CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

PhD THESIS SUMMARY

PhD supervisor:
PROF. UNIV. DR. BRĂTILĂ ELVIRA

PhD student:
NADĂ ELENA-SILVIA

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The impact of endometriosis on ovarian function in assisted human reproduction

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CONTENTS

Introduction

Endometriosis is a chronic benign disease characterized by the presence of endometrial tissue, glands and stroma, outside the uterine cavity [1]. Globally, the frequency of this disease is approximately 10% in the case of reproductive age women, reaching up to 30-50% in patients who complain of chronic pelvic pain or infertility [1].

Specialized studies demonstrate a delay in establishing the diagnosis up to 8-11 years from the onset of symptoms [1,2]. Ovarian function declines with age, especially after 35 years, and the delay in diagnosis and the subsequent need for surgery and recovery period translate clinically into decreased pregnancy rates.

The motivation underlying the choice of the doctoral research topic consists in the fact that endometriosis is one of the main causes of infertility at the present time, and this category of patients registers the lowest pregnancy rate compared to infertility of other etiologies. In the last decade, endometriosis has become a public health problem, a fact proven by the increased number of patients with this pathology who turn to infertility specialists and assisted human reproduction centers and thus constitute a current topic of interest to the medical community.

Patients with endometriosis frequently turn to in vitro fertilization, most of the time this being their only chance to get pregnant. The results of ovarian stimulation and pregnancy rates in this category of patients turned out to be inferior compared to in vitro fertilization in patients with other causes of infertility [3,4].

The doctoral thesis is structured into two parts. The first part includes the latest data on epidemiology, risk factors, methods of diagnosis and treatment, the impact of endometriosis on fertility and the management of endometriosis-related infertility. The special part includes the methodology, the analysis of the profile of the patient with endometriosis and infertility, and the core of the doctoral research focuses on the analysis of in vitro fertilization procedures performed in this category of patients. I analyzed the influence of the ovarian stimulation protocols, the gonadotropins, the ovulation triggering mechanism and the type of embryo transfer (fresh or frozen) on the clinical pregnancy rate compared to the results obtained in patients with tubal factor infertility.

I. GENERAL PART

1. Epidemiology and pathophysiology of endometriosis

Over 100 years have passed since the publication of the article "Perforating hemorrhagic (chocolate) cysts of the ovary" by John A. Sampson, article published in Archives of Surgery [5]. Sampson was the one who observed a history of infertility in patients with endometriosis, in whom no other cause of sterility could be detected [5].

The incidence and prevalence of endometriosis are difficult to estimate mainly due to underdiagnosis, but also due to the fact that patients are sometimes asymptomatic. In most studies, the incidence of endometriosis is estimated between 6-10% among patients of reproductive age and can reach up to 50% in the case of patients with infertility [6].

The etiopathogenesis of endometriosis, considered to be a multifactorial process, could be partially explained by several theories, some of them elaborated almost a century ago [7]. The etiopathogenic theories of endometriosis are: the retrograde menstruation theory, the hematogenous or lymphatic dissemination theory, the metaplasia of the coelomic epithelium, the induction theory and stem cells.

The profile of the patient with endometriosis includes early menarche, increased menstrual period length, short menstrual cycle length, nulliparity or low parity associated with short lactation period, advanced age at first childbirth, late menopause, low body mass index (BMI) and Caucasian race [8–10].

2. The diagnosis of endometriosis

The symptomatology in endometriosis is centered on pain, dysmenorrhea, dyspareunia, chronic pelvic pain associated most of the time with infertility, but also with irritable bowel syndrome, fatigue, interstitial cystitis, alternating constipation-diarrhea and the impairment of sexual life [11,12]. It is known from clinical practice that the severity of the symptoms does not correlate with the stage of the disease according to the classification of the American Society for Reproductive Medicine (ASRM - American Society for Reproductive Medicine) or the #ENZIAN classification, nor with the number or location of the lesions [13–15].

Transvaginal ultrasound is the first-line imaging investigation, which allows evaluating the mobility of pelvic structures, identifying painful areas and the presence of adhesions [16].

The endometrioma has the appearance of a well-demarcated, thick-walled cyst with a homogeneous ground-glass-like content without papillary projections [17]. A particular case is the appearance of "kissing ovaries" in which the ovaries are glued to the back of the uterus, a highly suggestive sign for the presence of deep endometriosis [16].

The assessment of the mobility of the uterus is performed by the "sliding sign" [16]. The negative "sliding sign", translated by the lack of free movement of the rectum in relation to the cervix and vagina, the rectosigmoid in relation to the posterior uterine wall, the ovaries in relation to the uterus or the uterus in relation to the urinary bladder, indicates the presence of adhesions and deep endometriosis [16] .

The European Society of Urogenital Radiology recommends magnetic resonance imaging as a secondary investigation in the diagnosis of endometriosis. MRI allows mapping the extension of endometriotic lesions, the presence of adhesions, compression, alteration of pelvic anatomy and the degree of infiltration of the intestinal wall [18].

The 2022 ESHRE guideline no longer recommends laparoscopy as the "gold standard" in the diagnosis of all patients, but only in cases where imaging methods (ultrasound and MRI) do not reveal the presence of the disease or empirical treatment has not been effective [19].

The benefit of laparoscopy in endometriosis lies in the direct visualization of the pelvis, with a good detection rate of adhesions, superficial implants, endometriomas and deep endometriosis lesions, followed by surgical cure and histological confirmation of the diagnosis [20]. Currently, diagnostic laparoscopy is indicated in patients with pelvic pain in whom the imaging is negative, in case the empirical pain treatment is ineffective and in patients who cannot benefit from hormonal treatment due to the desire to procreate [19].

3. Endometriosis-related infertility

The ovarian reserve refers to the number and quality of ovarian follicles, assessing a woman's reproductive potential [21,22]. The tests currently used to estimate ovarian reserve correlate with the number of follicles, but not with their quality [21]. Age is the best predictor of both oocyte quantity and quality [21].

AMH is the main biomarker currently used to assess the ovarian reserve [23,24]. AMH is an early marker of diminished ovarian reserve and, but which does not correlate with pregnancy rates [23–25]. A value < 1ng/mL is associated with a poor response to stimulation, low oocyte quality and low pregnancy rate [26,27].

The endometriotic ovarian cyst has a negative impact on the ovarian reserve even in non-operated patients [28]. The toxic content of the endometrioma creates a real cascade of events starting from the increase in oxidative stress markers and implicitly the accentuation of the production of reactive oxygen species that cause the increase in the degree of fibrosis in the ovarian tissue and finally the loss of the ovarian stroma with the entire cohort of follicles from this level [29,30]. Endometrioma produces a decrease in the ovarian reserve and surgical intervention accentuates this decrease, but also the absence of the surgical gesture with simple periodic monitoring will ultimately lead to the impairment of ovarian function [31,32].

The role of superficial endometriosis in infertility is debated by numerous studies and the results are contradictory due to the fact that this clinical entity is frequently diagnosed alongside the other clinical forms and rarely encountered as a singular location.

Studies have shown that patients with endometriosis have a higher volume of peritoneal fluid [33]. The peritoneal fluid has a direct toxic effect on the embryo regardless of the stage of the disease, the effect being related to the concentration of interleukins [34,35]. Decreased cleavage rate, increased deoxyribonucleic acid (DNA) fragmentation, and a higher percentage of developmental arrest have been observed in embryos from patients with endometriosis [34,35].

Deep endometriosis consists in the extension of lesions beyond 5 mm in the depth of the peritoneal serosa [36]. In particular, deep endometriosis alters the pelvic anatomy through the presence of adhesions and fibrosis, mechanically prevents ovulation, and affects the ability to capture and transport the oocyte by the fallopian tubes [36,37].

Endometriosis is a chronic disease that requires long-term monitoring and treatment [19]. The management of this pathology involves a multidisciplinary team to give the patient realistic expectations, starting even with lifestyle modification to be able to adapt to live with and control her pathology.

Surgical management of endometrioma involves cystectomy, ablation or a combination of these techniques, simple aspiration and coagulation are not recommended due to the high recurrence rate [38]. Cystectomy is associated with low recurrence rates, but has the disadvantage of decreasing ovarian reserve through inadvertent excision of healthy tissue and adjacent thermal injury [39].

Guidelines recommend excision or ablation of superficial endometriosis lesions, especially in patients with painful symptoms [40]. Laparoscopic treatment of superficial

peritoneal endometriosis and adhesiolysis increase the spontaneous pregnancy rate compared to diagnostic laparoscopy [41].

Deep endometriosis represents an advanced form of this pathology, associated with extensive fibrosis and involvement of retroperitoneal structures. Performing surgery requires advanced understanding of pelvic anatomy to identify anatomical landmarks and planes of dissection in a pelvis with profoundly distorted anatomy. [42].

In vitro fertilization is indicated in patients with endometriosis and infertility in the following situations: low ovarian reserve, impaired tubal permeability, the association of the male infertility factor, low EFI score (<5), failure to achieve a pregnancy naturally [19].

Ovarian stimulation in patients with endometriosis resulted in the collection of fewer mature oocytes and fewer total oocytes, but with implantation rates and pregnancy rates similar to controls [43]. The pregnancy rate is lower in this category of patients compared to patients with infertility of unknown cause (36% versus 55%) [44].

II. ORIGINAL PART – PERSONAL CONTRIBUTION

4. Study hypothesis and general objectives

The doctoral thesis aims to evaluate the management of patients with endometriosis and infertility who have performed in vitro fertilization in order to identify the factors influencing the pregnancy rate.

The objectives of the doctoral study are:

1. Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with endometriosis and infertility compared to patients with tubal factor infertility

2. Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with a history of ovarian surgery for endometrioma

I consider that the data highlighted by the doctoral research can have a favorable impact for the management of infertility associated with endometriosis through:

- Choosing the ovarian stimulation protocol
- Choosing the type of gonadotropins
- Identifying the factors that influence the pregnancy rate

5. General research methodology

The doctoral research includes two retrospective, observational studies. The research was carried out over a period of five years, between January 2019 and December 2023 in the Assisted Human Reproduction Department of the "Prof Dr Panait Sîrbu" Obstetrics-Gynecology Clinical Hospital, Bucharest. The study included patients with a history of minimally invasive surgery for endometriosis who underwent at least one in vitro fertilization procedure to achieve pregnancy.

The objectives, inclusion and exclusion criteria, research methodology, the number of included patients and statistical analysis were summarized as follows:

1. Objectives:

- Study 1 – Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with endometriosis and infertility compared to patients with tubal factor infertility in terms of the type of ovarian stimulation protocol, the types of gonadotropins used, the number of oocytes retrieved, the number of embryos obtained, the pregnancy rates in the two groups and the analysis of the factors that influenced the clinical pregnancy rate
- Study 2 – Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with a history of ovarian surgery for endometrioma in terms of the type of ovarian stimulation protocol, types of gonadotropins used, number of oocytes retrieved, number of embryos obtained, pregnancy rates and analysis of the factors that influenced the clinical pregnancy rate

2. The inclusion criteria of patients in the doctoral research studies were:

- Study 1 - the study group made up of patients with a history of minimally invasive surgery for endometriosis diagnosed with infertility and the control group made up of patients with tubal factor infertility documented by hysterosalpingography or after tubal patency testing by minimally invasive surgery
- Study 2 – patients with a history of minimally invasive surgery for endometrioma diagnosed with infertility
- Age between 18-42 years
- Patients who have undergone at least one in vitro fertilization procedure between January 2019 and December 2023
- The surgical intervention was performed in the Obstetrics-Gynecology Clinical Hospital "Prof Dr Panait Sîrbu" and in other hospitals in the country

3. The exclusion criteria of patients from the doctoral research studies were:

- Patients with associated pathologies (cardiovascular, hepatic, renal) with major impact on the reproductive function
- Patients who performed in vitro fertilization procedure with donated oocytes, donated embryos
- Patients whose partner has been diagnosed with teratospermia (normal forms of sperm < 4%)
- Incomplete data

Statistical analysis was performed using IBM SPSS Statistics 25 and the obtained data were illustrated using Microsoft Office Excel/Word 2021.

6. Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with endometriosis compared with patients with tubal factor infertility

6.1 Introduction

The objective of this study is to evaluate the results of ovarian stimulation in patients with endometriosis and infertility compared to patients with tubal factor infertility. The clinical characteristics of the patients, the influence of the ovarian stimulation protocol, the influence of the gonadotropins used, the number of oocytes and embryos obtained on the clinical pregnancy rate were analyzed.

6.2 Patients and methods

I performed a retrospective, observational study which included patients with a history of minimally invasive surgery for endometriosis who performed at least one in vitro fertilization procedure in order to achieve pregnancy. The results of the ovarian stimulation and embryo transfer procedure were compared with a group of patients with tubal factor infertility. According to the inclusion and exclusion criteria presented in chapter 5, 175 patients who performed 298 ovarian stimulation and embryo transfer cycles were included in the endometriosis group and in the tubal pathology group were included 189 patients who performed 303 ovarian stimulation and embryo transfer cycles.

6.3 Results

Following the statistical analysis I obtained the following data.

Table VI.1. Characteristics of the patients

Parameter (Mean ± SD, Median – IQR, Min-Max / No., %)	Endometriosis (no=175)	Tubal factor infertility (no=189)
Age	34.64 ± 3.82, 35 (32-38), 24-42	33.89 ± 4.08, 34 (31-37), 24-42
BMI	22.97 ± 3.58, 22.26 (20.83-24.5), 16.18-35.15	23.7 ± 3.44, 23.04 (21.32-25.79), 16.89-36.19
Menarche	13 ± 1.4, 13 (12-14), 9-17	13.25 ± 1.32, 14 (12-14), 10-17
Regular menstrual cycle	162 (92.6%)	177 (93.7%)
Dysmenorrhea	131 (74.9%)	105 (55.6%)
Dyspareunia	51 (29.1%)	13 (6.9%)
Chronic pelvic pain	64 (36.6%)	53 (28%)
Primary infertility	125 (71.4%)	76 (40.2%)
Miscarriage	48 (27.4%)	79 (41.8%)
Ectopic pregnancy	8 (4.6%)	62 (32.8%)
Smoking	52 (29.7%)	65 (34.4%)
Low-risk thrombophilia	32 (18.3%)	18 (9.5%)
Male factor infertility	73 (41.7%)	61 (32.3%)
AMH	1.63 ± 1.09, 1.47 (0.77-2.27), 0.05-4.98	2.55 ± 1.67, 2.05 (1.4-3.3), 0.31-10.17
FSH	8.08 ± 2.23, 7.72 (6.56-9.12), 3.31-14.93	7.23 ± 2, 6.8 (5.77-8.17), 4.1-14.69
History of ovarian surgery	115 (65.7%)	25 (13.2%)

The data in **Table VI.2** represents the comparison of the AMH values of the patients in the study groups

Table VI.2. Comparison of AMH values of the patients in the study groups

Group/AMH	Mean ± SD	Median (IQR)	Average rank	p*
Endometriosis (p<0.001)**	1.63 ± 1.09	1.47 (0.77-2.27)	150.45	**<0.001**
Tubal factor infertility (p<0.001)**	2.55 ± 1.67	2.05 (1.4-3.3)	212.17	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VI.3** represents the distribution of ovarian stimulation protocols and the medication used in the two analyzed groups.

Table VI.3. Distribution of ovarian stimulation protocol and the medication used

Parameter (Nr., %)	**Endometriosis (no=298)**	**Tubal factor infertility (no=303)**
Ovarian stimulation protocol		
SP – short antagonist protocol	263 (88.3%)	285 (94.1%)
LP – long agonist protocol	30 (10.1%)	13 (4.3%)
Luteal phase stimulation	5 (1.7%)	5 (1.7%)
Types of gonadotropins		
Menotropin	253 (84.90%)	251 (82.8%)
Follitropin alfa	167 (56%)	151 (49.8%)
Follitropin beta	40 (13.40%)	49 (16.2.1%)
Follitropin delta	38 (12.80%)	67 (22.1%)
Corifollitropin alfa	28 (9.40%)	25 (8.3%)
Letrozole	28 (9.40%)	22 (7.3%)
Follitropin alfa +lutropin alfa	22 (7.40%)	13 (4.3%)
IVF procedure		
Standard IVF	84 (29.4%)	105 (35.1%)
ICSI – intracytoplamatic sperm injection	198 (69.2%)	194 (64.9%)
Fertilization failure	4 (1.4%)	0

The data in **Table VI.4** shows the number of mature oocytes retrieved in the groups.

Table VI.4. Comparison of the number of mature oocytes retrieved in the study groups

Group/ No. mature oocytes	**Mean ± SD**	**Median (IQR)**	**Average rank**	**p***
Tubal factor infertility (p<0.001)**	8.41 ± 5.02	7 (5-11)	359.07	**<0.001**
Endometriosis (p<0.001)**	5.16 ± 3.14	5 (3-7)	241.95	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VI.5** represents the comparison of the number of blastocysts obtained in the study groups.

Table VI.5. Comparison of the number of blastocysts obtained in the study groups

Group/ No. blastocysts	**Mean ± SD**	**Median (IQR)**	**Average rank**	**p***
Tubal factor infertility (p<0.001)**	4.41 ± 3.15	4 (2-6)	345.14	**<0.001**
Endometriosis (p<0.001)**	2.38 ± 2.17	2 (0-4)	233.60	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Figure 6.1** represents the clinical pregnancy rates in the two groups. In the endometriosis group – 298 cases, the clinical pregnancy rate was 23.8%. In procedures that resulted in mature oocytes – 286 cases, the clinical pregnancy rate (cumulative) was 24.8%. In the tubal factor infertility group– 303 cases, the clinical pregnancy rate was 53.4%. In procedures that resulted in mature oocytes – 299 cases, the clinical pregnancy rate (cumulative) was 54.2%.

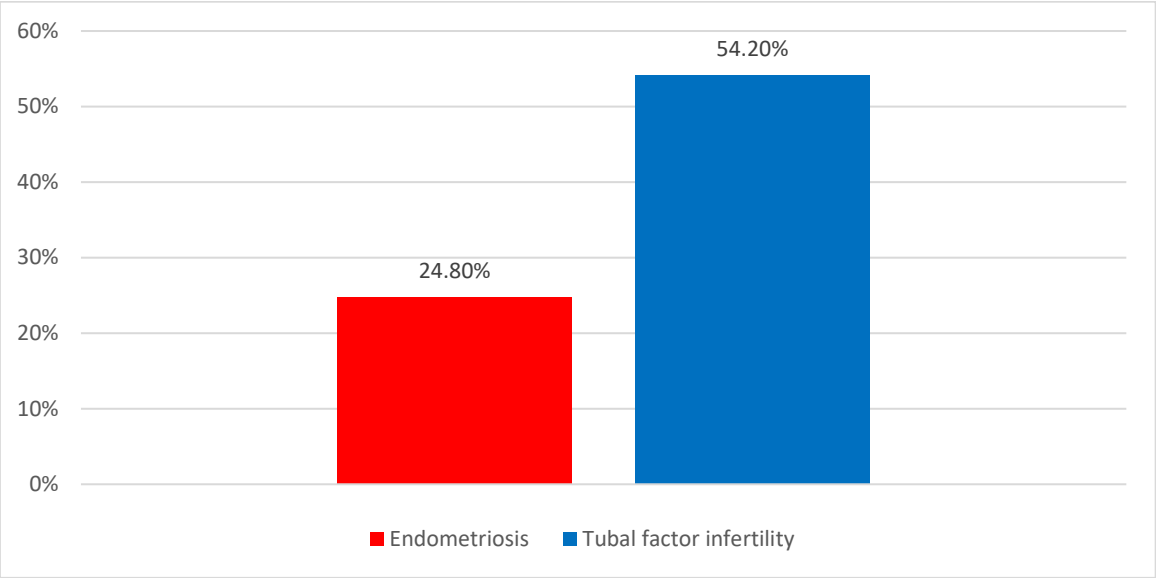

Figure 6.1. Clinical pregnancy rate

The data in **Table VI.6** shows the comparison of age related to the clinical pregnancy. The distribution of age values is non-parametric in the group of non-pregnant patients **(p=0.001)**. The differences in the age values between the groups are statistically significant **(p<0.001)** - patients who were pregnant had a significantly lower age compared to the non-pregnant patients in both groups.

Table VI.6. Comparison of age related to clinical pregnancy

Clinical pregnancy/Age	Mean ± SD	Median (IQR)	Average rank	p*
Endometriosis				
Absent (p=0.001**)	35.45 ± 3.9	36 (32.75-39)	99.18	**<0.001**
Present (p=0.131****)**	33.39 ± 3.35	33 (31-35)	70.83	
Tubal factor infertility				
Absent (p=0.051**)	35.72 ± 3.36	36 (33-39)	119.30	**<0.001**
Present (p=0.023)**	33.28 ± 4.13	33 (30-36)	86.96	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VI.7** represents the comparison of AMH values related to the clinical pregnancy rate. The distribution of AMH values is non-parametric in both **(p<0.05)**. The differences in AMH values between groups are statistically significant (**p=0.002** in the group with endometriosis and **p=0.003** in the tubal factor infertility group) - patients who were not pregnant had significantly lower AMH compared to patients who had a pregnancy.

Table VI.7. Comparison of AMH values related to the clinical pregnancy

Clinical pregnancy /AMH	Mean ± SD	Median (IQR)	Average rank	p*
Endometriosis				
Absent (p<0.001**)	1.46 ± 1.09	1.24 (0.59-1.98)	78.34	**0.002**
Present (p=0.041)**	1.91 ± 1.04	1.78 (1.2-2.54)	102.84	
Tubal factor infertility				
Absent (p<0.001**)	2.07 ± 1.72	1.61 (1.15-2.33)	74.39	**0.003**
Present (p<0.001)**	2.7 ± 1.63	2.21 (1.48-3.5)	101.82	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VI.8** represents the distribution of cases related to the existence of clinical pregnancy (cumulative pregnancy rate). The differences between the groups are significant **(p<0.001)**, thus noting that the patients who were pregnant were more frequently with tubal pathology than with endometriosis (54.2% vs. 24.8%), while the non-pregnant patients were more frequent with endometriosis than with tubal pathology (75.2% vs. 45.8%).

Table VI.8. Clinical pregnancy in the study groups (cumulative pregnancy rate)

Group / Clinical pregnancy	Endometriosis		Tubal factor infertility		p*
	No.	Percentage	No.	Percentage	
No pregnancy	215	75.2%	137	45.8%	**<0.001**
Pregnancy	71	24.8%	162	54.2%	

*Fisher's Exact Test

The data in **Table VI.9** represents the distribution of ovarian stimulation medication used in patients with endometriosis related to the clinical pregnancy. Differences between groups are not significant according to **Fisher tests (p>0.05)** for most of the analyzed gonadotropins, except for testing the association of clinical pregnancy with the administration of **corifollitropin alfa** where it was observed that the procedures where **corifollitropin alfa** was administered were significantly more frequently associated with the presence of clinical pregnancy (16.9% vs. 7%).

Table VI.9. Distribution of gonadotropins related to clinical pregnancy in patients with endometriosis

Follitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	95	41.9%	36	50.7%	0.218
With medication	132	58.1%	35	49.3%	
Follitropin alfa + lutropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	209	92.1%	67	94.4%	0.613
With medication	18	7.9%	4	5.6%	
Corifollitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	211	93%	59	83.1%	**0.019**
With medication	16	7%	12	16.9%	
Follitropin beta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	200	88.1%	58	81.7%	0.168
With medication	27	11.9%	13	18.3%	
Follitropin delta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	201	88.5%	59	83.1%	0.228
With medication	26	11.5%	12	16.9%	
Letrozole / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	202	89%	68	95.8%	0.104
With medication	25	11%	3	4.2%	
Menotropin / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	34	15%	11	15.5%	1.000
With medication	193	85%	60	84.5%	

*Fisher's Exact Test

The data in **Table VI.10** represents the distribution of ovarian stimulation medication used in patients with tubal factor infertility related to the clinical pregnancy. The differences between groups are not significant according to **Fisher tests (p>0.05)** for most of the analyzed gonadotropins, except for testing the association of clinical pregnancy with the administration of **follitropin alfa + lutropin alfa**, where it was observed that procedures in which **follitropin alfa + lutropin alfa** was used were significantly more frequently associated with the presence of clinical pregnancy (6.8% vs. 1.4%).

Table VI.10. Distribution of gonadotropins related to clinical pregnancy in patients with tubal factor infertility

Follitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	65	46.1%	87	53.7%	0.206
With medication	76	53.9%	75	46.3%	
Follitropin alfa + lutropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	139	98.6%	151	93.2%	**0.024**
With medication	2	1.4%	11	6.8%	
Corifollitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	128	90.8%	150	92.6%	0.677
With medication	13	9.2%	12	7.4%	
Follitropin beta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	114	80.9%	140	86.4%	0.212
With medication	27	19.1%	22	13.6%	
Follitropin delta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	116	82.3%	120	74.1%	0.097
With medication	25	17.7%	42	25.9%	
Letrozole / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	131	92.9%	150	92.6%	1.000
With medication	10	7.1%	12	7.4%	
Menotropin / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	21	14.9%	31	19.1%	0.362
With medication	120	85.1%	131	80.9%	

*Fisher's Exact Test

The data in **Table VI.11** represents the comparison of the number of mature oocytes in relation to the clinical pregnancy. The differences in the number of mature oocytes between groups are statistically significant **(p<0.001)**, a higher number of mature oocytes being observed in cases with pregnancy in both groups.

Table VI.11. Number of mature oocytes retrieved in relation to clinical pregnancy

Pregnancy/ No. mature oocytes	Mean ± SD	Median (IQR)	Average rank	p*
Endometriosis				
Absent (p<0.001)**	4.73 ± 3.13	4 (2-7)	137.10	**<0.001**
Present (p=0.007)**	6.52 ± 2.8	6 (4-9)	189.15	
Tubal factor infertility				
Absent (p<0.001)**	7.28 ± 4.66	6 (4-10)	132.90	**<0.001**
Present (p<0.001)**	9.39 ± 5.13	8 (5-13)	168.62	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VI.12** represents the distribution of the type of embryo transfer performed in patients with endometriosis in relation to the clinical pregnancy. Differences between groups are significant **(p<0.001)**, and **Z-tests with Bonferroni correction** show that procedures using fresh (22.5% vs. 12.6%) or frozen blastocysts (64.8% vs. 48.4%) were more frequently associated with pregnancy.

Table VI.12. Distribution of the type of embryo transfer in patients with endometriosis in relation to the clinical pregnancy

Embryo transfer / Clinical pregnancy	Absent		Present		p*
	No.	Percentage	No.	Percentage	
Fresh – Day 3 embryo	**45**	**23.7%**	**7**	**9.9%**	**<0.001**
Fresh – Blastocyst	**24**	**12.6%**	**16**	**22.5%**	
Frozen – Day 3 embryo	**29**	**15.3%**	**2**	**2.8%**	
Frozen - Blastocyst	**92**	**48.4%**	**46**	**64.8%**	

*Fisher's Exact Test

The data in **Table VI.13** represents the correlation between the AMH value and the number of mature oocytes collected. The correlation between the AMH value and the number of mature oocytes is significant and moderately positive (**p<0.001, R= 0.522** in the group with endometriosis and **p<0.001, R= 0.591** in the tubal pathology group) showing that in the cases of patients who had a high AMH value there was significantly more often a high number of mature oocytes and vice versa.

Table VI.13. Correlation between AMH value and number of mature oocytes

Correlation AMH (p<0.001**) x No. mature oocytes (p<0.001**)	p*
Endometriosis	**<0.001, R=0.522**
Tubal factor infertility	**<0.001, R=0.591**

*Spearman's rho Correlation Coefficient, **Shapiro-Wilk

The data in **Table VI.14** represents the logistic regression models in the prediction of clinical pregnancy using the number of mature oocytes and treatment with corifollitropin alfa for procedures performed in patients with endometriosis. In both univariable and multivariable models, both corifollitropin alfa treatment and mature oocyte count values were significant predictors of clinical pregnancy.

Table VI.14. Logistic regression models in clinical pregnancy prediction using the number of mature oocyte and corifollitropin alfa treatment in patients with endometriosis

Model/Parameter	**Univariable**		**Multivariable**	
	OR (95% C.I.)	**p**	**OR (95% C.I.)**	**p**
No. mature oocyes	1.195 (1.096-1.303)	**<0.001**	1.197 (1.097-1.306)	**<0.001**
Corifollitropin alfa	2.682 (1.203-5.983)	**0.016**	2.713 (1.186-6.207)	**0.018**

6.4 Discussion

The difference between the mean AMH value was statistically significant ($p<0.001$) between the two groups (1.63 ± 1.09 ng/mL in patients with endometriosis and 2.55 ± 1.67 ng/mL in patients with tubal pathology). The age over 35 years and the low ovarian reserve recorded in patients with endometriosis contributed significantly to the low pregnancy rate compared to the control group (24.8% and 54.2%). In both groups, age and AMH statistically significantly influenced the clinical pregnancy rate, with a positive correlation between AMH value and the number of mature oocytes and embryos, respectively.

The most used ovarian stimulation protocol was the short antagonist in both groups. The type of ovarian stimulation protocol did not influence the clinical pregnancy rate in any group. The most common gonadotropin used for ovarian stimulation was menotropin in both groups (84.9% and 82.8%), but taking into account that it was administered only in combination with other gonadotropins, and not as a single stimulation medication.

Endometriosis is frequently associated with a low ovarian reserve, translated both by a decreased number of retrieved oocytes and also by their impaired quality, which leads to a decrease in the fertilization rate or to low quality embryos and subsequently with reduced chances of implantation [45–47]. These results were also obtained in the present study where the results of ovarian stimulation in terms of total number of oocytes, mature oocytes, total number of embryos obtained and blastocysts were significantly lower ($p<0.001$) in the endometriosis group compared to those obtained in the tubal factor infertility group.

Regarding the gonadotropins, it is important to choose a certain medication according to the patient's characteristics, as this is almost the only element that can be modified in the ovarian stimulation protocol. In the doctoral study, most of the gonadotropins administered

to patients with endometriosis did not influence the clinical pregnancy rate, with the exception of corifollitropin alfa (p=0.019) which was more frequently associated with clinical pregnancy (16.9% versus 7%). In logistic regression models predicting clinical pregnancy, corifollitropin alfa treatment significantly (p=0.016) increased the odds of clinical pregnancy by 2,682-fold. I obtained a different result in the tubal pathology group. In these patients, the administration of follitropin alfa + lutropin alfa significantly increased (p=0.024) the clinical pregnancy rate (6.8% versus 1.4%). Some studies have identified a higher number of mature oocytes and embryos with the use of corifollitropin alfa compared with other recombinant FSH, but differences in pregnancy rates are conflicting [48–52].

6.5 Conclusions

1. Most patients in the endometriosis group were over 35 years old, but the difference between the mean age between the groups was not statistically significant (p=0.077).
2. The mean AMH value was 1.63 ± 1.09 ng/mL in the endometriosis group and 2.55 ± 1.67 ng/mL in the tubal pathology group (p<0.001).
3. Clinical pregnancy rate (cumulative) was 24.8% in the endometriosis group and 54.2% in the tubal pathology group (p<0.001).
4. Age influenced the clinical pregnancy rate in both groups, patients under 35 years had a higher pregnancy rate compared to those over 35 years (p<0.001).
5. The ovarian stimulation protocol did not influence the clinical pregnancy rate
6. Patients with endometriosis had a significantly (p<0.001) lower number of mature oocytes retrieved following ovarian stimulation compared to patients with tubal factor infertility (5.16 ± 3.14 versus 8.41 ± 5.02).
7. Patients with endometriosis had a significantly (p<0.001) lower number of blastocysts than patients with tubal factor infertility (2.38 ± 2.17 versus 4.41 ± 3.15).
8. Treatment with corifollitropin alfa in patients with endometriosis statistically significantly increased (p=0.016) the chance of clinical pregnancy by 2,682 times.
9. Treatment with follitropin alfa + lutropin alfa in patients with tubal pathology significantly increased (p=0.037) the chance of clinical pregnancy by 5,063 times.
10. The number of oocytes retrieved and the number of embryos obtained influenced the clinical pregnancy rate in both groups.
11. The AMH value positively correlates with the number of mature oocytes retrieved, with the number of embryos obtained and with the clinical pregnancy rate.
12. Most pregnancies were obtained after the embryo transfer of a frozen blastocyst in both groups.

7. Analysis of the ovarian response to controlled ovarian stimulation during in vitro fertilization procedures in patients with a history of ovarian surgery for endometrioma

7.1 Introduction

The objective of this study is the analysis of ovarian stimulation protocols and their results performed in patients with a history of ovarian surgery for endometrioma with the aim of identifying factors that are associated with an increased clinical pregnancy rate.

7.2 Patients and methods

I performed a retrospective, observational study which included patients diagnosed with endometriosis and with a history of minimally invasive surgery for endometrioma who performed at least one in vitro fertilization procedure in order to achieve pregnancy. The study was carried out in the Assisted Human Reproduction Department of the "Prof Dr Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, over a period of five years, between January 2019 and December 2023. According to the inclusion and exclusion criteria presented in chapter 5, the study included 115 patients with a history of ovarian surgery for endometrioma who underwent 193 cycles of ovarian stimulation and embryo transfer.

7.3 Results

Following the statistical analysis I obtained the following data. The clinical characteristics of the studied group can be found in **Table VII.1 and Figure 7.1**.

Table VII.1. Clinical characteristics of the patients

Parameter (Mean ± SD, Median – IQR, Min-Max / No., %)	**Endometrioma (no=115)**
Age	34.53 ± 3.86, 35 (32-38), 24-42
BMI	22.95 ± 3.55, 22.2 (20.83-24.62), 16.18-34.29
Menarche	13.1 ± 1.51, 13 (12-14), 9-17
Regular menstrual cycle	106 (92.2%)
Dysmenorrhea	84 (73%)
Dyspareunia	31 (27%)
Chronic pelvic pain	40 (34.8%)
Primary infertility	87 (75.7%)

Miscarriage	26 (22.6%)
Ectopic pregnancy	5 (4.3%)
Smoking	37 (32.2%)
AMH	1.41 ± 1.06, 1.22 (0.58-2.02) 0.05-4.98
FSH	8.38 ± 2.39, 7.96 (6.75-9.51), 4.1-14.93

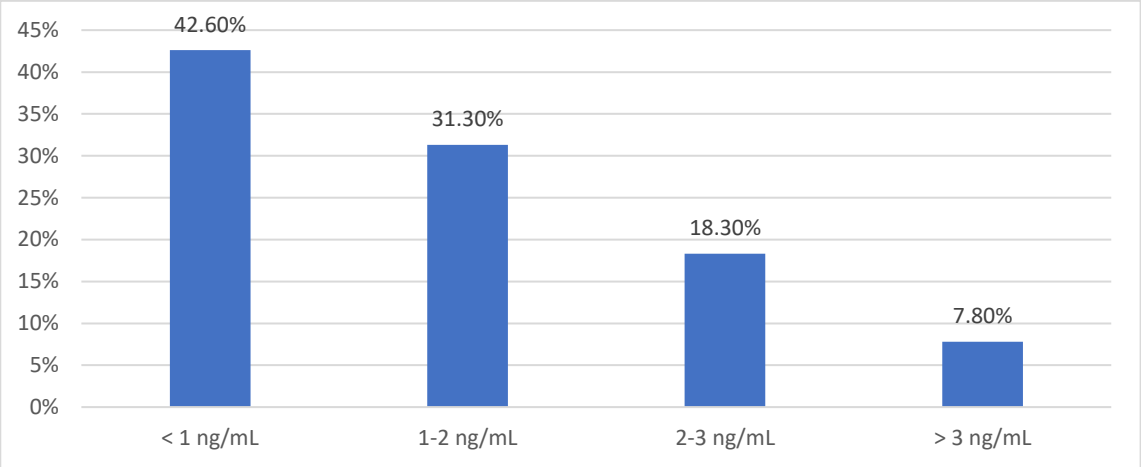

Figure 7.1. Distribution of patients related to the AMH value

The data in **Table VII.2** represents the distribution of ovarian stimulation protocols and the medication used. 193 cycles of ovarian stimulation were analyzed.

Table VII.2. Distribution of patients related to the type of ovarian stimulation protocol and the medication used

Parameter (No., %)	**Endometrioma (no=193)**
Ovarian stimulation protocol	
SP	169 (87.6%)
LP	19 (9.8%)
LUT	5 (2.6%)
Types of gonadotropins	
Menotropin	168 (87%)
Follitropin alfa	108 (56%)
Follitropin beta	25 (13%)
Follitropin delta	24 (12.4%)
Corifollitropin alfa	19 (9.8%)
Letrozole	16 (8.3%)
Follitropin alfa +lutropin alfa	15 (7.8%)

The data in **Table VII.3** represents the total number of oocytes and mature oocytes retrieved. In 9 cases (4.7%) no mature oocytes were obtained.

Table VII.3. Total number of oocytes and mature oocytes retrieved

Parameter	Mean ± SD	Median (IQR)	Min	Max
No. oocytes	6.05 ± 3.7	6 (3-8)	0	16
No. mature oocytes	4.67 ± 2.78	5 (3-6)	0	14

The data in **Table VII.4** represents the total number of embryos, day 3 embryos and blastocysts obtained. In 7 cases (3.9%) no embryos were obtained after fertilization.

Table VII.4. Total number of embryos, day 3 embryos and blastocysts obtained

Parameter	Mean ± SD	Median (IQR)	Min	Max
No. embryos	3.85 ± 2.28	3 (2-5)	0	9
No. day 3 embryos	0.78 ± 1.22	0 (0-2)	0	5
No. blastocysts	2.06 ± 2.08	2 (0-4)	0	8

The data in **Figure 7.2** represents the clinical pregnancy rate. Out of 70 cases in which there was a biochemical pregnancy, in 43 cases (61.4%) there was a clinical pregnancy. Out of the total number of analyzed cases – 193 cases, the clinical pregnancy rate was 22.3%. Taking into account the cases in which mature oocytes were obtained – 184 cases, the clinical pregnancy rate (cumulative) was 23.4%.

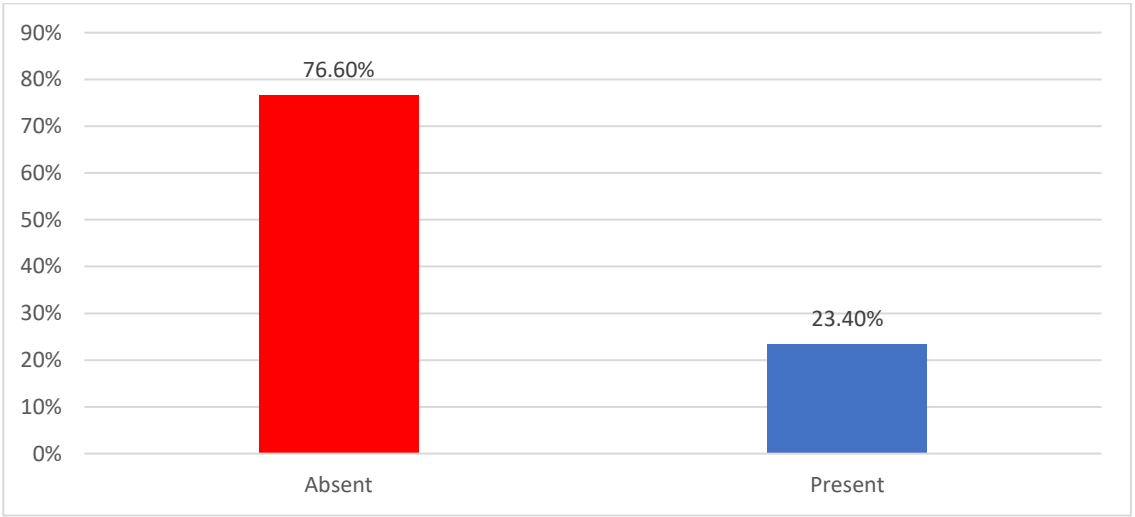

Figure 7.2. Clinical pregnancy rate

The data in **Table VII.5** represents the distribution of patients with endometriosis and a history of ovarian surgery related to the category of age greater than or equal to 35 years and clinical pregnancy. The differences between the groups are significant **(p=0.036)**, so patients with an age greater than or equal to 35 years had significantly less clinical pregnancy (59.5% vs. 39%) compared to patients under 35 years old (61% vs. 40.5%).

Table VII.5. Distribution of patients related to the category of age greater than or equal to 35 years and clinical pregnancy

Age / Clinical pregnancy	Absent		Present		p*
	No.	Percentage	No.	Percentage	
< 35 years	30	40.5%	25	61%	**0.036**
≥ 35 years	44	59.5%	16	39%	

*Pearson Chi-Square Test

The data in **Table VII.6** represents the correlation between the AMH value and the number of mature oocytes collected. The correlation between the AMH value and the number of mature oocytes is significant and moderately positive **(p<0.001, R= 0.537)** showing that in the cases of patients who had a high AMH value there is significantly more frequently a higher number of mature oocytes and vice versa.

Table VII.6. Correlation between AMH value and number of mature oocytes

Correlation	p*
AMH (p<0.001) x No. mature oocytes (p<0.001**)**	**<0.001, R=0.537**

*Spearman's rho Correlation Coefficient, **Shapiro-Wilk

The data in **Table VII.7** represents the correlation between the AMH value and the number of embryos obtained. Both variables have a non-parametric distribution **(p<0.05)**. The correlation between the AMH value and the number of embryos is significant and moderately positive **(p<0.001, R= 0.499)** showing that in the cases of patients who had a high AMH value there is significantly more frequently a higher number of embryos and vice versa.

Table VII.7. Correlation between AMH value and number of embryos

Correlation	p*
AMH (p<0.001) x No. embryos (p<0.001**)**	**<0.001, R=0.499**

*Spearman's rho Correlation Coefficient, **Shapiro-Wilk

The data in **Table VII.8** represents the distribution of ovarian stimulation medication related to the clinical pregnancy. Differences between groups are not significant according to **Fisher tests (p>0.05)** for most of the analyzed gonadotropins except for testing the association of clinical pregnancy with the administration of **corifollitropin alfa (p=0.016)**, where it was observed that the procedures in which **corifollitropin alfa** was used were associated significantly more frequently with the clinical pregnancy (20.9% vs. 6.7%).

Table VII.8. Distribution of gonadotropins related to clinical pregnancy

Follitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	62	41.3%	23	53.5%	0.168
With medication	88	58.7%	20	46.5%	
Follitropina alfa + lutropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	139	92.7%	39	90.7%	0.747
With medication	11	7.3%	4	9.3%	
Corifollitropin alfa / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	140	93.3%	34	79.1%	**0.016**
With medication	10	6.7%	9	20.9%	
Follitropin beta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	129	86%	39	90.7%	0.607
With medication	21	14%	4	9.3%	
Follitropin delta / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	133	88.7%	36	83.7%	0.432
With medication	17	11.3%	7	16.3%	
Letrozole / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	136	90.7%	41	95.3%	0.531
With medication	14	9.3%	2	4.7%	
Menotropin / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No medication	18	12%	7	16.3%	0.448
With medication	132	88%	36	83.7%	

*Fisher's Exact Test

The data in **Table VII.9** represents the relationship between the dual triggering of ovulation in the short antagonist protocol and clinical pregnancy. The dual triggering did not significantly influence the frequency of clinical pregnancy **(**p=0.072).

Table VII.9. Relationship between the dual ovulation triggering in the short antagonist protocol and clinical pregnancy

Dual triggering / Clinical pregnancy	**Absent**		**Present**		**p***
	No.	**Percentage**	**No.**	**Percentage**	
No dual triggering	64	47.4%	25	64.1%	0.072
With dual triggering	71	52.6%	14	35.9%	

*Fisher's Exact Test

The data in **Table VII.10** represents the relationship between the number of mature oocytes collected and the clinical pregnancy. The distribution of the number of mature oocytes is non-parametric in the group without pregnancy **(p<0.001)**. Differences in the number of mature oocytes between groups are statistically significant **(p<0.001)**, with a higher number of mature oocytes being observed in pregnant cases compared to non-pregnant cases.

Table VII.10. The number of mature oocytes related to clinical pregnancy

Pregnancy/No. mature oocytes	**Mean ± SD**	**Median (IQR)**	**Average rank**	**p***
Absent (p<0.001**)	4.28 ± 2.72	4 (2-6)	86.88	**<0.001**
Present (p=0.116****)**	6.05 ± 2.56	6 (4-8)	125.33	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VII.11** represents the relationship between the number of blastocysts obtained and the clinical pregnancy. The distribution of the number of blastocysts is non-parametric in both groups **(p<0.05)**. Differences in the number of blastocysts between groups are statistically significant **(p<0.001)**, with a higher number of blastocysts observed in pregnant cases compared to non-pregnant cases.

Table VII.11. Number of blastocysts related to the clinical pregnancy

Pregnancy/Blastocysts	**Mean ± SD**	**Median (IQR)**	**Average rank**	**p***
Absent (p<0.001**)	1.69 ± 1.97	1 (0-3)	81.75	**<0.001**
Present (p=0.011)**	3.26 ± 2	3 (2-5)	120.69	

*Mann-Whitney U, **Shapiro-Wilk

The data in **Table VII.12** represents the distribution of the type of embryo transfer and transferred embryo related to the clinical pregnancy. Differences between groups are significant **(p=0.006)**, and **Z tests with Bonferroni correction** show that procedures that used fresh day 3 embryos (26.4% vs. 11.6%) or frozen day 3 embryo (19.2% vs. 4.7%) were less often associated with pregnancy, while procedures using frozen blastocysts (67.4% vs. 44%) were more frequently associated with pregnancy.

Table VII.12. Distribution of the type of embryo transfer and transferred embryo related to the clinical pregnancy

Embryo transfer / Clinical pregnancy	Absent		Present		p*
	No.	Percentage	No.	Percentage	
Fresh – day 3 embryo	**33**	**26.4%**	**5**	**11.6%**	**0.006**
Fresh – Blastocyst	13	10.4%	7	16.3%	
Frozen – day 3 embryo	**24**	**19.2%**	**2**	**4.7%**	
Frozen - Blastocyst	**55**	**44%**	**29**	**67.4%**	

*Fisher's Exact Test

7.4 Discussions

Endometriosis is the prerogative of late diagnosis and repeated surgical interventions, but also an important cause of infertility, thus delaying the moment of conception. In accordance with these aspects, the majority of patients with a history of minimally invasive ovarian surgery for endometrioma who addressed the Department of Assisted Human Reproduction in order to obtain a pregnancy fell into the over 35 category (52.2%).

Ovarian surgery, as well as the simple presence of endometrioma, have a negative impact on the ovarian reserve and implicitly on the reproductive ovarian function. The AMH value correlates with the ovarian response to stimulation, but not with the pregnancy rate achieved by in vitro fertilization [23–25,53]. Most patients in the studied group (42.6%) had AMH below 1 ng/mL. This value is associated with poor response to ovarian stimulation, low oocyte quality and subsequently, low pregnancy rate [26,27]. The age over 35 years and the low AMH value constitute the premises of an impaired response to stimulation, with obtaining a low number of oocytes and implicitly a low clinical pregnancy rate.

The clinical pregnancy rate was 23.4%. Age represented a statistically significant factor (p=0.036) that influenced the clinical pregnancy rate, with patients under 35 getting pregnant more frequently.

Currently the most utilized ovarian stimulation protocol is the short antagonist, a fact that coincides with the present study, it was used in 87.6% of cases. The ovarian stimulation protocol did not influence neither the clinical pregnancy rate nor the delivery rate. Regarding the choice of a particular gonadotropin, in the present study most gonadotropins did not influence the pregnancy rate, except for the identification of a statistically significant increase (p=0.016) in the pregnancy rate in patients who received corifollitropin alfa (20.9%, respectively 6.7%). Some studies have identified a higher number of mature oocytes retrieved compared to cases receiving other recombinant FSH, but differences in pregnancy rates are conflicting [48,54–56].

The pregnancy rate was statistically significantly influenced by the total number of retrieved oocytes and mature oocytes, but also by the total number of embryos, mainly blastocysts. This indirectly highlights the importance of preserving ovarian reserve and minimizing the injury to healthy ovarian tissue during cystectomies. The pregnancy rate was positively influenced by the type of embryo transfer, with most pregnancies resulting from a frozen blastocyst embryo transfer.

7.4 Conclusions

1. Most patients were over 35 years old (52.2%).
2. The mean AMH value was 1.41 ± 1.06 ng/mL and 42.6% of the patients had an AMH value below 1 ng/mL.
3. The mean number of mature oocytes was 4.67 ± 2.78 and the mean number of blastocysts obtained was 2.06 ± 2.08.
4. Clinical pregnancy rate was 23.4%.
5. Age is a statistically significant factor that influenced the clinical pregnancy rate, patients older than or equal to 35 years having significantly less clinical pregnancy ($p=0.036$).
6. AMH did not influence the clinical pregnancy rate, but there is a positive correlation between its value and the number of mature oocytes collected, as well as the number of embryos obtained ($p<0.001$).
7. The most utilized ovarian stimulation protocol was the short antagonist (87.6%), but it did not influence neither the clinical pregnancy rate nor the delivery rate.
8. Treatment with corifollitropin alfa led to a higher clinical pregnancy rate (20.9%, respectively 6.7%, $p=0.016$).
9. The dual triggering of ovulation did not influence the clinical pregnancy rate, on the contrary it led to a lower number of oocytes ($p=0.026$) and embryos ($p=0.002$).
10. The clinical pregnancy rate was statistically significantly influenced by the number of oocytes ($p=0.001$), by the mature oocytes harvested ($p<0.001$), by the number of embryos ($p=0.014$) – mainly by blastocysts ($p<0.001$).
11. The highest clinical pregnancy rate was obtained following the transfer of a frozen blastocyst ($p=0.006$).

8. Final conclusions and personal contributions

Final conclusions

The doctoral research "The impact of endometriosis on ovarian function in assisted human reproduction" aimed to analyze the management of patients with endometriosis and infertility who underwent in vitro fertilization, in order to identify the factors that influence the clinical pregnancy rate. In other words, identifying an ovarian stimulation protocol and gonadotropin that leads to a superior response to stimulation translated into higher number of mature oocytes and embryos, and subsequently increased pregnancy rates.

I consider that the objectives of the doctoral research have been fulfilled by carrying out up-to-date studies on the management of infertility in patients with endometriosis and the evaluation of the response to ovarian stimulation during the in vitro fertilization procedure, with the identification of the factors that influence the clinical pregnancy rate.

The main advantages of the doctoral studies are represented by the analysis of gonadotropins and the most common combinations of gonadotropins used in ovarian stimulation in relation to the clinical pregnancy rate. This analysis led to the identification of statistically significant data regarding the treatment with corifollitropin alfa in patients with endometriosis and with the combination of follitropin alfa + lutropin alfa in patients with tubal factor infertility.

Limitations of the studies are that the embryo transfer protocol and embryo quality were not taken into account in the clinical pregnancy rate analysis. Also, the staging of the disease was not included in the doctoral study, as the patients had surgical interventions performed in different centers in Bucharest and in the country that did not perform the intraoperative staging of endometriosis lesions.

Patients with endometriosis represent a challenge for specialists in assisted human reproduction, and future research should focus on the relationship between the embryo and the endometrium by personalizing the embryo transfer protocol and studying the vaginal and intestinal microbiota. Even in cases where good quality embryos are obtained, pregnancy rates are still low compared to cases with infertility by other etiologies. Balancing the intestinal and vaginal microbiota with the aim of reducing the pro-inflammatory status is associated with a decrease in painful symptoms and a decrease in the level of reactive oxygen species, which can lead to a higher clinical pregnancy rate.

According to the results obtained, the following management recommendations for patients with endometriosis and infertility can be developed:

1. The clinical pregnancy rate is statistically significantly lower in patients with endometriosis than in patients with tubal factor infertility.
2. The main factors influencing pregnancy rate are age and AMH value.
3. The analysis of ovarian stimulation protocols (SP, LP and LUT) revealed that they do not influence the pregnancy rate, so the ovarian stimulation protocol can be chosen according to the characteristics of the patient and the experience of the infertility specialist.
4. Regarding the choice of a particular gonadotropin, treatment with corifollitropin alfa as part of ovarian stimulation led to a higher clinical pregnancy rate.
5. Dual ovulation triggering has no benefit in terms of oocyte count, embryo count, or clinical pregnancy rate.
6. Transfer of a frozen blastocyst leads to a higher clinical pregnancy rate.

The results obtained can be benchmarks for new research directions. The importance of treatment personalization in patients with endometriosis has been proven in the doctoral research, especially regarding the choice of the type of gonadotropins in the ovarian stimulation protocol. Studies on larger groups of patients should be carried out in order to stratify the pregnancy rate according to the administered gonadotropins.

Personal contributions

- I performed a literature review for the general part of the thesis, to evaluate the impact of endometriosis on fertility
- I conceived the design of the study
- I collected the data of the patients from the medical files which I entered into the Excel program to compile the two databases, of patients with endometriosis and of patients with tubal pathology
- I interpreted the statistical results obtained and made comparisons between the studied groups
- I compared the results obtained with the data published in the specialized studies
- I elaborated the final conclusions of the doctoral research in relation to the proposed objectives that can serve as a benchmark for current practice

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List of published scientific papers

1. **Nadă ES**, Bordea AE, Brătilă E. The Impact of Endometriosis on In Vitro Fertilization Outcome. Maedica (Bucur). 2022 Dec;17(4):757-761. doi: 10.26574/maedica.2022.17.4.757.
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2. **Nadă ES**, Coroleucă CB, Coroleucă CA, Brătilă E. Ovarian Stimulation for In Vitro Fertilization and Reproductive Outcome after Surgical Treatment of Endometriosis Compared with Tubal Factor Infertility. *Clinics and Practice*. 2024; 14(1):1-12. https://doi.org/10.3390/clinpract14010001
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3. **Nadă ES**, Coroleucă CA, Coroleucă CB, Brătilă E. Reproductive Outcome after In Vitro Fertilization in Endometriosis – Key Factors and Implications. J Med Life. 2024 Mar; 17(3):338-344. doi: 10.25122/jml-2024-0114
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