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# PhD THESIS

## POPULATIONAL STUDY ON ASSISTED REPRODUCTIVE TECHNIQUES IN ROMANIA

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# INTRODUCTION

The decline in the total fertility rate, which began in the second half of the 20th century in many European countries, is becoming increasingly important in determining the demographic composition of Europe and its individual member states. Although low fertility rates will have an impact on total population numbers, the changing age structure of the population is probably the most challenging factor facing the EU. Clear evidence suggests an aging population threatens future living standards and social cohesion. Thus, the management of demographic changes through an integrated policy response has become a component of EU legislation. However, current measures fail to capture the contribution of ART to increasing fertility rates.

Assisted human reproduction techniques are the solution for millions of couples suffering from infertility. In vitro fertilization has raised countless ethical, legal, economic and social dilemmas. Currently in Romania, the legislation in force regarding assisted human reproduction methods is still insufficiently regulated. Thus, couples of reproductive age with fertility problems do not benefit from adequate information both from a medical and legislative point of view regarding this condition. There are no social programs to inform the population about conception, fertility disorders or methods of assisted human reproduction, and no sufficient state subsidies are allocated for the treatment of infertility.

Worldwide, more than 80 million couples suffer from infertility, with the majority of couples from developing countries. In Romania, infertility is estimated to affect 1 couple out of 6, but unfortunately there is not sufficient data related to this subject. Romania faces a lack of facilities both in terms of informing the population and in terms of infertility diagnosis and treatment.

Since the beginning, the use of ART techniques has been accompanied by ethical, legal, social controversies. It was necessary to develop several directives to address these issues. However, the rapid evolution of ART requires frequent re-evaluations. Examining the literature on the ethical and legal aspects of ART, some of the most visible and challenging topics should be highlighted. Of specific interest are: reporting of ART procedures and outcomes; accessibility to ART procedures;

fertility preservation issues, preimplantation genetic testing, embryo donation, and reproductive outcomes after embryo transfer.

Improvements in ART reporting are needed nationally and globally. Reporting should include results that allow patients to make informed decisions. Improving access to ART and optimizing long-term outcomes, are challenges that must be addressed by the whole community and especially by people involved in the field, with the help of bioethicists, legal advisors and members of professional societies.

Many countries have already taken steps to regulate certain aspects of ART. Specifically, regulations and laws need to address ART reporting issues, social inequities that may arise, financial barriers to ART techniques, genetic testing, cryopreservation. A person's right to their genetic offspring are aspects of ART that will become increasingly controversial and will need to be debated in the future.

However, most of the ethical and legal issues surrounding ART have not yet been resolved. Society needs to rethink how to finance ART in a responsible and equitable manner to increase access to care. The multitude of unresolved issues surrounding gamete and embryo donation must be addressed in detail in the future through legal and social dialogues.

ART is a dynamic field that is constantly evolving and changing. In areas of ART, such as preimplantation genetic testing, new technologies are continually changing the capabilities of ART. Due to the rapidly evolving nature of ART, legislation is often unable to keep pace and address all the ethical and legal issues, and they remain constantly emerging in the field. Therefore, it is the duty of physicians to continuously monitor these issues and ensure that ART technologies are offered and delivered in a way that balances patient care with social and moral responsibility

## GENERAL PART

The problem of infertility has always been a primary challenge for reproductive medicine. According to the World Health Organization (WHO), infertility is a specific entity and, due to its prevalence, should be considered a social disease. However, the literature does not provide a uniform and concise definition. The UK's National Institute for Health and Clinical Excellence (NICE 2013) proposed that

infertility be defined as failure to conceive after 2 years of regular unprotected intercourse in the absence of known reproductive pathology.

The literature on the physiological consequences of infertility describes it as a devastating experience, especially for women. In addition, there are no clear answers to the question of what is the best method of diagnosis or what is the most effective and safe method of treatment. The average prevalence of infertility in developed countries is 3.5-16.7%, and in developing countries it is 6.9-9.3%. About one-third of cases of couple infertility are due to male factors, one-third to female factors, and one-third are related to a combination of male and female factors or have no identifiable cause. Although male factors contribute equally in all cases of infertility, this is rarely recognized and women are often responsible for the couple's inability to conceive. Two subcategories of infertility have been described in the literature. Primary infertility, which includes couples who have never been able to conceive, and secondary infertility, which includes couples who are currently unable to conceive, although they have not experienced this problem in the past.

Since the 1950s, demographic studies have indicated an important decline in the birth rate in all European countries, without considerable differences between regions or social classes. In a study conducted in 2017, it was found that 1 in 6 couples worldwide suffer from infertility. In Europe this number is estimated at 25 million citizens of reproductive age, a number that corresponds to an average fertility rate of 1.59. This average differs between countries, with Romania averaging 1.76, Malta 1.23, and France ranking first with 1.88. However, among the countries studied, the fertility rate remains below the limit set by Eurostat to maintain population size, which is 2.1 live births per woman.

The psychosocial consequences of couple infertility in high-income countries have been widely described and include symptoms of anxiety and depression, loss of self-esteem, difficulties in interpersonal relationships, loss of zest for life, and social isolation. The inability to procreate is frequently considered a personal tragedy and a stigma for the couple, affecting the entire family and often even the local community. In many cultures, femininity is defined by motherhood, and infertile women are usually blamed for the couple's inability to conceive. Childless women are frequently stigmatized, leading to isolation, neglect, violence and polygamy.

Worldwide, more than 70 million couples are affected by infertility. Since the first successful IVF procedure in 1978, the use of this and related technologies has expanded to become common throughout the world. Over the last decade, the use of ART services has grown at a rate of 5-10% annually. The total number of cycles presented to the ESHRE Consortium is currently increasing by approximately 7% per year, meaning that the consortium has monitored a cumulative total of nearly 9 million cycles since its formation in 1997 and over 1.6 million births.

## SPECIAL PART

The special part included an introductory chapter with premises, and the 2 studies. **The first study entitled THE IMPACT OF INDIVIDUAL AND ENVIRONMENTAL FACTORS ON FEMALE AND MALE INFERTILITY** was carried out in the **period 2017-2019** and was carried out on in an ambulatory setting (on outpatients), within a collaboration between five fertility clinics in university medical centers in Romania.

The study was built on a cross-sectional design and we opted for a convenience sampling technique to calculate the optimal sample size, which was estimated based on the prevalence of infertile couples to include at least 245 people for a confidence coefficient of 95% and a margin of error of 5%.

The questionnaire was also accessible online for ease of use and to ensure the completion and submission of the questionnaire. This made it available to patients who also presented in other Fertility Centers in the country, apart from the 5 mentioned above, but also for those who went for treatment outside the country. One-third of the data was collected from questionnaires available in the clinics, and two-thirds was collected online via a Google Forms questionnaire.

**A total of 829 eligible women** with a history of infertility successfully completed the surveys. Eligibility criteria included women of reproductive age in couples with a history of at least 12 months of unsuccessful pregnancy attempts. All respondents completed ART treatment and were subsequently asked by their physicians to answer a survey developed by the researchers to assess their overall experience.

Participants provided informed consent for data processing after being assured of confidentiality regarding personal identifiers and protection of data.

As for the male questionnaire, the group of patients was represented by the partners of patients resorting to ART and who agreed to complete this questionnaire, resulting a total of 230 completed questionnaires.

Regarding the educational level, almost 80% of the women included in the study graduated from the University. This shows that the level of education is important and can have an impact on how women deal with infertility problems. Higher education level was associated with an increase in female fertility impairment, independent of other demographic and behavioural characteristics. The correlation between female education and age at conception is well documented in many studies. There is a strong inverse relationship between education and fertility, with arguments highlighting that continued education could delay childbearing.

Our study clearly shows that people with a lower level of education are substantially more likely to be stressed than those with a higher level of education. This suggests that women with a college degree are more knowledgeable about the topic of infertility and the possibility of achieving a pregnancy through assisted reproductive treatments and therefore do not experience the same amount of stress as women without a college degree.

Regarding the correlation between the pregnancy rate and the degree of exposure to stress, it was found that in group of patients who achieved a pregnancy after assisted human reproduction procedures, exposure to stress was decreased in a high percentage of 81.4%. At the same time, in the group of women who did not achieve a pregnancy, the study revealed a similar percentage, i.e. 79.1% of the patients had reduced exposure to stress. These results mean that the degree of exposure to stress does not impact the rate of achieving a pregnancy.

**The second study entitled LAPAROSCOPIC SURGICAL MANAGEMENT OF DEEP INFILTRATING ENDOMETRIOSIS IN A MULTIDISCIPLINARY CENTER** retrospectively evaluated **74 patients**, with a mean age of 33.4 years (21-49 years), who underwent laparoscopic surgery for deep endometriosis.

Over a **period of 24 months (January 2014-December 2015)** all patients treated for DIE in the Department of Gynecological Surgery Premiere Hospital Timișoara were included and evaluated.

Patient parameters included age, associated sites of deeply infiltrative endometriosis, and previous surgery for endometriosis.

Hospital records and electronic databases were reviewed for intra- and post-operative complications and recurrent symptoms requiring further treatment, with or without colonoscopy and assessment of anti-Mullerian hormone (AMH) levels.

Pre-evaluation and preparation included a thorough clinical examination, exploration and imaging evaluation: transvaginal ultrasonography, pelvic MRI with or without colonoscopy, and assessment of anti-mullerian hormone (AMH) levels. Staging was performed according to the rAFS and the ENZIAN score. A complete laparoscopic management was planned in all patients that included resection of all visible disease in the pelvic sidewall, rectovaginal septum, and bowel. AMH levels decreased by 1.1-1.4 mU/dl after unilateral total cystectomy and by 1.8 mU/dl after bilateral cystectomy. AMH levels decreased by only 0.2–0.25 mU/dl when ovarian endometrioma evacuation was performed exclusively.

From the total of 74 patients, it was noted that an important percentage of 52.70% had at least one surgical intervention for the treatment of endometriosis: 44.59% - one intervention, 8.11% - 2 interventions. Endometriosis implants were discovered intraoperatively as follows: for 39 patients in the rectovaginal septum (63.5%), for 24 patients in the uterosacral ligaments (32.4%), for 8 patients in the bottom of the Douglas pouch (10, 8%), for 15 patients in the rectosigmoid (20.2%), for 2 patients in the appendix and for just 2 in the vagina. The ovaries were a frequent location of endometriosis, ovarian endometriomas being present in 33 patients (44.5%). Furthermore, 19 patients had ureter involvement (25.6%), 8 had bladder endometriosis (11%) and 2 patients had pelvic wall endometriosis. These intraoperative findings were consistent with existing guidelines.

Regarding infertility, 49 patients out of the 74 had the desire to conceive. The clinical pregnancy rate (CPR) was 37% (18 pregnancies). Spontaneous conception was achieved in 20% of patients (10 spontaneous pregnancies). 33% underwent in vitro fertilization, resulting in 8 pregnancies associated with reproductive techniques (ART) (17%). The total number of children born was 13 (26%).

## ORIGINAL CONTRIBUTIONS

***The original contributions*** of the present studies can be summarized as follows:

***FIRST STUDY OF THE THESIS:***

- ✓ 65.3% of the infertile patients who benefited from specialized treatment were younger than 35 years old. The average age of women using ART techniques is 33 years.
- ✓ 29.6% of the patients achieved a pregnancy through any of the following procedures: IUI-intrauterine insemination, IVF-in vitro fertilization, ICSI-intracytoplasmic sperm injection.
- ✓ Polycystic ovary syndrome was found in 139 patients from the studied group, with 2/3 of them simultaneously presenting fertility problems, but without a significant association p=0.105.
- ✓ History of sexually transmitted diseases is a significant risk factor for infertility disorders, OR=1.59 (95%, 1.14, 2.25).
- ✓ The association between female infertility and endometriosis was statistically significant, p=0.001, OR=1.81.
- ✓ For the educational level, almost 80% of the women included in the study graduated from university. Education level is important and can have an impact on how women deal with infertility problems.
- ✓ The proportion of male subjects with erectile disorders is significantly increased in the case of those who have a disordered lifestyle, p=0.018, OR=3.067.
- ✓ The proportion of men with an abnormal semen analysis result is significantly increased in the case of those exposed to occupational hazards, p=0.016, OR=3.595.
- ✓ Regarding the quality of ART, the results in Romania are good, comparable to the results in other European countries, which has a positive impact on the development of these technologies and encourages patients to trust Romanian fertility clinics. However, access is limited to a minority of infertile

couples with above-average incomes, and there is only general legislation covering ART procedures.

- ✓ There are significant differences between couples using assisted reproductive procedures, particularly in terms of stress levels, family income and governmental financial assistance.
- ✓ Because the techniques are expensive in Romania, high personal expenses and an above average income per household are important in achieving the desired pregnancy through ART. Lack of partner support and advanced age of women are to be considered.

**SECOND THESIS STUDY:**

- ✓ A percentage of 52.70% of the patients who benefited from surgical management of DIE had at least one surgical intervention for the treatment of endometriosis. Deeply infiltrative endometriosis is a disease that requires complex, long-term management, and surgical treatment, if necessary, must have a radical curative intent.
- ✓ A percentage of 68% of patients were staged preoperatively using the rAFS score in advanced stages III-IV, results similar to the staging performed laparoscopically in accordance with the ENZIAN classification. This concordance proves that transvaginal ultrasound can represent the investigation of first intention.
- ✓ In 97.4% of the patients, the surgical procedure was performed entirely by the minimally invasive surgical technique. The most common procedure was rectal shaving in 39.1%, while rectal resection was performed in 16.2%. Major complications were encountered in only 2 patients, a result similar to data from the literature. The minimally invasive technique is safe and ensures optimal postoperative recovery.
- ✓ In the advanced stage of infiltration, the surgical management of deeply infiltrative endometriosis requires high skills and therefore deserves a multidisciplinary setting, in a center of excellence dedicated to the treatment of patients with endometriosis and infertility**.**