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# Visualization of Breast Cancer and Safety: Review

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**Abstract**

Breast cancer remains a leading cause of mortality among women globally, with early detection playing a pivotal role in improving patient outcomes. The treatment and prognosis have improved significantly due to early detection. The rapid development of various imaging techniques has led to success in early detection. In this article, we will discuss the current options for breast cancer screening, including mammography (both film-screen and digital), breast magnetic resonance imaging, automated breast ultrasound, and other techniques such as digital breast tomography and breast computed tomography. In addition, we summarize the characteristic features of the modalities in a tabular view for better representation and comparability. The goal of this review is to highlight the progress made in breast cancer screening and its impact on survival rates. The review concludes that the progress in the screening techniques results in a much higher survival rate, in particular due to detections of earlier stages of tumors. In recent years, artificial intelligence has emerged as a powerful tool in the field of breast cancer management, revolutionizing detection, diagnosis, and treatment planning. The rapid growth in artificial intelligence technologies, particularly machine learning and deep learning, has enabled sophisticated analysis of imaging data, pathology, and clinical variables, significantly enhancing precision and efficiency. We highlight advancements in artificial intelligence for breast cancer in past five years, and discusses the challenges and future opportunities in integrating artificial intelligence into clinical workflows.

**Keywords:** Breast cancer screening, Mammography, (Automated breast) ultrasound, Digital breast tomosynthesis, MRI, Breast CT.

## 1. Introduction

Breast cancer (BC) is the most abundant form of cancers in women, the second most common cancer, and the fourth leading cause of death globally. In 2020, the World Health Organization reported 2.3 million new cases of BC worldwide, and 7.8 million women were alive with BC diagnosed in the past 5 years and 685,000 BC-related deaths were documented [1]. The incidence of breast cancer varies significantly across regions, often correlating with the level of economic development. In countries with a very high Human Development Index (HDI), about 1 in 12 women will be diagnosed with breast cancer during their lifetime, with 1 in 71 women dying from the disease. Conversely, in countries with a low HDI, 1 in 27 women is diagnosed with breast cancer, but 1 in 48 will die from it (according to WHO, see https://www.who.int/news-room/fact-sheets/detail/breast-cancer).

The global burden of breast cancer has been increasing, a trend attributed to factors such as population aging, lifestyle changes, and improved detection methods. Projections indicate a significant rise in both incidence and mortality by 2040, with an expected 40% increase in new cases and a 50% increase in deaths. This anticipated rise underscores the need for enhanced global efforts in breast cancer prevention, early detection, and treatment, particularly in transitioning countries where incidence rates are escalating rapidly, and mortality rates remain high.

The most preventing factor for BC cancer progression is the earlier detection [2]. The survival rate directly relates to the stage at diagnosis, as evidenced by 98% 10-year survival rate for patients with Stage 0 and Stage I of BC compared to 65% 10-year survival rate for patients with Stage III of the disease [3]. Routine screening reduced BC-associated mortality by 43% between 1989 and 2020 [4, 5]. The BC-associated death rate in the US decreased by ~1.8% annually between 2006 and 2015 and by ~1.3% annually between 2011 and 2020 [5].

Despite advancements in breast cancer management, disparities persist in outcomes between developed and developing regions. Women in low- and middle-income countries often face limited access to early detection and treatment services, leading to higher mortality rates. Addressing these disparities through improved healthcare infrastructure, education, and access to care is crucial for reducing the global burden of breast cancer.

Breast cancer continues to pose a significant global health challenge. Efforts to reduce its impact must focus on equitable access to early detection, effective treatment, and comprehensive education to address the varying incidence and mortality rates worldwide. The main criteria for a proper screening modality are good sensitivity, specificity, ease of use, acceptability (discomfort/pain and time), and low cost. We summarize here the benefits and limitations (prevalence in use, radiation dose, ranges of specificity and sensitivity) of the modalities used in BC screening (see also Table 1).

| Table 1 | Visualisation-methods | | | | | |
|---|---|---|---|---|---|---|
| Method of Visualization | Prevalence in screening | SPC *<br>SNS *<br>DA * | Radiation dose | Advantages and limitations | | Target patients |
| Film-screen mammography (FSM) | high (not in the US/Europe) | SPC: 40-100% (avg. ~77%)<br>SNS: 13-97% (avg. ~61%)<br>DA: high | low | Good for inpalpable, small, diffuse cancers<br>Limited sensitivity in dense breast<br>Can't detect small masses (<10 mm)<br>Needs breast compression | | Asymptomatic patients<br>Age 40-70 years<br>Non-dense breast |
| Full-Field Digital mammography (FFDM) | high (in the US/Europe) | SPC: 40-97% (avg. ~58%)<br>SNS: 43-95% (avg. ~77%)<br>DA: moderate | low | Faster acquisition, higher resolution vs. FSM<br>Needs breast compression | | Asymptomatic patients<br>Age 40-70 years<br>Pre/perimenopause<br>Non-dense breast |
| Ultrasound (US/ABUS) | moderate (used as supplement) | SPC: 75-95% (avg. ~85%)<br>SNS: 12-68% (avg. ~38%)<br>DA: moderate | - | No contraindications<br>More effective in dense breast vs. FSM/FFDM<br>No breast compression needed<br>Can't detect small masses (<10 mm), can't screen deeper than 10 cm | | Non-dence and dense breast<br>Supplement modality |
| Digital Breast Tomosynthesis (DBT) | moderate to high | SPC: 85-100% (avg. ~93%)<br>SNS: 81-90% (avg. ~86%)<br>DA: very high | moderate | 3D visualization<br>Less breast compression vs. FSM/FFDM<br>Relatively high dose vs. FSM/FFDM | | Dense breast |
| Magnetic Resonance Imaging (MRI) | low (only in high-risk groups) | SPC: 50-100% (avg. ~75%)<br>SNS: 65-100% (avg. ~87%)<br>DA: high | - | No radiation exposure<br>No breast compression needed<br>Can't detect microcalcifications | | High risk groups<br>Extremely dense breast |
| Computed Tomography (CT) low dose | rare (only in high-risk groups) | SPC: ~100%<br>SNS: ~85%<br>DA: very high | moderate | Primary breast cancer detection, can differentiate between structures and neoplasm<br>3D visualization<br>No breast compression needed<br>High dose compared to FSM, Comparable to FFDM + DBT | | Age 40-70 years<br>Dense breast<br>High risk groups |

* SPC – Specificity, * SNS – Sensitivity, * DA - Diagnostic accuracy, combined assessment of positive/negative prediction rates and/or diagnostic odds ratio, avg. = average value

## 2. Breast Cancer Screening Modalities

### 2.1. Film-Screen and Full-Field Digital Mammography

Mammography is a valuable tool for early detection of breast cancer because it can detect tissue abnormalities, such as dense formations and microcalcifications, in the breast. Initially, mammograms were taken using X-ray film screens, a process known as film-screen mammography (FSM). However, this method has been largely replaced by full-field digital mammography (FFDM), which uses sensors to capture the X-ray intensity map. This new technique has been approved for clinical use by the Food and Drug Administration (FDA). FFDM produces higher-quality images with less exposure time compared to FSM, making it a safer option for patients.

There have been several retrospective studies conducted to investigate whether FFDM provides better diagnostic results compared to FSM [6, 7]. Some earlier reports found little or no significant difference in cancer detection between these modalities [8, 9]. However, later studies, such as Heddson et al. (2007) and Skaane et al. (2007), found a significantly increased rate of cancer detection as well as a positive predictive value for FFDM screening [6, 10]. A recent meta-analysis of large datasets, consisting of over 11 million FSM images and 5.5 million digital mammograms, found that there was no significant difference in the overall cancer detection rate between the two methods [7]. Nevertheless, FFDM has become the most commonly used breast cancer screening method in Europe because up to 80% of the running screening programs utilize it [11]. In addition, according to a large multi-center study involving approximately 50,000 asymptomatic women with the use of both FFDM and FSM, showed that FFDM is a more accurate method for women under the age of 50, women with dense breasts on radiography, and pre-menopausal women [9].

The standard type of mammography is 2D imaging in two projections (Figure 1). Both FSM and FFDM provide good measures for true positive results and utilizing these methods for early screening of BC in women aged 40 years or older greatly reduces mortality rate [12]. Clinical trials for mammography screening run between 1960 and 2010 worldwide showed the decrease in BC-associated mortality by 20 to 30% [13,

14]. There are various assessments of false-positive rates for mammography. One study reported that it has a true positive rate of 83-95% and a false positive rate of 0.9-6.5%; however, these figures are from an idealized population of 27% of young women and the false positive rate in young women is known to be higher [3]. Another meta-analysis based on 117 different clinical studies concluded that the false-positive rate lies between 20 to 56% [13]. In general, for all groups of women, the false negative rate remains between 10 to 15% depending on a cohort study [15].
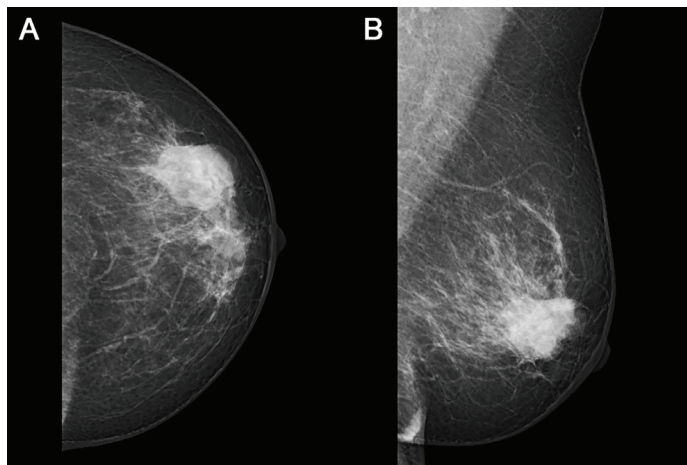


**Figure 1** – Digital mammography in 2 standard projections: (A) CC direct; (B) MLO oblique. On the left, on the border of the outer quadrants at a distance of 3 cm from the nipple can be seen a shadow of high density, irregular shape, with an indistinct contour (anterior, medial, and lateral contours are clear, the posterior contour is indistinct, stringy), up to 4.1x3.2 cm in size. On the left in the central section in the area of the areola, the skin is slightly thickened up to 0.3 cm. Conclusion: Nodular formation of the left breast

The sensitivity and specificity of mammography is lower in dense breast. As breast density itself depends on many factors like age, use of hormone replacement therapy (HRT), phase of the menstrual cycle, body mass index, and familial or genetic characteristics, the diagnostic reliability of mammography can vary between different groups of patients. For example, one study used over 460,000 screening mammograms from ~330,000 women aged between 40 and 89 years and reported that sensitivity / specificity of mammography is 87.0% / 96.9%, respectively, in women with entirely fatty breasts but amounted only to 62.9% / 89.1% in women with extremely dense breasts [16]. Another study reported similar data where the sensitivity of FFDM steadily declined from 100% in fatty breasts to 72.9% in heterogeneously dense breasts to 50% in extremely dense breasts [17]. Unlike FSM, FFDM still provides better cancer detection rate in dense breast patients and now is considered a primary screening modality for this case. In fact, despite the diminished sensitivity of mammography in dense breast, there is no absolute alternative for mammography as a screening tool and it remains a primary recommendation for all women, independent of age, breast density, and concomitant risks [18]. The use of supplemental screening methods to mammography, e.g. automated breast ultrasound (ABUS) or MRI, in dense breast women may improve the cancer detection rate; however, the data remains partially unclear. In addition, breast density is just a factor among many others that must be assessed during risk-based selection of a proper screening method for each individual. Age is another critical factor for BC occurrence and development, and therefore mammography is recommended for all women over the age of 40 or 50 (depending on different countries screening recommendations), since at this age the risk of developing cancer increases significantly [4].

The adverse attribute of mammography is an ionizing radiation dose. However, compared to standard doses in other uses like cardiovascular or nervous system imaging by computed tomography, the single radiation dose in mammography is times lower thus reducing possible adverse effects including death from cancer induced by the screening [13]. According to the United Nations Scientific Committee on the Effects of Atomic Radiation 2020/2021 Report, the typical effective radiation dose per single examination is 0.66 mSv, the order lower vs. the dose in a single chest CT scan. According to the Report, the weighing factor for breast tissue is 0.12, thus giving a value of typical absorbed dose to be ~5.5 mGy (~2.8 mGy per breast). Other reports provide similar data, ranging between 2.2 and 5.4 mGy per breast in two projections [19]. To date, it is speculated to use FFDM in combination with mammography with digital breast tomosynthesis (DBT) for better sensitivity, although this is accompanied by the increase in total radiation exposure as well.

FSM/FFDM have other certain limitations: they require some preparation to obtain the clearest and revealing data and they rely on patient's specific factors. The best option for passing the study is 5-10 days of the menstrual cycle. This modality is not optimal for detection of microcalcifications in dense breasts as well as in women with implants [20]. The notable disadvantage of mammography is that the breast must be compressed before screening which can produce pain and/or discomfort. However, mammography (now largely represented by FFDM) is the "gold standard" technique for primary screening for BC and is important modality of annual or biennial screening for average-risk groups aged 40 to 74 years [12].

### 2.2. Digital Breast Tomosynthesis

Mammography with digital breast tomosynthesis (DBT) acquires several images (layers) of the breast by rotating the X-ray tube along an arc. This method utilizes various numerical approaches to reconstruct a 3D layer-by-layer planes of the breast, contributes to a more detailed study of the structure of the dense mammary gland (BI-RADS C, D), and significantly expands the possibilities of early diagnosis of diseases.

It has been demonstrated that screening by tomosynthesis provides 16% more lesions detectable compared to a conventional mammogram and it has been reported to reduce false positive rate by 85% [21]. The higher sensitivity and specificity of DBT than FFDM alone were consistently found in most meta-regression analyses. Pooled data from twenty studies with ~45,000 patients demonstrated higher sensitivity and specificity of DBT alone (90% and 90%, respectively) vs. FFDM alone (76% and 83%, respectively) [22]. As similar, a multi-center comparative study on a smaller sample (~450 patients), which aimed to compare FFDM alone, DBT alone, and the combined DBT+FFDM, showed slightly greater sensitivity and specificity of DBT alone vs. FFDM alone: 89.1% vs. 86.6% for sensitivity and 84.6% vs. 81.4% for specificity, respectively [23]. Interestingly, the combined DBT+FFDM was more sensitive but less specific compared to DBT or FFDM alone. Another retrospective analysis summarized the results of comparison of examinations taken by FFDM alone (>280,000 images) and in combination with DBT (>170,000 images), over 450,000 images together [24]. The results indicate that screening by DBT+FFDM vs. FFDM alone provided: 1) a roughly two-fold lower recall and 1.5-fold smaller number of biopsies that were needed, and 2) a significant increase in the positive predictive value. Another study involving >14,500 women with a median age of 58 years and subdivided by groups according to the breast density concluded with higher sensitivity and lower specificity for DBT compared with FFDM for all breast density subgroups [25]. The investigators noted that DBT with increased sensitivity is most beneficial for those with the highest breast density while

at the cost of slightly lower specificity, and that their results may facilitate the use of DBT in individualized screening programs. On the other hand, a prospective cohort study of >340,000 women aged 40-79 years undergoing screening with DBT or FFDM revealed no difference in consistency of BI-RADS density between these modalities [26]. While DBT alone is partially replacing FFDM, it still can miss some invasive cancers in dense tissue. To overcome the problem, it might be recommended to combine DBT with automated breast ultrasound that will lead to levels of sensitivity and specificity as high as 100% [27].

Despite every single plane in DBT is about 10% of FFDM, the average glandular dose per total exposure for DBT full scan is higher by 25-35% [19]. This constitutes the main disadvantage of the method as the increased exposure dose may facilitate the occurrence of malignancies. DBT was approved by the FDA in 2011, but this modality is not yet considered the standard of care for BC screening [15]. It is used in BC screening centers; however more clinical experience is required to determine whether it will become a relevant screening test or become the diagnostic test of choice after screening mammography [3]. For example, it is still contradictory whether DBT in combination with FFDM is better than FFDM alone for visualization of subtle alterations like calcium deposits (microcalcifications) in breast tissue – this is an important issue because the deposits often relate to the initial stage of benign or malignant tumor [20].

### 2.3. Ultrasound

Ultrasound (US) can be effectively used as a screening method following palpable breast neoplasms or in a follow-up for abnormal mammography findings. Conventional hand-held US of the mammary glands allows the assessment of the size and structural features of tissues as well as the presence of pathological formations in the mammary gland like cysts and tumors (Figure 2). The modality is considered the more informative technique than mammography in cases of the examination of women younger than 30 years when denser glandular tissue. It is recommended to use in case of palpable lump, axillary adenopathy, nipple discharge or inversion, abnormalities in the presence of breast implants, skin retraction, and suspicious abnormalities on mammographic images that need percutaneous interventions as needle biopsy. Moreover, in some cases US can visualize a tumor whereas mammography is unable to do that [28].

Automated breast ultrasound (ABUS) is a relatively new modality (approved by FDA in 2012) which can be implemented in some systems. This modality allows for getting many images per procedure to cover as many area of the breast as possible, i.e. the imaging technique is based on tomographic-like quantitative profiles of various acoustic properties. Compared with standard B-mode US, it produces images with a large field-of-view whose quality is independent of the skill of the operator. However, the methods of image reconstruction in ABUS are based on approximate solutions to the acoustic wave equation which can result in reconstructed 3D pseudo images with poor resolution. Some investigators adopted automated computational methods and optimization-based image reconstruction algorithms, also with machine learning approaches, to solve this problem [29]. In fact, it has already been used in clinical screening [30] and some studies reports higher specificity but lower sensitivity of ABUS vs. FFDM [31]. It is typically used as an adjuvant method for women with dense breasts [32] and it is more suitable for dense breast screening compared to FSM or FFDM [33].

Pooled data for ABUS alone show the range of sensitivity between 89.9% and 93.8% and the range of specificity between 82.4% and 87% [34]. The specificity of US (conventional hand-held or ABUS), if applied alone, is at the level of mammography alone or slightly better, but with combined FFDM + ABUS
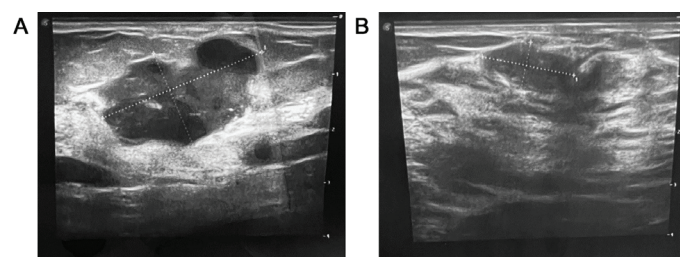


**Figure 2** – Ultrasonography of the mammary gland. (A) The glandular tissue is heterogeneous, hyperechogenic with moderately dilated milk ducts. On the border of the upper square, there is a hypoechoic formation with a smooth contour, 31.0x18.1 mm, avascular. (B) The left mammary gland has the fibroglandular structure with a predominance of glandular tissue, heterogeneous, hyperechogenic. The milk ducts are cystically dilated. In the upper-lower square, there is a hypoechoic formation with a smooth contour with a diameter of 16.7x8.0, avascular.

modality, the sensitivity increased up to 99-100% and specificity can be as high as ~87% [32].

The obvious advantages of US are as follows: it is radiation-free and breast-compression-free, and it is relatively inexpensive, compared to mammography. The specific advantage of the modality is that US of the mammary glands does not require special preliminary preparation and has no contraindications, for instance it can be done for pregnant and breast-feeding women. For a more relevant assessment of the condition of the breast, it is recommended to conduct an examination on 4-8 days from the onset of menstruation (if no hormonal contraceptives are taken or in menopause). The disadvantage of the method comes from the physics of sound wave penetration to and reflection from soft tissues. While the modern US scanners have a zero dead zone, the axiolateral resolutions in most of the instrumentals lie between 0.5 and 3 mm, and effective penetration depth ranges in 3 to 8 cm for linear scanners and >15 cm for convex heads [35]. Little changes in beam orientation can miss the neoplasm, which makes the ultrasound a highly device- and operator-dependent technique.

### 2.4. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not recommended as independent screening modality but in high-risk groups of women it seems to be the best alternative to mammography because of the sensitivity and the absence of ionizing radiation exposure [36]. However, in recent years, MRI screening has begun to be actively offered for the early detection of breast cancer in women at high risk and has been adopted based on evidence provided by comparative studies of test accuracy.

MRI allows for defining formations, cysts, and involutive changes of the mammary glands and helps to make a clear diagnosis of different neoplasms (Figure 3). According to numerous reports, the sensitivity of this imaging method ranges between 70 and 100% [37, 38] being the best among other visualization techniques including mammography and ultrasound. It has been reported that cancer yield from MRI alone is nearly 10 times higher vs. FSM/FFDM in average-risk women, and approximately twice higher in high-risk women [38]. Breast MRI is highly recommended annually as adjuvant to mammography for women with BRCA-1/BRCA-2 mutations or TP53/PTEN mutations, or to those who have already been diagnosed with BC; however, it is specifically not recommended for screening women at average risk for BC [36–38]. It can also be suggested as a prevailing screening method for women with extremely dense breast tissue because it is associated with an increased risk for BC and due to the poor sensitivity of mammography in such tissues [36]. The specificity of breast

MRI is much more variable between different trials and studies, with reported values ranged between >35% to ~100% [39]. This results in a relatively high rate of false-positive conclusions.
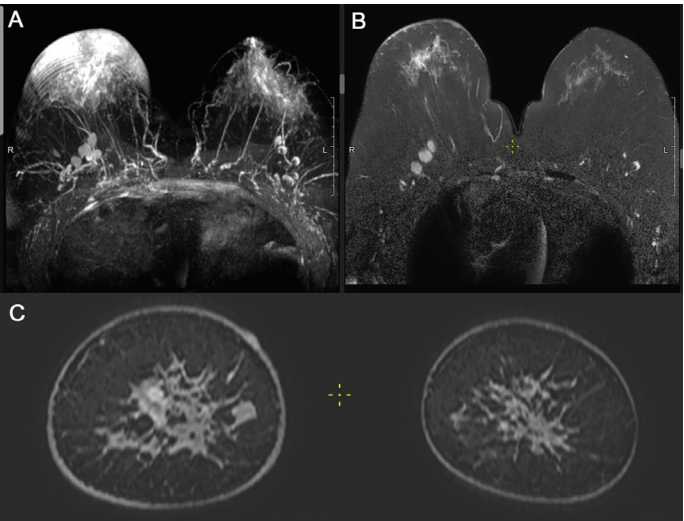


**Figure 3** – MRI scan of a diffuse-infiltrative formation of the right breast with skin thickening (BI-RADS 6). Multiple round and oval cysts have a diameter of 4.0 mm in the lower-outer quad-rant, with a diameter of 8.0 mm at the junction of the lower-outer and lower-inner quadrants. (A) MRI T2 STIR with fat suppression revealed a diffuse-infiltrative carcinoma in the upper-outer and lower-outer quadrants of the right mammary gland, with irregular shape, with fuzzy uneven stringy contours. (B) The contrast-enhanced T1-weighted images demonstrated the infiltrative formation in the right mammary gland. (C) Axial projection of the breast showed the isointense lesion in the right mammary gland in T2 images with the fat suppression option.

It was concluded that the combined MRI and mammography but not MRI + US could provide better efficiency [38]. While the potential advantage of the combined method is a more accurate selection of lesions for biopsy [40, 41], it remains open whether the specificity, sensitivity, and diagnostic predictability are affected by the actual size of the lesion. It has only been found that for lesions of 10 mm in size or larger the diagnostic effectiveness of MRI alone is enough to omit the need for biopsy [42].

The main disadvantages of breast MRI are high cost, complexity, and not quite a standardized technique. In addition, breast MRI is unable to visualize micro-calcifications that are often indicate the presence of malignancies [43]. Other disadvantages include longer times to acquire images (compared to mammography) and the fact that there is a small fraction (~15%) of individuals who do not tolerate MRI due to claustrophobia [44].

### 2.5. Breast computed tomography

Breast computed tomography (breast CT) takes a series of 2D images at different orthogonal planes with different slice thickness to reconstruct 3D image of the whole breast (Figure 4). The modality greatly facilitates locating and differentiation of structures and identification of neoplasm, its nature and degree of growth into the surrounding tissues, and changes in regional lymph nodes [45].

The high level of radiation dose during standard CT scan – as much as the order of magnitude compared to FSM/FFDM – initially prevented from using it as routine screening modality. However, a recently developed modality, cone beam breast CT (CB-BCT), has the average radiation dose as small as in conventional mammogram [46]. In the diagnosis of both malignant and benign lesions of the breast, the results obtained using the CT apparatus are superior to other diagnostic methods.
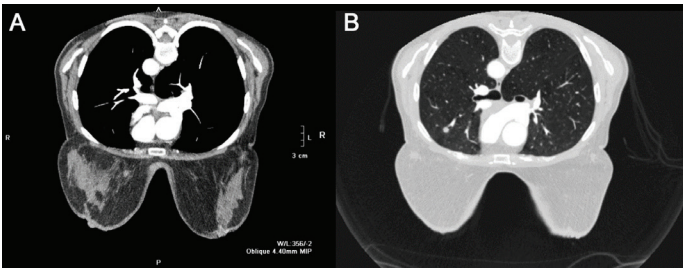


**Figure 4** – Different view modes help to check both breast and lungs. The reconstructed full data set gives high-resolution images of the breast in three dimensions (A); at the same time, it al-lows to examine the chest to determine the metastases (B).

Breast CT can diagnose completely unexpected early small malignant neoplasms, such as carcinomas, and differentiate potential precancerous lesions from benign fibrocystic breast disease [47]. Some studies reported that compared to other methods, breast CT provides the highest sensitivity and high specificity in the detection of breast tumors, including preclinical forms. For example, it was shown in a study involving 450 women that CT provides sensitivity, specificity, and accuracy for BC detection at the level of 84.2%, 99.3%, and 98.7% compared to 78.9%, 93.8%, and 93.2% for four-view mammography [45]. The evaluation by CT also provides definitive diagnostic help in the cases where mammography, ultrasound, and physical examinations are inconclusive.

Along with superior detection of malignancies, this modality is invariant to the duration of the menstrual cycle as well as does not need special preparation of patients for the screening. Next, breast compression is not required in this modality. Breast CT seems to be preferred in dense breasts but the greatest disadvantage of CT is a generally high radiation dose compared to FFDM [44], especially in several consecutive scans and in addition due to the extremely increased use of CT in clinics as a diagnostic instrumentation, often unnecessarily.

## 3. Artificial Intelligence in Breast Cancer: Advances, Applications, and Future Directions

AI-based algorithms have demonstrated the ability to address challenges of inter-observer variability, false negatives, and reduced sensitivity in dense breast tissue by improving detection rates and reducing false positives. Recent studies indicate that AI models outperform or complement radiologists in breast cancer detection. For example, a retrospective analysis comparing AI systems with human radiologists found that deep learning algorithms identified breast malignancies with accuracy comparable to experienced professionals, while reducing workload and recall rates [48]. Furthermore, AI systems have been particularly effective in identifying microcalcifications and subtle lesions that may be missed during conventional readings. AI-powered screening tools, such as convolutional neural networks (CNNs), have been integrated into mammography workflows. A study evaluating AI-assisted mammography screening reported a 20% increase in detection of invasive cancers and a reduction in false positives by 10% [49]. Additionally, AI algorithms have enhanced the performance of breast ultrasound in detecting lesions in women with dense breasts, an area where traditional methods often fall short. AI has also paved the way for personalized risk-based screening. Machine learning models trained on large-scale datasets, including mammographic density, genetic markers, and lifestyle factors, offer improved breast cancer risk prediction compared to traditional models like Gail or Tyrer-Cuzick scores [50].

Despite its promising applications, the implementation of AI in breast cancer care faces several challenges. AI models often require large, diverse datasets to perform optimally. Biases in training data can limit model generalizability across different populations and imaging systems. Ensuring patient privacy, addressing ethical concerns, and obtaining regulatory approvals remain significant hurdles for AI integration into healthcare. Seamlessly integrating AI tools into existing clinical workflows while maintaining accuracy and efficiency requires collaborative efforts between AI developers, clinicians, and healthcare institutions.

## 4. Conclusion

Breast cancer can be effectively diagnosed during routine screening. Although approximately 2/3 of all cancers are detected by mammography, other methods are needed, especially in high-risk groups. As a result of the methods, the mortality rate of breast cancer has decreased dramatically and the average survival rate has increased worldwide, mainly due to the early manifestation of malignancies. Recent advancements in AI technologies have demonstrated their potential to complement radiologists, pathologists, and oncologists, ultimately improving patient outcomes. However, overcoming challenges related to data, ethics, and interpretability is essential for widespread adoption.

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# Comparative Pathomorphological Characteristics of Placental Vessels from Pregnancies with High and Low Risk of Preeclampsia

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## Abstract

**Relevance:** Preeclampsia is a common multisystem specific pregnancy disorder accompanied by remodeling of placental vessels. Vascular structural changes are influenced by both systemic factors and local anomalies, such as umbilical cord pathology. The large variability and inconsistency of histomorphometric changes in placental vessels as markers of placental dysfunction emphasize the need for their further research using standardized methods of morphometric analysis.

The purpose of this work is to evaluate histomorphometric changes in the wall thickness and internal diameter of placental vessels during pregnancy with a different risk of preeclampsia based on screening in the first trimester and umbilical cord pathology.

**Methods:** A retrospective research included pregnant women grouped by preeclampsia risk (high and low) and additionally stratified by the presence of umbilical cord pathology. The placenta examination and the selection of fragments of placental tissue of the postpartum placenta were carried out in accordance with the consensus recommendations of the Amsterdam Placental Workshop Group. The sections were stained with hematoxylin and eosin and Masson trichrome. Morphometric measurements were performed using ImageJ software (version 1.52). The data were analyzed using the Mann-Whitney U-test with Bonferroni correction.

**Results:** Systemic and local factors had an impact on vascular remodeling, manifested in changes in wall thickness and diameter of macrovessels. In the low–risk group without umbilical cord pathology, the average vascular wall thickness was 14.4(11.6 - 17.8)μm, and the diameter of the vascular lumen was 124.9(98.4 – 142.6)μm. In placentas with a high risk of preeclampsia without umbilical cord pathology, a significant decrease in the wall thickness of placental vessels was observed to an average of 8.1(6.3 – 8.8)μm, accompanied by a significant expansion of the vascular lumen to 167.7(128.4 – 189.7)μm. The presence of umbilical cord pathology led to thickening of the wall of the proximal vessels 29.1(24.1-37.1)μm with a decrease in the lumen diameter to 93.7(82.7-105-5 )μm. The differences between the groups reached statistical significance (p<0.001).

**Conclusion:** This research highlights the combined effect of systemic factors (risk of preeclampsia) and local structural changes (umbilical cord pathology) on the remodeling of placental vessels. A decrease in the wall thickness of the placental vessels, accompanied by an increase in the internal diameter of the vessels, suggests significant structural changes that may be early diagnostic and prognostic markers of a newborn's predisposition to cardiovascular diseases.

**Keywords:** preeclampsia, chorionic villous vessels; histomorphometry, placenta.

## Introduction

Preeclampsia is a serious multisystem condition that affects approximately one in fifteen pregnant women [1]. Preeclampsia is associated with short-term and long-term risks to the mother, including cardiovascular complications, and adverse fetal outcomes such as growth restriction, preterm birth, and perinatal mortality [2–7]. An integrated

approach including risk monitoring, preventive measures and multidisciplinary collaboration is a key solution to reducing the burden of preeclampsia.

One of the important strategies for prevention is to use of low doses of acetylsalicylic acid from the first trimester of pregnancy, which, according to numerous researches, reduces the likelihood of developing preeclampsia in high-risk groups based on screening results [8–10]. Modern first trimester screening programs use a combination of clinical history data biochemical and sonographic indicators to assess the risk of preeclampsia. But despite the success in the development of screening programs, issue of the relationship between the identified risk and histopathological changes in the placenta remains open.

Pathological processes in the «mother-placenta» system, leading to prolonged hemodynamic disorders, may be accompanied by significant remodeling of placental vessels, exacerbating placental dysfunction [11, 12]. Researches of the vessels of the villous tree of the placenta in preeclampsia reveal significant differences in their morphometric parameters compared with physiological pregnancy. However, data on changes in the walls and lumen of blood vessels are contradictory: some authors point to thickening of the walls of blood vessels due to hypertrophy of smooth muscle cells or fibrous processes, others note their thinning and expansion of the diameter of blood vessels, and sometimes do not record significant changes at all [13–17]. The inconsistency of the data indicates the need for further researches of placental vessels in preeclampsia. Changes in the vascular network can act not only as a marker of placental perfusion disorders, but also as an independent factor affecting the outcome of pregnancy. The research of histomorphometric features of placental vessels depending on the risk of preeclampsia and concomitant factors is an important step in understanding the pathogenesis of preeclampsia and individualizing the approach to pregnancy follow-up with stratification of risk groups of women and newborns.

**The objective of this paper** is to evaluate histomorphometric changes in the wall thickness and internal diameter of placental vessels during pregnancy with a different risk of preeclampsia based on screening in the first trimester and umbilical cord pathology.

## Methods
## Research design

A retrospective study was performed from January 1, 2022 to January 1, 2024 in the Department of Pathology of the NJSC Karaganda Medical University (Kazakhstan). In the planning stage, the study was analyzed considering the current regulatory and legal acts governing compliance with ethical principles in research involving human subject.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki [18] and approved by the local bioethics commission of the Karaganda Medical University (09.25.2024). All participants signed a written informed consent, having received full information about this study. All research subjects were guaranteed anonymity.

Prenatal screening of the risk of preeclampsia was conducted in accordance with national standards and clinical protocols of the Republic of Kazakhstan [19, 20]. Screening was performed at gestation from 11 to 13 weeks and 6 days, and risk calculation was carried out using a highly sensitive fluorescent label using automated equipment and software AutoDELFIA, LifeCycle.

Preeclampsia was diagnosed as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) occurring after 20 weeks of gestation in a previously normotensive woman and accompanied by one or more of the following criteria: proteinuria (more than 300 mg in 24-hour urine or urine protein to creatinine ratio ≥ 0.3 mg/dL), maternal organ dysfunction (including liver, lung, kidney, or central nervous system disease), hematologic abnormalities, or dysfunction of the uteroplacental system [21, 22].

Inclusion criteria are as follows, written informed consent, delivery at a gestation period of more than 33 weeks, prenatal screening performed during pregnancy from 11 to 13 weeks and 6 days, risk factors for preeclampsia in the anamnesis, delivery of the placenta for histological examination.

Exclusion criteria are as follows, chronic arterial hypertension, rhesus-conflict pregnancy, mother's HIV infection, infection with SARS-CoV-2 during pregnancy, age less than 18 years, multiple pregnancies, intrauterine fetal growth restriction, congenital pathologies of the fetus.

The concomitant pathology of the mother included cardiovascular, endocrine, metabolic, autoimmune diseases, as well as chronic kidney diseases.

The umbilical cord pathology was determined by the presence of one or more of the following signs:
- anomalies of umbilical cord attachment: marginal or velamentous attachment;
- abnormal umbilical cord length: excessively long umbilical cord (more than 70 cm) or short umbilical cord (less than 35 cm);
- umbilical cord entanglement around parts of the fetus's body (single and multiple entanglements);
- anomalies in the number of vessels (single umbilical artery);
- true umbilical cord knot.

Four groups were identified as follows,

Group 1 – high risk of preeclampsia with umbilical cord pathology,

Group 2 – high risk of preeclampsia without umbilical cord pathology,

Group 3 – low risk of preeclampsia with umbilical cord pathology,

Group 4 – low risk of preeclampsia without umbilical cord pathology.

## Collection of clinical data

Clinical data were collected about patients from the patient medical records using software in an integrated health information system.

At the first prenatal visit, detailed demographic and clinical profiles were recorded for all participants. Key parameters included maternal age, pre-pregnancy body mass index (BMI), obstetric and medical history, gestational age, and blood pressure readings. For participants receiving prophylactic acetylsalicylic acid, data on the dosage and duration of therapy were collected from subsequent prenatal visits. In addition, information on pregnancy complications, gestational age at delivery, in particular, Apgar scores at 1 and 5 minutes postpartum were extracted from medical records.

The medical data were anonymized by coding each subject using a unique identifier.

Clinical data of women, and characteristics of the course of pregnancy of women in the study groups, including information on anthropometric indicators, medical history and concomitant diseases are presented in Table 1.

## Table 1 — Clinical characteristics of pregnancy, maternal and fetal/newborn outcomes

| Parameters | | Risk of preeclampsia | | p-value |
|---|---|---|---|---|
| | | high n = 21 | low n = 6 3 | |
| Mother's age, years | Me (Q1-Q3) | 38 ( 35-40 ) | 30 (26-34.5) | **0 .0001** |
| Gestation period according to ultrasound, weeks | Me (Q1-Q3) | 35 ( 34-36 ) | 35 ( 34-36 ) | - |
| Parity , n (%) | primiparous | 15 (71.4) | 18 (28.6) | **0.002** |
| | multiparous | 6 (28.6) | 45 (71.4) | |
| Body mass index , n (%) | underweight | 1 (4.8) | 7 (11.1) | |
| | normal weight | 5 (23.8) | 45 (71.4) | |
| | overweight | 7 (33.3) | 7 (11.1) | |
| | obesity | 8 (38.1) | 4 (6.4) | |
| Chronic diseases 1 , n (%) | Yes | 5 (23.8) | 9 (14.3) | 0.311 |
| | No | 16 (76.2) | 54 (85.7) | |
| Bad habits , n (%) | Yes | 1 (4.8) | 1 (1.6) | 0.409 |
| | No | 20 (95.2) | 62 (98.4) | |
| FGR , n (%) | Yes | - | - | - |
| | No | 21 (100.0) | 63 (100.0) | |
| Macrosomia , n (%) | Yes | - | 2 (3.2) | 0.409 |
| | No | 21 (100.0) | 61 (96.8) | |
| Antenatal fetal death , n (%) | Yes | - | - | - |
| | No | 21 (100.0) | 63 (100.0) | |
| Child's gender , n (%) | female | 10 (47.6) | 31 (49.2) | 0.900 |
| | male | 11 (52.4) | 32 (50.8) | |
| Apgar score (1 min) | Me (Q1-Q3) | 7 (7-8) | 8 (7-9) | 0.087 |
| Apgar score (5 min) | Me (Q1-Q3) | 8 (8-9) | 9 (8-9) | 0.122 |
| Placenta weight (g) | Me (Q1-Q3) | 344 (313-408) | 389 (345-427.5) | **0.033** |
| Pathology of the umbilical cord | Yes | 8 ( 38 . 1 ) | 19 (30.2) | 0.286 |
| | No | 13 (61.9) | 44 (69.8) | |
| Taking aspirin | Yes | 20 (95.2) | - | **0 .0001** |
| | No | 1 (4.8) | 63 (100.0) | |
| Preeclampsia | Yes | 2 (9.5) | 3 (4.8) | 0.425 |
| | No | 19 (90.5) | 60 (95.2) | |

*1 – diabetes type 1 or 2, obesity grade 2-3 , kidney disease or autoimmune diseases.*
*p <0.05- value indicating statistically significant differences between groups , calculated using the chi - square test , Fisher's exact test or Mann-Whitney U test, Student's t-test, depending on the data*

## Selection of placental tissues

Placental tissue collection was carried out in accordance with the internal policy of the organization, national and international recommendations [23].

Each placenta was transported for histological examination after the birth. If immediate analysis was possible, the sample was promptly transferred to the laboratory for excision. If immediate analysis was not possible, placentas were stored at 4°C in a refrigerator. Stored placentas were transported to the laboratory under controlled temperature conditions until the 48-hour storage period had expired. All stages, including collection, storage, transport, and laboratory processing were carefully documented to ensure transparency, compliance with safety standards, and adherence to protocol.

## Histological examination of the placenta

Placental tissue samples were fixed for 24 hours in 10% formalin at 4°C, then subjected to standard processing, including dehydration in increasing concentrations of alcohols and embedding in paraffin. Sections of 3–4 μm thickness

were deparaffinized and stained for histological examination. Histological sections were stained in Mayer's hematoxylin, then washed with water and stained with eosin according to a standard protocol.

To visualize and identify collagen fibers in the vessel wall, Masson trichrome staining was used with a commercial kit (Bio-Optica, Italy). Collagen fibers were stained dark blue and blue, contrasting with other tissue components, muscle fibers were stained red, and cell nuclei were stained black and dark brown.

## Histomorphometric analysis

Histomorphometric analysis of placental vessels was conducted according to the methodology described in a previously published work [24]. Histological identification of chorionic villi was carried out by the following this work [25].

Criteria for excluding sections:
- lack of vessel lumen;
- poorly distinguishable boundaries of the vessel walls;
- obliquely cut arteries (the ratio of perpendicular diameters is more than 1.3).

Histomorphometric examination of 20 arterioles was performed in each zone.

Digital images of histological sections were acquired using an EX30 microscope in ImageJ software. All equipment was calibrated to convert pixel size to micrometers before analysis. All measurements were performed manually by one trained, highly qualified investigator who was blinded to pregnancy outcomes, patient medical history, and placental risk group classification. The measured values were entered into a Microsoft Excel data spreadsheet for subsequent analysis.

Morphometric measurements were performed manually in software after calibration. For each vessel was measured:
- inner and outer diameters;
- the thickness of the placental arterioles, calculated as half the difference between the outer and inner vessel diameter.

Each measurement was taken in four standardized directions corresponding to 3, 6, 9, and 12 o'clock on a standard clock face. The values obtained in each direction were recorded and the arithmetic average of these measurements was calculated to obtain the wall thickness value for each vessel.

All morphometric measurements were performed manually by a single researcher who did not have access to information about pregnancy outcomes, the clinical history of patients, or the group to which each of the placentas belonged (high or low risk group).

## Statistical analysis

Data analysis and visualization were performed using IBM SPSS Statistics v.22 program (StatSoft, Inc., USA).

At the preliminary data analysis stage, the normality of distribution of quantitative variables was assessed using the Shapiro-Wilk test. The Levene test was utilized to test the uniformity of the variances. For quantitative traits with normal distribution, the mean and standard deviation were calculated. The sets of quantitative indicators, with a different distribution from the normal one, were presented as a median (Me) and first and third quartiles (Q1-Q3). Nominal data is presented in the form of absolute values and percentages. To compare the distribution frequencies by qualitative characteristics between groups, the statistical chi-square criterion with the Yates correction or the exact Fisher criterion was used. To compare groups with data without pattern of normal distribution, we used the Mann-Whitney U-test. To reduce the risk of type I errors in multiple comparisons, we use the Bonferroni correction. In the case of normal data distribution, comparisons between groups were made using Student's t-test.

## Results

Socio-demographic characteristics medical history data of women, clinical characteristics of pregnancies and newborns of high and low risk groups of preeclampsia are presented in Table 1.

The table data show that in the group of women with a high risk of preeclampsia, the age of women was higher (Me 38 years vs. 30 years, $p = 0.0001$), and the incidence of obesity was higher (38.1% vs. 6.4%). Also, a woman with a high risk of preeclampsia showed a decrease in placental mass (Me 344 g vs. 389 g, $p = 0.033$). Chronic diseases were more common in women at high risk of preeclampsia, but the differences did not reach statistical significance.

***Analysis of the wall thickness of the placenta vessels***

The results of measurements of the arterioles the placenta of the research groups are presented in Table 2 and Figure 1.

In the group with a high risk of preeclampsia and umbilical cord pathology, for proximal arterioles the median wall thickness was 29.1 (24.1 – 37.1)µm, the standard deviation is 11.4µm, the minimum value is 12.4µm, the maximum value is 47.2µm. For distal arterioles, the median wall thickness was 7.8(6.4 – 8.1) µm, the standard deviation was 3.4µm, the minimum value was 4.9µm, the maximum was 12.9µm.

In the group with a high risk of preeclampsia without umbilical cord pathology, for proximal arterioles the median wall thickness was 8.7(6.1–9.2)µm, the standard deviation was 11.0µm, the minimum value was 3.1µm, the maximum value was 43.1µm. For distal arterioles, the median wall thickness was 8.1(6.3 – 8.8)µm, the standard deviation was 1.7µm, the minimum value was 5.2µm, the maximum was 11.3µm.



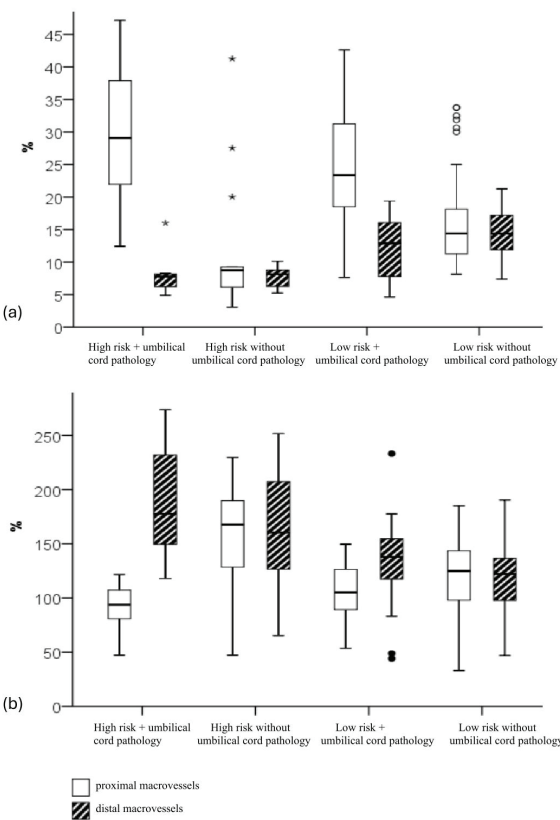**Figure 1** – Wall thickness and diameter of proximal and distal placental arterioles a. thickness of the walls of placental macrovessels, µm b. lumen diameter, µm

| Parameters, µm | | Group 1 | Group 2 | Group 3 | Group 4 | Groups with differences | p-value |
|---|---|---|---|---|---|---|---|
| | | High risk + umbilical cord pathology | High risk without umbilical cord pathology | Low risk + umbilical cord pathology | Low risk without umbilical cord pathology | | |
| | | n = 8 | n = 1 3 | n = 19 | n = 44 | | |
| **Proximal macrovessels** | | | | | | | |
| wall thickness | Median | 29.1 | 8.7 | 23.4 | 14.4 | 1 and 2, 1 and 4, 2 and 3, 3 and 4 | 0.0025 , 0.00 36 , 0.00 45 , 0.0 028 |
| | 25–75% | 24.1 – 37.1 | 6.1 – 9.2 | 18.5 – 31.3 | 11.6 – 17.8 | | |
| internal diameter | Median | 93.7 | 167.7 | 105.2 | 124.9 | 1 and 2, 2 and 3, 2 and 4, | <.001, 0.0016 , 0.0047 |
| | 25–75% | 82.7 – 105.5 | 128.4 – 189.7 | 89.2 – 126.4 | 98.4 – 142.6 | | |
| **Distal macrovessels** | | | | | | | |
| wall thickness | Median | 7.8 | 8.1 | 12.9 | 14.4 | 1 and 4, 2 and 4 | 0.00 4, 0.007 |
| | 25–75% | 6.4 – 8.1 | 6.3 – 8.8 | 7.8 – 16.1 | 11.9 – 17.0 | | |
| internal diameter | Median | 177.7 | 160.4 | 137.9 | 122.0 | 1 and 4, 2 and 4 | 0.0 04 , 0.00 47 |
| | 25–75% | 152.7 – 230.0 | 126.6 – 207.3 | 117.5 – 154.7 | 98.2 – 136.0 | | |

Table 2 — Morphometric measurements of proximal and distal vessels in placentas with different risks of preeclampsia and umbilical cord pathology

In the group with a low risk of preeclampsia and umbilical cord pathology, for proximal arterioles the median wall thickness was 23.4 (18.5 – 31.3)µm, the standard deviation is 9.6µm, the minimum value is 7.6µm, the maximum value is 42.6µm. For distal arterioles, the median wall thickness was 12.9(7.8 – 16.1)µm, the standard deviation was 5.0µm, the minimum value was 4.6µm, the maximum was 25.3µm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the wall thickness of the proximal arterioles was 14.4 (11.6 – 17.8)µm, the standard deviation was 7.5µm, the minimum value was 8.1µm, the maximum value was 33.8µm. For distal arterioles, the median wall thickness was 14.4(11.9 – 17.0)µm, the standard deviation was 3.7µm, the minimum value was 7.4µm, the maximum was 25.4µm.

### *Analysis of the lumen diameter of placental vessels*

In the group with a high risk of preeclampsia and umbilical cord pathology, the diameter of the proximal arterioles was 93.7(82.7 – 105.5)µm, the standard deviation was 27 µm, the minimum value was 47.2µm, the maximum value was 121.6µm. For distal arterioles, the median diameter of the vessels was 177.7(152.7 – 230.0)µm, the standard deviation was 53 µm, the minimum value was 117.9µm, the maximum was 273.7µm.

In the group with a high risk of preeclampsia without umbilical cord pathology, the diameter of the proximal arterioles was 167.7(128.4 – 189.7)µm, the standard deviation was 57.3µm, the minimum value was 47.1µm, the maximum value was 229.6µm. For distal arterioles, the median diameter was 160.4(126.6 – 207.3)µm, the standard deviation was 57.3µm, the minimum value was 65.3µm, the maximum was 251.7µm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the median diameter of the proximal arterioles was 105.2(89.2 – 126.4)µm, the standard deviation was 22.6µm, the minimum value was 53.6µm, the maximum value was 149.5µm. For distal arterioles, the median diameter was 137.9(117.5 – 154.7)µm, the standard deviation was 43.7µm, the minimum value was 44 µm, the maximum was 233.2µm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the diameter of the proximal arterioles was 124.9(98.4 – 142.6)µm, the standard deviation was 27.5µm, the minimum value was 33 µm, the maximum value was 185 µm. For distal arterioles, the median wall thickness was 122.0(98.2 – 136.0)µm, the standard deviation was 32 µm, the minimum value was 46.9µm, the maximum was 190.4µm (Table 2).

## Discussion

The present research presents a histomorphometric analysis of the placental vascular network with a different risk of preeclampsia based on the results of screening in the first trimester and the presence/absence of umbilical cord pathologies.

The obtained data show significant differences in the histomorphometric parameters of placental vessels between the study groups. In the high-risk group of preeclampsia without umbilical cord pathology, there was a significant thinning of the arteriolar wall of the proximal placenta with dilation of their lumen compared with low-risk groups (p<0.001). These changes may indicate compensatory vascular dilation aimed at maintaining placental perfusion. However, a decrease in vascular wall thickness indicates progressive structural changes that reduce the ability to adapt, accompanied by impaired vascular tone and elasticity. We believe that the observed diffuse dilation of blood vessels in combination with thinning of their walls indicates a violation of the normal process of vascular remodeling in which a decrease in the thickness of the muscular layer of blood vessels and dilation of their lumen may be the result of underdevelopment of the vascular wall in early pregnancy. This is confirmed by the systemic nature of the lesion, affecting both the proximal and distal parts of the placental vascular network. The results obtained are consistent with our previously published results [24].

In the high-risk group with umbilical cord pathology, signs of proximal fibromuscular sclerosis were observed, accompanied by vascular obliteration and compensatory dilation of distal vessels. Such changes indicate a prolonged exposure to a pathological factor, leading to a progressive loss of vascular adaptation. The revealed signs of ectatic macroangiopathy and proximal sclerosis expand the understanding of the systemic nature of damage to the placental vasculature in preeclampsia. Umbilical cord pathology associated with proximal fibromuscular sclerosis may act as an additional risk factor for vascular remodeling of the placenta. This confirms the hypothesis about the effects of systemic and local factors that enhance vascular dysfunction.

We believe that these structural changes reflect long-term and repeated exposure to a pathological factor that leads to disruption of the vascular remodeling process. This in turn causes obliteration of proximal vessels, limiting blood flow and compensatory dilation of distal vessels in order to maintain perfusion. However, such a compensatory mechanism may be insufficient to ensure blood flow, contributing to the development of placental hypoperfusion, chronic tissue ischemia and their dysfunction. These changes highlight the importance of studying the relationship between pathological vascular remodeling and ischemic processes in the placenta, as well as the impact on maternal and fetal health outcomes.

On the other hand, the observed structural changes in the placenta suggest similar pathological processes in the fetal vascular system. The morphological and functional relationship between the vessels of the placenta and the fetus indicates the likelihood of the fetus developing a predisposition to vascular pathologies, such as hypertension and cardiovascular diseases in the postnatal period.

The data of this research confirm that pathological remodeling of placental vessels is a systemic process that can be detected even in women without obvious clinical symptoms of preeclampsia, but with a high risk of preeclampsia. This makes it possible to consider a high risk during screening, even without subsequent clinical manifestation, as a possible indicator of ischemic processes in the placenta due to progressive vascular remodeling. However, this assumption requires further research.

Limitations of the research include fluctuations in data, which may be due to a small number of cases in subgroups, the single-center nature of the research, as well as the lack of long-term follow-up to assess the impact of identified structural changes in placental vessels on the health of the newborn and mother in the long term. Conducting multicenter researches with an increased sample will increase the representativeness and validity of the results. Further research in this area will contribute to the development of a personalized approach in obstetrics and pediatrics, clarifying the prognostic significance of the identified placental macrovascular changes and their integration into clinical practice for the prevention of long-term adverse effects for both mother and child.

## Conclusion

Significant differences in placental macrovascular remodeling were found in women at high risk of preeclampsia, including thinning of the vascular wall and dilation of the vascular lumen with thinning of the muscular layer in the vascular wall. These changes indicate a disruption of normal vascular remodeling processes, leading to a decrease in the adaptive potential of the placenta, limitation of its ability to respond to physiological and pathological changes, and an increase in vascular resistance. These changes may present the different temporal and spatial pattern of the action of pathological factors that limit the adaptive capabilities of blood vessels. These results emphasize the need for further research to clarify the mechanisms of development of pathological remodeling of placental vessels and their impact on the health of mother and child, which may contribute to the development of personalized approaches to the treatment of pregnancy complications.

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# Effect of Cilostazol on Myocardial Histomorphological Changes in Ischemia-Reperfusion Injury

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**Abstract**

Introduction: Protecting the myocardium from acute ischemia-reperfusion (IR) injuries during open-heart surgeries is vital for improving outcomes. This study aimed to compare the effects of cilostazol on the nature and extent of histomorphological changes in the myocardium in a rat IR injury model.

**Methods:** Wistar Albino rats were divided into three groups of eight. The Sham group underwent no coronary occlusion. In the IR group, the left anterior descending artery(LAD) was compressed for 45 minutes to induce acute ischemia, followed by 180 minutes of reperfusion. In the cilostazol group, 20 mg/kg/day cilostazol was administered orally for two weeks before IR induction. Rats were euthanized, and 3 mm myocardial slices were prepared for histomorphological analysis. Changes were assessed at four levels, and total, damaged, and necrotic areas were measured planimetrically. Comparisons were made using Student's t-test, with $P<0.05$ considered significant.

**Results:** Pathohistological changes in the IR and cilostazol groups were classified as "mild" in 37.5%/53.1% (P=0.008) and "moderate" in 50.0%/43.8% (P<0.05) respectively. "Severe" changes occurred in 12.5% of IR and 3.1% of cilostazol cases (P=0.006). Ischemic and necrotic areas in the IR group ($10.60\pm1.33$ mm² and $5.76\pm0.62$ mm²) were significantly reduced in the cilostazol group ($6.94\pm0.73$ mm² and $4.04\pm0.58$ mm², P<<0.01).

**Conclusion:** Cilostazol at 20 mg/kg/day for two weeks before IR injury significantly reduced myocardial ischemic and necrotic areas, showed positive results in histopathological examination demonstrating a strong cardioprotective effect.

**Keywords:** cilostazol, ischaemia-reperfusion injury, cardiac surgery.

## Introduction

Investigating the pathogenetic mechanisms of myocardial ischemia and reperfusion is crucial for developing diagnostic and therapeutic strategies to protect the myocardium [1–5]. Acute myocardial ischemia is characterized by depletion of high-energy compounds, disruption of electrolyte exchange, and anaerobic metabolism, leading to decreased oxygen ($O_2$) and ATP levels, acidosis, and cellular damage [6–10]. This causes cellular edema, increased vascular permeability, inflammation, and leukocyte infiltration. While cardiomyocyte contractility may recover within 15 minutes of ischemia, irreversible damage can begin after 20 minutes, depending on collateral blood supply [8].

The "no-reflow" phenomenon, described by Kloner et al. in 1974, shows that restoring blood flow after critical ischemia may not restore microcirculation or cell viability, especially when damage exceeds 40% of the left ventricle, leading to cardiogenic shock and arrhythmias [11].

Cilostazol (FK506), with its high lipophilic properties, can rapidly enter cells and inhibit the calcineurin-calmodulin (CaN–CaM) complex, reducing inflammation, platelet activation, and neutrophil adhesion during ischemia-reperfusion injury [12]. Given these effects, we hypothesized that cilostazol might offer protective benefits in the rat ischemia-reperfusion model, motivating this study.

## Methods

The study was conducted on 24 Wistar Albino rats as a single-blind, prospective scientific investigation using an in vivo ischemia-reperfusion (IR) injury model. Animals were randomized into Sham and comparison groups at baseline. This research adhered to the "Principles of Laboratory Animal Care" by the National Institutes of Health (1996) and received approval from the Gulhane Military Medical Academy Ethics Committee (November 2008 – 08/89 K-R).

Experiments were conducted under endotracheal isoflurane anesthesia. Thoracotomy and pericardiotomy were performed, and the left anterior descending coronary artery (LAD) was located immediately following the coronary artery exit (D1) (Figure 1). A 5/0 Vicryl thread was passed under the LAD, which was clamped to induce coronary occlusion, resulting in ischemia in the corresponding myocardial region. The development of ischemia was confirmed by ST segment changes, myocardial color alteration on ECG, decreased arterial blood pressure, and visibly weakened contraction in the LAD region (hypokinesia). According to protocol, animals were randomized by multiple parameters into three groups, each consisting of eight rats:

• Sham Group: All surgical manipulations were performed, but ischemia was not induced.

• IR Group: After acute ischemia was induced by clamping the LAD for 45 minutes, occlusion was removed, and reperfusion was applied for 180 minutes to model IR injury.

• Cilostazol Group: Animals received 20 mg/kg/day of cilostazol (Pletal), dissolved in 30% dimethyl sulfoxide, administered via gastric gavage each morning for two weeks prior to IR injury induction.
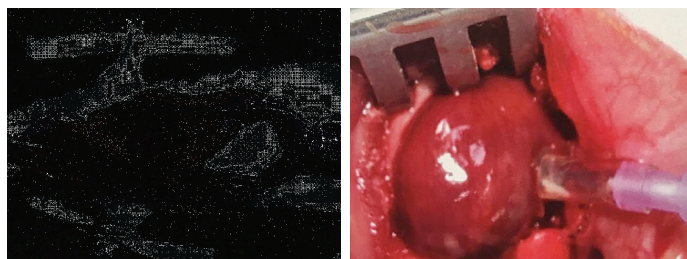


**Figure 1** – A) Rat After Tracheostomy and Thoracotomy B) Rat Heart After LAD Occlusion with a Snare

The IR injury model employed is widely accepted and continues to be commonly used [3, 13–15]. Analgesia was maintained with isoflurane anesthesia during the procedure, with rats connected to a mechanical ventilator (Datex-Ohmeda Excell 410) under artificial ventilation. Respiratory parameters were adjusted to norms (respiratory rate of 60 per minute, minute volume of 1.5 ml per 150 grams of body weight, and 40% oxygen concentration). Anesthesia adequacy was monitored continuously through ECG, arterial pressure, $SO_2$, and body temperature. The methylene blue test was performed to confirm the IR model and to delineate the ischemic area. At the end of reperfusion, the LAD was re-occluded, and 1.5 ml of 2% methylene blue was injected into the right atrium, allowing reperfusion for three minutes. During this procedure, the non-ischemic myocardium stained dark blue, while the ischemic area retained its color, indicating successful IR model creation.

After the heart was excised and frozen at -30°C for 15 minutes, it was sectioned into 4 transverse slices, each 2 mm thick, from the LAD ligature region to the left ventricular apex. The slices were rinsed in a physiological solution, stained with Triphenyl tetrazolium chloride (TTC), fixed in 10% formalin, and sent to the pathology laboratory for histomorphological and planimetric analysis.

Twenty-four myocardial samples from each group were examined microscopically (Optika B-66, light microscope) for intratissue hemorrhages (hematomas), polymorphonuclear infiltration, edema, and necrosis (myolysis) of cardiomyocytes. Total, ischemic, and necrotic areas of each sample (in mm²) were measured using a computer-assisted planimetric program (Axio Vision Rel 4.7, Zeiss, Germany) at the GATA Histology and Embryology Laboratory.

Pathohistological changes were graded using the methodology of Şahin et al. (2021) [15], as follows:

• G0 (none): No pathological changes detected.

• G1 (mild): Myocardiocyte edema (smoky edema), hydropic degeneration, and localized cell necrosis.

• G2 (moderate): Myofibrillar disarray and focal necrosis.

• G3 (severe): Structural disarray, widespread myocardial necrosis, edema, and inflammatory cell infiltration.



**Figure 2** – Myocardial sections with no infarct area - A, minimally affected (cilostazol) - B, and those with extensive necrotic areas (IR group) - C (from left to right).

Statistical analysis was conducted using Student's t-test in MS Excel 2003 and SPSS for Windows Version 15.0 (SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant at P<0.05.

## Results

First, the histomorphological examination results of myocardial samples from animals in the comparison groups were analyzed (Table 1). As expected, there were no signs of tissue damage in the samples from animals that did not undergo coronary occlusion. However, in all samples from the other groups, we observed different levels of damage caused by ischemia-reperfusion, indicating that the condition had a significant impact on the tissues (P<0.001).

In the IR group, histomorphological changes were observed as mild in 12 samples (37.5%), moderate in 16 samples (50%), and severe in 4 samples (12.5%). In contrast, more than half of the samples (17 out of 32, or 53.1%) from rats treated with Cilostazol showed only mild changes (P1=0.008). Additionally, 43.8% (14 samples) displayed moderate changes (P<0.05), while severe changes were seen in only 1 sample (3.1%) (P1=0.006).

**Table 1**     Classification of changes detected in myocardial samples taken from comparison groups according to degree*.

| Comparison groups | Manifestation rates of changes | | | |
|---|---|---|---|---|
| | No (G-0) | Weak (G-1) | Moderate (G-2) | Severe (G-3) |
| IR model (n=32) | 0 (0.0%) | 12 (37.5%) P<0.001 | 16 (50.0%) P<0.001 | 4 (12.5%) P<0.001 |
| Cilostazol (n=32) | 0 (0.0%) | 17 (53.1%) P<0.001 P1=0.008 | 14 (43.8%) P<0.001 P1<0.05 | 1 (3.1%) P<0.001 P1=0.006 |

*Note: \*4 myocardial slices (samples) were prepared from each heart. P – compared with Sham group, P1 – IR group.*

**Table 2**     Area (mm²) of total, damaged and necrotic areas in myocardial samples from Sham, IR and Cilostazol groups.

| Indicators | Sham qrup (n=32) | IR group (n=32) | Cilostazol group (n=32) | Statistical indicators |
|---|---|---|---|---|
| Total area (mm2) | 74.81±6.91 | 69.76±5.73 | 72.99±5.83 | P=0.663 |
| Damaged area (mm2) | No | 10.60±1.33 | 5.76±0.62 | P<0.01 |
| Area of necrosis (mm2) | No | 6.94±0.73 | 4.04±0.58 | P<0.01 |

Using the planimetric method, we measured the total, damaged, and necrotic areas in myocardial sections from all three groups. The results were then compared and analyzed. In the Sham group, the total area of the section was 74.81±6.91 mm², and no ischemic or necrotic areas were observed (Table 2).
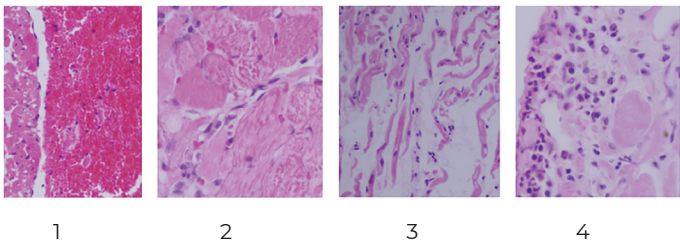


**Figure 3** – Hematoxylin and eosin staining of tissues under a light microscope (Optika B-66)."
1.     Hemorrhagic areas expanding the muscle fibers between myocardial fibers (X200 H&E)
2.     Mild myocytolysis (X400 H&E)
3.     Myocardial edema (X200 H&E) (separation and dilation of muscle fibers is noticeable)
4.     Polymorphonuclear leukocyte (PMNL) infiltration (X20 H&E) (neutrophil infiltrating between muscle fibers in the subepicardial area)

Here, we see that the dimensions of the damage and necrosis areas detected in all myocardial samples taken from rats with the IR model were 10.60±1.33 and 5.76±0.62 mm2, respectively (Table 2). Beside of that, we observed that a similar process occurred in the planimetric measurements made in animals given cilostazol, but these areas were significantly smaller than in the IR group (6.94±0.73 and 4.04±0.58 mm2) (P<0.001). The fact that the ischemia and necrosis area dimensions in the cilostazol group were significantly smaller than the indicators in the IR group (P<0.01) can only be explained by the fact that this drug has a sufficiently strong cardioprotective effect.

The examination of the ratios between the total, damaged and necrotic areas of the myocardial samples taken from the IR and Cilostazol groups and the comparative analysis of the results confirmed this idea once again. For this, the ratios of the damaged area to the total area, the necrosis area to the total area and the necrosis area to the damaged area were calculated (Table 3). As can be seen from the table, it is worth noting that the size of the areas exposed to ischemic damage in the rats in the IR group was 15.19±1.49% of the total area, while this ratio was 2 times less in the Cilostazol group (7.89±0.82%) (P<0.001).

Similar results were also found when calculating the ratio of the size of the necrotic areas to the total area. Thus, while this ratio was 10.41±1.20% in IR model rats, it was significantly lower in cilostazol-treated animals - 5.67±1.93% (P<0.001). Contrary to the above, no reliable difference was found between the groups according to the ratio of the necrotic area to the ischemic damaged area - 65.47±3.12% and 70.14±4.34% (P>0.05).

## Discussion

The main finding of this study is the marked reduction in the extent of myocardial injury in the Cilostazol-treated group. More than half of the myocardial samples from Cilostazol-treated rats showed only mild changes (53.1%), compared to the IR group, where the majority of samples displayed moderate to severe damage.

Based on cilostazol's cardioprotective effects in the IR model and its ability to reduce infarct size, it is believed that the drug increases interstitial ATP and nitric oxide (NOx) levels, opens $K^+$-ATP channels, accelerates superoxide dismutase (SOD) synthesis, and inhibits lipid peroxidation [16–19, 21]. Recent experimental studies (2019–2023) have shown convincingly that cilostazol raises cAMP levels in myocardial cells, enhances interstitial areas and cell viability, promotes angiogenesis, and positively affects the inflammatory response in animals with IR damage models. Notably, cell death (apoptosis) and fibrosis are significantly slowed [14, 15, 19]. Our research findings from the myocardial IR damage model fully align with these conclusions. Specifically, histomorphological changes in myocardial samples from the IR group showed "moderate" and "severe" gradings in 50.0% and 12.5% of samples, respectively, while these rates decreased to 43.8% (P1<0.05) and 3.1% (P1=0.006) in the cilostazol group, suggesting that cilostazol effectively protects the myocardium from ischemia-reperfusion injury.

As expected, myocardial samples from the Sham group showed no signs of tissue damage, confirming the validity of our experimental model. In contrast, myocardial samples from the IR group displayed varying degrees of ischemic damage, with 37.5% of the samples showing mild changes, 50% showing moderate changes, and 12.5% showing severe damage.

In a similar study on rats with an IR model [20], cilostazol and clopidogrel were shown to exert strong antioxidant and cardioprotective effects, especially when used in combination, a finding that aligns with our results. Another study by Japanese scientists demonstrated that intravenous administration of 1 mg/kg and 5 mg/kg cilostazol in two groups of rabbits, 5 minutes before 30 minutes of anoxic ischemia and 30 minutes of reperfusion, significantly reduced the infarct size, with a dose-dependent increase in effect [3]. Our comparative planimetric examination results further validated these findings: in myocardial samples from cilostazol-treated animals, the ischemia-reperfusion damage area was 4.66 mm², and the necrotic area was 2.52 mm² smaller than those in the IR group. This provides solid evidence of cilostazol's potent cardioprotective effect and infarct-reducing capacity.

These findings confirm the results of another research group, which observed significant infarct reduction in myocardial samples from rats treated with cilostazol before IR model establishment [22].

## Conclusion

Administering 20 mg/kg/day of cilostazol to rats for two weeks prior to establishing the myocardial IR injury model significantly reduces the severity of histomorphological changes and the size of ischemic and necrotic areas.

Cilostazol is can be effective for use in "open heart" surgeries to protect the myocardium from acute ischemia-reperfusion injury. Additional research is required to further explore this topic.

## Limitations

This study involved a small sample size of 24 male Wistar Albino rats, and larger samples could provide more robust and generalizable results. Cilostazol was administered at a fixed dose, and exploring different dosages or regimens may offer a better understanding of its effects. Finally, while the findings are valuable in an experimental setting, further clinical trials in humans are needed to confirm cilostazol's therapeutic potential in patients with myocardial ischemia-reperfusion injury.

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# Are Women of Reproductive Age Aware of Gynecological Cancers?

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## Abstract

**Objective:** This descriptive study aimed to determine the awareness levels of women of reproductive age regarding gynecological cancers.

**Methods:** The study was conducted with 379 women aged between 15 and 49 registered at two separate Family Health Centers in Tekirdağ city center between May 2022 and April 2023. Data were collected using the "Gynecological Cancers Awareness Scale" and an "Introductory Information Form." Descriptive statistics including number, minimum, maximum, percentage, mean, and standard deviation were provided using the SPSS 21 package program. Shapiro-Wilk normality test, Independent Sample T-test, One Way ANOVA, Pearson correlation test, and Bonferroni test were used for data analysis. A statistical significance level of p <0.05 was accepted.

**Results:** The mean age of the women in the study was 34 ±11 years, with 61.5% being married. The average Gynecological Cancers Awareness Scale (GCAS) score was 157.1 ±17.1 (range 106-205). Sub-dimension scores were: "Early Diagnosis and Information Awareness" 17.1 ±2.3 (range 10-20), "Risk Awareness" 28.4 ±5.3 (range 13-45), "Prevention Awareness" 22.4 ±3.4 (range 12-30), and "Routine Checks and Serious Illness Perception" 89.0 ±11.9 (range 45-110).

In the study, 48.5% of the women knew about early diagnosis methods for gynecological cancers, and 76% were aware of the Cancer Early Diagnosis Screening and Education Center (KETEM). Women who were aware of risky health behaviors and cancer symptoms had higher awareness levels (p <0.05). There was no significant difference between the number of pregnancies and births and awareness levels (p >0.05).

**Conclusion:** The result shows that women have a moderate level of awareness about gynecological cancers; however, their knowledge of gynecological cancer symptoms and awareness of risky health behaviors is higher. Additionally, more than half of the participants (60.7%) have never had a gynecological examination.

**Keywords:** Gynecological cancer,reproductive age women, awareness levels, nurse.

## Introduction

Cancer stands as one of the most critical health challenges globally in today's world. The high mortality and morbidity rates of cancer cases today, along with the long duration and cost of treatment, emphasize the importance of cancer cases. Among the leading causes of death, lung cancer is the most prevalent among men, whereas breast cancer is the most common among women. When gynecological cancer types are ranked according to the number of new cases, cervical cancer ranks fourth, and corpus uteri cancer ranks sixth. According to the Turkish Public Health Institute Cancer Statistics for 2018, common cancers in women of all age groups are reported as breast cancer 48.6%, uterine corpus cancer 11.1%, ovarian cancer 6.5%, and cervical cancer 4.2% [1–4]. Cancers have specific risk factors. Generally, the risk factors for gynecological cancers include age, socioeconomic status, and education level, genetic characteristics, having multiple births, unwanted pregnancies, intentionally induced abortions, inadequate health services during prenatal and postnatal periods, adolescent marriages, history of infections, sexually transmitted infections, personal and environmental factors. The most important factor

in reducing the frequency and mortality of cancers is early diagnosis practices considering the risk factors [3–6].

Body image, reproductive ability, and problems in sexual life in women adversely affect both themselves and family members. In this respect, gynecological cancers can lead to negative effects on women's lives in social, physical, psychological, and economic dimensions [7, 8].

Gynecological cancers, like other types of cancer, are preventable diseases with early diagnosis and treatment. Factors such as insufficient knowledge of women about cancer screening programs, financial constraints in accessing services, and low educational levels reduce the chances of early diagnosis and treatment [9,10]. However, significant decreases in mortality and morbidity rates of women are observed with the effective implementation of early diagnosis and treatment methods today [11,12]. Studies investigating the knowledge levels and awareness of women about gynecological cancers report that these rates are quite low [3, 13–16].

## Methods

**Type of Study:** This descriptive cross-sectional study was conducted between May 2022 and April 2023 to assess the awareness of gynecological cancers among women of reproductive age (15-49 years) at the 100th Year Family Health Center and Rüstem Paşa Family Health Center (FHC), which operate under the Tekirdağ Public Health Directorate in the Süleymanpaşa central district.The data were collected by face-to-face interviews with the researchers in the appropriate areas of the planned FHCs' Maternity-Puerperium follow-up rooms or in a different suitable area of the FHC.

Study Population/Sample: The study population included the 100th Year FHC and Rüstem Paşa FHC located in the Süleymanpaşa District of Tekirdağ Province. The sample consisted of 379 voluntary women aged 15-49 who visited the selected FHCs and consented to participate in the study.

## Data Collection

**Participant Information Form:** The questionnaire developed by the researchers includes questions regarding personal characteristics such as occupation, age, education level, income level, and chronic disease status, as well as questions related to the women's gynecological and obstetric history.

**Gynecological Cancers Awareness Scale (GCAS):** The sub-dimensions of the scale are as follows; "Awareness of Risks in Gynecological Cancers" (items 3-11) with a Cronbach's alpha value of 0.843, "Awareness of Prevention from Gynecological Cancers" (items 14-19) with a Cronbach's alpha value of 0.778. Although the scale is evaluated based on the total score, a minimum of 41 and a maximum of 205 points can be obtained from GCAS [17]. The Cronbach's alpha value of the scale is 0.944, and in this study, it is 0.918.

**Ethical Aspect of the Study:** Ethical approval for the implementation of the research was obtained from the Ethics Committee. (Date:15.06.2022, Decision: 170617). In addition, compliance with the "Helsinki Declaration" was ensured at every stage of the research.

**Data Analysis:** Descriptive statistics, including frequency, minimum, maximum, and standard deviation percentages, were provided. The Shapiro-Wilk normality test was used to assess data distribution. For normally distributed data, One-Way ANOVA, Pearson correlation analysis, and Independent Sample T-test were applied.

## Findings

The mean age of the women included in the study is $34.4\pm11.0$ years, with 74.4% having a university degree or higher education level, 61.5% being married, 62.0% having income matching their expenses, 84.2% belonging to a nuclear family, 72.3% not smoking, and 85.2% not consuming alcohol. The average duration of smoking among smokers is $14.5\pm9.4$ (min.1-max.38) years, with an average daily cigarette consumption of $12.7\pm8.0$ (min.1-max.40) cigarettes. 78.4% of women do not have any chronic illnesses, and 74.4% do not use regular medication. The participants' BMI average is $24.3\pm4.8$ (min.15.21-max.50.78), the average age of first menstruation is $13.5\pm2.9$ (min.8-max.43) years, the average age of first sexual intercourse is $23.2\pm4.0$ (min.13-max.37) years, the average number of pregnancies is $2.0\pm1.9$), and the average number of births is $1.6\pm0.7$). (Table 1).

| Table 1 | Distribution of Some Characteristics of Women (n=379) | |
|---|---|---|
| Characteristics | Number (n) | Percentage (%) |
| Average Age | 34.4±11.0 (min.16-max.64) | |
| Education Level | | |
| Primary School | 15 | 4.0 |
| Middle School | 11 | 2.9 |
| High School | 70 | 18.5 |
| University and above | 283 | 74.4 |
| Marital Status | | |
| Married | 233 | 61.5 |
| Single | 146 | 38.5 |
| Occupation | | |
| Homemaker | 90 | 23.7 |
| Worker | 40 | 10.6 |
| Civil Servant | 122 | 32.2 |
| Other | 127 | 33.5 |
| Income Level | | |
| Income less than expenses | 87 | 23.0 |
| Income equal to expenses | 237 | 62.0 |
| Income more than expenses | 57 | 15.0 |
| Family Type | | |
| Nuclear Family | 319 | 84.2 |
| Extended Family | 41 | 10.8 |
| Broken Family | 19 | 5.0 |
| Smoking Status | | |
| Yes | 105 | 27.7 |
| No | 274 | 72.3 |
| Average years of smoking* | 14.5±9.4 (min.1-max.38) | |
| Average number of cigarettes smoked per day* | 12.7±8.0 (min.1-max.40) | |
| Alcohol Consumption Status | | |
| Yes | 56 | 14.8 |
| No | 323 | 85.2 |
| Average years of alcohol consumption** | 8.8±6.6 (min.1-max.25) | |
| BMI Average | 24.3±4.8 (min.15.21-max.50.78) | |
| Having a Chronic Disease | | |
| Yes | 80 | 21.1 |
| No | 299 | 78.9 |
| Regular Use of Medication | | |
| Yes | 97 | 25.6 |
| No | 282 | 74.4 |
| Average age of first menstruation | 13.5±2.9 (min.8-max.43) | |
| Average age of first sexual intercourse*** | 23.2±4.0 (min.13-max.37) | |
| Average number of pregnancies**** | 2.0±1.9 (min.1-max.9) | |
| Average number of births***** | 1.6±0.7 (min.1-max.4) | |
| Total | 379 | 100 |

*averages are among smokers. ** averages are among alcohol consumers.*** averages are among those who have had sexual intercourse before, **** among those who have experienced pregnancy, ***** among those who have given birth.

The mean score of the GCAS scale for women is 157.1±17.1 (min.106-max.205), with a mean score of 17.1±2.3 for the "Early Diagnosis and Knowledge Awareness in Gynecological Cancers" subscale, a mean score of 28.4±5.3 for the "Awareness of Gynecological Cancer Risks" subscale, a mean score of 22.4±3.4 for the "Awareness of Preventing Gynecological Cancers" subscale, and a mean score of 89.0±11.9 for the "Awareness of Routine Checks and Perception of Serious Illness in Gynecological Cancers" subscale.

There is a statistically significant difference between the use of birth control pills and the total score of GCAS, as well as the awareness of prevention and awareness of routine checks and perception of serious illness sub-dimension scores (p<0.05). There were no statistically significant differences between the use of birth control pills and the subscale scores of early diagnosis and knowledge awareness, and awareness of cancer risks (p>0.05), as well as similar total and subscale scores of GCAS concerning menopausal status, hormone therapy, family history of gynecological cancer and HPV vaccination status (p>0.05).

Having a regular sexual life does not show statistically significant differences between the awareness of prevention, early diagnosis and knowledge, and awareness of cancer risks sub-dimensions concerning barriers to testing or examination, previous knowledge of gynecological cancer, knowledge of screening at FHC and Cancer Early Diagnosis Screening and Education Unit (CEDSEU) and the most recent PAP smear (p>0.05).

There is a statistically significant relationship between having a regular sexual life and the total score of GCAS, as well as the awareness of routine checks and perception of serious illness sub-dimensions concerning barriers to testing or examination, previous knowledge of gynecological cancer, knowledge of screening at FHC and CEDSEU and the most recent PAP smear test (p<0.05) (p<0.001). There is also a statistically significant relationship between knowing the factors affecting gynecological cancer and the total score of GCAS, as well as all sub-dimensions, and knowing the symptoms of gynecological cancer and the total score of GCAS, and all sub-dimension scores (p<0.001) (Table 2).

| Table 2 | Comparison of total and subscale scores of GCAS scale according to some gynecological-obstetric characteristics of the participants. (n=379) |

| Characteristics | Number (n) | Percentage (%) | GCAS Ort.±SS | Early Diagnosis and Knowledge AwarenessOrt.±SS | Cancer Risk AwarenessOrt.±SS | Awareness of Prevention Ort.±SS | Awareness of Routine Checkups and Perception of Serious Illness Ort.±SS |
|---|---|---|---|---|---|---|---|
| Usage of Birth Control Pills | | | | | | | |
| Yes | 107 | 28.2 | 160.4±15.1 | 17.5±2.1 | 28.4±5.5 | 24.0±3.1 | 91.5±10.0 |
| No | 272 | 71.8 | 155.7±17.7 | 17.0±2.3 | 28.4±5.3 | 22.2±3.5 | 88.0±12.5 |
| Test1/p | | | t=2.409 p=0.016 | t=1.769 p=0.078 | t=-0.118 p=906 | t=2.026 p=0.044 | t=2.621 p=0.009 |
| Entering Menopause | | | | | | | |
| Yes | 50 | 13.8 | 159.2±17.3 | 17.4±2.4 | 28.4±5.4 | 22.9±3.3 | 90.4±11.8 |
| No | 329 | 86.8 | 156.8±17.1 | 17.1±2.2 | 28.4±5.3 | 22.3±3.4 | 88.7±11.9 |
| Test1/p | | | t=0.925 p=0.356 | t=0.690 p=0.480 | t=-0.076 p=0.940 | t=1.077 p=0.282 | t=0.919 p=0.359 |
| Receiving Hormone Therapy | | | | | | | |
| Yes | 46 | 12.1 | 160.3±20.5 | 17.7±2.2 | 28.0±6.4 | 22.4±4.0 | 92.1±12.1 |
| No | 333 | 87.9 | 156.6±16.6 | 17.1±2.3 | 28.5±5.2 | 22.4±3.3 | 88.5±11.9 |
| Test1/p | | | t=1.358 p=0.175 | t=1.865 p=0.063 | t=-0.609 p=0.543 | t=-0.027 p=0.978 | t=1.878 p=0.061 |
| History of Sexually Transmitted Infections | | | | | | | |
| Yes | 10 | 2.6 | 153.9±12.2 | 16.8±2.9 | 26.9±4.5 | 22.2±2.6 | 88.0±9.9 |
| No | 369 | 97.4 | 157.2±17.3 | 17.2±2.2 | 28.4±5.4 | 22.4±3.4 | 89.0±12.0 |
| Test1/p | | | t=-0.600 p=549 | t=-0.541 p=0.589 | t=-0.925 p=0.356 | t=-0.250 p=0.803 | t=-0.270 p=0.787 |
| Having a Regular Sexual Life | | | | | | | |
| Yes | 220 | 58.0 | 159.0±16.8 | 17.0±2.3 | 28.5±5.4 | 22.7±3.4 | 90.6±11.1 |
| No | 159 | 42.0 | 154.4±17.3 | 17.3±2.2 | 28.3±5.3 | 22.0±3.4 | 86.7±17.7 |
| Test1/p | | | t=2.578 p=0.011 | t=-0.938 p=0.349 | t=0.466 p=0.641 | t=1.863 p=0.063 | t=3.146 p=0.002 |
| Attending Gynecological Examinations | | | | | | | |
| Never attended | 230 | 60.7 | 157.6±16.1 | 17.0±2.3 | 28.2±5.2 | 22.5±3.3 | 89.8±10.8 |
| Once a year or more frequently | 132 | 34.8 | 155.7±17.7 | 17.4±2.1 | 28.4±5.3 | 22.2±3.5 | 87.3±13.0 |
| Less often than once a year | 17 | 4.5 | 162.2±24.5 | 17.3±2.4 | 31.0±7.5 | 23.0±4.0 | 90.9±16.2 |
| Test2/p | | | t=1.479 p=0.229 | t=1.662 p=0.191 | t=2.083 p=0.126 | t=0.679 p=0.508 | t=2.067 p=0.128 |
| Barriers to Undergoing Gynecological Testing or Examination | | | | | | | |
| Disregard/ Perceived Unimportance (a) | 140 | 36.9 | 151.3±16.9 | 17.1±2.3 | 28.3±5.6 | 21.5±3.5 | 84.2±11.9 |

| | n | % | | | | | |
|---|---|---|---|---|---|---|---|
| Fear of Examination (b) | 72 | 19.0 | 163.2±17.5 | 17.2±2.4 | 28.1±6.0 | 23.3±3.4 | 94.4±11.3 |
| Sense of Privacy/ Embarrassment (c) | 101 | 26.6 | 160.3±15.8 | 17.2±2.3 | 28.6±4.9 | 23.1±3.1 | 91.2±10.8 |
| Physician's Gender (d) | 31 | 8.2 | 157.0±15.4 | 17.1±1.6 | 28.3±4.4 | 22.4±2.9 | 89.0±10.4 |
| Lack of Knowledge (e) | 35 | 9.2 | 158.5±16.1 | 17.0±2.2 | 28.9±5.1 | 22.2±3.7 | 90.3±10.9 |
| Test2/p | | | t=7.728 p=0.000 | t=0.90 p=0.986 | t=0.161 p=0.958 | t=4.780 p=0.001 | t=11.374 p=0.000 |
| Difference | | | a<b, a<c | | | a<b, a<c | a<b, a<c, a<e |
| **Awareness of Gynecological Cancer Information** | | | | | | | |
| Yes | 160 | 42.5 | 154.2±12.8 | 17.0±2.1 | 28.5±5.2 | 21.9±3.5 | 86.6±12.6 |
| No | 219 | 57.5 | 159.2±16.0 | 17.2±2.3 | 28.3±5.4 | 28.8±3.3 | 90.7±11.2 |
| Test1/p | | | t=-2.795 p=0.005 | t=-0.807 p=0.401 | t=0.335 p=0.738 | t=-2.457 p=0.014 | t=-3.306 p=0.001 |
| **Sources of Information Regarding Gynecological Cancer** | | | | | | | |
| Healthcare Personnel | 10 | 2.6 | ± | ± | ± | ± | ± |
| Television | 8 | 2.1 | ± | ± | ± | ± | ± |
| Internet | 9 | 2.4 | ± | ± | ± | ± | ± |
| Family/Friends | 7 | 1.8 | ± | ± | ± | ± | ± |
| Other | 5 | 1.3 | ± | ± | ± | ± | ± |
| Test2/p | | | t= p= | t= p= | t= p= | t= p= | t= p= |
| **Family History of Gynecological Cancer** | | | | | | | |
| Yes | 33 | 8.7 | 156.7±16.8 | 17.2±2.1 | 29.0±6.0 | 22.1±3.9 | 88.2±12.9 |
| No | 346 | 91.3 | 157.1±17.2 | 17.1±2.3 | 28.3±5.3 | 22.5±3.4 | 89.0±11.8 |
| Test1/p | | | t=-0.139 p=0.890 | t=0.136 p=0.892 | t=0.711 p=0.478 | t=-0.605 p=0.545 | t=-0.370 p=0.712 |
| **Awareness of Factors Affecting Gynecological Cancer** | | | | | | | |
| Yes | 190 | 50.1 | 163.5±17.0 | 17.7±2.2 | 29.8±5.7 | 23.4±3.3 | 92.5±11.6 |
| No | 189 | 49.9 | 156.0±14.7 | 16.6±2.2 | 27.0±4.6 | 21.5±3.2 | 85.4±11.2 |
| Test1/p | | | t=7.879 p=0.000 | t=5.050 p=0.000 | t=5.287 p=0.000 | t=5.581 p=0.000 | t=5.961 p=0.000 |
| **Awareness of Symptoms of Gynecological Cancer** | | | | | | | |
| Yes | 183 | 48.5 | 163.2±17.0 | 17.6±2.3 | 29.8±5.9 | 23.4±3.2 | 92.2±12.1 |
| No | 195 | 51.5 | 151.3±15.2 | 16.7±2.2 | 27.1±4.3 | 21.5±3.4 | 85.9±11.0 |
| Test1/p | | | t=7.161 p=0.000 | t=4.151 p=0.000 | t=5.189 p=0.000 | t=5.428 p=0.000 | t=5.288 p=0.000 |
| **Awareness of Cancer Screening Services Offered at Family Health Centers** | | | | | | | |
| Yes | 288 | 76.0 | 159.4±17.3 | 17.2±2.3 | 28.8±5.4 | 22.8±3.4 | 90.4±11.8 |
| No | 91 | 24.0 | 149.6±14.3 | 16.8±2.2 | 27.0±4.7 | 21.1±3.3 | 84.5±11.3 |
| Test1/p | | | t=4.893 p=0.000 | t=1.634 p=103 | t=2.801 p=0.005 | t=4.184 p=0.000 | t=4.164 p=0.000 |
| **Time Since Last PAP Smear Test** | | | | | | | |
| Never undergone (a) | 185 | 48.8 | 153.5±17.5 | 17.0±2.3 | 28.2±5.3 | 21.8±3.6 | 86.2±15.5 |
| Less than 1 year ago (b) | 75 | 19.8 | 162.1±17.2 | 17.0±2.5 | 28.8±5.7 | 23.6±3.3 | 92.6±11.3 |
| 1-3 years ago (c) | 53 | 14.0 | 160.8±15.2 | 17.5±2.0 | 28.1±5.2 | 22.8±2.8 | 92.2±10.5 |
| 3-5 years ago (d) | 32 | 8.4 | 158.4±14.6 | 17.3±2.0 | 28.4±4.9 | 22.7±3.2 | 89.8±10.5 |
| More than 5 years ago (e) | 34 | 9.0 | 159.2±16.5 | 17.6±2.1 | 29.1±5.4 | 22.2±3.1 | 90.3±10.2 |
| Test2/p | | | t=4.772 p=0.001 | t=0.864 p=0.486 | t=0.341 p=0.851 | t=3.765 p=0.005 | t=5.697 p=0.000 |
| Difference | | | a<b, a<c | | | a<b | a<b, a<c |
| **Status of Receiving HPV Vaccination** | | | | | | | |
| Yes | 22 | 5.8 | 155.9±16.4 | 17.0±2.0 | 28.8±5.3 | 21.6±2.9 | 88.4±11.4 |
| No | 357 | 94.2 | 157.1±17.2 | 17.2±2.3 | 28.4±5.3 | 22.5±3.4 | 89.0±12.0 |
| Test1/p | | | t=-0.328 p=0.743 | t=-0.397p=0.691 | t=0.327 p=0.744 | t=-1.102 p=0.271 | t=-0.224 p=0.823 |

*1Independent Sample T testi, 2One Way Anova*

|  | GCAS | Early Detection and Knowledge Awareness | Cancer Risk Awareness | Prevention Awareness | Awareness of Routine Checkups and Perception of Serious Illness |
|---|---|---|---|---|---|
| Age | r=0.147 p=0.004 | r=0.019 p=0.719 | r=0.000 p=0.995 | r=0.124 p=0.016 | r=0.172 p=0.001 |
| Age at Menarche | r=-0.057 p=0.272 | r=-0.062 p=0.227 | r=0.008 p=0.876 | r=0.012 p=0.817 | r=-0.076 p=0.138 |
| BMI | r=-0.003 p=0.951 | r=-0.076 p=0.139 | r=0.000 p=0.993 | r=-0.021 p=0.677 | r=-0.016 p=0.724 |
| Mean Age of First Sexual Intercourse | r=0.099 p=0.105 | r=0.087 p=0.155 | r=0.092 p=0.134 | r=0.207 p=0.001 | r=0.207 p=0.241 |
| Mean Number of Pregnancies | r=-0.086 p=0.179 | r=-0.030 p=0.643 | r=-0.003 p=0.969 | r=-0.103 p=0.107 | r=-0.092 p=0.151 |
| Mean Number of Births | r=-0.076 p=0.243 | r=-0.186 p=0.185 | r=0.046 p=0.485 | r=-0.085 p=0.191 | r=-0.090 p=0.166 |

r=Pearson Korelasyon Katsay

Age and GCAS total score, awareness of prevention, and awareness of routine checks and perception of serious illness sub-dimension score averages showed a weak level of statistically significant correlation (p<0.005, p<0.001). With the exception of the awareness of prevention sub-dimension, no statistically significant correlation was found between the age at first sexual intercourse and the total GCAS score, as well as the averages of all other sub-dimension scores. (p>0.005). A weak but statistically significant positive correlation was found between the age at first sexual intercourse and the awareness of prevention sub-dimension score averages (p<0.001). However, no statistically significant relationship was observed between age at menarche, BMI, average number of pregnancies, average number of births, and the GCAS total score or sub-dimension score averages. (p>0.005) (Table 3).

## Discussion

Early diagnosis in gynecological cancers is among the most crucial criteria for improving women's quality of life and ensuring a successful treatment process. High levels of awareness among women regarding gynecological cancers play a significant role in regularly attending screenings and not overlooking potential symptoms. In our study, the mean age of women was found to be 34 ± 11 years, and the average total score obtained from the GCAS scale was 157.1 ± 17.1. Given that the GCAS scale allows for a minimum score of 41 and a maximum score of 205, the results of our study suggest that women's awareness of gynecological cancers is above the moderate level. In a study by Atlas and Güneri (2022) with 400 women, the mean GCAS score was 160.3 ± 22.4, while Öztürk et al. (2021) reported an average score of 147.4 ± 22.31 from a sample of 554 women. Similarly, Burucu and Kıyak (2022) found a median total score of 154, and Gözüyeşil et al. (2020) reported an average GCAS score of 153 in a large-scale study involving 2000 women [4, 10, 18, 19].

Upon reviewing the current literature, it is observed that, similar to our study, although the average score on the GCAS scale is above the average value, it is not at the desired level [4, 10, 18, 19].

In our study, it was found that 48.5% of women were knowledgeable about early diagnosis methods in gynecological cancers, and 76% of women knew about the CEDSCS. In a study by Alp Dal et al. (2020), it was reported that 74.5% of women knew about CEDSCS, and 87.3% were knowledgeable about early diagnosis methods in gynecological cancers [16]. Despite being married and having an active sexual life, only 51.2% of women in our study underwent Pap smear tests. When examining the rates of undergoing Pap smear tests in Turkey, Uysal and Toprak (2022) reported a rate of 37.9%, Akyüz et al. (2006) reported 51.3%, Uğur et al. (2019) reported 42.3%, and Pehlivanoğlu et al. (2019) reported 38.6% [20–23]. Similar to our study, ıt can be observed that the rates of undergoing Pap smear tests are not at the desired level. The low rates of Pap smear testing among the women in the study may be attributed to a lack of knowledge and education on the subject. It is important to instill healthy lifestyle behaviors to increase awareness of gynecological cancers. In our study, it was found that 60.7% of the women had never undergone a gynecological examination. When the reasons for women not undergoing gynecological examinations were examined, it was found that neglect (36.9%), embarrassment (26.6%), and fear of examination (19.0%) were the main reasons. In the literature, reasons for not undergoing gynecological examinations include embarrassment due to the examination position, the genital area being exposed, and fear and pain. Regular health check-ups and screenings play an important role in maintaining and improving women's health. Gynecological examination is important in the prevention and early diagnosis of gynecological cancers. Health professionals' facilitating and supportive attitudes will have a significant impact on women's habit of undergoing regular gynecological examinations [24–27].

One of the most important steps in preventing gynecological cancers is knowing risky health behaviors that could lead to gynecological cancers and creating awareness of healthy living [28].

In our study, it was found that married women with active sexual lives had higher awareness of risky behaviors that could lead to gynecological cancers and gynecological cancer symptoms, indicating that their awareness of gynecological cancers was higher. In studies by Kaya Şenol et al. (2021), and Kızılırmak & Kocaöz (2018), it was reported that women who were knowledgeable about gynecological cancers and were married had statistically higher GCAS scores and sub-scale scores. It can be said that the awareness of married women positively affects their awareness of cancer [3, 29]. In our study, no significant relationship was found between the number of pregnancies and births and the level of awareness of gynecological cancers.

In contrast to our study, Atlas and Güneri (2022) and Baltacı et al. (2023) reported that as the number of pregnancies, births, and children increased, women's awareness of gynecological cancers decreased [10, 28]. Conversely, Kaya Şenol et al.

(2021) found that the awareness of women who had given birth was higher than that of women who had not given birth [3]. It is thought that the differences in the study results in the literature may be due to factors such as the regions where the studies were conducted, access to health services, and socio-cultural factors.

## Conclusion

It was determined that awareness levels of risky health behaviors that could lead to gynecological cancers and knowledge of gynecological cancer symptoms are higher. It is important to promote healthy lifestyle behaviors and increase knowledge about gynecological cancers to enhance awareness regarding gynecological cancers. Nurses, as key healthcare professionals, play a crucial role in enhancing women's knowledge and awareness of gynecological cancers through education and counseling. Studies assessing women's awareness of gynecological cancers remain limited, highlighting the need for broader, community-based, and comprehensive research on this topic.

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# Ultrasound Characteristics of the Urethro-Vesical Segment in Women with Stress Urinary Incontinence

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**Abstract**

**Introduction:** Acute cerebrovascular disorders are a major contributor to adult disability. The underlying processes that contribute to their development include inflammation, excitotoxicity, oxidative stress, and dysregulation of the tryptophan–kynurenine pathway, which is essential for neuronal survival. However, the precise mechanisms and significance of these processes are not fully comprehended, and their influence on the efficacy of therapeutic approaches remains uncertain.

**The aim** of this study is to investigate the role of the tryptophan-kynurenine metabolic pathway in the development of stroke and its potential as a biomarker and therapeutic target.

**Results and Conclusions:** Tryptophan metabolism primarily occurs through the kynurenine pathway. Among its metabolites, kynurenine, kynurenic and choline acids are the most significant. Them have both neuroprotective and neurotoxic effects. Activation of the kynurenine pathway is linked to chronic inflammation, increasing the risk of cardiovascular and neurodegenerative conditions. Kynurenic and choline acids regulate N-methyl-D-aspartate receptor activity and oxidative stress. The increased production of choline and 3-hydroxyanthranilic acid due to oxidative stress is a major mechanism of neuronal damage under ischemic. The regulation of the balance between the neuroprotective and neurotoxic properties of metabolites produced by the kynurenine pathway is essential for normal brain function.

**Keywords:** Cerebrovascular Disorders, Kynurenine, Tryptophan, Inflammation, Oxidative Stress, NMDA Receptors.

## Introduction

Stress urinary incontinence (SUI) is characterized by the involuntary leakage of urine during everyday activities (such as coughing), occurring when the pressure in the bladder surpasses the urethra's ability to stay sealed [1]. This condition affects approximately 20-40% of individuals and significantly impacts both the physical and mental well-being of patients, as well as their social interactions [2]. If the SUI symptoms are combined with the urine leakage on the way to the toilet during a strong urge, it is considered to be a mixed urinary incontinence (MUI). The combination of the two is quite common (29%) [3].

According to the prevailing theories, SUI is caused by a mixture of abnormalities in the supporting connective tissues of the bladder and urethra, along with the reduction in the strength of the pelvic floor muscles, bladder neck, and sphincters of urethra, lead to a decrease in urethral closure pressure and reduction in lower abdominal leak point pressure. (ALPP) [4]. Two interdependent and often coexisting mechanisms that explain SUI include urethral hypermobility (UH) and internal sphincter deficiency (SD) [5], which could be defined by urodynamic investigation (UDI), and ALPP (also called Valsalva leak point pressure (VLPP)) [6,7]. At the same time, UDI is a rather complicated method and preoperative office assessment is as effective as UDI on surgical outcomes in women with uncomplicated, severe SUI [8,9,10]. Moreover, some office assessment tools, such as the incontinence questionnaire-short form (ICIQ-SF) have been reported to distinguish UH from SD in the patients with SUI and negatively correlate with VLPP [11]. Despite the need to simplify diagnostic algorithms, methods and parameters are required to be in place to determine anatomical changes in pelvic floor structures to make an accurate diagnosis.

Ultrasound (US) is a recommended method of examination for the pelvic floor and periurethral tissues in pelvic organ prolapse (POP) and SUI. In line with the recommendations of the European Association of Urology (EAU), ultrasound has been used to assess urinary incontinence and pelvic floor since 1980 [12]. The following indicators in particular bladder neck descent (BND), UH, funneling of urethra, the bladder neck's internal angle (BIA), α angle (measured between the axis of the proximal urethra and the central axis of the pubic symphysis), the rectovesical angle (β angle), and the deviation of these angles are measured at rest and Valsalva maneuver. These parameters indicate the hypermobility of the urethra and bladder neck. All of the above parameters can be used all together to diagnose SUI, which has been recently confirmed by numerous studies [13,14,15,16]. There is no standardized research methodology, and the data obtained by different researchers are contradictory. Thus, the conclusive diagnosis continues to rely on physical examination findings. Therefore, the objective of this study aimed to determine if ultrasound parameters are linked to symptom severity in SUI.

## Methods

This clinical randomized trial started in December 2023, was conducted during 2024 as a pilot project at a single medical center, and included seventy-six (76) women, including 38 women with SUI. The control group, of the same size, was age- and parity-matched with volunteers from healthy patients who did not report urinary incontinence and sought examination for reasons unrelated to genital pathology. The patients were grouped based on whether they had SUI or not, which was registered as the clinical data (patient complaints, positive/negative cough test in lithotomic and orthostatic position with the bladder filled) and The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) after assessment of eligibility criteria. ICIQ-SF is a validated self-administered tool designed to assess the severity of urinary incontinence and its impact on quality of life. It consists of a few concise questions that evaluate the frequency, severity, and type of incontinence, alongside its effect on daily activities. Scoring ranges from 0 to 21, with higher scores indicating greater severity. Individuals with a previous pelvic surgery (uterus removal surgery, colporrhaphy, etc.), pelvic masses or ovarian, uterine, and rectal cancer, pregnant and postpartum women as well as non-pregnant women, patients with POP extending beyond the hymen, cases of abnormal urinalysis, overactive bladder and an increase in residual urine volume exceeding 100 ml were excluded from the research.

The study was conducted with permission from the local bioethics commission. All participants were informed about ongoing study and provided their written informed consent before being recruited into the study.

## Transperineal Ultrasound Procedure

An radiologist specializing in pelvic ultrasound with 31 years of experience conducted all the ultrasound tests of the patients by using a Samsung HERA W10 scanner with a 2-11MHz vaginal transducer and a 2-9MHz convex transducer wrapped in a sterile sheath during examination. The choice of the sensor was determined by the patient's body-build and individual access. No principal difference was revealed when performing measurements. The quality of visualization of the studied structures was considered to be the main criteria. The ultrasound testing was performed in the standard position for gynecologic examination – lying on the back with the legs bent at the knees and the full bladder (120-400 ml). In comparison with the transvaginal US, the transperineal US does not require a transducer to be inserted into vagina as it is performed at the level of the vaginal vestibule.

If need be, the study was supplemented with transvaginal access. The topography of the front vaginal wall and the back bladder wall, urethra, bladder fundus, and surrounding tissues and organs were also studied.

After exposing the inferior edge of the symphysis pubis in the sagittal axis, the urethra, bladder and urethra-vesical junction were exposed. The image was positioned on the left half of the screen and α angle, BIA and β angle were measured. The same position and the same bladder volume were used for further tests to measure of bladder neck funneling (BNF), bladder neck symphyseal distance (BSD), bladder neck descent (BND), the length of the urethra (UL) and its diameter in the proximal third (urethral diameter, (UD)), and the span from the pubic symphysis to the anterior wall of the urethra in its middle third (pubo-urethral distance, PUD) was measured. All these parameters were evaluated in a relaxed state and during the Valsalva maneuver (VM). At the conclusion of the study, postvoid residual urine (PVR) was assessed following the patient's voiding.

## Statistical Analysis

All the obtained data were analyzed with the SPSS 23 statistical software. A p-value of 0.05 was considered statistically significant. The Data normality was evaluated using the Kolmogorov-Smirnov test. Continuous data with a normal distribution were presented as the mean ± standard deviation and analyzed using the t-test. On the other hand, non-normally distributed data were represented as the median and interquartile ranges and compared using the Mann-Whitney U test. The data from both groups, before and after the Valsalva maneuver, were compared using the nonparametric Wilcoxon test.

## Results

A total of 76 women participated in the study, with 38 in the main group and 38 in the control group. The average age of all participants was $50.0 \pm 9.93$ years. No notable differences were observed in age, BMI, pregnancies, parity numbers and bladder volume (BV) during the examination between the case and control group as well as UL, BSD and angle β parameters showed no significant differences either at rest or in the VM. However, PUD, UD, α angle and its deviation and the deviation of β angle in the SUI group were significantly higher than those in the control group (Refer to the Table 1).

When studying the changes in the US parameters within groups, in the majority of cases (n=28; 73.6%), the SUI patients had significant urethral shortening in the VM, whereas no significant differences in this parameter were found in the control group.

PUD as an indicator of urethral hypermobility was not significantly different in both groups, although an increase in this distance was observed in almost half of the SUI group (n=20; 52.6%) and to a lesser extent in the control group (n=17; 44.7%). The α angle got significantly increased after the VM in most members of the SUI group (n=20;76.3%) and in the control group (n=22; 57.8%), whereas the retro-vesical angle got significantly changed only in the SUI group toward the decrease in the angle size (n=26; 38.4%).

According to the ICIQ-SF in terms of the severity, the patients were distributed as follows: there were no patients with slight severity, Grade 2 (Moderate severity) – n=8 (21.01%), Grade 3 (Severe) – n=22 (57.8%), and Grade 4 (Extremely severe) – n=8 (21.01%). No significant differences in any of the UT parameters were found in reference to the severity of symptoms neither at rest nor in VM (Refer to the Table 2-3).

## Table 1 — Comparison of characteristics between the SUI group and control group.

| Group | SUI (n=38) Median [IQR] | Normal (n=38) Median[IQR] | Z | p-value |
|---|---|---|---|---|
| Age (years) | 49.0 (41.7-60.2) | 46.5 (42.0-54.2) | -.614 | 0.539 |
| BMI (kg/m2) | 26.2 (24.0-31.2) | 26.6 (23.7-33.0) | -.270 | 0.787 |
| Pregnancy number (n) | 3 (2.0-4.0) | 3 (2.0-4.2) | -.453 | 0.651 |
| Parity number (n) | 2.0 (1.0-2.0) | 2.0 (1.0-2.2) | -.531 | 0.596 |
| UD at rest, mm | 10.5 (9.0-13.1) | 9.9 (8.5-11.4) | 1.478 | 0.139 |
| UD (VM), mm | 10.9 (10.0-13.4) | 10.1 (9.0-11.2) | 2.123 | 0.033 |
| UL at rest, mm | 32.7 (29.0-38.0) | 34.0 (30.3-39.0) | .702 | 0.483 |
| UL (VM), mm | 30.9 (27.1-34.2) | 33.6 (29.0-38.0) | 1.861 | 0.062 |
| PUD at rest, mm | 10.4 (8.9-12.8) | 8.7 (7.0-10.0) | -3.263 | 0.001 |
| PUD (VM), mm | 10.25 (8.3-13.2) | 9.1 (7.6-10.0) | -2.583 | 0.010 |
| BSD at rest, mm | 21.45 (18.9-25.7) | 23.0 (20.0-25.8) | 1.055 | 0.291 |
| BSD (VM), mm | 22.3 (18.2-25.0) | 23.3 (20.1-26.1) | 1.039 | 0.299 |
| BND, mm | 0.15 (-2.0-1.1) | 0.3 (-0.4-1.0) | -0.624 | 0.533 |
| BIA at rest, mm | 74.0 (57.7-81.2) | 67.5 (52.7-84.7) | -.468 | 0.640 |
| BIA (VM), mm | 67.0 (54.2-80.0) | 68.0 (52.7-86.2) | -.036 | 0.971 |
| α angle at rest (°) | 23.8 (21.0-29.0) | 20.0 (15.0-25.0) | -2.693 | 0.007 |
| α angle (VM) (°) | 31.3 (26.8-37.0) | 21.5 (17.2-26.0) | -4.589 | 0.000 |
| α angle deviation (Δα) | 6.58 (14.0-2.0) | 1.0 (3.0-0.9) | 3.381 | <0.001 |
| β angle at rest (°) | 148.0 (134.0-157.0) | 141.5 (133.0-152.0) | -1.315 | 0.188 |
| β angle (VM) (°) | 131.0 (116.0-150.0) | 140.0 (136.0-149.0) | -1.814 | 0.700 |
| β angle deviation (Δβ) | 15.0 (2.0-23.0) | 1.50 (3.00-7.0) | 2.837 | 0.004 |
| BV, ml | 231.5 (116.5-383.0) | 187.5 (120.0-220.0) | -1.663 | 0.096 |
| PVR, ml | 13.5 (5.0-31.2) | 10.0 (5.0-18.0) | -.676 | 0.499 |
| ICIQ-SF | 15.0 (13.0-18.0) | - | - | - |
| Cystocele Green's type: | | | | |
| 0 | - | - | - | - |
| I | 1 (2.6%) | - | - | - |
| II | - | - | - | - |
| III | 7 (18.4%) | - | | |

Note: SUI – stress urinary incontinence, BMI – body mass index, UD – urethral diameter, UL –urethral length, PUD – pubo-urethral distance, VM – Valsalva maneuver, BIA – bladder neck internal angle, BSD – bladder neck symphyseal distance, BV – bladder volume, PVR – post-void residual, ICIQ-SF – International Consultation on Incontinence Questionnaire-Short Form.

## Table 2 — Comparison of ultrasound test parameters in terms of the severity of symptoms

| UT parameters | ICIQ-SF score | n | Mean Rank | χ2 | p-value |
|---|---|---|---|---|---|
| UD at rest, mm | moderate | 8 | 18.63 | 2.568 | 0.277 |
| | severe | 22 | 21.66 | | |
| | extremely severe | 8 | 14.44 | | |
| UD (VM), mm | moderate | 8 | 18.13 | 1.866 | 0.393 |
| | severe | 22 | 21.45 | | |
| | extremely severe | 8 | 15.50 | | |
| UL at rest, mm | moderate | 8 | 20.06 | .218 | 0.897 |
| | severe | 22 | 19.89 | | |
| | extremely severe | 8 | 17.88 | | |
| UL (VM), mm | moderate | 8 | 20.75 | .351 | 0.839 |
| | severe | 22 | 18.59 | | |
| | extremely severe | 8 | 20.75 | | |
| PUD at rest, mm | moderate | 8 | 22.44 | .713 | 0.700 |
| | severe | 22 | 18.80 | | |
| | extremely severe | 8 | 18.50 | | |
| PUD (VM), mm | moderate | 8 | 23.00 | 1.481 | 0.477 |
| | severe | 22 | 19.41 | | |
| | extremely severe | 8 | 16.25 | | |
| BSD at rest, mm | moderate | 8 | 22.19 | .729 | 0.713 |
| | severe | 22 | 17.68 | | |
| | extremely severe | 8 | 21.81 | | |
| BSD (VM), mm | moderate | 8 | 21.94 | .694 | 0.700 |
| | severe | 22 | 18.25 | | |
| | very severe | 8 | 20.50 | | |
| BIA at rest, mm | moderate | 8 | 21.06 | .519 | 0.771 |
| | severe | 22 | 19.77 | | |
| | extremely severe | 8 | 17.19 | | |
| BIA (VM), mm | moderate | 8 | 17.06 | 1.411 | 0.494 |
| | severe | 22 | 18.98 | | |
| | extremely severe | 8 | 23.38 | | |
| α angle at rest (°) | moderate | 8 | 17.81 | .376 | 0.829 |
| | severe | 22 | 20.41 | | |
| | extremely severe | 8 | 18.69 | | |
| α angle (VM) (°) | moderate | 8 | 19.13 | .026 | 0.987 |
| | severe | 22 | 19.45 | | |
| | extremely severe | 8 | 20.00 | | |
| β angle at rest (°) | moderate | 8 | 19.44 | .577 | 0.750 |
| | severe | 22 | 18.59 | | |
| | extremely severe | 8 | 22.06 | | |
| β angle (VM) (°) | moderate | 8 | 18.00 | .329 | 0.848 |
| | severe | 22 | 20.36 | | |
| | extremely severe | 8 | 18.63 | | |

Note: ICIQ-SF – International Consultation on Incontinence Questionnaire-Short Form (range 0-21) is given in the four scoring categories: slight (1-5), moderate (6-12), severe (13-18) and extremely severe (19-21); UD – urethral diameter, UL – urethral length, PUD – pubo-urethral distance, VM – Valsalva maneuver, BIA – bladder neck internal angle, BSD – bladder neck symphyseal distance.

| | ICIQ-SF score | n | Mean Rank | χ2 | p-value |
|---|---|---|---|---|---|
| Age | moderate | 8 | 14.94 | 2.819 | 0.244 |
| | severe | 22 | 19.43 | | |
| | extremely severe | 8 | 24.25 | | |
| BMI | moderate | 8 | 15.56 | 3.662 | 0.160 |
| | severe | 22 | 18.66 | | |
| | extremely severe | 8 | 25.75 | | |
| Pregnancies | moderate | 8 | 22.81 | 2.008 | 0.366 |
| | severe | 22 | 17.39 | | |
| | extremely severe | 8 | 22.00 | | |
| Parity number | moderate | 8 | 19.13 | .037 | 0.982 |
| | severe | 22 | 19.77 | | |
| | extremely severe | 8 | 19.13 | | |

Note: BMI – body mass index, ICIQ-SF – International Consultation on Incontinence Questionnaire-Short Form.

## Discussion

Since SUI is viewed as a significant health issue, its diagnosis is of great importance. Transperineal (TPUS) ultrasound demonstrated some diagnostic value in identifying SUI, with the potential to become a routine examination to aid clinical decision-making. Yet, there is no standardized research methodology, and the data obtained by different researchers are quite contradictory. Up to the present moment, the diagnosis of SUI has been based on some physical examination and objectification of symptoms using questionnaires [15, 16]. In this pilot study, the UT parameters of the urethro-vesical segment and the dynamics of their changes were analyzed during the VM in the patients with and without SUI by 2D TPUS. SUI was pre-diagnosed by physical examination and the ICIQ-SF questionnaire. Furthermore, all participants underwent the TPUS examination, and the results were evaluated against the control group. Notable differences between the groups were observed in parameters such as PUD, UD, α angle and its deviation as well as the deviation of β angle, which were significantly higher in the SUI group.

The frequency of episodes and severity of SUI symptoms positively correlated with age, BMI, number of pregnancies and childbirths, and the higher proportion occurring at menopause [17]. In this study, women were not in accordance with the onset of menopause and no positive correlation between age was observed [49.0(41.7-60.2), 46.5(42.0-54.2), p=0.539], BMI [26.2(24.0-31.2), 26.6(23.7-33.0), p=0.787], number of pregnancies [3(2.0-4.0), 3(2.0-4.2), p=0.651] and parity [2.0(1.0-2.0), 2.0(1.0-2.2), p=0.596] in the main and control groups, respectively.

UD in the proximal urethra measured by TPUS during the VM is a suitable measure to differentiate between patients with urinary incontinence and might indicate the intrinsic sphincter deficiency. This parameter did not change significantly within the SUI group [p =.257] and between the main and control groups at rest [10.5(9.0-13.1); 9.9(8.5-11.4), p=0.139], but was significantly higher in the SUI group compared to the control one during the VM [10.9(10.0-13.4); 10.1(9.0-11.2), p=0.033].

The results of the studies regarding UL are contradictory. Authors have reported both shorter [11], longer [19,20], and no difference [21,22,23] in the urethral length between women with SUI and healthy women. In this study, the SUI patients and control groups had no significant differences in UL either at rest [32.7(29.0-38.0); 34.0 (30.3-39.0), p=0.483] or at VM [30.9(27.1-34.2); 33.6(29.0-38.0), p=0.062]. However, the SUI patients had significantly shortened urethra at VM [p=.001].

The variation in BSD measurements at rest and during VM indicates the BND value, which indicates urethral mobility. The mobility at > 2cm is considered clinically significant [24]. The obtained data do not agree with the data submitted by the most authors in reference to the BND, which makes this indicator reliable for diagnosing SUI [25, 26]. In this study, BND did not show a significant difference between groups [SUI 0.15 (-2.0-1.1); Normal 0.3(-0.4-1.0), p=0.533] and was much less than 2 cm. On the other hand, it is not the only way to measure BND as the authors used different techniques [27] to demonstrate some evidence that the bladder neck and proximal urethra respond differently to the stress test in the horizontal and vertical positions [28]. In addition, data from some studies have shown that issue in SUI is not bladder neck instability, but rather the instability of the mid-urethra [29], which is consistent with the data in this study. The PUD, which reflects the mobility of the mid-urethra, was significantly higher in the SUI group, both at rest [p=0.001] and during VM [p=0.010].

One of the less discussed parameters of the urethro-vesical segment is BIA, the decrease, which is associated with relaxation of the supporting structures around the urethra in the SUI patients [11]. In the given study there was no significant difference observed in BIA between the SUI group and the control group either at rest [74.0(57.7-81.2); 67.5(52.7-84.7), p=0.640] or during VM [67.0(54.2-80.0); 68.0 (52.7-86.2), p=0.971]. This fact might also indicate the bladder neck stability in the SUI patients in this study.

Other commonly measured parameters in the literature are the α and β angles. Some previous studies have proven that the measurements of these angles and their deviation are significantly larger in the SUI patients at rest and during VM and the sizes of the corners increase during VM [30]. In this study, the median α angle at both rest [SUI 23.8(21.0-29.0); normal range 20.0(15.0-25.0), p=0.007] and VM [SUI 31.3(26.8-37.0); normal range 21.5(17.2-26.0), p=0.000] were significantly higher in the SUI group. The α angle deviation (Δα) was also measured within groups during VM, and it was significantly higher in the SUI group [6.58(14.0-2.0); 1.0(3.0-0.9), p=<0.001]. However, the size of the β angle, both at rest and during VM, was not significantly different between groups [p=0.188; p=0.700] and this does not agree with the data of other authors. At the same time, this suggests bladder neck immobility in the studied patients and is consistent with the BND measurement. Another difference was a decrease in the size of the beta angle during VM, which may be due to the presence of Green's type III cystocele in the SUI group [n=7; 18.4%], which resulted in lowering of the anterior vaginal wall during VM and a decrease in the value of the β angle, with the deviation of the angle (Δβ) being higher in the SUI group [15.0 (2.0-23.0); 1.50 (3.00-7.0), p=0.004]. It should be noted that the presence of a cystocele showed no significant impact on the measurements of bladder neck mobility. in the SUI patients [31]. The cystocele type affects the risk of occult SUI. Type III cystocele (intact retro-

vesical angle) associates with occult SUI [32]. In this study, type III cystocele was diagnosed only in the SUI patients, and was associated with urinary incontinence.

With the increase in BND, and the α and β angles, the SUI became more severe [33]. However, no significant differences were observed in all UT parameters as well as in age, BMI, number of pregnancies and parities, studied in term of symptoms' severity on the ICIQ-SF scale. This may be due to the small number of patients studied and their distribution of symptoms' severity.

## Clinical Implications

The data from the current pilot study suggest the possibility of routine use of TPUS to determine the causes of stress urinary incontinence, such as urethral hypermobility and intrinsic sphincter deficiency. This may be the basis for choosing the tactics of surgical intervention and predicting possible effectiveness.

## Limitations of the study

There is no doubt that this study has many limitations that need to be acknowledged. This is the sample size, which was minimal for the significant differences obtained. Another aspect is the performance of TPUUS only in the supine position, as well as the exclusion of women with urinary incontinence and severe pelvic organ prolapse and a history of surgery.

## Conclusion

The findings validated that TPUS can be recommended as an appropriate diagnostic tool for identifying SUI. The recommended parameters to be used for diagnosis according to our data are PUD, UD, α angle and its deviation as well as the deviation of β angle. However, further studies are required to obtain the UT indicators in the larger quantity of the SUI patients, including the combination with anatomical changes of the pelvic floor. The function of TPUS in assessing the severity of SUI also still needs to be investigated.

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# Is Spirituality a Source of Support or Conflict for Infertility? A Qualitative Study

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## Abstract

**Background:** Infertility has become an important public health problem in developing countries due to its high prevalence. Infertility is a difficult crisis situation with psychological and spiritual dimensions.

**Aims:** The aim of this study is to determine whether religion provides support or conflict for the infertility process in women.

**Methods:** This research was designed as a descriptive qualitative study. This study was conducted in a governmental hospital's infertility outpatient clinic in Istanbul, Turkey. Twenty participants participated in the face-to-face, in-depth interview technique used to gather the research data. A semi-structured interview and a comprehensive information form were used to gather data.

**Results:** In line with the interviews with the participants, 2 main themes, 9 sub-themes and 12 codes for the sub-themes were determined as the findings obtained based on the content analysis in the study, positive religious behaviors and negative religious behaviors.

**Conclusions:** In our study, it was found that women felt unhappy, hopeless and helpless and could not accept not being able to have children. Women blamed religion for their infertility. Religion first caused infertile women to experience conflict. After the conflict, women with religious affiliation perceived religious support as a source of conflict for others.

**Keywords:** Conflict; infertility treatment; spirituality; support.

## Introduction

The World Health Organization (WHO) defines infertility as the inability to achieve fertilization despite engaging in regular unprotected sexual intercourse for a duration of at least one year or more. The identification of environmental determinants, particularly nutrition, that affect fertility is of significant importance from both clinical and public health perspectives. Globally, it is estimated that approximately one in every six couples experiences infertility [1].

Women experience psychological and social issues as a result of infertility, which manifests as a crisis in life and is influenced by a variety of factors, including cultural, religious, and class [2, 3]. For many years in the historical process, procreation or ensuring the continuation of the generation has a different importance with its psychological, sociological, religious and spiritual dimensions beyond being a basic instinct. Although the meaning of having a child has taken on different dimensions in this process, it still maintains its importance today [2, 4]. While birth or

fertility in the woman's body is a biological process, being a mother in cases of postponement, absence, loss or medicalization of fertility creates its cultural and religious dimension. In this context, the effect of cultural values and religious dimensions on infertile should be questioned [5, 6]. Dealing with this crisis is one of the most difficult things for women who have fertility issues. People look to religion for solace, hope, and respite from distress when confronted with life-altering events. Their beliefs can serve as their main coping mechanism for stressors in their lives, including illness, pain, and crises [7, 8]. Strong religious convictions can help infertile women cope and recover. While some women may view infertility as a punishment from a higher power, others may find comfort in the idea that it is a part of a divine design [4, 8].

The number of studies evaluating the positive or negative effects of religion on infertility is very limited. It has not been fully clarified how infertile women see religion as a support for themselves or how religion negatively affects their infertility attitude [6, 7]. Women

who develop negative religious coping mechanisms tend to come into conflict with God. Since parenthood is considered sacred in Turkish culture, childlessness is perceived as a test or punishment given by God [8]. However, the literature on how positive or negative coping mechanisms affect infertile women is very limited. It is very important for the health personnel who care for infertile people to determine how the infertile woman is affected by the religion she believes in. Because the religious meaning that women attribute to infertility directly affects treatment options, treatment continuation, perception of stress and perception of success [9, 10]. Sometimes the religious feelings of the woman can stand in front of the health personnel as a set. In this case, the maintenance process may not start at all. Determining how religion affects the perception of being infertile is also necessary in terms of determining spiritual care needs [11, 12]. Therefore, in this study, unlike the literature, it was aimed to discuss the positive and negative religious behaviors developed by infertile women and how these behaviors affect the infertility process.

## Methods

This qualitative study was carried out at a university hospital's infertility outpatient clinic. 250 women who applied to the university hospital's infertility polyclinic between January 20, 2022, and February 20, 2023, made up the study's sample. Women who had been receiving infertility treatment for at least two years were included in the study. Purposive sampling was used to choose study participants. In keeping with our objective of reaching data saturation in in-depth interviews, we conducted our study with 20 willing participants.

## Data Collection

Age, length of marriage, level of education, length of infertility treatment, work status, financial condition, and the cause of infertility were all inquired about in the introductory information form. Infertile women were asked four questions on the semi-structured interview form, with extra questions added according to how the interview went (Table 1).

| Table 1 | Semi-structured interview questions. |

1. To cope with this situation, praying, perform prayer, going to the shrine, making a vow, etc. Do you make apps?
2. What do you attribute your infertility to?
3. How does the religious value affect your acceptance of infertility and your treatment?
4. Do your feelings conflict with your religious values?

Face-to-face in-depth interviews were used to gather research data. On average, the interviews lasted between forty-five and sixty minutes. Interviews with participants who allowed audio recording were conducted by a researcher. The resulting audio recordings were transcribed and reported. Interviews with the participants who did not allow audio recording were made with two researchers. While one of the two researchers was doing the interview, the other researcher took notes.

## Data analysis

The data were coded line by line and then submitted to content analysis by the researchers in accordance with the literature. The researchers then collaborated to reevaluate and come to a consensus on the themes and sub-themes. Four researchers who were specialists in their domains and had

academic studies on qualitative research verified the percentage of consistency between the codes and themes in order to guarantee the validity and reliability of the study. The acquired value of 0.85 was assessed as proof of the consistency of the categories [21].

## Results

### Participants' Demographic and Obstetric Characteristics

After analyzing the causes of infertility, it was found that 45% of women, 25% of men, 20% had an unknown cause, and 10% were both male and female. The average duration of infertility among women was 5±1.75. (Table 2).

| Table 2 | Descriptive Characteristics of the Participants |

| Participants | Age | Marriage duration (years) | Infertility treatment duration (years) | Cause of infertility |
|---|---|---|---|---|
| Participant A | 30 | 6 | 3 | Woman |
| Participant B | 32 | 7 | 5 | Woman |
| Participant C | 33 | 6 | 2 | Man |
| Participant D | 37 | 8 | 5 | Woman |
| Participant E | 32 | 8 | 4 | Man |
| Participant F | 26 | 6 | 4 | Infertility of Unknown Cause |
| Participant G | 39 | 3 | 2 | Infertility of Unknown Cause |
| Participant H | 39 | 12 | 5 | Both woman and man |
| Participant I | 26 | 6 | 4 | Woman |
| Participant J | 37 | 10 | 6 | Man |
| Participant K | 29 | 5 | 4 | Man |
| Participant L | 30 | 7 | 3 | Infertility of Unknown Cause |
| Participant M | 36 | 13 | 4 | Woman |
| Participant N | 30 | 3 | 2 | Woman |
| Participant O | 29 | 4 | 2 | Man |
| Participant P | 42 | 9 | 8 | Woman |
| Participant R | 33 | 7 | 6 | Infertility of Unknown Cause |
| Participant S | 25 | 4 | 3 | Woman |
| Participant T | 27 | 5 | 4 | Woman |
| Participant U | 41 | 7 | 5 | Both woman and man |

According to the participant interviews, two primary themes, nine sub-themes, and twelve codes for the sub-themes—"Positive Religious Behaviors" and "Negative Religious Behaviors"—were identified as the study's content analysis findings (Table 3).

**Main Theme 1. Positive Religious Behaviors**

The opinions of the participants on positive religious coping activities were coded, and 3 sub-themes: religiosity, surrender to fate, religious worship, and 6 codes for sub-themes were formed (Table 3).

**Sub-Theme 1. Religiosity**

While the majority of the participants stated that they prayed more often during the infertility treatment, their belief and devotion to God increased more, some of the participants stated that they were not very attached to religious values and that the solution to having a child was medical treatment and a scientific approach. The findings of this sub-theme show that they take refuge in God by taking refuge in religion and they are aware that they are not alone. The statements of some of the participants are given below:

**Table 3** Analysis of Sub-Themes and Codes Regarding the Main Themes of Positive And Negative Religious Behaviors

| Main Theme 1 (*n folded) Positive Religious Behaviors | | |
|---|---|---|
| Sub-Themes | Codes | n* |
| Religiosity | Knowing that you are not alone | 7 |
| | Feeling peaceful | 8 |
| | Trusting in God | 9 |
| Surrender to Fate | Positive self-perception | 5 |
| | Purpose in life | 4 |
| Religious Worship | Social support | 6 |
| **Main Theme 2 Negative Religious Behaviors** | | |
| Sub-Themes | Codes | n* |
| To revolt | Feeling sinful | 14 |
| Perceiving it as punishment by God | Feeling worthless | 12 |
| Conflict with God | Lack of social support | 14 |
| Staying away from God | Abandoning religious practices | 8 |
| Feeling guilty | Experiencing anxiety and stress | 13 |
| Fear of being punished by God | Fear of giving birth to a disabled baby | 11 |

Participant I (26 years old) *"...Since I started infertility treatment, I started to do my prayers more regularly, I covered my head. I started wearing sheets. I feel closer to God."*

Participant H (39 years old) *"...I am not very attached to my religious values. Getting medical help and being treated relieves me. I think the solution will be by getting scientific and medical help. I cannot conceive at the moment because it is caused by the problems that both my wife and I have."*

### Sub-Theme 2. Surrender to Fate

Most of the participants stated that the reason for not being able to have children was fate, destiny and fortune, and that the situation of not having a child was their destiny and they agreed to this situation and were tested as the purpose of existence in life. This sub-theme caused women to see infertility as a part of the sacred plan and to develop a positive self-perception. The statements of some of the participants are given below:

Participant I (26 years old) *"...I dream that I am pregnant. I trust God. I believe I will be a mother."*

Participant D (age 37) *"...May Allah protect us from the weakness of faith. If there is a weakness in faith, this situation cannot be mentioned. God's judgment. Thank goodness for this. This is how God wants it."*

### Main Theme 2. Negative Religious Behaviors

The participants' views on negative religious coping activities were coded, and 6 sub-themes and 6 codes were created for sub-themes: rebelling, perceiving punishment by God, conflict with God, turning away from God, feeling guilty, and fearing punishment by God (Table 2).

### Sub-Theme 1. Revolt

Most of the participants stated that they rebelled and repented after rebelling, did not want to rebel, but continued to rebel. A few of the participants stated that rebelling is a very sin, and they never rebelled. The majority of the participants experience the feeling of sinfulness. The statements of some of the participants are given below:

Participant P (42 years old) *"... I always rebel. I have been in treatment for 8 years. The result is always negative. I say rebelling is a sin, but what's the use? Constant rebellion, constant rebellion. Anger, resentment inside me. I am very unhappy."*

Participant E (32 years old) *"... I try not to rebel. But there are many times when I rebel. When I see my friends' children or when I see a beautiful child while walking outside, it hurts and I start to rebel even though I have repented."*

### Sub-Theme 2. Perception as Punishment by God

Although most of the participants do not want to say, they stated that not realizing their desire to be a mother could be a punishment method by God. Some of the participants stated that they could not get pregnant due to purely medical reasons, as this was not a punishment. This situation has caused women to feel worthless. The statements of some of the participants are given below:

Participant F (26 years old) *"... I wonder if someone bad damn to me. I think God punished me. Why did this happen, I can't get out of it."*

Participant R (33 years old) *"... I say it came from God. Sometimes I think that this is a punishment for me. Maybe the child I gave birth to will be very unhappy in this life? God is great, it knows something."*

### Sub-Theme 3. Conflict with God

The majority of the participants stated that they constantly questioned the inability to have children, everyone had children, there were people who became pregnant right after marriage without any treatment, and they did not know why they could not get pregnant. They are in constant conflict even though they believe it is a test from God. A few of the participants stated that their infertility situation came from God and that there should be no conflicts. It was determined that this conflict had a negative impact on women's psychological well-being, and it was determined that it caused women to experience a lack of social support. The statements of some of the participants are given below:

Participant C (33 years) *"... I think that my pregnancy was only due to the malfunctions in my body. Only medical aid will be the solution. I do not experience any conflict situations"*

Participant K (29 years old) *"... I often ask myself if I am not a good servant who fulfills God's orders. Are my prayers not accepted? Women get pregnant immediately after marriage, why can't I get pregnant?.*

Participant S (25 years old) *"... I have conflicts from time to time. I have not already fully accept. I'm running after my destiny, trying to make an effort. I always say to myself that there is a good thing that came from God. I try not to rebel, but I do rebel."*

## Discussion

In this study, it was determined that women in the infertility process developed positive and negative religious behaviors. It was determined that these behaviors caused women to experience different emotions such as loneliness, social support, guilt, sinfulness, anxiety, stress, increase in religious affiliations, and psychological well-being within the scope of religious values. They attributed their infertility to being a punishment from God. Because of this, they became angry and rebelled against fate [13, 14]. In a qualitative study conducted in Turkish culture, female infertility was found to be a reflection of God's will [5]. In a

previous study in Turkey, it was found that positive religious coping levels of women decreased their psychological distress levels due to infertility [3]. In another study, it underlines that religion affects mental health and that health professionals should consider it in the infertility process [15]. In their 2022 study in Finland, Halkola et al. reported that women trust in God and accept not being a mother as their destiny [22]. In this study, it was seen that infertile women worship and prayer, and go to the shrine. In women's infertility situations, feelings of spirituality can be a tool to help the individual accept the situation and cope with the stress. Religious commitment, self-esteem or positive personality may have increased feelings of dominance, and this may have been reflected in health indicators. For example, religious affiliations may have encouraged infertility treatment [4, 13]. There appears to be a positive relationship between religious participation and psychological well-being. It can be explained by the awareness of patience, acceptance, compassion and the adoption of religious approaches in the events that are perceived as a problem in the religion of Islam [3]. As a result, women can go through the infertility treatment process more easily by believing that they are with God. In the literature on the subject, it has been emphasized that there are positive relationships between aspects of religious commitment and self-esteem or personal competence [13, 16]. Sormunen et al. In their 2018 study, it was stated that infertility treatment negatively affected women psychologically, and women felt stressed and lonely [23]. In this study, women with infertility were also angry at their infertility and clashed with God. Women could not cope with the stressful situation and cognitively felt alone in this regard. The stress experienced by women may have disrupted strong religious-moral norms, and their sterility may have brought along a fear of holy punishment [17]. Six of the women participating in this study said they felt anger. In a similar study, it was emphasized that negative emotions such as anger towards God constitute an obstacle in the infertility process, and religion is perceived as a negative coping method [15]. In situations where religious identity is not good, the development of low self-esteem can create negative emotions such as anger. In this case, women used the negative coping mechanism in their infertile processes. In our study, it was determined that women who developed positive religious behaviors perceived religion as social support. Few studies emphasize the importance of spiritual support (e.g., sharing religious views, praying for others) that provides informal socio-emotional support to people participating in religious activities [18, 19]. The thought of a holy punishment by divine decision can lead to a dead end in women who are infertile. The tension caused by various anxiety and fear behind this questioning prevents women from coping with this situation [17]. In one study, it was emphasized that religion and spirituality have the ability to improve or harm mental health [10]. Religious devotions and practices can provide solace, hope, and strong surrender, they are often intricately intertwined with psychological disorders. It is difficult to decide whether religious devotion or spirituality is a source of consolation or a responsibility [13, 20]. In our study, it was found that women felt unhappy, hopeless and helpless and could not accept not

being able to have children. It was also seen that how women perceive these things is more important than what God says in religions. Religions generally advocate for people to take shelter in God in difficult situations, to be patient, to behave towards the purpose of existence, tolerance and social support. As a result of this study, it can be recommended to provide spiritual care support to infertile women so that women can cope with infertility effectively.

## Conclusion

In our study, it was found that women felt unhappy, hopeless and helpless and could not accept not being able to have children. As a result; It was found that most of the participants saw infertility as a part of the divine plan, not as a biological process related to the bodies. Although this seemed to help them to accept this process, it caused them to experience very different opposite emotions. While women who stated that they had strong religious beliefs developed positive religious behaviors, religion created more confusion in women who were not. Nurses need to take infertile women's psychological needs into account and consider their personal feelings and values.

## Strengths and Limitations

One strength of this study is that it clearly reveals whether religion is an interest or support for infertility. The only limitation of the study is that it has a qualitative design and that obtained findings cannot be generalized to the whole society.

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# The Relationship between Women's Beliefs about Mental Illnesses in the Prenatal Period and Their Attitudes towards Seeking Psychological Help

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## Abstract

**Aim:** This study was conducted as a descriptive and correlational study to examine the relationship between prenatal women's beliefs about mental illness and their attitudes towards seeking psychological help.

**Methods:** The study was conducted in a state hospital in Aksaray between March 18 and May 18, 2024. The population of the study consisted of pregnant women who applied to the gynecology and obstetrics outpatient clinics of the hospital, and the sample consisted of 215 pregnant women who met the research criteria and agreed to participate. Data were collected using the Information Form, Beliefs about Mental Illness Scale and Attitudes towards Seeking Psychological Help Scale. The data were collected using a questionnaire method previously tested by the researchers with a small group. After explaining the purpose of the study, data collection tools were distributed to the pregnant women who agreed to participate in the study and they were asked to fill them out. SPSS (Statistical Package for Social Sciences) 26 package statistical program was used to evaluate the data.

**Result and Conclusion:** It was found that beliefs about mental illness scale total score and helplessness sub-dimension scale scores were higher in the first trimester and attitude towards seeking psychological help scale total scores were higher in the second trimester. Identifying factors related to seeking psychological help during pregnancy may benefit the implementation of interventions, and identifying women who are less likely to seek help may increase the rates of diagnosis and treatment of pregnancy mental health problems.

**Keywords:** Pregnant; mental illness; psychological help.

## Introduction

The mental health of pregnant women has garnered significant attention in recent years, particularly in light of changes to the biopsychosocial model of medicine [1]. The period between the onset of pregnancy and the onset of labor is referred to as the prenatal period [2]. Pregnant women constitute a unique group with specific needs, given the challenging physiological processes associated with pregnancy and childbirth. In addition to these physical challenges, they undergo substantial changes in their living circumstances and social roles, which can render them more susceptible to psychological disorders such as anxiety, insomnia, and stress-induced depression [3].

Psychological disorders in pregnant women not only harm the mental well-being of the mother, but they also have long-term detrimental effects on the baby, including premature birth, low birth weight, and potential impairments in future development, cognition, behavior, and emotional health. These issues also extend to the family unit [4, 5]. Therefore, psychological help-seeking behavior and perinatal mental health literacy among pregnant women facing mental health challenges are critical for ensuring that they receive appropriate and effective psychological care. According to Fischer and Turner, help-seeking behavior is defined as "seeking solutions from external sources due to the inadequacy of individual resources when facing a problem that the individual perceives as directed towards themselves" [6]. It has been noted that many pregnant women rely on social support from those around them, without seeking medical assistance, and attempt to manage their mental health challenges independently [7].

Several barriers to seeking psychological help among pregnant women have been identified, including lack of time, trust, stigma, and the normalization of symptoms [8]. Other contributing factors include male dominance in marriages, religious beliefs, cultural practices, and financial constraints. Furthermore, limited access to services and the high cost of care have also been recognized as significant obstacles to seeking psychological support [8, 9]. Stigmatization, one of the negative factors that impede help-seeking behavior, typically involves the adoption of derogatory attitudes and beliefs that can result in discrimination against others [10]. Stigma is also associated with the concept of mental health literacy. Mental health literacy (MHL) was initially defined as " knowledge and beliefs about mental disorders which aid recognition, management or prevention". A more recent operationalization of the MHL concept includes the sub-components attitudes and help-seeking. This definition does not only add the concept of stigma but also the concept of help-seeking efficacy to the definition of MHL. Low MHL has been identified as one of the reasons for the limited use of mental health services. Stigmatization of pregnant women reduces their positive perception of professional medical support and contributes to a broader issue of social mistrust [11]. These emerging challenges may impact how pregnant women approach mental health concers and influence their attitudes toward seeking help. To proactively identify women who may be less inclined to seek treatment during this critical period, it is crucial to develop a more comprehensive understanding of the factors that influence the decision to seek psychological assistance during pregnancy. Attitudes toward mental illness are also shaped by negative views and beliefs. Research has shown that negative attitudes and beliefs about mental disorders significantly affect individuals' willingness to seek psychiatric help [12, 13].

Health professionals play a critial role in supporting and empowering pregnant women to enhance their coping skills, self-confidence, and overall well-being [14]. Awareness and education can help communities adopt a more open and supportive approach to mental health issues. This, in turn, can reduce the stigma and taboos associated with mental illness, encourage individuals to seek help, and foster a healthier society. It is believed that pregnant women's awareness of their mental health challenges during the prenatal period, which significantly impacts their lives, and their recognition of the need for psychological support, will have a positive effect on both maternal and fetal mental health during pregnancy and after childbirth. A review of the literature revealed no studies addressing the attitudes of pregnant women toward seeking psychological help. Therefore, the aim of this study was to explore the relationship between prenatal women's beliefs about mental illness and their attitudes toward seeking psychological assistance.

*Research Questions*

• What is the level of women's beliefs in the prenatal stage about mental illnesses?

• What is the level of women's attitudes in the prenatal stage towards receiving psychological help?

• Do women's beliefs about mental illnesses change according to socio-demographic characteristics in the prenatal stage?

• Do women's attitudes in the prenatal stage towards receiving psychological help change according to socio-demographic characteristics?

• Do women's beliefs about mental illness in the prenatal stage affect their attitudes toward searchingfor psychological help?

## Methods

*Study Design*

This study was conducted as a descriptive and correlational research to examine the relationship between prenatal women's beliefs about mental illness and their attitudes toward seeking psychological support.

*Population and Sample*

The population of this study consisted of pregnant women who visited the gynecology and obstetrics outpatient clinics of a public hospital. A random sampling method, which is one of the non-probability sampling techniques, was employed to determine the sample group for this study. In cases where the total population is unknown, the sample size was calculated using a sample size formula [15]. The mean score and standard deviation of the Attitudes Toward Seeking Psychological Help Scale in the study by Gül Yildiz and Sariçam (26.14±3.56) were used to estimate the population standard deviation [16]. The sample size was determined to be 195, with a 95% confidence level and an effect size of d=0.5 [17]. To account for potential data loss, the sample group for this study was formed with 215 pregnant women, considering a 10% increase over the calculated sample size [18].

n=t2. σ/d2

n= Number of people to be sampled

σ = Universe standard deviation. Since it is mostly unknown, their standard deviation is used.

t= Theoretical value in the table in the degree of freedom and the determined burning level.

d= The desired performance according to the event is symbolized as +. (ss=n-1) [15].

Data were collected by the researchers through a questionnaire method at a public hospital between March 18 and May 18, 2024. After explaining the purpose of the study, the data collection instruments were distributed to pregnant women who consented to participate and were asked to complete them.

*Instrumentation*

Research data were collected using the Information Form, Beliefs about Mental Illness Scale and Attitudes Towards Seeking Psychological Help Scale. The data collection forms were applied by the researcher to ten people outside the study population before the research, and the statements that were not understood in the information form not found.

1. Information Form

The information form was developed by the researcher based on the literature and consists of 13 questions [19, 20]. It includes inquiries regarding socio-demographic characteristics, as well as feelings, knowledge, and attitudes towards mental illness.

2. Beliefs towards Mental Illness Scale (BMI)

The scale developed by Hirai and Clum [21] was adapted into Turkish, and its validity and reliability were conducted by Bilge and Çam [22]. The scale consists of 21 items and three sub-dimensions: Dangerousness, Incurability and Disturbance in Interpersonal Relationships, and Shame. The Turkish validity and reliability study resulted in a Cronbach's alpha coefficient of 0.82 for the scale. The Beliefs about Mental Illness Scale uses a 6-point Likert type format, with scores ranging from "I completely disagree: 0" to "I completely agree: 5."

*Incurability and Disturbance in Interpersonal Relationships:* This subscale includes 11 items, specifically items 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, and 21. The lowest possible score on this subscale is 0, and the highest is 55. A higher score indicates feelings of helplessness and obstacles in interpersonal relationships with individuals with mental health disorders.

*Dangerousness:* This subscale contains 8 items, numbered 1, 2, 3, 4, 5, 6, 7, and 13. The maximum score for this subscale is 40. It measures the perceived dangerousness of individuals with mental illness.

*Shame:* This subscale consists of items 12 and 15, with the highest possible score being 10. It addresses the perception that mental illness is a shameful condition. A lower score on this subscale indicates that the participant does not view mental illness as something to be ashamed of.

3. Attitudes Towards Seeking Professional Psychological Help Scale (ATSPPHS-SF)

The Attitudes Toward Seeking Psychological Help Scale-Short Form (ATSPPHS-SF) was developed by Fischer and Farina [23]. This version of the scale is a revised form of the original 29-item scale [6]. The Cronbach's alpha coefficient of the scale was found to be 0.76. The adaptation of the Short Form of the PSRAS into Turkish was carried out by Topkaya [24]. The scale items are rated on a 4-point Likert scale, ranging from (3) agree to (0) disagree. Four items on the scale are reverse-scored: items 2, 8, 9, and 10. During the validity and reliability analyses of the scale, it was noted that the item-total test correlation for item 4, "It is an admirable attitude for a person to want to deal with his/her conflicts and fears without seeking support from an expert when needed," was below 0.30, and the t-statistic for the item was not significant in the confirmatory factor analysis. The scale consists of a total of 9 questions and a single dimension. The lowest possible score on the scale is 0, and the highest score is 27. A higher score on the scale indicates more positive attitudes toward seeking psychological help.

*Data Analysis*

The data obtained from the research were statistically analyzed using the SPSS (Statistical Package for the Social Sciences) version 26 software. Descriptive statistics, including percentages, means, and standard deviations, were employed for data evaluation. The normal distribution of the data used depends on the skewness and kurtosis values being between ±2 [15]. It was observed that the scales showed normal distribution. Therefore, parametric tests were used. Parametric tests, including one-way analysis of variance (ANOVA) and independent samples t-test, were applied. The Tukey HSD test was used to identify differences between groups. Pearson correlation analysis, a parametric test, was utilized to examine the relationship between two continuous variables that did not follow a normal distribution. The results were evaluated at a 95% confidence interval with a significance level of $p < 0.05$.

*Ethical Considerations*

Prior to the study, ethical approval was obtained from the Necmettin Erbakan University Health Sciences Scientific Research Ethics Committee, with decision number 2024/690, dated 06.03.2024, as well as official approval from the institution where the research was conducted. Permissions were granted for the use of the Beliefs Towards Mental Illness Scale and the Attitudes Toward Seeking Psychological Help Scale. Informed consent forms were obtained from pregnant women who agreed to participate in the study. Pregnant women who chose not to participate were not pressured to take part. This study is limited to data collected from 215 pregnant women who attended the gynecology and obstetrics outpatient clinics of a state hospital.

# Results

Overall, among the 227 women who participated in the study, 215 had complete data and were included in the data analysis. The average age of the expectant mothers was 27.56±5.49 years, 34.4% had completed high school, 80.9% did not have a job, and 80.5% thought their income was moderate. 53% had been married for less than 5 years, 35.8% had their first pregnancy and 44.7% were in the third trimester.11.2% of pregnant women were found to have applied to a psychiatrist clinic throughout their pregnancy, 71.6% shared their mental problems with their families and 28.8% felt pity, 44.2% felt uneasiness, 19.1% felt fear, 5.1% felt embarrassment, 69.3% felt compassion and 22.3% felt curiosity towards individuals with mental illness. The main cause of mental illnesses; 68.4% of the pregnant women stated that they thought that they were caused by events experienced in childhood (Table 1).

| Table 1 | Socio-demographic Characteristics of Pregnant Women (n=215) |

| Variables | | Mean ±SD | Min-Max |
|---|---|---|---|
| **Age** | | **27.56±5.49** | **18-44** |
| | | n | % |
| Education Status | Primary school | 28 | 15.0 |
| | Middle school | 46 | 21.40 |
| | High school | 74 | 34.40 |
| | Undergraduate and above | 67 | 31.20 |
| Employment Status | Working | 41 | 19.10 |
| | Not Working | 174 | 80.90 |
| Duration of marriage | Less than 5 years | 114 | 53.0 |
| | 5 years and more | 101 | 47.0 |
| Income status | Low | 23 | 10.70 |
| | Middle | 173 | 80.50 |
| | High | 19 | 8.80 |
| Place of residence | Village | 51 | 23.70 |
| | City Center | 164 | 76.30 |
| How many pregnancies | 1st pregnancy | 77 | 35.80 |
| | 2nd pregnancy | 61 | 28.40 |
| | 3rd and more pregnancies | 77 | 35.80 |
| Pregnancy week | 1-13 weeks (1st trimester) | 39 | 18.10 |
| | 14-26 weeks (2nd trimester) | 80 | 37.20 |
| | 27-41 weeks (3rd trimester) | 96 | 44.70 |
| Feelings for individuals with mental illness | Pity | 62 | 28.80 |
| | Anxiety | 95 | 44.20 |
| | Fear | 41 | 19.10 |
| | Shame | 11 | 5.10 |
| | Compassion | 149 | 69.30 |
| | Curiosity | 48 | 22.30 |
| The cause of mental illness | Hereditary predisposition | 52 | 24.20 |
| | Events in childhood | 147 | 68.40 |
| | Supernatural powers such as magic | 6 | 2.80 |
| | Traumatic events | 127 | 59.10 |
| | Family conflicts | 129 | 60.0 |
| | Previous infectious diseases | 23 | 10.70 |
| Referral to a psychiatric clinic | Yes | 24 | 11.20 |
| | No | 191 | 88.80 |
| Family psychiatric history | Yes | 29 | 13.50 |
| | No | 186 | 86.50 |
| The person with whom he shares the most mental problems | Family | 154 | 71.60 |
| | Friend | 56 | 26.00 |
| | Mental health specialist | 5 | 2.30 |

SD: Standard Deviation;
Min: Minimum;
Max: Maximum

Pregnant women's ATSPPHS-SF scores ranged between 8-27, with a mean of 20.68±3.85, and their BMI scores ranged between 0-105, with a mean of 44.89±18.11. The mean scores of the subscales of BMI were 22.64±10.62 for incurability and disturbance in interpersonal relationships, 20.70±8.09 for dangerousness and 1.53±2.28 for shame (Table 2).

According to the gestational age of the pregnant women, the mean total score (51.94±18.60; p=0.023) and the mean incurability and disturbance in interpersonal relationships subscale score (26.59±10.34; p=0.029) of the BMI of those in the first trimester were statistically significantly higher than those in the other trimesters. The scores of pregnant women in the second trimester (22.10±3.29) were significantly higher than those in the first and third trimesters (p=0.05) between the mean scores of the expectant mothers on the ATSPPHS-SF and BMI and their employment status, educational status, duration of marriage, perceived income level, place of residence, psychiatric clinic referral status, family history of psychiatric treatment and the person with whom they shared their mental problems the most (Table 3)

| Table 2 | Means cores of the pregnant women in the ATSPPHS-SF, BMI and subscales (n=215) | | |
|---|---|---|---|
| Scales | | Mean±SD | Min-Max |
| ATSPPHS-SF | | 20.68±3.85 | 8-27 |
| BMI Subscales | Incurability and Disturbance in Interpersonal Relationships | 22.64±10.62 | 0-55 |
| | Dangerousness | 20.70±8.09 | 0-40 |
| | Shame | 1.53±2.28 | 0-10 |
| BMI Total | | 44.89±18.11 | 0-105 |

| Table 3 | Comparison of the means cores of the ATSPPHS-SF, BMI and subscale scores according to the socio-demographic characteristics of pregnant women (n=215) |

| Variables | | N | ATSPPHS-SF | BMI Subscales | | | BMI Total |
|---|---|---|---|---|---|---|---|
| | | | | Incurability and Disturbance in Interpersonal Relationships | Dangerousness | Shame | |
| Education Status | Primary School | 28 | 21.46±2.85 | 24.32±11.39 | 21.25±8.78 | 1.39±2.47 | 46.96±20.02 |
| | Middle School | 46 | 20.30±4.15 | 21.24±11.39 | 19.50±8.74 | 1.50±2.04 | 42.24±18.55 |
| | High School | 74 | 20.16±4.36 | 24.69±10.92 | 21.71±8.12 | 1.68±2.61 | 48.08±18.98 |
| | Undergraduate and above | 67 | 21.19±3.32 | 20.65±9.001 | 20.19±7.29 | 1.46±2.01 | 42.31±15.52 |
| | F | | 1.383 | 2.235 | 0.855 | 0.154 | 1.686 |
| | P | | 0.249 | 0.085 | 0.465 | 0.927 | 0.171 |
| Employment Status | Working | 41 | 21.24±3.57 | 20.66±8.94 | 19.22±7.61 | 1.71±1.81 | 41.58±16.28 |
| | Not Working | 174 | 20.55±3.91 | 23.11±10.95 | 21.05±8.18 | 1.49±2.39 | 45.66±18.46 |
| | T | | 1.035 | -1.334 | -1.311 | 0.536 | -1.301 |
| | P | | 0.302 | 0.223 | 0.743 | 0.478 | 0.968 |
| Duration of marriage | Less than 5 years | 114 | 20.82±3.51 | 22.46±11.15 | 21.30±7.47 | 1.51±2.25 | 45.28±18.25 |
| | 5 years and more | 101 | 20.52±4.21 | 22.85±10.05 | 20.03±8.72 | 1.56±2.34 | 44.44±18.02 |
| | T | | 0.569 | -0.266 | 1.156 | -0.178 | 0.337 |
| | P | | 0.570 | 0.696 | 0.328 | 0.525 | 0.658 |
| Income status | Low | 23 | 20.30±4.26 | 26.26±12.58 | 21.04±8.20 | 2.04±2.74 | 49.34±20.91 |
| | Middle | 173 | 20.85±3.64 | 22.25±10.38 | 20.94±8.14 | 1.44±2.19 | 44.64±17.79 |
| | High | 19 | 19.58±5.07 | 21.84±9.98 | 18.10±7.43 | 1.79±2.59 | 41.73±17.34 |
| | F | | 1.065 | 1.511 | 1.080 | 0.838 | 1.002 |
| | P | | 0.346 | 0.223 | 0.342 | 0.434 | 0.369 |
| Place of residence | Village | 51 | 20.47±3.63 | 24.31±11.68 | 20.25±8.06 | 1.80±2.69 | 46.37±16.59 |
| | City Center | 164 | 20.75±3.93 | 22.12±10.25 | 20.84±8.12 | 1.45±2.14 | 44.42±17.65 |
| | T | | -0.451 | 1.285 | -0.456 | 0.963 | 0.669 |
| | P | | 0.652 | 0.302 | 0.690 | 0.268 | 0.547 |
| How many pregnancies | 1st pregnancy | 77 | 20.64±3.61 | 21.32±11.30 | 21.27±7.55 | 1.55±2.25 | 44.14±18.09 |
| | 2nd pregnancy | 61 | 20.52±3.76 | 24.28±10.21 | 20.54±8.39 | 1.34±2.02 | 46.16±18.41 |
| | 3rd and more pregnancies | 77 | 20.84±4.18 | 22.67±10.18 | 20.27±8.44 | 1.68±2.53 | 44.62±18.06 |
| | F | | 0.121 | 1.320 | 0.310 | 0.356 | 0.223 |
| | P | | 0.886 | 0.269 | 0.734 | 0.701 | 0.800 |
| Pregnancy week | 1st trimester | 39 | 19.97±3.75 | 26.59±10.34 | 23.43±8.32 | 1.92±2.73 | 51.94±18.60 |
| | 2nd trimester | 80 | 22.10±3.29 | 21.19±10.83 | 20.06±8.08 | 1.36±2.17 | 42.61±18.42 |
| | 3rd trimester | 96 | 19.79±4.01 | 22.26±10.27 | 20.13±7.86 | 1.52±2.19 | 43.92±17.08 |
| | F | | **9.311** | **3.590** | 2.756 | 0.791 | **3.834** |
| | P | | **0.000** | **0.029** | 0.066 | 0.455 | **0.023** |
| Referral to a psychiatric clinic | Yes | 24 | 21.58±3.45 | 23.21±8.24 | 18.41±7.67 | 1.75±3.01 | 43.37±16.75 |
| | No | 191 | 20.57±3.89 | 22.57±10.90 | 20.99±8.11 | 1.51±2.19 | 45.07±18.30 |
| | T | | 1.215 | 0.274 | -1.475 | 0.488 | -0.434 |
| | P | | 0.226 | 0.237 | 0.353 | 0.122 | 0.590 |
| Family psychiatric history | Yes | 29 | 19.65±4.88 | 22.34±9.93 | 19.58±6.54 | 1.38±1.82 | 43.31±14.86 |
| | No | 186 | 20.84±3.65 | 22.69±10.75 | 20.88±8.31 | 1.56±2.35 | 45.13±18.58 |
| | T | | -1.551 | -0.164 | -0.801 | -0.393 | -0.504 |
| | P | | 0.122 | 0.686 | 0.113 | 0.403 | 0.237 |
| The person with whom he shares the most mental problems | Family | 154 | 20.64±4.04 | 21.80±10.43 | 20.49±8.30 | 1.45±2.09 | 43.74±17.87 |
| | Friend | 56 | 20.75±3.43 | 24.93±11.27 | 21.30±7.53 | 1.75±2.67 | 47.98±18.78 |
| | Mental health specialist | 5 | 21.00±2.55 | 23.00±4.85 | 20.80±8.87 | 1.60±3.58 | 45.40±16.89 |
| | F | | 0.031 | 1.791 | 0.208 | 0.343 | 1.127 |
| | P | | 0.969 | 0.169 | 0.812 | 0.710 | 0.326 |

SD: Standard Deviation;
t: Dependent Sample t Test
F:One-Way Anova

| Parameter | | ATSPPHS-SF | BMI Subscales | | | BMI Total |
|---|---|---|---|---|---|---|
| | | | Incurability and Disturbance in Interpersonal Relationships | Dangerousness | Shame | |
| Age | r | 0.119 | -0.100 | -0.099 | -0.061 | -0.111 |
| | p | 0.083 | 0.142 | 0.149 | 0.370 | 0.105 |

**Table 4** Correlation test results for the relationship between age and ATSPPHS-SF, BMI and BMI subscales

r: Analysis of Pearson Correlation

The mean scores of BMI and its subscales did not show a statistically significant correlation with age (p>0.05). The ATSPPHS-SF and BMI did not significantly correlate, according to the correlation test results (Table 4).

## Discussion

In this study, the majority of pregnant women (69.3%) expressed compassion toward individuals with mental illness. It is suggested that those who demonstrate compassion toward individuals with mental disorders may also extend the same compassion for themselves and their unborn children, thereby increasing their willingness to seek psychological help. More than half of the participants attributed mental health issues to family conflicts and childhood trauma. Notably, psychiatric problems during pregnancy were found to be five times more prevalent among women with a history of childhood trauma compared to those without [25]. These findings underscore the critical role of familial emotional bonds in mental health.

The majority of pregnant women (71.6%) shared their mental health concerns with family members. Research suggests that individuals with strong social support, particularly from spouses or family, are more likely to seek psychological help [26]. Consequently, pregnant women with such support may be more inclined to actively utilize mental health services.

Although not statistically significant, 68.8% of the pregnant women had an education level below undergraduate, and 80.9% were unemployed. Research indicates that higher maternal education levels are associated with more positive attitudes toward seeking psychological help [27]. In this study, the absence of a significant relationship may be attributed to limited access to mental health resources among women with lower education levels.

The mean total ATSPPHS-SF score among pregnant women was 20.68±3.85, consistent with findings from other studies using the same scale [28]. Although no specific research has focused on pregnant women's attitudes toward psychological seeking help, these findings suggest that social support from family facilitates help-seeking behavior. Identifying factors influencing this behavior could enhance the early diagnosis and treatment of mental health issues. Research indicates that prenatal depression rates range from 7% to 20% in high-income countries and exceed 20% in low- and middle-income countries [29]. Despite the high prevalence of mental illness, only 11.2% of participants had visited a psychiatric clinic, and just 2.3% had sought help from a specialist, highlighting a gap in mental health service utilization. Notably, one study suggests that consulting a spiritual counselor may be as important as seeking support from a psychologist or social worker [30].

Pregnant women in the second trimester had higher ATSPPHS-SF scores than those in the first and third trimesters. Seeking psychological help may not be a priority during early pregnancy due to the initial excitement and the process of adapting to pregnancy. In later stages, increasing physical discomfort and concerns about childbirth may take precedence. [31]. By the second trimester, women may have adjusted to pregnancy and experienced reduced distress, making them more likely to seek psychological help. Previous research indicates that just over one-third of women seek professional mental health care during the first trimester [32]. Hamilton and Lobel observed that pregnant women often rely on spiritual coping strategies in the first and second trimester [33]. Additionally, Nordin-Remberger et al. identified several barriers to seeking psychological help during pregnancy, including stigma, previous negative experiences with healthcare providers, fear of not being believed, and discomfort in confronting personal fears. Notably, more than half of those who received treatment reported finding it ineffective or only minimally helpful [34]. Furthermore, Arslantaş et al. found that lack of social support during pregnancy, combined with increased knowledge about childbirth, contributed to greater fear of childbirth, which may be a risk factor for postpartum depression [35].

The average BMI total score for pregnant women in our study was 44.89±18.11. This score was comparable to findings from other studies using the same measure in different populations [36]. Our results, which align with previous research, suggest that pregnant women hold relatively positive attitudes toward mental illnesses, despite the lack of studies specifically examining their beliefs on this topic. It is suggested that the psychological distress experienced during pregnancy may influence levels of shame and stigmatization. Additionally, societal prejudices against mental illness may shape pregnant women's perspectives on this issue.

In our study, pregnant women in the first trimester had higher BMI scores as well as higher subscale scores for incurability and interpersonal relationship disturbance, compared to those in the second and third trimesters. Various biological, psychological, and social factors may contribute to stronger perceptions of mental illness during early pregnancy. Hormonal fluctuations, coupled with the need to adapt to new responsibilities, may heighten emotional sensitivity during this period. Additionally, uncertainty regarding the baby's health, the progression of the pregnancy, and the future may contribute to feelings of incurability. Previous research has shown that pregnant women often experience profound shame and stigmatization related to mental health issues, leading to reluctance in discussing their psychological difficulties [5]. One study reported that some pregnant women believed they were vulnerable to harm through spiritual attacks, such as witchcraft [37]. However, in our study, only 2.8% of participants attributed mental illness to supernatural causes, suggesting cultural variations in beliefs about mental health. These findings highlight the importance of incorporating belief systems into prenatal mental health prevention and intervention programs.

A review of the literature suggests that depression screening in pregnant women can reduce depression prevalence and improve treatment outcomes [38, 39], while psychosocial

or psychological interventions, such as cognitive behavioral therapy and interpersonal psychotherapy, can significantly lower the risk of postpartum depression, particularly for those at higher risk [40].

The mean total scores of the BMI and the ATSPPHS-SF were found to be unaffected by the following factors: age, educational attainment, employment status, length of marriage, perceived income level, place of residence, admission status to a psychiatric clinic, family history of psychiatric treatment, and the people with whom the pregnant women shared their mental problems the most. This study has some limitations that should be acknowledged. First, the data were collected only in one state hospital, which resulted in the similarity of the low level of education of the pregnant women. Second, it was seen that the fact that the pregnant women shared a common culture and had similar social support networks could affect their belief systems and lead to similar results in terms of psychological help-seeking behavior.

The ATSPPHS-SF and BMI did not significantly correlate, according to the correlation test results (Table 4). Overall, this result suggests that the factors influencing help-seeking behavior may be more complex and multifaceted than simply being determined by one's beliefs about mental illness. Further research could explore additional variables or more specific subcomponents of both scales to gain a deeper understanding of the relationship.

## Conclusion and recommendations

BMI total scores and helplessness subscale scores were higher in the first trimester, whereas the total scores of the ATSPPHS-SF total scores were higher in the second trimester.

These findings provide valuable insights into psychological help-seeking behaviors during pregnancy and inform the development of targeted supportive interventions. Accordingly, cognitive-behavioral therapy (CBT)-based group interventions could be implemented in the first trimester to enhance psychological resilience. Specifically, structured educational programs focused on stress management and coping strategies may help mitigate feelings of helplessness among pregnant women. In the second trimester, regular psychoeducation sessions led by healthcare providers could be beneficial in promoting help-seeking behaviors. These sessions should include information on accessing mental health services and the potential benefits of such support.

In addition, psychological screening tests can be administered to pregnant women at family health centres to identify at-risk groups and referral mechanisms to mental health professionals can be strengthened for high-risk pregnant women [41]. To enhance healthcare professionals' awareness, training modules on psychological help-seeking behaviors can be developed for obstetricians, nurses, and family physicians and implemented periodically. Furthermore, integrating mental health assessments into pre-pregnancy counseling services and expanding early intervention programs, such as mindfulness-based stress reduction programs, may help reduce the risk of postpartum depression and anxiety. Regarding this; Bukhali practices, which begin in the pre-pregnancy period and include the post-pregnancy period, are seen as an important guide for optimizing mental health [42]. Considering the relationship between pre-pregnancy, during pregnancy and postpartum psychological distress and birth outcomes and subsequent behavioural problems in mothers and children, there is a need to investigate women's mental health before pregnancy planning and to provide interventions aimed at improving mental health. According to Lim et al. (2023), by monitoring the mental health of young women in the pre-pregnancy, pregnancy or postpartum period, high-risk or treatment-requiring groups can be discovered and appropriate management can be provided to prevent or improve mental health and quality of life [43]. A more comprehensive study is needed to understand the mental health outcomes and experiences of women who contacted mental health services during pregnancy and to bring more context to this discussion. It is recommended to be re-studied in different sample groups.

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# A Rare Hardware-related Complication After Deep Brain Stimulation: Two Cases of Twiddler's Syndrome

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## Abstract

Twiddler's syndrome is an uncommon complication of deep brain stimulation, arising from the inadvertent rotation of the implanted pulse generator, which results in lead coiling, displacement, or fracture. This results in stimulation failure and symptom recurrence, often necessitating surgical revision. While well-documented in cardiac devices, Twiddler's syndrome remains infrequent in operations. Early diagnosis through radiographic imaging and impedance abnormalities is crucial for prompt intervention.

We report two cases of Twiddler's syndrome in patients with movement disorders: a 73-year-old male with Parkinson's disease and a 55-year-old female with multifocal dystonia, both of whom had bilateral deep brain stimulation with left-sided dual-channel implanted pulse generator. After years of effective symptom control, both patients presented with worsening motor symptoms. Device examination revealed abnormal impedance readings, and imaging confirmed extensive lead coiling. Surgical revision was performed, including lead replacement and implanted pulse generator repositioning under the pectoralis fascia. Both patients demonstrated significant symptom improvement postoperatively, with restored impedance levels and functional recovery.

Twiddler's syndrome is a rare but critical complication of deep brain stimulation, leading to hardware failure and clinical deterioration. Early diagnosis through imaging and impedance monitoring is essential. Preventive strategies, including secure implanted pulse generator fixation and careful pocket sizing, are key to minimizing risk and improving patient outcomes.

**Keywords:** deep brain stimulation, movement disorders, Twiddler's syndrome, hardware complications, extension fracture.

## Introduction

Twiddler's syndrome is a rare but serious hardware-related complication following deep brain stimulation (DBS) surgery. It is characterized by unintended rotation of the implanted pulse generator (IPG) within its subcutaneous pocket, leading to excessive coiling, displacement, or fracture of the leads [1]. This results in stimulation failure, loss of therapeutic benefit, or even neurological worsening.

Originally described in cardiac pacemakers by Bayliss in 1968, Twiddler's syndrome has since been reported in various neurostimulation devices, including DBS [2].

Although well-documented in cardiac implantable electronic devices, where it occurs in approximately 1.2% of cases [3], Twiddler's syndrome remains an infrequent but clinically significant complication in DBS, with an estimated prevalence of 0.07% to 1.4%. [4–6].

The condition is often associated with rapid symptom recurrence, stimulation inefficacy, and abnormal impedance readings. Radiographic evaluation, particularly chest X-ray, may reveal coiled, displaced, or fractured leads—often in a double-helical pattern [7].

Several risk factors have been implicated, including an oversized implantation pocket, insufficient device fixation, and patient-related behaviors such as compulsive manipulation of the IPG. Additional predisposing factors identified in cardiac patients—such as female sex, high body mass index (BMI), and antidepressant use—may also be relevant in the DBS population [3, 5].

From a neurosurgical perspective, Twiddler's syndrome presents both diagnostic and management

challenges. Lead displacement compromises clinical outcomes and often necessitates surgical revision. Prevention strategies, including optimal IPG placement, secure anchoring techniques, and patient education on device care, are critical in minimizing this complication. Despite these considerations, Twiddler's syndrome in DBS remains underreported, limiting consensus on best management practices.

While direct evidence linking individual genetic and neurobiological factors to hardware-related complications in neuromodulation therapies is currently limited, emerging research suggests that patient-specific factors, including genetic predispositions and neurobiological responses, may influence outcomes. For instance, genetic factors influencing BMI and compulsive behaviors have been implicated in conditions like obsessive-compulsive disorder (OCD), which shares phenotypic similarities with behaviors that could lead to hardware manipulation. Furthermore, variations in genes related to neurotransmitter systems, particularly those involved in serotonin and dopamine signaling, have been associated with compulsive behaviors. Some of the key genetic factors include: **HTR2A** and **HTR1B** (serotonin signaling), as well as **DRD2** and **DAT1** (dopamine regulation).These genetic insights suggest a potential link between neurobiological predispositions and hardware-related complications in neuromodulation therapies. However, further investigation is warranted to clarify their specific roles and clinical implications in patient management [8].

In this report, we present two cases of Twiddler's syndrome in movement disorder patients: one with Parkinson's disease undergoing bilateral subthalamic nucleus (STN) DBS and another with multifocal dystonia undergoing bilateral globus pallidus internus (GPi) DBS. Through these cases, we aim to highlight the clinical course, radiographic findings, surgical management, and preventive strategies for this uncommon complication. Over an 11-year follow-up period, during which 620 neuromodulation procedures were performed, these cases remained exceptionally rare.

## Case presentation

**Illustrative case 1.** A 73-year-old male patient with a Stage 5 Parkinson's Disease diagnosis according to the Hoehn & Yahr scale underwent bilateral STN DBS using a left dual-channel IPG (Activa PC). The initial programming of the DBS system resulted in significant improvement in symptoms for over 6 years.

Recently, the patient experienced discomfort in the left clavicular region and a gradual worsening of his condition, including increased stiffness and tremors in the limbs and a decrease in self-care skills over a three-week period. Upon evaluation, impedance and current measurements for electrodes 0, 1, and 2 were within normal ranges with current output (4.1mA), suggesting that the circuitry was intact, however, electrode 3 displayed low impedance level (234), indicating a potential problem with the lead.

To determine the cause of the suspected malfunction, the patient underwent diagnostic imaging, including cranial and chest X-rays. The X-rays revealed twisting of the IPG and extension leads around their axis (figure 1a-c).

A surgical intervention was performed, during which twisting of the DBS extension leads was observed, necessitating replacement of the extension leads. Additionally, the IPG was repositioned under the pectoralis fascia to reduce the risk of future displacement and coiling.
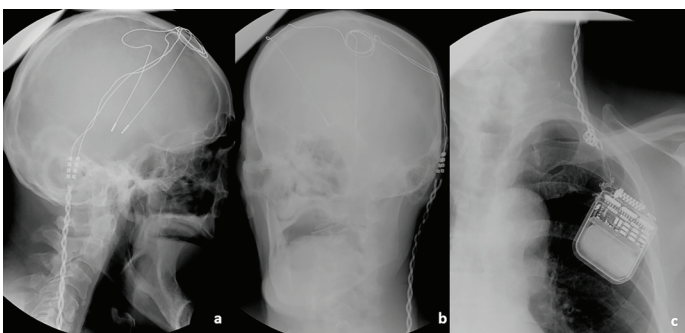


**Figure 1** – Cranial (a, b) and Chest (c) X-ray show coiling of extension wires.

This intervention significantly improved the patient's symptoms, and follow-up examinations showed that impedance levels had returned to normal.

**Illustrative case 2.** The patient is a 55-year-old female diagnosed with multifocal dystonia, which has manifested as cervical and torsion dystonia for the past 11 years. She has experienced significant improvement in symptoms following bilateral GPi DBS and the placement of a left dual-channel IPG (Activa PC). This treatment has effectively managed her condition for ten years. The IPG has required battery replacements 5.5 years and 3.5 years prior due to low capacity of battery.

The patient was readmitted to the hospital due to worsened uncontrolled muscle cramps, spasms, and difficulties with speaking and swallowing, indicating a worsening of her dystonia.

During evaluation, impedance and current measurements for electrodes 0, 1, and 2 were within normal ranges, suggesting the circuitry was intact. However, electrode 3 showed significantly increased impedance levels (10700-12400) and decreased current output (0.6mA), indicating a potential issue with the lead. Subsequent chest X-rays (figure 2a) revealed extensive coiling of the DBS extension leads, a mechanical complication that could affect the effectiveness of the DBS.
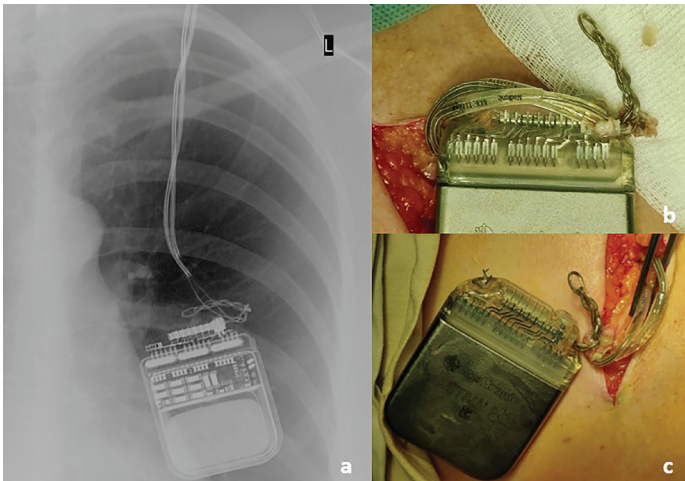


**Figure 2** – Chest X-ray showing IPG and coiling of extension wires (a). Intraoperative view of the IPG and coiled of extension wires (b,c).

An urgent surgical revision was required. During the procedure, it was observed that the DBS extension leads had twisted (Figure 2b, c), necessitating replacement. Additionally, the IPG was repositioned securely beneath the pectoralis fascia to reduce the risk of future displacement and coiling.

This intervention resulted in significant improvement in the patient's dystonic symptoms, with follow-up examinations showing normalization of impedance levels.

## Discussion

Deep brain stimulation is a neuromodulatory intervention that applies a neurostimulator to deliver electrical impulses to specific regions of the brain. For decades, DBS has been predominantly treating for managing motor symptoms for patients with advanced Parkinson's disease and dystonia.

While DBS provides the benefit of reversibility, it also has a few limitations. These include high costs, the requirement for continuous follow-ups, periodic battery replacements, and possible device-associated complications [9]. Among them, hardware-related complications continue as a cause for serious concern [10, 11], including.Twiddler's syndrome, a rare but potentially serious complication characterized by device manipulation leading to lead displacement or fracture. Although Twiddler's syndrome has been well-documented in cardiac devices, its occurrence in DBS patients has only recently gained recognition as DBS implantations have become more common [12]. Twiddler's syndrome occurs due to excessive movement of the IPG within an oversized pocket, allowing for repetitive twisting of the device until leads are tightly coiled or displaced [1].

The condition often presents with rapid symptom recurrence, loss of stimulation efficacy, and abnormal impedance readings, leading to deterioration in motor function or exacerbation of psychiatric symptoms [6]. Additionally, Twiddler's syndrome can cause localized pain along the course of the lead wires, particularly in the postauricular region [13].

Various risk factors have been associated with Twiddler's syndrome, including psychiatric conditions such as obsessive-compulsive disorder, anxiety, and paranoia, as well as physical factors like weight loss, female sex, advanced age, and excessive subcutaneous fat reduction in previously obese individuals [14–16].

Additionally, younger patients with high mobility and repetitive motor behaviors may be predisposed to Twiddler's syndrome due to inadvertent lead twisting [17]. However, our cases did not present with behavioral disorders, high BMI, or significant physical activity, suggesting alternative mechanisms for lead displacement.

Radiographic screening plays a crucial role in early detection, with studies showing that plain X-rays can reveal twisted extension wires in most cases [4]. In our cases, early X-ray imaging enabled prompt identification and surgical intervention. All patients with Twiddler's syndrome-related hardware malfunction underwent revision surgery, underscoring the importance of timely diagnosis and intervention.

Preventative measures include surgical techniques to secure the IPG, such as fixating the device within a tight-fitting subcutaneous pocket using nonabsorbable sutures or anchoring it to the pectoralis fascia [15, 16]. Limiting pocket size and ensuring adequate closure of the pseudocapsule around the IPG may further minimize the risk of rotation [18]. The TYRX™ Absorbable Antibacterial Envelope has also been proposed as a protective measure against device migration [5]. In some cases, subpectoral or subfascial placement of the IPG within polyester pouches has been suggested, however, these methods may not entirely prevent manipulation [13].

A potential solution to eliminating these complications is the development of a wireless IPG, eliminating the risk of lead twisting. On the other hand, making IPGs that are specific to each person's anatomy might help them fit better in the subcutaneous pocket, limiting movement and the chance of displacement.

Looking ahead, targeted gene therapy may provide a device-free solution for treating movement disorders. This field is already advancing, with multiple Phase I and early Phase II clinical trials underway. These early studies have played a crucial role in shaping the next generation of gene therapy trials, which continue to evolve and hold significant promise for more effective and long-lasting treatments [19].

Currently, due to the unpredictable nature of Twiddler's syndrome, routine follow-up with screening X-rays during the initial postoperative period is recommended to enable early detection before complications occur. Additionally, patients should be advised on activity restrictions during this period to minimize mechanical stress on the system and support stable encapsulation of the IPG [13].

Emerging evidence suggests that genetic and neurobiological factors may influence susceptibility to hardware-related complications in DBS. Genetic predispositions related to foreign body response, wound healing, and compulsive behaviors associated with neurotransmitter signaling may contribute to Twiddler's syndrome risk [8, 17]. Understanding these factors may allow for personalized DBS strategies, including patient-specific surgical techniques and postoperative monitoring plans.

## Conclusion

Twiddler's syndrome is a rare but serious complication of DBS, leading to hardware failure, symptom recurrence, and the need for surgical revision. Our study identified two cases, emphasizing the importance of early diagnosis through radiographic imaging and impedance abnormalities. Preventive strategies, such as secure fixation of the IPG and careful pocket sizing, are crucial in reducing risk.

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# Subclinical Hypothyroidism After a Three-Month Course of Low-Dose Amiodarone

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## Abstract

This case report describes a 64-year-old male who developed subclinical hypothyroidism after three months of low-dose amiodarone (100 mg/day). Routine monitoring showed a TSH increase to 44.40 mU/L with normal FT4 and FT3 levels. Based on the Naranjo scale (score: 7), amiodarone was deemed a probable cause of SCH. This case highlights the importance of routine thyroid monitoring during amiodarone therapy, even at low doses.

**Keywords:** side effects of amiodarone, amiodarone induced subclinical hypothyroidism, low dose of amiodarone, ablation, cryobaloon isolation, atrial fibrillation.

## Introduction

Amiodarone is a widely used drug known for its efficacy in managing atrial fibrillation and other arrhythmias. However, due to its high iodine content and direct effects on thyroid metabolism, it is also associated with a range of thyroid dysfunctions, including subclinical hypothyroidism (SCH) [1].

SCH, characterized by an elevated thyroid-stimulating hormone (TSH) level with normal free thyroxine (FT4), is a frequent overlooked consequence of amiodarone therapy. Amiodarone-induced thyroid dysfunction (AIT) is observed in 14% of patients and often presents as SCH in iodine-replete areas [2]. This report presents a case of SCH following short-term low-dose amiodarone therapy.

## Case presentation

A 64-year-old man with hypertension was admitted to the hospital with shortness of breath, dizziness, heart palpitations, and arrhythmic episodes. He has had atrial fibrillation since February 2022. An electrocardiogram (ECG) upon admission showed AF with a ventricular rate of 68 bpm. Echocardiography revealed left ventricular and biatrial dilation, with a left ventricular ejection fraction (LVEF) of 55%. Coronary angiography did not show hemodynamically significant stenoses.

On September 7, 2023, the patient underwent cryoballoon pulmonary vein isolation, and a subcutaneous cardiac monitor was implanted. Sinus rhythm was restored on the second post-procedure day. The patient was prescribed amiodarone (100 mg), perindopril (5 mg), rivaroxaban (20 mg), and atorvastatin (20 mg) for outpatient management.

In December 2023, routine testing revealed elevated TSH levels, prompting consultation with a cardiologist and an arrhythmologist. The patient had no symptoms of hypothyroidism (fatigue, constipation, cold intolerance) and no history of thyroid disease. Thyroid hormone levels were within normal limits.

Differential diagnoses included autoimmune thyroiditis and anemia. Anemia was excluded based on normal hemoglobin, iron studies (serum iron, ferritin, transferrin saturation, total iron binding capacity), vitamin B12, and folic acid levels. Autoimmune thyroiditis was ruled out due to normal thyroid peroxidase antibody (TPOAb) levels.

Given the thyroid dysfunction, amiodarone was discontinued, and bisoprolol (5 mg) was prescribed. An endocrinology consultation was obtained. Thyroid examination did not reveal enlargement, a fine-grained texture, and an elastic consistency, with no nodules or eye symptoms. Thyroid ultrasound showed diffuse

parenchymal changes, classified as Thyroid Imaging Reporting and Data System (TIRADS) 1/1.

TSH initially increased to 18.80 mMU/mL, leading to the initiation of levothyroxine (25 mcg/day). Despite ongoing levothyroxine therapy, TSH continued to rise after amiodarone withdrawal, peaking at 44.40 mMU/mL on day 9. In March 2024, the patient independently increased the levothyroxine dose to 37.5 mcg/day, leading to a decrease in TSH to 16.70 mMU/mL. After an endocrinology follow-up, the levothyroxine dose was further adjusted to 50 mcg/day. Thyroid function monitoring was recommended after two months, followed by an endocrinologist evaluation. Thyroid hormone level changes are presented in the graph [Figure 1].
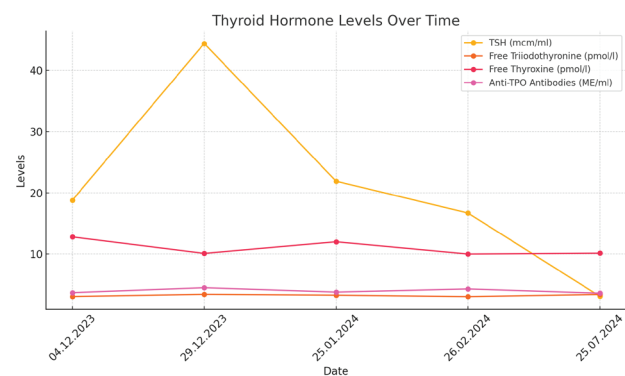


**Figure 1** – Control of thyroid hormones in dynamics

## Discussion

Subclinical hypothyroidism is a common thyroid disorder that can occur to patients taking amiodarone. This medication belongs to class III antiarrhythmic agents and is rich in iodine, a key element for thyroid hormone production. Due to its chemical structure, which resembles the natural thyroid hormones triiodothyronine (T3) and thyroxine (T4), amiodarone affects thyroid function in multiple ways. One of its primary effects is the suppression of an enzyme called type II 5'-deiodinase, which is responsible for converting T4 into the active form T3 in the pituitary gland. As a result, T3 levels decrease, leading to a compensatory increase in TSH by the pituitary gland [1, 2].

Amiodarone is exceptionally rich in iodine, containing about 37% iodine by weight. A single 200 mg tablet releases more than 70 times the recommended daily iodine intake. This excess iodine can temporarily suppress thyroid hormone production—a process known as the Wolff-Chaikoff effect. This mechanism serves as a protective response to iodine overload, preventing excessive thyroid hormone synthesis. However, in some patients, this adaptation is prolonged, leading to persistent elevation of TSH, which is a hallmark of subclinical hypothyroidism [3, 4].

Beyond its iodine-related effects, amiodarone and its active metabolite, desethylamiodarone, exert direct cytotoxic effects on thyroid follicular cells, which can lead to destructive thyroiditis. This direct toxicity contributes to both hypothyroidism and thyrotoxicosis, depending on the extent of tissue damage and hormone release. Additionally, amiodarone can act as a competitive antagonist of T3 at the cardiac cellular level, interfering with its normal receptor function, which may have direct cardiac implications independent of thyroid function [1–3].

Based on the Naranjo Adverse Drug Reaction Probability Scale, the adverse drug reaction (ADR) was assessed as "Probable" with a total score of 7 points. The reaction occurred within a reasonable timeframe following the administration of the drug, aligned with a known response pattern to the suspected medication, and was confirmed upon withdrawal. However, re-exposure to the drug was not attempted, and the reaction could not be adequately attributed to other known aspects of the patient's clinical condition [5].

Amiodarone-induced thyroid dysfunction requires regular monitoring. The European Thyroid Association (ETA) recommends a baseline thyroid function test (TFT) before initiation, including TSH, FT4, and thyroid peroxidase antibodies. During therapy, TFTs should be performed every 3–6 months [4].

For subclinical hypothyroidism (TSH 4.0–10.0 mIU/L), asymptomatic patients require monitoring, while symptomatic individuals or those at cardiovascular risk may need levothyroxine therapy. For overt hypothyroidism (TSH >10.0 mIU/L), levothyroxine is recommended, with TSH reassessment after 2 months to ensure proper dosing [4, 6]. This approach aligns with the management in this case. Despite the short duration of amiodarone therapy in this case, thyroid dysfunction persisted even after drug withdrawal, consistent with amiodarone's long half-life (~100 days) and prolonged storage in adipose tissue [1, 3, 4].

The decision to continue or discontinue amiodarone treatment should be made on an individual basis, in collaboration between cardiologist and endocrinologist.

While most studies focus on amiodarone-induced hyperthyroidism and overt hypothyroidism, subclinical hypothyroidism (SCH) remains less frequently discussed despite its clinical significance. Given this gap, we analyzed existing studies and clinical guidelines on SCH management in amiodarone-treated patients. Our review revealed inconsistencies in diagnostic thresholds and treatment strategies, particularly regarding when to initiate levothyroxine therapy. While recommendations vary, most sources, including the 2023 Korean Thyroid Association (KTA) and 2018 European Thyroid Association (ETA) guidelines, recommend intervention when TSH levels exceed 10 mU/L to prevent progression to overt hypothyroidism, whereas treatment decisions for lower TSH elevations remain controversial [4–7].

This case underscores the importance of structured thyroid monitoring and individualized levothyroxine therapy in amiodarone-treated patients. While SCH is known complication, data on its management in similar cases are limited. As a single case, it does not allow broad conclusions, highlighting the need for further research. Effective management requires close collaboration between cardiologists and endocrinologists for timely intervention and optimal outcomes.

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# A Case from Battery Replacement to Epicardial Pacemaker Implantation

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## Abstract

Globally, the prevalence of Cardiac implantable electronic devices (CIED) continues to increase every year. With the increase in device implantation, the incidence of device-related infections has also increased. CIED infection is seen with a frequency of 0.5% to 2.2%. CIED infections can present with a large spectrum ranging from erythema due to skin site inflammation to infective endocarditis, which can be fatal. Whether the pocket infection is complicated or not and whether there are signs of systemic infection are important in the prognosis and treatment of patients. In this case report, we present a patient with high comorbidity who underwent pacemaker battery replacement and developed a complicated pocket infection and difficulties in management.

**Keywords:** Cardiac implantable electronic device, infection, epicardial pacemaker.

## Introduction

CIED infections remain a popular problem due to the high mortality risk, high cost, and increasing number of CIED implantations over the years. A study of 4,144,683 device-related procedures showed that CIED infection has increased over the years, reaching 3.41 % [1]. In our country, CIED infection was found to be 8.5% in the study reported by Deniz et al. [2].

When the risk factors for developing device-related infection are analyzed, it is known that there are various patient-related, operation-related, and a device-related risk factors [3] . We will present a case with risk factors and comorbidities for device-related infection.

## Case report

A 41-year-old male patient had a history of ischemic cerebrovascular disease after deep vein thrombosis 10 years ago. After cardiac evaluation, atrial septal defect and atrial fibrillation were found and atrial septal defect repair was performed surgically. The patient underwent dual pacemaker implantation 9 years ago due to atrioventricular complete block and syncope. The patient was using rivaroxaban 20 mg qd , metoprolol 50 mg qd , furosemide 40 mg qd , levetiracetam 1000 mg bid. ECG showed atrial fibrillation. Echocardiography showed an Ejection Fraction: 55%, right heart chambers were extremely wide, no residual migration through the interatrial septum was observed, tricuspid valve insufficiency was advanced. and pulmonary artery pressure 45 mmHg.

The patient, whose battery was found to be end of life on battery measurement, was interrupted by rivaroxaban tablets for two days and the battery was replaced. Rivaroxaban treatment was started again at the 8th hour after battery replacement. The patient was treated with IV cefazolin for two days after follow-up and wound dressings were made with rifampicin. The patient was discharged with cefuroxime 500 mg bid on the 3d day after the procedure and was advised to have regular dressings for 10 days and come for follow-up visits for suture removal.

The patient, who did not make his dressings regularly and had his sutures taken at a primary healthcare institution, came to the pacemaker control in the 2nd month because of abdominal pulsation. In the pacemaker control, it was observed that the atrial lead impedance was high. When the anamnesis was detailed, it was learned that the patient had a hematoma at the pocket site 1 week after suture removal and then there was drainage from the suture lines. When the pocket site was checked, it was observed that there was erosion at the pocket site and the battery was visible through the skin (Figure 1). The patient was hospitalized with the diagnosis of pocket site infection and erosion. Vancomycin 1 gr qd, piperacillin + tazobactam 4,5 gr tid were started. Since battery and lead extraction was planned, rivaroxaban treatment was interrupted and enoxaparin sc 6000 IU bid was started. C-reactive protein (CRP) 1,7 (0-5 mg/L), sedimentation rate (Sedim) 4 (0-15 mm/h) and was within normal range.

**Figure 1** – Erosion at the pocket site and view of the battery through the skin

A temporary pacemaker was implanted and the battery and leads were removed with a lead extraction device. The new RV lead was inserted into the apicoseptum through the contralateral pectoral region and the dual pacemaker was implanted. The temporary pacemaker was not removed for 48 hours because of the stability problem of the RV lead during implantation. After 48 hours, the temporary pacemaker was removed as no problem was observed in the controls.

Hematoma and erosion were observed in the infected battery pocket site where the battery was removed (Figure 2). Dermatology and plastic surgery opinions were obtained and graft was not planned.



**Figure 2** – Hematoma at the pocket site

The patient went into ventricular fibrillation 5 days after the procedure and was defibrillated. The patient's ECG showed a complete AV block. RV lead was observed to be dislodged on scopy images (Figure 3). A temporary pacemaker was implanted and pacemaker lead revision was performed. After 48 hours, the temporary pacemaker was removed.

In the follow-up, it was seen that the RV lead was again thrown on the 9th day after the first procedure. Temporary pacemaker was placed again and epicardial pacemaker implantation was planned. The epicardial pacemaker was implanted on the 12th day (Figure 4). The cultures performed from the patient showed no growth. The patient was dicharged after 2 weeks of iv antibiotherapy.
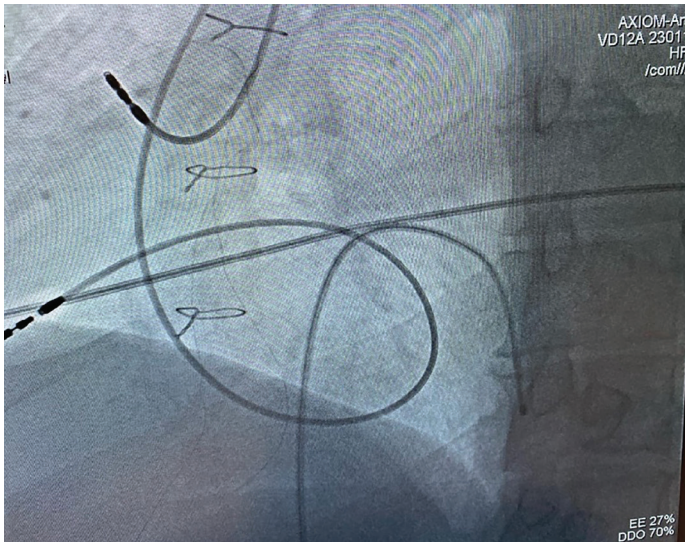


**Figure 3** – The RV lead appears to be thrown.
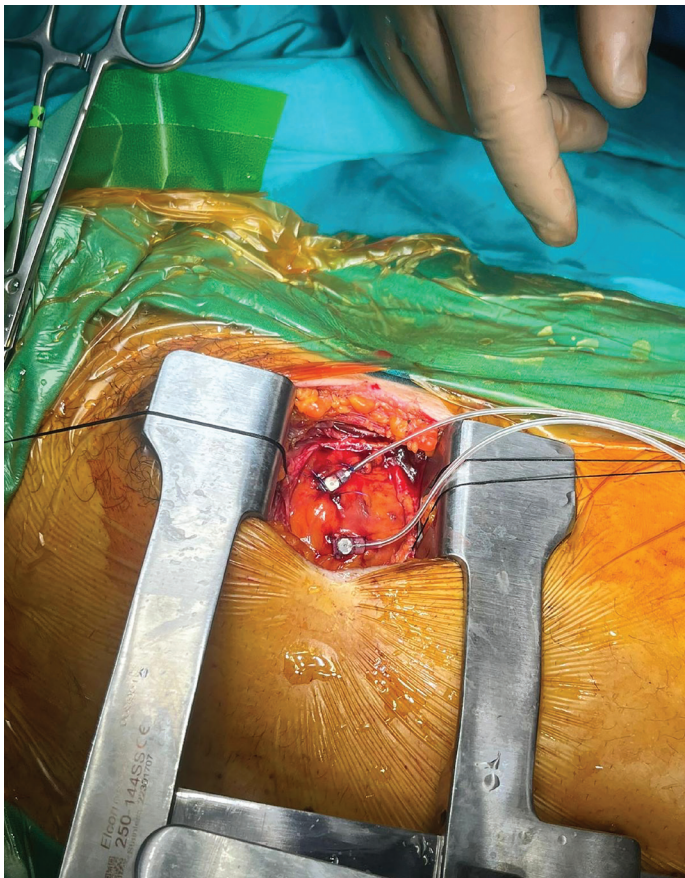


**Figure 4** – Epicardial lead implantation.

## Discussion

CIED infections may be limited to pocket site infection or may lead to systemic infection (4). When the risk factors for CIED infections are considered, it is known that infection increases as the number of implanted leads increases [4, 5]. Having a CRT device implanted, reoperation, male gender, being a young patient, and having a history of previous valve operation are risk factors in the development of CIED infections [3, 4]. In addition, heart failure, diabetes mellitus, corticosteroid use, and malignancy are among other risk factors [3, 4, 6]. One of the most important risk factors associated with CIED infections is postoperative hematoma [7]. A meta-analysis by Kewcharoen et al. showed that hematoma increased the risk of developing CIED infection by 6.3 times [8]. When the risk factors in our patient

were looked at, male gender, anticoagulant therapy, history of cardiac surgery due to congenital disease, and most importantly a history of postoperative hematoma were present.

Patients on antiaggregants or anticoagulants should be careful for pocket hematoma. Since antiplatelet drugs increase the likelihood of bleeding, it is recommended to take a break 5–10 days before, depending on the half-life of the drug [9, 10]. Bridging between anticoagulants is not recommended as it has been shown to increase the risk of bleeding [9, 11]. It is recommended to continue oral anticoagulant therapy in patients with high thromboembolic events [9]. In our patient, rivaroxaban treatment was interrupted for a short time without bridging in the first procedure, but in the second procedure, enoxaparin treatment was switched to enoxaparin because of the high risk of bleeding due to the extraction procedure to be performed in the patient and because the patient would be followed up with a temporary pacemaker and would undergo surgery. This was one of the factors that increased the risk of hematoma in the second procedure.

To reduce pocket hematoma, the duration of standard sandbagging can be extended, a sub-pocket small hole drainage method can be applied, a compression device can be used or a negative pressure vacuum drainage system can be applied if there is concurrent infection in the area. In our patient, prolonged standard sandbagging was applied [12–14].

In patients diagnosed with CIED infection; the crucial next step is to determine whether the device and leads should be removed or not. If there is a presentation of isolated erythema without drainage due to early inflammation after implantation, the patient should be followed up with careful observation. Lead and device removal is recommended in the presence of isolated pocket infection in which the device or leads are visible through the skin, cellulitis affecting the battery site without systemic infection findings, uncomplicated pocket infection in which the battery and lead are visible through the skin or abscess or fistula is present, or complicated pocket infection in which there are systemic infection findings or blood culture positivity or involvement on the lead. Antibiotics should be given for 14 days if there is no endocardial vegetation and for 4-6 weeks if there is [15]. In our patient, while there was no evidence of systemic infection, the battery and leads were visible through the skin. Therefore, the patient underwent lead and battery removal.

Epicardial pacemakers are usually implanted in pediatric patients. In adults; it is implanted in patients who have difficulty in endocardial lead placement, congenital heart disease, AV blocks, or bradycardia after valve and coronary revascularization operations [16]. Our patient had a previously existing congenital atrial septal defect with large right heart chambers and signs of right-sided overload. Since RV lead stabilization could not be achieved at the apex despite repeated attempts, a lead was placed in the apicoseptum, but during follow-up, it was observed that the patient's lead stabilization was constantly failing due to right ventricular structure and function. As the patient had a diagnosis of AV block, a dual pacemaker lead was implanted epicardially because RV lead stabilization could not be achieved despite repeated attempts.

## Conclusıon

Battery replacement of CIED is a relatively simple procedure compared to implantation, but caution is required in terms of infection. Especially in patients on anticoagulants, attention should be paid to hematoma, which is among the important risk factors for CIED infections.

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# Aspirin Intolerance in the Setting of Acute Coronary Syndrome: Case Report and Review of Literature

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## Abstract

Acute coronary syndrome (ACS) requires prompt intervention to prevent myocardial ischemia. This case report describes a patient's clinical journey, highlighting the challenges associated with aspirin intolerance and the necessity of an alternative antithrombotic approach. The patient, who presented with ACS and a documented history of aspirin-induced asthma and angioedema, was unable to undergo standard dual antiplatelet therapy (DAPT) with aspirin. Given the urgency of intervention and failed prior aspirin desensitization, ticagrelor and rivaroxaban were selected as alternative agents. The patient underwent successful percutaneous coronary intervention (PCI) with stent placement and was managed postoperatively using a modified antithrombotic regimen. The case underscores the importance of individualized therapy in aspirin-intolerant ACS patients and suggests a viable alternative strategy for anticoagulation and platelet inhibition. Patient outcomes were favorable, demonstrating effective ischemic risk mitigation without aspirin-related hypersensitivity reactions.

**Keywords:** acute coronary syndrome, aspirin intolerance, percutaneous coronary intervention.

## Introduction

Acute coronary syndrome (ACS) is a critical condition requiring immediate medical intervention to prevent myocardial ischemia and improve clinical outcomes [1]. Acetylsalicylic acid (aspirin) is a cornerstone in managing ischemic heart disease and preventing cardiovascular events [2]. Current guidelines recommend a standard dual antiplatelet therapy (DAPT) comprising aspirin and an oral P2Y12 platelet inhibitor, for example, clopidogrel (prasugrel) or ticagrelor (cangrelor), after percutaneous coronary interventions (PCIs) [3, 4]. However, managing patients with cardiovascular diseases who exhibit aspirin intolerance poses significant challenges, compromising the safety of standard treatment therapy [5, 6]. Although most European protocols indicate either low-dose aspirin challenge or aspiring desensitization as a management routine in clinical settings [7], acute administration of PCI in an emergency setting has not been included in practical guidelines and remains understudied [8, 9]. This case demonstrates an alternative therapeutic approach for aspirin-intolerant patients requiring urgent intervention. It highlights the feasibility of using a combination of ticagrelor and rivaroxaban and provides insights into individualized treatment strategies for such complex cases.

## Presentation of clinical case
### Demographics

A 54-year-old man arrived at the emergency department by ambulance with chest pain.

### Medical History

The patient had no history of chronic illnesses, prior myocardial infarctions, or cerebrovascular events. His family history was unremarkable. He had a documented allergy to aspirin, manifesting as aspirin-induced asthma and angioedema. A previous aspirin desensitization attempt in 1999 was unsuccessful. He had a 30-year smoking history (one pack per day).
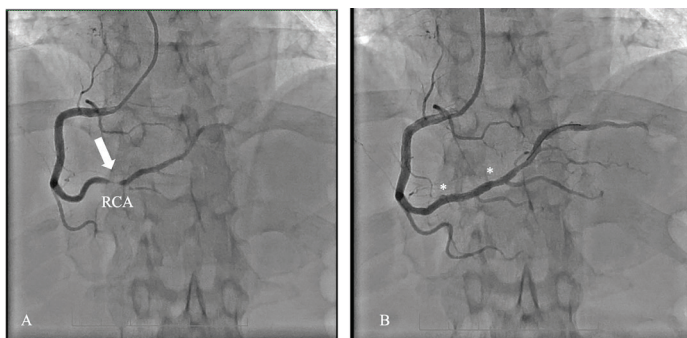
**Figure 1** – no text

## Presenting Complaint

The patient reported chest pain radiating to the left arm and jaw, lasting over 15 minutes. Symptoms progressively worsened over three days, prompting urgent medical attention.

## Diagnostic Assessment

- **Electrocardiogram (ECG):** Sinus rhythm (74 bpm), no ST-segment changes.
- **Laboratory Tests:** Troponin I increased from 0.07 ng/mL to 0.16 ng/mL within two hours, confirming non-ST elevation myocardial infarction (NSTEMI).
- **Echocardiography:** Left ventricular ejection fraction (LVEF) 62%, normal systolic function, mild mitral and tricuspid regurgitation, no pericardial effusion.

## Initial Management

The patient received ACS protocol-based care, including ticagrelor (180 mg) and heparin (5000 IU), while aspirin was omitted due to his allergy. He was transferred to a multidisciplinary hospital for further management.

## Interventions

Given his intolerance to aspirin and prior failed desensitization, an alternative strategy was adopted, excluding aspirin from the regimen. The patient underwent urgent percutaneous coronary intervention (PCI), placing an *Ultimaster Tansei* 3.5 × 18 mm stent in the RCA, restoring TIMI 3 flow. Additional anticoagulation included heparin (7500 IU, activated clotting time 255 sec).

## Follow-Up and Outcome

The patient remained stable after the procedure without complications. The post-PCI regimen included ticagrelor (180 mg), enoxaparin (0.1 mg/kg), and lipid-lowering therapy (rosuvastatin/ezetimibe 20/10 mg). Given his aspirin intolerance and refusal of repeat desensitization, he was discharged on ticagrelor (90 mg BID) and rivaroxaban (2.5 mg BID) for one year, with renal function monitoring to prevent adverse effects.

## Discussion

Aspirin intolerance in ACS patients poses a significant challenge, necessitating individualized management. Aspirin remains the gold standard for antithrombotic therapy due to its role in reducing myocardial infarction recurrence and cardiovascular complications [10]. However, allergic reactions may preclude its use, requiring alternative strategies to balance thrombotic and bleeding risks [11].

Recent studies found that a P2Y12 inhibitor in pair with a small dose of direct oral anticoagulant (DOAC) showed comparable thrombotic protection to DAPT while reducing bleeding risk [12]. Similarly, the ADRIFT trial (2020) demonstrated that rivaroxaban effectively maintained thrombin generation risk mitigation in patients in contrast to DAPT in the settings of PCI interventions [13]. In this case, due to an intolerance to aspirin, a ticagrelor-rivaroxaban regimen was used instead. Based on the PRECISE-DAPT score [14] (10 points), the patient required standard DAPT for one year. The selected treatment strategy minimized thrombotic risk while avoiding aspirin-related hypersensitivity reactions. This approach underscores the importance of personalized treatment strategies in aspirin-intolerant ACS patients. Future research should further evaluate aspirin-free antithrombotic regimens' long-term safety and efficacy through randomized controlled trials and real-world cohort studies [15].

## Conclusion

This case demonstrates a viable management approach for an ACS patient with aspirin intolerance and a history of failed desensitization intervention. We emphasize the importance of personalized management and the growing evidence supporting aspirin-free antithrombotic regimens in high-risk patients.

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