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PHYSIOTHERAPY-BASED EXERCISE INTERVENTION IN INFERTILITY CARE FOR WOMEN WITH DIMINISHED OVARIAN RESERVE

PhD Thesis

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LIST OF ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists

ADIM: abdominal drawing-in maneuver

AFC: antral follicle count

AMA: advanced maternal age

AMH: anti-Müllerian hormone

ART: assisted reproductive technology

BMI: body mass index

CoQ10: coenzyme Q10

CSE: core stabilization exercise

DB: diaphragmatic breathing

DOR: diminished ovarian reserve

E2: estradiol

e.g.: exempli gratia (for example)

ESHRE: European Society for Human Reproduction and Embryology

FSH: follicle-stimulating hormone

HFEA: Human Fertilization and Embryology Authority

ICSI: intracytoplasmic sperm injection

IVF: in vitro fertilization

IVF-ET: in vitro fertilization - embryo transfer

LAM: levator ani muscle

LBP: low back pain

LH: luteinising hormone

LM: lumbar multifidus muscle

LPHC: lumbar-pelvic-hip complex

MET: metabolic equivalent method

MI: myo-inositol

OS: oxidative stress

PA: physical activity

PCOS: polycystic ovary syndrome

PIA: physical inactivity

PFM: pelvic floor muscle

POI: premature ovarian insufficiency
RCT: randomised controlled trial
ROS: reactive oxygen species
SEM: standard error of the mean
SB: sedentary behavior
TLF: thoracolumbar fascia
TrA: transversus abdominis muscle
WHO: World Health Organization

1. INTRODUCTION

1.1. Historical background of physical exercise in relation to fertility

Human reproduction, covering all aspects from conception to fertility and infertility, has long been a central subject of scientific, medical, and social inquiry.-Throughout history, a woman's social value was frequently linked to her reproductive capacity, and childlessness often resulted in social marginalization and stigma. With the development of medical science, particularly the emergence of assisted reproductive technologies (ART), both the clinical understanding and the societal perception of infertility have undergone profound changes. In recent decades, increasing attention has been directed toward holistic, lifestyle-based approaches that integrate nutrition, mental health, and physical activity into infertility care (1).

The therapeutic use of physical exercise has deep historical roots. In ancient Egypt, the Kahun Gynecological Papyrus (c. 1825 BC) already recommended dietary modifications and targeted physical exercises to support conceptio (2, 3). Similarly, in ancient India, Susruta (c. 600 BCE) emphasized individualized, moderate-intensity physical activity for both prevention and treatment, while warning against sedentary lifestyle and excessive caloric intake (4). These early sources reflect an intuitive recognition of the interconnection between movement, metabolic balance, and reproductive health. Classical Greek medicine further systematized the therapeutic application of exercise. Physicians such as Herodicus, Hippocrates, and Galen laid the foundations of Western exercise-based therapy (5), consistently promoting moderation and balance. Hippocrates was among the first to describe the association between obesity and infertility, thereby identifying body composition as a determinant of reproductive health (6). This principle continues to hold a central role in contemporary reproductive medicine. During the medieval period, Arab scholars significantly expanded lifestyle-oriented medical thinking. Avicenna (980–1037 AD), in his Canon Medicinae, described physical activity, nutrition, sleep, and psychological well-being as fundamental determinants of health and fertility (7). He also recognized the relationship between obesity and infertility and suggested that a lower body mass index (BMI) could improve reproductive outcomes (8, 9). In parallel, the European Trotula manuscript (12th century) emphasized hygiene, balanced nutrition, regular physical activity, and stress reduction as key elements in the management of female infertility (10), highlighting the early integration of movement and lifestyle factors into gynecological care. The Renaissance marked a turning point through the rapid advancement of anatomical and biomechanical knowledge. Leonardo da Vinci (1452–1519) made exceptional contributions to the understanding of reproductive anatomy, posture, gait, and muscle function (11-14). Among his most significant achievements was the precise identification of the human body's center of gravity in standing posture and during various phases of walking and running (15). He also accurately depicted the central tendon and musculature of the diaphragm, providing an advanced understanding of its role in respiration (16). These observations, remarkably precise for their time, have remained scientifically valid for centuries and form an important conceptual bridge between movement science and physiological function.

From a historical perspective, infertility treatment can thus be regarded as an evolving process in which physical exercise has consistently played a therapeutic role, albeit with varying degrees of emphasis. As summarized by historical analyses (1), physical activity - whether applied intuitively or based on empirical observation - has long been considered an integral component of fertility support. Despite this long-standing tradition, the relationship between structured exercise and reproductive health remains insufficiently explored within a rigorous scientific framework. This historical gap provides a strong conceptual foundation for the contemporary investigation of physiotherapy-based interventions in infertility care.

Female fertility encompasses biological, emotional, and social dimensions. Beyond its biological aspects, childbearing carries profound psychological and existential significance; consequently, infertility is increasingly conceptualized as a complex biopsychosocial condition with substantial psychological consequences (17) and a growing social and public health burden worldwide (18).

Drawing on the preceding historical and scientific context, the present dissertation focuses on ovarian rejuvenation, examining whether a targeted physiotherapy-based exercise programme can contribute to the regeneration and optimization of ovarian function. The central hypothesis is that specific forms of physical activity may not only support general health but also exert a regulatory and facilitating effect on reproductive function.

The therapeutic exercise programme is rooted in the European body culture of the 19th and 20th centuries. It incorporates the principles of Ling’s Swedish gymnastics, including conscious breathing, body awareness, and anatomically informed movement, while drawing inspiration from early 20th-century women’s “harmonic gymnastics” traditions (Stebbins, Ali, Stack), which emphasize posture, relaxation, fluid transitions, and psychophysical balance (19, 20). The programme also integrates selected elements of yoga, while remaining firmly grounded in the European physiotherapeutic tradition. Furthermore, the methodological foundations are informed by Bess Mensendieck’s approach, which linked posture correction and muscular awareness to women’s health, as well as by its Hungarian adaptation developed by Alice Madzsar (21, 22). As a Hungarian physiotherapist, both my professional identity and the structure of the programme are deeply shaped by this heritage. Accordingly, the method places particular emphasis on conscious transitions, bodily awareness, and the integration of physical and mental processes.

1.2. Infertility as a public health issue

Infertility affects approximately 10–15% of couples of reproductive age globally, and has emerged as a significant public health issue (23, 24). Beyond its profound emotional and psychological impact on affected individuals and families, infertility presents considerable challenges for healthcare systems due to the growing demand for assisted reproductive technologies, which are often costly and not universally accessible (25). This complex condition is influenced by a combination of epidemiological, demographic, and biological factors. In the following sections, the epidemiology of infertility will be examined, alongside key trends such as the phenomenon of delayed childbearing and physiological factors including diminished ovarian reserve, which collectively contribute to the increasing prevalence and public health relevance of infertility.

1.2.1. The epidemiology of infertility as a public health problem

Infertility is a condition of the male or female reproductive system, defined as failure to conceive after 12 months or more of regular unprotected sexual intercourse (26). Infertility can be categorised as primary or secondary. Primary infertility is defined as the inability to conceive, while secondary infertility is characterised by the failure to conceive after at least one previous pregnancy. Infertility can be caused by factors affecting either the male or the female (26). The etiological distribution of infertility varies across different sources, with the proportions of male, female, and unexplained infertility showing considerable variation. These discrepancies partly reflect differences in the populations studied as well as methodological variations (27). Beyond biological determinants, infertility is increasingly recognised as a multifactorial condition influenced by lifestyle, behavioural, and psychosocial factors, which may affect reproductive function even in the absence of identifiable structural pathology (26, 28).

Data reported by the World Health Organization (WHO) indicate a lifetime infertility prevalence of 17.5% and an intermittent prevalence of 12.6%, underscoring the significant public health impact of this condition (26). The WHO's first global guideline on infertility (2025) emphasizes that prevention and management of infertility should be integrated into health systems and highlights the role of lifestyle factors—such as healthy diet, physical activity, and avoidance of risk behaviours—in individuals planning or attempting conception. Although these guidelines do not provide specific therapeutic recommendations (e.g., structured exercise programs), they generally support lifestyle interventions as part of preventive strategies to enhance reproductive health and fertility (29).

Globally, there is a rising trend in the utilization of assisted reproductive technologies (ART) (25, 30-32) partly related to delayed childbearing (33-35). The increasing global use of ART reflects both rising demand and delayed family formation; however, access remains limited in many countries, underscoring the potential significance of inexpensive, non-invasive lifestyle interventions during the pre-ART period (29, 36).

Infertility linked to late childbearing age is a distinct form of infertility. This condition is not idiopathic, as the underlying cause is maternal advanced age itself, which is linked to diminished reproductive potential (37). Delayed childbearing combined with modifiable lifestyle factors influences reproductive health, which is particularly relevant for the prevention of infertility and the study of natural conception-supportive interventions (29).

1.2.2. The late childbearing phenomenon

In the case of late childbearing or advanced maternal age (AMA), the mother is aged 35 or over at the time of childbirth (38). Late childbearing is associated with a sharp decline in a woman's ability to conceive. AMA is thus a significant risk factor associated with adverse pregnancy outcomes in both high and low income countries (33, 39).

The postponement of childbirth is one of the salient demographic changes that has occurred in developed countries in recent decades. A significant outcome of delayed childbearing is the rise in subfertility and infertility rates among both women and men (40, 41).

This phenomenon has begun to affect Hungarian families on a massive scale in recent decades. In our country, childbearing behaviour has changed fundamentally over the past two decades. Society is changing, and birth trends are beginning to change as well. The postponement of childbearing is a complex phenomenon. While the causes are primarily social, the consequences are largely health and demographic (42), with a relatively high failure rate (partly for biological reasons) to achieve these late childbearing plans. Delayed childbearing has a negative impact on both population numbers (demographic indicators) and socio-economic factors (43). In Hungary, the largest absolute increase in fertility in the decade since 2010 has been among women in their 30s, including those aged 34-35, but the rate of increase is highest around the age of 40 and in the few years after. Overall, the role of the over-40s is becoming increasingly important both in terms of numbers and proportions: from 0.5% of all live births in 1990 to 1.5% in 2010 and 3.3% in 2020 (44). According to KSH data, childlessness in Hungary has nearly doubled in a short period of time. While childlessness among women born in 1967 was 10.4% at age 44, 18.4% of women born in 1977 (at age 44) were childless. Among women born in 1983, 24.8% will still be childless in 2022, when they will be 39 years old. The chances are high that more than 20% of this cohort will remain childless (45).

Similar trends are observed across Europe, where EUROSTAT 2023 data show an increasing average age of first childbirth alongside a declining fertility rate, reflecting a broader shift towards delayed parenthood and its associated reproductive challenges (34). According to the National Vital Statistics Reports, delayed childbearing in the United States has steadily increased over the past three decades, with women aged 35 and older contributing a growing share to the overall fertility rates. This demographic shift corresponds with observed declines in fertility among younger age groups and highlights the increasing relevance of age-related infertility (35). In addition to Europe and the United States, rising infertility rates linked to delayed childbearing are also observed in East Asia, notably in China (33). Socioeconomic shifts, urbanization, and evolving reproductive behaviors have contributed to increasing maternal age at first childbirth, which is closely associated with diminished fertility and higher infertility prevalence. Recent demographic analyses estimate infertility rates in China to be around 12-15%, reflecting a growing public health concern that parallels global trends (42). This highlights the widespread nature of reproductive aging challenges and underscores the importance of developing accessible interventions across diverse populations.

1.2.3. Diminished ovarian reserve

One of the earliest ageing organs is the ovary, as it ages at a faster rate than other body systems. Ovarian aging is widely regarded as the primary catalyst of female bodily aging, driving the process of aging in multiple organs (46). The process of ovarian ageing is a multifaceted phenomenon influenced by numerous factors, including lifestyle, medical, genetic, autoimmune, environmental and idiopathic factors. Therefore, the process of ovarian ageing can be categorised as physiological ovarian ageing, which is characterised by an age-related decline in the functional ovarian reserve and the onset of premature ovarian failure (POF) due to the aforementioned factors (47).

An age-related decline in follicle numbers and a concomitant decline in egg quality lead to a gradual decline in fertility (48). The term "ovarian reserve" is used to describe the quantity of oocytes a woman possesses at a given point in her life. Beyond its quantitative aspect, ovarian reserve reflects a dynamic functional parameter that is shaped by age, genetic background, and environmental factors (49). The process of ovarian senescence is characterised by a gradual decline in the quality of oocytes over time. This phenomenon is associated with a reduction in the probability of a fertilised oocyte resulting in a live birth (50).

Advanced maternal age is associated with a progressive decline in ovarian reserve (DOR) (51), which is commonly assessed by measuring anti-Müllerian hormone (AMH) levels, antral follicle count (AFC), and basal follicle-stimulating hormone (FSH) concentrations (52). Ovarian reproductive potential can be predicted by both ultrasound imaging and biochemical measurements of serum AMH and FSH (50, 53, 54).

AMH is secreted by granulosa cells and is widely used as a biomarker of ovarian reserve. AMH concentrations decrease progressively with advancing age and correlate with the size of the follicular pool, as well as with the remaining number and quality of oocytes. In contrast, basal FSH levels tend to rise as ovarian reserve diminishes over time (51, 55, 56).

In infertility care, DOR is recognized as a clinical diagnosis reflecting reduced ovarian reproductive capacity. In affected patients, this reduction is typically associated with a lower number of retrieved oocytes, fewer embryos available for transfer, and a decreased likelihood of obtaining high-quality embryos, which may adversely influence pregnancy outcomes (57). Significant global problem has emerged due to the rise in infertility caused by diminished ovarian reserve. Although the prevalence and incidence of DOR is increasing (51, 58), there is currently no effective treatment for this condition.

Internationally established clinical guidelines provide a framework for assessing ovarian response and diagnosing diminished ovarian reserve. The European Society for Human Reproduction and Embryology (ESHRE) recommends testing AFC or AMH (using the Bologna criterion of AMH < 1.1 ng/mL) to predict ovarian response and diagnose reduced ovarian reserve (59). According to the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM), threshold values such as AMH levels below 1 ng/mL and FSH levels above 10 mIU/mL are commonly used benchmarks for identifying diminished ovarian reserve and poor ovarian response (50, 54, 60).

Given that no singular metric of ovarian reserve possesses 100% specificity in detecting DOR, this study employs a mix of biochemical and transvaginal ultrasound assessments (including FSH, LH, E2, AMH and AFC) to evaluate alterations in ovarian reserve.

1.3. Current approaches in reproductive medicine

While assisted reproductive technologies have revolutionized infertility treatment worldwide, their effectiveness remains limited in certain patient groups. For instance, women with DOR often experience poor outcomes even with advanced reproductive interventions (61-64). These limitations have prompted growing interest in adjunctive strategies, including lifestyle-based interventions that may enhance reproductive outcomes by modulating oxidative stress. This section reviews international ART data alongside the role of oxidative stress in reproductive health, with a particular focus on interventions such as dietary supplementation and exercise, which may influence oxidative balance and fertility.

1.3.1. International ART data

According to the latest 2019 data from the European Society for Human Reproduction and Embryology (ESHRE), the average pregnancy rate per embryo transfer in Europe was 34.6% after IVF, 32.1% after ICSI, 35.9% after frozen embryo transfer and 50.5% after egg donation (25).

The Human Fertilisation and Embryology Authority (HFEA) reports a notable improvement in IVF outcomes over the past three decades. The overall pregnancy rate for fresh embryo transfers rose from 10% in 1991 to 29% in 2021. The increase was also evident in older age groups: for women aged 40–42, the pregnancy rate per embryo transferred climbed from 6% to 16% between 1991 and 2021, while for women aged 43–50, it grew from 1% to 6% during the same timeframe. The HFEA data further indicate that the average age of IVF patients reached 36 years in 2021, and the average age of those undergoing donor insemination (DI) was 34 years (31).

According to data from the british Human Fertilisation and Ebryology Authority 2021, the proportion of live births from IVF interventions using the patient's own eggs was as follows by age range: 33% between 18-34 years, 25% between 35-37 years, 17% between 38-39 years, 10% between 40-42 years and 4% from age 43 years (31).

Data from the United States Society for Assisted Reproductive Technology (SART) show that the average rate of live births from IVF treatments using their own eggs were 54 % under the age of 35, 40.5 % between 35-37 years, 26 % between 38-40 years, 13.3 % between 41-42 years and 4 % for patients over 42 years (32).

International data clearly indicate that even with IVF, live birth rates remain suboptimal in women of advanced maternal age**,** especially in those over 35. This suggests that assisted reproductive technologies cannot fully compensate for the age-related decline in ovarian function and reproductive potential.

In recent years, ovarian rejuvenation - aimed at restoring or improving previously reduced ovarian function - has emerged as a topic of growing interest within reproductive and regenerative medicine (46, 65-69). Despite the growing interest in various experimental therapies such as intraovarian platelet-rich plasma (PRP) injection, stem cell-based interventions, or melatonin supplementation (70-73),

There is still no widely accepted or standardized medical treatment for age-related diminished ovarian reserve, one of the leading causes of infertility. Given this unmet clinical need, our study aims to evaluate the effectiveness of a novel, non-invasive combined approach—oral antioxidant therapy and a fertility-oriented exercise program—as a potential strategy to support ovarian function in women with DOR. Although the present pilot study does not directly measure oxidative stress markers, its underlying hypothesis is rooted in the assumption that modulating oxidative stress may be a key mechanism contributing to ovarian rejuvenation. This assumption is supported by a growing body of literature indicating that oxidative stress plays a central role in ovarian ageing (74, 75), and that both targeted antioxidant supplementation and moderate-intensity exercise may help restore redox balance. These theoretical foundations are explored in more detail in the following sections, which discuss the relationship between oxidative stress and ovarian ageing, and the role of physical exercise and antioxidant supplementation in redox homeostasis.

1.3.2. Oxidative stress and dietary supplements

Oxidative stress (OS) has been recognized as a significant contributor to the pathophysiology of female infertility (76). Oxidative stress is characterized by an imbalance between the generation of reactive oxygen species (ROS) and the organism's capacity to mitigate or rectify their detrimental consequences. ROS are involved in several physiological processes; however, excessive accumulation may induce oxidative damage and disturb cellular homeostasis. Elevated oxidative stress has been associated with impaired reproductive function. Lifestyle modifications, including a healthy diet, adequate antioxidant intake and exercise, can be key to reducing oxidative stress and optimising reproductive health (77).

There is currently no established “gold standard” treatment for ovarian rejuvenation. However, given that oral antioxidant supplementation was provided to all participants, it was considered ethically appropriate to use this intervention as the reference and control condition and to compare the novel physiotherapy-based reproductive exercise program against it. Vitamin and micronutrient deficiencies are frequently observed in women with diminished ovarian reserve (78), making supplementation a commonly applied and clinically justified standard supportive approach in this population. For this reason, oral antioxidant supplementation was used as the reference intervention and as the control condition for comparison with the physiotherapy-based exercise program in the present study.

A number of studies have demonstrated that specific vitamins and supplements have the capacity to exert a favourable influence on reproductive health by sequestering reactive oxygen species (79).

It has been shown that myo-inositol enhances ovarian function and improves the quality of oocytes, especially in women with polycystic ovary syndrome (PCOS), increasing the likelihood of conception (80, 81). The use of myo-inositol (MI) delays ovarian ageing. MI administration improves the function of the granulosa cells and the cumulus-corana complex and increases the influx of information necessary for the formation of high-quality oocytes through the gap junctions between the oocytes and the granulosa cells (82, 83). It may also have a preventive role when administered during pregnancy (84).

Preconceptional folic acid supplementation (≥400 μg/day) has demonstrated higher fecundability rates than those not receiving supplementation (85).

Melatonin is mainly involved in the control of circadian rhythms, but more and more is known about its relationship with fertility. Sleep deprivation and poor sleep quality are increasingly cited as causes of failure (86-88). Sleep disorders affect the secretion of sex hormones. Sleep deprivation suppresses melatonin production and disrupts circadian rhythms, which may adversely affect the pulsatile secretion of sex hormones (89). Several recent studies have concluded that good sleep quality may be associated with more effective ART treatment (90-92).

It also exerts antioxidant effects that may reduce oxidative damage in oocytes and support oocyte quality (70-72, 93, 94). They detail how endogenous production in oocytes and surrounding cells, along with exogenous supplementation, counteracts oxidative stress, supports mitochondrial function, reduces deoxyribonucleic acid (DNA) damage, and thereby protects fertility in older females. The authors suggest melatonin supplementation could preserve ovarian function and reduce the need for assisted reproduction among women delaying childbearing. In the 2012 article, Tamura and colleagues reported that patients undergoing assisted reproductive procedures who were administered 3 mg of melatonin orally in the evening from the fifth day of the previous menstrual cycle until the day of egg retrieval experienced a 4-fold increase in follicular concentrations of melatonin (95).

A clinical study conducted by Tamura et al. in 2013 demonstrated that the administration of melatonin to infertile women resulted in increased concentrations of melatonin within follicles, accompanied by a reduction in oxidative damage within these structures. The study further revealed that melatonin treatment led to an enhancement in fertilisation and pregnancy rates. Additionally, melatonin treatment was observed to improve progesterone production in the corpus luteum of infertile women afflicted with luteal phase deficiency. Consequently, melatonin treatment emerges as a promising avenue for enhancing oocyte quality and luteal function in infertile women (96).

Rizzo and his fellow researchers looked for a correlation between melatonin and egg quality. The study group was administered melatonin in combination with inositol and folic acid, while the control group received folic acid alone. The melatonin-treated group exhibited a significantly higher number of mature cells and a significantly higher number of high-quality oocytes (73). These findings align with the prevailing perspective that pharmacologically administered melatonin enhances follicular melatonin concentrations, reduces oxidative damage within the follicles, and potentially benefits fertilisation and pregnancy rates (PGR) in assisted reproductive technology (ART) procedures. Tong et al. (97) established a positive correlation between follicular melatonin levels and ovarian reserve markers (baseline levels of anti-Muellerian hormone and FSH) in women undergoing IVF. The same research group reported a comparable association between follicular fluid melatonin concentrations and IVF outcomes, including oocyte quality. Espino et al. (2019) (72) have reported a positive change in women with idiopathic infertility. This change was characterised by an improvement in intrafollicular oxidative capacity and oocyte quality in IVF protocols following melatonin supplementation.

In women receiving fertility treatment, higher consumption of antioxidants, such as vitamin C, is favorably correlated with ovarian reserve (98). In a randomised controlled trial, researchers used selenium and vitamin E supplements to reduce oxidative stress in the ovaries, thereby helping to increase ovarian reserve in patients with premature ovarian insufficiency (POI). The intervention group received 200 µg selenium and 400 IU vitamin E, and the control group received a placebo for 3 months. Measurements were taken 12 months after the start of the interventions: AMH, AFC and measurement of ovarian volume (MOV) in both groups. In the intervention group, AMH levels were significantly increased, antral follicle count (AFC) and ovarian volume were increased compared to the placebo group (99). According to this study, POI patients' ovarian reserve can be increased and ROS overexpression decreased by taking antioxidant supplements containing selenium and vitamin E.

Vitamin D3 contributes to immune regulation and reproductive function, and insufficient levels have been associated with unfavorable fertility outcomes (100). Vitamin D has been reported to influence AMH production, with higher circulating concentrations associated with a slower decline in ovarian reserve (101). Findings from a 2022 prospective cross-sectional study suggest that vitamin D supplementation could be integrated into fertility care for women with DOR, given its reported associations with higher AFC and AMH levels and lower FSH concentrations (102-104).

Although a meta-analysis in 2021 did not find a significant association between serum vitamin D levels and ovarian reserve markers, it did confirm a significant association for AFC, LH and LH/FSH ratio. The results suggest that lower AFC may be associated with vitamin D insufficiency/deficiency (105).

Coenzyme Q10 (CoQ10) contributes to mitochondrial activity and energy production within oocytes, and its supplementation has been linked to more favorable ovarian response and embryo developmental outcomes (106, 107). A recent meta-analysis (107) has indicated that the administration of oral CoQ10 may improve clinical pregnancy rates in women with infertility who are treated with assisted reproductive technology. Moreover, recent meta-analyses have demonstrated that the administration of CoQ10 prior to ovarian stimulation has been shown to be an effective intervention to improve IVF/ICSI outcomes in women with DOR (108).

All these parameters are also reflected in our study as the "gold standard" per os rejuvenation therapy. Over a 3-month period (3 consecutive menstrual cycle), the oral intake of a formulation containing myo-inositol, folic acid and melatonin, which Rizzo and colleagues found to be effective, a dose of 3 mg of melatonin as recommended by

Tamura and his collegues, and the intake of vitamin C, vitamin D3, 400 IU of vitamin E and coenzyme Q10.

1.3.3. Oxidative stress and exercise

The initial documentation of exercise-induced oxidative stress in human research was conducted in 1978. While regular physical activity and intense exercise offer numerous health benefits, they concomitantly induce oxidative stress. In recent decades, there has been a growing body of scientific literature investigating the sources of reactive oxygen species generation in skeletal muscle, the role and effects of muscle-derived ROS, and the reduction of oxidative stress through the use of antioxidants (109, 110).

According to the study summary by Simioni et al, antioxidant supplementation combined with moderate exercise may be a useful tool to reduce oxidative stress and alleviate age-related pathophysiological disorders. Low levels of oxidative stress-derived ROS, or free radicals, are required for many important physiological functions, including muscle contraction. A dramatic increase in ROS is observed during strenuous exercise (111).

Research indicates that physical activity modulates oxidative stress and antioxidant defense, and that intensity, exercise type, and individual factors determine whether physical activity has an overall beneficial or stress-inducing effect on the body (109, 112-114). According to a Hungarian study, moderate pre-treatment physical activity may enhance pregnancy rates in IVF patients despite an associated increase in oxidative stress, suggesting that the beneficial effects of exercise on reproductive outcomes can outweigh the potential negative impact of elevated oxidative markers (115). A 2017 publication suggests that while per os antioxidant therapy can effectively reduce ROS levels, it cannot comprehensively control them. In contrast, yoga and meditation not only reduce ROS levels, but can also regulate them. Yoga can be a preventive and therapeutic strategy to reduce damage to ROS and DNA, potentially preventing health disorders such as infertility (116).

A number of animal studies are currently underway to investigate this relationship. Rahayu and colleagues studied the effects of different intensities of exercise on folliculogenesis in female mice. Different intensities of exercise affected the number of follicles and primary follicles in different ways. Studies in female mice have shown that moderate-intensity exercise improves corona radiata and granulosa cell function, improving ovarian stimulability and oocyte quality (117). This improvement may be indicated by increased AMH levels and optimized basal FSH levels. Additionally, exercises enhancing pelvic circulation may further improve these parameters. This could increase pregnancy chances and enhance follicle count during fertility treatments (118).

The effects of oxidative stress induced by different intensities of exercise on male reproductive function have also been studied in mice. In a study of obese male mice, moderate-intensity exercise was shown to be effective in reducing body fat, alleviating obesity-induced high oxidative stress in testicular tissue, increasing testosterone biosynthesis and improving sperm quality. Although high-intensity exercise reduced body fat more in the obese male mice in this study, it had no beneficial effects on high oxidative stress levels, testicular tissue inflammatory response, testosterone biosynthesis and sperm quality (119). Available evidence suggests that exercise intensity may differentially influence reproductive function, potentially through modulation of oxidative stress.

1.4. Professional aspects of exercise programme design

In the context of infertility, targeted exercise programmes are increasingly recognized as adjunctive interventions that may contribute to hormonal regulation, oxidative balance, and mental well-being. However, designing effective and safe programmes for women affected by infertility requires careful attention to both physiological and psychological factors.

This chapter outlines the key professional principles of exercise programme design, beginning with the global health implications of physical inactivity and the musculoskeletal and postural consequences of a sedentary lifestyle. It then explores the biomechanical importance of lumbar stability and core function, with a special focus on the synergistic role of the pelvic floor, diaphragm, and transversus abdominis. Furthermore, the significance of stretching and mobilisation techniques is discussed in the context of restoring functional movement. Finally, the psychological burden of infertility and the potential stress-reducing effects of physical activity are addressed as integral components of a holistic therapeutic approach.

1.4.1. Sedentary behavior and physical inactivity as a global health issue

A global rise in sedentary behavior (SB) and physical inactivity (PIA) has been reported since the COVID-19 pandemic (120-122), with the literature suggesting a higher susceptibility among women (123, 124).

According to a Hungarian study published in 2023, the average daily sitting time of the Hungarian population exceed 7 hours. The Sedentary Behaviour Questionnaire (SBQ) was utilised in the study, and the results indicated that Hungarians typically spend an average of 7.81 hours seated during weekdays and 7.01 hours on weekends (125). The researchers identified the groups with the highest levels of sedentary behaviour, categorised as follows: men, young adults, inhabitants of the capital city and sedentary workers. Among Hungarian women of reproductive age, both physical inactivity and sedentary behavior remain prevalent, with the majority not meeting the WHO's recommended levels of physical activity. These patterns may have adverse implications for reproductive health and fertility. Notably, significant discrepancies were observed between self-reported and objectively measured physical activity levels, with self-assessments tending to overestimate actual activity (126).

Sedentary behaviour is defined as sedentary activity during waking hours, such as sitting, leaning or lying down, with minimal energy expenditure (≤1.5 metabolic equivalents (METs)) (127). MET is an established technique for the more precise calculation of the intensity of physical activity. The level of energy expenditure while resting quietly is equivalent to 1 MET. The classification of physical activity is based on the MET value, with activities designated as follows: sedentary behavior (1.0–1.5 METs), light-intensity (0–3 METs), moderate-intensity (3–6 METs) and vigorous-intensity (> 6 METs) (128, 129). Further quantified data to define sedentary behaviour. A sedentary lifestyle is defined as ≤5000 steps/day, whereas ≈3500 steps/day is associated with an extremely low activity level (130).

Physical inactivity is typically defined as the failure to meet established minimum recommendations for moderate-to-vigorous physical activity (MVPA) (150–300 min per week) (131). One of the main risk factors for non-communicable diseases is a lack of physical activity. Physical inactivity is a major and expanding public health hazard, according to the World Health Organization. WHO's latest estimates indicate that almost 31% of adults globally—approximately 1.8 billion individuals—fail to achieve the recommended levels of weekly physical activity, thereby markedly elevating their risk of heart disease, stroke, type 2 diabetes, and specific malignancies (132).

Complementary findings by Strain (2024) further highlight that over 25% of adults are physically inactive, with a marked gender gap: 31.7% of women compared to 23.4% of men fail to meet activity guidelines (123). The situation is even more concerning among adolescents, with 81% of individuals aged 11–17 classified as physically inactive (133). According to the European Union's official website, when asked how often they exercise or play sport, almost half (45%) of EU citizens said they never do. The situation is worse in Hungary, where 59% of respondents said they never exercise (134).

Sedentary behaviour is conceptually distinct from physical inactivity. These two behaviours coexist in some cases and sometimes not (135). Sedentary behavior and physical inactivity represent distinct constructs; an individual may achieve recommended levels of physical activity yet accumulate excessive sedentary time, such as prolonged sitting, which independently impacts health outcomes.

A considerable number of studies do not adequately differentiate between sedentary behavior and physical inactivity, frequently using the terms interchangeably. This lack of conceptual clarity contributes to inconsistent and conflicting results across the literature, making it challenging to accurately assess the independent effects of each behavior on infertility.

In a case–control design, Foucault reported that women with more than 7 hours of sedentary behaviour per day had a markedly higher likelihood of idiopathic infertility (Odds Ratio [OR] = 3.61; 95% CI: 1.58–8.24). Additionally, a high body fat percentage (OR = 3.16) and low fat-free mass (OR = 2.65) were independently associated with infertility. However, physical inactivity alone was not significantly linked to infertility in women. The results further indicated that sedentary behavior and physical inactivity should be regarded as separate and independent risk factors within both research and clinical practice (136).

Zhang et al. identified a nonlinear association between leisure-time physical activity and infertility among reproductive-age women. Moderate activity levels were associated with reduced infertility risk, but excessive exercise beyond a certain threshold (e.g., >6 hours/week) was linked to increased risk. This U-shaped pattern highlights the importance of balanced physical activity in reproductive health strategies (137) . To date, numerous studies have explored the relationship between physical activity and infertility; however, findings remain inconclusive and contradictory**.** Most studies have not demonstrated a statistically significant association between physical activity and infertility (136, 138, 139).

1.4.2. Musculoskeletal and postural consequences of inactivity

Incorrect posture, when maintained for prolonged periods, in conjunction with a sedentary lifestyle, has been demonstrated to rapidly induce weakness in the muscles responsible for spinal stabilisation (140, 141). The consequence of these imbalances is a displacement of the head, which exerts an increased load on the cervical and lumbar regions of the spine (142). During prolonged sitting, reduced activation of the lumbar stabilizing musculature shifts the mechanical load toward passive spinal structures, including ligaments and facet joints (140)**.** The muscles involved in stabilisation rapidly weaken and then atrophy (143), leading to deconditioning of the lumbar spine, which may contribute to the development of low back pain (144, 145).

Research has demonstrated that sitting for a minimum of seven hours a day and engaging in less than 150 minutes of physical activity per week can lead to a reduction in thoracic spine mobility (146). It can contribute to the dysfunction of adjacent spinal regions. Furthermore, adopting a poor posture whilst sitting can also lead to alterations in the pelvic position, characterised by a backward rotation of the pelvis, a flattening of lumbar lordosis, and a reduction in hip joint mobility (147, 148).

The altered position and muscle function of the pelvic-lumbar region also affects the function of the pelvic floor muscles (149, 150) and the respiratory diaphragm (151, 152), and thus presumably also the function of the reproductive organs. The nervous system very quickly switches on the compensatory muscles, leading to the development of faulty motion stereotypes, muscle imbalances and chronic musculoskeletal problems (e.g. low back pain) (153, 154).

Prolonged sitting in a suboptimal posture has been identified as a significant risk factor for non-specific low back pain (NSLBP). However, other contributing factors may include overuse of spinal muscles, sleep disturbances, stress, prolonged static standing, low levels of physical activity and being overweight (155, 156). According to WHO, low-back pain is the most common problem among all work-related illnesses, accounting for

37% of the total. The proportion of non-specific LBP in total back pain is close to 90% (157). Low Back Pain can cause irreversible damage to the spinal structure, making its prevention and consequence reduction an important physiotherapy and public health challenge.

Physiological posture and its teaching are the basis of physiotherapy. The correct posture (posture re-education) is achieved by adjusting the neutral position of the lumbar spine and pelvis and by using active elongation. In the postural literature, elongation is defined as the active axial extension of the spine and its maintenance (158). Elongation is the active stretching along the axis of the spine, with the aim of increasing the distance between the vertebrae, thereby releasing the load on the discs and the small joints. This simple active movement produces visible changes in the sagittal curves of the spine. According to the results of Kondor et al, elongation exercises have an acute effect on posture and morphological changes in the spinal column. The data suggest that an increase in tonicity and contraction of the multifidus muscles occurs with elongation (159).

1.4.3. Lumbar spine stability and core muscle function

According Panjabi's work published in 1992, the stability of the spine is maintained by three distinct subsystems: the nervous system (neuromuscular control), the passive subsystem (ligaments, joint capsule, etc.), and the active subsystem (muscles). The integrity of these three systems is paramount for achieving optimal stability (160).

The "core" is essentially the central part of the body, made up of the trunk, pelvic and shoulder girdle and their musculature, as well as connective tissue and bony structures. The core is intrinsically linked to the body's centre of gravity (COG), a dynamic centre around which the body maintains its balance, which is always dependent on the body's position at any given moment. The relative position of the centre of gravity is constantly changing as the limbs move or change spatially, and therefore the core is an integrated functional unit that synergistically adjusts the whole body to maintain balance, postural stability and mobility (161).

Faries and Greenwood, in their comprehensive analysis published in 2007, describe that the "core" muscles have the primary function of supporting the pelvico-lumbo-hip complex in order to stabilize the spine, pelvis and kinetic chains during functional movements, and therefore knowledge of the specific characteristics of these muscles is essential for therapeutic and preventive activities. The core is the centre of the functional kinetic chain, which provides the proximal stability necessary for distal mobility and function of the limbs. An essential prerequisite for spinal stability and injury prevention is adequate muscular strength, endurance and an adequate activation pattern of the trunk muscles (162).

Based on the location and main function of the muscles, Bergmark established a classification of local and global muscles for the lumbar spine in 1989. Local muscles, which have their origin and/or attachment on a lumbar vertebra, with the exception of the m. psoas major, are involved in adjusting the position of the lumbar vertebrae and controlling the lumbar spinal curvature. They also provide the sagittal and lateral stiffness necessary for the mechanical stability of the spine. The synergic contraction of the m. multifidus, m. transversus abdominis, m. levator ani (LAM) and respiratory diaphragm increases intra-abdominal pressure and stiffness of the "core" and provides inter-segmental stability, which allows for an even distribution of external and internal forces on the intervertebral joints. The transmission of forces acting on the trunk and body between the pelvis and the rib cage is achieved by a combination of the muscles forming the global system and changes in intra-abdominal pressure (163). To maintain stability, adequate activation and timing of local and global stabilizer muscles is essential to ensure coherent functioning of the muscles to ensure even distribution of forces (164).

Lumbar spinal stabilizer muscles develop reflex motoneuron inhibition in response to low back pain, resulting in atrophy and reduced strength of muscle fibres, as well as altered physiological patterns of myoelectric activation (165). Because the muscles responsible for trunk stability and mobility are activated in a specific sequence and at a specific rate during each movement, late and/or different sequences of weakened contraction do not ensure intervertebral joint stability (153, 162, 166, 167).

The major contributor to maintaining normal function and stability of the lumbar spine is the lumbar multifidus (LM) muscle (168). This muscle provides segmental stabilization during functional activities by maintaining a neutral intervertebral position and provides more than two-thirds of the spinal rigidity (169). The fibres of the LM contain a large number of proprioceptors responsible for sensing muscle tension and joint position, so its atrophy, contraction delay and reduced proprioceptive capacity put it at high risk of developing intervertebral instability.

Muscle atrophy is a sign of degeneration due to reflex-inhibition of m. multifidus. Hides et al. found that in patients with chronic LBP, multifidus muscles' atrophy persists after pain has resolved and spontaneous regeneration of muscle function is not expected. Subjects who did not receive specific LM activity rehabilitation exercises had m. multifidus atrophy even 10 weeks after "complete" recovery (170) and were more likely to have recurrence of Low Back Pain (171). This residual non-physiological state of the lumbar multifidus muscle may explain why many patients with back pain suffer from recurrence of symptoms and re-experiencing of pain (172). Once the pain resolves, the muscle condition can be improved by targeted and very precise exercises, and even irreversible lesions may develop if therapy is not given (173). Tong and colleagues concluded that individuals with low back pain have a clear impairment in lumbar proprioception (joint position perception and muscle tone adjustment), which is most associated with prolonged sitting in a neglected posture (174), and therefore it is worth considering the integration of exercises that affect the proprioceptive system.

In the case of back pain, other spinal conditions, sedentary lifestyle and rehabilitation to develop a functionally well-functioning body, local stabilizers training should also be a priority. The exercise programme should focus on both the sensation and mastery of voluntary and isolated contraction, the correct timing of activation, and the increase in muscle strength and cross-section (173).

Segmental trunk stabilisation is widely regarded as a fundamental exercise in preventing and treating low back pain, as well as in eliminating problems caused by a sedentary lifestyle (175) and improving reproductive function.

Effective pelvic–lumbar (core) stabilisation depends on the integrated performance of the diaphragm, pelvic floor muscles, transversus abdominis (TrA), and multifidus muscles, playing a critical role in maintaining spinal integrity, facilitating respiration and movement, preventing injury, transmitting forces, supporting the pelvic floor and pelvic organs (ovaries, uterus), and ensuring proper sexual function. Effective pelvic–lumbar (core) stabilisation results from the integrated training of the deep spinal stabilisation system combined with correct breathing mechanics (176). Conscious segmental pelvic-lumbar stabilization can be effectively developed with the abdominal drawing-in maneuver (ADIM) in the neutral position of the lumbar spine. The ADIM technique induces recruitment of the transverse abdominal muscle with minimal activation of the superficial trunk muscles (177). In addition to the multifidus (MF) muscles, the transversus abdominis is the other primary segmental spinal stabilizing muscle (178). Core stabilization exercise (CSE) using the ADIM technique has been found to be more effective than general core muscle strengthening (179) and protective against low back pain from prolonged sitting (177). One study found that 4 weeks of targeted TrA training can improve muscle activation and the timing of activation (neural changes) whether or not you have Lower Back Pain, but not enough time to achieve maximum effectiveness. Muscle strength increases are only detectable 6-8 weeks after the start of training programs (180).

To stabilize the lumbar vertebrae, a complex myofascial and aponeurotic belt surrounding the trunk is also required. The central part of this "belt" is the thoracolumbar fascia (FTL), which is connected to several muscles and plays an important role in posture, load transmission and breathing (166). Rehabilitation of all these interconnected anatomical structures must be addressed in a complex manner. According to Hodges et al, FTL also contributes to pelvic-lumbar stability as an intersegmental stabiliser, as it can control vertebral rotation and translation by attachment to the processus transversus (181).

1.4.4. Synergy of the pelvic floor, diaphragm and transversus abdominis

Pelvic and lumbar stability, along with the normalization of breathing patterns, depends substantially on the proper function of the transversus abdominis muscle and its synergistic co-contraction with the pelvic floor muscles. TrA contributes to pelvic-lumbar stability by increasing internal abdominal pressure and tension on the thoracolumbar fascia, but this is only fully achieved through the combined action of the diaphragm and pelvic floor muscles (PFMs). During limb movements or increased stability demand, the diaphragm, transverses abdominis muscle and pelvic floor muscles engage in a feed-forward mechanism and stabilize the pelvic-lumbar region, regardless of the direction of the movements (151, 152). It means that activation of the muscles involved in stabilising the trunk precedes limb movements.

Studies have also shown that a 15% contraction of the pelvic floor muscles is sufficient to activate the TrA muscle. This co-contraction can also be demonstrated in an inverse manner, with contraction of the TrA muscle activating the PFMs (149). This co-contraction is most pronounced in the neutral position of the lumbar spine. In addition, the combined activation of PFM and TrA can increase IAP, thereby stabilising the pelvic and lumbar region. The pelvic floor muscles are not only responsible for urogenital functions, but also play a major role in stabilising the pelvic-lumbar region and increasing internal abdominal pressure. Their function is interdependent on the other muscles of the system (151). Studies by Hodges et al have demonstrated the role of pelvic floor muscles in postural and respiratory function (152). Findings from an electromyographic (EMG) investigation indicate that spinal posture influences pelvic floor muscle activation, with the neutral lumbar alignment eliciting the greatest activity (150). Sitting in a prolonged poor position also reduces pelvic floor muscle activity and the correct positioning of the diaphragm and pelvic floor relative to each other for optimal function is not maintained. Recent evidence supports the role of pelvic floor muscle function in female sexual and reproductive health, providing a rationale for including pelvic floor muscle activation within physiotherapy-based interventions (182, 183).

The role of breathing in relation to the pelvic floor has undergone significant changes in the past few decades, with different and sometimes conflicting opinions being expressed regarding the ideal contraction pattern of the pelvic floor muscles. Specifically, there has been a lack of consensus on whether the PFMs should ideally contract during inhalation or exhalation, or whether they should contract independently of breathing. Recent scientific research has confirmed that the physiological role of the pelvic floor muscles is to contract simultaneously with the anterolateral abdominal muscles during exhalation (152, 184, 185). However, there is a curious discrepancy between this scientific consensus and the views of scientists and therapists. The gold standard for researchers and health professionals working on these topics, as set out in the joint the International Urogynecological Association (IUGA) and International Continence Society (ICS) reports on the terminology, assessment and treatment of PFM functions and dysfunctions, does not mention the relationship between PF and breathing (186, 187). The PFM rehabilitation guidelines provide precise instructions. These guidelines primarily emphasize concentric strengthening strategies, while the integration of respiratory phases and abdominal co-activation appears to receive comparatively limited focus (186).

In contrast, recent years have seen a growing body of research focused on the coordinated function of the respiratory system and the core musculature, including the diaphragm, transversus abdominis, multifidus, and the pelvic floor muscles. This emerging perspective suggests that these muscle groups do not operate in isolation, but rather as part of an integrated system responsible for postural control, pressure regulation, and dynamic stability, particularly in relation to breathing mechanics.

Recent evidence highlights a synergistic relationship between pelvic floor muscles and diaphragmatic function during respiration. Task-specific EMG studies demonstrate increased activation of both deep and superficial PFMs in response to respiratory demands (188). Moreover, (189) found that this synergy is influenced by body position, with the strongest interaction occurring in the crawling (quadruped) posture. Their findings suggest that combining diaphragmatic breathing (DB) with PFM training, especially in the crawling position, may enhance muscle coordination and optimize rehabilitation outcomes for women with pelvic floor dysfunction.

Stress-induced superficial breathing has been shown to disrupt the coordination between the diaphragm and pelvic floor muscles (190). As this synergy supports pelvic organ function, persistent PFM tension due to stress may impair relaxation, reducing their ability to respond effectively (191). Therefore, training both contraction and relaxation of the pelvic floor is essential in fertility-focused exercise programs. Optimising breathing is an important part of the musculoskeletal therapy. Breathing is a movement pattern that can be developed through conscious, focused practice. Breathing is a fundamental physiological process generated through the coordinated, rhythmic contraction and relaxation of the muscles of the thoracic and abdominal walls, working in synergy with the diaphragm (191).

Recent meta-analytic evidence confirms that restoring normal breathing patterns through targeted exercises significantly improves pain and functional outcomes in individuals with low back pain (192). This aligns with earlier studies demonstrating altered breathing patterns in chronic low back pain patients (193) and highlights the importance of integrating breathing retraining into trunk stabilization programs (194).

1.4.5. The role of stretching and mobilisation in functional recovery

The maintenance of optimal mobility of the hip joint, stability of the pelvico-lumbar joints and the functionality of core muscles are also essential for the effective functioning of the pelvic organs (ovaries, uterus). The stability of this area is of paramount importance for a functionally well-functioning body. A decrease in physical activity has been shown to increase the stiffness and reduce the flexibility of the tendons, muscles, and ligaments of any given joint (for example, the ankle joint-foot complex). This is associated with an increased risk of musculoskeletal pathologies (195). The hip flexor muscles have been shown to be of significant importance in the maintenance of lumbar spine stability. Tight hip flexors have been demonstrated to be a contributing factor to pain in the lumbar spine, and consequently, to an impairment in performance. Sedentary behaviour has been demonstrated to be a contributing factor to reduced hip extension and, consequently, increased flexor tightness (196). It can therefore be hypothesised that a significant proportion of the sedentary population may exhibit tight hip flexors. This assertion is further substantiated by the findings of Mettler et al (197)., who reported that two-thirds of the investigated population demonstrated limited hip extension and tight hip flexors. In addition, research also shows that chest mobility is reduced in individuals who sit for more than 7 hours a day and perform less than 150 minutes of physical activity per week (146).

Dynamic and static stretching exercises have been proposed as a method of reducing muscle tightness and addressing the aforementioned issues (196).

1.4.6. Physiotherapy in infertility-related stress reduction

Stress is a response reaction that occurs when the body is faced with emotional, psychological or physical stress. This response can help you cope with everyday challenges, but if it is excessive or persistent it can lead to a range of negative consequences. Stress has been referred to as the "modern-day hidden epidemic" due to its high and increasing prevalence as well as its global health effects. Symptoms of stress are wide-ranging and can take many forms, including: fear, anxiety and difficulty relaxing, tachycardia, breathing problems and altered sleep, eating and lifestyle habits (198, 199).

One of the leading models in reproductive psychology is the psychological consequence model of infertility, which conceptualizes infertility as a complex experience of loss, an acute or chronic life crisis, associated with adverse psychological outcomes (17). Clinical interventions, such as the Mind/Body Program, have been tested to mitigate these psychological consequences (200). According to this theory, fertility problems lead to infertility-specific distress. Several studies have identified a high incidence of anxiety and depression in patients diagnosed with infertility. The prevalence of anxiety was higher in the infertility group than in other groups diagnosed with serious chronic diseases, such as HIV-positive patients, patients with cancer or heart disease (201). Assisted reproductive therapy has also been associated with elevated anxiety and depression compared to individuals who have not undergone such treatment (202, 203).

Although infertility is inherently associated with heightened stress and anxiety, evidence indicates that sedentary behaviour is related to poorer mental health, including increased symptoms of anxiety and depression (204, 205). These factors may further contribute to the psychological burden experienced by women facing fertility challenges.

Diaphragmatic breathing is essentially a more precise professional term for diaphragmatic breathing; both refer to the same fundamental breathing technique. According to Bradley (2014) (206), diaphragmatic breathing is characterised by the coordinated movement of the upper and lower rib cage as well as the abdomen, involving slow, deep inhalations and exhalations with proper diaphragm engagement. Diaphragmatic breathing, when implemented as a slow-paced breathing technique (approximately 4–7 breaths per minute), consistently activates the parasympathetic nervous system and reduces physiological and psychological stress (207-209). Slow breathing techniques—particularly at a rate of approximately six breaths per minute—have been shown to increase parasympathetic activation, improve heart rate variability, and enhance emotional regulation and subjective well-being (210). Importantly, controlled DB has also demonstrated immediate reductions in perceived pain and state anxiety even following a single session in individuals with chronic pain (211). Bradley and colleagues demonstrated that individuals employing a diaphragmatic-dominant breathing pattern achieved significantly better results on the Functional Movement Screen (FMS), supporting the role of diaphragmatic breathing not only in parasympathetic nervous system activation but also in enhancing core stability and postural control (206, 212). It is used in both physiotherapy and yoga. Together, these data underpin the inclusion of DB in fertility-focused exercise protocols to enhance mental well-being and potentially support reproductive outcomes.

In summary, the professional considerations outlined above highlight that a sedentary lifestyle detrimentally affects not only reproductive health but also various facets of physical and mental well-being. Extended periods of sitting have been associated with adverse changes in postural alignment, dysfunction of the spinal stabilising system, altered respiratory mechanics, and an increased risk of pelvic floor dysfunction and low back pain. These interconnected consequences formed the foundation for designing an exercise protocol aimed at supporting fertility alongside overall musculoskeletal and functional health. Moreover, the exercise programme incorporates crucial elements such as postural re-education and active elongation, neuromuscular control and movement pattern development, pelvic floor rehabilitation, optimization of diaphragm function, joint mobility restoration, and stress-relief through parasympathetic activation. Integrating these professional aspects into a targeted, comprehensive, and multidimensional training approach ensures a holistic support system that addresses both fertility and broader health concerns. This investigation adopts a novel conceptual approach by placing conventional and integrative therapeutic approaches within a unified interpretative framework.

2. OBJECTIVES

The aim of the present doctoral dissertation was to contribute to the scientific foundation of complex, interdisciplinary interventions supporting female fertility, with particular emphasis on the integration, evaluation, and clinical relevance of a physiotherapy-based exercise program for women with diminished ovarian reserve (DOR). Within this framework, the primary objective of the pilot study was to evaluate the effectiveness of a combined intervention consisting of a supervised physiotherapy-based exercise program and oral antioxidant supplementation on ovarian reserve (as reflected by serum AMH levels) and ovarian function (as reflected by basal FSH levels), as well as on spontaneous pregnancy rates in women with DOR. Secondary objectives included the assessment of the safety, feasibility, and acceptability of the physiotherapy-based exercise program in this population. In addition, the study aimed to generate preliminary clinical and reproductive outcome data to inform the design and development of future large-scale, controlled clinical trials in women with diminished ovarian reserve.

Research Questions:

1. Does the combined intervention (physiotherapy-based exercise program plus oral antioxidant therapy) result in greater improvement in ovarian reserve (as reflected by AMH) and ovarian function (as reflected by basal FSH levels) compared with oral antioxidant therapy alone in women with DOR?
2. Does the combined intervention increase the rate of spontaneous pregnancies compared with oral antioxidant therapy alone in women with DOR?
3. Is the physiotherapy-based exercise program safe, feasible and clinically applicable for women with DOR?
4. Does the randomized controlled study provide evidence supporting the potential usefulness of integrating a physiotherapy-based exercise program into comprehensive fertility treatment for women with diminished ovarian reserve?
5. Do the findings of the randomized controlled study support the rationale for integrating a physiotherapy-based exercise intervention into comprehensive fertility care for women with diminished ovarian reserve?

It is hypothesized that oral antioxidant therapy positively influences ovarian function by enhancing granulosa and corona radiata cell activity, thereby contributing to improved ovarian responsiveness and oocyte quality. Furthermore, supplementing oral antioxidant therapy with a targeted, supervised physiotherapy-based exercise program is expected to result in more pronounced improvements in ovarian reserve (as reflected by higher serum AMH levels) and ovarian function (as reflected by lower basal FSH levels), and to increase the likelihood of spontaneous conception in women with diminished ovarian reserve.

It is additionally hypothesized that the physiotherapy-based exercise program is safe, feasible, and well-tolerated in this patient population. Finally, it is hypothesized that the findings of the first clinical target-searching provide sufficient preliminary clinical, feasibility, and acceptability evidence to support the integration of a physiotherapy-based exercise program into comprehensive, interdisciplinary fertility care models for women with diminished ovarian reserve.

3. METHODS

Integration of study components and source publications

This doctoral dissertation is based on two peer-reviewed publications that form a structured research framework. The first publication presents a randomized controlled trial protocol detailing the design of a physiotherapy-based exercise intervention for women with diminished ovarian reserve (213). This protocol proposed a randomized controlled trial involving three study arms: a group receiving oral therapy alone, another group recieving oral therapy plus walking and a group receiving oral therapy combined with a supervised, targeted physiotherapeutic exercise program. This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting template. The study protocol received approval and registration from the Human Reproduction Committee of the Hungarian Medical Research Council (25489-8/2021/EÜIG).

The second publication reports on a clinical study involved limited number of patients, (214) conducted to evaluate the feasibility, preliminary effects, and clinical applicability of the intervention originally described in the protocol. Due to its exploratory nature, the pilot study was conducted with a smaller sample size and included only two groups: a control group receiving oral therapy alone and an intervention group receiving oral therapy in combination with the physiotherapy-based exercise. Despite the reduced complexity, the methodological principles, intervention content, inclusion and exclusion criteria, and outcome measures were consistent with those described in the original protocol.

The present dissertation primarily focuses on the methodology and findings of the clinical study, integrating these results to evaluate the feasibility and preliminary effectiveness of the intervention. The results of the pilot informed refinements in recruitment, compliance monitoring, and outcome selection, thereby strengthening the design and future implementation of the full-scale trial.

3.1. Clinical study setting

This doctoral dissertation is based on a prospective, randomized, two-arm pilot study designed to explore the effects of a physiotherapy-based exercise programme, in combination with oral rejuvenation therapy, on ovarian reserve markers and spontaneous pregnancy outcomes in women diagnosed with diminished ovarian reserve. The study was conducted between 2021 and 2025 at Semmelweis University. Participants were allocated to either a control group receiving oral therapy alone or an intervention group receiving oral therapy in combination with a supervised, targeted physiotherapeutic exercise program.

3.2. Recruitment process

The Assisted Reproduction Center at Semmelweis University in Hungary served as the source of participants. Eligible patients were identified by the treating physicians during routine clinical visits. The study protocol and its objectives were explained to each candidate both verbally and in writing, including the voluntary nature of participation and the possibility to withdraw at any time. Patients were informed that the collected data would be anonymized and analyzed only for research purposes. After providing sufficient time for consideration, participants who agreed to join the study signed written informed consent.

3.3. Participants, Eligibility criteria

The study population consisted of women diagnosed with diminished ovarian reserve who sought infertility treatment at the center. Participants were categorised as having primary or secondary infertility according to their reproductive history. Within the intervention group, primary infertility predominated (9 vs. 3), while the control group exhibited an equal distribution of primary and secondary infertility (6:6).

Eligibility for the pilot study was defined based on reproductive age and ovarian reserve markers. Women aged 20–42 years with regular menstrual cycles and a body mass index (BMI) between 18.5 and 30 kg/m^2 were considered eligible. In addition, participants were required to have an anti-Müllerian hormone (AMH) level below 1.1 ng/mL. and hormone values within predefined limits (TSH < 2.5 mIU/mL, vitamin D3 > 75 nmol/L, prolactin < 24 ng/mL). These criteria were selected to ensure a relatively homogeneous study population and to reduce confounding factors that could influence ovarian function.

Exclusion criteria were established to avoid including women with severe ovarian insufficiency or other conditions affecting ovarian reserve. Patients were excluded if they had an antral follicle count (AFC) below 3 on cycle days 2–4, or if they had experienced multiple failed stimulation cycles resulting in cancellation. Women with allergies to the medications used in the oral rejuvenation therapy, or those with a history of multiple ovarian surgeries leading to significant ovarian reserve depletion (e.g., iatrogenic POI or DOR), were also excluded. Structural uterine abnormalities were considered an additional exclusion criterion.

3.4. Implementation

After eligibility was confirmed, the principal investigator or an appointed sub-investigator entered the required patient data into the web-based allocation system. Baseline data collection included demographic and medical history, anthropometric measurements (weight, height, BMI), menstrual cycle characteristics, and antral follicle count (AFC) measured on cycle days 2–4. In addition, baseline hormonal parameters (AMH, FSH, LH, E2, prolactin, TSH, vitamin D3, and progesterone) were recorded to characterize ovarian reserve and endocrine status at study entry. These baseline measures were used to describe the study population and to confirm eligibility.

3.5. Randomization

Participants were randomly allocated to one of two study groups in a 1:1 ratio:

- Arm A: oral antioxidant therapy (control group)
- Arm B: oral therapy combined with the targeted physiotherapeutic exercise program (intervention group)

Randomization was performed using a computer-based random sequence generator managed by a third-party statistician who was not involved in the clinical management of participants. This procedure was implemented to reduce selection bias and to ensure that allocation remained concealed.

Outcome assessment was blinded where feasible. Laboratory personnel analyzing hormone levels were not informed of group allocation, as samples were processed centrally without identifying information. Antral follicle count measurements were performed by sonographers who, whenever possible, were not informed about the participants' group assignment. These measures aimed to reduce measurement bias and strengthen the methodological rigour of the pilot study. The trial design of the pilot study is summarized in Figure 1 (214).

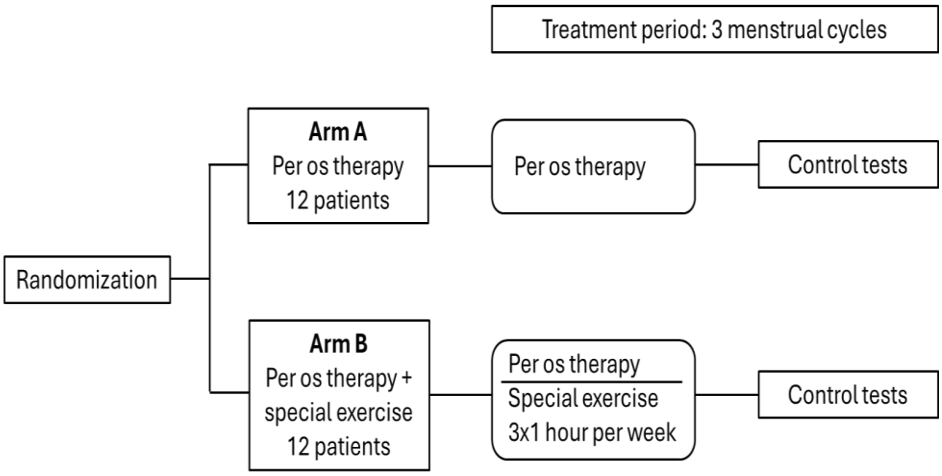

Figure 1. Study design of the pilot study

Randomized pilot study design showing the allocation of participants into two arms. Arm A received oral therapy only, while Arm B received oral therapy combined with a supervised physiotherapy-based exercise program. The intervention period lasted for three menstrual cycles, followed by follow-up assessments and control tests.

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3.6. Intervention

All participants received the same baseline oral supplementation throughout the study. The daily regimen included myo-inositol combined with folic acid taken twice daily, melatonin (3 mg) at bedtime, and a set of antioxidants and vitamins (vitamin C 1000 mg slow-release, vitamin E 400 mg, vitamin D3 2500 IU/day, and coenzyme Q10 200 mg). Participants assigned to the control group (Arm A) were instructed to continue their usual daily activities and to avoid starting any new structured exercise program during the study period.

Participants in the intervention group (Arm B) additionally attended a supervised physiotherapy-based exercise program, delivered three times per week for 70 minutes per session over a period of three consecutive menstrual cycles. The program was developed to support reproductive health by combining postural correction, pelvic-lumbar stabilization, pelvic floor muscle re-education, and diaphragmatic breathing with mobility, stretching, and relaxation elements. It integrated concepts from physiotherapy, yoga, and dance therapy, with a focus on improving pelvic circulation, reducing musculoskeletal tension, and enhancing autonomic regulation through breathing.

Each session followed a structured sequence, including warm-up, core stabilization, breathing exercises, functional movement training, and lumbar - pelvic - hip complex mobilization. The warm-up prepared the body through posture correction, joint mobilization, and activation of the core and gluteal muscles. The core stabilization phase emphasized coordinated activation of the deep stabilizing system of the spine, including the diaphragm, transverse abdominal, multifidus, and pelvic floor muscles, synchronized with breathing. The breathing segment employed diaphragmatic breathing in various positions to promote relaxation and parasympathetic activation, while supporting functional balance and gentle stretching of the lumbo-pelvic-hip complex.

The next phase prior to the final part consolidates the previous exercises, focusing on postural alignment, stretching, core stabilization, and breathing techniques to enhance mobility, support pelvic floor function, and improve pelvic circulation. The final part of the session included controlled movement patterns derived from dance, aimed at mobilizing the lumbar–pelvic–hip complex through hip rotations and pelvic tilts. Improved mobility of this region supports functional movement and may contribute to reproductive health.

The exercise program was designed to address both physical and psychological factors that may affect fertility. By combining controlled breathing, posture correction, core stabilization, stretching and relaxation techniques, the intervention aimed to reduce stress, improve neuromuscular balance and pelvic organ circulation, and support a functionally optimized female body. The program required no specific equipment beyond an exercise mat and optional support tools (pillow or yoga block). Sessions were supervised by a physiotherapist to ensure correct technique, progression, and consistency across participants, and the program was developed and led by the author (physiotherapist).

The present dissertation focuses on the study design, intervention principles, and outcomes rather than providing a step-by-step training manual. The exercise program was standardized and supervised, and its key components are described, while detailed exercise protocols are available in the original publication.

Attendance at the exercise sessions was recorded by the supervising physiotherapist. According to the protocol, participants in the intervention arm were required to attend at least 75% of the scheduled sessions; failure to meet this threshold constituted a criterion for discontinuation. In the study, all participants in the intervention group achieved attendance above this threshold, therefore no discontinuation occurred due to non-adherence. Other discontinuation criteria included withdrawal of consent, spontaneous pregnancy, initiation of other treatments or surgery that could influence study outcomes, and adverse events preventing continuation.

3.7. Outcome measures

The primary outcome of the pilot study were: changes in FSH and AMH levels, compared to baseline. In addition, spontaneous pregnancy during the intervention and the 6-month post-intervention follow-up period were recorded as a primary outcome measure. The secondary outcomes included the post-intervention E2, TSH, prolactin and LH levels.

3.8. Baseline and follow-up assessments

Baseline evaluations conformed to the trial’s standard operating procedure (SOP). The initial examination was scheduled between menstrual cycle days 2 and 4, corresponding to the early follicular phase. During this visit, venous blood samples were collected to determine serum concentrations of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), thyroid-stimulating hormone (TSH), and 25-hydroxyvitamin D3, providing an evaluation of ovarian reserve, hypothalamic–pituitary–ovarian axis function, and endocrine status. Mid-luteal progesterone levels were assessed on cycle days 21–22 of the same menstrual cycle to confirm ovulatory function. Throughout the intervention and follow-up period, participants were prospectively monitored for spontaneous conception. After completion of three consecutive post-treatment menstrual cycles, serum AMH, FSH, LH, E2, PRL, and TSH levels were re-evaluated to assess potential endocrine adaptations associated with the intervention. Spontaneous pregnancies as well as successful in vitro fertilization (IVF) outcomes were subsequently followed for an additional six months or until live birth (Table 1). All samples were analyzed in the same certified laboratory.

3.9. Efficacy assessments

The effectiveness of the intervention was assessed using a comprehensive set of outcome measures obtained at the 3–6-month follow-up evaluation. Participants were monitored for an overall duration of approximately nine months, comprising a treatment phase spanning three consecutive menstrual cycles, followed by a six-month observational follow-up period or until live birth in cases where spontaneous conception occurred.
Spontaneous pregnancies were initially self-reported by participants and subsequently verified through biochemical confirmation of serum beta-human chorionic gonadotropin (β-hCG) levels and/or transvaginal ultrasonography performed between 6 and 8 weeks of gestation. Throughout the entire study period, no assisted reproductive technologies (ART) were applied.

Table 1. Schedule of study procedures and outcome assessments across the screening, baseline, post-treatment, and follow-up phases.
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	Screening	Baseline (cycle days 2–4)	Baseline (cycle days 21–22)	Post-treatment (3 cycles; cycle days 2–4)	Follow-up (up to 6 months)
Investigator meeting	✓				
Informed consent	✓				
Demographics, medical and family history	✓				
Anthropometric measurements	✓				

(weight, height, BMI)					
Menstrual cycle characteristics	✓				
Hormone levels (AMH, FSH, LH, E2, PRL, TSH, 25-OH-vitamin D3)		✓		✓	
progesterone			✓		
AFC		✓			
Spontaneous pregnancy				✓	✓
IVF outcome					✓

3. 10. Criteria for discontinuation

The criteria for the discontinuation of the trial are as follows: if the participant refuses to continue or withdraws consent, if the entire study is terminated, or if a spontaneous pregnancy occurs during the study. Additionally, discontinuation will occur if the participant fails to adhere to the study rules, attends fewer than 75% of the exercise sessions in the intervention group, or undergoes any other intervention or surgery during the study period that may alter the study outcome. The trial may also be discontinued in the case of undesirable events related to the treatment, such as acute pain, musculoskeletal complaints, or acute mental or physical trauma that prevents the continuation of the study. The study may also be discontinued in the event of a newly diagnosed malignancy or if the treating physician and physiotherapist determine that continuation of oral therapy or physiotherapy is no longer appropriate.

3. 11. Statistical analysis

All statistical analyses were performed using GraphPad Prism (version 10.3.1.509, GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics (version 25, IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. Variables with normal distribution are presented as mean ± standard error of the mean (SEM), while non-normally distributed variables are presented as median with 95% confidence interval (CI). Categorical variables are reported as absolute numbers and percentages.

Baseline characteristics were compared between groups using independent t-tests or Mann–Whitney U-tests for continuous variables and Fisher's exact tests for categorical variables. Within-group pre–post changes were evaluated using paired t-tests or Wilcoxon signed-rank tests, as appropriate.

For all hormonal outcomes (AMH, FSH, LH, E2, PRL, and TSH), analysis of covariance (ANCOVA) was performed using SPSS to compare follow-up values between the treatment (exercise + oral therapy) and control (oral therapy only) groups, while adjusting for baseline values and body mass index (BMI). In each model, the follow-up measurement was the dependent variable, study group was the fixed factor, and baseline value and BMI were entered as covariates. This adjustment allowed estimation of between-group differences that were independent of initial hormone levels and BMI. Adjusted mean differences and their 95% confidence intervals (CI) are reported. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

3. 12. Ethics approval

Ethical approval for the study was obtained from the Human Reproduction Committee of the Hungarian Medical Research Council under reference number 25489-8/2021/EÜIG on 12 July 2021. The research procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Prior to enrolment, all participants provided written informed consent.

3. 13. Discontinuation of the study

The study will be prematurely concluded if the Institutional Review Board (IRB) detects any of the following: severe adverse medication reactions, a newly diagnosed cancer, or participants facing unforeseen, substantial, or intolerable risks (including mortality). There was no patient discontinued the study.

4. RESULTS

Table 2 presents the baseline characteristics of the control and treatment groups, including age, BMI, and hormone levels at both baseline and post-treatment assessment. The BMI of the control group was significantly higher than that of the treatment group.

Table 2. Baseline and 3-month hormonal parameters in the intervention group (exercise combined with oral therapy) and the control group (oral therapy only). Data are presented as mean ± SEM for normally distributed variables and median (95% CI) for non-normally distributed variables, according to the Shapiro–Wilk test. Between-group differences were evaluated using independent t-tests or Mann–Whitney tests, as appropriate. Sample size: n = 12 per group (214).

	Control group	**Treatment group**	***p* value**
Age	38.00 ± 0.60	35.25 ± 1.47	0.104
BMI	25.64 ± 0.96	21.49 ± 0.61	0.0014
AMH	0.50 ± 0.07	0.54 ± 0.08	0.695
FSH	10.83 ± 0.74	12.16 ± 1.36	0.397
LH	4.83 ± 0.69	5.82 ± 0.57	0.281
E2	42.25 (38.00–62.20)	40.01 (25.30–63.70)	0.370
prolactin	11.51 (8.45–33.62)	11.29 (7.24–15.30)	0.525
TSH	2.06 ± 0.29	1.83 ± 0.20	0.515
3-month AMH	0.28 (0.10–0.82)	0.85 (0.32–1.40)	0.0075
3-month FSH	13.07 ± 2.04	9.39 ± 0.90	0.122
3-month LH	4.30 (2.82–10.40)	4.55 (3.50–7.00)	0.877
3-month E2	47.60 (34.10–95.70)	43.45 (33.70–80.95)	0.349
3-month prolactin	10.85 ± 1.143	9.90 ±1.82	0.659
3-month TSH	1.47 (0.21–3.86)	1.48 (1.08–3.54)	>0.999

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To mitigate BMI-related distortion, we conducted an ANCOVA analysis. When evaluating hormonal parameters together with pregnancy and age, while adjusting for BMI and baseline AMH levels, AMH was significantly higher in the treatment group than in the control group at the 3-month assessment (Fig. 1).

The incidence of spontaneous pregnancy during both the intervention and follow-up periods was significantly higher in the treatment group than in the control group (Fisher's exact test, p = 0.0272; Figure 2). This difference remained statistically significant in the multivariate ANCOVA model (p = 0.013). No significant between-group differences were detected in post-treatment FSH, LH, E2, prolactin, or TSH levels, either in the unadjusted comparisons or in the ANCOVA-adjusted analyses (Table 2).

Across the study period, spontaneous conception was documented in more than half of the participants assigned to the treatment group (7/12), whereas only one case was observed among controls (1/12).

Within the treatment group, three spontaneous pregnancies occurred during the active intervention phase; none of these resulted in live birth. By contrast, four additional spontaneous pregnancies were recorded after completion of the intervention, during the 6-month follow-up period, and all culminated in live births. In the control group, a single spontaneous pregnancy was documented during the active study period and resulted in a live birth. Taken together, the total number of live births was four in the treatment group and one in the control group.

During the follow-up period, only 2 IVF treatments were performed in the intervention group, both of which were unsuccessful. In contrast, 9 IVF treatments were conducted in the control group, with 2 successful IVF procedures resulting in live births, despite only one spontaneous pregnancy.

We conducted an ANCOVA on AMH levels, adjusting for BMI, and confirmed that AMH was higher in the treatment group compared with the control group at post-treatment assessment. However, when AMH was analyzed separately using an ANCOVA model adjusted only for BMI, the between-group difference did not reach statistical significance (p = 0.086), potentially due to limited statistical power arising from the small sample size. Notably, BMI had no significant or clinically meaningful effect on AMH levels (p = 0.756). While the data suggest a potential increase in AMH levels following exercise, the limited sample size precludes definitive conclusions, and the observed difference may be attributable to random variation.

The ANCOVA test was also performed separately for spontaneous pregnancies, taking into account BMI and baseline AMH. Difference in spontaneous pregnancy rates between the treatment and control groups plus the effect of BMI were also filtered out here. When spontaneous pregnancy was analyzed separately in an ANCOVA model adjusting for BMI and baseline AMH, the between-group difference was still significant (p = 0.034), and BMI showed no significant association (p = 0.998). In other words, exercise did indeed increase the chance of spontaneous pregnancy, and this was not caused by differences in BMI.

After adjustment for baseline AMH and BMI, the addition of the 3-month structured exercise program to oral therapy resulted in higher post-intervention AMH levels compared with oral therapy alone. The incidence of spontaneous pregnancy was also higher in the intervention group. No statistically significant differences were observed in the remaining hormonal parameters. The intervention demonstrated good tolerability and feasibility. Attendance rates exceeded 85–90% of the scheduled supervised exercise sessions. Missed sessions were predominantly attributable to minor and transient conditions, including short episodes of dysmenorrhea (1–2 days), brief febrile illnesses, or short-term absences such as vacations lasting up to one week. Overall adherence rates indicate a high level of participant compliance and support the feasibility of implementing this supervised intervention protocol in larger-scale studies.

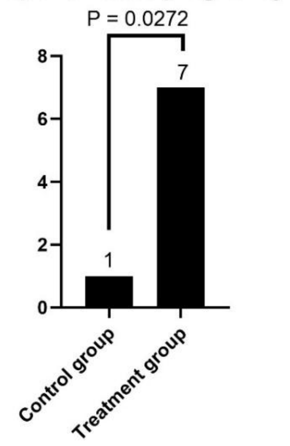

Figure 2. Incidence of spontaneous pregnancy in the intervention group receiving combined exercise and oral antioxidant therapy compared with the control group receiving oral antioxidant therapy alone across the intervention and follow-up periods. Bars represent the number of women achieving spontaneous pregnancy in each group. Between-group differences were statistically significant in both unadjusted (Fisher's exact test) and adjusted ANCOVA models controlling for baseline AMH, BMI, and age ($p \leq 0.034$). Sample size: n = 12 per group.

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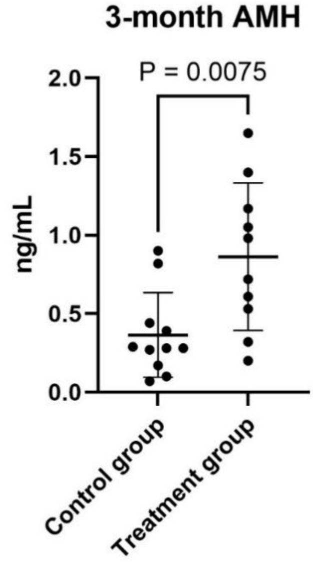

Figure 3. Post-treatment serum AMH levels in the intervention group (exercise combined with oral therapy) and the control group (oral therapy only). Data are presented as median values with 95% confidence intervals. A significant difference between groups was observed in the unadjusted Mann–Whitney test ($p = 0.0075$) and persisted in a multivariate ANCOVA model including all hormonal parameters, spontaneous pregnancy, and age, adjusted for baseline AMH and BMI ($p = 0.008$). In a separate ANCOVA model including only AMH and adjusting for BMI, the difference was not statistically significant ($p = 0.086$), likely due to the limited sample size. Sample size: 12 participants per group.

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5. DISCUSSION

5.1. Background and Rationale

This dissertation builds upon the previously published study protocol (213) and its corresponding clinical pilot study (214). Although the clinical study was conducted with a reduced sample size and a simplified design, it preserved the key methodological elements of the planned full-scale trial and provided valuable preliminary data regarding feasibility, adherence, and potential efficacy. The primary aim of the clinical study was to explore whether a structured, physiotherapy-based exercise program targeting the pelvic region could improve ovarian reserve markers and increase spontaneous pregnancy rates in women with diminished ovarian reserve. To our knowledge, this represents the first study specifically investigating the reproductive effects of such a targeted intervention in this patient population.

5.2. Summary of clinical findings

In this exploratory clinical study, participation in the combined intervention was associated with a statistically significant increase in anti-Müllerian hormone levels and a higher incidence of spontaneous pregnancies compared to the control group. Basal FSH levels demonstrated a decreasing trend, although this did not reach statistical significance. While IVF-related outcomes were not predefined endpoints, fewer assisted reproductive treatments were required in the intervention group, which also exhibited a higher rate of natural conception during the follow-up period.

5.3. Interpretation and conceptual considerations

Interpretation of these findings requires careful consideration of the potential physiological mechanisms involved. In particular, it is important to distinguish between true ovarian rejuvenation and delayed ovarian ageing, as these processes carry different implications for follicular dynamics, ovulatory function, and long-term fertility potential. The observed increase in AMH levels and spontaneous pregnancy rates suggests a favorable modulation of ovarian function; however, the clinical study was not designed to definitively determine whether these effects reflect genuine rejuvenation or a temporary functional enhancement. Potential mechanisms may include improved pelvic perfusion, enhanced neuromuscular coordination, reduced oxidative stress, and modulation of autonomic balance through targeted exercise and diaphragmatic breathing.

5.4. Potential mechanisms underlying the observed effects

The observed trends in ovarian reserve and spontaneous pregnancy in the clinical study may be mediated by several interrelated physiological and psychological mechanisms. Targeted physiotherapy exercises and specific physical activities—particularly those focusing on the pelvic region, such as pelvic floor activation, diaphragmatic breathing, and yoga postures—may enhance local blood flow to reproductive organs. Improved pelvic perfusion can facilitate oxygen and nutrient delivery, supporting follicular development, oocyte quality, and hormonal regulation.

Although direct evidence in DOR is limited, several related studies provide indirect support for these mechanisms. For example, yoga has been shown to enhance uterine artery perfusion (215), and altered vascular resistance in hypoestrogenic amenorrhea illustrates the link between hormonal milieu and circulation (216). Observational and interventional data also indicate that moderate exercise positively affects ovarian reserve markers such as AMH and antral follicle count, and may improve assisted reproductive outcomes (217, 218).

Beyond local circulation, the coordinated function of core muscles—including the diaphragm, transversus abdominis, multifidus, and pelvic floor—is essential for lumbar-pelvic stability, postural control, and optimal support of reproductive organs (151, 219). Targeted exercises strengthening these deep stabilizing muscles may improve pelvic floor function, support anatomical positioning of reproductive organs, and enhance circulation (220). Proper diaphragmatic breathing can further optimize neuromuscular control and trunk stabilization, contributing to overall pelvic function (188, 221).

Beyond their role in postural control and pelvic stability, pelvic floor muscles may also influence female sexual function and sexual response, potentially contributing indirectly to reproductive outcomes. A recent systematic review and meta-analysis demonstrated a consistent association between pelvic floor muscle function and multiple domains of female sexual health, while randomized controlled trial evidence indicates that targeted pelvic floor muscle training can lead to clinically meaningful improvements in sexual function in women of reproductive age (182, 183). Although sexual function was not assessed in the present pilot study, the available evidence supports including pelvic floor activation and coordination within physiotherapy-based reproductive exercise programs. Importantly, the pelvic floor and diaphragm function as an integrated unit, and improved neuromuscular coordination within this system may simultaneously enhance pelvic organ support, circulation, and autonomic regulation. This shared pathway provides a conceptual link between pelvic floor–focused training and stress-regulating breathing practices. These mechanisms may contribute indirectly to reproductive outcomes and will be further explored in the planned full-scale randomized trial using validated patient-reported outcome measures, such as the Female Sexual Function Index (FSFI).

These findings align with our pilot study observations and suggest that stress-regulating interventions may further support reproductive outcomes. Infertility-related stress, considered a negative life event and a complex experience of loss, is highly prevalent in women undergoing fertility evaluation or treatment (17, 201, 202). Diaphragmatic breathing (DB) and yoga-based mind-body interventions offer effective strategies for stress reduction. DB activates the parasympathetic nervous system, reducing physiological and psychological stress (207-209), while yoga reinforces resilience and may improve reproductive outcomes (200, 222).

Furthermore, beyond stress modulation, physical activity may also influence fertility through oxidative stress regulation. Oxidative stress plays a central role in ovarian ageing and reduced reproductive potential. Elevated levels of reactive oxygen species can damage cellular structures, impair folliculogenesis, reduce oocyte quality, and contribute to subfertility (74). Lifestyle interventions, including moderate-intensity exercise, can positively influence oxidative stress and enhance endogenous antioxidant defenses, supporting ovarian function (114, 116).

Overall, our findings suggest that physiotherapy-based movement interventions likely exert a multifaceted, holistic impact on reproductive health. By improving pelvic circulation, optimizing musculoskeletal function, mitigating oxidative stress, and addressing psychological wellbeing, such programs may enhance both physical and emotional health. These mechanisms provide a biologically and psychologically plausible explanation for the trends observed in ovarian reserve and spontaneous pregnancy in the study, supporting the value of structured, targeted, and supervised physiotherapy-based exercise programs in women with DOR.

5.5. Context within existing literature

Previous interventional studies examining the effects of exercise on female fertility have predominantly focused on women with polycystic ovary syndrome (PCOS). In this population, both moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) have been shown to improve insulin sensitivity, menstrual cyclicity, androgen levels, and, in some cases, ovulatory and pregnancy outcomes (223-225). Lifestyle programs combining exercise with dietary or pharmacological interventions yielded the most robust improvements in BMI, hormonal normalization, and reproductive function (226).

A large reduction in body weight, excessive exercise, and/or elevated stress levels are associated with an increased risk of developing hypothalamic amenorrhoea. Suppression of gonadotrophin-releasing hormone (GnRH) pulsatility reduces LH, leading to oestradiol decline, anovulation, and cessation of menstruation. Dysfunction of the hypothalamic-pituitary-ovarian axis results in a hypoestrogenic state, negatively affecting sexual function and fertility (227, 228).

In contrast, women with diminished ovarian reserve (DOR) remain largely understudied, and no prior trials have specifically evaluated physiotherapy-based exercise interventions in this population. The present pilot study thus provides novel preliminary evidence that a structured, pelvic-focused exercise program may positively influence ovarian reserve and spontaneous conception in women with DOR (214).

It is important to note that many prior studies use heterogeneous definitions of physical activity, exercise, or training, which complicates comparisons. In contrast, the present study implemented a structured, targeted, and supervised physiotherapy-based exercise program specifically designed to optimize pelvic function and ovarian reserve in women with DOR, distinguishing it from general or unmonitored physical activity interventions (214).

Data on the association between physical activity and fertility remain inconsistent. PA encompasses all skeletal muscle–driven activities that increase energy expenditure, including occupational, leisure, conditioning, household, and other forms (131). Exercise is a planned, structured, and repetitive subcategory of PA, typically aimed at improving health, well-being, or performance (229). These distinctions are often conflated in existing RCTs and meta-analyses, contributing to heterogeneity in the literature (230).

Therefore, structured, supervised, and targeted exercise interventions, like the present program, are needed to clarify the effects of moderate-intensity physical activity on ovarian function and fertility outcomes.

While moderate-intensity activity appears to support ovarian reserve and optimize hormonal balance (217, 231), frequent high-intensity exercise may increase the risk of subfertility, particularly in ovulatory disorders (232). Currently, the literature does not provide a clear consensus regarding the impact of pre-ART physical activity on pregnancy outcomes (139, 233-235). In a small Hungarian cohort study, moderate-intensity physical activity was positively associated with the number of oocytes retrieved and pregnancy outcomes (218) supporting our pilot study observations. A recent systematic review of 34 studies concluded that evidence remains insufficient to determine the relationship between physical activity and male and female fertility (236). Conflicting results were also reported when examining associations between daily walking duration and female fertility.

Mind-body approaches, such as yoga and diaphragmatic breathing, have been linked to reductions in psychological stress, improvements in autonomic balance, and enhanced reproductive outcomes (198, 200, 207, 222), suggesting potential pathways through which exercise may influence fertility.

Additionally, combining diaphragmatic breathing with trunk-stabilizing exercises may improve neuromuscular control and trunk stability, supporting optimal pelvic function, as demonstrated in studies showing rapid postural stabilization after fatigue in healthy adults (188, 221).

While physical exercises and yoga share many movement characteristics, yoga further emphasizes breathing, mindfulness, and precise postures. Clinical evidence indicates that yoga can be equally or more effective than conventional physical exercise in promoting physiological and psychological well-being, which may, in turn, enhance ART success rates (237, 238).

Other mechanistic pathways potentially contributing to improved ovarian function include enhanced pelvic blood flow (215), increased pelvic-lumbar stability (151, 176), and reductions in oxidative stress (110, 116). Despite growing evidence, heterogeneity in study populations, intervention types, duration, and outcome measures limits direct comparisons (236).

Importantly, no prior study has investigated a comprehensive physiotherapy intervention specifically targeting pelvic rehabilitation in women with DOR. This underlines the novelty and clinical relevance of the present pilot findings (214). Additionally, recommendations by the World Health Organization (131) and the American College of Obstetricians and Gynecologists (60) advocating at least 150 minutes of moderate physical activity per week for women planning pregnancy are consistent with the exercise parameters employed in this pilot study.

5.6. Strengths of the clinical study

The clinical study presented in this dissertation demonstrates several notable strengths. First, the study design preserved key elements of a controlled trial, comparing an intervention group receiving a structured, targeted, and supervised physiotherapy-based exercise programme in addition to per os therapy with a control group receiving per os therapy alone. Despite the limited sample size inherent to a pilot design, the study applied strict inclusion criteria and implemented close monitoring of participant adherence, particularly regarding exercise sessions and diaphragmatic breathing protocols. This careful supervision increases confidence that the observed effects can be attributed to the intervention itself rather than to variability in participant compliance or execution of exercises. In addition, the study included a six-month follow-up period, allowing preliminary evaluation of both short-term and longer-term trends in ovarian reserve markers and spontaneous pregnancy outcomes. The inclusion of both hormonal parameters and reproductive events allows for a more comprehensive evaluation of potential effects, thereby increasing the interpretative value and clinical relevance of the findings.

5.7. Limitations

Nevertheless, several limitations should be acknowledged. The small sample size, which is inherent to pilot studies, reduces statistical power and limits the generalisability of the findings. Although statistically significant changes were observed in AMH levels and spontaneous pregnancy rates, other hormonal markers did not show significant between-group differences, underscoring the exploratory and preliminary nature of the results. The follow-up period, although sufficient to capture early trends, may not fully reflect long-term effects on ovarian function or fertility outcomes. Furthermore, the study did not include direct assessments of oxidative stress or advanced imaging of uterine or ovarian perfusion, meaning that mechanistic explanations remain hypothetical and are based on existing literature rather than on direct measurement. Finally, although the structured exercise programme was carefully designed and supervised, individual variability in baseline fitness, lifestyle factors, and psychosocial stress levels may have influenced the outcomes, reflecting the complex and multifactorial nature of female fertility. Although the distribution of primary and secondary infertility differed between the study groups, the higher proportion of primary infertility in the intervention group would be expected to be associated with a less favourable reproductive prognosis. Therefore, this baseline difference is unlikely to explain the observed improvements in ovarian function and spontaneous conception.

5.8. Clinical relevance of the study

Despite the limitations discussed above, the findings of this study may have potential clinical relevance. Women with diminished ovarian reserve often have limited therapeutic options, making non-invasive and well-tolerated interventions particularly valuable. The pilot findings suggest that structured physiotherapy-based exercise programmes may serve as a promising adjunctive approach to support ovarian function, facilitate spontaneous conception, and promote overall reproductive health. By integrating elements aimed at improving circulation, core and pelvic stabilization, stress reduction, and antioxidant support, the programme addresses multiple pathways implicated in fertility, offering a holistic, lifestyle-oriented complement to conventional medical therapies. Moreover, the programme appeared feasible and acceptable to participants in the pilot setting, indicating that it could be adapted for use in both clinical practice and community-based care, although its effectiveness should be confirmed in larger, controlled studies. Importantly, the present research represents a proof-of-concept investigation demonstrating the clinical relevance of a structured, physiotherapy-based supportive intervention in women with diminished ovarian reserve.

5.9. Future research directions

As an exploratory pilot study, these results may provide a preliminary basis for larger, adequately powered trials. Future studies should aim to replicate and further characterize the observed trends, explore potential underlying mechanisms using direct physiological assessments (e.g., oxidative stress markers, uterine and ovarian perfusion imaging), and evaluate longer-term reproductive outcomes. While definitive conclusions cannot be drawn at this stage, such research may contribute to the development of evidence-informed clinical perspectives regarding the potential role of physiotherapy-based exercise as an adjunctive, non-invasive component of fertility care, offering women with diminished ovarian reserve additional options to support their reproductive health.

Lifestyle factors are increasingly recognized as important contributors to reproductive health, including physical activity levels (236), dietary pattern (239), body weight (226, 240), sleep patterns (86, 88), smoking (241) and psychosocial stress. Within this broader context, the present pilot findings suggest that targeted, structured exercise may represent one modifiable lifestyle component with potential relevance for women with diminished ovarian reserve**.** By emphasizing early intervention, health education, and supportive lifestyle strategies, future research may further clarify how such approaches can be systematically integrated into comprehensive fertility care. From a clinical and implementation perspective, future research could support the development of interdisciplinary care models in which physiotherapy-based interventions are integrated into comprehensive fertility care, helping to establish reproductive physiotherapy as a recognized discipline within this framework.

6. CONCLUSIONS

This study provides preliminary evidence that a targeted, and supervised physiotherapy-based exercise intervention combined with oral antioxidant supplementation may support ovarian function and facilitate spontaneous conception in women with diminished ovarian reserve. A statistically significant increase in AMH levels and a higher likelihood of spontaneous pregnancy were observed, while basal FSH showed a decreasing tendency without reaching statistical significance. This intervention, relevant to women's health physiotherapy and fertility care, was safe, feasible, and well-tolerated, highlighting its clinical relevance as a non-invasive adjunct to conventional fertility treatments. The program's beneficial effects are likely mediated through enhanced pelvic circulation, optimized neuromuscular function, stress reduction, and modulation of oxidative balance. These results are consistent with a holistic perspective on reproductive health recognizing the complex interplay of physiological, psychological, and lifestyle factors in influencing fertility potential**.** The present research represents a proof-of-concept investigation, providing initial clinical evidence that a structured, physiotherapy-based supportive intervention is feasible, safe, and clinically relevant in the context of diminished ovarian reserve. Despite limitations such as the small sample size and short follow-up period, the results provide a foundation for larger, adequately powered controlled trials. Future studies should aim to confirm efficacy, elucidate the underlying mechanisms more directly, and evaluate long-term reproductive outcomes. Ultimately, integrating a structured, physiotherapy-based supervised exercise programme into fertility care and women's health physiotherapy practice may represent a promising strategy to enhance reproductive outcomes and overall wellbeing in women facing the challenges of DOR.

7. SUMMARY

Infertility affects approximately 15–17% of couples worldwide, with diminished ovarian reserve (DOR) representing a major contributing factor for which no widely accepted, effective treatment currently exists. In recent years, increasing attention has been directed toward lifestyle-related determinants of reproductive health, including lifestyle factors that are increasingly recognized as modifiable influences on fertility potential. Against this background, the present dissertation introduces a structured, supervised physiotherapy-based exercise programme combined with oral antioxidant supplementation, developed as an interdisciplinary supportive intervention designed to enhance ovarian function in women diagnosed with DOR. In this study, participants receiving the combined intervention showed a statistically significant increase in AMH levels and higher spontaneous pregnancy rates than controls. Basal FSH levels exhibited a decreasing trend, although the change did not reach statistical significance. These findings suggest that the observed benefits may be partly mediated through improved pelvic perfusion, optimized neuromuscular function, reduction of psychological stress, and modulation of oxidative balance.

The intervention proved to be safe, feasible, and well tolerated, underscoring its potential clinical relevance as a supportive strategy for women with limited therapeutic options. While the small sample size and relatively short follow-up period limit definitive conclusions, the results provide preliminary, proof-of-concept evidence supporting the role of physiotherapy-based exercise in reproductive health.

Future studies with larger sample sizes and longer follow-up are warranted to confirm these findings, clarify underlying mechanisms through direct physiological measurements, and optimize intervention protocols. Overall, this work highlights the potential of supervised physiotherapy exercise programmes as a non-invasive, integrable component of comprehensive fertility care for women with DOR.

8. REFERENCES

1. Kovács BP, Várbíró S, Forrai J. A meddőség kezelési módjai az ókortól napjainkig / Infertility treatment methods from ancient times to the present day. Kaleidoscopehistory. 2023;13(27):100-19.
2. Haimov-Kochman R, Sciaky-Tamir Y, Hurwitz A. Reproduction concepts and practices in ancient Egypt mirrored by modern medicine. Eur J Obstet Gynecol Reprod Biol. 2005;123(1):3-8.
3. Trindade Lopes H, Gurgel Pereira R. The Gynaecological Papyrus Kahun. In: Trindade Lopes H, Gurgel Pereira R, editors. The Gynecological Papyrus Kahun. London: IntechOpen; 2021.
4. Tipton CM. Susruta of India, an unrecognized contributor to the history of exercise physiology. J Appl Physiol (1985). 2008;104(6):1553-6.
5. Saint-Fleur J, Persaud NA, Ganti L. Herodicus: The Father of Sports Medicine. Cureus. 2024;16(11):e74224.
6. Abbasnejad F, Golzari SE, Ghabili K, Aslanabadi S, Rikhtegar R, Ranjbar Y. Obesity-related female infertility in medieval persian manuscripts. Obes Surg. 2013;23(4):574-6.
7. Aligabi Z. Reflections on Avicenna's impact on medicine: his reach beyond the middle east. J Community Hosp Intern Med Perspect. 2020;10(4):310-2.
8. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol. 2018;16(1):22.
9. Pasalar M, Mosaffa-Jahromi M, Amooee S, Daneshfard B. Obesity and Infertility: Persian Medicine Perspective. J Reprod Infertil. 2021;22(1):73-4.
10. Green MH. The Trotula: An English translation of the medieval compendium of women’s medicine. Philadelphia: University of Pennsylvania Press; 2001.
11. Keele KD. Leonardo da Vinci: Anatomical drawings from the Royal Collection. London: Royal Academy of Arts; 1977.
12. Bowen G, Gonzales J, Iwanaga J, Fisahn C, Loukas M, Oskouian RJ, et al. Leonardo da Vinci (1452–1519) and his depictions of the human spine. Child's Nervous System. 2017;33(12):2067-70.

13. Kemp M. Revisiting Leonardo on Muscles: Intimations of Mathematical Biology and Biomechanics. Biological Theory. 2023;18(1):7-19.

14. Carroll M. The Renaissance of Reproductive Science: Leonardo da Vinci's Anatomical Contributions. Reprod Sci. 2025;32(3):575-99.

15. Novell JR. From Da Vinci to Harvey: the development of mechanical analogy in medicine from 1500 to 1650. J R Soc Med. 1990;83(6):396-8.

16. Harkányi L. Leonardo da Vinci a légzőrendszerről. Orvosi Hetilap. 1989;130(30):1614-6, 9.

17. Lakatos E, Pápay N, Ádám S, Balog P. Paradigmák a meddőség értelmezésében. Pszichológia. 2014;34(3):261-87.

18. Liu J, Qin Y, Liu H, Liu Y, Yang Y, Ning Y, et al. Global, regional, and national burden of female infertility and trends from 1990 to 2021 with projections to 2050 based on the GBD 2021 analysis. Sci Rep. 2025;15(1):17559.

19. Singleton M. Yoga Body: The Origins of Modern Posture Practice. Oxford: Oxford University Press; 2010.

20. Kovács BP. A testmozgás gyógyító ereje / The healing capacity of physical exercise. Kaleidoscopehistory. 2023;13(26):477-92.

21. Veder R. Seeing your way to health: the visual pedagogy of Bess Mensendieck's physical culture system. Int J Hist Sport. 2011;28(8-9):1336-52.

22. Zaletnyik Z, Repiszky T. A gyógyító mozgás művésze: Madzsar Alice emlékének. Budapest, Magyarország: Semmelweis Kiadó; 2012.

23. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018;62:2-10.

24. Deshpande PS, Gupta AS. Causes and Prevalence of Factors Causing Infertility in a Public Health Facility. J Hum Reprod Sci. 2019;12(4):287-93.

25. Smeenk J, Wyns C, De Geyter C, Kupka M, Bergh C, Cuevas Saiz I, et al. ART in Europe, 2019: results generated from European registries by ESHRE. Hum Reprod. 2023;38(12):2321-38.

26. World Health Organization. Infertility Prevalence Estimates, 1990-2021 Geneva: World Health Organization; 2023 [updated 2023-04-03; cited 2026-01-31]. Available from: https://www.who.int/publications/i/item/978920068315.

27. Walker MH, Tobler KJ. Female infertility. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.

28. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update. 2015;21(4):411-26.

29. World Health Organization. Guideline for the prevention, diagnosis and treatment of infertility Geneva: World Health Organization; 2025 [updated 2025-11-28; cited 2026-01-31]. Available from: https://www.who.int/publications/i/item/9789240115774.

30. Chambers GM, Dyer S, Zegers-Hochschild F, de Mouzon J, Ishihara O, Banker M, et al. International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology, 2014†. Hum Reprod. 2021;36(11):2921-34.

31. Authority HFaE. Fertility treatment 2021: preliminary trends and figures London: Human Fertilisation and Embryology Authority; 2023 [cited 2023-12-21]. Available from: https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2021-preliminary-trends-and-figures/#section-2.

32. Technology SfAR. Preliminary national summary report for 2022. Birmingham (AL); 2022.

33. Li H, Nawsherwan, Fan C, Mubarik S, Nabi G, Ping YX. The trend in delayed childbearing and its potential consequences on pregnancy outcomes: a single center 9-years retrospective cohort study in Hubei, China. BMC Pregnancy Childbirth. 2022;22(1):514.

34. Eurostat. Fertility statistics: 2023 [cited 2025-07-24]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics.

35. Driscoll AK, Hamilton BE. Effects of Age-specific Fertility Trends on Overall Fertility Trends: United States, 1990–2023. Natl Vital Stat Rep. 2024;74(3):1–19.

36. Adamson GD, Zegers-Hochschild F, Dyer S. Global fertility care with assisted reproductive technology. Fertil Steril. 2023;120(3 Pt 1):473-82.

37. Owen A, Carlson K, Sparzak PB. Age-Related Fertility Decline. StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.

38. Gantt A, Metz TD, Kuller JA, Louis JM, Cahill AG, Turrentine MA. Obstetric Care Consensus #11, Pregnancy at age 35 years or older. Am J Obstet Gynecol. 2023;228(3):B25-b40.

39. Ding X, Li H, Yang Q, Nawsherwan. The Trend in Delayed Childbearing Age and Its Potential Impact on Adverse Maternal-Perinatal Outcomes in Developed and Developing Countries: A Narrative Review. Iran J Public Health. 2025;54(1):1-12.

40. Delbaere I, Verbiest S, Tydén T. Knowledge about the impact of age on fertility: a brief review. Ups J Med Sci. 2020;125(2):167-74.

41. Beaujouan E. Latest-Late Fertility? Decline and Resurgence of Late Parenthood Across the Low-Fertility Countries. Popul Dev Rev. 2020;46(2):219-47.

42. Liang Y, Huang J, Zhao Q, Mo H, Su Z, Feng S, et al. Global, regional, and national prevalence and trends of infertility among individuals of reproductive age (15-49 years) from 1990 to 2021, with projections to 2040. Hum Reprod. 2025;40(3):529-44.

43. Spéder Z, Bálint L. Realization of Short-Term Fertility Intentions in a Comparative Perspective: Which Macro-Level Conditions Matter? Population Research and Policy Review. 2024;43(5):72.

44. Monostori Judit ŐPSZ. Demográfiai portré 2021. Budapest: Központi Statisztikai Hivatal Népességtudományi Kutatóintézet; 2021. 39-56. p.

45. Monostori J, Őri P. Demográfiai portré 2024. In: Spéder Z, editor. Budapest, Magyarország: KSH Népességtudományi Kutatóintézet (KSH NKI); 2024. p. 39-56.

46. Sadeghi MR. Ovarian Rejuvenation: Turning Dreams into Reality. J Reprod Infertil. 2024;25(1):1-2.

47. Zhang J, Chen Q, Du D, Wu T, Wen J, Wu M, et al. Can ovarian aging be delayed by pharmacological strategies? Aging (Albany NY). 2019;11(2):817-32.

48. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev. 2009;30(5):465-93.

49. Tal R, Seifer DB. Ovarian reserve testing: a user's guide. Am J Obstet Gynecol. 2017;217(2):129-40.

50. Medicine PCotASfR. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020;114(6):1151-7.

51. Choi R, Park W, Chun G, Lee SG, Lee EH. Investigation of the Prevalence of Diminished Ovarian Reserve in Korean Women of Reproductive Age. J Clin Med. 2023;12(15):5099.

52. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010;16(2):113-30.

53. Parry JP, Koch CA. Ovarian Reserve Testing. Endotext. Treasure Island (FL): StatPearls Publishing; 2020.

54. Carson SA, Kallen AN. Diagnosis and Management of Infertility: A Review. JAMA. 2021;326(1):65-76.

55. Moolhuijsen LME, Visser JA. Anti-Müllerian Hormone and Ovarian Reserve: Update on Assessing Ovarian Function. J Clin Endocrinol Metab. 2020;105(11):3361-73.

56. Liao S, Pan W, Dai WQ, Jin L, Huang G, Wang R, et al. Development of a Dynamic Diagnosis Grading System for Infertility Using Machine Learning. JAMA Netw Open. 2020;3(11):e2023654.

57. Han S, Zhai Y, Guo Q, Qin Y, Liu P. Maternal and Neonatal Complications in Patients With Diminished Ovarian Reserve in In-Vitro Fertilization/Intracytoplasmic Sperm Injection Cycles. Front Endocrinol (Lausanne). 2021;12:648287.

58. Devine K, Mumford SL, Wu M, DeCherney AH, Hill MJ, Propst A. Diminished ovarian reserve in the United States assisted reproductive technology population: diagnostic trends among 181,536 cycles from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System. Fertil Steril. 2015;104(3):612-19.e3.

59. Ovarian Stimulation T, Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Hum Reprod Open. 2020;2020(2):hoaa009.

60. ACOG Committee Opinion No. 762: Prepregnancy Counseling. Obstet Gynecol. 2019;133(1):e78-e89.

61. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder--a plea for universal definitions. J Assist Reprod Genet. 2015;32(12):1709-12.

62. Li S, Hu L, Zhang C. Effect of chronological age of patients with diminished ovarian reserve on in vitro fertilization outcome. J Obstet Gynaecol. 2022;42(4):654-7.

63. Wald KA, Shahine LK, Lamb JD, Marshall LA, Hickok LR. High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients. Gynecol Endocrinol. 2020;36(12):1079-81.

64. Yin J, Chang H, Li R, Leung P. Recent progress in the treatment of women with diminished ovarian reserve. Gynecol Obstet Clin Med. 2021;1(4):186–9.

65. Fraidakis M, Giannakakis G, Anifantaki A, Skouradaki M, Tsakoumi P, Bitzopoulou P, et al. Intraovarian Platelet-Rich Plasma Injections: Safety and Thoughts on Efficacy Based on a Single Centre Experience With 469 Women. Cureus. 2023;15(5):e38674.

66. Sills ES. The Scientific and Cultural Journey to Ovarian Rejuvenation: Background, Barriers, and Beyond the Biological Clock. Medicines (Basel). 2021;8(6):29.

67. Sills ES, Wood SH. Progress in human ovarian rejuvenation: Current platelet-rich plasma and condensed cytokine research activity by scope and international origin. Clin Exp Reprod Med. 2021;48(4):311-5.

68. Polonio AM, García-Velasco JA, Herraiz S. Stem Cell Paracrine Signaling for Treatment of Premature Ovarian Insufficiency. Front Endocrinol (Lausanne). 2020;11:626322.

69. Serdarogullari M, Raad G, Makieva S, Liperis G, Fraire-Zamora JJ, Celik-Ozenci C. Revitalizing female fertility: platelet-rich plasma - hype or hope? Reprod Biomed Online. 2024;49(2):103813.

70. Reiter RJ, Sharma R, Romero A, Manucha W, Tan DX, Zuccari D, et al. Aging-Related Ovarian Failure and Infertility: Melatonin to the Rescue. Antioxidants (Basel). 2023;12(3):695.

71. Tamura H, Jozaki M, Tanabe M, Shirafuta Y, Mihara Y, Shinagawa M, et al. Importance of Melatonin in Assisted Reproductive Technology and Ovarian Aging. Int J Mol Sci. 2020;21(3):1135.

72. Espino J, Macedo M, Lozano G, Ortiz Á, Rodríguez C, Rodríguez AB, et al. Impact of Melatonin Supplementation in Women with Unexplained Infertility Undergoing Fertility Treatment. Antioxidants (Basel). 2019;8(9):338.

73. Rizzo P, Raffone E, Benedetto V. Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid

on oocyte quality and pregnancy outcome in IVF cycles. A prospective, clinical trial. Eur Rev Med Pharmacol Sci. 2010;14(6):555-61.

74. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol. 2012;10:49.

75. Yan F, Zhao Q, Li Y, Zheng Z, Kong X, Shu C, et al. The role of oxidative stress in ovarian aging: a review. J Ovarian Res. 2022;15(1):100.

76. Kaltsas A, Zikopoulos A, Moustakli E, Zachariou A, Tsirka G, Tsiampali C, et al. The Silent Threat to Women's Fertility: Uncovering the Devastating Effects of Oxidative Stress. Antioxidants (Basel). 2023;12(8):1490.

77. Walke G, Gaurkar SS, Prasad R, Lohakare T, Wanjari M. The Impact of Oxidative Stress on Male Reproductive Function: Exploring the Role of Antioxidant Supplementation. Cureus. 2023;15(7):e42583.

78. Jeon GH. The Associations of Vitamin D with Ovarian Reserve Markers and Depression: A Narrative Literature Review. Nutrients. 2023;16(1).

79. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol. 2013;11:66.

80. Katyal G, Kaur G, Ashraf H, Bodapati A, Hanif A, Okafor DK, et al. Systematic Review of the roles of Inositol and Vitamin D in improving fertility among patients with Polycystic Ovary Syndrome. Clin Exp Reprod Med. 2024;51(3):181-91.

81. Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. Gynecol Endocrinol. 2012;28(7):509-15.

82. Díaz-Muñoz M, de la Rosa Santander P, Juárez-Espinosa AB, Arellano RO, Morales-Tlalpan V. Granulosa cells express three inositol 1,4,5-trisphosphate receptor isoforms: cytoplasmic and nuclear Ca2+ mobilization. Reprod Biol Endocrinol. 2008;6:60.

83. Gullo G, Carlomagno G, Unfer V, D'Anna R. Myo-inositol: from induction of ovulation to menopausal disorder management. Minerva Ginecol. 2015;67(5):485-6.

84. Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS. Myo-Inositol as a Key Supporter of Fertility and Physiological Gestation. Pharmaceuticals (Basel). 2021;14(6).

85. Cueto HT, Jacobsen BH, Laursen ASD, Riis AH, Hatch EE, Wise LA, et al. Dietary folate intake and fecundability in two preconception cohorts. Hum Reprod. 2022;37(4):828-37.

86. Lateef OM, Akintubosun MO. Sleep and Reproductive Health. J Circadian Rhythms. 2020;18:1.

87. Zhao F, Hong X, Wang W, Wu J, Wang B. Effects of physical activity and sleep duration on fertility: A systematic review and meta-analysis based on prospective cohort studies. Front Public Health. 2022;10:1029469.

88. Caetano G, Bozinovic I, Dupont C, Léger D, Lévy R, Sermondade N. Impact of sleep on female and male reproductive functions: a systematic review. Fertil Steril. 2021;115(3):715-31.

89. Sciarra F, Franceschini E, Campolo F, Gianfrilli D, Pallotti F, Paoli D, et al. Disruption of Circadian Rhythms: A Crucial Factor in the Etiology of Infertility. Int J Mol Sci. 2020;21(11).

90. Du CQ, Zhang DX, Chen J, He QF, Lin WQ. Men's Sleep Quality and Assisted Reproductive Technology Outcomes in Couples Referred to a Fertility Clinic: A Chinese Cohort Study. Nat Sci Sleep. 2022;14:557-66.

91. Liu Z, Zheng Y, Wang B, Li J, Qin L, Li X, et al. The impact of sleep on in vitro fertilization embryo transfer outcomes: a prospective study. Fertil Steril. 2023;119(1):47-55.

92. Reschini M, Buoli M, Facchin F, Limena A, Dallagiovanna C, Bollati V, et al. Women's quality of sleep and in vitro fertilization success. Sci Rep. 2022;12(1):17477.

93. Olcese JM. Melatonin and Female Reproduction: An Expanding Universe. Front Endocrinol (Lausanne). 2020;11:85.

94. Reiter RJ, Tan DX, Osuna C, Gitto E. Actions of melatonin in the reduction of oxidative stress. A review. J Biomed Sci. 2000;7(6):444-58.

95. Tamura H, Takasaki A, Taketani T, Tanabe M, Kizuka F, Lee L, et al. The role of melatonin as an antioxidant in the follicle. J Ovarian Res. 2012;5:5.

96. Tamura H, Takasaki A, Taketani T, Tanabe M, Kizuka F, Lee L, et al. Melatonin as a free radical scavenger in the ovarian follicle. Endocr J. 2013;60(1):1-13.

97. Tong J, Sheng S, Sun Y, Li H, Li WP, Zhang C, et al. Melatonin levels in follicular fluid as markers for IVF outcomes and predicting ovarian reserve. Reproduction. 2017;153(4):443-51.

98. Maldonado-Cárceles AB, Souter I, Li MC, Mitsunami M, Dimitriadis I, Ford JB, et al. Antioxidant Intake and Ovarian Reserve in Women Attending a Fertility Center. Nutrients. 2025;17(3).

99. Safiyeh FD, Mojgan M, Parviz S, Sakineh MA, Behnaz SO. The effect of selenium and vitamin E supplementation on anti-Mullerian hormone and antral follicle count in infertile women with occult premature ovarian insufficiency: A randomized controlled clinical trial. Complement Ther Med. 2021;56:102533.

100. Iervolino M, Lepore E, Forte G, Laganà AS, Buzzaccarini G, Unfer V. Natural Molecules in the Management of Polycystic Ovary Syndrome (PCOS): An Analytical Review. Nutrients. 2021;13(5).

101. Merhi ZO, Seifer DB, Weedon J, Adeyemi O, Holman S, Anastos K, et al. Circulating vitamin D correlates with serum antimüllerian hormone levels in late-reproductive-aged women: Women's Interagency HIV Study. Fertil Steril. 2012;98(1):228-34.

102. Bacanakgil BH, İlhan G, Ohanoğlu K. Effects of vitamin D supplementation on ovarian reserve markers in infertile women with diminished ovarian reserve. Medicine (Baltimore). 2022;101(6):e28796.

103. Aramesh S, Alifarja T, Jannesar R, Ghaffari P, Vanda R, Bazarganipour F. Does vitamin D supplementation improve ovarian reserve in women with diminished ovarian reserve and vitamin D deficiency: a before-and-after intervention study. BMC Endocr Disord. 2021;21(1):126.

104. Yin WW, Huang CC, Chen YR, Yu DQ, Jin M, Feng C. The effect of medication on serum anti-müllerian hormone (AMH) levels in women of reproductive age: a meta-analysis. BMC Endocr Disord. 2022;22(1):158.

105. Karimi E, Arab A, Rafiee M, Amani R. A systematic review and meta-analysis of the association between vitamin D and ovarian reserve. Scientific Reports. 2021;11.

106. Bentov Y, Casper RF. The aging oocyte--can mitochondrial function be improved? Fertil Steril. 2013;99(1):18-22.

107. Florou P, Anagnostis P, Theocharis P, Chourdakis M, Goulis DG. Does coenzyme Q(10) supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. J Assist Reprod Genet. 2020;37(10):2377-87.

108. Lin G, Li X, Jin Yie SL, Xu L. Clinical evidence of coenzyme Q10 pretreatment for women with diminished ovarian reserve undergoing IVF/ICSI: a systematic review and meta-analysis. Ann Med. 2024;56(1):2389469.

109. Powers SK, Deminice R, Ozdemir M, Yoshihara T, Bomkamp MP, Hyatt H. Exercise-induced oxidative stress: Friend or foe? J Sport Health Sci. 2020;9(5):415-25.

110. Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev. 2008;88(4):1243-76.

111. Simioni C, Zauli G, Martelli AM, Vitale M, Sacchetti G, Gonelli A, et al. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. Oncotarget. 2018;9(24):17181-98.

112. Galli D, Carubbi C, Masselli E, Vaccarezza M, Presta V, Pozzi G, et al. Physical Activity and Redox Balance in the Elderly: Signal Transduction Mechanisms. Applied Sciences. 2021;11:2228.

113. Thirupathi A, Wang M, Lin JK, Fekete G, István B, Baker JS, et al. Effect of Different Exercise Modalities on Oxidative Stress: A Systematic Review. Biomed Res Int. 2021;2021:1947928.

114. Kozakiewicz M, Rowiński R, Kornatowski M, Dąbrowski A, Kędziora-Kornatowska K, Strachecka A. Relation of Moderate Physical Activity to Blood Markers of Oxidative Stress and Antioxidant Defense in the Elderly. Oxid Med Cell Longev. 2019;2019:5123628.

115. Prémusz V, Lendvai-Emmert D, Makai A, Amrein K, Chauhan S, Bódis J, et al. Pre-Treatment Physical Activity Could Positively Influence Pregnancy Rates in IVF despite the Induced Oxidative Stress: A Cohort Study on Salivary 8-Hydroxy-2'-deoxyguanosine. Antioxidants (Basel). 2022;11(8).

116. Tolahunase M, Sagar R, Dada R. Impact of Yoga and Meditation on Cellular Aging in Apparently Healthy Individuals: A Prospective, Open-Label Single-Arm Exploratory Study. Oxid Med Cell Longev. 2017;2017:7928981.

117. Rahayu FK, Dwiningsih SR, Sa'adi A, Herawati L. Effects of different intensities of exercise on folliculogenesis in mice: Which is better? Clin Exp Reprod Med. 2021;48(1):43-9.

118. Xie F, You Y, Guan C, Gu Y, Yao F, Xu J. Association between physical activity and infertility: a comprehensive systematic review and meta-analysis. Journal of Translational Medicine. 2022;20(1):237.

119. Yi X, Tang D, Cao S, Li T, Gao H, Ma T, et al. Effect of Different Exercise Loads on Testicular Oxidative Stress and Reproductive Function in Obese Male Mice. Oxid Med Cell Longev. 2020;2020:3071658.

120. Stockwell S, Trott M, Tully M, Shin J, Barnett Y, Butler L, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. BMJ Open Sport Exerc Med. 2021;7(1):e000960.

121. Wilke J, Rahlf AL, Füzéki E, Groneberg DA, Hespanhol L, Mai P, et al. Physical Activity During Lockdowns Associated with the COVID-19 Pandemic: A Systematic Review and Multilevel Meta-analysis of 173 Studies with 320,636 Participants. Sports Med Open. 2022;8(1):125.

122. Musa S, Elyamani R, Dergaa I. COVID-19 and screen-based sedentary behaviour: Systematic review of digital screen time and metabolic syndrome in adolescents. PLoS One. 2022;17(3):e0265560.

123. Strain T, Flaxman S, Guthold R, Semenova E, Cowan M, Riley LM, et al. National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: a pooled analysis of 507 population-based surveys with 5·7 million participants. Lancet Glob Health. 2024;12(8):e1232-e43.

124. Nienhuis CP, Lesser IA. The Impact of COVID-19 on Women's Physical Activity Behavior and Mental Well-Being. Int J Environ Res Public Health. 2020;17(23).

125. Bácsné Bába É, Müller A, Pfau C, Balogh R, Bartha É, Szabados G, et al. Sedentary Behavior Patterns of the Hungarian Adult Population. Int J Environ Res Public Health. 2023;20(3).

126. Premusz V, Makai A, Veress R, Doczi T, Rocha P, Acs P. P06-05 Physical activity patterns of Hungarian women of reproductive age, preliminary study of the EUPASMOS project. Eur J Public Health. 2022;32(Suppl 2).

127. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act. 2017;14(1):75.

128. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. Jama. 1995;273(5):402-7.

129. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab. 2012;37(3):540-2.

130. Tudor-Locke C, Hatano Y, Pangrazi RP, Kang M. Revisiting "how many steps are enough?". Med Sci Sports Exerc. 2008;40(7 Suppl):S537-43.

131. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451-62.

132. World Health Organization. Nearly 1.8 billion adults at risk of disease from not doing enough physical activity: World Health Organization; 2024 [updated 2024-06-26; cited 2025-07-26]. Available from: https://www.who.int/news/item/26-06-2024-nearly-1.8-billion-adults-at-risk-of-disease-from-not-doing-enough-physical-activity.

133. Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1·6 million participants. Lancet Child Adolesc Health. 2020;4(1):23-35.

134. European Commission D-GfC. Special Eurobarometer SP525: Sport and physical activity (v1.00). In: Commission E, editor. 2022.

135. Matusiak-Wieczorek E, Lipert A, Kochan E, Jegier A. The time spent sitting does not always mean a low level of physical activity. BMC Public Health. 2020;20(1):317.

136. Foucaut AM, Faure C, Julia C, Czernichow S, Levy R, Dupont C. Sedentary behavior, physical inactivity and body composition in relation to idiopathic infertility among men and women. PLoS One. 2019;14(4):e0210770.

137. Zhang H, Hua L, Liu D, Su X, Chen J, Chen J. Effects of physical activity on infertility in reproductive females. Reproductive Biology and Endocrinology. 2024;22(1):62.

138. Tempest N, France-Ratcliffe M, Al-Lamee H, Oliver ER, Slaine EE, Drakeley AJ, et al. Habitual physical activity levels in women attending the one stop infertility clinic: A prospective cross-sectional observational study. Reprod Fertil. 2022;3(3):231-7.

139. Läänelaid S, Ortega FB, Kunovac Kallak T, Joelsson L, Ruiz JR, Hreinsson J, et al. Physical and Sedentary Activities in Association with Reproductive Outcomes among Couples Seeking Infertility Treatment: A Prospective Cohort Study. Int J Environ Res Public Health. 2021;18(5).

140. Kett AR, Sichting F, Milani TL. The Effect of Sitting Posture and Postural Activity on Low Back Muscle Stiffness. Biomechanics [Internet]. 2021; 1(2):[214-24 pp.].

141. Marijančić V, Grubić Kezele T, Peharec S, Dragaš-Zubalj N, Pavičić Žeželj S, Starčević-Klasan G. Relationship between Physical Activity and Sedentary Behavior, Spinal Curvatures, Endurance and Balance of the Trunk Muscles-Extended Physical Health Analysis in Young Adults. Int J Environ Res Public Health. 2023;20(20).

142. Susilowati IH, Kurniawidjaja LM, Nugraha S, Nasri SM, Pujiriani I, Hasiholan BP. The prevalence of bad posture and musculoskeletal symptoms originating from the use of gadgets as an impact of the work from home program of the university community. Heliyon. 2022;8(10):e11059.

143. Hides JA, Belavý DL, Stanton W, Wilson SJ, Rittweger J, Felsenberg D, et al. Magnetic resonance imaging assessment of trunk muscles during prolonged bed rest. Spine (Phila Pa 1976). 2007;32(15):1687-92.

144. Jung KS, Jung JH, In TS, Cho HY. Effects of Prolonged Sitting with Slumped Posture on Trunk Muscular Fatigue in Adolescents with and without Chronic Lower Back Pain. Medicina (Kaunas). 2020;57(1).

145. Waongenngarm P, Rajaratnam BS, Janwantanakul P. Internal Oblique and Transversus Abdominis Muscle Fatigue Induced by Slumped Sitting Posture after 1 Hour of Sitting in Office Workers. Saf Health Work. 2016;7(1):49-54.

146. Heneghan NR, Baker G, Thomas K, Falla D, Rushton A. What is the effect of prolonged sitting and physical activity on thoracic spine mobility? An observational study of young adults in a UK university setting. BMJ Open. 2018;8(5):e019371.

147. Cho IY, Park SY, Park JH, Kim TK, Jung TW, Lee HM. The Effect of Standing and Different Sitting Positions on Lumbar Lordosis: Radiographic Study of 30 Healthy Volunteers. Asian Spine J. 2015;9(5):762-9.

148. Boukabache A, Preece SJ, Brookes N. Prolonged sitting and physical inactivity are associated with limited hip extension: A cross-sectional study. Musculoskelet Sci Pract. 2021;51:102282.

149. Sapsford RR, Hodges PW, Richardson CA, Cooper DH, Markwell SJ, Jull GA. Co-activation of the abdominal and pelvic floor muscles during voluntary exercises. Neurourol Urodyn. 2001;20(1):31-42.

150. Tim S, Mazur-Bialy AI. The Most Common Functional Disorders and Factors Affecting Female Pelvic Floor. Life (Basel). 2021;11(12).

151. Richardson CA, Hodges P, Hides JA. Therapeutic Exercise for Lumbopelvic Stabilization: A Motor Control Approach for the Treatment and Prevention of Low Back Pain. London, United Kingdom: Churchill Livingstone; 2004.

152. Hodges PW, Sapsford R, Pengel LH. Postural and respiratory functions of the pelvic floor muscles. Neurourol Urodyn. 2007;26(3):362-71.

153. Hodges PW, Richardson CA. Inefficient muscular stabilization of the lumbar spine associated with low back pain. A motor control evaluation of transversus abdominis. Spine (Phila Pa 1976). 1996;21(22):2640-50.

154. Hides JA, Stokes MJ, Saide M, Jull GA, Cooper DH. Evidence of lumbar multifidus muscle wasting ipsilateral to symptoms in patients with acute/subacute low back pain. Spine (Phila Pa 1976). 1994;19(2):165-72.

155. Bontrup C, Taylor WR, Fliesser M, Visscher R, Green T, Wippert PM, et al. Low back pain and its relationship with sitting behaviour among sedentary office workers. Appl Ergon. 2019;81:102894.

156. Baradaran Mahdavi S, Riahi R, Vahdatpour B, Kelishadi R. Association between sedentary behavior and low back pain; A systematic review and meta-analysis. Health Promot Perspect. 2021;11(4):393-410.

157. Csuhai É A, Nagy AC, Váradi Z, Veres-Balajti I. Functional Analysis of the Spine with the Idiag SpinalMouse System among Sedentary Workers Affected by Non-Specific Low Back Pain. Int J Environ Res Public Health. 2020;17(24).

158. Drzał-Grabiec J, Snela S, Wyszyńska J, Podgórska-Bednarz J, Truszczynska-Baszak A. The influence of elongation exercises on the anterior-posterior spine curvatures. Biomedical Human Kinetics. 2014;6:1-4.

159. Kondor J, Széll A, Tihanyi J. Az aktív elongációs technika hatása a gerincoszlop morfológiai jellemzőire. Biomechanica Hungarica. 2018;11(2):31-41.

160. Panjabi MM. The stabilizing system of the spine. Part II. Neutral zone and instability hypothesis. J Spinal Disord. 1992;5(4):390-6; discussion 7.

161. Csuhai ÉA. Doktori (PhD) értekezés tézisei: A derékfájás megelőzését és kezelését célzó munkahelyi egészségfejlesztési program kidolgozása és hatásai ülő munkát végző munkavállalók körében. Debrecen: Debreceni Egyetem EGÉSZSÉGTUDOMÁNYOK DOKTORI ISKOLA; 2023.

162. Faries MD, Greenwood MC. Core Training: Stabilizing the Confusion. Strength and Conditioning Journal. 2007;29:10-25.

163. Bergmark A. Stability of the lumbar spine. A study in mechanical engineering. Acta Orthop Scand Suppl. 1989;230:1-54.

164. Dougherty JJ. The anatomical "core": a definition and functional classification. Osteopathic Family Physician. 2011;3(6):239-45.

165. Russo M, Deckers K, Eldabe S, Kiesel K, Gilligan C, Vieceli J, et al. Muscle Control and Non-specific Chronic Low Back Pain. Neuromodulation. 2018;21(1):1-9.

166. Willard FH, Vleeming A, Schuenke MD, Danneels L, Schleip R. The thoracolumbar fascia: anatomy, function and clinical considerations. J Anat. 2012;221(6):507-36.

167. Cholewicki J, VanVliet JJt. Relative contribution of trunk muscles to the stability of the lumbar spine during isometric exertions. Clin Biomech (Bristol). 2002;17(2):99-105.

168. Kim C, Gottschalk L, Eng C, Ward S, Lieber R. The Multifidus Muscle is the Strongest Stabilizer of the Lumbar Spine. Spine Journal - SPINE J. 2007;7.

169. Wilke HJ, Wolf S, Claes LE, Arand M, Wiesend A. Stability increase of the lumbar spine with different muscle groups. A biomechanical in vitro study. Spine (Phila Pa 1976). 1995;20(2):192-8.

170. Hides JA, Richardson CA, Jull GA. Multifidus muscle recovery is not automatic after resolution of acute, first-episode low back pain. Spine (Phila Pa 1976). 1996;21(23):2763-9.

171. Panjabi MM. Clinical spinal instability and low back pain. J Electromyogr Kinesiol. 2003;13(4):371-9.

172. Hides JA, Jull GA, Richardson CA. Long-term effects of specific stabilizing exercises for first-episode low back pain. Spine (Phila Pa 1976). 2001;26(11):E243-8.

173. Csuhai É A, Nagy AC, Szőllősi GJ, Veres-Balajti I. Impact Analysis of 20-Week Multimodal Progressive Functional-Proprioceptive Training among Sedentary Workers Affected by Non-Specific Low-Back Pain: An Interventional Cohort Study. Int J Environ Res Public Health. 2021;18(20).

174. Tong MH, Mousavi SJ, Kiers H, Ferreira P, Refshauge K, van Dieën J. Is There a Relationship Between Lumbar Proprioception and Low Back Pain? A Systematic Review With Meta-Analysis. Arch Phys Med Rehabil. 2017;98(1):120-36.e2.

175. Si X, Zhang L, Li F, Liang H. The effectiveness of pelvic floor muscle training on lumbar function and muscle performance in sedentary women with lower back pain: a randomized controlled trial. BMC Womens Health. 2025;25(1):125.

176. Ki C, Heo M, Kim HY, Kim EJ. The effects of forced breathing exercise on the lumbar stabilization in chronic low back pain patients. J Phys Ther Sci. 2016;28(12):3380-3.

177. Saiklang P, Puntumetakul R, Swangnetr Neubert M, Boucaut R. The immediate effect of the abdominal drawing-in maneuver technique on stature change in seated sedentary workers with chronic low back pain. Ergonomics. 2021;64(1):55-68.

178. Panjabi MM. The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. J Spinal Disord. 1992;5(4):383-9; discussion 97.

179. Sipaviciene S, Kliziene I. Effect of different exercise programs on non-specific chronic low back pain and disability in people who perform sedentary work. Clin Biomech (Bristol). 2020;73:17-27.

180. Selkow NM, Eck MR, Rivas S. TRANSVERSUS ABDOMINIS ACTIVATION AND TIMING IMPROVES FOLLOWING CORE STABILITY TRAINING: A RANDOMIZED TRIAL. Int J Sports Phys Ther. 2017;12(7):1048-56.

181. Hodges P, Kaigle Holm A, Holm S, Ekström L, Cresswell A, Hansson T, et al. Intervertebral stiffness of the spine is increased by evoked contraction of transversus abdominis and the diaphragm: in vivo porcine studies. Spine (Phila Pa 1976). 2003;28(23):2594-601.

182. Faucher S, Déry-Rouleau G, Bardin M, Morin M. Investigating the role of the pelvic floor muscles in sexual function and sexual response: a systematic review and meta-analysis. J Sex Med. 2024;21(3):217-39.

183. Tekbaş S. The effect of pelvic floor muscle exercise on sexual function in women of reproductive age: A randomized controlled trial. Medicine (Baltimore). 2025;104(37):e44324.

184. Hodges PW, Gandevia SC. Changes in intra-abdominal pressure during postural and respiratory activation of the human diaphragm. J Appl Physiol (1985). 2000;89(3):967-76.

185. Neumann P, Gill V. Pelvic floor and abdominal muscle interaction: EMG activity and intra-abdominal pressure. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(2):125-32.

186. Bo K, Frawley HC, Haylen BT, Abramov Y, Almeida FG, Berghmans B, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. Int Urogynecol J. 2017;28(2):191-213.

187. Frawley H, Shelly B, Morin M, Bernard S, Bø K, Digesu GA, et al. An International Continence Society (ICS) report on the terminology for pelvic floor muscle assessment. Neurourol Urodyn. 2021;40(5):1217-60.

188. Aljuraifani R, Stafford RE, Hall LM, van den Hoorn W, Hodges PW. Task-specific differences in respiration-related activation of deep and superficial pelvic floor muscles. J Appl Physiol (1985). 2019;126(5):1343-51.

189. Korkmaz Dayican D, Keser I, Celiker Tosun O, Yavuz O, Tosun G, Kurt S, et al. Exercise Position to Improve Synergy Between the Diaphragm and Pelvic Floor Muscles in Women With Pelvic Floor Dysfunction: A Cross Sectional Study. J Manipulative Physiol Ther. 2023;46(4):201-11.

190. Park H, Han D. The effect of the correlation between the contraction of the pelvic floor muscles and diaphragmatic motion during breathing. J Phys Ther Sci. 2015;27(7):2113-5.

191. Talasz H, Kremser C, Talasz HJ, Kofler M, Rudisch A. Breathing, (S)Training and the Pelvic Floor-A Basic Concept. Healthcare (Basel). 2022;10(6).

192. Zhai H, Zhang L, Xia J, Li C. The Efficiency of Respiratory Exercises in Rehabilitation of Low Back Pain: A Systematic Review and Meta-Analysis. J Sport Rehabil. 2024;33(3):189-200.

193. Roussel N, Nijs J, Truijen S, Vervecken L, Mottram S, Stassijns G. Altered breathing patterns during lumbopelvic motor control tests in chronic low back pain: a case-control study. Eur Spine J. 2009;18(7):1066-73.

194. Chaitow L. Breathing pattern disorders, motor control, and low back pain. Journal of Osteopathic Medicine. 2004;7(1):33-40.

195. Charmode S, Mehra S, Mishra AK. Causal Relationships Between Physical Activity and Arthrokinematic Integrity of the Ankle Joint-Foot Complex Across Normal and Pathological Phenomena: A Case-Control Analysis. Cureus. 2024;16(5):e59578.

196. Konrad A, Močnik R, Titze S, Nakamura M, Tilp M. The Influence of Stretching the Hip Flexor Muscles on Performance Parameters. A Systematic Review with Meta-Analysis. Int J Environ Res Public Health. 2021;18(4).

197. Mettler JH, Shapiro R, Pohl MB. Effects of a Hip Flexor Stretching Program on Running Kinematics in Individuals With Limited Passive Hip Extension. J Strength Cond Res. 2019;33(12):3338-44.

198. Khajuria A, Kumar A, Joshi D, Kumaran SS. Reducing Stress with Yoga: A Systematic Review Based on Multimodal Biosignals. Int J Yoga. 2023;16(3):156-70.

199. World Health Organization. COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide Geneva: World Health Organization; 2022 [updated 2022-03-02; cited 2025-08-16]. Available from: https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide.

200. Szigeti FJ, Kazinczi C, Szabó G, Sipos M, Ujma PP, Purebl G. The clinical effectiveness of the Mind/Body Program for Infertility on wellbeing and assisted

reproduction outcomes: a randomized controlled trial in search for active ingredients. Hum Reprod. 2024;39(8):1735-51.

201. Simionescu G, Doroftei B, Maftei R, Obreja BE, Anton E, Grab D, et al. The complex relationship between infertility and psychological distress (Review). Exp Ther Med. 2021;21(4):306.

202. Cousineau TM, Domar AD. Psychological impact of infertility. Best Pract Res Clin Obstet Gynaecol. 2007;21(2):293-308.

203. Greil AL, McQuillan J, Lowry M, Shreffler KM. Infertility treatment and fertility-specific distress: A longitudinal analysis of a population-based sample of U.S. women. Soc Sci Med. 2011;73(1):87-94.

204. Jiang L, Cao Y, Ni S, Chen X, Shen M, Lv H, et al. Association of Sedentary Behavior With Anxiety, Depression, and Suicide Ideation in College Students. Front Psychiatry. 2020;11:566098.

205. Santana EES, Neves LM, Souza KC, Mendes TB, Rossi FE, Silva AAD, et al. Physically Inactive Undergraduate Students Exhibit More Symptoms of Anxiety, Depression, and Poor Quality of Life than Physically Active Students. Int J Environ Res Public Health. 2023;20(5).

206. Bradley H, Esformes J. Breathing pattern disorders and functional movement. Int J Sports Phys Ther. 2014;9(1):28-39.

207. Tavoian D, Craighead DH. Deep breathing exercise at work: Potential applications and impact. Front Physiol. 2023;14:1040091.

208. Hopper SI, Murray SL, Ferrara LR, Singleton JK. Effectiveness of diaphragmatic breathing for reducing physiological and psychological stress in adults: a quantitative systematic review. JBI Database System Rev Implement Rep. 2019;17(9):1855-76.

209. Fincham GW, Strauss C, Montero-Marin J, Cavanagh K. Effect of breathwork on stress and mental health: A meta-analysis of randomised-controlled trials. Sci Rep. 2023;13(1):432.

210. Zaccaro A, Piarulli A, Laurino M, Garbella E, Menicucci D, Neri B, et al. How Breath-Control Can Change Your Life: A Systematic Review on Psycho-Physiological Correlates of Slow Breathing. Front Hum Neurosci. 2018;12:353.

211. Serrano-Ibáñez E, Czub M, Ortega Cordero C, López-Martínez A, Ramírez-Maestre C, Piskorz J, et al. Effect of a controlled diaphragmatic breathing session on

perceived pain and state anxiety in people with chronic pain. Current Psychology. 2024;43(40):31650-60.

212. Masroor S, Tanwar T, Aldabbas M, Iram I, Veqar Z. Effect of Adding Diaphragmatic Breathing Exercises to Core Stabilization Exercises on Pain, Muscle Activity, Disability, and Sleep Quality in Patients With Chronic Low Back Pain: A Randomized Control Trial. J Chiropr Med. 2023;22(4):275-83.

213. Kovács BP, Balog J, Sebők B, Keszthelyi M, Várbíró S. Unlocking Female Fertility with a Specific Reproductive Exercise Program: Protocol of a Randomized Controlled Clinical Trail. Life (Basel). 2024;15(1):18.

214. Kovács BP, Balog J, Szigeti JF, Sebők B, Török M, Várbíró S. Effects of Supervised Physiotherapy-Based Exercise on Ovarian Reserve and Spontaneous Pregnancy in Women with Diminished Ovarian Reserve: A Controlled Pilot Study. Life (Basel). 2026;16(1):120.

215. Rakhshani A, Nagarathna R, Mhaskar R, Mhaskar A, Thomas A, Gunasheela S. Effects of yoga on utero-fetal-placental circulation in high-risk pregnancy: a randomized controlled trial. Adv Prev Med. 2015;2015:373041.

216. Pellizzari P, Esposito C, Siliotti F, Marchiori S, Gangemi M. Colour Doppler analysis of ovarian and uterine arteries in women with hypoestrogenic amenorrhoea. Human Reproduction. 2002;17(12):3208-12.

217. Kiranmayee D, Praveena T, Himabindu Y, Sriharibabu M, Kavya K, Mahalakshmi M. The Effect of Moderate Physical Activity on Ovarian Reserve Markers in Reproductive Age Women Below and Above 30 Years. J Hum Reprod Sci. 2017;10(1):44-8.

218. Prémusz V, Makai A, Perjés B, Máté O, Hock M, Ács P, et al. Multicausal analysis on psychosocial and lifestyle factors among patients undergoing assisted reproductive therapy - with special regard to self-reported and objective measures of pre-treatment habitual physical activity. BMC Public Health. 2021;21(Suppl 1):1480.

219. Thabet AA, Alshehri MA. Efficacy of deep core stability exercise program in postpartum women with diastasis recti abdominis: a randomised controlled trial. J Musculoskelet Neuronal Interact. 2019;19(1):62-8.

220. Espiño-Albela A, Castaño-García C, Díaz-Mohedo E, Ibáñez-Vera AJ. Effects of Pelvic-Floor Muscle Training in Patients with Pelvic Organ Prolapse Approached with Surgery vs. Conservative Treatment: A Systematic Review. J Pers Med. 2022;12(5).

221. Amiri B, Zemková E. Trunk stability and breathing exercises superior to foam rolling for restoring postural stability after core muscle fatigue in sedentary employees. Scientific Reports. 2025;15(1):13909.

222. Domar AD, Rooney KL, Wiegand B, Orav EJ, Alper MM, Berger BM, et al. Impact of a group mind/body intervention on pregnancy rates in IVF patients. Fertil Steril. 2011;95(7):2269-73.

223. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2011;17(2):171-83.

224. Patten RK, McIlvenna LC, Levinger I, Garnham AP, Shorakae S, Parker AG, et al. High-intensity training elicits greater improvements in cardio-metabolic and reproductive outcomes than moderate-intensity training in women with polycystic ovary syndrome: a randomized clinical trial. Hum Reprod. 2022;37(5):1018-29.

225. Patten RK, Pascoe MC, Moreno-Asso A, Boyle RA, Stepto NK, Parker AG. Effectiveness of exercise interventions on mental health and health-related quality of life in women with polycystic ovary syndrome: a systematic review. BMC Public Health. 2021;21(1):2310.

226. Ruiz-González D, Cavero-Redondo I, Hernández-Martínez A, Baena-Raya A, Martínez-Forte S, Altmäe S, et al. Comparative efficacy of exercise, diet and/or pharmacological interventions on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity: a systematic review and network meta-analysis. Hum Reprod Update. 2024;30(4):472-87.

227. Huhmann K. Menses Requires Energy: A Review of How Disordered Eating, Excessive Exercise, and High Stress Lead to Menstrual Irregularities. Clin Ther. 2020;42(3):401-7.

228. Morrison AE, Fleming S, Levy MJ. A review of the pathophysiology of functional hypothalamic amenorrhoea in women subject to psychological stress, disordered eating, excessive exercise or a combination of these factors. Clin Endocrinol (Oxf). 2021;95(2):229-38.

229. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.

230. Dasso NA. How is exercise different from physical activity? A concept analysis. Nurs Forum. 2019;54(1):45-52.

231. Cong J, Li P, Zheng L, Tan J. Prevalence and Risk Factors of Infertility at a Rural Site of Northern China. PLoS One. 2016;11(5):e0155563.

232. Mussawar M, Balsom AA, Totosy de Zepetnek JO, Gordon JL. The effect of physical activity on fertility: a mini-review. F S Rep. 2023;4(2):150-8.

233. Sõritsa D, Mäestu E, Nuut M, Mäestu J, Migueles JH, Läänelaid S, et al. Maternal physical activity and sedentary behaviour before and during in vitro fertilization treatment: a longitudinal study exploring the associations with controlled ovarian stimulation and pregnancy outcomes. J Assist Reprod Genet. 2020;37(8):1869-81.

234. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol. 2006;108(4):938-45.

235. Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, et al. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod. 2008;23(3):642-50.

236. Brinson AK, da Silva SG, Hesketh KR, Evenson KR. Impact of Physical Activity and Sedentary Behavior on Spontaneous Female and Male Fertility: A Systematic Review. J Phys Act Health. 2023;20(7):600-15.

237. Govindaraj R, Karmani S, Varambally S, Gangadhar BN. Yoga and physical exercise - a review and comparison. Int Rev Psychiatry. 2016;28(3):242-53.

238. Dumbala S, Bhargav H, Satyanarayana V, Arasappa R, Varambally S, Desai G, et al. Effect of Yoga on Psychological Distress among Women Receiving Treatment for Infertility. Int J Yoga. 2020;13(2):115-9.

239. Eskew AM, Bedrick BS, Chavarro JE, Riley JK, Jungheim ES. Dietary patterns are associated with improved ovarian reserve in overweight and obese women: a cross-sectional study of the Lifestyle and Ovarian Reserve (LORe) cohort. Reprod Biol Endocrinol. 2022;20(1):33.

240. Fichman V, Costa R, Miglioli TC, Marinheiro LPF. Association of obesity and anovulatory infertility. Einstein (Sao Paulo). 2020;18:eAO5150.

241. Dhage VD, Nagtode N, Kumar D, Bhagat AK. A Narrative Review on the Impact of Smoking on Female Fertility. Cureus. 2024;16(4):e58389.

9. BIBLIOGRAPHY OF PUBLICATIONS

Publications related to the thesis:

Kovács BP, Balog J, Sebők B, Keszthelyi M, Várbíró S. Unlocking Female Fertility with a Specific Reproductive Exercise Program: Protocol of a Randomized Controlled Clinical Trail. *Life*. 2025; 15(1):18. https://doi.org/10.3390/life15010018

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Kovács BP, Balog J, Szigeti JF, Sebők B, Török M, Várbíró S. Effects of Supervised Physiotherapy-Based Exercise on Ovarian Reserve and Spontaneous Pregnancy in Women with Diminished Ovarian Reserve: A Controlled Pilot Study. *Life*. 2026; 16(1):120. https://doi.org/10.3390/life16010120

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