miscarriage rate (MR) and live birth rate (LBR) were performed.

3. Patients and Methods

We conducted a prospective analysis of 231 consecutively enrolled women (mean age: 34 years, range: 21–44 years) who underwent IVF treatment at our center. A thorough endocrinological investigation of each patient requesting IVF treatment in this cohort was performed. The patients were considered overweight with a body mass index (BMI) over 25, and obese in case of BMI of more than 30. Serum cholesterol and triglyceride were recorded. As part of the infertility work-up, regardless of IVF indication, we tested the following endocrinological parameters: serum levels of FSH, LH, E2, PRL supplemented with macro-PRL if PRL was elevated, TSH, fT3, fT4, TPOAb, TGAb, spermium antibody, TT, fasting glucose and insulin and AMH on days 2–4 of the menstrual cycle.

The diagnosis of PCOS was established according to the Rotterdam criteria, with consideration to new additions by different associations.

The Bologna criteria served as a basis to define the levels of hormones (FSH, LH and E2) for diagnosing diminished ovarian reserve (DOR), together with AMH and AFC. Hyperprolactinaemia was defined as elevated PRL after having taken away the macroPRL. If PRL exceeded 100 ng/ ml, magnetic resonance imaging (MRI) of the sella was performed.

Oral glucose tolerance test (OGTT; 0, 60 and 120-min measurements of glucose and insulin) was performed to reveal insulin resistance (IR). MRI evaluation of the sella and an investigation of the pituitary gland's hormone secretion (FSH, LH, TSH, ACTH, GH and PRL) served as the basis of making the differential diagnosis of central hypogonadotropic hypogonadism. Hyperandrogenic symptoms and elevated 17-OHP levels prompted us to carry out an adrenocorticotropic hormone (ACTH) stimulation test for verification of congenital adrenal hyperplasia (CAH). The number of oocytes retrieved (NOR), clinical pregnancy rate and the number of cycles required to achieve pregnancy. We also evaluated the outcomes of IVF treatments in each group after age adjustment.

During IVF treatment, patients were monitored and managed according to our standardized clinical protocol. The stimulation protocol and recombinant follicle-stimulating hormone dose were determined on an individual basis according to characteristics of the patient's basic hormone levels and AMH level. Patients underwent transvaginal ultrasonography and hormonal monitoring during hyperstimulation three times. When the leading follicle reached 18 mm, 250 μg of recombinant human chorionic gonadotropin (hCG) was administered subcutaneously. Oocyte retrieval was performed transvaginally 36 h after hCG injection.

Embryo transfer was performed. Patients received vaginal, oral and subcutaneous progesterone supplementation therapy along with low-molecular-weight heparin (LMWH) therapy. On day 12-14, serum hCG levels were measured.

The research was approved by the Regional and Institutional Research Ethics Committee of the Clinical Centre of the University of Debrecen (DE RKEB/IKEB 5684–2021). The design, analysis, data interpretation, drafting and revisions followed the Helsinki Declaration and strengthened the reporting of observational studies in epidemiology (STROBE) statement, available through the enhancement of the quality and transparency of health research (EQUATOR) network Reproductive Sciences 1 3 (www.equator-network.org). Each patient enrolled in this study signed an informed consent form for all procedures and to allow data and biological sample collection and analysis for research purposes. No remuneration was offered for study participation.

Statistical Analysis:

For descriptive statistics, we used absolute and relative frequencies for categorical variables and mean and standard deviation for continuous variables. Associations between categorical outcomes and other variables were assessed using Fisher's exact tests in unadjusted analysis and logistic regression in analysis adjusted for confounders. Patient groups were compared in terms of continuous outcomes using Student's t tests (if distributional assumptions were satisfied) or Wilcoxon's rank sum tests (otherwise). The significance criterion was set at the conventional $p<0.05$. Data handling and analysis were performed using version 15 of the Stata statistical package (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Age-adjusted comparisons of TAI positive and negative subjects in terms of pregnancy, miscarriage, live birth (binary categorical) were performed using logistic and ordered logistic multiple regression, respectively. Ordinary least-squares multiple linear regression was used to analyze the continuous outcomes of fertilization rate and oocyte count in the same relation. Additional explanatory terms included age squared or an interaction term between age (used as a continuous variable) and the TAI group identifier if such additions substantially improved model fit. All available variables were exploratively assessed as potential confounders to adjust for. The models for pregnancy, miscarriage, and live birth were thus adjusted for natural log-transformed FSH, while the model for egg cell count was adjusted for log-transformed AMH.

Estimates were expressed as odds ratios (categorical outcomes) or additive differences (continuous outcomes) in TAI positives versus negatives, with 95% confidence intervals and p-values, either as a single estimate or a series of age-specific estimates.

4. Results:

4.1. Main indications of the IVF treatment

Of the 231 patients enrolled in this study, the main indications for IVF treatment in order of frequency were as follows: male factor (n=70; 30.3%), DOR (n=55; 23.8%), tubal factor (n=43; 18.6%), chronic anovulation (n=32; 13.8%), unexplained idiopathic infertility (n=18; 7.7%) and endometriosis (n=13; 5.6%).

4.2. Endocrinological disorders as main or coindications for IVF

Endocrinological diseases were identified in 161 patients (69.7%, average age: 35 years, range: 19–45), while 70 patients (30.3%, average age: 32 years, range 21–44) had no underlying endocrine disorder. The main indication for IVF treatment was anovulatory dysfunction in 87 cases (DOR n=55, PCOS n=29, hypogonadotropic hypogonadism n=2 and congenital adrenal hyperplasia n=1), while in 74 cases endocrinological disease appeared as a co-factor.

4.3. Prevalence and association of endocrinological disorders in IVF

The breakdown of underlying endocrinological disorders among IVF patients was as follows: thyroid disorders (n = 75/231, 32.5%), DOR (n = 55/213, 23.8%), IR (n = 52/231, 22.5%), PCOS (n = 35/231, 15.2%), hyperprolactinaemia (n = 31/231, 13.4%), overweight or obesity (n = 83/231, 35.93 %), hypogonadotropic hypogonadism (n = 2/231, 0.8%) and congenital adrenal hyperplasia (n=1/231, 0.2%).

Thyroid disorders represented almost half (46.6%) of the endocrine-positive patients. Among patients with thyroid disease, the most frequent disorder was Hashimoto's thyroiditis (52 cases, 69.3%).

DOR was diagnosed in 55 women, which accounted for 23.8% of all patients enrolled in the study and for 34.16% of patients with endocrinopathy. Concomitant endocrine comorbidity was found in 39 cases (70.9%) of patients with DOR assessed for polyglandular endocrinopathy. Most frequent disorders were thyroid disease (n=21, 38.18%), Hashimoto's thyroiditis (n=14, 25.45%), IR (n=10, 18.18%) and hyperprolactinaemia (n=6, 10.9%). Only 29.09% of the DOR patients had no co-existing endocrine disorder.

PCOS was detected in 15.15% (n=35) of patients overall, which accounted for 21.7% of the endocrine-positive group. In 14 cases (40%) thyroid disease was diagnosed as a co-morbidity for PCOS, of which Hashimoto's thyroiditis was present in 7 cases (20%). IR was detected in 68.6%, overweight (BMI over 25) in 54% and obesity (BMI over 30) in 17.1%. Hyperprolactinaemia was diagnosed in 31 patients (13.4% of all patients and 19.3% of endocrine-positive patients), in whom hypophyseal microadenoma was diagnosed in 4 cases (12.9%) with MRI. PCOS and IR co-morbidities were both present in 6 cases (19.4%). In 19.4% of the cases with hyperprolactinaemia, drug use (anti-epileptic therapy: 1; antidepressant therapy: 2 and antihypertensive therapy: 3) was the underlying reason. There was no specific reason of hyperprolactinaemia identified in 48.38% of the cases. Thyroid disease in 45%, hypothyreosis in 19.35 %, Hashimoto's thyroiditis in 25.8%. PCOS and DOR in 19.4% were found as comorbidities in this group.

4.4. Comparison of infertile women with and without endocrinopathies

Average age, BMI and serum triglyceride level were significantly higher in the endocrine positive group. There were no significant differences in serum levels of LH, E2, prolactin, TSH, fT3, fT4, TT, DHEAS, androstendione, 17-OHP and SHBG between the endocrine negative and endocrine positive patients. Assessing carbohydrate metabolism, baseline glucose level at baseline insulin level and 120-min glucose level and 120-min insulin level were significantly higher in endocrine-positive group. No significant difference was observed in vitamin D levels between the two groups. There was no significant difference between the two groups for the number of cycles performed. Average number of retrieved oocytes was significantly lower in endocrine-positive group, as compared with the control group. Pregnancy rate (61.43% vs. 34.16%; p=0.003) was also significantly lower in the endocrine-positive group, compared with the control group, and this difference (p=0.0151) was observed in age-corrected rates, as well.

4.5. Comparison of patients with PCOS and women without endocrinopathies

Average age was significantly lower in the PCOS group, as compared to the control. BMI value, serum triglyceride level and AMH level were significantly higher in PCOS group. FSH level was significantly lower, and the LH level was significantly higher is PCOS group. However, a significant difference was not found in levels of E2, TSH, fT3, fT4, DHEAS and

androstendione. Total testosterone and 17-OHP were significantly higher in PCOS group. Serum SHBG level was significantly lower in the endocrine-positive group. Serum baseline glucose level and baseline insulin level, 120-min glucose level and 120-min insulin level were significantly higher in study group, but there was no significant difference between glucose and insulin levels at 60 min.

There was no significant difference between the two groups for the number of cycles performed and the average number of retrieved oocytes in the PCOS group, compared with controls. Pregnancy rate (61.43% vs. 40.0%; p=0.061) was lower in the endocrine-positive group, but this difference was not significant. There was no significant difference in pregnancy rate. However, the difference in age correlated rate was significant (p=0.0027) for those under 35 years old. In the subgroup of over 35, the age correlated difference was not significant (p=0.26).

4.6. Comparison of women with hypothyroidism without TAI and women without endocrinopathies

The average age was significantly higher and AMH level was significantly lower in patients with hypothyroidism without TAI, as compared to the control group. There was no significant difference in average, BMI and in levels of FSH, LH, E2, prolactin, androgen levels, SHBG, TSH, free thyroid-hormones, vitamin-D, serum glucose and insulin between the two groups. Furthermore, there was no significant difference between the two groups in the number of cycles performed. However, the number of retrieved oocytes was significantly lower in the hypothyroidism group. The pregnancy rate was also lower in the hypothyroidism group (61.43% vs. 33.33%; p=0.83), and this non-significant difference could also be observed in age-corrected rates as well (p=0.13).

4.7. Comparison of women with Hashimoto's thyroiditis and women without endocrinopathies

The average age was significantly higher and AMH level was significantly lower in the TAI positive group. There was no significant difference in BMI of the two groups. There were also no differences observed in start-of-cycle FSH, LH, E2, prolactin, androgen hormones, SHBG, vitamin D, TSH and fT3 levels. The fT4 level was higher within the normal range in the TAI-

positive group. Serum baseline glucose, baseline insulin level and 120-min glucose level, and 120-min insulin level were significantly higher in the study group, but there were no differences between glucose and insulin levels at 60 min. There was no significant difference between the two groups for the number of cycles performed. However, the number of retrieved oocytes was significantly lower in the TAI group. Pregnancy rate was significantly lower in the endocrine-positive group, compared to the control group (61.43% vs. 29.41%; p=0.001), and this difference was significant in age-corrected rates as well (p=0.0095).

4.8. Comparison of patients with DOR and women without endocrinopathies

Average age and BMI were higher in DOR patients, while AMH level was lower. The FSH level was higher in the DOR group. No differences were found in levels of LH, E2, prolactin, TSH, FT3, FT4, androgen hormones and SHBG. However, serum baseline glucose level and 120-min glucose level were higher in the DOR group. With no difference in the number of cycles performed, the average number of retrieved oocytes was much less in the DOR group, compared to the endocrine negative patients. Pregnancy rate (61.43% vs.21.82%; p<0.001) was significantly lower in the DOR group, compared with controls, and this difference remained significant (p=0.0109) in age-corrected rates as well.

4.9. Comparison of patients with hyperprolactinaemia and women without endocrinopathies

There were no differences in average age and BMI. AMH level was lower, and prolactin level was slightly higher in patients with hyperprolactinaemia, both within the normal range. Further, no differences were observed in start-of-cycle FSH, LH, E2, TSH, fT3, fT4, androgen hormones, SHBG, vitamin-D and serum glucose and insulin levels. The number of cycles was significantly higher in the hyperprolactinaemia group without difference in the average number of oocytes retrieved. Pregnancy rate (61.43% vs. 29.03%; p=0.005) was significantly lower, and this difference remained significant (p=0.0072) in age-corrected cohort rates as well.

4.10. Hashimoto's thyroiditis negatively influences ICSI outcome in euthyroid women on T4 substitution therapy

The number of oocytes retrieved was significantly lower in the TAI positive group, however this difference did not persist after adjusting for age and AMH.

The fertilization rate (FR) was similar between the two groups (62.9% vs. 69.12%; p=0.12) but was significantly higher in the age adjusted analysis of TAI negative subjects younger than 35 at each cut-off point. Fertilization rates at age 25 (p=0.0061), age 27.5 (p= 0.0052), age 30 (p=0.0064) and age 32.5 (p=0.023) were significantly lower in TAI positive compared to TAI negative group. No statistically significant differences, however, were found in subjects aged 35 years (p=0.21), 37,5 years (p=0.82), 40 years (p=0.21), or 42.5 years (p=0.21) between the TAI positive and negative treatment groups.

The clinical pregnancy rate (CPR) (69.56% vs. 36.04%; p<0.001) was significantly higher in the TAI negative group, and this difference (p<0.001) was consistently observed in age-and FSH adjusted rates as well.

The miscarriage rate (MR) was significantly higher (12.5 % vs. 35.48%; p=0.024) and the live birth rate (LBR) was significantly lower (60.86% vs. 23.25 %; p<0.001) in the TAI positive treatment group. After adjusting for age and FSH, the MR remained significantly higher (p=0.035) and the LBR remained significantly lower (p<0.001) in the TAI positive cohort.

5. Discussion

1. Endocrine diseases are often present in patients participating in IVF programs with a higher prevalence at elevated age. ART outcome is adversely affected by various underlying concomitant endocrinopathies regardless of optimal treatment and despite proper correction of laboratory parameters. Endocrinological disease has a basic effect on the success of IVF treatment. Therefore, the correction of an endocrinological change is a must prior to the start of IVF treatment.
2. Our results show that despite providing complex treatment, we cannot achieve equally high pregnancy rates in the groups of patients with endocrinological diseases, during the IVF program. Regarding the above fact and to achieve success, patients should be enrolled in the IVF program as soon as possible, paying special attention to DOR, autoimmune thyroiditis and hyperprolactinaemia, and, also, considering the age of the patients.
3. We conclude based on our results that TAI has a major adverse impact on reproductive health. TAI positive patients diagnosed with subclinical or overt hypothyroidism receiving treatment with thyroxine hormone replacement have lower reproductive parameters in the ICSI program. Although TAI positive patients are older and have lower ovarian reserve resulting in a significantly lower number of retrieved oocytes during IVF, after age adjustment the difference disappeared suggesting that age is the major contributing factor. In contrast, although the presence of TAI did not make difference in the overall fertilization rate, after age adjustment we conclude that Hashimoto's thyroiditis negatively impacts fertilization rates in women younger than 35. With increased age the adverse impact of age for the fertilization rate exceeds that of TAI as a contributing factor. A lower clinical pregnancy rate and lower live birth rate can be expected in TAI positive patients, while the higher miscarriage rate can be explained with the higher average age of TAI patients. Normal thyroid function is essential for the success of assisted reproductive techniques (ART). Since thyroid autoimmunity fundamentally affects the outcome of ICSI, it is recommended add autoantibody titers to laboratory tests for assessing thyroid function and screening for autoimmunity in subfertile women. These procedures are especially recommended in cases of subfertile patients having multiple miscarriages or multiple unsuccessful IVF programs (RIF-recurrent implantation failure) in their history. Autoimmune thyroid disease is only considered as a partial indication for in vitro fertilization programs. Based on our results, if IVF treatment is recommended for patients

with Hashimoto thyroiditis, beyond the impact of age the TAI also must be taken into account as a contributing factor of diminished reproductive indicators.

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Registry number: DEENK/14/2024.PL
Subject: PhD Publication List

Candidate: Tünde Herman
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Herman, T.**, Török, P., Laganà, A. S., Chiantera, V., Venezia, R., Jakab, A.: Hashimoto's thyroiditis negatively influences ICSI outcome in euthyroid women on T4 substitution therapy; a retrospective study.
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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