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Multifactoriality and its impact on female infertility

ABSTRACT OF THE DOCTORAL THESIS

PhD supervisor:

PROF. UNIV. DR. LIANA PLEȘ

Doctoral student:

POMANĂ (POPESCU) CRISTINA DIANA

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Summary

Introduction

Infertility is defined as the inability to get pregnant after 6 or 12 months of unprotected sexual contact. The period is defined according to the age of the partners, so couples under the age of 35 are advised to start investigations after 12 months of unprotected sexual contact without achieving pregnancy, as opposed to couples over 35 who are limited to 6 months. [1]

It has been found that worldwide between 8 and 12% of couples of childbearing age are diagnosed with infertility, in 85% of cases the cause of infertility is known; 15% of couples experience "infertility of unknown cause" [2]. Studies show that 1 in 8 women aged between 18 and 48 seek health services for infertile couples, but successful pregnancy depends on several factors, the most important being age, type of infertility, cause of infertility, associated diagnoses, and daily medication when appropriate. [3] The identification of the causes of infertility among women seeking medical attention needs to be carried out systematically and rapidly so that all the factors involved are defined. [4]

In recent years there has been an increase in the number of women wishing to become pregnant after the age of 30, so that the delay in the age of childbearing, as well as lifestyle, environment, stress generated by the workplace, are interlinked and adversely affect the chances of achieving a pregnancy. [5] An increase in the average age of giving birth to the first child has a significant impact on the quality and quantity of oocytes, and systemic diseases that occur with advancing age also have a negative impact on fertility in both women and men. [6] The diagnosis of infertility in itself is associated with additional emotional stress, feelings of isolation, sadness, even depression, all of which are felt much more intensely by women than men. [7]

The main causes of female infertility include advancing age, ovarian dysfunction, tubal pathology associated or not with upper genital infections, uterine pathology, cervical pathology, endometriosis, polycystic ovaries, but also weight gain or emotional factors. [8] Ovulation can be documented by measuring serum progesterone on day 21 of the menstrual cycle or by home kits. [9] A relevant blood test in testing ovarian reserve is Anti Mullerian Hormone (AMH). Pelvic ultrasonography and hysterosalpingography easily assess the uterus and fallopian tubes, and can be supplemented by hysteroscopy, laparoscopy, laparotomy, nuclear magnetic resonance, chromopertubation.[10] Premature

ovarian failure is the loss of ovarian function before the age of 35; it can be spontaneous or iatrogenic and is an important cause of female infertility. [11]

Infertility is classified as primary or secondary infertility. In women with primary infertility, they have never achieved a pregnancy, in contrast to those diagnosed with secondary infertility who have had a pregnancy in the past but are unable to conceive again. [12]

The choice of the research topic was motivated by a concern for identifying and understanding the complexity of the diagnosis of infertility, given its significant consequences on quality of life. The importance of this theme lies in the need to develop early diagnosis and personalized treatment strategies for couples affected by infertility.

The novelty and timeliness of the topic are evident in the context of rapidly evolving medical techniques and technologies that open new perspectives in approaching infertility.

This research aims to make significant contributions to the literature by exploring interdisciplinary aspects that support a comprehensive approach to infertility.

Based on the hypothesis that infertility is the result of the interaction of several factors, the scientific objectives of this work are to identify the main mechanisms involved, to evaluate methods of diagnosis and treatment and to develop recommendations for improving fertility.

The proposed research method consists of an exhaustive review of the literature, the study of three groups of patients and statistical analysis, with the aim of obtaining the most complete and truthful picture possible of the diagnosis of infertility. The content of the work will cover aspects related to the pathophysiology of infertility, risk and protective factors, available diagnostic and treatment methods, as well as the psycho-emotional implications for the patients concerned.

Research limitations include restricted access to some data or resources, but the possibility of expanding the patient pool is unlimited, as is the possibility of interdisciplinary collaborations or tackling new research directions.

I. GENERAL PART

1.Infertility per se

1.1. Short history

Humans are defined by evolution through natural selection, on a par with all species; the defining step in this selection is reproduction. [13]

Robert Edwards (1925 - 2013) was the innovator of in vitro fertilization and together with his partner, gynecologist Patrick Steptoe, they succeeded in conceiving the first "test-tube baby" as it was called at the time, in 1978. The documents recount their battles with the medical establishment of the time, with leading biologists and doctors, and with anti-abortion theorists. [14] [15]

In 1978, when the first in vitro fertilization was performed, this technology underwent a marked development and became more accessible over time, with significant advances; at that time the success of the procedure was achieved on an unstimulated menstrual cycle, by laparoscopic removal of a single oocyte which was then fertilized in vitro and transferred into the patient's uterus as an embryo. [16]

Infertility has been defined as a health problem affecting 48 million couples and an estimated 186 million people worldwide. The evolution of mankind has been intensively associated with the increase in the number of couples diagnosed with infertility, and endocrine factors have been frequently associated in the causes of infertility, in direct relation to chemicals in the food industry. [17]

Assisted reproductive technologies have enabled more than 5 million births worldwide between 1978-2013. [18] Significant progress has been made over time in increasing the rates of pregnancies carried to term, reducing multiple pregnancies, reducing complications associated with these pregnancies and delivering healthy babies. [19]

1.2. Fertility and reproduction

Fertility is the ability to conceive, and the monthly probability of achieving pregnancy is about 20-25%, so the average time to achieve pregnancy is about 4 months; all couples within this percentage should achieve pregnancy at the end of one year of unprotected sexual contact, talking about couples without other associated pathologies. [20]

Infertility is a common pathology in the general population. It has been found that the prevalence of infertility over the last 40 years has remained relatively constant; the

demand for its investigation and treatment has increased and the hope of achieving the ultimate goal has increased considerably. [21]

Examination of the infertile couple is a challenge for the specialist. The successful achievement of pregnancy is characterized by complex events including ovulation, oocyte uptake by the fallopian tube, fertilization, transport of the fertilized egg into the uterine cavity and implantation. Educating couples about the term fertile window is essential; the chance of conception is high on the periovulatory days and highest on the day of ovulation. [22]

1.3. Evaluating infertile couples

Infertility is attributed to the female partner in one third of cases, to the male partner in one third of cases, and infertility involving both partners accounts for one third of cases, emphasizing the importance of assessing both partners before therapy is instituted. [23]

For women, the complete gynecologic and obstetric history, personal medical and surgical pathological history, drug therapy administered, as well as social and hereddocollateral factors, should be discussed during the first consultation. [24] Of the gynecological history, the physician should consider questions about the characters of the menstrual cycle, namely menstruation in terms of duration, frequency, recent changes in their duration or interval, any associated symptoms such as hot flushes or dysmenorrhea, previous contraception, and the duration of infertility. The history of cystic ovarian pathology, diagnosis of endometriosis where applicable, uterine fibroids, sexually transmitted diseases or possible pelvic inflammatory diseases, as well as obstetric history such as previous pregnancies, time to conception, complications of previous pregnancy such as miscarriage, premature birth, chorioamnionitis, fetal abnormalities, and questions about uterine curettage or possible (elective) termination of pregnancy will be discussed during the history. The anamnesis also includes a history of Pap smears, whether previous interventions such as diathermy loop electrosection or conization have been performed, which may result in a decrease in the quality of cervical mucus or changes in the anatomy of the cervical canal. [25] The doctor should obtain information about the frequency of unprotected sexual intercourse and its synchronization with ovulatory periods, as well as about symptoms such as dyspareunia or, less commonly, even the inability to have sexual intercourse in patients with vaginismus. [26]

1.4. Primary infertility

Primary infertility is defined as the inability to conceive in couples who have never been able to achieve pregnancy. This is a complex medical problem of concern with significant biological, psychological and social implications for both partners. Primary infertility is distinguished from secondary infertility, which involves couples who have previously achieved at least one pregnancy. [27]

Diagnosis of primary infertility involves a detailed assessment of the patient and combines medical history, physical examination and laboratory tests.[28] Imaging investigations are crucial to assess the reproductive anatomy and allow the identification of possible structural abnormalities that may influence fertility. [29]

Treatment of primary infertility is complex and depends on the cause identified. Therapeutic options range from pharmacologic interventions to surgical procedures. In some cases assisted reproduction techniques may be necessary. Lifestyle changes, adjusting body weight and physical activity, giving up alcohol or tobacco, can significantly improve outcomes. [30]

1.5. Secondary infertility

Secondary infertility is defined as a woman's inability to conceive after a previous pregnancy, whether achieved naturally or with assisted reproduction techniques and affects a considerable number of couples, with a prevalence of between 30 and 50% of all infertility cases. [31] Secondary infertility can occur from multiple causes including both physiological and psychosocial aspects.

The assessment of secondary infertility involves a similar approach to that for primary infertility but with increased attention to previous obstetric history. The medical history includes information about previous pregnancies, complications of previous pregnancies, contraceptive methods used, and recently diagnosed pathologies when appropriate. Laboratory and imaging tests are similar to those used in women diagnosed with primary infertility. [32]

1.6. Infertility of undetermined cause

Infertility of undetermined cause is a complex diagnosis in which a detailed assessment of both partners does not lead to the identification of obvious causes that could explain the difficulty in conceiving. This diagnosis affects between 15 and 30% of infertile

couples and is often challenging because in some cases the therapeutic approach is targeted without a specific cause. [33]

Treatment of infertility of undetermined cause can often be challenging. Therapeutic options vary and include assisted reproductive techniques such as intrauterine insemination or in vitro fertilization; these are applied in the hope of overcoming unexplained obstacles. [34] Another important aspect is the integration of psychological support that can reduce associated anxiety or depression; thus, the health of couples could be improved and with it the chance of conceiving. [35]

2. Causes of infertility. Solutions.

2.1. Ethiology of female infertility and necessary investigations

Female infertility remains a public health problem with multiple implications, significantly affecting women's personal and social lives. From hormonal dysfunctions to environmental and lifestyle factors, every aspect plays a crucial role in the ability to conceive. Advances in diagnostic technologies have allowed a more nuanced assessment of the reproductive health status of these women, and innovative guidelines are essential for developing effective treatment plans. [36] The approach requires an integrated and comprehensive view and a full understanding of the complexity of this pathology can have significant results in improving outcomes and quality of life for the women involved.

2.2. Male infertility

Male infertility has widespread implications for reproductive health and family dynamics. Recent advances in diagnostic technologies have impacted positively the approach to male infertility, allowing a more accurate assessment. Advanced techniques such as detailed morphological analysis of spermatozoa or genetic evaluation have made essential contributions in personalizing treatment strategies and better understanding the long-term implications of male infertility. It is essential that the therapeutic approach is multidimensional, integrating medical interventions with psychological support. [37]

2.3. Human assisted reproduction techniques

Assisted reproduction techniques have evolved significantly in recent decades with the aim of supporting infertile couples. These methods can be classified into several categories, depending on the interventions used and the characteristics of each case.

Assisted reproductive methods not only improve the chances of achieving pregnancy, but also contribute significantly to a deeper understanding of the biological mechanisms involved in reproduction. They represent a complex and evolving field with diverse applications, responding to the varied needs of infertile couples. [38]

II. PERSONAL CONTRIBUTIONS

3. Working hypothesis and general objectives

This study aims to demonstrate that infertility is a multifactorial pathology that requires a multidisciplinary approach. [39] [40] This research will explore how the multitude of interconnected factors contribute to infertility and their impact on the couple's reproductive decisions.

A secondary objective of the study includes analysing the psycho-emotional impact of the infertility diagnosis on patients as well as its impact on family life. [41]

The working hypothesis of this paper is based on the premise that infertility is a multifactorial phenomenon resulting from complex interactions between biological, psychological, social and environmental variables. This research argues that there is not a single factor responsible for infertility, but a complex web of influences affecting fertility.

The overall objectives of the paper are as follows:

1. To explore the multifactoriality of infertility diagnosis by: identifying and analysing the various biological, psychological and socioeconomic causes contributing to infertility, assessing the interactions between these factors and how they influence fertility in both women and men, investigating the prevalences of these factors in the study population;

2. Evaluation of the role of hysteroscopy in the diagnosis and treatment of infertility by: analysing the effectiveness of hysteroscopy as a method of diagnosing uterine pathologies associated with infertility, examining the clinical results obtained by hysteroscopy and their impact on the success rates in terms of women's fertility, analysing the group of patients who achieved pregnancy following appropriate treatment, and the complications associated with pregnancy;

3. Investigating the psychological and emotional impact on infertile women by: assessing the level of stress and emotional problems experienced by women coping with infertility, analysing how psychological issues influence reproductive decisions and access to treatment, identifying psychological support strategies that can help infertile women manage stress and anxiety;

4. Study on financial stress and its impact on infertile women by: assessing the perception of financial stress among women seeking infertility treatments, analysing the correlation between financial difficulties and optimism for the future;

5. Development of integrated interventions to address infertility: proposing intervention strategies based on the data obtained from the study that address both the medical and psychosocial aspects of infertility, recommending personalized treatment protocols that integrate regular psychological, social and financial assessments of patients, creating educational resources for both patients and health care providers aimed at improving awareness of the multifactoriality of infertility.

The objectives are designed to provide a holistic and integrated approach to infertility, reflecting the complexity of this condition.

4. General research methodology

The study evaluates relevant variables in the context of infertility, corresponding to the identification of correlations between biological, psychological, socioeconomic factors of infertility. In the context of the desire to reflect the variability in the causes of infertility, the study included women diagnosed with infertility selected mostly from the clinic but also from the online environment.

The patients included in the first two studies were selected among those who presented to the Bucur Maternity, Hospital Clinic of Emergency ,,St John's", Bucharest and who had approached the obstetrics-gynecology physicians with the aim of achieving a pregnancy. All data were collected from the clinic and analysed in two prospective cohort studies. All patients signed consents for medical investigations and participation in medical education, were informed about the purpose of the research and understood how the data would be used. The data obtained were handled confidentially, with participant identification protected by coding.

In the case of the third study the data collection was created and completed electronically and the questionnaire included the study participants' voluntary consent to the processing of personal data. All responses from participants with a diagnosis of infertility over 18 years of age were accepted for analysis. The questionnaire was distributed online via social media and also via Whatsapp mobile application.

Before the beginning of the research, the approval of the study was obtained by the ”Ethics Commission" of the ,”St. John's” Emergency Clinical Hospital No. 9082/12.04.2023.

The IBM SPSS Statistics version 21 program IBM SPSS Statistics version 21 was used to perform the statistical analysis, $p \leq 0.05$ values were considered statistically significant. The statistical tests used were: Chi-Square test, Mann - Whitney U test, Spearman correlation indicator, Phi correlation coefficient, Kolmogorov-Smirnov and Shapiro-Wilk tests, and visual analysis.

5. STUDY I: "Infertility - a single cause or a multifactorial entity?"

5.1. Introduction

Reproduction is a complex process involving numerous biological processes, including hormone production, meiosis and mitosis. [42] Infertility can occur when there is an imbalance in one of these processes and is defined as a major reproductive pathology affecting about one in seven couples of childbearing age worldwide. [43]

Medical genetics has undergone significant advances, with multiple advantages also in reproductive endocrinology. [44] Technological advances are represented by methods such as pre-implantation genetic testing, exome sequencing, which bring numerous benefits and increase efficiency and accuracy. [45]

5.2. Material and methods

The objective of the study was to evaluate infertility as a multifactorial entity in a group of patients who presented at the Bucur Maternity, ”St. John's” Emergency Clinical Hospital, Bucharest.

The prospective study included patients diagnosed with primary or secondary infertility over a 12-month period in 2022 (January 3–December 15, 2022). Parameters such as patients' personal data (age, weight, personal medical history, family medical history, medication administered), as well as data from blood tests, menstrual cycle characteristics, ultrasound, hysteroscopic, or hysterosalpingographic investigations were collected.

Inclusion criteria for the study were female patients over 18 years of age, desire to conceive, established diagnosis of infertility (primary or secondary infertility), and transvaginal ultrasound as the first investigation.

Exclusion criteria were the patient's desire to postpone pregnancy (they only wanted to preserve their oocytes – they did not have a partner), total or partial lack of data, and infertility exclusively due to male factors.

The study was approved by the Ethics Committee (12.04.2023, number 9082).

The data obtained were statistically analysed using IBM SPSS Statistics 21, with $p \leq 0.05$ values considered statistically significant. The data were collected using Excel version 2007. The statistical tests used in the data analysis were Chi-Square, Mann-Whitney U, Spearman's correlation coefficient, and Phi correlation coefficient.

The normality of the distributions was established using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as visual analysis.

5.3. Results

Following the application of the inclusion and exclusion criteria, the study included 204 patients aged between 20 and 48 years, with a mean age of 35.98 years. Of the total number of patients, 68.63% (n=140) were diagnosed with primary infertility, while 31.37% (n=64) of patients had secondary infertility.

Patients with primary infertility were aged between 20 and 48 years, with a mean age of 35.45 years, while patients with secondary infertility were aged between 28 and 48 years, with a mean age of 37.13 years.

In terms of weight, most of the patients included in the study group were of normal weight. The body mass index (BMI) ranged from 16.71 to 46.98, with a mean value of 24.11. Of the patients included in the analysed group, 81.68% were non-smokers (n=167), while 18.14% were smokers (n=37).

Half of the patients had a personal medical history (50%, n=102), with a significantly higher incidence among women with secondary infertility (n=43) than among those with primary infertility (n=59) (67.19% versus 42.14%) (p=0.001). It was noted that hypothyroidism was significantly more common in women with secondary infertility than in those with primary infertility (p=0.045): 2.86% among women with primary infertility (n=4) and 9.38% among women with secondary infertility (n=6).

Of the patients included in the study, 90.69% were nulliparous (n=185), while 9.31% had a history of childbirth (n=19). Regarding previous elective abortions, 74.51% of patients (n=152) had none, but there were also women who had at least one abortion on request in their history (25.49%, n=52, 1 in 4 patients had a history of elective abortions).

Most of the patients - 87.75%, had no history of missed abortions (n=179), but there was a proportion of women who had at least one missed abortion in their history (12.25%, n=25). 95.10% of the women included in the group had no history of ectopic pregnancy (n=194), but 2.45% of them had a history of ectopic pregnancy (n=5).

The patients analysed had menarche between the ages of 10 and 17, half of them before the age of 12. The average age of onset of the first menstruation was 12.49 years. Only 2.5% of the patients analysed reported irregular menstrual cycles (n=5), with the majority of patients in the group having regular menstruation (97.5%, n=199). Among the symptoms associated with menstruation, dysmenorrhea was frequently reported in the analysed group, with 60.29% of patients affected by dysmenorrhea (n=123), while 39.71% of patients denied the association with dysmenorrhea (n=81). Regarding dyspareunia, approximately half of the patients included in the group responded positively (43.14% of patients reported dyspareunia, n=88), while 56.86% of patients denied it.

The patients included in the group had AMH (Anti-Mullerian hormone) values ranging from 0.04 ng/ml to 17.80 ng/ml, with a mean value of 2.42 ng/ml. Half of the women had AMH results above 1.50 ng/ml, 19.57% had low ovarian reserve indicating the onset of menopause (n=36), and 17.93% had AMH levels low enough to confirm the onset of menopause (n=33).

All patients included in the group underwent ultrasound examination. It was found that 1 in 3 patients had changes on ultrasound examination. Thus, 63.24% of patients had normal ultrasound results (n=129), while 36.76% had abnormal results (n=75). Regarding the hysteroscopic evaluation of the patients included in the study group, it was observed that 2 out of 5 patients with abnormal ultrasound scans (39.06%, n=25) had abnormal hysteroscopy results, and less than 1 out of 25 patients with normal ultrasound results (3.19%, n=3) had abnormal hysteroscopy results.

Fibromatous uterus was diagnosed by ultrasound in approximately 1 in 5 patients with abnormal ultrasound (17.33%, n=13) and less than 1 in 100 patients with normal ultrasound results (0.78%, n=1).

In patients with polycystic ovary syndrome (PCOS), suggestive images were observed in approximately 1 in 10 patients with abnormal ultrasound scans (12%, n=9), and 3 in 100 patients with normal ultrasound results had PCOS (3.10%, n=4). Endometriosis was diagnosed in more than one-third of patients with abnormal ultrasound scans (37.33%, n=28) and in 1 out of 100 patients with normal ultrasound results (1.55%,

n=2). Adhesions were diagnosed in more than 1 in 20 patients with abnormal ultrasound scans (5.33%, n=4) and in none of the patients with normal ultrasound scans.

Regarding the investigations performed, 65.68% (n=134) of the patients included in the cohort underwent hysterosalpingography (HSG), while 34.31% did not undergo this investigation (n=70). The results obtained indicated that almost half of the patients who underwent the investigation were diagnosed with blocked fallopian tubes - 47.01% (n=63), while 52.99% of patients had normal results (n=71).

Of the 204 patients included in the study, 158 underwent hysteroscopy, with normal results in most cases: 82.28% of patients had favorable results, with no changes observed during hysteroscopy (n=130), while 17.72% of patients had abnormal results following hysteroscopy (n=28).

5.4. Discussions

The study was conducted to identify the cause of female infertility among patients who came to the clinic hoping to become pregnant. The age range of the sample was between 20 and 48 years, half of whom were over 36 years old, with an average age of 35.98 years. It was found that patients with secondary infertility were slightly older, but there was no significant difference. Studies in the literature show that the average age of couples conceiving their first child has increased significantly in the last 10 years, due to the desire for professional success, late marriages, but also to widespread access to contraception and longer life expectancy. [46] It has been found that women over the age of 35 have a significantly higher risk of infertility, miscarriage, pregnancy-related pathologies, or congenital malformations. [47]

Clinical studies have shown that smoking is associated with decreased fertility. [48] In the study group, no significant association was found between tobacco use and the type of primary or secondary infertility, with most patients being non-smokers (81.86%).

All patients included in the study group underwent transvaginal ultrasound examination - 1 in 3 patients had abnormal ultrasound results (36.76%). It was noted that the percentage of patients with abnormal ultrasound results and a diagnosis of primary infertility (41.45%) was significantly higher than that of patients with abnormal ultrasound results and secondary infertility (26.56%). Uterine fibroids are the most common benign tumors in women of reproductive age, with transvaginal ultrasound being the first-line investigation. [49]

A large proportion of the patients included in the cohort underwent hysterosalpingography (65.68%); of those who underwent the investigation, 47.01% had blocked fallopian tubes, more than half of them bilaterally. According to the literature, HSG examinations showed that the most frequently diagnosed pathology in patients with infertility was tubal obstruction, and this type of investigation is essential in the evaluation of patients with infertility. [50]

Of the total number of patients included in the study, 158 underwent hysteroscopic evaluation, with 17.72% having abnormal results. Regardless of the pathology detected in patients with abnormal hysteroscopy, it was found that hysteroscopy plays a remarkable role in the diagnosis and treatment of uterine pathologies,[51] and the results after operative hysteroscopy showed a 39% increase in the conception rate. [52] Transvaginal ultrasound correlated with hysteroscopic results significantly increased the chances of correct treatment of gynecological pathologies. [53]

5.5. Partial conclusions

The study highlights that infertility is a multifactorial pathology, with both female and male causes. The paper focuses on female infertility, which requires a multidisciplinary approach. Age is an important prognostic factor in achieving pregnancy, directly related to the number and quality of oocytes. In addition to the personal medical history of each patient included in the study, particular attention is paid to various gynecological conditions. All of this highlights the importance of early diagnosis and personalized therapeutic intervention.

Following the analysis carried out in the first study, it can be concluded that female infertility is a complex problem involving multiple factors, ranging from the age of the patients and the quality of the oocytes to the presence of various pathologies. It has been shown that primary and secondary infertility do not differ significantly in terms of associated pathologies, suggesting the need for a standardized approach to diagnosis and treatment. Paraclinical investigations allow the diagnosis of patients, enabling physicians to adopt an appropriate therapeutic plan. Also, correctly identifying and treating non-gynecological conditions that can affect fertility is a vital part of infertility management. So, it is important for the treatment strategy to be personalized, considering that each patient has a unique medical history.

6. Study II: "The role of hysteroscopy in diagnosing infertility in young women"

6.1. Introduction

Infertility is a complex condition caused by a variety of mechanisms, [54] which is why it does not usually appear as a single pathology and correct diagnosis and treatment are the main objectives in order to achieve pregnancy. [55]

Transvaginal ultrasound and hysteroscopy are the most important non-invasive techniques for evaluating infertile patients. [56] Transvaginal ultrasound is the first-line technique for evaluating the uterus and adnexa, and color Doppler examination significantly increases the accuracy of the technique. [57] Hysteroscopy combines high diagnostic value and allows, in addition to diagnosis and treatment, histopathological evaluation of tissues. [58]

The aim of the study was to identify potential uterine causes of infertility in women evaluated hysteroscopically and to evaluate the results obtained after operative hysteroscopy where appropriate.

6.2. Material and methods

The objectives of the study were to evaluate the particularities of hysteroscopic examinations in patients diagnosed with infertility, based on the idea that gynecological pathology is common among women with infertility, and that correct diagnosis and treatment of the causes can significantly improve the final results.

The main goal was to evaluate the results of hysteroscopies available in the clinic and analyse the data obtained, with the ultimate goal of identifying associated pathologies and comparing the long-term results obtained from operative hysteroscopies. To this end, the inclusion and exclusion criteria were followed.

The prospective study was conducted at the Bucur Maternity Hospital, "Saint John" Emergency Clinical Hospital, Bucharest and included patients diagnosed with infertility who underwent hysteroscopic evaluation at our clinic. The study period was 24 months starting in February 2021. Available data from patient observation notes, transvaginal ultrasound results, hysteroscopy, hysterosalpingography, MRI or chromopertubation, postoperative results where applicable, as well as obstetric results and pregnancy-related pathologies were analysed.

The inclusion criteria were age over 18 years, diagnosis of infertility, and hysteroscopy performed as a diagnostic or treatment method.

The exclusion criteria were total or partial lack of available data, age under 18 years, and unavailability of patient contact details in the observation sheets (email or phone number).

The study was approved by the Ethics Committee (12.04.2023, number 9082).

All parameters obtained were statistically analysed using IBM SPSS Statistics version 21, and quantitative variables were expressed as mean and standard deviation. The data were collected using Excel version 2007. The statistical test used in the data analysis was the Chi-square test.

6.3. Results

The study included 75 patients diagnosed with primary infertility (n=21) and secondary infertility (n=54). Patients with primary infertility accounted for 28% of cases, and those with secondary infertility accounted for 72% of cases.

Most of the patients diagnosed with infertility had pelvic pain, menometrorrhagia, or amenorrhea, but a significant proportion of them were asymptomatic. Symptomatic patients accounted for 64% of cases (i.e., 2 out of 3 patients) (n=48), and asymptomatic patients accounted for 36% of cases (n=27).

The association of menometrorrhagia was frequently reported by the women included in the cohort, with 54.67% of them reporting the association of menometrorrhagia (n=41) (more than 1 in 2 patients), most often among patients with secondary infertility. In the study group, 17.33% of patients reported pelvic-abdominal pain (n=13), which was reported more frequently by women with secondary infertility. The incidence of amenorrhea was low in the study population, occurring in 6.67% of patients (n=5), with no association between amenorrhea and the type of infertility.

All patients included in the group underwent transvaginal ultrasound (100%, n=75), supplemented by other investigations. Hysteroscopy was performed in 80% of cases (n=60), respectively in 71.43% of patients with primary infertility (n=15) and in 83.33% of those with secondary infertility (n=45). Hysterosalpingography was performed in 12% of the total number of patients (n=9); the investigation was recommended significantly more frequently to patients with primary infertility, being performed in 28.57% of these (n=6) and only 5.56% of those with secondary infertility (n=3) (χ^2=7.585, p=0.006). 9.33% of

patients (n=7) underwent MRI, and chromopertubation was performed in 6.67% of cases (n=5).

Following ultrasound examination, 41.33% of patients were diagnosed with endometrial polyps (n=31), with a significantly higher incidence among those with secondary infertility. Following hysteroscopy, endometrial polyps were diagnosed in 18.67% of patients (n=14), with a higher incidence among patients with secondary infertility. Transvaginal ultrasound and hysteroscopy allowed the diagnosis of endometrial polyps in 60% of the patients included in the study (n=45), with a higher incidence among women with secondary infertility (χ^2=8.642, p=0.003).

Uterine fibroids were identified in 14.67% of patients (n=11), with a higher incidence among patients with secondary infertility. Tubal pathology was associated only with patients with secondary infertility, being diagnosed in 11.11% of them (n=6).

After treatment for the cause of infertility, the long-term outcome was analysed: 40% of the patients included in the group achieved at least one pregnancy (n=30), while 32% failed to conceive (n=24); for 28% of the patients, no information was available (n=21). No significant differences were noted in terms of achieving pregnancy between patients with or without endometrial polyps, with both groups of patients conceiving in 40% of cases. Among the patients who achieved pregnancy, 1 in 2 had associated pathologies during pregnancy: HTA in 20% of cases (n=6), anemia in 10% of cases (n=3), gestational diabetes in 10% of cases (n=3), obesity in 6.67% of cases (n=2), thyroid pathology in 3.33% of cases (n=1). Most pregnant women had no complications during pregnancy, but a significant proportion (40% of pregnant women, 2 out of 5 pregnant women) were diagnosed with placenta previa in 20% of cases (n=6), threatened miscarriage in 13.33% of cases (n=4), and preeclampsia in 6.67% of cases (n=2).

6.4. Discussions

The study was conducted to evaluate the impact of hysteroscopy in the diagnosis of infertility in patients who presented at the clinic; the results were evaluated in the short and long term. Hysteroscopy is considered an important and necessary step in counselling infertile patients, with high sensitivity and specificity compared to other assessment methods. [59]

In the study group, it was found that patients with secondary infertility were significantly more numerous than those who presented with primary infertility (n=54, 72% of patients with secondary infertility versus n=21, 28% of patients with primary infertility).

Among the patients who underwent hysteroscopy, most of those with associated endometrial polyps had secondary infertility (1 in 5 patients, n=12, 22.22%) and a small proportion had primary infertility (n=2, 9.52%). Endometrial polyps are one of the most common pathologies diagnosed during uterine cavity evaluation in patients diagnosed with infertility; endometrial polyps have been found to negatively influence the chances of achieving pregnancy, and the rate of pregnancies achieved through in vitro fertilization was negatively affected by the presence of endometrial polyps. [60]

A study published in 2023 reported that the spontaneous pregnancy rate after operative hysteroscopy was 27.9%, with 50% of cases achieving IVF success following the procedure in patients who had previously undergone another assisted reproductive procedure without success. Among patients who achieved pregnancy, spontaneous delivery or spontaneous abortion occurred in 12.7% of cases. [61]

6.5. Partial conclusions

Secondary infertility was diagnosed more frequently than primary infertility in the patients included in the study group, and the most common symptoms reported by patients were menorrhagia, metrorrhagia, pelvic pain, or secondary amenorrhea, most often associated with patients with secondary infertility. Endometrial polyps and uterine fibroids are the gynecological conditions most commonly associated with infertility. Transvaginal ultrasound was correlated with hysteroscopy, and the results of operative hysteroscopies were subsequently analysed and found to be favorable regardless of the size or location of endometrial polyps or uterine fibroids in the patients included in the present study.

The study confirms that hysteroscopy plays an essential role in the diagnosis of infertility in young women, having a significant impact on the management of these cases; due to its minimally invasive nature, this technique not only helps to identify abnormalities that are difficult to diagnose using other techniques, but also allows direct surgical treatment when necessary, which can increase the chances of successful fertility treatments.

Another important aspect of the study is that early identification of the causes of infertility using hysteroscopy can significantly contribute to reducing patient anxiety and to faster and more effective treatment.

These observations underscore the importance of integrating hysteroscopy into standard protocols for the evaluation of infertile patients, especially in young women, for whom early treatment can have a significant impact on the success of achieving pregnancy.

7. STUDY III - "The psycho-emotional impact and financial stress of infertility diagnosis. How strong is the impact on patients?"

7.1. Introduction

Studies in the literature have attributed stress to problems related to the inability to conceive, including women's fear of the unknown, social isolation, stigmatization, and financial pressure. [62] In some cases, the consequences have led to discontinuation of treatment and instability in the couple's relationship. Anxiety, depression, and a reduced quality of life have also been reported. [63]

A study reviewing publications from the last 10 years in the literature on infertility as a primary diagnosis and the psychological impact of this diagnosis found, after analysing 7,947 articles, that anxiety, depression, and decreased quality of life are significant among infertile couples, both men and women, with similar experiences regardless of culture. [64] Studies report that good relationships with family, support, and partners are the main protective factors. [65] The prevalence of stress in infertile couples undergoing assisted reproductive treatment was twice as high as in the general population. [66]

The high cost of treatment for infertile couples and the lack of insurance coverage for related treatments limit access to medical services [67], but total costs vary from country to country. [68]

7.2. Material and methods

The study aimed to include patients with infertility and identify the impact that this diagnosis has on them from a psychological, emotional, relationship, and financial perspective.

The working hypothesis was the need to further explore the data already available in the literature, with the study targeting patients in Romania.

The prospective study was conducted by distributing a questionnaire via social media over a period of four months (January 20 to May 25, 2024). The questionnaire was addressed to women diagnosed with infertility in Romania and included 35 questions aimed at highlighting the impact of this diagnosis.

The inclusion criteria were age over 18 and inability to conceive for at least six months; all women participating in the questionnaire were married or in a stable relationship with a diagnosis of infertility or were already undergoing treatment to conceive.

Exclusion criteria were age under 18, unprotected sexual intercourse for less than 6 months and infertility in the couple due only to male factors (no female infertility).

The data obtained were statistically analysed using IBM SPSS Statistics 21 and Excel version 2007. The statistical tests used were the Chi-square test, the Mann-Whitney U test, and the Kruskal-Wallis H test.

7.3. Results

The study included 523 women aged between 19 and 43, as follows: under 20 years of age, 0.76% of women who responded to the questionnaire (n=4); between 21 and 30 years of age, 29.64% of the total number of women (n=155), between 31 and 40 years old 58.89% (n=308), and over 40 years old 10.71% of the women participating in the study (n=56). Most of the respondents came from urban areas (79.92%, n=418) and less frequently from rural areas (20.08%, n=105).

The patients who completed the questionnaire weighed between 47 and 89 kg, 10.13% of the participants (n=53) weighed less than 50 kg and 13.19% of the women who responded to the questionnaire (n=69) weighed over 80 kg.

The questionnaire included a question about cigarette consumption, which showed that non-smokers predominated among the patients included in the group (70.17%, n=367), with less than one-third of respondents being smokers (29.83%, n=156 – approximately 1 in 3 women were smokers).

Dysmenorrhea was reported frequently, with approximately 4 out of 5 women with infertility reporting this symptom (frequently or occasionally). In the case of dyspareunia,

more than 1 in 2 women with infertility reported being affected frequently or occasionally. Respondents reported being diagnosed with endometriosis in 34.23% of cases (n=179), polycystic ovaries in 19.12% of cases (n=100), or pelvic inflammatory disease in 11.47% of cases (n=60).

Most of the respondents had never managed to conceive spontaneously (without the help of assisted reproductive techniques), representing 59.08% of cases (n=309, 3 out of 5 women). 91.20% of participants said they were hopeful about the future with regard to their family (n=477), while 8.80% said they were pessimistic (n=46). It was observed that perceptions of the future of the family varied significantly depending on the age of the respondent, with younger women looking to the future with more hope, while as they get older, their optimism about getting pregnant tends to decrease (χ^2=43.479, φ =0.288, $p \leq 0.001$). Religion also influences the confidence with which respondents view their family's future, with 75.47% of women with a positive perception of the future stating that religion is a source of moral support (n=360), while among women who are less optimistic about the future, only 54.35% said they find support in religion (n= 25).

In 81.45% of cases, the study participants said they sleep between 6 and 9 hours per night (n=426) and in 1.53% of cases more than 9 hours per night (n=8). A significant proportion of women with infertility reported sleeping less than 6 hours per night (17.02%, n=89, i.e., 1 in 6 women sleep less than 6 hours per night).

The diagnosis of infertility was found to induce considerable stress for most respondents. Most women reported that the impact was major (score 5, 37.48%, n=196), and a considerable percentage of them estimated that the level of stress was high (score 4, 27.15%, n=142) or medium (score 3, 25.81%, n=135).

It was relevant that the stress of infertility-related expenses (diagnosis, treatment, procedures) contributes to the overall level of stress caused by the diagnosis itself. The patients who responded to the questionnaire mentioned that their main fears at the moment are that they will never be able to have a child (56.79%, n=297), the significant stress caused by the infertility diagnosis itself (41.68%, n=218), the impact of infertility on their relationship (31.74%, n=166), or their advanced age (30.78%, n=161). Patients were confident that their infertility problem would be resolved within the next 12 months, with most of them being optimistic (score 5, 39.39%, n=206) and only 11.09% being pessimistic about their diagnosis (score 1, 11.09%, n=58). It was noted that the association of health problems (in general) contributes to a decrease in the respondents' optimism regarding the resolution of infertility.

7.4. Discussions

Infertility is a chronic and poorly controlled stress factor with negative psychological impact and long-lasting social consequences. Studies conducted on infertile couples who have been unable to conceive show that most women have managed to adapt psycho-emotionally, although they stated that the absence of a child represents a major loss. [69]

A study analysing several articles published between 1955 and 2019 concluded that psychological distress in both women and men diagnosed with infertility has negative consequences on the fertility of both sexes and alters the proper functioning of the endocrine glands and the immune system. [70]

Most of the young patients who responded to the questionnaire are hopeful about the future, but as they get older, their optimism about getting pregnant decreases. Solid studies already published in the literature associate advancing age with decreased fertility and increased fears; there is an accelerated decline in the chances of achieving pregnancy after the age of 35. [71]

The most commonly recommended psychological methods for women with infertility are based on cognitive behavioural therapy and various stress reduction techniques; studies recommend psychological assistance throughout the course of infertility treatment in order to achieve better results. [72]

7.5. Partial conclusions

This study found that patients who received psychological support, regardless of the type, showed a greater ability to cope with stress and adopt a more positive attitude. Psychological support is essential for managing negative emotions and strengthening motivation to persevere in the face of difficulties. It was also highlighted that religious and spiritual support plays an essential role in facilitating the adaptation process in patients with infertility. Faith and support from the religious community can help reduce anxiety and increase resilience by providing meaning and a broader perspective on life experiences. This becomes a source of comfort in times of distress and prayer can deepen feelings of hope and confidence in the possibility of a solution.

In conclusion, the study highlights the complexity of infertility, which is not limited to the medical aspect, but extends significantly to psycho-emotional and financial aspects. A comprehensive approach to infertility treatment includes both medical interventions and

psychological and social support and is essential for improving the well-being of affected patients.

8. Final conclusions and personal contributions

The research presented in this paper highlights the complexity of infertility, a phenomenon that cannot be attributed to a single factor, but rather represents a multifactorial entity influenced by the complex interaction between biological, psychological, socioeconomic, and cultural factors. These interconnected dimensions require a holistic and integrated approach to the assessment and treatment of infertility, with the main aim of the research being to highlight the importance of a multidisciplinary strategy.

One of the main strengths of this research is that it highlights the fact that infertility is a challenge that has profound implications for the psychological health of patients and multiple socioeconomic implications. Thus, the studies included in this thesis emphasize the need for personalized assessment and treatment that takes into account all the influences of this condition, from initial diagnosis to long-term monitoring of patients.

The first study highlighted that infertility cannot be attributed to a single cause, but is a complex condition influenced by a combination of biological, genetic, and physiological factors that interact with each other in a complex way. Infertility cannot be reduced to a simple deficiency of a function or organ, but involves multiple levels of influence that affect the ability to conceive. All these variables combine in different ways depending on each individual case, which means that diagnosis and treatment need to be personalized and adapted to each patient. So, there's no standard approach to infertility, but rather a need for detailed assessment and specific intervention that takes into account all the elements involved.

The second study on the effectiveness of hysteroscopy explored its essential role in the diagnosis and treatment of uterine conditions that can contribute to infertility, demonstrating its effectiveness in both assessing causes and therapeutic interventions. The study highlighted that hysteroscopy is extremely useful in identifying specific conditions such as endometrial polyps, submucosal or intramural fibroids that mark the uterine cavity, uterine synechiae, or congenital uterine malformations that can have a significant impact on fertility. It was also highlighted that many of these conditions can be effectively treated by hysteroscopic interventions, improving the chances of subsequent conception.

Regarding the implementation of hysteroscopy in practice, the study suggests that it should be part of the initial evaluation of patients with infertility, especially in young patients or those diagnosed with unexplained infertility. It was also highlighted that hysteroscopy, in addition to its usefulness in the direct treatment of uterine pathologies, can contribute significantly to better planning of assisted reproduction treatments. Thus, hysteroscopy has the potential to optimize the chances of conception through personalized treatments and rapid interventions.

Regarding the psycho-emotional impact and financial stress on infertile women, the **third study** explored in depth the psycho-emotional and financial consequences of infertility, highlighting how they can significantly influence patients' well-being and decisions regarding fertility treatments.

In addition to physical challenges, infertility causes significant stress and anxiety, profoundly affecting patient's emotional state. Often, the diagnosis of infertility generates negative feelings, which are exacerbated by social or family pressure that emphasizes a woman's role as a mother. All of this can lead to social isolation and interpersonal conflicts, especially within the couple's relationship.

The study also highlighted that, in addition to the emotional impact, infertility treatments also bring a significant financial burden. Assisted reproduction procedures are often expensive and can lead to significant financial stress, especially when treatments are needed over a long period of time.

In this context, the study highlighted that there is a close correlation between the psycho-emotional and financial impact, and that patients facing financial difficulties are at greater risk of developing disorders such as anxiety or depression.

This study highlighted the need for adequate psychological support to help patients cope with the stress and anxiety associated with infertility, as well as financial support to reduce the economic burden of treatment.

In the **general conclusion** of the thesis, I highlighted the importance of implementing integrated infertility management that addresses not only medical aspects, but also psychological and socioeconomic aspects. A holistic approach would contribute to improving the chances of conception and optimising the quality of life of these patients throughout the treatment process. In this regard, the integration of a multidisciplinary framework in infertility treatment is essential for maximum success. Thus, treatment teams should be made up of professionals from different fields (gynecologists, psychologists, social workers) who work together to provide comprehensive support to patients.

This research provides a solid basis for the development of personalized treatment protocols, taking into account the complexity and particularities of each case of infertility.

As **personal contributions**, the research has made a number of significant contributions to the field of infertility, highlighting the complexity of the subject and the need for integrated approaches. The text has expanded the literature through a detailed analysis of infertility as a multifactorial phenomenon. The studies were characterized by a rigorous research methodology that included multiple data analyses. Through the use of a questionnaire, we were able to obtain varied and relevant data that reflects the condition of the patients.

The data studied highlighted the interconnection between biological, psychological, and social factors, promoting a holistic approach to the assessment and treatment of infertility. By highlighting these complex relationships, the thesis contributes significantly to the development of a theoretical framework that can guide future research in the field. Thus, the results obtained have not only deepened our understanding of the phenomenon of infertility, but also created a starting point for exploring innovative solutions in the field of reproductive health.

Another important contribution of the research is the proposal of more personalized and integrated approaches to infertility management, taking into account not only the medical dimension but also psychological, social, and economic aspects. This can provide a framework for action that can support both health professionals and patients in adapting therapeutic strategies to individual needs. In this regard, the thesis promotes a multidisciplinary model for optimizing treatments and supporting patients in a comprehensive manner.

The thesis highlights the need for a better structured support system at the level of health institutions to facilitate patients' access to the necessary resources. This would include financial support as well as counselling and education services. The research proposes directions for the development of public health policies to ensure the management of these cases.

The personal contributions of this research include the proposal of longitudinal studies to track the long-term evolution of patients. These studies could deepen the understanding of how integrated interventions influence both therapeutic success and the quality of life of the subjects.

I believe that **future research** should focus on evaluating the effectiveness of integrated investigations.

Longitudinal studies tracking patients' long-term outcomes could provide valuable insights into how different types of patient support influence outcomes. These data could contribute to the development of more effective protocols tailored to individual needs.

Another important aspect is promoting public awareness of infertility. Informing the public can help reduce the stigma and social isolation experienced by many of these women.

Future research could also explore the effects of integrative approaches on the family and interpersonal relationships, given the significant impact that infertility can have on a couple's life.

Through all these contributions, the research presented in this thesis advances the scientific understanding of infertility as a multifactorial phenomenon, but also proposes concrete solutions for improving clinical interventions and support strategies. Thus, the thesis opens new perspectives for future research and the development of more effective approaches to infertility management.

One of the essential proposals for the future management of infertility is the creation of an approach protocol that includes the psychosocial assessment of women with infertility. An important first step in this direction would be to create a detailed psychosocial profile of the patient, allowing for a clearer understanding of her emotional, psychological, and social context. This profile should be developed at the beginning of the diagnosis and treatment process to help the multidisciplinary team adapt their interventions accordingly.

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