SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Changes in the etiological background of premature ovarian insufficiency and the importance of early recognition, with special emphasis on bone health

by Szilvia Csehely, MD

Supervisor: Attila Jakab, MD, PhD

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF CLINICAL MEDICINE

DEBRECEN, 2025.

Changes in the etiological background of premature ovarian insufficiency and the importance of early recognition, with special emphasis on bone health

By Szilvia Csehely, MD

Supervisor: Attila Jakab, MD, PhD,

Doctoral School of Clinical Medicine, University of Debrecen

Head of the **Defense Committee**:	Gabriella Szűcs, MD, DSc
Reviewers:	Berta Eszter, MD, PhD Szabolcs Varbíró, MD, DSc
Members of the Defense Committee:	Ádám László, MD, PhD Attila Keresztúri, MD, PhD

The PhD defense takes place at the Lecture Hall of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Debrecen, on 24 November 2025 at 2:00 p.m.

1. Introduction

Premature ovarian insufficiency (POI) is an endocrine disorder associated with partial or complete loss of ovarian function before the age of 40 years. Although it is a rare condition, it affects around 1-3% of women and recent international meta-analyses suggest that the true prevalence is around 3.5-3.7%.

Hypoestrogenism, which is a major feature of POI, can lead to accelerated bone loss and the development of osteoporosis, as oestrogen plays a key role in regulating bone metabolism and maintaining bone mass. Lindsay's pioneering work early on highlighted the bone-protective effects of synthetic oestrogen therapy in oophorectomized women, emphasizing the essential role of oestrogen in maintaining bone health. In POI, bone density is significantly reduced and the incidence of osteoporosis ranges from 8-27%, which is about 2.5 times the risk compared to normal menopausal age. Menopause before the age of 45 increases the risk of fractures by 1.5-3 times.

In the short term, hypoestrogenism can be associated with menstrual irregularities, infertility, hot flushes, mood swings and a poorer quality of life. In the long term, it is associated with increased risk of osteoporosis, cardiovascular and cognitive decline and premature mortality. Timely detection of POI and proactive management of bone metabolism are key to preventing osteoporosis and its associated complications.

The development of POI may be due to a number of factors. The aetiological classification distinguishes between forms of genetic origin, most commonly associated with Turner syndrome and other chromosomal abnormalities (e.g. X-chromosomal deletions, mosaicism, FMR1 premutation), and autoimmune origin, involving autoimmune attack of ovarian tissue and other associated endocrine autoimmune diseases (e.g. Hashimoto's thyroiditis, Addison's disease, Graves' disease).

Iatrogenic POI develops mainly after chemotherapy, radiotherapy or radical pelvic surgery, especially in the context of oncological indications. In addition, gynaecological surgery such as ovarian resection for endometriosis may also contribute.

Environmental factors such as toxic exposures or certain viral infections also play a role, although the exact mechanism is not fully understood. However, despite detailed, targeted

investigations, no clear cause can be identified in up to 50% of cases; these are idiopathic cases, which remain the most challenging part of the aetiological spectrum of POI.

Recognition and differentiation of the different aetiological forms not only helps in patient counselling and prognosis, but is also crucial for the prevention of long-term complications, in particular bone health impairment, and for the planning of targeted hormone replacement therapy.

2. Objectives

The aim of this dissertation is to comprehensively explore the complex clinical and aetiological background of premature ovarian insufficiency (POI), with a particular focus on bone health and the importance of timing of detection.

1. Comparative analysis of the aetiological distribution of POI and the evolution of reproductive outcomes in two different time periods

Mapping changes in aetiological distribution by comparing the historical (1978-2003) and contemporary (2017-2024) cohorts.

To identify factors contributing to the temporal aetiological shift in POI, with a particular focus on the increase in the proportion of iatrogenic cases (e.g. increase in oncological survivors, more frequent surgical interventions).

To compare reproductive outcomes in the two cohorts.

2. To assess the bone health status of POI and early menopausal patients and to investigate the association

To determine the prevalence of baseline bone status (osteoporosis, osteopenia) at diagnosis.

To analyse the relationship between serum estradiol levels and bone mineral density (BMD).

To investigate the relationship between body mass index (BMI) and BMD.

To explore the relationship between time to diagnosis (time from onset of symptoms to diagnosis) and bone health, with particular attention to the timing and effectiveness of

detection. To investigate the prevalence of osteoporosis and osteopenia in patients with POI, particularly in the primary and secondary amenorrhoeic subgroups. To evaluate variations in bone density in POI cases with different aetiological backgrounds (spontaneous and iatrogenic). To compare the diagnostic value of BMD and T-score in the detection of reduced bone density.

3. Patients and methods

The aim of our study was to map the clinical and hormonal features of primary ovarian insufficiency (POI) and early menopause (EM), the temporal changes in the aetiological background and the bone health status. Two complementary study phases were performed: in the first part, we analysed temporal variations in the aetiology, detection rate and reproductive outcomes of POI based on a comparison of two cohorts of patients (aetiological study) that were temporally distinct. In the second part of our study, we focused on the evaluation of bone density abnormalities and their determinants in women with POI and EM diagnosis (bone health study).

3.1 Study population and data collection

We retrospectively analysed data from 168 women (mean age: 36.52 ± 8.89 years) diagnosed with premature ovarian insufficiency (POI) or premature menopause (EM) between January 2017 and June 2024 at the Department of Obstetrics and Gynaecology, University of Debrecen, between January 2017 and June 2024. Inclusion criteria included that the patient had not received either hormone replacement therapy (HRT) or hormonal contraception since her last menstrual period. Diagnosis was based on the 2015 NICE guidelines (revised in 2019), which state that amenorrhoea of at least four months' duration over the age of 40 years and two elevated FSH levels (>30 U/L) measured at least four weeks apart are required to establish POI. Women under 40 who met these criteria were classified as POI, while women aged 40-45 were classified as EM.

Patient data were obtained from the electronic hospital system (eMedSolution and UDMed). We recorded age, date of last menstruation, body mass index (BMI), baseline hormone profile (FSH, LH, E2, PRL, TSH, T3, T4) and medical history (pregnancy, parity, oncological and surgical history). For autoimmune screening, anti-TPO, anti-Tg and adrenal cortex antibodies were tested. In case of suspected genetic background, karyotyping and FMR1 premutation

testing were also performed. Transvaginal ultrasound examinations were performed as an additional orientation to describe uterine and ovarian morphology.

3.1.1 Etiological classification and comparative analysis

In the first part of the study, data from the contemporary (2017-2024) POI cohort (111 patients) were compared with data from a previous cohort of patients (172 patients) cared for at the same institution between 1978 and 2003, the results of which were published by Zs. Molnár and colleagues in 2004 (Molnár, 2004). Comparable sample size, diagnostic criteria and methodological consistency were important considerations in the selection of the two cohorts. For the diagnosis of POI, in accordance with the clinical practice at the time, the definition of POI in the previous study was based on FSH values ≥40 U/L, and for the contemporary cohort, a value of ≥30 U/L was used based on the NICE guideline.

Etiologies were categorised into four groups as follows:

- Genetic POI: this included chromosomal abnormalities (e.g. Turner syndrome, triple X syndrome) and cases with FMR1 premutation.

- Autoimmune POI: included cases with adrenocortical antibodies (21OH-Ab), clinically proven Hashimoto's thyroiditis with anti-TPO and/or anti-thyroglobulin (Tg) positivity, and other known autoimmune diseases (e.g. Addison's disease, systemic lupus erythematosus, Graves' disease). Classification was based on the 2016 ESHRE guidelines, which at that time also supported the testing of thyroid autoimmunity.

- Iatrogenic POI: those cases that were associated with chemotherapy, radiotherapy or surgical ovarian injury.

- Idiopathic POI: cases of unidentified aetiology for which the underlying cause has not been identified despite full investigation.

3.1.2 Bone health assessment in POI and EM patients

A total of 125 patients had an evaluable DXA scan available, so the analysis of bone metabolism status was performed on the basis of data from these patients. The selection process is illustrated in the figure below (Figure 1). Bone density measurements (DXA) were

performed within one month of diagnosis using GE Lunar Prodigy Encore (2003). BMD and T-score values (g/cm²) were determined at specific points on the lumbar spine (L1-L4) and left femur, as the system used did not provide Z-score data. The actual BMI values of the patients (kg/m²) were also recorded.

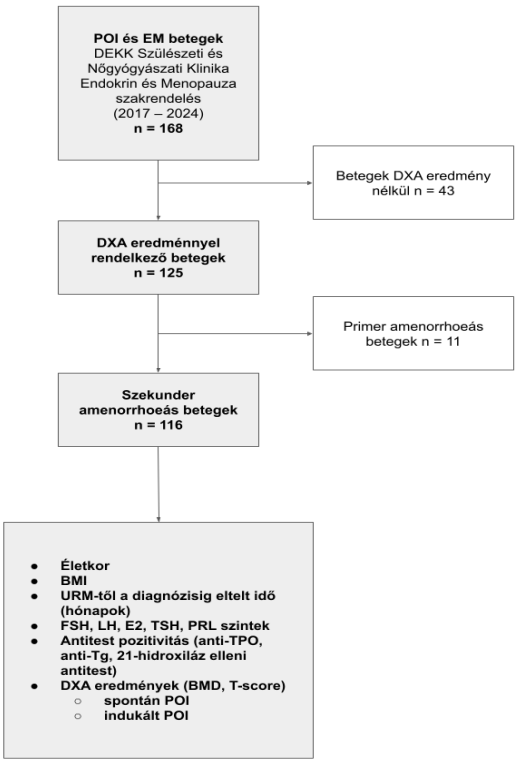

Figure 1. Flowchart of Bone Mineral Density Assessment in POI and EM Patients

To assess the impact of diagnostic delay on bone density, the number of months between the last menstrual period (LMP) and diagnosis was examined as an indicator of detection efficiency. Bone status was assessed not only in terms of time to diagnosis but also in terms of E2 levels at diagnosis, by classifying patients into three categories: below 5 ng/L, between 5-30 ng/L and above 30 ng/L. Etiologically, patients were classified into three main groups: primary amenorrhoeic cases and spontaneous and induced (iatrogenic) forms of POI with secondary amenorrhoea. The primary amenorrhoeic group was mainly composed of patients with underlying genetic abnormalities (e.g. Turner syndrome, other chromosomal abnormalities). Patients with secondary amenorrhoea were divided into two broad subgroups: spontaneous and induced POI. The spontaneous group included cases with idiopathic,

autoimmune and other non-iatrogenic causes. The induced POI group included women who developed secondary amenorrhoea as a consequence of surgical or oncological interventions.

3.2 Statistical analysis

Patient data were stored and managed in PostgreSQL 16.2 database for reliable and structured data processing. We used Python 3.12 for statistical analyses of our studies, the pandas library for data management, NumPy for numerical operations, and the statsmodels library for modelling. Chi-square test, Fisher exact test, Z-test, two-sample t-test for data with normal distribution, Mann-Whitney U-test for data with non-normal distribution were used to assess differences between groups; normality of distribution was tested using Shapiro-Wilk test. Linear relationships between continuous variables were tested using Pearson correlation. $p < 0.05$ was considered statistically significant.

4. Results

4.1 Comparative etiological analysis

The contemporary cohort included 111 women diagnosed with POI for whom complete etiological data were available. In the contemporary POI cohort diagnosed between 2017 and 2024, the mean age was 32.85 ± 8.81 years. Secondary amenorrhoea was identified in 84.7% of patients and primary amenorrhoea in 15.3%. The onset of symptoms occurred before the age of 30 years in 40.5% and between 30-40 years in 59.5%. According to the etiological distribution, the proportion of idiopathic cases was 36.9%, iatrogenic cases 34.3%, the prevalence of POI of autoimmune origin 18.9%, and the proportion of cases of genetic origin 9.9%.

In the previous cohort (1978-2003), Molnár et al. reported 172 POI patients, where etiological data were also available. The mean age of the patients was 30.17 ± 5 years. Based on the type of amenorrhoea, a secondary form was identified in 89.5% and a primary form in 10.5%. Symptoms occurred before 30 years in 48.3% of cases and between 30-40 years in 51.7%. In this cohort, the proportion of idiopathic cases was higher (72.1%), while the proportion of iatrogenic (7.6%), autoimmune (8.7%) and genetic (11.6%) forms was lower.

Comparing the two cohorts, we found that the incidence of POI detection increased significantly in the contemporary group (mean 13.9 new cases/year), compared with an average of 6.6 cases/year in the former period (odds ratio = 2.10; 95% CI: 1.65-2.66; $p < 0.0001$). The mean age of presentation and the distribution by age (under 30 years vs. over 30 years) did not show significant differences.

The analysis of the aetiological rates indicated a significant time shift. The proportion of POI of iatrogenic origin increased significantly from 7.6% (13/172) in the former cohort to 34.3% (38/111) in the contemporary group ($z = -5.70$; $p < 0.0001$; $\chi^2 = 30.71$; $p < 0.0001$). Logistic regression analysis showed that diagnosis between 2017-2024 was significantly more likely to be associated with an iatrogenic aetiology (OR = 6.37; 95% CI: 3.20-12.67; $p < 0.0001$), reflecting the evolution of gynaecological and oncological surgical interventions and oncotherapies.

The proportion of cases of autoimmune origin also showed an increase, from 8.7% (15/172) in the former cohort to 18.9% (21/111) in the contemporary group ($z = -2.51$; $p = 0.012$; $\chi^2 = 5.43$; $p = 0.020$). This is partly due to improved diagnostic facilities and screening for thyroid autoimmunity.

In contrast, the rate of idiopathic POI decreased significantly, from 72.1% (124/172) in the former cohort to 36.9% (41/111) in the contemporary cohort ($z = 5.86$; $p < 0.0001$; $\chi^2 = 32.87$; $p < 0.0001$), indicating the effectiveness of more targeted screening. The proportion of genetic cases did not change significantly over time (11.6% vs. 9.9%).

The vast majority of POI cases with genetic background in both cohorts were Turner syndrome and mosaic forms, with Triple X syndrome, FMR1 premutation and ovarian agenesis also present in the contemporary cohort. Among the idiopathic cases, a positive family history was found in nine patients, but no genetic mismatch was confirmed.

In the contemporary cohort, the most common background of autoimmune cases was Hashimoto's thyroiditis (15 cases), but also Addison's disease, isolated 21OH-Ab positivity, Graves' disease, SLE and non-specific connective tissue disease (NDC) were found. The previous cohort was dominated by Hashimoto's thyroiditis (7 cases) and SLE (4 cases), and cases of type 1 diabetes mellitus and myocarditis were also documented, the latter possibly indicative of polyglandular autoimmune syndrome.

The development of iatrogenic POI in the contemporary cohort was dominated by treatments of oncological origin (76%), mainly as a consequence of radical surgery and adjuvant therapies for pelvic tumours and haematological malignancies. Among non-oncological surgical cases, the most common indication was surgery for endometriosis, with ovarian cystectomies, adnexectomies and uterine artery embolizations. In contrast, in the previous cohort, pelvic surgery was predominant (69%), while haematological origin accounted for 31%. In the contemporary cohort, the proportion of pelvic surgical cases continued to increase (79%), of which 55.3% were oncological and 23.7% non-oncological indications, with endometriosis being the underlying cause in more than half of the latter (55%).

In terms of **reproductive outcomes**, ten pregnancies were documented in the contemporary cohort: two were spontaneously conceived and eight were achieved by assisted reproduction (including two cases of oocyte donation). Three of the IVF pregnancies ended in miscarriage, and one was medically indicated abortion due to malformation. The live birth rate was 6.3% (7/111), reflecting the fact that despite advances in reproductive medicine, childbearing remains a significant challenge in this patient population. In the previous cohort, ten pregnancies were registered, five of which ended in live births, for a total of six children.

During the study period, data from 168 female patients were analysed, of whom 111 were diagnosed with primary ovarian insufficiency (POI) and 57 with early menopause (EM). The mean age of the POI group was 32.85 ± 8.8 years, while the mean age of the EM group was 43.67 ± 2.23 years. Primary amenorrhea was associated with 10.1% (17 cases) of POI, while the remaining 94 POI and all EM cases were associated with secondary amenorrhea. Body mass index (BMI) was similar in both groups (POI: 25.5 ± 5.81 kg/m²; EM: 25.23 ± 4.71 kg/m²).

No significant differences were found in hormonal parameters between the groups: mean FSH in the POI group was 83.65 ± 42.25 IU/L, LH 44.75 ± 18.76 IU/L, and median E2 10.24 ng/L (IQR: 5-25.29). In the EM group, FSH was 84.79 ± 38.76 IU/L, LH 44.78 ± 18.81 IU/L, and median E2 was 10.91 ng/L (IQR: 6.17-28).

4.2 Study of bone health in POI and EM patients

Bone metabolism analysis was performed in 125 patients, who also had DXA scans within one month of diagnosis. Cases with primary POI (9) were excluded from the analysis as it was not

possible to accurately determine the time to diagnosis in these cases and standardised BMD and T-score reference values are not available for the population under 20 years of age. The final analysis therefore included data from 116 individuals (secondary POI and EM).

The median time between no menstrual period and diagnosis was 9 months in the whole population (IQR: 5-23.5 months), reflecting the low efficiency of early detection. Among patients with secondary POI and EM, 34% were diagnosed within 6 months of symptom onset, 22% within 6-12 months, while 27% were diagnosed after 1-3 years and 12% after 3-10 years. Notably, in 5% of cases, diagnosis took more than a decade.

Densitometric studies revealed a significant proportion of osteoporosis in all groups: osteopenia was diagnosed in 31% of the total population and osteoporosis in 10.1%. The prevalence of osteoporosis in patients with primary POI was 55.6% (5/9), compared with 12.7% (9/71) in patients with secondary POI. Overall, the rate of osteoporosis in the POI group was 17.5% (14/80) compared to 6.7% (3/45) in the EM group. Although the difference did not reach the level of statistical significance ($p = 0.108$), the data are considered to represent a clinically relevant trend.

When examining the etiological subgroups, osteoporosis was found in 20% (10/50) of patients with induced POI and 9.3% (7/75) of spontaneous POI/EM cases. Although the difference was not statistically significant ($p = 0.112$), the trend was towards more severe bone loss in induced cases. However, a significant difference was found in the prevalence of non-normal bone density status (osteopenia or osteoporosis) in the first year after diagnosis: 70% in the induced group and 47.8% in the spontaneous group showed abnormal densitometry results ($p < 0.05$).

Within the POI group, 43.1% of patients had osteopenia, 10.3% osteoporosis and 46.6% normal bone density. A negative correlation was observed between time to diagnosis and lumbar spine BMD ($r = -0.255$; $p = 0.022$) and T-score ($r = -0.21$; $p = 0.031$). This relationship was also similar for femoral neck, but did not reach statistical significance (BMD: $r = -0.18$; $p = 0.06$; T-score: $r = -0.17$; $p = 0.08$).

When subgrouped by baseline E2 levels, a stronger negative correlation was found between time to diagnosis and BMD ($r = -0.401$; $p = 0.026$) and T-score ($r = -0.377$; $p = 0.036$) for patients with low estradiol levels (≤ 5 ng/L). The prevalence of reduced bone density was 61.5% in the low E2 level group, 54.5% in the medium (5-30 ng/L) level group and 44.4% in

the higher (>30 ng/L) level group. Although the differences between the groups did not prove statistically significant, the trend of decreasing E2 levels suggests an increased risk of bone loss.

Analysis by BMI showed a weak negative correlation between time to diagnosis and BMD in both the ≤25 kg/m² (r = -0.225; p = 0.109) and >25 kg/m² (r = -0.234; p = 0.113) groups. A similar trend was also found for T-score (≤25 kg/m²: r = -0.217; p = 0.121; >25 kg/m²: r = -0.230; p = 0.121). Although these relationships did not reach statistical significance, the weak negative trend may indicate an independent effect of BMI on bone mass development.

The prevalence of bone mass loss (osteopenia or osteoporosis) was 60.3% in the BMI ≤25 kg/m² group and 47.2% in the >25 kg/m² group. This trend suggests that patients with lower BMI may be at higher risk of bone loss.

Overall, our results indicated that a delay in diagnosis may be associated with an increased risk of bone loss, especially in the presence of low E2 levels and lower BMI. The comprehensive densitometry data confirm the importance of early detection and treatment in preserving long-term bone health in POI and EM patients.

5. Discussion

5.1. Discussion of the results of the etiological comparative study

The aim of the first phase of this study was to map the temporal changes in the aetiology of premature ovarian insufficiency (POI), with a particular focus on the increasing rate of iatrogenic cases and the prevention options that can be applied in clinical practice. Between 1978 and 2003, 172 patients with POI were diagnosed at our institution over a 25-year period, whereas between 2017 and 2024, 111 cases were detected over an eight-year period, representing an increase in annual incidence of approximately 2.1-fold.

The proportion of cases with genetic origin and primary amenorrhoea showed no significant difference between the two cohorts, highlighting the current limitations of genetic diagnostic options and the likelihood that many POI cases with a monogenic or complex genetic background remain hidden. Although karyotype testing and screening for FMR1 premutation

are recommended, the routine use of targeted gene testing (e.g. NGS or WGS) is limited by financial and technical difficulties.

Our results show a significant aetiological shift: while the proportion of idiopathic cases in the previous cohort was 72%, this fell to less than 37% in the contemporary group. This decrease is partly explained by an increase in cases of iatrogenic and autoimmune origin. The high rate of familial accumulation (22%) in the idiopathic group may also suggest hidden genetic causes and supports the need for a detailed family history and more genetic testing.

The rate of POI of autoimmune origin increased to 18.9% in the contemporary cohort, which is in line with international data. These suggest that about one quarter of women with POI have a confirmed autoimmune co-morbidity. Autoimmune polyendocrine syndromes (PAS), especially type I, play a prominent role in the pathogenesis of POI. Although the routine use of corticosteroid treatments and immunomodulatory therapies is not yet established, new experimental guidelines (e.g. Treg/Th17 regulation) may offer promising possibilities for the future.

The rate of iatrogenic POI has increased significantly from 7.6% to 34% of the previous cohort. This is partly a consequence of the increase in pelvic surgery (in particular ovarian surgery for endometriosis) and the spread of oncological treatments (chemotherapy, radiotherapy). Fertility counselling prior to oncotherapies and preventive interventions such as egg or embryo freezing, ovarian transplantation or GnRH analogue protection are key to fertility preservation and long-term hormonal health.

Improving clinical awareness, advances in laboratory technology and changes in diagnostic criteria (e.g. lowering the FSH threshold) are also contributing to the increased frequency of POI detection. The reduction in the proportion of idiopathic cases reflects the more accurate aetiological classification and the effectiveness of more targeted screening.

From a reproductive perspective, POI remains a serious challenge: the 6.3% survival rate documented in the contemporary cohort is low in line with international data and underlines the importance of early personalised family planning strategies and assisted reproductive technologies (e.g. egg donation).

Overall, our results support the importance of a detailed exploration of the aetiological background, the need for prevention-focused clinical practice, and the prominent role of multidisciplinary care in optimising long-term health and reproductive outcomes for women affected by POI.

5.2. Discussion of bone health assessment

In this study, we showed that delay in diagnosis of premature ovarian insufficiency (POI) and early menopause (EM) has a significant negative impact on bone metabolism. The results showed a clear, albeit moderate negative correlation of time to diagnosis with bone density parameters (BMD and T-score), especially in the lumbar spine (L1-L4) region, where trabecular bone stock responds more rapidly to hormonal changes.

It is noteworthy that more than half of the patients already had impaired bone metabolism at the time of diagnosis, largely as a consequence of prolonged untreated hypoestrogenism. The median delay was 9 months (IQR: 5-23.5 months), reflecting the shortcomings in clinical recognition. Late diagnosis not only accelerates the rate of bone loss, but also increases the risk of fracture, which has a major impact on patients' quality of life and long-term health outcomes.

Patients with primary amenorrhoea have the worst bone metabolism status. This is due to the failure to develop adequate peak bone mass (PBM) during adolescence, which determines long-term bone strength and fracture risk. This is further exacerbated by genetic abnormalities such as Turner syndrome or other chromosomal abnormalities, which can cause not only hormonal but also structural bone development disorders.

In the induced (iatrogenic) POI group, we found more rapid and severe bone loss, mainly after oncological or surgical interventions, which can be explained by the sudden onset of oestrogen deficiency. Compared to spontaneous POI, significantly lower E2 levels were measured in induced cases, further increasing the risk of bone loss. Close metabolic monitoring and targeted preventive measures, such as timely initiation of hormone replacement, are therefore particularly warranted in iatrogenic cases.

The EM group had a lower rate of bone metabolism disorders, partly due to a shorter diagnostic delay and partly due to the fact that they had already reached their maximum bone mass before the onset of oestrogen deficiency. This observation underlines the importance of PBM and the

greater medical awareness and diagnostic skills for menstrual disorders among women approaching menopause.

In our analysis, we observed that in the most severe hypoestrogenic state (E2 ≤ 5 ng/L), diagnostic delay was associated with even more pronounced bone mass loss, especially in the lumbar spine region. In contrast, the femoral neck, which is mainly composed of cortical bone, showed less significant correlation with lag time, in line with previous literature.

Body mass index (BMI) also influenced bone metabolism: patients with lower BMI (BMI < 25 kg/m²) were found to have more severe bone loss and lower BMD- values. In the group with higher BMI, aromatization in adipose tissue and increased mechanical loading may have partially counteracted the adverse effects of estrogen deficiency, which could be interpreted as a protective factor.

Our results underline the importance of early screening for menstrual disorders and amenorrhoea. Prompt diagnosis and appropriate hormone replacement can reduce bone loss, reduce fracture risk and contribute to improving long-term quality of life.

Although the correlations between BMD and T-score were statistically weak, the clinical relevance of the trends shown is undisputed. As part of comprehensive care, regular bone density analysis (DXA) is recommended, especially in women with low E2 levels and low BMI, who are at particularly high risk of bone loss.

Overall, our results support that delayed diagnosis and persistent hypoestrogenism in POI and EM can lead to significant impairment of bone metabolism. Early detection, targeted hormone replacement therapy and risk-based, individualized care are key to preventing and mitigating bone loss.

6. Summary

Premature ovarian insufficiency (POI) is one of the most significant hypoestrogenic conditions in women under 40 years of age, leading not only to infertility but also to serious long-term health consequences affecting quality of life and survival, including osteoporosis and increased fracture risk.

Our aetiological study, uniquely based on retrospective data from a single centre over a four-decade time span, has highlighted the dynamic changes in the causes of POI. We showed a significant decrease in the proportion of idiopathic cases (from 72.1% to 36.9%), a nearly fourfold increase in the proportion of iatrogenic cases (from 7.6% to 34.2%), and a doubling in the incidence of autoimmune cases (from 8.7% to 18.9%). In contrast, the proportion of POI of genetic origin remained unchanged (~10%). These changes reflect the evolution of the diagnostic tools, the increase in the number of gynaecological and oncological surgical procedures, and the increasing health awareness of patients and physicians.

Reproductive outcomes in both cohorts have remained unfavourable, with low survival rates, underlining the urgent need to develop and expand the use of fertility preservation strategies.

Our bone mineral density study was the first to our knowledge to specifically analyse the relationship between time to diagnosis and bone metabolism parameters (BMD, T-score) in POI and EM. Based on data from 168 patients studied from 2017-2024, we identified osteopenia in 43.1% and osteoporosis in 10.3% of patients at the time of diagnosis. We detected a significant negative correlation between the diagnostic delay and bone density, especially in patients with severe hypoestrogenic state ($E2 \leq 5$ ng/L). Although statistical significance was not confirmed for low BMI, a clear clinically relevant trend was observed, confirming the increased risk of bone loss in women with a leaner body mass.

Our results highlight the significant impact of diagnostic delay on the bone metabolism status of women with POI and underscore the importance of early detection and prompt, targeted hormone replacement and bone protection strategies. Mapping the aetiological background not only helps to better understand the pathomechanism but also lays the foundation for a personalised approach to prevention and care.

Although treatment options targeting the aetiology are currently limited, a more detailed understanding of the underlying mechanisms is key to identifying preventable risk factors and designing targeted prevention.

In the future, prospective, long-term follow-up studies are needed to classify iatrogenic cases in more detail, including more precise mapping of the effects of specific chemotherapy protocols and surgical techniques on ovarian function. In addition, the development of genetic diagnostics, the clinical validation of immunomodulatory therapeutic options and the strengthening of multidisciplinary, individualised oncofertility care are fundamental objectives.

Overall, our results may contribute to improving the long-term reproductive and general health outcomes of women with POI, thereby reducing the burden of complications and quality of life deterioration caused by hypoestrogenic conditions.

Summary of new findings

Etiological spectrum shift – over a four-decade comparison:

Our study was unique in presenting changes in the aetiological distribution of POI over four decades, based on data from a single centre. The proportion of idiopathic cases decreased significantly (from 72% to 37%), while the proportion of iatrogenic cases quadrupled (from 7.6% to 34%) and the proportion of autoimmune cases doubled (from 9% to 19%). According to our findings, the frequency of POI diagnoses has more than doubled over the past decades, which may reflect a shift in the etiological spectrum and an improvement in diagnostic recognition.

Reproductive outcomes:

Low live birth rates were observed in both cohorts, highlighting the infertility challenges associated with POI and reinforcing the need for fertility preservation approaches.

Our results support the key role of early detection, targeted aetiological screening and personalised multidisciplinary care in improving long-term health and reproductive outcomes in POI and EM.

Effect of delay in diagnosis on bone metabolism:
Our study clearly demonstrated, for the first time to our knowledge, an association between diagnostic delay and bone density in POI and EM, particularly in severe hypoestrogenic state (E2 ≤ 5 ng/L). This highlights the paramount importance of early detection in preventing bone loss.

Relationship between BMI and bone loss:

Although statistical significance was not confirmed for low BMI, a clear negative trend was observed, which can be evaluated as a clinically relevant indication of increased risk in leaner patients.

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/442/2025.PL
Subject: PhD Publication List

Candidate: Szilvia Csehely
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Csehely, S.**, Kun, A., Orbán, E., Katona, T., Orosz, M., Krasznai, Z. T., Deli, T., Jakab, A.: Changing Etiological Spectrum of Premature Ovarian Insufficiency over the Past Decades: a Comparative Analysis of Two Cohorts from a Single Center.
Diagnostics. 15 (13), 1-18, 2025.
DOI: http://dx.doi.org/10.3390/diagnostics15131724
IF: 3.3 (2024)

2. **Csehely, S.**, Kun, A., Orbán, E., Katona, T., Orosz, M., Herman, T., Krasznai, Z. T., Deli, T., Jakab, A.: Prevalence of Impaired Bone Health in Premature Ovarian Insufficiency and Early Menopause and the Impact of Time to Diagnosis.
J Clin Med. 14 (12), 1-17, 2025.
DOI: http://dx.doi.org/10.3390/jcm14124210
IF: 2.9 (2024)

List of other publications

3. Jakab, A., **Csehely, S.**: Az asszisztált reprodukcióval fogant terhességek szülészeti vonatkozásai. In: Szeretnénk, ha megszületnél! A meddőség orvosi, lélektani és társadalmi vonatkozásai. Szerk.: Bátki Anna, Mészáros Krisztina, Oriold és Társai Kft., Budapest, 215-225, 2024.

4. Jakab, A., **Csehely, S.**: Az asszisztált reprodukcióval született gyermekek egészsége. In: Szeretnénk, ha megszületnél! A meddőség orvosi, lélektani és társadalmi vonatkozásai. Szerk.: Bátki Anna, Mészáros Krisztina, Oriold és Társai Kft., Budapest, 341-348, 2024.

5. Orosz, M., Borics, F., Rátonyi, D., Krasznai, Z. T., Vida, B., Herman, T., **Csehely, S.**, Jakab, A., Lukács, L., Lampé, R., Deli, T.: Endocrine Characteristics and Obstetric Outcomes of PCOS Patients with Successful IVF and Non-IVF Pregnancies.
J Clin Med. 13 (18), 1-13, 2024.
DOI: http://dx.doi.org/10.3390/jcm13185602
IF: 2.9

6. Orosz, M., Borics, F., Rátonyi, D., Vida, B., **Csehely, S.**, Jakab, A., Lukács, L., Lampé, R., Deli, T.: Pre-Conception Androgen Levels and Obstetric Outcomes in Polycystic Ovary Syndrome: a Single-Center Retrospective Study.
Diagnostics. 14, 1-15, 2024.
DOI: http://dx.doi.org/10.3390/diagnostics14192241
IF: 3.3

7. **Csehely, S.**, Orosz, M., Deli, T., Krasznai, Z. T., Jakab, A.: A korai petefészek-elégtelenség időben történő felismerésének jelentősége.
Magy Noorv Lapja. 86 (5), 283-286, 2023.

8. Herman, T., **Csehely, S.**, Orosz, M., Bhattoa, H. P., Deli, T., Török, P., Laganà, A. S., Chiantera, V., Jakab, A.: Impact of endocrine disorders on IVF outcomes: results from a large, single-centre, prospective study.
Reprod. Sci. 30 (6), 1878-1890, 2023.
DOI: https://doi.org/10.1007/s43032-022-01137-0
IF: 2.6

9. Török, P., Naem, A., **Csehely, S.**, Chiantera, V., Sleiman, Z., Laganà, A. S.: Reproductive outcomes after expectant and surgical management for tubal pregnancy: a retrospective study.
Minim. Invasive Ther. Allied Technol. 32 (3), 127-135, 2023.
DOI: http://dx.doi.org/10.1080/13645706.2023.2181091
IF: 1.7

10. Herman, T., **Csehely, S.**, Orosz, M., Bhattoa, H. P., Deli, T., Török, P., Jakab, A.: Endokrin kórképek előfordulása és társulása in vitro fertilizációs programban részt vevő nők körében.
Orv. hetil. 163 (18), 712-719, 2022.
DOI: http://dx.doi.org/10.1556/650.2022.32372
IF: 0.6

11. Berczi, A., Sakamoto, S., **Csehely, S.**, Herman, T., Jakab, A.: Genetic concerns and other offsping health safety issues of assisted reproduction: a literature review = Az asszisztált reprodukcióval fogant terhességeivel és az abból született utódok genetikai, valamint egyéb betegségeivel kapcsolatos ismeretek - irodalmi áttekintés.
Magyar Androl. 2022 (1), 15-27, 2022.

12. Csécsei, K., **Csehely, S.**, Póka, R., Zádor, Z., Németh, I., Ringelhan, B., Deliné Molnár, S., Jakab, A.: Haemangioma a méhnyakban: 4 eset ismertetése és irodalmi áttekintés.
Orv. hetil. 163 (5), 187-194, 2022.
DOI: http://dx.doi.org/10.1556/650.2022.32317
IF: 0.6

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

13. Póka, R., Barna, L., **Csehely, S.**, Damjanovich, P. G., Farkas, Z., Molnár, S., Nagyházi, O., Orosz, G. B., Orosz, M., Ördög, L., Sipos, A. G., Juhász, A. G., Török, O., Tóth, Z.: Szülés módja és neonatális eredmények: terminuson túl szinguláris fejvégű magzattal spontán vajúdó, először szülő nők körében.
Magyar Nőorv. Lap. 82, 228-234, 2019.

14. Póka, R., Barna, L., **Csehely, S.**, Damjanovich, P. G., Farkas, Z., Molnár, S., Nagyházi, O., Orosz, G. B., Orosz, M., Ördög, L., Sipos, A. G., Juhász, A. G., Török, O., Tóth, Z.: Születési súly és császármetszés kapcsolata: 37. hetet betöltött, szinguláris fejvégű magzattal spontán vajúdó először szülő nőkben.
Magyar Nőorv. Lap. 82 (2), 56-61, 2019.

15. Póka, R., Barna, L., **Csehely, S.**, Damjanovich, P. G., Farkas, Z., Molnár, S., Nagyházi, O., Orosz, G. B., Orosz, M., Ördög, L., Sipos, A., Újvári, B., Tóth, Z.: A császármetszés frekvenciájának Robson-féle klasszifikáció szerinti elemzése a Debreceni Egyetem Szülészeti és Nőgyógyászati Klinika tízéves anyagában.
Magy. Nőorv. Lapok. 80, 76-85, 2017.

Total IF of journals (all publications): 17,9
Total IF of journals (publications related to the dissertation): 6,2

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

07 July, 2025

DEBRECENI EGYETEM
Egyetemi és Nemzeti Könyvtár