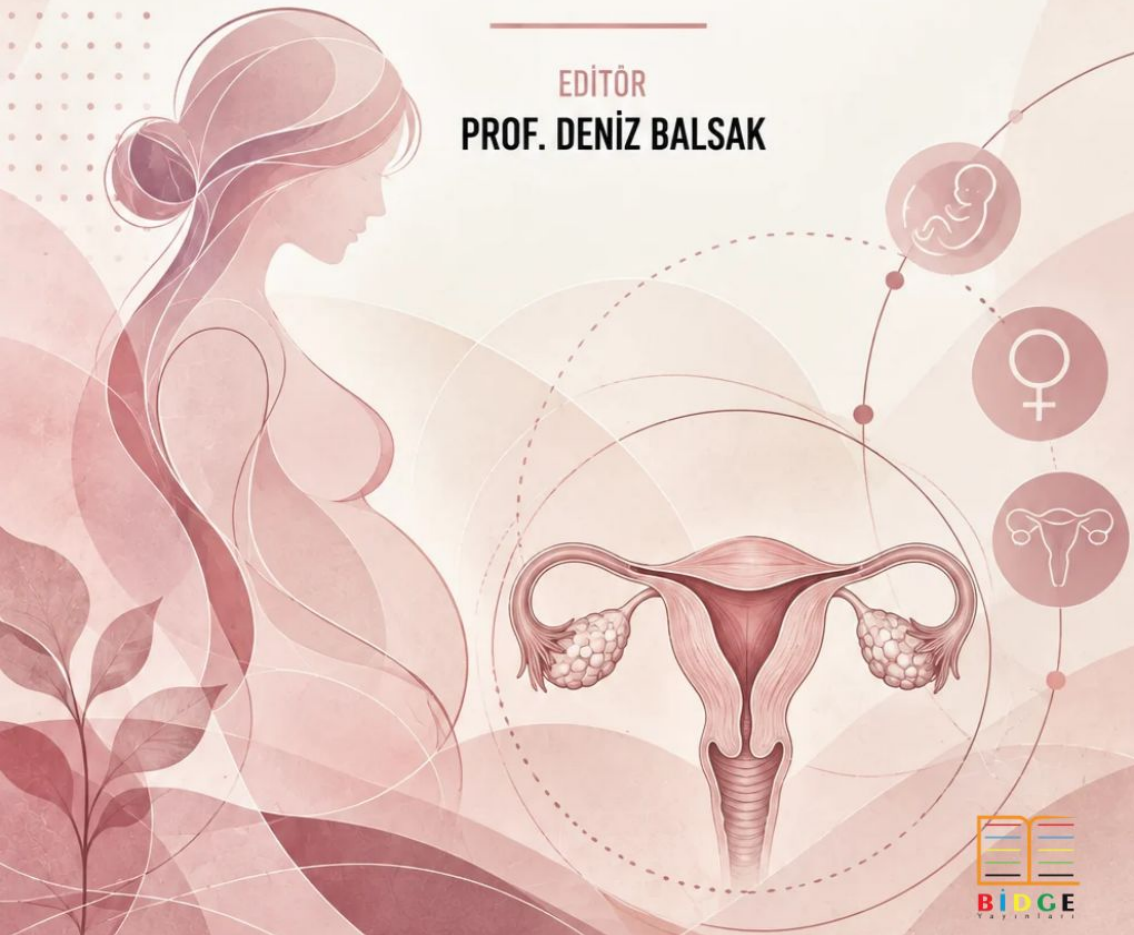
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CLINICAL ASSESSMENT AND THERAPEUTIC APPROACHES

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PROF. DENİZ BALSAK



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CHAPTER 1

ULTRASONOGRAPHIC ASSESSMENT OF AMNIOTIC FLUID VOLUME

ÖZGE ÖZTÜRK[1]

Introduction

Amniotic fluid is a fundamental component of the environment in which the fetus develops in utero. In addition to allowing fetal movement, contributing to protection of the umbilical cord from compression, and playing a role in fetal lung development, alterations in amniotic fluid volume may be associated with various maternal, fetal, and placental conditions (Brace, 1997; Brace & Cheung, 2014). Therefore, assessment of amniotic fluid volume is a fundamental component of obstetric ultrasonography (Salomon et al., 2022).

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Amniotic fluid volume (AFV) is not constant throughout pregnancy. The relative contribution of the mechanisms responsible for fluid production and removal changes at different stages of gestation. During the second half of pregnancy, fetal urine production and pulmonary fluid secretion are the major sources of fluid entering the amniotic cavity, whereas fetal swallowing and intramembranous absorption play important roles in fluid removal (Brace, 1997; Brace & Cheung, 2014).

Direct measurement of actual amniotic fluid volume is not feasible in routine clinical practice. Although dye-dilution techniques can be used in research to determine actual fluid volume, their invasive nature makes them unsuitable for routine obstetric practice (Magann et al., 2000). Clinical assessment therefore relies on ultrasonographic methods.

Amniotic fluid may be assessed subjectively by ultrasonography or semiquantitatively using the single deepest pocket (SDP; also termed the deepest vertical pocket, DVP) or the amniotic fluid index (AFI) (Salomon et al., 2022). Although both methods are widely used, neither directly measures actual amniotic fluid volume.

The choice between AFI and DVP is not merely a technical distinction. Randomized studies have shown that the method used can influence the frequency of oligohydramnios diagnosis and the associated obstetric interventions (Nabhan & Abdelmoula, 2008; Kehl et al., 2016). Accordingly, interpretation of amniotic fluid assessment should consider not only the numerical value obtained but also the measurement method, technique, gestational age, and clinical context.

This chapter reviews the physiological basis and gestational changes of amniotic fluid, sonographic assessment methods, AFI and DVP measurement techniques, factors affecting measurement reliability, evidence comparing AFI and DVP, the sonographic approach to decreased and increased amniotic fluid volume, special pregnancy settings, and recent developments.

Physiological Basis of Amniotic Fluid Volume

The formation and circulation of amniotic fluid change across gestation. Early in pregnancy, before complete keratinization of the fetal skin, fluid and solutes can pass between the fetal compartment and the amniotic cavity. As fetal skin keratinization progresses, the importance of this pathway decreases and fetal urine production becomes one of the principal sources of amniotic fluid (Brace, 1997).

During the second half of pregnancy, fetal urine production, fetal pulmonary fluid secretion, fetal swallowing, and intramembranous absorption are central to the regulation of amniotic fluid volume. Fetal urine and pulmonary fluid secretion contribute fluid to the amniotic cavity, whereas fetal swallowing and intramembranous absorption remove fluid from it (Brace, 1997; Brace & Cheung, 2014).

This physiological balance is important when evaluating abnormalities of amniotic fluid volume. Marked oligohydramnios or anhydramnios may develop when fetal renal function is severely impaired or when urine does not enter the amniotic cavity from the urinary tract. Conversely, conditions that impair fetal swallowing may be associated with increased amniotic fluid volume (Brace, 1997; Brace & Cheung, 2014).

Intramembranous absorption is an important mechanism involved in the transfer of fluid and solutes between the amniotic fluid and the fetal circulation. Regulation of amniotic fluid volume is therefore not simply a balance between fetal urine production and fetal swallowing; intramembranous transport mechanisms also contribute to volume regulation (Brace & Cheung, 2014).

Consequently, decreased or increased amniotic fluid volume detected on ultrasonography should not be regarded as an etiologic diagnosis in itself. Findings should be interpreted together with gestational age, fetal anatomy, fetal growth, and the clinical context.

Normal Amniotic Fluid Volume and Gestational Changes

Amniotic fluid volume and the ultrasonographic parameters used to estimate it change throughout pregnancy (Brace, 1997; Phelan et al., 1987; Moore & Cayle, 1990; Owen et al., 2019).

One of the classic studies evaluating changes in AFI throughout pregnancy was conducted by Phelan et al. A total of 262 AFI measurements were obtained in 197 pregnancies; AFI increased between 11 and 26 weeks of gestation, subsequently remained at approximately 16.2 ± 5.3 cm until term, and showed a tendency to decrease after 38 weeks (Phelan et al., 1987).

Moore and Cayle defined gestational age-specific AFI reference values, and their nomogram became one of the principal reference standards used in clinical studies for many years (Moore & Cayle, 1990).

More recently, Owen et al. used data from the NICHD Fetal Growth Studies-Singletons to develop a contemporary US reference standard (Owen et al., 2019). The analysis included 1,719 low-risk singleton pregnancies with available measurements. Both AFI and

SDP varied across gestation; AFI reached its maximum at approximately 26 weeks and SDP at approximately 33 weeks (Owen et al., 2019).

The same study identified statistically significant differences in AFI and SDP among maternal racial/ethnic groups; however, the absolute differences were small and were considered to be of limited clinical significance (Owen et al., 2019).

These data highlight the need to distinguish gestational age-specific reference percentiles from the clinical thresholds used to diagnose oligohydramnios or polyhydramnios. Reference curves describe the physiological distribution in a healthy population, whereas clinical thresholds are used for obstetric assessment and risk classification.

Sonographic Assessment of Amniotic Fluid

Amniotic fluid volume may be assessed subjectively or semiquantitatively. According to the ISUOG guideline for the routine mid-trimester fetal ultrasound scan, amniotic fluid can be assessed subjectively as normal or abnormal (decreased/increased) or measured semiquantitatively using DVP or AFI (Salomon et al., 2022).

For subjective assessment, the uterus is systematically surveyed to evaluate the overall amount and distribution of fluid surrounding the fetus. Marked oligohydramnios or polyhydramnios may be readily recognized by an experienced examiner; however, semiquantitative methods provide a more standardized assessment when measurements are near threshold values.

Single Deepest Vertical Pocket

The single deepest vertical pocket method is referred to in the literature as SDP, DVP, or maximum vertical pocket (MVP). The basic principle is to measure the largest vertical pocket of fluid that contains no fetal parts or umbilical cord (Salomon et al., 2022).

In the ISUOG mid-trimester guideline, DVP ≤2.0 cm is classified as decreased amniotic fluid volume, DVP >2.0 to ≤8.0 cm as normal amniotic fluid volume, and DVP >8.0 cm as increased amniotic fluid volume (Salomon et al., 2022).

In the ACOG document on antenatal fetal surveillance, isolated oligohydramnios is defined as a single deepest vertical pocket <2 cm (American College of Obstetricians and Gynecologists [ACOG], 2021).

Thus, "≤2 cm" and "<2 cm" are used for DVP/SDP in different guidelines. This small distinction is particularly relevant in academic writing, and the guideline on which a threshold is based should be specified.

Amniotic Fluid Index

AFI is a semiquantitative method based on assessment of the uterus in four quadrants. An appropriate vertical fluid pocket is measured in each quadrant, and the four measurements are summed to obtain the AFI (Phelan et al., 1987).

According to the ISUOG mid-trimester guideline, AFI can be calculated from approximately 18 weeks of gestation by measuring vertical fluid pockets free of umbilical cord and fetal parts in the four uterine quadrants (Salomon et al., 2022).

The AFI and DVP thresholds used to diagnose polyhydramnios differ slightly among guidelines. SMFM defines

polyhydramnios in singleton pregnancies as DVP ≥8 cm or AFI ≥24 cm (Society for Maternal-Fetal Medicine [SMFM] et al., 2018). In the ISUOG mid-trimester guideline, DVP >8 cm is classified as increased amniotic fluid volume (Salomon et al., 2022).

Because of these differences, particularly for borderline measurements, the guideline on which the definition is based should be stated.

Grading of Polyhydramnios

ACOG classifies polyhydramnios as mild, moderate, or severe according to its degree (ACOG, 2021):

Table 1. Ultrasonographic grading of polyhydramnios

Grade	DVP	AFI
Mild	8-11 cm	24.0-29.9 cm
Moderate	12-15 cm	30.0-34.9 cm
Severe	≥16 cm	≥35 cm

Source: American College of Obstetricians and Gynecologists (2021).

These values are clinical classification thresholds and should not be equated with gestational age-specific percentiles in a normal population.

Factors Affecting Measurement Reliability

Although amniotic fluid measurement appears technically straightforward, fetal movements, the position of the umbilical cord within fluid pockets, and observer-related differences can affect the measurement.

The DVP selected for measurement should contain no fetal parts or umbilical cord (Salomon et al., 2022). Color Doppler may be helpful when it is unclear on grayscale imaging whether the

umbilical cord lies within a fluid pocket. However, color Doppler use has been shown to affect measurement results.

Magann et al. measured AFI and SDP with and without color Doppler in 67 pregnancies and compared the results with actual amniotic fluid volume determined by dye dilution (Magann et al., 2001). Without color Doppler, 3% of cases were classified as having low fluid volume by AFI, whereas this proportion increased to 21% when color Doppler was used. Color Doppler did not improve detection of truly low fluid volume and resulted in nine pregnancies with normal actual fluid volume being classified as low fluid volume by AFI (Magann et al., 2001).

These findings indicate that color Doppler may assist in excluding the umbilical cord from a measured pocket, but routine use may increase the ultrasonographic classification of low fluid volume (Magann et al., 2001).

Intraobserver and Interobserver Variability

Both intraobserver and interobserver variability occur in amniotic fluid measurements.

Rutherford et al. evaluated the reproducibility of AFI measurements in 23 term and post-term pregnancies (Rutherford et al., 1987). For low or normal fluid volumes, the mean variability between repeated AFI measurements by the same observer was 1.0 cm, whereas mean variability between different observers was 2.0 cm. At above-normal fluid volumes, variability increased by 2.5- to 3-fold (Rutherford et al., 1987).

In the study by Peedicayil et al., the intraobserver intraclass correlation coefficient (ICC) for AFI was >0.8, whereas the interobserver ICC was 0.67. When AFI was categorized as <8 cm or

≥8 cm, disagreement in classification between observer pairs reached 22-28% (Peedicayil et al., 1994).

These data indicate that technical and observer-related variability should be considered, particularly when measurements are close to clinical thresholds.

How Accurately Do AFI and DVP Reflect Actual Amniotic Fluid Volume?

A fundamental limitation of AFI and DVP is that both are indirect indicators of actual amniotic fluid volume.

Magann et al. compared AFI and SDP measurements with actual amniotic fluid volume determined by dye dilution after amniocentesis in 179 singleton pregnancies (Magann et al., 2000). For identifying pregnancies with actual fluid volume below the gestational age-specific 5th percentile, AFI ≤5 cm had a sensitivity of 10% and specificity of 96%, whereas SDP ≤2 cm had a sensitivity of 5% and specificity of 98%.

For identifying high actual fluid volume, AFI >20 cm had a sensitivity of 29% and specificity of 97%, whereas SDP >8 cm had a sensitivity of 29% and specificity of 94% (Magann et al., 2000).

These findings demonstrate that both AFI and SDP have limited sensitivity for detecting truly abnormal amniotic fluid volume. Ultrasonographic measurements should therefore be regarded as semiquantitative indicators developed for clinical use rather than as direct measures of actual fluid volume.

AFI or DVP? Evidence from Randomized Studies

One of the most clinically relevant differences between AFI and DVP is the frequency with which oligohydramnios is diagnosed.

The PubMed-indexed 2008 Cochrane systematic review by Nabhan and Abdelmoula included four randomized trials with a total of 3,125 pregnant women (Nabhan & Abdelmoula, 2008). Oligohydramnios was diagnosed more frequently when AFI was used than when DVP was used (RR 2.33; 95% CI 1.67-3.24). Labor induction (RR 2.10; 95% CI 1.60-2.76) and cesarean delivery for fetal distress (RR 1.45; 95% CI 1.07-1.97) were also more frequent in the AFI group (Nabhan & Abdelmoula, 2008).

In contrast, neither method was shown to be superior with respect to neonatal intensive care unit admission, umbilical artery pH <7.1, meconium, a 5-minute Apgar score <7, or overall cesarean delivery rate (Nabhan & Abdelmoula, 2008).

The SAFE trial conducted by Kehl et al. also compared AFI and SDP in a randomized design (Kehl et al., 2016). The study included 1,052 term singleton pregnancies at four centers in Germany.

There was no significant difference between the groups in the primary outcome of neonatal intensive care unit admission. However, oligohydramnios was diagnosed in 9.8% of the AFI group and 2.2% of the SDP group; induction of labor for oligohydramnios occurred in 12.7% and 3.6%, respectively (Kehl et al., 2016).

In the SAFE trial, oligohydramnios was defined as AFI ≤5 cm in the AFI group and as the absence of a fluid pocket measuring at least 2 × 1 cm in the SDP group (Kehl et al., 2016). This methodological detail indicates that the SDP criterion used in SAFE is not identical to the criterion of a vertical diameter <2 cm used in some current guidelines.

Taken together, randomized data indicate that AFI use is associated with more diagnoses of oligohydramnios and more obstetric interventions than DVP use, while AFI has not demonstrated superiority for the major peripartum outcomes evaluated (Nabhan & Abdelmoula, 2008; Kehl et al., 2016).

The ISUOG mid-trimester guideline also states that AFI may be preferred for assessment of polyhydramnios and DVP for assessment of oligohydramnios; this is a Grade C recommendation (Salomon et al., 2022).

Sonographic Approach to Decreased Amniotic Fluid Volume

Oligohydramnios is not an etiologic diagnosis in itself. When decreased fluid volume is identified, the finding should be interpreted in relation to gestational age and the clinical context.

The source of the threshold used is important. ISUOG classifies DVP ≤2.0 cm as decreased amniotic fluid volume (Salomon et al., 2022), whereas the ACOG antenatal fetal surveillance document uses SDP <2 cm as the criterion for isolated oligohydramnios (ACOG, 2021).

When decreased amniotic fluid is detected, fetal anatomy should be reassessed. Particularly when marked oligohydramnios or anhydramnios is present at an early gestational age, the fetal kidneys, bladder, and urinary tract should be carefully examined. The possibility of membrane rupture should be included in the clinical evaluation.

When fetal growth restriction is present, amniotic fluid measurement should not be interpreted independently of fetal biometry and Doppler assessment. ACOG considers pregnancies with fetal growth restriction accompanied by oligohydramnios or

maternal comorbidity within a distinct clinical risk context for antenatal surveillance (ACOG, 2021).

Isolated Oligohydramnios

The ACOG antenatal fetal surveillance document defines isolated oligohydramnios as SDP <2 cm and notes that the natural history of this condition remains incompletely understood (ACOG, 2021).

Accordingly, decreased amniotic fluid volume associated with fetal growth restriction, fetal anomaly, membrane rupture, or maternal disease should be distinguished from isolated oligohydramnios.

Because this chapter focuses on ultrasonographic assessment, the frequency of antenatal surveillance and timing of delivery are not discussed in detail.

Borderline AFI

An AFI of 5.1-8.0 cm is frequently described in the literature as “borderline oligohydramnios” or “borderline AFI.” However, there is no established consensus that this range constitutes an independent clinical disease category or regarding its management.

The 2025 systematic review and meta-analysis by Sgayer et al. included eight observational studies, comparing 799 cases of borderline oligohydramnios with 1,512 singleton pregnancies with normal AFI (Sgayer et al., 2025).

Borderline oligohydramnios was associated with overall cesarean delivery (OR 2.20; 95% CI 1.70-2.84), cesarean delivery for fetal distress (OR 2.70; 95% CI 1.70-4.30), a 5-minute Apgar score <7 (OR 2.18; 95% CI 1.38-3.44), low birth weight (OR 2.32;

95% CI 1.27-4.25), and neonatal intensive care unit admission (OR 2.63; 95% CI 1.63-4.24) (Sgayer et al., 2025).

However, the studies included in the meta-analysis were observational. These findings therefore do not establish that borderline AFI causes the reported adverse outcomes or that a specific obstetric intervention improves outcomes in these pregnancies.

Sonographic Approach to Increased Amniotic Fluid Volume

Thresholds used to define polyhydramnios may differ slightly among guidelines.

SMFM Consult Series #46 defines polyhydramnios in singleton pregnancies as DVP ≥8 cm or AFI ≥24 cm (SMFM et al., 2018). This SMFM document was reaffirmed in 2024.

ACOG classifies polyhydramnios as mild when DVP is 8-11 cm or AFI is 24.0-29.9 cm, moderate when DVP is 12-15 cm or AFI is 30.0-34.9 cm, and severe when DVP is ≥16 cm or AFI is ≥35 cm (ACOG, 2021).

When polyhydramnios is identified, assessment should not be limited to grading the amount of fluid. SMFM states that detection of polyhydramnios should prompt evaluation for an underlying etiology. Although a substantial proportion of mild cases are idiopathic, the most common pathological causes are maternal diabetes and fetal anomalies; congenital infection and alloimmunization are also possible causes (SMFM et al., 2018).

Therefore, when polyhydramnios is detected, fetal anatomy should be systematically reassessed and potential maternal and fetal causes should be investigated in the appropriate clinical context.

Assessment of Amniotic Fluid in Special Clinical Settings

Second Trimester

The ISUOG mid-trimester ultrasound guideline states that AFI can be measured using the four-quadrant technique from approximately 18 weeks of gestation (Salomon et al., 2022).

When severe oligohydramnios or anhydramnios is detected in the early second trimester, the fetal urinary tract and bladder should be evaluated in detail, and the possibility of membrane rupture should be considered in the clinical context.

Multiple Pregnancy

In multiple pregnancies, amniotic fluid should be assessed separately for each fetal amniotic compartment.

According to the updated 2025 ISUOG guideline on twin pregnancy, amniotic fluid volume should be assessed for both fetuses at every ultrasound examination. In monochorionic diamniotic twin pregnancies, the amniotic fluid volume of each fetus should be assessed and documented using DVP for screening for twin-to-twin transfusion syndrome (TTTS) (Khalil et al., 2025).

This approach underscores the importance of assessing each amniotic compartment separately rather than using a single uterine AFI value, particularly in diamniotic twin pregnancies.

Contemporary Reference Values: 2026 Data from Türkiye

A substantial proportion of classic AFI reference data were established many years ago. Consequently, studies developing gestational age-specific reference curves in different populations using contemporary ultrasound technology are valuable.

The prospective cross-sectional study by Karaduman et al., published in 2026, included 507 healthy singleton pregnancies at 14-28 weeks of gestation in Türkiye (Karaduman et al., 2026). One measurement was obtained from each pregnancy, and AFI and SDP measurements were performed by two perinatologists using a shared written protocol.

Gestational age-specific P3-P97 percentile curves were constructed. AFI increased from 105 mm at 14 weeks to 163 mm at 28 weeks ($r = 0.609$; $p < 0.001$), while SDP increased from 38 mm to 55 mm over the same period ($r = 0.581$; $p < 0.001$) (Karaduman et al., 2026).

Median AFI values between 16 and 28 weeks were 1.7 cm higher than the classic Moore-Cayle reference, with the difference reaching 2.3 cm at some gestational ages (Karaduman et al., 2026).

Interobserver reliability was reported as ICC 0.976 for AFI and ICC 0.920 for SDP (Karaduman et al., 2026).

This study provides contemporary second-trimester AFI and SDP reference curves for healthy singleton pregnancies in Türkiye. However, gestational age-specific reference curves and the clinical thresholds used for oligohydramnios and polyhydramnios serve different purposes and should not be used interchangeably.

Emerging Technologies and Automated Measurement

With the development of artificial intelligence applications in obstetric ultrasonography, studies have explored automation of fetal biometry and amniotic fluid assessment.

In a 2023 study by Slimani et al., deep-learning models were developed to automate fetal biometry and amniotic fluid

measurements (Slimani et al., 2023). The models were trained using a database of 172,293 de-identified fetal ultrasound images together with additional open datasets and were subsequently evaluated on prospectively acquired ultrasound videos from 172 pregnant women at four healthcare centers in Morocco.

The investigators reported that the 95% limits of agreement between model and operator measurements were narrower, across the evaluated parameters, than previously reported expert intraobserver and interobserver variability limits (Slimani et al., 2023).

These findings suggest that automated measurement systems may contribute to standardization of ultrasonographic measurements in the future. However, current evidence is insufficient to support replacement of standard obstetric ultrasonographic assessment performed by an experienced operator.

Sonographic Approach in Clinical Practice

When assessing amniotic fluid, the uterus should first be surveyed globally and the distribution of fluid evaluated. When a semiquantitative measurement is required, DVP or AFI may be used according to the clinical setting.

Randomized evidence supports the use of DVP in the assessment of oligohydramnios. Compared with AFI, DVP use is associated with fewer diagnoses of oligohydramnios and fewer obstetric interventions, while AFI has not demonstrated superiority for the major peripartum outcomes evaluated (Nabhan & Abdelmoula, 2008; Kehl et al., 2016).

An appropriate fluid pocket free of fetal parts and umbilical cord should be selected for measurement (Salomon et al., 2022).

Color Doppler may be helpful when the umbilical cord is difficult to distinguish on grayscale imaging; however, its use may increase classification of low fluid volume (Magann et al., 2001).

Measurement variability should be considered for values close to clinical thresholds. Both intraobserver and interobserver differences in AFI have been shown to be large enough to affect clinical classification (Rutherford et al., 1987; Peedicayil et al., 1994).

When abnormal fluid volume is detected, assessment should not end with reporting the AFI or DVP value alone. Findings should be interpreted together with gestational age, fetal anatomy, fetal growth, and the clinical context.

Conclusion

Ultrasonographic assessment of amniotic fluid volume is a fundamental component of obstetric ultrasonography. Although AFI and DVP are widely used in clinical practice, neither directly measures actual amniotic fluid volume, and both have limitations in identifying truly abnormal fluid volume (Magann et al., 2000).

Ultrasonographic measurements of amniotic fluid change with gestational age. In addition to classic reference studies, the NICHD Fetal Growth Studies and data published from Türkiye in 2026 demonstrate that AFI and SDP vary throughout pregnancy (Owen et al., 2019; Karaduman et al., 2026). Gestational age-specific physiological reference values should therefore be distinguished from clinical diagnostic thresholds.

Randomized data comparing AFI and DVP show that AFI use results in more diagnoses of oligohydramnios and more obstetric interventions, whereas superiority of AFI over DVP has not been

demonstrated for the major peripartum outcomes evaluated (Nabhan & Abdelmoula, 2008; Kehl et al., 2016).

Guidelines differ slightly in their threshold values. Values used by ISUOG, ACOG, and SMFM should therefore be interpreted with reference to their respective sources (Salomon et al., 2022; ACOG, 2021; SMFM et al., 2018). These differences should not be merged into a single universal definition in academic writing; the threshold used and the guideline on which it is based should be clearly stated.

In conclusion, amniotic fluid measurement should not be interpreted as an isolated numerical parameter. A measurement obtained using the correct technique should be interpreted together with gestational age, fetal anatomy, fetal growth, and the clinical context.

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CHAPTER 2

Pelvic Floor Muscle Spasm And Its Neurophysiological Evaluation: Literature Review

Running Head: Neurophysiology And Pelvic Floor Muscle Spasm

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ABSTRACT

Pelvic floor muscle spasm is a condition characterized by involuntary and persistent contractions of the muscles that make up the pelvic floor, which can lead to pain, urinary and bowel problems, and sexual dysfunction. The literature indicates that neurophysiological methods play a significant role in the evaluation of this condition. Methods such as electromyography (EMG), nerve conduction studies, and reflex tests help determine the source and severity of the spasm by examining the activity of the pelvic floor muscles and the neuromuscular relationship. These assessments provide important information in the diagnosis of pelvic floor dysfunctions, differentiating them from other neurological or muscular disorders, and developing an appropriate treatment plan. Literature reviews show that neurophysiological assessment techniques are a valuable tool for better understanding pelvic floor muscle spasm and improving treatment processes.

Keywords: Neurophysiology, Pelvic Floor ,Muscle Spasm, Urogynecology

What is already known on this topic?

- Pelvic floor muscle spasm is associated with chronic pelvic pain, urinary and bowel dysfunction, and sexual dysfunction.
- Neurophysiological assessment methods such as electromyography (EMG), nerve conduction studies, and reflex testing are used to evaluate pelvic floor muscle function and neuromuscular control.

- Accurate diagnosis of pelvic floor muscle spasm is often challenging because its symptoms overlap with other pelvic, neurological, and musculoskeletal disorders.

What this study adds?

- This review summarizes current evidence regarding the neurophysiological mechanisms underlying pelvic floor muscle spasm.
- It highlights the clinical value of neurophysiological assessment methods in the diagnosis and differential diagnosis of pelvic floor muscle spasm.
- The review emphasizes the importance of integrating neurophysiological findings into multidisciplinary evaluation and treatment planning and identifies future research directions for standardized assessment protocols.

Introduction

The pelvic floor muscles consist of a complex structure of muscle and connective tissue that plays a crucial role in supporting pelvic organs, maintaining urinary and fecal continence, and sustaining sexual function. The pelvic floor comprises muscles, ligaments, and fascial structures that support pelvic organs such as the bladder, uterus, prostate, and rectum. These structures work in coordination with the nervous system to contribute to maintaining continence and pelvic stability (1). Dysfunctions in the pelvic floor muscles can lead to various clinical conditions known as pelvic floor dysfunctions. These conditions include urinary incontinence, fecal incontinence, pelvic organ prolapse, chronic pelvic pain, and sexual dysfunction (2). Pelvic floor muscle spasm, a significant cause of pelvic floor dysfunctions, is characterized by involuntary and continuous contraction of the pelvic floor muscles and is often associated with symptoms such as pelvic pain, difficulty urinating, and defecation problems (3). Changes in neuromuscular control mechanisms and increased muscle tone play an important role in the occurrence of this condition. Therefore, understanding the anatomy, physiology and neurophysiological characteristics of the pelvic floor muscles is of great importance for correctly identifying pelvic floor muscle spasm and determining appropriate treatment approaches (4).

2. Anatomy and Physiology of the Pelvic Floor

The pelvic floor is a complex anatomical region located at the lower part of the pelvic cavity and consists of muscles, ligaments, fascia, and neural structures. This structure plays a crucial role in supporting pelvic organs such as the bladder, rectum, and in women the uterus and vagina. In addition, it contributes to several essential physiological functions, including urinary and fecal continence, sexual function, and the mechanisms involved in childbirth (5).The main structural component of the pelvic floor is the pelvic diaphragm. The primary muscles of the pelvic diaphragm are the levator ani and coccygeus muscles. The levator ani muscle group is composed of the puborectalis, pubococcygeus, and iliococcygeus muscles. These muscles attach to the inner walls of the pelvis and help maintain the position of the pelvic organs while providing support during increases in intra-abdominal pressure (6). The levator ani muscle also plays a functional role in regulating urination, defecation, and sexual activity (7). Another important function of the pelvic floor is its contribution to the continence mechanism while supporting the pelvic organs. Pelvic floor muscles surround openings such as the urethra, vagina, and anus, helping to maintain closure of these structures and thereby assisting in the control of urine and feces (8). Contraction of these muscles elevates the pelvic organs, whereas relaxation allows physiological processes such as urination and defecation to occur. The innervation of the pelvic floor muscles is largely provided by nerves originating from the sacral plexus. In particular, the pudendal nerve plays a significant role in both motor and sensory control of the pelvic floor muscles. Through this neural regulation, pelvic floor muscles are able to function both voluntarily and reflexively (9). From a physiological perspective, the pelvic floor muscles work in coordination with other muscle groups in the body. In particular, they function together with the diaphragm, abdominal muscles, and paraspinal muscles to regulate intra-abdominal pressure. This coordination is important for maintaining lumbopelvic stability and supporting the spine.During inhalation, the movement of the diaphragm is accompanied by relaxation of the pelvic floor muscles, while during exhalation these muscles contract again, helping to maintain pressure balance within the abdominal cavity. The anatomical and functional integrity of the pelvic floor can be influenced by various factors. Pregnancy, childbirth trauma, aging, hormonal changes, and obesity may lead to weakening of the pelvic floor muscles. Such weakening can result in clinical conditions including pelvic organ prolapse, urinary incontinence, and sexual dysfunction. Therefore, understanding the anatomy and physiology of the pelvic floor is essential for preventing pelvic floor disorders and developing effective treatment strategies.

3. Definition and Pathophysiology of Pelvic Floor Muscle Spasm

Pelvic floor muscle spasm is a condition characterized by involuntary and persistent contraction of the muscles forming the pelvic floor, particularly the levator ani muscle, and is often associated with chronic pelvic pain syndrome. This condition can lead to symptoms such as pain in the pelvic region, difficulty urinating and defecating, and sexual dysfunction. Pathophysiologically, pelvic floor muscle spasm is a multifactorial process; neuromuscular dysfunction results in increased muscle tone and decreased relaxation capacity, while prolonged pain stimuli cause central and peripheral sensitization, contributing to the chronicity of pain (10,11). This mechanism is similar to myofascial pain syndrome. Furthermore, factors such as stress and anxiety increase sympathetic activity via the autonomic nervous system, raising muscle tone, and this can occur in conjunction with functional disorders such as irritable bowel syndrome. Local ischemia and metabolic changes developing in persistently contracted muscles lead to lactate accumulation and the release of pain mediators, further worsening symptoms (12). In addition, viscerosomatic reflexes resulting from pelvic organ diseases such as endometriosis can also contribute to the development of reflex spasms in the pelvic floor muscles.

4. Clinical Manifestations and Symptoms

The clinical signs and symptoms of pelvic floor muscle spasm manifest across a wide spectrum depending on the underlying muscle hypertonicity. Patients frequently complain of chronic pain in the pelvic region that is dull, burning, or pressure-like, and this pain may worsen with sitting, prolonged standing, or sexual activity. Continuous contraction of the muscles forming the pelvic floor, particularly at the level of the levator ani muscle, can lead to lower urinary tract symptoms such as difficulty urinating, frequent urge to urinate, or incomplete emptying. Similarly, anorectal complaints such as difficulty defecating, constipation, or incomplete emptying are also common. Sexual dysfunction, such as dyspareunia in women and pain during ejaculation in men, may accompany the condition (13). Furthermore, in some patients, the pain may radiate to the perineum, lower abdomen, lower back, or inner thigh, creating a clinical presentation that overlaps with chronic pelvic pain syndrome. The severity of symptoms generally increases with factors such as stress, anxiety, and fatigue, significantly affecting the patients' quality of life.

5. Diagnostic Approaches

The diagnostic approach to pelvic floor muscle spasm involves a detailed history, careful physical examination, and, if necessary, the combined evaluation of auxiliary diagnostic

methods. Patients should be thoroughly questioned about the character and duration of their pain, triggering factors, and any accompanying urinary, bowel, or sexual dysfunction. Physical examination particularly assesses tenderness, increased muscle tone, and trigger points in the levator ani muscle. Digital pelvic examination plays a significant role in determining the relaxation capacity of the muscles and their pain response. Methods such as superficial electromyography (EMG), anorectal manometry, and ultrasound can be used to support the diagnosis. Furthermore, chronic pelvic pain syndrome, infections, or structural pathologies that may cause similar symptoms should be ruled out. Therefore, the diagnostic process generally requires a multidisciplinary approach, and accurate diagnosis is critical for establishing an appropriate treatment plan.

6.Neurophysiological Evaluation Methods

Pelvic floor muscle spasm is a condition characterized by an abnormal increase in the resting tone of these muscles, often presenting with symptoms such as chronic pelvic pain, urinary incontinence, and bowel dysfunction (14). Neurophysiological evaluation methods are critical for identifying the underlying neurogenic causes of these spasms (nerve damage, reflex arc abnormalities) and for objectively measuring the dysfunction (15-17).

- **Major Neurophysiological Assessment Methods**

The primary methods used to evaluate pelvic floor function are categorized below. These methods can be summarized as follows (18):

Electromyography (EMG): This is the most commonly used method. It measures the electrical activity of the muscle during rest, contraction, and relaxation.

Concentric Needle EMG (CNEMG): It is considered the "gold standard" for detecting signs of denervation (nerve loss) or reinnervation (re-nerving) in muscle fibers. Changes in motor unit potentials (MUPs) are examined in cases of spasm.

Kinesiological EMG (kEMG): It evaluates muscle coordination during functions such as urination or defecation (e.g., dyssynergia, where the sphincter fails to relax while the detrusor contracts).

Surface EMG (sEMG): Less invasive; it is typically used to monitor muscle activity during biofeedback and rehabilitation processes.

Sacral Reflex Studies: Tests the integrity of the sacral reflex arc (S2–S4 segments).

Bulbocavernosus Reflex (BCR): Measures sphincter contraction in response to clitoral or penile stimulation. Delayed or absent responses may indicate lesions of the nerve root or conus medullaris.

Somatosensory Evoked Potentials (pSEP): Assesses the integrity of sensory pathways from the pudendal nerve to the cerebral cortex. Used to detect nerve compression or spinal cord lesions.

Motor-Evoked Potentials (pMEP): Assesses central motor pathways by measuring the motor response of the pelvic floor muscles to magnetic stimulation delivered from the brain or lumbosacral roots.

Pudendal Nerve Terminal Motor Latency (PNTML): Measures the conduction velocity in the fastest motor fibers of the pudendal nerve. However, its routine use is controversial because its reproducibility and clinical correlation are currently considered low (18,19).

Perineal Sympathetic Skin Response (pSSR): Assesses the function of the sympathetic autonomic nervous system and the activity of sweat glands in the pelvic region (20).

- **Other Complementary Assessment Tools**

In addition to neurophysiological tests, the following methods are also used to measure the mechanical and anatomical effects of spasm (19):

Manometry: Objectively assesses muscle tone (hypertonicity) by measuring pressure within the vaginal or anal canal.

Urodynamics: Identifies spasm-related voiding disorders by examining the pressure-flow relationship between the bladder and the sphincter.

Imaging (MRI and Ultrasound): Helps dynamically monitor structural damage, asymmetries, or changes in pelvic organ position caused by spasm.

To determine which of these methods is appropriate for you, a detailed clinical evaluation by a urogynecologist or pelvic floor physical therapist is recommended (21,22).

7. Differential Diagnosis

Pelvic floor muscle spasm is generally not a disease in its own right but rather arises as a result of or in conjunction with another underlying condition. In the differential diagnosis of this condition, systemic, gynecological, and neurological diseases that cause similar symptoms (pain, urinary/bowel problems) but operate through different mechanisms must be carefully evaluated (23).

- **Major Differential Diagnosis Groups**

In a patient presenting with pelvic pain and dysfunction, the following conditions should be ruled out (24,25).

Urological Conditions:

Interstitial Cystitis (Painful Bladder Syndrome): Characterized by suprapubic pain that increases with bladder fullness and decreases upon voiding. This condition may be diagnosed concurrently in up to 90% of patients with pelvic floor spasm.

Recurrent Urinary Tract Infections (UTIs): In the presence of infection, muscles may spasm as a protective response; culture results are diagnostic.

Prostatitis / Prostatodynia (in men): Symptoms of pelvic floor dysfunction are nearly identical to those of this condition; it is distinguished based on the presence of infection or inflammation.

Gynecological Conditions:

Endometriosis: Deep pain associated with the menstrual cycle (cyclic) is typical. Inflammation caused by endometriotic lesions leads to chronic "protective" muscle spasms (guarding) in the pelvic floor muscles.

Vulvodynia: Chronic burning and pain in the external genital area that worsens with touch.

Pelvic Organ Prolapse: The descent of organs due to muscle weakness or overstretching; spasms sometimes originate from fatigued muscles attempting to provide support against this prolapse.

Neurological and Neurogenic Conditions:

Pudendal Neuralgia: A burning and stabbing pain that worsens when sitting, resulting from compression of the pudendal nerve. The Nantes criteria are used to establish this diagnosis.

Lumbar Disc Herniation and Lumbosacral Disc Disorders: Pain radiating from the lower back may mimic spasms in the pelvic region.

Pudendal Nerve Injury: May develop following childbirth trauma or surgical interventions.

Gastrointestinal Conditions:

Irritable Bowel Syndrome (IBS): Bloating and changes in bowel habits may coincide with pelvic floor spasms.

Anorectal Disorders: Anal fissures or fistulas trigger spasms in the sphincter and pelvic muscles in response to pain (26).

- **Key Differences in Diagnosis**

In differential diagnosis, clinicians focus on the following characteristics:

Nature of the Pain: While muscle spasms typically feel like "pressure, heaviness, or a tight band," nerve pain is described as "an electric shock or burning sensation."

Triggering Factors: Endometriosis pain typically peaks during menstruation, whereas muscle spasm can be triggered by prolonged sitting or physical activity.

Physical Examination: Direct tenderness of the muscles during a single-finger vaginal or rectal examination is the strongest finding distinguishing spasm from pain originating in other organs (27, 28).

8. Treatment Approaches

Treatment for pelvic floor muscle spasm (hypertonicity) typically requires a multidisciplinary approach rather than a single method. The primary goal of treatment is to relax tense muscles, break the pain cycle, and normalize pelvic organ function (29).

- **Pelvic Floor Physical Therapy (Gold Standard)**

This is the most effective treatment method. Unlike traditional exercises (such as Kegels), the focus here is on relaxation.

Manual Therapy: The physical therapist locates "trigger points" in the muscles via the vaginal or rectal route and releases these points using stretching and massage techniques.

Biofeedback: Sensors are used to display muscle activity on a screen. This helps the patient recognize which muscle they are contracting or relaxing.

Dilatator Training: The tolerance of the muscles is increased and spasms are reduced using devices that gradually expand (30).

- **Medications**

Used to manage pain and reduce muscle tension:

Muscle Relaxants: Can be administered systemically (orally) or topically (vaginal/rectal suppositories). Local applications reduce side effects.

Neuropathic Pain Medications: Medications such as gabapentin or amitriptyline may be prescribed to alleviate nerve sensitivity associated with spasms.

Topical Creams: Creams containing muscle relaxants or anesthetics are applied directly to the affected area (31).

- **Interventional Methods**

These are preferred in cases that do not respond to conservative treatments:

Botox (Botulinum Toxin) Injections: These are injected into overactive or spastic pelvic muscles to temporarily paralyze and relax the muscle (for 3–6 months).

Trigger Point Injections: These involve the direct administration of a mixture of local anesthetic or steroids into painful trigger points.

Neuromodulation (TENS or Sacral Nerve Stimulation): This method uses mild electrical currents to modulate nerve signals, thereby controlling muscle spasms (32,33).

- **Lifestyle and Self-Management**

Education and Awareness: Breaking the habit of unconsciously tightening the pelvic floor muscles (guarding) throughout the day.

Heat Therapy: Warm sitz baths or applying heat to the lower abdomen can help relax the muscles.

Nutrition: Preventing constipation (fiber-rich foods, plenty of water) reduces spasms caused by straining during bowel movements.

Stress Management: The pelvic floor is an area directly affected by stress. Yoga, meditation, or breathing exercises enhance treatment success (34).

5. Psychosexual Support

Chronic pain and spasms often lead to sexual dysfunction or anxiety. Working with a sex therapist or psychologist during this process can help manage emotional triggers (35).

9. Future Perspectives and Research Directions

Although studies on the pathophysiology and neurophysiological characteristics of pelvic floor muscle spasm have increased in recent years, significant knowledge gaps still remain in this area. Future research should focus on elucidating the neuromuscular control mechanisms of the pelvic floor muscles in more detail. In particular, the use of advanced neurophysiological assessment methods, high-resolution electromyography techniques, and neuroimaging methods can contribute to a better understanding of the underlying mechanisms

of pelvic floor muscle spasm. Furthermore, the development of standardized neurophysiological assessment protocols for the diagnosis of pelvic floor muscle spasm is of great importance for clinical practice. Establishing such standards will increase the comparability of data obtained from different centers and make the diagnostic process more reliable. In addition, large-scale, controlled clinical trials evaluating the effectiveness of physiotherapy, biofeedback, neuromodulation, and pharmacological treatment approaches will contribute to the development of treatment strategies. In conclusion, multidisciplinary research and the use of advanced diagnostic technologies will lead to a better understanding of pelvic floor muscle spasm, significantly contributing to the improvement of both diagnostic and treatment processes. It is believed that future studies in this area will enable the development of more effective and individualized treatment approaches in the management of pelvic floor dysfunctions.

Conclusion

Pelvic floor muscle spasm is a significant but often underrecognized cause of chronic pelvic pain and pelvic floor dysfunction. Understanding the neurophysiological mechanisms underlying pelvic floor muscle activity is crucial for accurate diagnosis and effective management of this condition. Neurophysiological assessment methods, particularly electromyography and nerve conduction studies, provide valuable information about the functional status and neural control of the pelvic floor muscles. These techniques contribute to differentiating pelvic floor muscle spasm from other neuromuscular disorders and developing targeted treatment strategies. The current literature emphasizes the importance of a multidisciplinary approach combining clinical assessment, neurophysiological testing, and individualized therapeutic interventions. Future research focusing on standardized diagnostic protocols and advanced neurophysiological techniques may further improve the understanding, diagnosis, and treatment of pelvic floor muscle spasm.

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CHAPTER 3

MANAGEMENT OF VASOMOTOR SYMPTOMS IN MENOPAUSE: CURRENT HORMONAL AND NONHORMONAL APPROACHES

SENA ÜNLÜ[1]

Abstract

Hot flashes and night sweats can disrupt sleep, impair concentration, and interfere with everyday life for years after the menopausal transition. Treatment decisions therefore depend on the burden of symptoms as well as their frequency. This narrative review brings together current guidelines, randomized trials, and prescribing information to examine hormonal and nonhormonal approaches to management. Systemic menopausal hormone therapy offers the greatest symptom relief for women who are suitable candidates. Its use requires careful selection of the dose and route, with adequate endometrial protection when the uterus is present. For women who cannot or prefer not to use hormones, options include selected antidepressants, gabapentin, oxybutynin, and neurokinin receptor antagonists. Fezolinetant and elinzanetant have expanded these choices, although their prescribing requirements, interactions,

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and safety profiles differ. Menopause-specific cognitive behavioral therapy and clinical hypnosis also have a role. Because trial populations and outcome measures vary, treatment effects cannot be ranked reliably across separate studies. The practical aim is to choose a treatment that fits the woman's health, priorities, and access to care, then reassess its benefit and tolerability over time.

Keywords: Menopause; vasomotor symptoms; menopausal hormone therapy; nonhormonal treatment; fezolinetant; elinzanetant.

Introduction

Hot flashes and night sweats are among the most troublesome symptoms of the menopausal transition. Episodes typically begin with a sudden sensation of heat in the face, neck, or chest, accompanied by flushing and sweating; some women also describe palpitations or chills afterward. For many, the consequences extend beyond the episode itself. Interrupted sleep, difficulty concentrating, and interference with work or social activities often drive the decision to seek treatment. Assessment should therefore begin with how symptoms affect the woman's life. The same number of daily episodes may be manageable for one woman and debilitating for another (Avis et al., 2015; National Institute for Health and Care Excellence, 2026).

Counseling also needs to reflect the duration of symptoms. In the Study of Women's Health Across the Nation (SWAN), frequent vasomotor symptoms lasted a median of 7.4 years overall and persisted for a median of 4.5 years after the final menstrual period. These estimates describe a cohort rather than an individual prognosis: the stage at onset, personal characteristics, and the study definition of frequent symptoms all matter. Nevertheless, the findings make a useful point for clinical practice. Women should not be left expecting symptoms to disappear within a few months, and

treatment plans should allow for adjustment over time (Avis et al., 2015).

This chapter follows the decisions that arise in practice, from assessing symptom burden and treatment eligibility to choosing a regimen and reviewing its effects. It considers the evidence for hormonal and nonhormonal treatments alongside the safety and monitoring requirements that determine whether a treatment is appropriate for a particular woman.

Scope of the Review

This narrative review draws on a targeted assessment of literature and official documents accessed through October 20, 2026. Sources included PubMed/Europe PMC records, accessible primary publications, recommendations from the North American Menopause Society (NAMS), the National Institute for Health and Care Excellence (NICE), and the International Menopause Society (IMS), and official prescribing information. Search terms were menopause, vasomotor symptoms, hormone therapy, nonhormonal treatment, neurokinin antagonist, fezolinetant, and elinzanetant. Guidelines and randomized trials informed the discussion of treatment selection, while prescribing information informed the sections on drug safety. The review had no registered protocol, comprehensive systematic search, independent selection by two reviewers, or formal risk-of-bias assessment.

Pathophysiology and the Development of Targeted Therapy

Declining estrogen levels affect hypothalamic networks involved in temperature regulation. Within the arcuate nucleus, neurons expressing kisspeptin, neurokinin B, and dynorphin—the KNDy neurons—connect reproductive signaling with thermoregulatory pathways. Reduced estrogen feedback may change the activity of these neurons and make heat-loss responses easier to trigger. Peripheral vasodilation and sweating are the outward

manifestations of that response. This model helps explain vasomotor symptoms without assuming that every episode has the same trigger or a single underlying mechanism (Rance et al., 2013).

Two lines of evidence helped move this model toward treatment. Administration of neurokinin B to healthy women produced physiological responses resembling hot flashes, and an early randomized trial of an NK3 receptor antagonist subsequently showed that symptoms could improve without estrogen administration. Together, these findings provided the rationale for developing neurokinin-targeted therapies (Jayasena et al., 2015; Prague et al., 2017).

Clinical Assessment

The first consultation should establish the menstrual history and the pattern of symptoms: when they began, whether they occur mainly during the day or at night, how severe they are, and what they prevent the woman from doing. A diary of episodes and sleep over one or two weeks can help clarify the baseline. Treatment goals can then be made specific. Sleeping through more of the night, completing a working day without repeated interruptions, or feeling comfortable in social situations may matter more than reaching a particular episode count. Menopause-specific quality-of-life measures can support this assessment and provide a consistent basis for follow-up (International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026).

For women older than 45 years with typical symptoms and menstrual changes, diagnosis of the menopausal transition is usually clinical; routine FSH testing adds little. Younger age at presentation, possible alternative causes of amenorrhea, or diagnostic uncertainty calls for a different approach. Contraception deserves a separate discussion during perimenopause because menopausal hormone

therapy does not prevent pregnancy (National Institute for Health and Care Excellence, 2026).

Atypical sweating, abrupt symptom onset, fever, unintentional weight loss, marked tachycardia, or a history that does not fit the menopausal transition should prompt consideration of other diagnoses. Tests for thyroid disease, medication effects, and other systemic causes are guided by these findings. Before prescribing, the clinician also needs a clear history of breast and endometrial disease, unexplained bleeding, thromboembolism, cardiovascular disease, and hepatic or renal disease, together with a review of prescription medicines and herbal products (International Menopause Society, 2026; The North American Menopause Society, 2022).

Hormonal Treatments

Patient Selection and Benefit–Risk Assessment

Systemic hormone therapy remains the most effective treatment for vasomotor symptoms. The prescribing decision, however, depends on whether its benefits outweigh its risks for the woman seeking relief. In symptomatic women without contraindications, that balance is generally more favorable before age 60 or within 10 years of menopause onset. Neither criterion replaces a review of medical history, symptom burden, and treatment preferences. Starting therapy later requires closer attention to absolute cardiovascular and thromboembolic risks (The North American Menopause Society, 2022).

The WHI remains central to this discussion, but its findings need to be applied to the treatment it actually studied. The estrogen–progestin arm evaluated oral conjugated equine estrogens with medroxyprogesterone acetate across a broad postmenopausal age range. It did not support using that regimen for primary prevention of chronic disease. Applying the same risk profile to every

preparation or to all younger women seeking symptom relief overlooks differences in formulation, dose, population, and treatment purpose (Rossouw et al., 2002).

The distinction between regimens is particularly relevant to breast cancer counseling. In long-term WHI follow-up, conjugated equine estrogens alone were associated with lower breast cancer incidence and mortality among women with prior hysterectomy. Conjugated equine estrogens with medroxyprogesterone acetate were associated with higher incidence among women with a uterus. These were separate trial populations; the findings do not justify prescribing estrogen to prevent breast cancer or assuming that other regimens have identical effects. A useful risk discussion identifies the preparation, expected duration of use, and the woman's baseline risk (Chlebowski et al., 2020).

Route of Administration and Endometrial Protection

The choice between oral and transdermal estrogen takes account of preference, metabolic characteristics, and thromboembolic risk. Large observational database studies found an association between oral hormone therapy and venous thromboembolism, without a comparable increase for transdermal therapy. This supports considering transdermal estrogen in selected women, although residual confounding remains possible and absence of an observed increase does not mean absence of risk. In particular, changing the route does not by itself make treatment appropriate after a thromboembolic event (Vinogradova et al., 2019).

For women with a uterus, adequate progestogen exposure is an essential part of systemic estrogen treatment because it reduces the risk of endometrial hyperplasia and cancer. Protection depends on dose, duration, and adherence in relation to the estrogen regimen. Transdermal progesterone creams should not be relied on for this purpose. After total hysterectomy, estrogen alone is usually

sufficient, with separate consideration needed for conditions such as residual endometriosis (International Menopause Society, 2026; The North American Menopause Society, 2022).

Selecting a Dose and Regimen

Examples of a low-dose starting regimen include oral 17β-estradiol at 0.5–1 mg/day or a transdermal patch delivering 25 micrograms of estradiol per 24 hours. The transdermal dose may be increased to 50 micrograms per 24 hours when needed. The patch strength describes its daily delivery rate; replacement intervals follow the individual product information. Oral and transdermal doses are not directly interchangeable. Symptom burden, metabolic characteristics, and thromboembolic risk guide the initial choice, with response reviewed at 6–12 weeks. If control is inadequate, adherence and application technique should be checked before changing the dose or preparation (International Menopause Society, 2026; Joffe et al., 2014; The North American Menopause Society, 2022).

A sequential regimen is often a better fit during perimenopause or when cyclical bleeding is expected. Estrogen is taken continuously, with oral micronized progesterone commonly added at 200 mg/day for 12–14 days of each 28-day cycle. After menopause, women seeking a bleed-free regimen may prefer continuous combined treatment. With low or standard estrogen doses, oral micronized progesterone is commonly given at 100 mg/day. These examples are starting points rather than proof of adequate protection at every estrogen dose. Higher estrogen exposure, progestogen intolerance, or persistent bleeding requires a fresh review of the regimen (International Menopause Society, 2026; The North American Menopause Society, 2022).

Medroxyprogesterone acetate offers an alternative in an appropriate preparation, either at 2.5 mg/day continuously or at 10

mg/day for 12–14 days each month sequentially. Comorbidities, tolerability, and preferences about bleeding help determine the choice. A 52-mg levonorgestrel-releasing intrauterine system may be useful when both contraception and endometrial protection are needed. Its permitted duration for protection during hormone therapy should be checked locally rather than inferred from its contraceptive duration (International Menopause Society, 2026).

Clear instructions are as important as regimen selection. With sequential treatment, estrogen continues on days when progestogen is not taken; with continuous combined treatment, both components are used daily. Women need to understand the expected withdrawal bleed and which changes warrant assessment. Dose adjustment is usually guided by symptom relief and tolerability, without routine serum estradiol measurement (International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026).

Table 1 brings these prescribing decisions together.

Table 1 Clinical Selection of Hormonal Therapy

Clinical situation	**Treatment approach**	**Key consideration**
Uterus present	Systemic estrogen with sufficient progestogen or appropriate endometrial protection	Assess estrogen dose, regimen, adherence, and bleeding pattern together.
Total hysterectomy	Usually systemic estrogen alone	Endometriosis or an oncological history may require a different approach.
Increased thromboembolic risk	Consider the transdermal route in an appropriate patient	Observational evidence favors this route in selected patients; a history of thromboembolism still requires separate assessment.

Clinical situation	Treatment approach	Key consideration
Initiation at an older age	More detailed individual benefit–risk assessment	Consider age, time since menopause, medical history, and alternatives together.
Genitourinary symptoms only	Consider local treatment	Low-dose vaginal estrogen does not replace systemic vasomotor symptom treatment.

Source: Synthesized from the cited publications (International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026; The North American Menopause Society, 2022; Vinogradova et al., 2019).

Contraindications and Follow-up

The 2022 NAMS statement identifies unexplained vaginal bleeding, liver disease, a history of estrogen-sensitive cancer, coronary heart disease, prior myocardial infarction, stroke or venous thromboembolism, and a personal or inherited high risk of thromboembolism as contraindications to oral or transdermal systemic hormone therapy. Observational evidence favoring the transdermal route does not override these exclusions. A family history of breast cancer, by contrast, is not equivalent to a personal history. Controlled hypertension, diabetes, or obesity is assessed in the context of coexisting vascular disease and overall risk (International Menopause Society, 2026; The North American Menopause Society, 2022).

An initial review at about three months allows the clinician and patient to assess benefit, adverse effects, and bleeding; follow-up is then undertaken at least annually. Heavy or prolonged bleeding, new postmenopausal bleeding, or persistent bleeding that the regimen does not explain needs timely assessment. Its relation to treatment initiation or dose changes and the woman's endometrial cancer risk guide investigation. Continuing therapy is a decision to revisit, rather than one determined automatically by age. Low-dose vaginal estrogen may be appropriate for genitourinary symptoms,

but it does not treat systemic vasomotor symptoms (International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026; The North American Menopause Society, 2022).

Nonhormonal Pharmacological Treatments

SSRIs and SNRIs

Certain selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors offer symptom relief when hormone therapy is unsuitable or not wanted. Coexisting mood symptoms may help guide the choice, although the dose used for hot flashes may not adequately treat a psychiatric disorder. Current psychiatric treatment, blood pressure, sexual adverse effects, tolerability, and withdrawal symptoms all deserve attention. Explaining why an antidepressant is being prescribed can also prevent confusion about the treatment goal (Freeman et al., 2011; Simon et al., 2013; The North American Menopause Society, 2023).

Low-dose paroxetine at 7.5 mg/day reduced vasomotor symptom frequency in two placebo-controlled trials. Its strong inhibition of CYP2D6 is a practical limitation in women taking tamoxifen: paroxetine and fluoxetine should be avoided in favor of options with less interaction potential. The US approval applies to the low-dose formulation and does not establish approval of all antidepressants for vasomotor symptoms or availability of that formulation in Türkiye (Legacy Pharma Inc., 2025; Simon et al., 2013; The North American Menopause Society, 2023).

One eight-week trial provides a direct comparison between venlafaxine and low-dose oral estradiol. Frequency fell from baseline by 52.9% with estradiol, 47.6% with venlafaxine, and 28.6% with placebo. These findings support venlafaxine as an effective option without establishing equivalence to hormone therapy as a whole. They also show why reductions within an active

treatment arm need to be read alongside the placebo response (Joffe et al., 2014).

Escitalopram at 10–20 mg/day produced a greater reduction in daily hot flash frequency than placebo at week 8 in a randomized trial. Nausea, headache, changes in sleep, and sexual adverse effects can influence whether treatment remains acceptable. SNRIs require additional attention to blood pressure and other noradrenergic effects. When discontinuing treatment, a gradual taper is planned, particularly after longer use or at higher doses (Freeman et al., 2011; The North American Menopause Society, 2023; Wyeth Pharmaceuticals LLC, 2022).

Gabapentin

Gabapentin can be a useful choice when nighttime symptoms are prominent or neuropathic pain is also present. In a randomized trial of 420 women with breast cancer, 900 mg/day significantly improved hot flash severity scores compared with placebo. Starting low and titrating according to tolerance may help manage dizziness and somnolence. Renal function, fall risk, and concurrent sedatives affect prescribing. The results obtained with divided doses should not be assumed to apply equally to a low dose given only at bedtime (Pandya et al., 2005; The North American Menopause Society, 2023; U.S. Food and Drug Administration, 2025).

Oxybutynin and Other Options

Oxybutynin reduced hot flash scores at 2.5 or 5 mg twice daily in a short randomized trial involving women with and without breast cancer. Dry mouth, constipation, and difficulty urinating may limit its usefulness. The broader anticholinergic burden is especially relevant in older women, those with cognitive complaints, and those taking several medicines. The trial's short-term efficacy findings cannot establish long-term cognitive safety (Leon-Ferre et al., 2020).

Clonidine and pregabalin are not preferred for routine management of vasomotor symptoms. When an initial treatment fails, reviewing the diagnosis, adherence, and treatment goal is more useful than adding medicines to a regimen that has provided little benefit (The North American Menopause Society, 2023).

Fezolinetant

Fezolinetant targets the NK3 receptor. In the phase 3 SKYLIGHT 1 trial, 45 mg/day reduced daily moderate-to-severe symptom frequency more than placebo. DAYLIGHT extended placebo-controlled evidence to 24 weeks in women considered unsuitable for hormone therapy. That category included both medical reasons for avoiding hormones and an informed preference not to use them, so it should not be read as a single, uniformly high-risk population (Lederman et al., 2023; Schaudig et al., 2024).

Hepatic safety has a direct bearing on whether fezolinetant is a practical choice. US prescribing information calls for liver tests before treatment, monthly during the first three months, and at months 6 and 9. Treatment must not begin if ALT, AST, or total bilirubin is at least twice the upper limit of normal. Cirrhosis, severe renal impairment, and concomitant CYP1A2 inhibitors are contraindications, making a medication review part of the baseline assessment (Astellas Pharma US, Inc., 2026).

The US Food and Drug Administration (FDA) added a boxed warning after serious liver injury was reported during postmarketing use. Women should know to stop treatment and seek assessment for jaundice, dark urine, pruritus, or new marked fatigue. Treatment is also discontinued if transaminases exceed five times the upper limit of normal, or exceed three times the upper limit together with total bilirubin above twice the upper limit. Clinical use must follow the current local prescribing information (Astellas Pharma US, Inc., 2026; U.S. Food and Drug Administration, 2024).

Elinzanetant

Elinzanetant acts at both NK1 and NK3 receptors. In OASIS 1 and 2, 120 mg/day improved symptom frequency and severity at weeks 4 and 12 compared with placebo. At week 12, the additional reduction in frequency was about 3.2 episodes/day in each trial, alongside improvements in sleep and quality of life (Pinkerton et al., 2024).

OASIS 3 added a longer placebo-controlled observation period: 628 women were randomized to elinzanetant or placebo for 52 weeks. The adjusted additional reduction with elinzanetant was 1.6 daily episodes at week 12. Treatment-emergent adverse events led to discontinuation in 12.5% of the elinzanetant group and 4.1% of the placebo group, an important consideration when discussing persistence with treatment (Panay et al., 2025).

US prescribing information recommends 120 mg at bedtime. It includes hepatic assessment at baseline and month 3, warnings about central nervous system depression and daytime impairment, and attention to seizure risk. Strong CYP3A4 inhibitors and strong or moderate inducers should be avoided; with a moderate inhibitor, the bedtime dose is reduced to 60 mg. Elinzanetant is contraindicated in pregnancy (Bayer HealthCare Pharmaceuticals Inc., 2026).

Clinical Use and Access in Türkiye

Evidence of efficacy and access to treatment are separate considerations. Before prescribing in Türkiye, the clinician needs to confirm the product's authorization, approved indication, available strength and formulation, and reimbursement conditions. An antidepressant or gabapentin authorized for another disorder is not necessarily authorized for vasomotor symptoms. The Turkish Medicines and Medical Devices Agency (TİTCK) authorization records and summaries of product characteristics, together with the Social Security Institution (SGK) Health Implementation

Communiqué and medicine lists, provide the relevant local framework (Social Security Institution, n.d.; Turkish Medicines and Medical Devices Agency, n.d.).

The fezolinetant and elinzanetant regimens described here come from US prescribing information; they do not establish authorization, availability, or reimbursement in Türkiye. Until local status is confirmed, neither should be presented as a routinely accessible option. Monitoring costs and access to the required tests also affect whether treatment can be maintained (Astellas Pharma US, Inc., 2026; Bayer HealthCare Pharmaceuticals Inc., 2026).

Table 2 summarizes the practical considerations for selecting a nonhormonal medicine.

Table 2 Comparison of Nonhormonal Medicines

Agent and studied dose	**Clinical rationale for selection**	**Main limitation or monitoring**
Paroxetine 7.5 mg/day	The low-dose formulation has demonstrated efficacy for vasomotor symptoms.	CYP2D6 interaction with tamoxifen; authorization and formulation vary by country.
Escitalopram 10–20 mg/day	Coexisting mood symptoms may influence selection.	Nausea, sexual adverse effects, other serotonergic medicines, and a discontinuation plan.
Venlafaxine XR 75 mg/day	An option when hormones are unsuitable or not desired.	Monitor blood pressure and tolerability; plan a gradual taper. Trial dosing does not replace individual prescribing.
Gabapentin 900 mg/day in divided doses	May be considered for nighttime symptoms with coexisting neuropathic pain.	Somnolence, dizziness, fall risk, and renal dose adjustment.

Agent and studied dose	Clinical rationale for selection	Main limitation or monitoring
Oxybutynin 2.5–5 mg twice daily	An option for selected patients who can tolerate anticholinergic effects.	Dry mouth, constipation, difficulty urinating, cognitive risk, and total anticholinergic burden.
Fezolinetant 45 mg/day	A treatment targeting the NK3 receptor.	Hepatic testing at baseline, monthly for the first 3 months, and at months 6 and 9; CYP1A2 interactions.
Elinzanetant 120 mg at bedtime	Targets NK1/NK3 receptors; trials report benefits for vasomotor symptoms and sleep.	Hepatic assessment at baseline and month 3; daytime impairment, seizure risk, and CYP3A4 interactions.

Source: Synthesized from the cited publications (Astellas Pharma US, Inc., 2026; Bayer HealthCare Pharmaceuticals Inc., 2026; Freeman et al., 2011; Joffe et al., 2014; Legacy Pharma Inc., 2025; Leon-Ferre et al., 2020; Pandya et al., 2005; Pinkerton et al., 2024; Simon et al., 2013; U.S. Food and Drug Administration, 2025; Wyeth Pharmaceuticals LLC, 2022).

Doses reflect trial regimens and prescribing information; local authorization and individual patient characteristics should guide clinical use.

Nonpharmacological Approaches

Cognitive Behavioral Therapy and Clinical Hypnosis

Menopause-specific cognitive behavioral therapy addresses thoughts about symptoms, responses to bodily sensations, and coping. In MENOS 2, group treatment and guided self-help reduced how problematic women found their hot flashes and night sweats. This distinction matters when judging response: fewer episodes and less distress are different outcomes. Improved sleep or a return to social activities can be worthwhile even when episodes continue (Ayers et al., 2012).

Clinical hypnosis also has trial support. A controlled study of 187 postmenopausal women found improvements in hot flash scores

and related outcomes. Its use depends on trained practitioners and structured protocols, as well as the woman's preference, available time, cost, and access to a service (Elkins et al., 2013).

Lifestyle and Complementary Interventions

Physical activity, healthy eating, smoking cessation, and weight management remain part of good menopausal care. Their general health value should be distinguished from evidence that they directly reduce hot flash frequency. A cool room or layered clothing may make symptoms easier to tolerate, but these measures should not substitute for effective treatment when it is needed. Herbal products require particular care because composition varies and interactions and safety concerns may be difficult to predict (International Menopause Society, 2026; The North American Menopause Society, 2023).

Table 3 outlines the place of these approaches in care. It reflects a clinical reading of guidelines and trials rather than a new formal grading of evidence.

Table 3 Clinical Role of Nonpharmacological Approaches

Approach	**Clinical role**	**Comment**
Menopause-specific cognitive behavioral therapy	Evidence-supported option	Addresses symptom bother and coping; these outcomes differ from episode frequency.
Clinical hypnosis	Supportive trial findings with structured delivery	Trained practitioner, protocol, and patient preference are important.
Weight management and physical activity	Part of overall health management	Some evidence supports weight loss. The general benefits of exercise do not establish a direct effect on hot flashes.

Approach	Clinical role	Comment
Cool environment and individual triggers	Individual adjustments for comfort	May improve comfort, but strong evidence for treating symptoms is lacking.
Herbal products and supplements	Not recommended as routine effective therapy	Consider inconsistent efficacy, nonstandardized composition, and interactions.

Source: Synthesized from the cited publications (Ayers et al., 2012; Elkins et al., 2013; International Menopause Society, 2026; The North American Menopause Society, 2023).

Special Clinical Situations

Breast Cancer and Endocrine Therapy

For women with a history of breast cancer, systemic hormone therapy is generally avoided and symptom management is coordinated with oncological treatment. Tamoxifen makes CYP2D6 interactions especially important. Gabapentin or a suitable antidepressant may be selected according to sleep disturbance, pain, mood symptoms, and the existing regimen. Relieving treatment-related symptoms is itself an important part of the woman's experience of cancer care (Pandya et al., 2005; The North American Menopause Society, 2023).

OASIS 4 specifically examined elinzanetant in 474 women receiving endocrine therapy for hormone receptor-positive breast cancer or for prevention because of high risk. The additional reduction in daily moderate-to-severe symptom frequency was approximately 3.4 episodes at week 12 compared with placebo. This is evidence of symptom benefit in the studied population, not evidence establishing long-term safety with respect to cancer recurrence (Cardoso et al., 2025).

Early and Surgical Menopause

Premature ovarian insufficiency and early menopause require a broader discussion than symptom relief alone. When there is no contraindication, hormone replacement is considered for bone and general health as well as hot flashes until the expected age of natural menopause. After bilateral oophorectomy, symptoms may begin abruptly, making counseling before surgery and an early follow-up plan especially valuable. The surgical indication, uterine status, and pathological findings remain central to treatment selection (International Menopause Society, 2026; The North American Menopause Society, 2022).

Multimorbidity and Older Age

Obesity, hypertension, or diabetes does not dictate the same choice for every woman. Control of these conditions and the presence of vascular disease are more informative than a diagnostic label alone. New sweating in an older woman warrants reassessment rather than an automatic diagnosis of menopausal symptoms. With polypharmacy, cumulative anticholinergic effects, sedation, and pharmacokinetic interactions may determine whether a treatment is acceptable. Suspected major depression, sleep apnea, or another sleep disorder should be assessed on its own merits (International Menopause Society, 2026; Leon-Ferre et al., 2020; National Institute for Health and Care Excellence, 2026).

Individualized Decision Algorithm and Follow-up

The following sequence brings together the main decisions discussed in this chapter. It is a clinical synthesis of guidelines and prescribing information, not a validated risk score (Astellas Pharma US, Inc., 2026; Bayer HealthCare Pharmaceuticals Inc., 2026; International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026; The North American Menopause

Society, 2022; The North American Menopause Society, 2023; U.S. Food and Drug Administration, 2024).

1. Establish the symptom pattern and its effect on daily life. Confirm that the presentation fits the menopausal transition and investigate alternative diagnoses when it does not.
2. Agree on a treatment goal. Counseling and follow-up may be sufficient for mild, tolerable symptoms; bothersome symptoms warrant a discussion of active treatment.
3. Review eligibility for systemic hormone therapy, considering age, time since menopause, bleeding, cancer, thromboembolism, and organ disease.
4. If hormone therapy is suitable and preferred, select the route and dose and ensure adequate endometrial protection when a uterus is present.
5. Otherwise, choose a nonhormonal option according to coexisting symptoms, interactions, and access. Cognitive behavioral therapy may be used alone or alongside medication when appropriate.
6. Reassess benefit using the baseline measures, with drug-specific early safety monitoring and a review of overall response at about 6–12 weeks.
7. For an inadequate response, revisit adherence, dose, adverse effects, and diagnosis before changing treatment or seeking specialist advice.

Follow-up is most useful when it returns to the goals set at the first visit. Alongside episode counts, ask about sleep, daily functioning, and satisfaction with treatment. A partial reduction may be enough; escalating the dose without a meaningful additional goal

can increase adverse effects. A new diagnosis, medicine, or episode of vaginal bleeding may change the balance. Women should also know that symptoms can recur after treatment stops and when to return for review (International Menopause Society, 2026; National Institute for Health and Care Excellence, 2026).

Comparative Trial Findings and Limitations of the Evidence

Table 4 summarizes selected randomized trials. It separates the population, regimen, and follow-up period from the main finding and its limitations. Frequency, severity scores, and patient-reported bother measure different aspects of symptoms; percentage changes from baseline and placebo-adjusted differences likewise answer different questions.

Table 4 Comparison of Selected Randomized Trials

Trial and sample	Studied regimen and duration	Main finding and limitation
Joffe et al. n=339	Estradiol 0.5 mg/day; venlafaxine XR 75 mg/day; placebo. 8 weeks.	Frequency decreased from baseline by 52.9%, 47.6%, and 28.6%, respectively. Short follow-up and one estrogen regimen; not an equivalence trial.
Pandya et al. n=420; breast cancer	Gabapentin 300 or 900 mg/day in three divided doses; placebo. 8 weeks.	At week 8, severity scores decreased by 46% in the 900-mg arm and 15% with placebo. Severity-score endpoint; cannot be generalized to a low bedtime dose.
ACCRU SC-1603 n=150	Oxybutynin 2.5 or 5 mg twice daily; placebo. 6 weeks.	Both doses reduced hot flash scores more than placebo. Short duration and anticholinergic adverse effects; long-term cognitive safety was not established.
SKYLIGHT 1 n=527 randomized	Fezolinetant 30 or 45 mg/day; placebo. 12 controlled weeks plus a 40-week active extension.	45 mg improved frequency and severity versus placebo. Only the first 12 of the total 52 weeks were placebo-controlled.

Trial and sample	Studied regimen and duration	Main finding and limitation
DAYLIGHT n=453 randomized	Fezolinetant 45 mg/day; placebo. 24 weeks.	An additional placebo-adjusted reduction of 1.93 episodes/day at week 24. Included women who declined hormones and women considered medically unsuitable.
OASIS 1 and 2 n=396 and n=400	Elinzanetant 120 mg/day; placebo for 12 weeks, then active treatment. 26 weeks in total.	Additional reduction in frequency of approximately 3.2 episodes/day versus placebo at week 12 in both trials. No active comparator.
OASIS 3 n=628	Elinzanetant 120 mg/day; placebo. 52 weeks.	Adjusted additional reduction in frequency of 1.6 episodes/day at week 12. No minimum baseline episode threshold; safety beyond one year was not assessed.
OASIS 4 n=474; endocrine therapy	Elinzanetant 120 mg/day; placebo for 12 weeks, then active treatment. 52 weeks in total.	An additional reduction of approximately 3.4 episodes/day at week 12. Endocrine therapy for breast cancer treatment/prevention; long-term safety regarding recurrence was not established.

Source: Synthesized from the cited publications (Cardoso et al., 2025; Joffe et al., 2014; Lederman et al., 2023; Leon-Ferre et al., 2020; Panay et al., 2025; Pandya et al., 2005; Pinkerton et al., 2024; Schaudig et al., 2024).

Reading across these trials requires care. Baseline symptom frequency, participant characteristics, placebo responses, and follow-up periods differ, so the results do not support a simple ranking of treatments. The estradiol–venlafaxine trial offers a direct comparison, but only for one low-dose estrogen regimen over eight weeks. Direct comparisons of newer neurokinin antagonists with hormone therapy, or with one another, remain limited (Cardoso et al., 2025; Joffe et al., 2014; Lederman et al., 2023; Panay et al., 2025; Pinkerton et al., 2024; Schaudig et al., 2024).

Further evidence is needed on longer-term use in routine care, particularly among older women, those with several medical conditions, and populations less well represented in trials. Hepatic and neurological safety, sleep, treatment persistence, and cost all matter to clinical use. Manufacturer support for many phase 3 trials also makes funding and conflicts of interest relevant to interpretation. Future studies should give the same attention to the functional outcomes women value as they give to episode counts (Cardoso et al., 2025; Lederman et al., 2023; Pinkerton et al., 2024; Schaudig et al., 2024).

Conclusion

Managing vasomotor symptoms begins with understanding what the woman wants treatment to change. Systemic hormone therapy provides the greatest symptom relief for suitable candidates, with route, dose, and endometrial protection considered together. Evidence-supported nonhormonal medicines and behavioral approaches provide alternatives when hormones are unsuitable or not preferred. The best choice is one that offers worthwhile relief with acceptable adverse effects, manageable monitoring, and realistic access to care. Regular review keeps that choice aligned with the woman's health and priorities.

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