

KADIN SAĞLIĞINDA GELİŞMELER:

ANNE-FETAL SONUÇLARDAN
JİNEKOLOJİK BAKIMA

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Önsöz

Kadın saęlığı; biyomedikal teknolojilerdeki hızlı ilerlemeler, dijital dönüşüm ve kanıta dayalı tıbbın ışığında her geçen gün daha dinamik ve multidisipliner bir yapı kazanmaktadır. *"Kadın Saęlığında Gelişmeler: Anne-fetal Sonuçlardan Jinekolojik Bakıma"* başlıklı bu eser, obstetrik ve jinekoloji alanındaki köklü klinik yaklaşımları; vajinal mikrobiyotadan yapay zeka uygulamalarına, modern tanı yöntemlerinden güncel tedavi kılavuzlarına uzanan en son yeniliklerle harmanlamayı amaçlamaktadır. Maternal-fetal tıp süreçlerinden jinekolojik bakıma kadar kadının yaşam döngüsündeki kritik evreleri kapsamlı ve vizyoner bir bakış açısıyla ele alan bu kitabın, literatürdeki en güncel gelişmeleri yakından takip etmek isteyen tüm klinisyenler, asistan hekimler ve araştırmacılar için zengin, yol gösterici ve kalıcı bir akademik başvuru kaynağı olmasını temenni ediyorum.

Prof. Dr. Deniz Balsak

Mardin Artuklu Tıp Fakóltesi

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REMZİ KARASUNGUR

Abnormal Uterine Bleeding: Etiological Classification and Clinical Assessment

BÖLÜM 1

BERKAY DEYİRMENCİ¹

Introduction

Abnormal uterine bleeding (AUB) is one of the most common gynecological complaints encountered in clinical practice and accounts for a substantial proportion of outpatient gynecologic consultations worldwide. It encompasses any variation from normal menstrual cyclicity, frequency, duration, or volume of bleeding and may affect women throughout the reproductive lifespan, including adolescence, reproductive age, and the perimenopausal transition. AUB has a significant impact on physical health, psychological well-being, social functioning, and overall quality of life. Furthermore, excessive or prolonged uterine bleeding may contribute to iron deficiency anemia, reduced work productivity, and increased healthcare utilization. (Munro et al., 2018).

Historically, the terminology used to describe abnormal menstrual bleeding was inconsistent, leading to considerable variation in clinical communication and research reporting. To address these limitations, the International Federation of Gynecology and Obstetrics (FIGO) developed a standardized classification system for the causes of AUB in non-pregnant women of reproductive age. (Munro et al., 2011). This system, known as the PALM–COEIN classification, categorizes etiologies into structural and non-structural causes, thereby facilitating accurate diagnosis, effective communication among clinicians, and evidence-based management strategies.

The structural causes included within the PALM component consist of endometrial polyps, adenomyosis, leiomyomas, and malignancy or hyperplasia. In contrast, the COEIN component encompasses non-structural causes, including coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic factors, and conditions that remain not yet classified. (Munro et al., 2011). This classification has become the cornerstone of contemporary evaluation and management of AUB and has been widely adopted in both clinical practice and scientific research. (Jain et al., 2023).

Given the broad spectrum of underlying etiologies, the diagnostic approach to AUB requires careful clinical assessment, including detailed history taking, physical examination, laboratory investigations, and appropriate imaging studies. Identification of the underlying cause is essential not only for symptom control but also for the early detection of

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premalignant and malignant conditions. This chapter reviews the current etiological classification of abnormal uterine bleeding and summarizes the principles of clinical assessment that guide diagnostic and therapeutic decision-making. (Munro et al., 2023)

Classification of Abnormal Uterine Bleeding: The FIGO PALM–COEIN System

The etiological spectrum of abnormal uterine bleeding is broad and includes a variety of structural, hormonal, systemic, and iatrogenic disorders. Historically, inconsistent terminology and heterogeneous diagnostic criteria created challenges in both clinical practice and scientific research. To establish a standardized approach, the International Federation of Gynecology and Obstetrics (FIGO) introduced the PALM–COEIN classification system, which has become the internationally accepted framework for categorizing the causes of abnormal uterine bleeding in non-pregnant women of reproductive age. (Jain et al., 2023).

The PALM–COEIN classification divides the etiologies of AUB into structural and non-structural categories. The acronym PALM refers to structural abnormalities that can generally be identified through imaging techniques or histopathological evaluation. These include endometrial polyps (P), adenomyosis (A), leiomyomas (L), and malignancy and hyperplasia (M). Structural lesions frequently alter the anatomy of the uterine cavity or myometrium and are commonly associated with heavy menstrual bleeding, intermenstrual bleeding, or both.

Endometrial polyps are localized overgrowths of endometrial glands and stroma that may cause irregular or prolonged uterine bleeding. Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium and often presents with heavy menstrual bleeding, dysmenorrhea, and uterine enlargement. Leiomyomas, commonly referred to as uterine fibroids, represent the most prevalent benign tumors of the female reproductive tract and are an important cause of abnormal bleeding, particularly when they distort the endometrial cavity. (Leal et al., 2024). Malignancy and endometrial hyperplasia constitute the most clinically significant structural causes, particularly among perimenopausal and postmenopausal women, where prompt diagnosis is essential to prevent disease progression and improve outcomes.

The COEIN component includes non-structural causes of AUB. These encompass coagulopathy (C), ovulatory dysfunction (O), endometrial disorders (E), iatrogenic causes (I), and conditions not yet classified (N). Unlike structural abnormalities, these disorders are often identified through clinical assessment, laboratory testing, and exclusion of other etiologies. (American College of Obstetricians and Gynecologists, 2024).

Coagulopathies may account for a significant proportion of heavy menstrual bleeding cases, particularly in adolescents and young women. Ovulatory dysfunction is among the most common causes of AUB and may result from conditions such as polycystic ovary syndrome, thyroid disorders, hyperprolactinemia, obesity, or the hormonal fluctuations

associated with the perimenopausal transition. Endometrial causes are diagnosed when abnormal local endometrial hemostatic mechanisms contribute to excessive bleeding despite normal ovulatory function and the absence of structural pathology. Iatrogenic bleeding may occur secondary to hormonal therapies, anticoagulants, intrauterine devices, or other medical interventions. The final category, not yet classified, includes rare or poorly understood disorders for which insufficient evidence exists to support inclusion within the established categories.

The FIGO PALM–COEIN system provides a practical and reproducible framework for the evaluation of women presenting with abnormal uterine bleeding. By facilitating accurate etiological classification, this system improves diagnostic precision, guides individualized management strategies, and enhances the comparability of clinical studies. Consequently, PALM–COEIN remains the cornerstone of modern AUB assessment and serves as the basis for subsequent discussions of specific etiological factors. (Bahamondes et al., 2022).

Structural Causes of Abnormal Uterine Bleeding (PALM)

Structural abnormalities constitute an important group of etiologies responsible for abnormal uterine bleeding and are represented by the PALM component of the FIGO classification system. These conditions are generally identifiable through imaging modalities, hysteroscopic evaluation, or histopathological examination and often contribute to heavy menstrual bleeding, prolonged bleeding episodes, intermenstrual bleeding, or a combination of these symptoms. (Munro et al., 2018)

Endometrial polyps are localized overgrowths of endometrial glands, stroma, and blood vessels that protrude into the uterine cavity. Although many polyps remain asymptomatic, they frequently present with irregular menstrual bleeding, intermenstrual spotting, or postmenopausal bleeding. The prevalence of endometrial polyps increases with age and is particularly notable during the perimenopausal period. Transvaginal ultrasonography, saline infusion sonography, and hysteroscopy play important roles in diagnosis, with hysteroscopy remaining the gold standard for both visualization and treatment.

Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium, resulting in diffuse or focal uterine enlargement. The condition predominantly affects multiparous women in their late reproductive years and frequently manifests with heavy menstrual bleeding, dysmenorrhea, chronic pelvic pain, and pressure symptoms. Advances in imaging techniques, particularly transvaginal ultrasonography and magnetic resonance imaging, have significantly improved the diagnostic accuracy of adenomyosis. Although the exact pathogenesis remains incompletely understood, disruption of the endometrial–myometrial interface and chronic inflammatory processes are believed to play central roles in disease development. (Leal et al., 2024)

Leiomyomas, commonly referred to as uterine fibroids, represent the most prevalent benign tumors of the female reproductive tract. Their contribution to abnormal uterine bleeding

depends largely on size, number, and anatomical location. Submucosal fibroids are particularly associated with heavy menstrual bleeding because of their direct effect on the endometrial cavity and uterine contractility. In addition to menstrual disturbances, leiomyomas may cause pelvic pressure, urinary symptoms, infertility, and reproductive complications. Ultrasonography remains the first-line diagnostic modality, while magnetic resonance imaging may be useful in selected complex cases. (Munro et al., 2011)

Malignancy and endometrial hyperplasia constitute the most clinically significant structural causes of abnormal uterine bleeding. Endometrial hyperplasia develops as a consequence of prolonged unopposed estrogen exposure and may progress to endometrial carcinoma, particularly when cytological atypia is present. Risk factors include obesity, chronic anovulation, polycystic ovary syndrome, diabetes mellitus, and advancing age. Endometrial carcinoma should always be considered in women presenting with abnormal uterine bleeding during the perimenopausal transition and in all postmenopausal women with uterine bleeding. Endometrial sampling remains the cornerstone of diagnosis and should be performed whenever clinical suspicion exists. Early recognition of premalignant and malignant conditions is essential for improving prognosis and optimizing patient outcomes. (Leal et al., 2024)

Collectively, the structural causes of abnormal uterine bleeding encompass a diverse group of disorders with varying clinical presentations and prognostic implications. Accurate identification of these pathologies through appropriate imaging and histological assessment forms a critical component of the diagnostic evaluation and guides subsequent management strategies.

Non-Structural Causes of Abnormal Uterine Bleeding (COEIN)

Non-structural causes of abnormal uterine bleeding are represented by the COEIN component of the FIGO classification system and comprise disorders that cannot be attributed to identifiable anatomical abnormalities. These conditions are frequently diagnosed through clinical evaluation, laboratory testing, and exclusion of structural pathology. Despite the absence of detectable uterine lesions, non-structural causes account for a substantial proportion of abnormal uterine bleeding cases encountered in gynecological practice.

Coagulopathies are important yet often underrecognized causes of heavy menstrual bleeding. Inherited bleeding disorders, particularly von Willebrand disease, represent the most common hematological abnormalities associated with excessive menstrual blood loss. Acquired coagulation disorders may also contribute to abnormal bleeding patterns. Women with coagulopathies frequently report heavy menstrual bleeding since menarche and may have a personal or family history of easy bruising, epistaxis, prolonged bleeding after surgical procedures, or postpartum hemorrhage. Identification of an underlying bleeding disorder is essential because management strategies often differ from those used for structural causes of AUB. (Bahamondes et al., 2022)

Ovulatory dysfunction is among the most common etiologies of abnormal uterine bleeding and results from disturbances in the normal cyclic production of ovarian hormones. Irregular or absent ovulation leads to prolonged estrogen exposure without adequate progesterone-mediated endometrial stabilization, resulting in unpredictable endometrial shedding. Common causes include polycystic ovary syndrome, thyroid dysfunction, hyperprolactinemia, obesity, stress, and the hormonal fluctuations characteristic of the perimenopausal transition. Clinically, patients often present with irregular menstrual cycles, prolonged intervals between bleeding episodes, or episodes of excessive and prolonged bleeding.(American College of Obstetricians and Gynecologists, 2024)

Endometrial causes refer to abnormalities in local endometrial hemostatic mechanisms occurring despite regular ovulation and the absence of structural pathology. The normal menstrual process requires a complex interaction between inflammatory mediators, vasoconstrictive factors, coagulation pathways, and tissue repair mechanisms. Dysregulation of these processes may result in excessive menstrual bleeding. Although the diagnosis is often one of exclusion, increasing evidence suggests that alterations in prostaglandin metabolism, inflammatory cytokines, and angiogenic factors contribute to the pathophysiology of endometrial AUB. (Leal et al., 2024)

Iatrogenic causes encompass bleeding abnormalities resulting from medical interventions or pharmacological treatments. Hormonal contraceptives, menopausal hormone therapy, anticoagulant medications, selective serotonin reuptake inhibitors, and certain intrauterine devices may all be associated with abnormal uterine bleeding. The bleeding pattern varies according to the specific intervention and duration of use. Careful medication review is therefore an essential component of patient assessment.

The category of “not yet classified” includes rare, poorly understood, or newly recognized conditions that do not fit within the established PALM–COEIN categories. As understanding of menstrual physiology and reproductive disorders continues to evolve, additional etiologies may ultimately be incorporated into future revisions of the FIGO classification system.

Recognition of non-structural causes is critical because treatment is frequently directed toward correction of the underlying systemic, hormonal, or pharmacological factor rather than surgical intervention. Consequently, comprehensive clinical assessment remains fundamental to distinguishing these disorders from structural causes of abnormal uterine bleeding and ensuring appropriate patient management.

Clinical Assessment of Abnormal Uterine Bleeding

The evaluation of abnormal uterine bleeding begins with a comprehensive clinical assessment aimed at identifying the underlying etiology and excluding serious pathology. A detailed menstrual history should include the onset, duration, frequency, regularity, and volume of bleeding, as well as associated symptoms such as pelvic pain, dysmenorrhea, pressure symptoms, or postcoital bleeding. Information regarding reproductive history, contraceptive

use, medication exposure, systemic diseases, and family history of bleeding disorders or gynecologic malignancies should also be obtained. (Jain et al., 2023)

Physical examination plays a crucial role in the assessment of women presenting with AUB. General examination may reveal signs of anemia, obesity, thyroid dysfunction, or systemic disease. Pelvic examination allows evaluation of the cervix, uterus, adnexa, and potential lower genital tract sources of bleeding. Particular attention should be given to identifying pelvic masses, uterine enlargement, or suspicious cervical lesions. (Munro et al., 2023)

Laboratory investigations are guided by clinical findings and commonly include a pregnancy test, complete blood count, and assessment of iron status. Additional testing such as thyroid function tests, coagulation studies, or hormonal evaluation may be indicated in selected patients. Transvaginal ultrasonography remains the first-line imaging modality for the evaluation of structural abnormalities and provides valuable information regarding endometrial thickness, uterine morphology, and adnexal pathology. (Munro et al., 2018).

Endometrial sampling should be considered in women aged 45 years and older presenting with abnormal uterine bleeding, as well as in younger women with risk factors for endometrial hyperplasia or carcinoma, including obesity, chronic anovulation, or persistent symptoms despite medical therapy. Histopathological assessment remains essential for excluding premalignant and malignant endometrial disease. Through a systematic approach combining clinical evaluation, laboratory testing, imaging, and histological assessment when indicated, clinicians can accurately determine the cause of abnormal uterine bleeding and develop individualized management strategies. (American College of Obstetricians and Gynecologists, 2024).

Conclusion

Abnormal uterine bleeding is a common gynecological condition with a broad range of underlying etiologies that may significantly affect women's health and quality of life. The FIGO PALM–COEIN classification system has provided a standardized framework for categorizing both structural and non-structural causes of AUB, thereby improving diagnostic accuracy and facilitating evidence-based management. (Munro et al., 2023) Structural abnormalities such as endometrial polyps, adenomyosis, leiomyomas, and malignancy must be distinguished from non-structural causes including coagulopathies, ovulatory dysfunction, endometrial disorders, and iatrogenic factors. A thorough clinical assessment incorporating detailed history taking, physical examination, laboratory investigations, imaging studies, and endometrial evaluation when appropriate remains fundamental for establishing the correct diagnosis. Continued advances in diagnostic techniques and a deeper understanding of menstrual physiology are expected to further improve the evaluation and management of women presenting with abnormal uterine bleeding. (Munro et al., 2011; Jain et al., 2023).

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BÖLÜM 2

VAGINAL MICROBIOTA IN OBSTETRICS AND GYNECOLOGY: PHYSIOLOGY, DYSBIOSIS, AND CLINICAL OUTCOMES

ZAHİDE KÜÇÜK¹

Introduction

The vaginal microbiota is now recognized as a central determinant of female reproductive tract health rather than a passive microbial background. In most reproductive-age women, a vaginal ecosystem dominated by **Lactobacillus** species contributes to host defense through lactic acid production, maintenance of a low vaginal pH, competitive exclusion of pathogenic organisms, and modulation of mucosal immune responses. This balanced microbial environment supports epithelial barrier integrity and helps preserve local homeostasis across the menstrual cycle, sexual activity, and pregnancy, although substantial interpersonal and temporal variation is well established (1, 2).

Conversely, disruption of this ecological balance, commonly referred to as **vaginal dysbiosis**, has been associated with a broad spectrum of gynecologic and obstetric disorders. The best-known clinical correlate of dysbiosis is bacterial vaginosis, which remains the most common cause of vaginal discharge in clinical practice and is characterized by depletion of protective lactobacilli and overgrowth of diverse anaerobic organisms. Beyond symptomatic vaginitis syndromes, growing evidence indicates that vaginal

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dysbiosis is linked to persistent genital inflammation, altered innate and adaptive immune signaling, greater susceptibility to sexually transmitted pathogens, and recurrence-prone lower genital tract disease. Current clinical guidance still relies mainly on syndrome-based diagnosis and conventional treatment algorithms, underscoring the gap between rapidly evolving microbiome science and routine bedside practice (3, 4).

In obstetrics and gynecology, interest in the vaginal microbiota has intensified because its relevance appears to extend far beyond local infection. Recent reviews and systematic syntheses suggest that microbiota composition may influence major reproductive outcomes, including preterm birth risk, assisted reproduction outcomes, human papillomavirus persistence, and progression of cervical dysplasia. These observations have shifted the field toward a more integrated model in which the vaginal microbiota interacts dynamically with hormonal status, epithelial biology, and host immunity to shape reproductive health and disease. Accordingly, understanding the physiology of the vaginal microbiota, the mechanisms and patterns of dysbiosis, and their clinical consequences has become essential for modern obstetric and gynecologic practice (5-7).

Physiology of the Vaginal Microbiota

The vaginal microbiota is a dynamic mucosal ecosystem that plays a central role in maintaining lower genital tract homeostasis. In healthy reproductive-age women, this ecosystem is most commonly characterized by relative dominance of *Lactobacillus* species, particularly *Lactobacillus crispatus*, *L. gasseri*, *L. jensenii*, and, in many women, *L. iners*. Although interindividual variation is substantial and not every healthy vagina is uniformly *Lactobacillus*-dominant, lactobacilli-rich community states are generally

associated with a low vaginal pH, reduced colonization by opportunistic pathogens, and a more stable mucosal environment. This physiologic state is now understood not as a static “normal flora,” but as a hormonally responsive and immunologically active microbial system (8-10).

A key determinant of vaginal microbial physiology is the estrogen-dependent maturation of the vaginal epithelium. Under estrogenic influence, epithelial cells accumulate glycogen, which is subsequently metabolized through host and microbial pathways into substrates that support lactobacilli and related metabolic networks. The end result is abundant production of lactic acid, which maintains the vaginal pH in an acidic range and creates conditions that are unfavorable for many anaerobic and sexually transmitted pathogens. This acidic microenvironment is one of the most important features of vaginal health because it contributes not only to microbial selection but also to biochemical and immunologic defense at the mucosal surface (11-13).

The protective role of lactobacilli extends beyond pH regulation alone. Vaginal lactobacilli contribute to host defense through multiple complementary mechanisms, including competitive adherence to the vaginal epithelium, exclusion of exogenous and endogenous pathogens, production of antimicrobial metabolites, and modulation of local immune responses. Lactic acid itself appears to have direct antimicrobial and virucidal properties and may also shape the vaginal immune milieu by dampening excessive inflammation while preserving barrier defense. In addition, lactobacilli influence epithelial integrity and mucus-associated protection, thereby helping to maintain a biologic barrier against ascending infection (11, 12, 14, 15).

Vaginal microbial physiology is not fixed across the life course. In childhood and after menopause, reduced estrogen exposure is associated with lower glycogen availability, diminished

lactobacillary dominance, and a higher vaginal pH. By contrast, during the reproductive years, hormonal cycling, sexual activity, semen exposure, menstrual bleeding, hygiene practices, pregnancy, and antibiotic use may all influence microbial composition and temporal stability. Pregnancy is often associated with a more stable and *Lactobacillus*-enriched vaginal ecosystem, whereas menstruation and exogenous perturbations may transiently alter community structure. Thus, physiologic variation should be distinguished from true dysbiosis, even though the boundary between adaptation and pathology may at times be clinically subtle (8).

Another important concept in vaginal physiology is that “normality” does not necessarily imply a single universal microbial pattern. Culture-independent sequencing studies have shown that healthy women may exhibit different community state types, some dominated by a single *Lactobacillus* species and others showing greater diversity. However, communities depleted of lactobacilli and enriched with anaerobic organisms are, in general, more often associated with elevated pH, mucosal inflammation, and clinical syndromes such as bacterial vaginosis. Accordingly, the physiology of the vaginal microbiota is best interpreted as a balance among microbial composition, metabolic output, epithelial biology, and host immunity rather than as the mere presence or absence of specific taxa (16).

From a clinical perspective, understanding the physiology of the vaginal microbiota is essential because many gynecologic and obstetric disorders begin with disruption of this finely regulated ecosystem. The healthy vaginal microenvironment depends on the interaction of sex steroids, epithelial glycogen metabolism, *Lactobacillus*-driven acidification, mucosal barrier integrity, and immune homeostasis. When these physiologic relationships are preserved, the vagina remains relatively resistant to pathogen

overgrowth and ascending infection; when they are disturbed, the risk of dysbiosis and its reproductive consequences increases substantially (8, 11).

Factors Shaping the Vaginal Microbial Ecosystem

The vaginal microbial ecosystem is not biologically static; rather, it is continuously shaped by endocrine status across the female life course. Puberty, the reproductive years, pregnancy, and menopause each create distinct hormonal environments that influence epithelial glycogen availability, mucosal acidity, and the relative abundance of *Lactobacillus*-dominant communities. In broad terms, estrogen-rich states tend to favor a more protective vaginal milieu, whereas hypoestrogenic states are more often associated with reduced lactobacillary dominance, greater microbial diversity, and increased mucosal vulnerability (8, 17).

Menstrual cycling is another major determinant of vaginal microbial dynamics. Longitudinal studies indicate that the composition of the vaginal microbiota may fluctuate over time, with shifts related to menstrual bleeding, cyclical hormonal variation, and short-term ecological perturbation (18). These changes are not necessarily pathologic; however, they help explain why the same individual may exhibit temporal variation in microbial stability and why cross-sectional sampling can sometimes misrepresent the true physiologic range of the vaginal ecosystem (19).

Sexual behavior and partner-related microbial exchange also appear to influence vaginal microbiota composition. Increasingly, the field recognizes that microbial transfer between sexual partners, semen exposure, and broader sexual practices may contribute to transient or sustained ecological shifts in the lower genital tract (20). This has led to growing interest in the concept of a shared genital microbial environment, in which the vaginal microbiota is shaped

not only by host factors but also by interpersonal microbial exchange and sexual network effects (21).

Pregnancy exerts a particularly important effect on the vaginal ecosystem. Available evidence suggests that healthy pregnancy is often associated with greater microbial stability and, in many women, a relative enrichment of *Lactobacillus*-dominant communities, especially during later gestation (22). This relative stabilization is thought to be biologically advantageous because it may help preserve mucosal defense and reduce ascending infectious risk during a period in which reproductive tract homeostasis is especially critical for maternal and fetal health (23).

Daily practices and external exposures can also modulate the vaginal microbial environment. Hygiene behaviors such as vaginal douching, irritant cleansing practices, and certain vulvovaginal care habits may disrupt the epithelial surface and alter local microbial balance (24). More broadly, antibiotics, contraceptive use, smoking, psychosocial stress, and other environmental or behavioral factors may either destabilize or support eubiosis, depending on the exposure context and the host background. Accordingly, the vaginal microbiota should be understood as an ecosystem shaped by the interaction of biologic, behavioral, and environmental determinants rather than by microbial factors alone (25).

Mechanisms and Patterns of Vaginal Dysbiosis

Vaginal dysbiosis refers to a pathobiological shift away from a stable, protective vaginal ecosystem toward a state characterized by loss of *Lactobacillus* predominance, increased microbial diversity, and altered metabolic output. Rather than representing a single uniform condition, dysbiosis encompasses a spectrum of microbial community disturbances that differ in composition, severity, persistence, and clinical expression. This broader concept

is important because not all dysbiotic states are identical in their biologic behavior, and not all are captured fully by traditional syndromic diagnoses such as bacterial vaginosis (26).

One of the central mechanistic features of dysbiosis is the depletion of lactic acid-producing lactobacilli and the consequent rise in vaginal pH. As acidity declines, the vaginal niche becomes more permissive to anaerobic and facultative anaerobic organisms, including taxa commonly associated with bacterial vaginosis. This altered biochemical environment is accompanied by changes in metabolite production, mucin interaction, and epithelial surface ecology, thereby promoting microbial persistence and weakening the physiologic barriers that normally restrict pathogen overgrowth (26, 27).

A further hallmark of dysbiosis is polymicrobial biofilm formation, particularly in biofilm-associated vaginosis. In this setting, organisms such as *Gardnerella* may act as early colonizers that facilitate the adhesion, stratification, and cooperative survival of additional anaerobic species. The resulting polymicrobial consortia create a structurally organized microbial layer on the vaginal epithelium that is more resistant to host clearance and antimicrobial therapy than planktonic organisms, helping to explain both chronicity and recurrence (28, 29).

Dysbiosis is also an immunobiologic phenomenon. As protective microbial dominance is lost, the vaginal microenvironment shifts toward epithelial stress, inflammatory signaling, and impaired mucosal homeostasis. This inflammatory state may promote tissue vulnerability, facilitate ascending microbial effects, and contribute to adverse reproductive outcomes. In pregnancy, for example, dysbiosis-associated communities enriched with anaerobes such as *Gardnerella* and *Prevotella* have been linked to inflammatory activation and premature cervical remodeling, supporting the view that microbial imbalance can influence disease

through immune and barrier-mediated pathways rather than simple infection alone (30, 31).

Clinically, patterns of vaginal dysbiosis may be transient, recurrent, or persistent. Some women experience short-lived fluctuations that resolve spontaneously, whereas others develop stable dysbiotic community states associated with recurrent symptoms, treatment failure, or reproductive complications. This heterogeneity is one reason why current definitions based solely on discharge, odor, microscopy, or pH remain insufficient to capture the full biologic complexity of dysbiosis. Contemporary microbiome research therefore increasingly frames vaginal dysbiosis as a dynamic ecological disorder involving microbial succession, host susceptibility, and context-specific clinical expression (28, 30).

Vaginal Dysbiosis in Gynecologic Disease

Vaginal dysbiosis has increasingly been implicated in a wide spectrum of gynecologic disorders, extending its relevance beyond bacterial vaginosis and symptomatic vaginitis. In contemporary gynecology, dysbiosis is best viewed as a disturbance of the cervicovaginal microenvironment that may influence epithelial integrity, mucosal immunity, inflammatory tone, and susceptibility to disease persistence or progression. This broader framework has shifted the discussion from isolated infectious syndromes toward a systems-based model in which microbial imbalance may function as both a marker and mediator of gynecologic pathology (13).

One of the strongest and most consistently discussed associations is with human papillomavirus infection and cervical neoplasia. Current reviews indicate that *Lactobacillus* depletion and increased microbial diversity are more frequently observed in women with persistent HPV infection, cervical intraepithelial neoplasia, and cervical cancer. The proposed mechanisms include

impaired viral clearance, chronic low-grade inflammation, disruption of mucosal barrier function, and creation of a pro-oncogenic cervical microenvironment. Although causality remains incompletely resolved, the relationship between vaginal dysbiosis and HPV-related cervical disease is now considered one of the most important translational areas in gynecologic microbiome research (32, 33).

A second major field of interest is infertility and assisted reproduction. Emerging evidence suggests that dysbiotic vaginal communities may be associated with impaired reproductive efficiency, possibly through cervical barrier disruption, altered endometrial receptivity, subclinical inflammation, or reduced implantation potential. Studies in assisted reproduction settings have further suggested that vaginal microbiota profiles may correlate with IVF outcomes, although the exact direction and strength of these associations vary across cohorts. These findings support the idea that the vaginal microbiota may represent a clinically relevant component of the reproductive microenvironment rather than an incidental bystander (34, 35).

Vaginal dysbiosis has also been linked to endometriosis and other non-neoplastic gynecologic disorders, although this area is still more exploratory than the HPV literature. Recent analyses suggest that women with endometriosis may exhibit altered vaginal microecology, and these changes may interact with inflammatory and estrogen-dependent pathways that are central to disease biology. At present, however, the literature remains heterogeneous, and it is not yet clear whether dysbiosis contributes directly to disease pathogenesis, reflects systemic reproductive tract disturbance, or varies according to phenotype and disease burden (36, 37).

From a clinical standpoint, these observations underscore a larger shift in gynecology: vaginal dysbiosis is no longer relevant only as a cause of discharge or odor, but as a potential modifier of

infection persistence, reproductive function, and gynecologic disease risk. The challenge now is to determine which microbial patterns are truly actionable, which are merely associative, and how microbiota-informed diagnostics or interventions might eventually be integrated into routine gynecologic practice (38).

The Vaginal Microbiota in Pregnancy and Adverse Obstetric Outcomes

Pregnancy is accompanied by distinctive changes in the vaginal microbial ecosystem, and in many women this period is characterized by relative enrichment of *Lactobacillus*-dominant communities and greater temporal stability compared with the nonpregnant state. This pattern is generally interpreted as biologically adaptive, since a more stable and acid-producing vaginal environment may help preserve epithelial integrity and reduce ascending microbial risk at a time when reproductive tract homeostasis is critical for fetal development (39, 40).

Despite this physiologic tendency toward stability, vaginal dysbiosis during pregnancy has been repeatedly associated with adverse obstetric outcomes, particularly spontaneous preterm birth. Recent systematic and narrative reviews indicate that depletion of protective lactobacilli, increased microbial diversity, and enrichment with anaerobic taxa such as *Gardnerella* and *Prevotella* are linked to a higher likelihood of preterm delivery, although the strength of association varies by population, sampling time, and analytic method (7, 31).

Preterm prelabor rupture of membranes represents another major obstetric condition in which the vaginal microbiota appears to be clinically relevant. Current evidence suggests that dysbiotic vaginal communities may promote membrane weakening through inflammatory signaling, biofilm-associated persistence, proteolytic

activity, and disruption of local barrier defenses. In this model, vaginal dysbiosis is not merely a coincidental finding but a plausible upstream contributor to membrane fragility and premature rupture (1, 41).

The relationship between the vaginal microbiota and early pregnancy loss is less settled than the preterm birth literature, but recent work suggests that miscarriage and recurrent pregnancy loss may also be influenced by lower genital tract microbial patterns. Reviews in this area indicate that non-Lactobacillus-dominant communities, microbial diversity shifts, and associated immune dysregulation may be linked to early pregnancy failure in at least a subset of patients, although causality remains incompletely established and the evidence base is still developing (42, 43).

From a clinical perspective, these findings support the view that the vaginal microbiota is not simply a local microbial descriptor in pregnancy, but a biologically meaningful component of obstetric risk architecture. The major challenge now is translational: to determine whether microbiota-informed screening, risk stratification, or targeted interventions can improve outcomes such as preterm birth, PPROM, or pregnancy loss without overinterpreting associative data that remain context dependent and methodologically heterogeneous (1, 44).

Diagnostic Approaches and Emerging Technologies

The diagnostic assessment of the vaginal microbiota has traditionally relied on clinical and microscopy-based methods such as symptom evaluation, vaginal pH measurement, Amsel criteria, wet mount examination, and Nugent scoring. These approaches remain important in routine practice because they are inexpensive, rapid, and clinically accessible; however, they primarily identify syndromic patterns such as bacterial vaginosis rather than providing

a detailed ecological profile of the vaginal microbiome. As a result, they often fail to capture microbial complexity, strain-level variation, and biologically relevant dysbiotic states that may not fit neatly within conventional diagnostic categories (45).

More recently, molecular diagnostics have expanded the field beyond morphology-based classification. Targeted PCR and multiplex qPCR assays can identify key bacterial taxa, estimate relative community shifts, and improve the detection of dysbiosis-associated organisms with greater analytic precision than conventional microscopy. These methods are particularly attractive because they offer a bridge between research-grade microbiome analysis and clinically deployable testing, potentially allowing faster and more standardized microbiota-informed assessment in gynecologic practice (46, 47).

High-resolution sequencing technologies now provide a much deeper view of the vaginal microbial ecosystem. 16S rRNA gene sequencing remains widely used for taxonomic profiling, while metagenomic next-generation sequencing can deliver species- and sometimes strain-level resolution together with functional information. These tools are especially valuable in research and translational settings because they can identify community state types, detect mixed microbial consortia, and reveal functional signatures that are invisible to routine clinical tests. At the same time, their broader clinical adoption is limited by cost, turnaround time, host-DNA contamination, and the need for standardized sampling and bioinformatic pipelines (45, 48).

Emerging technologies are now moving the field toward more actionable and personalized diagnostics. Recent work highlights shallow shotgun sequencing, optimized protocol standardization, and integrated computational approaches as promising strategies for improving reproducibility and clinical interpretability. In parallel, digitally enabled care models and remote

microbiome-guided management platforms suggest that vaginal microbiota assessment may eventually become more scalable, longitudinal, and patient-centered rather than remaining confined to episodic in-clinic testing (49, 50).

From a translational perspective, the central challenge is no longer whether the vaginal microbiota can be measured, but how to convert increasingly sophisticated microbial data into clinically meaningful decisions. The future of diagnostics in this field will likely depend on assays that are not only analytically robust but also standardized, affordable, and linked to validated clinical endpoints such as recurrence risk, treatment response, infertility outcomes, or adverse pregnancy events. Until then, emerging microbiome technologies should be viewed as highly promising tools whose full clinical utility is still being defined (51).

Therapeutic Perspectives and Microbiota-Modulating Strategies

The treatment of vaginal dysbiosis has traditionally centered on antimicrobial therapy, particularly in the setting of bacterial vaginosis, where oral or intravaginal metronidazole and intravaginal clindamycin remain the standard evidence-based options in routine practice. These therapies are effective for short-term symptom control and clinical remission; however, they do not reliably restore a durable *Lactobacillus*-dominant ecosystem, which helps explain why recurrence remains a major therapeutic limitation. In this sense, conventional treatment often suppresses dysbiotic overgrowth without fully re-establishing microbial resilience (52).

This limitation has driven growing interest in probiotics as microbiota-modulating adjuncts or alternatives. Recent reviews suggest that selected ***Lactobacillus***-containing probiotic regimens, delivered orally or vaginally, may help reduce recurrence, improve

microbial balance, and support reconstitution of a more protective vaginal environment, although strain selection, dosing, formulation, and treatment duration remain insufficiently standardized across studies. Accordingly, probiotics appear promising, but they have not yet achieved the level of protocol uniformity needed for universal integration into guideline-driven care (53, 54).

Another emerging therapeutic frontier is vaginal microbiota transplantation, which aims to restore eubiosis by transferring vaginal microbial communities from healthy donors to recipients with persistent dysbiosis. Recent scoping and narrative reviews describe this strategy as biologically compelling, particularly for refractory or recurrent bacterial vaginosis, because it attempts ecological restoration rather than repeated suppression. At present, however, the field is still early in development, and questions remain regarding donor screening, safety, durability, regulatory oversight, and the reproducibility of clinical benefit (55, 56).

A parallel line of innovation involves more targeted ecosystem-based strategies, including combination regimens that pair antibiotics with probiotic restoration, biofilm-disrupting approaches, and nontraditional microbial interventions designed to reduce relapse. Recent therapeutic reviews increasingly emphasize that recurrent dysbiosis should not be viewed simply as repeated infection, but as an ecological failure of recovery after treatment. This conceptual shift is important because it redirects management away from repeated empiric retreatment alone and toward sustained microbiome reconstitution (57, 58).

Looking ahead, the most advanced therapeutic vision is a personalized one. Newer work in vaginal pharmacomicrobiomics suggests that host–microbiome–drug interactions may influence treatment response, persistence, and recurrence, raising the possibility that future therapy could be tailored according to microbial composition, functional activity, and predicted drug–

microbiome behavior. Such an approach remains investigational, but it reflects the broader transition of the field from symptom-based management toward precision microbiota medicine in obstetrics and gynecology (13, 59).

Conclusion

The vaginal microbiota has emerged as a fundamental component of female reproductive health, with relevance that extends far beyond the traditional boundaries of infectious disease. Rather than functioning as a passive microbial population, it represents a dynamic and biologically active ecosystem that interacts closely with hormonal regulation, epithelial integrity, mucosal immunity, and reproductive physiology. When this ecosystem remains balanced, it contributes to vaginal homeostasis and host defense; when disrupted, it may influence a broad range of gynecologic and obstetric disorders.

Current evidence has made it increasingly clear that vaginal dysbiosis should be understood not merely as a local microbial abnormality, but as a clinically meaningful disturbance with potential implications for cervical health, fertility, pregnancy outcomes, and long-term reproductive well-being. At the same time, the field remains in transition. Although microbiome science has advanced rapidly, routine clinical practice still relies largely on conventional diagnostic frameworks and treatment strategies that do not fully capture the ecological complexity of the vaginal environment.

For obstetrics and gynecology, the significance of this field lies in its translational promise. Improved characterization of the vaginal microbiota may refine risk assessment, enhance understanding of disease mechanisms, and support the development of more precise preventive and therapeutic approaches. However,

meaningful clinical integration will require standardized diagnostics, stronger longitudinal evidence, and careful distinction between association and causation. As research continues to evolve, the vaginal microbiota is likely to become an increasingly important element of personalized reproductive medicine, linking microbial ecology with clinical decision-making in a way that may reshape the future of women's health.

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BÖLÜM 3

GENITOURINARY SYNDROME OF MENOPAUSE: DIAGNOSIS, TREATMENT, AND QUALITY OF LIFE

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Introduction

Genitourinary syndrome of menopause (GSM) is a chronic clinical condition that encompasses genital, sexual, and lower urinary tract symptoms and signs related to the decline in estrogenic and androgenic stimulation of urogenital tissues during the menopausal transition and after menopause (Kaufman et al., 2025; Portman & Gass, 2014). The term GSM was introduced to replace older expressions such as vulvovaginal atrophy and atrophic vaginitis because those terms did not adequately describe the broader involvement of the vulva, vestibule, vagina, urethra, bladder, and sexual function (Portman & Gass, 2014). GSM is not limited to vaginal dryness; it includes a spectrum of symptoms such as vulvovaginal burning, irritation, itching, dyspareunia, decreased lubrication, dysuria, urinary urgency, recurrent urinary tract infections, and postcoital bleeding or discomfort (Danan et al., 2024a; Kaufman et al., 2025).

The prevalence of GSM varies widely across studies because of heterogeneity in diagnostic criteria, study populations, menopausal stage, symptom thresholds, and assessment instruments (Danan et al., 2024a; Simon et al., 2026). The North American

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Menopause Society reported that GSM affects approximately 27% to 84% of postmenopausal women and may significantly impair health, sexual function, and quality of life (The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Recent expert recommendations also indicate that the presence of at least one GSM symptom may range from 14% to 87% among postmenopausal women, with vaginal dryness and dyspareunia being among the most frequently reported symptoms (Simon et al., 2026). Despite this high prevalence, GSM remains underdiagnosed and undertreated because many women do not volunteer symptoms, many clinicians do not proactively ask about them, and sexual or urogenital complaints may be normalized as an unavoidable aspect of aging (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024a).

The clinical importance of GSM lies in its persistence and its effect on daily functioning, sexual well-being, intimate relationships, and self-perception (Nappi & Palacios, 2014; Parish et al., 2013). Unlike vasomotor symptoms, which often improve over time in many women, GSM symptoms commonly persist and may progress without appropriate treatment (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Simon et al., 2026). Therefore, GSM should be approached as a treatable, patient-centered condition rather than as an inevitable or trivial consequence of menopause (Kaufman et al., 2025).

Pathophysiology and Biological Basis

The pathophysiology of GSM is primarily driven by reduced estrogen and androgen exposure in urogenital tissues, which are hormonally responsive throughout adult life (Kaufman et al., 2025; Simon et al., 2026). Estrogen deficiency leads to thinning of the vaginal epithelium, decreased epithelial glycogen content, reduced lubrication, diminished tissue elasticity, increased vaginal pH, and alterations in the vaginal microbiome (Danan et al., 2024a; Sarmiento et al., 2021). Reduced glycogen availability limits the substrate for

lactobacilli, and the resulting decrease in lactic acid production contributes to elevation of vaginal pH and vulnerability to irritation, dysbiosis, and infection-like symptoms (Danan et al., 2024a; Sarmiento et al., 2021).

The vulva, vestibule, clitoris, vagina, urethra, bladder trigone, and pelvic floor tissues contain hormone-responsive receptors, which explains why GSM may present with genital, urinary, and sexual symptoms simultaneously (Simon et al., 2026; Portman & Gass, 2014). The vestibule and periurethral region are particularly relevant in women with introital pain, superficial dyspareunia, urinary urgency, and urethral discomfort (Simon et al., 2026). Collagen remodeling, reduced vascularity, decreased mucosal secretions, loss of rugal folds, and narrowing of the introitus may collectively produce pain, dryness, fissuring, and reduced sexual comfort (Sarmiento et al., 2021; The NAMS 2020 GSM Position Statement Editorial Panel, 2020).

Urinary symptoms in GSM are clinically important but diagnostically complex because urgency, frequency, dysuria, and recurrent urinary tract infections may overlap with overactive bladder, urinary infection, pelvic floor dysfunction, and age-related lower urinary tract changes (Danan et al., 2024a; Kaufman et al., 2025). In hypoestrogenic women with recurrent urinary tract infections, vaginal estrogen has been associated with reduction in future urinary tract infection risk, supporting a biologically plausible link between the estrogenized vaginal environment and urogenital host defense (Chen et al., 2021; Tan-Kim et al., 2023). However, not every urinary symptom in a postmenopausal woman should automatically be attributed to GSM, and alternative or coexisting causes should be evaluated when symptoms are severe, atypical, persistent, or treatment-resistant (Danan et al., 2024a; Kaufman et al., 2025).

Clinical Presentation

The clinical presentation of GSM can be organized into vulvovaginal, sexual, and urinary domains (Kaufman et al., 2025; Portman & Gass, 2014). Vulvovaginal symptoms include dryness, burning, itching, irritation, soreness, decreased lubrication, abnormal discharge perception, fissuring, and postcoital spotting (Danan et al., 2024a; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Sexual symptoms include superficial dyspareunia, reduced arousal related to discomfort, avoidance of intercourse, decreased sexual satisfaction, and distress related to loss of sexual spontaneity or intimacy (Nappi & Palacios, 2014; Parish et al., 2013). Urinary symptoms include dysuria, urgency, frequency, recurrent urinary tract infections, urethral discomfort, and sometimes worsening urinary incontinence symptoms (Danan et al., 2024a; Kaufman et al., 2025).

Physical findings may include pale or hypopigmented vaginal mucosa, loss of rugae, reduced moisture, petechiae, mucosal friability, narrowing of the introitus, labial resorption, clitoral hood changes, urethral caruncle, vestibular tenderness, and fissuring at the posterior fourchette (Danan et al., 2024a; Sarmiento et al., 2021). Importantly, the severity of visible physical findings does not always correlate with symptom severity, and some women with marked atrophic changes may report few symptoms while others with subtle findings may experience substantial pain or distress (Danan et al., 2024a). This discrepancy highlights the need to evaluate GSM through both clinical examination and patient-reported symptom burden rather than relying on appearance alone (Kaufman et al., 2025).

GSM may occur not only after natural menopause but also in women with iatrogenic or functional hypoestrogenism, including those receiving aromatase inhibitors, gonadotropin-releasing hormone analogues, chemotherapy, pelvic radiation, bilateral oophorectomy, or prolonged lactational hypoestrogenism (Beste et

al., 2025; Simon et al., 2026). Cancer survivors deserve particular attention because oncologic treatments may intensify GSM symptoms and because therapeutic decisions often require balancing symptom relief, cancer recurrence concerns, patient values, and multidisciplinary communication (Beste et al., 2025; Faubion et al., 2018).

Diagnosis and Differential Diagnosis

GSM is primarily a clinical diagnosis based on compatible symptoms, menopausal or hypoestrogenic status, and exclusion of alternative or coexisting pathology (Kaufman et al., 2025; Danan et al., 2024a). Current evidence does not establish a single required number or type of symptoms for diagnosis, and there is no universally accepted requirement that physical findings must be present in order to diagnose GSM (Danan et al., 2024a; Kaufman et al., 2025). A structured history should ask about vaginal dryness, burning, itching, dyspareunia, lubrication, sexual avoidance, urinary urgency, dysuria, recurrent urinary tract infections, postcoital bleeding, prior treatments, cancer history, medications, and patient goals (Kaufman et al., 2025; Simon et al., 2026).

Pelvic examination should assess the vulva, vestibule, introitus, vagina, cervix when present, urethral meatus, pelvic floor tenderness, and signs of dermatoses or infection (Danan et al., 2024a; Sarmiento et al., 2021). Vaginal pH and vaginal maturation index may support the assessment of hypoestrogenic vaginal changes, but they are not mandatory for routine clinical diagnosis and are used more frequently in clinical trials than in everyday practice (Danan et al., 2024a). Clinical trials often define postmenopausal vaginal atrophy using vaginal pH greater than 5 and low superficial cell percentage on vaginal maturation index, but such thresholds should not replace individualized clinical assessment (Danan et al., 2024a).

Validated patient-reported outcome tools can improve recognition of symptom burden and treatment response (Huang et al., 2015; Mastroianni et al., 2020). The Day-to-Day Impact of Vaginal Aging questionnaire was developed to measure the functional and emotional impact of vaginal symptoms in postmenopausal women (Huang et al., 2015). Clinical screening tools may be particularly helpful because many women hesitate to initiate conversations about sexual pain, dryness, or urinary symptoms unless clinicians ask directly and respectfully (Mastroianni et al., 2020; The NAMS 2020 GSM Position Statement Editorial Panel, 2020).

The differential diagnosis includes infectious vaginitis, vulvovaginal candidiasis, bacterial vaginosis, urinary tract infection, vulvar lichen sclerosus, lichen planus, contact dermatitis, vulvodynia, pelvic floor myalgia, desquamative inflammatory vaginitis, malignancy, trauma, foreign body, and medication-related mucosal changes (Danan et al., 2024a; Kaufman et al., 2025). Postmenopausal bleeding, persistent ulceration, unexplained discharge, visible lesions, severe vulvar architectural changes, or treatment-refractory symptoms require further evaluation and may require biopsy or specialist referral (Kaufman et al., 2025). A diagnosis of GSM should not prevent clinicians from investigating coexisting pathology when clinical features are atypical or disproportionate (Danan et al., 2024a).

General Principles of Treatment

Treatment should be individualized according to symptom severity, dominant symptom domain, contraindications, patient preference, cost, availability, sexual activity, cancer history, and willingness to use local or systemic therapy (Kaufman et al., 2025; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Shared decision-making is central because GSM is chronic, symptoms vary in meaning and priority across individuals, and

adherence is influenced by formulation, route, expectations, perceived safety, and partner-related factors (Kaufman et al., 2025; Parish et al., 2013). The goal of treatment is not merely to normalize pH or cytology but to reduce bother, improve comfort, preserve sexual function when relevant, reduce urinary morbidity when possible, and improve quality of life (Danan et al., 2024a; Nappi & Palacios, 2014).

For mild symptoms, nonhormonal vaginal lubricants and moisturizers are generally recommended as first-line therapy because they are accessible, low risk, and may provide sufficient relief for many women (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024b). Lubricants are used at the time of sexual activity to reduce friction and dyspareunia, whereas moisturizers are used regularly to improve hydration and reduce baseline dryness (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024b). Products should ideally be selected to minimize irritants, fragrances, and high osmolality formulations that may worsen mucosal discomfort in sensitive patients (Simon et al., 2026).

For moderate to severe symptoms, persistent dyspareunia, recurrent symptoms despite nonhormonal therapy, or prominent objective hypoestrogenic changes, prescription therapies such as low-dose vaginal estrogen, vaginal dehydroepiandrosterone, or oral ospemifene should be considered (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024b). The 2025 AUA/SUFU/AUGS guideline emphasizes that local low-dose vaginal estrogen has the most robust evidence base among available GSM therapies (Kaufman et al., 2025). Current guideline-based care does not require a rigid stepwise progression through all hormonal options before choosing an appropriate therapy, and treatment should be selected according to the patient's symptoms, safety considerations, and preferences (Kaufman et al., 2025).

Nonhormonal and Behavioral Interventions

Vaginal moisturizers and lubricants are appropriate for women with mild GSM symptoms, those who prefer nonhormonal care, those with contraindications or concerns regarding hormonal therapy, and those needing adjunctive symptom relief during sexual activity (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024b). A 2024 systematic review found that vaginal moisturizers may improve vulvovaginal dryness, although the certainty of evidence was generally low and effects on dyspareunia or dysuria were less consistent (Danan et al., 2024b). Nonhormonal products may be particularly useful when expectations are realistic and patients understand the difference between transient lubrication and tissue-directed hormonal restoration (The NAMS 2020 GSM Position Statement Editorial Panel, 2020).

Vaginal hyaluronic acid has gained attention as a nonhormonal option because of its hydrating and tissue-supportive properties (Agrawal et al., 2024). In a randomized pilot trial of women with GSM, vaginal hyaluronic acid and vaginal estrogen both improved vulvovaginal symptom questionnaire scores after 12 weeks, and no clinically meaningful difference between treatment arms was observed in that small study (Agrawal et al., 2024). These findings support vaginal hyaluronic acid as a promising nonhormonal option, but larger trials with longer follow-up are needed before it can be considered equivalent to estrogen-based treatment across broader populations (Agrawal et al., 2024; Danan et al., 2024b).

Behavioral measures include avoidance of irritants, use of gentle vulvar care, maintenance of sexual activity if desired and comfortable, pelvic floor physical therapy when pelvic floor overactivity is present, and counseling for sexual pain or avoidance (Simon et al., 2026; Kaufman et al., 2025). Pelvic floor physical

therapy is not a primary tissue-restorative treatment for GSM, but it may be valuable when dyspareunia is amplified by pelvic floor muscle hypertonicity, vestibular guarding, or secondary pain sensitization (Simon et al., 2026). Dilator therapy may help selected women with introital narrowing, vaginismus-like guarding, or post-radiation vaginal stenosis, but it should be introduced sensitively and paired with adequate lubrication or local therapy when mucosal fragility is present (Simon et al., 2026).

Complementary and alternative therapies remain an area of active interest, but many interventions have limited evidence, small sample sizes, heterogeneous formulations, and inconsistent outcome reporting (Danan et al., 2024a; Ullman et al., 2024). Patients should be asked about over-the-counter botanical products, supplements, oils, or compounded preparations because these may cause irritation, interact with other treatments, or delay effective therapy (Danan et al., 2024a). Clinicians should avoid overstating the benefits of unregulated or inadequately studied products and should frame them within the limits of available evidence (Danan et al., 2024a).

Local Hormonal Therapy, Prasterone, and Ospemifene

Low-dose vaginal estrogen is one of the best-supported treatments for GSM and is available in several formulations, including creams, tablets, inserts, and rings (Biehl et al., 2019; Kaufman et al., 2025). Vaginal estrogen improves local estrogenization, reduces vaginal dryness, improves epithelial maturation, lowers vaginal pH, and may improve dyspareunia and recurrent urinary tract infection risk in hypoestrogenic women (Biehl et al., 2019; Chen et al., 2021). Low-dose vaginal estrogen is generally used without progestogen co-therapy, but unexplained postmenopausal bleeding should always be evaluated rather than attributed to treatment (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024a).

The AHRQ systematic review concluded that vaginal estrogen may improve vulvovaginal dryness and treatment satisfaction, while evidence for some outcomes such as dyspareunia, dysuria, and quality of life varied by comparator and certainty level (Danan et al., 2024b). These findings do not negate the clinical role of vaginal estrogen; rather, they emphasize that trial outcomes, placebo effects, symptom heterogeneity, and measurement limitations complicate evidence interpretation (Danan et al., 2024a). In clinical practice, symptom improvement is often assessed after several weeks of therapy, and maintenance treatment is usually required because GSM symptoms may recur when therapy is discontinued (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Simon et al., 2026).

Vaginal dehydroepiandrosterone, also known as prasterone, is an intravaginal therapy that is converted locally into active sex steroids within target tissues and is used for moderate to severe dyspareunia associated with menopause-related vulvovaginal changes (Labrie et al., 2016; Simon et al., 2026). Randomized trial evidence supports improvement in dyspareunia and objective vaginal parameters with intravaginal DHEA in women with vulvovaginal atrophy or GSM (Labrie et al., 2016). The 2024 systematic review concluded that vaginal DHEA may improve dryness, dyspareunia, and quality-of-life-related outcomes, although certainty of evidence and long-term safety data remain limited (Danan et al., 2024b).

Ospemifene is an oral selective estrogen receptor modulator used for moderate to severe dyspareunia or vaginal dryness associated with postmenopausal vulvovaginal atrophy and GSM (Portman et al., 2014; Archer et al., 2019). Phase III evidence has shown that ospemifene can improve vaginal dryness, dyspareunia, vaginal maturation index, and vaginal pH in appropriately selected postmenopausal women (Portman et al., 2014; Archer et al., 2019).

Ospemifene may be attractive for women who prefer oral therapy over vaginal administration, but contraindications, thromboembolic risk factors, vasomotor adverse effects, and endometrial considerations should be assessed before prescribing (Danan et al., 2024a; The NAMS 2020 GSM Position Statement Editorial Panel, 2020).

Systemic menopausal hormone therapy may improve GSM when used for vasomotor symptoms or broader menopausal indications, but systemic therapy alone may not adequately treat persistent urogenital symptoms in all women (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; The NAMS 2022 Hormone Therapy Position Statement Advisory Panel, 2022). Women receiving systemic therapy may still require local vaginal therapy if dryness, dyspareunia, or urinary symptoms persist (The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Conversely, isolated GSM without vasomotor symptoms generally does not require systemic hormone therapy when local options are appropriate (The NAMS 2022 Hormone Therapy Position Statement Advisory Panel, 2022).

Urinary Symptoms and Recurrent Urinary Tract Infection

The urinary domain of GSM is clinically relevant because hypoestrogenic changes may contribute to dysuria, urgency, frequency, urethral discomfort, and recurrent urinary tract infections (Danan et al., 2024a; Kaufman et al., 2025). However, urinary symptoms require careful evaluation because overactive bladder, stress urinary incontinence, recurrent bacterial cystitis, bladder pain syndrome, pelvic floor dysfunction, and medications may mimic or coexist with GSM (Danan et al., 2024a). Urinalysis and urine culture should be used when infection is suspected, particularly in women with acute dysuria, hematuria, systemic symptoms, or recurrent episodes (Kaufman et al., 2025).

Vaginal estrogen has evidence for reducing recurrent urinary tract infections in postmenopausal or hypoestrogenic women (Chen et al., 2021; Tan-Kim et al., 2023). A meta-analysis found that vaginal estrogen reduced the number of recurrent urinary tract infections and lowered vaginal pH in postmenopausal women compared with placebo (Chen et al., 2021). A large retrospective study of hypoestrogenic women prescribed vaginal estrogen found a reduction in urinary tract infection frequency during the following year, supporting its use as part of recurrent urinary tract infection prevention in appropriately selected patients (Tan-Kim et al., 2023).

Urinary urgency and frequency may improve in some women when GSM is treated, but persistent symptoms should prompt assessment for overactive bladder, pelvic organ prolapse, incomplete bladder emptying, recurrent infection, or neurologic contributors (Danan et al., 2024a; Kaufman et al., 2025). Behavioral bladder strategies, pelvic floor physical therapy, and pharmacologic overactive bladder treatment may be required when urinary symptoms are not fully explained by GSM (Kaufman et al., 2025). The best outcomes are achieved when clinicians avoid forcing all symptoms into a single diagnosis and instead address overlapping urogenital syndromes in an integrated manner (Danan et al., 2024a).

Special Populations: Breast Cancer Survivors and High-Risk Patients

Women with a history of breast cancer or those receiving endocrine therapy often experience severe GSM because chemotherapy, ovarian suppression, aromatase inhibitors, and antiestrogen therapy may intensify hypoestrogenic urogenital changes (Beste et al., 2025; Faubion et al., 2018). Nonhormonal therapies are generally considered first-line in breast cancer survivors because of safety concerns and patient or clinician reluctance regarding estrogen exposure (Faubion et al., 2018; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). When

nonhormonal treatments are inadequate, individualized discussion with the oncology team is appropriate, especially for women receiving aromatase inhibitors or those with hormone receptor-positive disease (Faubion et al., 2018; The NAMS 2020 GSM Position Statement Editorial Panel, 2020).

A 2025 systematic review and meta-analysis of observational studies found that vaginal estrogen use in breast cancer survivors was not associated with increased breast cancer recurrence, breast cancer-specific mortality, or overall mortality, but the authors emphasized the observational nature of the available evidence (Beste et al., 2025). These findings are reassuring but should not be interpreted as eliminating the need for individualized risk assessment, shared decision-making, and oncology collaboration (Beste et al., 2025). For women with severe GSM whose quality of life is substantially impaired, the balance between symptom burden and theoretical risk should be discussed clearly and compassionately (Faubion et al., 2018; Beste et al., 2025).

Gynecologic cancer survivors, women after pelvic radiation, and women with surgical menopause may also require tailored management because GSM may coexist with stenosis, fibrosis, dyspareunia, urinary morbidity, and psychosexual distress (Simon et al., 2026; Danan et al., 2024a). In these patients, local therapy, pelvic floor rehabilitation, dilator programs, sexual counseling, and survivorship care should be coordinated according to cancer type, treatment history, recurrence risk, and patient priorities (Simon et al., 2026). A narrow medication-only approach is often insufficient for patients whose GSM is embedded within broader cancer survivorship concerns (Faubion et al., 2018; Simon et al., 2026).

Energy-Based Therapies and Emerging Interventions

Energy-based interventions, including fractional carbon dioxide laser, Er:YAG laser, and radiofrequency devices, have been

investigated as nonhormonal approaches for GSM, particularly among women who cannot or do not wish to use hormonal treatments (Pessoa et al., 2024; Zerzan et al., 2025). Proposed mechanisms include induction of controlled microtrauma, neovascularization, collagen remodeling, and epithelial changes, but clinical efficacy and safety remain uncertain because of variability in devices, protocols, sham controls, follow-up duration, and outcome measures (Pessoa et al., 2024; Zerzan et al., 2025). A 2024 systematic review and meta-analysis reported that CO₂ laser may increase vaginal health index scores and reduce dyspareunia, dryness, and burning compared with sham laser, but the certainty of evidence was low and did not support a general recommendation for routine use (Pessoa et al., 2024). A 2025 systematic review of energy-based interventions similarly concluded that benefits and harms are not sufficiently established and that evidence does not demonstrate efficacy across key GSM outcomes (Zerzan et al., 2025).

Energy-based therapies should therefore be discussed as investigational or evidence-limited rather than as established replacements for low-dose vaginal estrogen, DHEA, ospemifene, or moisturizers (Danan et al., 2024a; Zerzan et al., 2025). Patients considering these treatments should be informed about cost, uncertain long-term safety, lack of standardized protocols, and the possibility of adverse effects such as pain, bleeding, discharge, scarring, or worsening symptoms (Pessoa et al., 2024; Zerzan et al., 2025). Future trials should include adequate sham controls, standardized diagnostic criteria, validated patient-reported outcomes, longer follow-up, and safety monitoring in diverse patient populations (Danan et al., 2024a; Zerzan et al., 2025).

Quality of Life and Sexual Health

GSM can impair quality of life through physical discomfort, sexual pain, avoidance of intimacy, reduced self-confidence, sleep

disturbance from urinary symptoms, anxiety about recurrent infections, and distress related to perceived loss of femininity or sexual identity (Nappi & Palacios, 2014; Parish et al., 2013). Survey-based evidence has shown that vulvovaginal symptoms can adversely affect interpersonal relationships, sexual function, and daily well-being (Parish et al., 2013). Women may experience embarrassment, fear of discussing sexual symptoms, or the belief that symptoms are too minor or too expected to merit medical attention (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Domoney et al., 2020).

Sexual quality of life should be assessed in a nonjudgmental way that respects women who are sexually active, not sexually active, partnered, unpartnered, heterosexual, LGBTQ+, widowed, divorced, or not interested in sexual activity (Simon et al., 2026). The clinical goal is not to impose sexual activity but to reduce symptoms that interfere with the patient's desired level of comfort, intimacy, and function (Simon et al., 2026). For sexually active women, treatment may restore comfort, reduce dyspareunia, improve lubrication, and decrease avoidance behaviors (Nappi & Palacios, 2014; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). For women who are not sexually active, treatment may still be important for daily dryness, burning, recurrent urinary symptoms, vulvar irritation, and comfort during examination (Kaufman et al., 2025; Danan et al., 2024a).

Quality-of-life assessment should include patient-defined outcomes such as comfort during daily activities, ability to sit or exercise without irritation, confidence with intimacy, reduction in urinary episodes, satisfaction with treatment route, and willingness to continue therapy (Huang et al., 2015; Danan et al., 2024a). Validated tools can support research and clinical follow-up, but routine care can also use simple questions such as “Which symptom bothers you most?” and “What would meaningful improvement look

like for you?” (Kaufman et al., 2025). A patient-centered approach is essential because the same physical symptom may have different emotional and functional significance for different women (Nappi & Palacios, 2014; Simon et al., 2026).

Follow-Up and Long-Term Management

Follow-up should assess symptom response, adherence, adverse effects, satisfaction, correct use of the chosen product, and emergence of red-flag symptoms such as postmenopausal bleeding (Danan et al., 2024a; Kaufman et al., 2025). Many effective interventions show improvement within weeks to months, but long-term data remain limited for several therapies, especially regarding comparative effectiveness, endometrial safety, and sustained quality-of-life outcomes (Danan et al., 2024a; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Because GSM is often chronic, discontinuation of treatment may lead to symptom recurrence, and patients should be informed that maintenance therapy may be required (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Simon et al., 2026).

Routine endometrial surveillance is not generally required solely because a woman uses low-dose vaginal estrogen, but any unexplained postmenopausal bleeding should be evaluated according to standard gynecologic practice (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024a). Long-term safety evidence for vaginal estrogen, vaginal DHEA, and ospemifene beyond one year remains incomplete, which should be acknowledged during counseling without unnecessarily deterring symptomatic women from effective therapy (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024a). Follow-up intervals should be individualized because evidence does not define one optimal schedule for all patients (Danan et al., 2024a).

Conclusion

GSM is a prevalent, chronic, and treatable condition that affects vulvovaginal comfort, sexual health, lower urinary tract symptoms, and quality of life in peri- and postmenopausal women (Kaufman et al., 2025; The NAMS 2020 GSM Position Statement Editorial Panel, 2020). Diagnosis is clinical and should be based on symptom inquiry, focused examination, assessment of patient bother, and exclusion of alternative or coexisting disorders (Danan et al., 2024a; Kaufman et al., 2025). Treatment should be individualized, beginning with education and nonhormonal options for mild symptoms and progressing to evidence-supported prescription therapies such as low-dose vaginal estrogen, vaginal DHEA, or ospemifene when symptoms are moderate, severe, persistent, or quality-of-life limiting (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Danan et al., 2024b).

The most important clinical message is that GSM should be actively identified rather than silently endured (Kaufman et al., 2025). Clinicians can improve outcomes by asking about symptoms routinely, normalizing discussion of urogenital and sexual health, offering evidence-based treatment, and respecting patient preferences and risk context (The NAMS 2020 GSM Position Statement Editorial Panel, 2020; Simon et al., 2026). Future research should refine diagnostic criteria, standardize outcome measures, generate longer-term safety data, and include diverse populations, cancer survivors, and women with complex urinary or sexual pain presentations (Danan et al., 2024a; Zerzan et al., 2025).

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BÖLÜM 4

ANTI-MÜLLERIAN HORMON (AMH) TESTİNİN KLİNİKTE KULLANIMI

BURAK ÜN¹

Giriş

Anti-Müllerian hormon (AMH), günümüzde over rezervinin değerlendirilmesinde yaygın olarak kullanılan biyobelirteçlerden biridir. Özellikle yardımcı üreme teknolojileri kapsamında uygulanacak tedavilerin planlanmasında ve kontrollü over stimülasyonuna verilecek yanıtın öngörülmesinde klinisyene yol gösterici bilgiler sağlamaktadır. Bu nedenle AMH ölçümü, üreme tıbbı pratiğinde giderek daha fazla önem kazanmıştır.

AMH düzeyleri kadınlarda genellikle erken erişkin dönemde en yüksek seviyelerine ulaşmakta, ilerleyen yaşla birlikte ise kademeli olarak azalmaktadır. Menopoza yaklaşıldıkça serum AMH konsantrasyonlarında belirgin bir düşüş izlenirken, menopoz sonrasında çoğu kadında ölçülemeyecek düzeylere gerilemektedir. Bu yaşa bağlı değişim, over rezervindeki doğal azalmayı yansıtması nedeniyle AMH'nin üreme potansiyelinin değerlendirilmesinde

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değerli bir belirteç olarak kullanılmasına olanak sağlamaktadır (Nelson et al., 2009; van Rooij et al., 2005).

AMH

AMH transforme edici büyüme faktörü-beta (TGF- β) süper ailesinin bir üyesi olan homodimerik bir glikoproteindir. Kadınlarda başlıca over korteksinde yer alan preantral ve küçük antral foliküllerin granüloza hücreleri tarafından sentezlenmektedir.

AMH, kadın üreme fizyolojisindeki işlevlerinin yanı sıra erkek cinsiyet farklılaşmasında da kritik bir göreve sahiptir. Erkek fetüste testislerin Sertoli hücrelerinden salgılanan AMH, embriyonik dönemde Müllerian kanalların gerilemesini sağlayarak normal erkek genital sistem gelişimine katkıda bulunmaktadır.

İnsan AMH proteini, 19p13.3 kromozomunda yer alan AMH geni tarafından kodlanmaktadır. AMH'nin biyolojik etkileri ise 12. kromozomda bulunan AMHR2 geni tarafından kodlanan AMH reseptör tip 2 (AMHR2) aracılığıyla gerçekleşmektedir. AMH-AMHR2 sinyal yolu, erkek cinsiyet gelişiminin düzenlenmesinde temel mekanizmalardan biri olarak kabul edilmektedir.

İlk olarak erkek fetus gelişimindeki etkileri nedeniyle tanımlanan AMH'nin, daha sonraki yıllarda kadınlarda over fonksiyonunun değerlendirilmesinde de yararlı bir biyobelirteç olduğu gösterilmiştir.

AMH, foliküler gelişimin düzenlenmesinde görev alan önemli faktörlerden biridir. Folikülogenez sürecinde primordial foliküllerin aktivasyonunu ve erken dönem foliküler büyümeyi baskılayarak folikül havuzunun tüketilmesini sınırlandırdığı düşünülmektedir. Bu sayede her ovulatuvar döngüde kullanılabilir folikül havuzunun korunmasına katkı sağlamakta ve over rezervinin sürdürülmesinde rol oynamaktadır. Bu düzenleyici etkinin, kadının üreme yaşamı boyunca foliküler rezervin devamlılığında önemli

olduğu kabul edilmektedir (Dewailly et al., 2014; Fanchin et al., 2003; van Rooij et al., 2005).

Overde AMH ekspresyonu, foliküler gelişim sürecine paralel olarak değişkenlik göstermektedir. AMH başlıca primer foliküllerden küçük antral foliküllere kadar olan gelişim evrelerindeki foliküllerin granüloza hücrelerinde üretilmektedir. Bu ekspresyon örüntüsü, insan dahil birçok türde benzer özellikler göstermektedir. AMH düzeyleri yaklaşık 8 mm çapa ulaşan foliküllere kadar artış göstermekte, bu aşamadan sonra ise belirgin şekilde azalmaktadır. Benzer bir dağılım foliküler sıvıdaki AMH konsantrasyonlarında da gözlenmektedir.

AMH ekspresyonu foliküler gelişimin farklı evrelerinde değişiklik göstermektedir. Folikül seçilimini takiben ve folikül uyarıcı hormonun (FSH) etkisiyle granüloza hücrelerinde AMH üretimi azalırken, preovulatuvar foliküllerin kumulus hücrelerinde sınırlı düzeyde ekspresyon devam edebilmektedir. Buna karşılık AMH ekspresyonu atretik foliküllerde ve korpus luteumda saptanmamaktadır. Bu bulgular, AMH'nin folikülogenez sürecindeki işlevinin gelişim evrelerine göre farklılık gösterdiğini düşündürmektedir.

AMH ekspresyonunun foliküler gelişim boyunca gösterdiği değişimlerin ortaya konulması, over fizyolojisinin daha iyi anlaşılmasına katkı sağlamıştır. AMH düzeyleri ile foliküler gelişim evreleri arasındaki ilişkinin değerlendirilmesi sayesinde over fonksiyonu non-invaziv olarak değerlendirilebilmekte ve üreme potansiyeli hakkında bilgi edinilebilmektedir. Günümüzde AMH; over rezervinin değerlendirilmesi, kontrollü over stimülasyonunun planlanması ve polikistik over sendromunun (PKOS) değerlendirilmesi gibi birçok alanda kullanılmakta olup hem klinik

uygulamada hem de arařtırmalarda önemli bir yer edinmiřtir (Jeppesen et al., 2013; Moolhuijsen & Visser, 2020).

AMH düzeyleri, over rezervi ve kontrollü over stimölasyonuna verilebilecek yanıt hakkında yol gösterici bilgiler saęlayabilmektedir. Ancak, AMH deęerlerinin yorumlanmasında kullanılan eřiklerin, ölçüm yöntemi ve deęerlendirilen popölasyona göre deęiřebileceęi göz önünde bulundurulmalıdır. Genel olarak serum AMH düzeyinin 1 ng/mL'nin altında olması azalmıř over rezervi ile iliřkilendirilirken, yüksek AMH düzeyleri artmıř over yanıtını düşündürebilmektedir. Özellikle 3,5 ng/mL'nin üzerindeki deęerlerde kontrollü over stimölasyonu sırasında aşırı over yanıtı ve ovaryan hiperstimölasyon sendromu (OHSS) riski açısından dikkatli olunması önerilmektedir.

Over rezervi, overlerde bulunan oosit havuzunun büyüklüęü ile iliřkili olup kadının yařamı boyunca belirgin deęiřiklikler göstermektedir. Fetal yařamda oosit sayısı gebelięin yaklaşık 20. haftasında en yüksek düzeye ulařmakta ve 7–8 milyon civarında olduęu bildirilmektedir. Bu dönemden sonra bařlayan fizyolojik atrezi süreci ile oosit sayısında ilerleyici bir azalma meydana gelmektedir. Puberte dönemine gelindięinde her iki overdeki toplam oosit sayısının yaklaşık 300.000–500.000'e geriledięi kabul edilmektedir.

Fertilite Göstergesi Olarak AMH

Granölöza hücreleri tarafından üretilen AMH, kadın üreme yařamı boyunca dolařıma salgılanmaktadır. Doğumda serum AMH düzeyleri oldukça düşük olmakla birlikte, puberte döneminde belirgin bir artış göstermektedir. Reprodüktif dönemde ise AMH konsantrasyonları yařla birlikte kademeli olarak azalmakta ve menopoz sonrasında çoęu kadında ölçülemeyecek düzeylere gerilemektedir (Lee et al., 1996; Rajpert-De Meyts et al., 1999).

Plazmada kolaylıkla ölçülebilmesi nedeniyle AMH, over rezervinin değerlendirilmesinde yaygın olarak kullanılmakta olup menopoz zamanlamasının öngörülmesinde de araştırılan biyobelirteçlerden biridir.

AMH düzeylerinin fertilite potansiyelini öngörmedeki değeri değerlendirilirken hasta grubunun özellikleri dikkate alınmalıdır. Özellikle infertilite öyküsü bulunmayan, daha önce gebelik elde etmiş veya henüz gebe kalmayı denememiş reproduktif çağıdaki kadınlarda AMH düzeylerinin doğal fertiliteyi ve gebelik sonuçlarını öngörmedeki katkısı sınırlı görünmektedir. Bu nedenle infertil olmayan kadın popülasyonunda AMH sonuçları yorumlanırken dikkatli olunmalı ve test sonuçları tek başına fertilite göstergesi olarak değerlendirilmemelidir ("ACOG Committee Opinion No. 773: The Use of Antimüllerian Hormone in Women Not Seeking Fertility Care," 2019).

AMH, bazı klinik durumlarda over rezervi hakkında yararlı bilgiler sağlamakla birlikte, bilinen bir üreme problemi olmayan kadınlarda fertilite potansiyelini tek başına yansıtmamaktadır. Bu nedenle kadınlara fertilite konusunda danışmanlık verilirken AMH düzeylerinin yaş, over rezervi, eşlik eden klinik durumlar ve diğer bireysel özelliklerle birlikte değerlendirilmesi önerilmektedir (Peigné et al., 2023).

Serum AMH düzeyleri, yardımcı üreme teknolojileri (YÜT) uygulamalarında over yanıtının öngörülmesi açısından yararlı bilgiler sağlamaktadır. Bunun yanı sıra, kümülatif canlı doğum olasılığını belirleyen tek faktör olarak değerlendirilmemelidir. Mevcut veriler, başarılı bir YÜT sonucunu dışlayacak belirli bir AMH alt sınırının bulunmadığını göstermektedir. Bu nedenle AMH düzeyleri, tedaviye uygunluğun değerlendirilmesinde tek başına kullanılmamalı; hastanın yaşı, over yanıt potansiyeli ve diğer klinik özellikleri ile birlikte yorumlanmalıdır. Bu durum özellikle genç yaş grubundaki kadınlarda daha belirgindir; düşük AMH düzeylerine

rağmen başarılı gebelik sonuçları elde edilebilmektedir (Umarsingh et al., 2020).

AMH, over rezervinin değerlendirilmesinde yaygın olarak kullanılan ve kalan oosit havuzu hakkında dolaylı bilgi sağlayan biyobelirteçlerden biridir. Öte yandan, AMH düzeylerinin oosit kalitesini doğrudan yansıtmadığı ve gebelik sonuçlarını öngörmedeki değerinin sınırlı olduğu bilinmektedir. Fertilite başarısı ile elde edilen oosit sayısı arasındaki ilişki karmaşık olup çok sayıda faktörden etkilenmektedir. Genel olarak daha fazla oosit elde edilmesi, canlı embriyo gelişimi olasılığını artırabilmekte ve buna bağlı olarak canlı doğum şansına katkı sağlayabilmektedir. Ancak gebelik ve canlı doğum sonuçları yalnızca oosit sayısına bağlı olmayıp yaş, embriyo kalitesi, uterin faktörler ve eşlik eden klinik durumlar gibi birçok değişkenden etkilenmektedir (La Marca et al., 2010).

Yardımcı Üreme Teknolojilerinde (YÜT) AMH

Over rezervi, kadınlarda yaşla birlikte azalma gösteren dinamik bir süreçtir ve esas olarak overlerdeki mevcut oosit havuzunun büyüklüğünü yansıtmaktadır. Bu süreçle paralel olarak serum AMH düzeylerinde de zaman içinde kademeli bir düşüş meydana gelmektedir. Folikül uyarıcı hormon (FSH) ve östradiol (E2) gibi geleneksel belirteçlere kıyasla AMH düzeyleri menstrüel siklus boyunca daha sınırlı değişkenlik göstermektedir. Bu nedenle AMH, over rezervinin değerlendirilmesinde yaygın olarak kullanılan biyobelirteçlerden biri haline gelmiştir (Iliodromiti et al., 2015). Ayrıca serum AMH düzeylerinin, over rezervi değerlendirmesinde sık kullanılan parametrelerden biri olan antral folikül sayısı (AFC) ile yakın ilişki gösterdiği bildirilmiştir (Yates et al., 2011).

Yardımcı üreme teknolojileri uygulamalarında AMH ölçümü, kontrollü over stimülasyonunun planlanmasında önemli bir araç olarak kullanılmaktadır. AMH düzeyleri, hastanın gonadotropin tedavisine verebileceği yanıt hakkında bilgi sağlayarak tedavinin bireyselleştirilmesine katkıda bulunmaktadır. Böylece aşırı over yanıtı ve ovaryan hiperstimülasyon sendromu (OHSS) riskinin azaltılması ile yetersiz yanıt nedeniyle siklus iptali olasılığının öngörülmesinde klinisyene yardımcı olabilmektedir (Karkanaki et al., 2011; Tokura et al., 2013).

Kanser ve AMH

AMH, kanser tanısı alan kadınlarda over rezervinin değerlendirilmesi ve fertilitenin korunmasına yönelik planlamada yararlanılan biyobelirteçlerden biridir. Özellikle kemoterapi ve radyoterapinin gonadotoksik etkileri, reproduktif çağıdaki kadınlarda prematür over yetmezliği (POY) gelişimine ve buna bağlı fertilite kaybına neden olabilmektedir. Kanser tedavilerindeki gelişmeler ile sağkalım sürelerinin uzaması, fertilitenin korunmasına yönelik yaklaşımların önemini artırmıştır.

Tedavi öncesinde ölçülen AMH düzeylerinin, tedavi sonrasında kalan over rezervi ile ilişkili olduğu ve gelecekteki üreme potansiyeli hakkında bilgi sağlayabileceği bildirilmiştir (Dillon et al., 2013; Dunlop & Anderson, 2015). Özellikle meme kanseri hastalarında tedavi öncesi AMH düzeylerinin, kemoterapiye bağlı amenore riskinin değerlendirilmesinde yardımcı olabileceği gösterilmiştir. Bu durum, fertilite koruyucu yöntemlerin planlanması ve hastaların bireysel risklerinin belirlenmesi açısından klinisyene yol gösterebilmektedir. Ancak, gonadotoksik tedavilere karşı bireysel duyarlılığın farklılık gösterebildiği unutulmamalıdır (Cobo et al., 2016; Decanter et al., 2018; Sermondade et al., 2019). Ayrıca AMH ölçümünün, kanser tedavisine bağlı over yetmezliği ve

infertilite açısından daha yüksek risk taşıyan kadınların belirlenmesine katkı sağlayabileceği bildirilmektedir. Bu sayede uygun hastaların fertilite koruma merkezlerine zamanında yönlendirilmesi ve tedavi öncesi danışmanlık süreçlerinin planlanması mümkün olabilmektedir (Fabbri et al., 2014).

Polikistik Over Sendromunda (PKOS) ve AMH

Polikistik over sendromu (PKOS), reproduktif çağıdaki kadınlarda en sık görülen endokrin bozukluklardan biri olup oligo-ovulasyon, hiperandrojenizm ve infertilite ile ilişkilidir ("ACOG Practice Bulletin No. 194: Polycystic Ovary Syndrome," 2018). Klinik ve biyokimyasal bulguların değişkenlik gösterebilmesi nedeniyle tanı sürecinde farklı biyobelirteçlerin kullanımı araştırılmaya devam etmektedir.

Son yıllarda AMH, PKOS değerlendirmesinde üzerinde en fazla çalışılan biyobelirteçlerden biri haline gelmiştir (Lauritsen et al., 2014). Çeşitli çalışmalar, PKOS'lu kadınlarda serum AMH düzeylerinin sağlıklı kadınlara kıyasla daha yüksek olduğunu göstermiştir. Bu durumun, PKOS'ta sıklıkla görülen artmış küçük antral folikül sayısı ile ilişkili olduğu düşünülmektedir. Bu nedenle AMH ölçümünün, PKOS tanısına katkı sağlayabilecek ve hastalığın fenotipik özelliklerini yansıtabilecek ek bir belirteç olabileceği öne sürülmüştür (Bungum et al., 2013).

Her ne kadar mevcut veriler serum AMH düzeylerinin PKOS ile ilişkili olduğunu gösterse de, AMH ölçümü güncel tanı kriterleri içerisinde yer almamaktadır. Bu nedenle AMH'nin PKOS tanısındaki yeri henüz tam olarak netleşmemiş olup, klinik kullanıma ilişkin standartların belirlenebilmesi için daha fazla çalışmaya ihtiyaç bulunmaktadır ("ACOG Committee Opinion No. 773: The Use of Antimüllerian Hormone in Women Not Seeking Fertility Care," 2019).

Over Neoplazilerinde AMH

AMH, özellikle granüloza hücreli tümörlerde tanı ve takip amacıyla kullanılan biyobelirteçlerden biridir. Yetişkin tip granüloza hücreli tümörlerde serum AMH düzeylerinin yüksek bulunduğu ve olguların büyük bölümünde tümör yükü ile ilişkili olduğu bildirilmiştir (Färkkilä et al., 2015). Bu nedenle AMH ölçümü, granüloza hücreli tümörlerin izleminde yararlı bir belirteç olarak kabul edilmektedir.

Son yıllarda yapılan çalışmalar, AMH'nin epitelyal over kanserleri üzerindeki olası biyolojik etkilerine de odaklanmıştır. Deneysel veriler, AMH'nin hücre proliferasyonunu baskılayabileceğini ve apoptotik mekanizmaları uyarabileceğini düşündürmektedir. Önerilen mekanizmalar arasında kök hücre faktörünün inhibisyonu, apoptozun uyarılması ve hücre döngüsünün G1/S fazında durdurulması yer almaktadır (Zhang et al., 2018). Ancak, bu etkilerin klinik öneminin ve alтта yatan moleküler mekanizmaların daha ayrıntılı olarak ortaya konulmasına ihtiyaç bulunmaktadır.

AMH'nin olası terapötik kullanım alanları da araştırılmaktadır. Özellikle tümör büyümesi, invazyon ve tedavi direnci ile ilişkili bazı yolaklar üzerindeki etkileri nedeniyle rekombinant AMH'nin hedefe yönelik tedavi yaklaşımlarında kullanılabileceği öne sürülmektedir. Ancak mevcut verilerin büyük bölümü deneysel çalışmalara dayanmakta olup, klinik uygulamaya geçilebilmesi için daha kapsamlı çalışmalara ihtiyaç vardır.

Güncel bulgular, AMH'nin over neoplazilerindeki rolünün yalnızca tanısal bir belirteç olmanın ötesine geçebileceğini düşündürmektedir. Bununla birlikte, AMH'nin terapötik potansiyelinin netleştirilebilmesi için ileri klinik ve translasyonel araştırmalara gereksinim bulunmaktadır.

Menopoz Prediksiyonunda AMH

AMH düzeyleri ile üreme fonksiyonundaki yaşa bağlı değişiklikler arasındaki ilişki son yıllarda yoğun olarak araştırılan konulardan biri olmuştur. Over rezervindeki azalmayı yansıtan AMH düzeylerinin yaşla birlikte kademeli olarak düşmesi, bu hormonun menopoz zamanlamasının öngörülmesinde kullanılabilecek bir biyobelirteç olup olamayacağı sorusunu gündeme getirmiştir (Shrikhande et al., 2020).

Öte yandan, AMH'nin tek başına menopoz yaşını öngörmedeki değeri halen tartışmalıdır. Özellikle 40 yaşın altındaki kadınlarda yapılan tahminlerde güven aralıklarının oldukça geniş olduğu ve öngörülerin birkaç yıldan on yılı aşkın süreye kadar değişebildiği bildirilmektedir (Laven & Louwers, 2024).

Yapılan bir çalışmada AMH düzeyindeki her 0,10 ng/mL'lik azalmanın prematür over yetmezliği riskinde artış ile ilişkili olduğu bildirilmiştir (Bertone-Johnson et al., 2018). Ayrıca AMH ölçümlerinin yaş ile birlikte değerlendirilmesinin, erken menopoz riskinin tahmin edilmesinde tek başına yaş kullanımına göre daha iyi sonuçlar sağlayabileceği bildirilmiştir (Depmann et al., 2018).

Menopoza yaklaşıldıkça AMH'nin öngörü gücünün arttığı düşünülmektedir. Bunun yanı sıra, menopoz zamanlamasının yalnızca AMH düzeyleri ile açıklanamayacağı ve genetik, çevresel ve bireysel birçok faktörden etkilendiği göz önünde bulundurulmalıdır. Ayrıca doğal menopozun çoğu kadında 45–55 yaş arasında gerçekleştiği bilinmektedir (Nelson et al., 2023).

Mevcut veriler, AMH'nin üreme yaşlanmasının değerlendirilmesinde yararlı bir biyobelirteç olabileceğini düşündürmektedir. Ancak menopoz zamanlamasının öngörülmesinde tek başına kullanımı için mevcut kanıtlar yeterli

değildir. Bu nedenle AMH sonuçları yorumlanırken yaş ve diğer klinik özelliklerle birlikte değerlendirilmelidir.

Pediatric Üreme Endokrinolojisinde AMH

AMH üreme biyolojisi ve pediatrik endokrinoloji pratiğinde önemli klinik kullanım alanlarına sahip bir biyobelirteçtir. Erkek fetüste Müllerian yapıların gerilemesindeki rolü uzun yıllardır bilinmekle birlikte, günümüzde çocukluk ve adölesan döneme ait çeşitli klinik durumların değerlendirilmesinde de yararlanılmaktadır. AMH, testislerde sertoli hücreleri, overlerde ise granüloza hücreleri tarafından sentezlenmektedir.

Erkeklerde sertoli hücreleri tarafından fetal yaşamdan ergenlik başlangıcına kadar yüksek düzeylerde AMH üretimi devam ederken, kız çocuklarında AMH üretimi primer ve küçük antral foliküllerin granüloza hücrelerinden kaynaklanmakta ve daha düşük düzeylerde seyretmektedir.

Pediatric üreme endokrinolojisinde AMH'nin başlıca kullanım alanları şunlardır:

- Testis dokusunun varlığının değerlendirilmesi: Kriptorşidizm ve cinsiyet gelişim bozukluklarında (CGB) AMH düzeyleri, fonksiyonel testis dokusunun varlığı hakkında bilgi sağlayabilmektedir.

- Virilizasyon nedenlerinin ayırıcı tanısı: Yüksek AMH düzeyleri testiküler kaynaklı virilizasyonu düşündürebilirken, normal veya düşük düzeyler diğer etiyolojik nedenlerin değerlendirilmesine katkı sağlayabilmektedir.

- Ovotestiküler CGB olgularının değerlendirilmesi: AMH ölçümü, testiküler dokunun belirlenmesinde yardımcı olabilir ve cerrahi planlamaya katkı sağlayabilir.

- Klinefelter sendromu: AMH düzeyleri testiküler fonksiyon hakkında bilgi verebilmekte ve gonadal disfonksiyonun değerlendirilmesinde yardımcı olabilmektedir.

- Turner sendromu: AMH ölçümü, over rezervinin değerlendirilmesinde ve prematür over yetmezliği riskinin öngörülmesinde kullanılabilmektedir.

Bu kullanım alanları, AMH'nin pediatrik üreme endokrinolojisinde tanısal değerlendirmeyi destekleyen yararlı biyobelirteçlerden biri olduğunu göstermektedir (Josso et al., 2013; Lindhardt Johansen et al., 2013).

Düşük Riski ve AMH

AMH'nin gebelik sonuçları ile ilişkisi son yıllarda araştırılan konulardan biridir. Özellikle düşük AMH düzeylerinin gebelik kaybı riski ile ilişkili olup olmadığına yönelik çalışmaların sayısı giderek artmaktadır.

Doğal yolla gebe kalan ve infertilite öyküsü bulunmayan kadınlarda yapılan bir çalışmada, çok düşük AMH düzeylerinin ($\leq 0,4$ ng/mL) artmış düşük riski ile ilişkili olabileceği bildirilmiştir. Bu bulgu, AMH düzeyleri ile gebelik sonuçları arasında olası bir ilişki bulunduğunu düşündürmektedir (Lyttle Schumacher et al., 2018).

Mevcut çalışmalar, AMH ile düşük riski arasındaki ilişkiyi henüz net olarak ortaya koyamamıştır. Bazı çalışmalar düşük AMH düzeyleri ile artmış gebelik kaybı riski arasında ilişki bildirirken, diğer çalışmalarda benzer sonuçlar elde edilememiştir. Ayrıca mevcut verilerin önemli bir kısmı ileri yaş veya infertilite öyküsü bulunan kadınlardan elde edildiğinden, sonuçların genel popülasyona genellenmesi güçtür. Yüksek AMH düzeylerinin düşük

riski üzerindeki etkisi de henüz yeterince açıklığa kavuşmamıştır (Zhou et al., 2022).

Güncel kılavuzlar doğrultusunda, gebelik kaybı riskinin öngörülmesi amacıyla rutin AMH ölçümü önerilmemektedir. AMH'nin farklı hasta gruplarında düşük riski ile ilişkisini ve olası klinik kullanımını ortaya koyabilmek için daha geniş kapsamlı çalışmalara ihtiyaç bulunmaktadır (Tokura et al., 2013).

Sonuç

AMH, günümüzde over rezervinin değerlendirilmesinde en yaygın kullanılan biyobelirteçlerden biridir. Menstrüel siklus boyunca sınırlı değişkenlik göstermesi ve antral folikül sayısı ile yakın ilişki göstermesi nedeniyle, özellikle yardımcı üreme teknolojileri uygulamalarında klinik karar verme sürecine katkı sağlamaktadır. Bunun yanı sıra PKOS, fertilitenin korunması, over neoplazileri ve menopoz zamanlamasının değerlendirilmesi gibi farklı klinik alanlarda da kullanım potansiyeline sahiptir.

Ancak, AMH düzeylerinin öncelikle oosit havuzu hakkında bilgi sağladığı, oosit kalitesini ve gebelik sonuçlarını tek başına yansıtmadığı göz önünde bulundurulmalıdır. Bu nedenle AMH sonuçları yorumlanırken hastanın yaşı, klinik özellikleri ve diğer üreme parametreleri ile birlikte değerlendirilmelidir.

Mevcut veriler, AMH'nin üreme endokrinolojisindeki yerini giderek güçlendirmektedir. Ancak farklı klinik kullanım alanlarındaki rolünün daha net ortaya konulabilmesi ve yeni uygulama alanlarının belirlenebilmesi için ileri çalışmalara ihtiyaç bulunmaktadır.

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BÖLÜM 5

LEİOMYOMU BULUNAN POSTMENOPÖZAL KADINLARDA HORMON REPLASMAN TEDAVİSİ: KLİNİK YAKLAŞIM VE PROSPEKTİF OLGU SERİSİ

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GİRİŞ

Uterin leiomyomlar, kadın genital sisteminin en sık görülen benign düz kas tümörleri olup reproduktif çağıdaki kadınların yaklaşık %20–40'ında saptanmaktadır (1,2). Leiomyom gelişiminde genetik yatkınlık, büyüme faktörleri, ekstrasellüler matriks değişiklikleri ve özellikle steroid hormonlar önemli rol oynamaktadır (3,4). Östrojen ve progesteron reseptör yoğunluğu leiomyom dokusunda normal myometriuma göre daha yüksek olduğundan tümör büyümesi hormonal çevreden doğrudan etkilenmektedir (5).

Menopoz sonrasında over fonksiyonlarının azalması ile birlikte çoğu leiomyom küçülme eğilimindedir. Bununla birlikte bazı olgularda leiomyomlar stabil kalabilmekte, nadiren büyüyebilmekte ya da semptomatik hâle gelebilmektedir (6,7). Günümüzde yaşam süresinin uzaması nedeniyle kadınların menopoz sonrası dönemde geçirdikleri süre artmış, buna paralel olarak hormon replasman tedavisi gereksinimi de yükselmiştir.

Vazomotor semptomlar, osteoporoz riski, uyku bozuklukları, ürogenital atrofi ve yaşam kalitesinde azalma nedeniyle hormon replasman tedavisi etkili bir seçenek olmaya devam etmektedir (8,9). Ancak uterin leiomyomu bulunan postmenopozal kadınlarda

hormon replasman tedavisinin leiomyom boyutu, uterin volüm ve uterin kan akımı üzerine etkileri klinik açıdan önem taşımaktadır.

Bu bölümde postmenopozal leiomyomlu hastalarda hormon replasman tedavisinin etkileri, literatür verileri ve yazarın uzmanlık tezinden elde edilen prospektif randomize kontrollü çalışma sonuçları olgu serisi biçiminde sunulmuştur (10).

LEİOMYOM VE MENOPOZ SONRASI DÖNEM

Leiomyomlar çoğunlukla fertil çağ hastalığı olarak kabul edilse de menopoz sonrası dönemde tamamen kaybolmazlar. Özellikle obezite, periferik aromatzasyon artışı, metabolik sendrom ve eksojen östrojen kullanımı leiomyom devamlılığı ile ilişkilidir (11).

Menopoz sonrası dönemde yeni büyüyen uterin kitlelerde ayırıcı tanıda aşağıdaki durumlar mutlaka düşünölmelidir:

Leiomyosarkom

Endometrial patolojiler

Adneksiyal kitleler

Adenomyozis

Dejeneratif leiomyom

Bu nedenle hormon replasman tedavisi (HRT) başlanmadan önce ayrıntılı jinekolojik değerlendirme zorunludur.

HORMON REPLASMAN TEDAVİSİ VE LEİOMYOMLAR

Leiomyomlu hastalarda hormon replasman tedavisi ile ilgili temel klinik sorular şunlardır:

Leiomyom büyür mü?

Kanama yapar mı?

Cerrahi gereksinimi artırır mı?

Kullanılan preparata göre fark var mı?

Literatürde özellikle oral yüksek doz kombine rejimlerde hafif hacim artışı bildirilmiş, düşük doz ve transdermal rejimlerde ise etkinin daha sınırlı olduğu gösterilmiştir (12–15).

GEREÇ VE YÖNTEM

Bu bölümde sunulan veriler, Mart 2003–Eylül 2004 tarihleri arasında yürütülen prospektif randomize kontrollü çalışmadan uyarlanmıştır (10).

Dahil Edilme Kriterleri

40–60 yaş arası postmenopozal kadın

Son adet tarihinden en az 1 yıl geçmiş olması

FSH >40 IU/L

LH >25 IU/L

Estradiol <30 pg/mL

Transvajinal ultrasonografi ile en az 15 mm leiomyom saptanması

BMI <30 kg/m²

Son 6 ay hormonal ilaç kullanmamış olması

Çalışma Grupları

Toplam 33 hasta çalışmaya alınmış, sekiz hasta takipten ayrılmıştır. Analize 25 hasta dâhil edilmiştir.

Grup A (n=14):

1 mg estradiol hemihidrat + 0.5 mg norethisterone asetat

Grup B (n=11):

2 mg estradiol hemihidrat + 1 mg norethisterone asetat

Değerlendirilen Parametreler

Leiomyom hacmi

Uterus hacmi

Endometrial kalınlık

Sağ ve sol uterin arter PI

Sağ ve sol uterin arter RI

Ölçümler tedavi öncesinde, 6. ayda ve 12. ayda yapılmıştır.

Tablo 1. Yaş, doğum sayısı, BMI, menopoz süresine göre vakaların tanımlayıcı özellikleri

Özellikler	Tüm vakalar	Düşük doz HRT	Standart Doz HRT	p
Vaka sayısı	25	14	11	-
Yaş	51,9	51,6	52,2	0,64
Doğum sayısı	2,4	2,5	2,3	0,84
BMI (Kg/m ²)	26	24,5	27,6	0,73
Menopoz süresi (yıl)	3,9	2,7	5,5	0,04

Kaynak: Altındağ T. Leiomyomu bulunan postmenopozal kadınlarda hormon replasman tedavisinin leiomyom üzerine etkileri. Uzmanlık tezi. Dokuz Eylül Üniversitesi; 2004.

OLGU SERİSİ SONUÇLARI

Düşük Doz Hormon Replasman Tedavisi Alan Hastalar
(n=14)

Bir yıllık takip sonunda uterus hacmi başlangıçta 71.6 cm³ iken 6. ayda 80.9 cm³, 12. ayda 72.4 cm³ olarak ölçülmüş ve fark istatistiksel olarak anlamlı bulunmamıştır (p=0.40).

Leiomyom hacmi başlangıçta 9.3 cm³, 6. ayda 9.0 cm³ ve 12. ayda 11.1 cm³ olarak saptanmış, anlamlı artış izlenmemiştir (p=0.60).

Endometrial kalınlık başlangıçta 4.4 mm iken 6. ayda 5.4 mm, 12. ayda 4.9 mm olarak değerlendirilmiş ve anlamlı değişiklik gözlenmemiştir (p=0.60).

Sağ ve sol uterin arter PI ve RI değerlerinde anlamlı değişiklik izlenmemiştir.

Bu bulgular, düşük doz hormon replasman tedavisinin leiomyom boyutu, uterin hacim ve endometrium üzerine belirgin olumsuz etkisinin olmadığını düşündürmektedir.

Standart Doz Hormon Replasman Tedavisi Alan Hastalar (n=11)

Uterus hacmi başlangıçta 63.1 cm³, 6. ayda 62.1 cm³ ve 12. ayda 67.4 cm³ olarak ölçülmüş olup anlamlı fark saptanmamıştır (p=0.76).

Leiomyom hacmi sırasıyla 5.5 cm³, 5.8 cm³ ve 6.9 cm³ olarak bulunmuş, artış istatistiksel anlam taşımamıştır (p=0.52).

Endometrial kalınlık başlangıçta 4.1 mm, 6. ayda 4.1 mm ve 12. ayda 3.6 mm olarak değerlendirilmiştir (p=0.69).

Sol uterin arter PI değerinde istatistiksel olarak anlamlı azalma izlenmiştir (2.6 → 1.9 → 2.1; p=0.01). Diğer vasküler parametrelerde anlamlı değişiklik bulunmamıştır.

Bu sonuçlar standart doz tedavi grubunda leiomyom hacminde hafif artış olabileceğini, ancak bunun klinik açıdan sınırlı düzeyde kaldığını göstermektedir.

Tablo 2. Düşük doz ve standart doz HRT uygulanan hastalarda tedavi öncesi, 6. ay ve 12. ayda uterus hacmi, leiomyom hacmi ve endometrial kalınlık değerleri

HRT	Düşük doz	6. ay	p	12. ay	p	Standart doz	6. ay	p	12. ay	p
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	Tedavi öncesi					Tedavi öncesi				
Uterus hacmi (cm ³)	71,6	80,9	0,4	72,4	0,4	63,1	62,1	0,76	67,4	0,76
Leiomyom hacmi (cm ³)	9,3	9,0	0,6	11,1	0,6	5,5	5,8	0,52	6,9	0,52
Endometrial kalınlık (mm)	4,4	5,4	0,6	4,9	0,6	4,1	4,1	0,69	3,6	0,69

Kaynak: Altındağ T. Leiomyomu bulunan postmenopozal kadınlarda hormon replasman tedavisinin leiomyom üzerine etkileri. Uzmanlık tezi. Dokuz Eylül Üniversitesi; 2004.

Tablo 3. Uterin arter Doppler parametreleri

Ölçümler		Düşük doz HRT (n=14)				Standart doz HRT (n=11)					
		Tedavi öncesi	6. ay	p	12. ay	p	Tedavi öncesi	6. ay	p	12. ay	p
Sağ uterin arter	PI	2,5	2,4	0,5	2,3	0,5	2,5	2,0	0,09	2,0	0,09
	RI	0,8	0,7	0,1	0,7	0,1	0,7	0,7	0,36	0,8	0,36
Sol uterin arter	PI	2,1	2,1	0,5	2,0	0,5	2,6	1,9	0,01	2,1	0,01
	RI	0,7	0,7	0,1	0,7	0,1	0,8	0,7	0,26	0,7	0,26

Kaynak: Altındağ T. Leiomyomu bulunan postmenopozal kadınlarda hormon replasman tedavisinin leiomyom üzerine etkileri. Uzmanlık tezi. Dokuz Eylül Üniversitesi; 2004.

LİTERATÜRLE KARŞILAŞTIRMA

Postmenopozal dönemde HRT'nin leiomyomlar ve uterin arter Doppler bulguları üzerindeki etkisini inceleyen çalışmaların sonuçları tam olarak birbiriyle uyumlu değildir. Bunun başlıca nedeni; çalışmalarda kullanılan östrojen ve progesteron preparatlarının farklı olması, hormonların oral ya da transdermal yolla verilmesi, tedavi sürelerinin değişmesi, olgu sayılarının sınırlı olması ve değerlendirilen sonlanım ölçütlerinin aynı olmamasıdır. Bu nedenle literatür genel olarak incelendiğinde, HRT'nin leiomyom ve uterin arter akımları üzerindeki etkisinin tek tip değil, kullanılan rejime ve hasta özelliklerine göre değişebilen bir özellik gösterdiği anlaşılmaktadır.

Uterin arter Doppler bulguları açısından değerlendirildiğinde, Tanawattanacharoen ve arkadaşlarının çalışmasında postmenopozal hastalara 0.625 mg konjuge östrojen ve 2.5 mg MPA içeren HRT verilmiş, tedavi sonrasında sağ ve sol uterin arter RI değerlerinde anlamlı değişiklik saptanmamıştır (16). Benzer şekilde Exacoustos ve arkadaşlarının 50 mikrogram transdermal östradiol ve 10 mg didrogesteron kullandıkları çalışmada da uterin arter PI ve RI değerlerinde istatistiksel olarak anlamlı fark gösterilememiştir (18). Jarvela ve arkadaşlarının levonorgestrel intrauterin sistem ile kombine transdermal östradiol kullandıkları çalışmada da PI açısından anlamlı değişiklik bildirilmemiştir (19). Bu çalışmalar birlikte değerlendirildiğinde, özellikle bazı HRT rejimlerinde uterin arter Doppler parametrelerinin stabil kalabildiği görülmektedir.

Buna karşılık Battaglia ve arkadaşları, 50 mikrogram transdermal östradiol ve 2.5 mg MPA verilen olgularda uterin arter PI değerinde anlamlı azalma göstermiştir (17). Doren ve arkadaşları da daha uzun süreli HRT uygulanan postmenopozal kadınlarda hem

PI hem de RI deęerlerinde anlamlı azalma bildirmiřtir (20). Bu sonular, bazı hasta gruplarında HRT'nin uterin arter vasküler direncini azaltabileceęini dūřündürmektedir. zellikle strojenin vazodilatr etkisi gz nne alındıęında, uterin arter akımlarında iyileřme biyolojik olarak beklenen bir sonutur. Ancak btn alıřmaların aynı sonuca ulařmamıř olması, bu etkinin yalnızca strojen varlıęı ile deęil; doz, uygulama yolu, tedavi sresi ve eřlik eden progestin tipi ile de iliřkili olduęunu gstermektedir.

Leiomyom hacmi ve uterus hacmi aısından yapılan alıřmalarda da benzer bir heterojenlik dikkat ekmektedir. Frigo ve arkadaşlarının alıřmasında bir yıllık HRT sonrasında leiomyom hacmi, uterus byklę ve endometrial kalınlıkta anlamlı artıř saptanmıřtır (12). řener ve arkadaşlarının alıřmasında ise iki farklı HRT rejimi karřılařtırılmıř; transdermal stradiol ve oral MPA kullanan grupta leiomyom boyutunda artıř izlenirken, konjuge strojen ve MPA kullanan grupta benzer artıř saptanmamıřtır (13). Bu sonu, yalnızca hormon verilmesinin deęil, verilen hormonun tipi ve uygulama yolunun da belirleyici olduęunu gstermesi bakımından nemlidir.

Gregoriou ve arkadaşlarının tibolon kullandıkları alıřmada, bir yıllık takip sonunda leiomyom hacminde anlamlı artıř saptanmamıřtır (21). Benzer řekilde řimřek ve arkadaşlarının tibolon ve transdermal HRT sistemini karřılařtırdıkları alıřmada da her iki grupta leiomyom hacminde anlamlı fark bulunmamıřtır (24). Bu sonular, zellikle tibolonun leiomyom bymesi aısından daha ntr bir profile sahip olabileceęini dūřündürmektedir.

Buna karşılık Fedele ve arkadaşlarının çalışmasında, transdermal östradiol ve oral MPA kullanan grupta leiomyom hacmi, uterus hacmi ve leiomyom sayısında artış gösterilmiş, tibolon grubunda ise bu artış izlenmemiştir (14). Polatti ve arkadaşlarının iki yıl süreli çalışmasında da oral estradiol valerat ve siproteron asetat kullanan grupta leiomyom hacminde artış saptanmazken, transdermal östradiol ve oral MPA verilen grupta büyüme gözlenmiştir (15). Bu iki çalışma özellikle transdermal östrojen ve belirli progestin kombinasyonlarının leiomyom büyümesi üzerinde daha belirgin etkili olabileceğini düşündürmektedir.

Colacurci ve arkadaşlarının çalışmasında ise 50 mikrogram transdermal 17 beta östradiol ve nomegestrol asetat verilen postmenopozal kadınlarda leiomyom hacminde artış izlenmemiştir (22). Bu bulgu, transdermal yolun tek başına belirleyici olmadığını, progestin türünün ve toplam hormonal etkinin de sonucu etkileyebileceğini göstermektedir. Aynı şekilde Palomba ve arkadaşlarının çalışmasında 2.5 mg MPA ile 5 mg MPA karşılaştırılmış, daha yüksek progesteron dozu verilen grupta leiomyom hacminde artış saptanmıştır (23). Bu sonuç, progesteronun leiomyom biyolojisindeki rolünü destekleyen önemli bulgulardan biridir. Gerçekten de leiomyomların yalnızca östrojen bağımlı yapılar olmadığı, progesteronun da proliferasyon, mitoz ve ekstraselüler matriks birikimi üzerinde belirgin etkileri bulunduğu artık daha iyi bilinmektedir (5,11).

Bu çalışmalar topluca değerlendirildiğinde, literatürde üç temel eğilim görülmektedir. Birinci grup çalışmalarda HRT'nin leiomyom hacmi veya uterin arter akımları üzerinde anlamlı etkisi olmadığı bildirilmektedir (16,18,19,21,22,24). İkinci grup çalışmalarda özellikle bazı rejimlerde uterin arter direnç

indekslerinde azalma saptanmakta, yani vasküler düzeyde etkilenme gösterilmektedir (17,20). Üçüncü grup çalışmalarda ise belirli östrojen-progestin kombinasyonlarıyla leiomyom hacminde artış gözlenmektedir (12–15,23). Bu nedenle literatür, HRT'nin leiomyomlu postmenopozal hastalarda tamamen güvenli ya da tamamen sakıncalı olduğu yönünde tek bir sonuca işaret etmemektedir; daha çok, tedavi rejimine bağlı değişken bir etki profilini ortaya koymaktadır.

Literatürdeki çelişkili sonuçların birkaç olası açıklaması vardır. Öncelikle hasta sayılarının çoğu çalışmada sınırlı olması küçük hacim değişikliklerinin istatistiksel olarak gösterilmesini güçleştirmektedir. İkinci olarak, leiomyomların başlangıçtaki sayısı, lokalizasyonu ve hacmi çoğu çalışmada homojen değildir. Üçüncü olarak, tedavi süresi kısa olan çalışmalarda uzun dönem büyüme etkileri yeterince ortaya çıkmamış olabilir. Dördüncü olarak, oral ve transdermal preparatlar serum hormon düzeyleri, karaciğer ilk geçiş etkisi ve doku düzeyindeki biyoyararlanım açısından aynı değildir. Son olarak, kullanılan progestinlerin birbirinden farklı farmakolojik özellikleri bulunmaktadır; bu durum özellikle leiomyom büyümesi açısından önemli olabilir.

Sonuç olarak mevcut literatür, postmenopozal dönemde HRT'nin leiomyomlar ve uterin arter Doppler bulguları üzerindeki etkisinin tek boyutlu olmadığını göstermektedir. Bazı çalışmalarda leiomyom hacminde artış ve uterin arter akımlarında değişiklik bildirilirken, bazı çalışmalarda anlamlı fark saptanmamıştır. En dikkat çekici nokta, sonucun yalnızca HRT kullanımı ile değil; östrojenin dozu, verilış yolu, progesteronun tipi ve dozu, tedavi süresi ve hasta seçimi ile yakından ilişkili olmasıdır. Bu nedenle literatür ışığında en doğru yaklaşım, leiomyomu bulunan

postmenopozal hastalarda HRT kararının bireyselleştirilmesi ve düzenli ultrasonografik izlem ile desteklenmesidir.

Tablo 4. Postmenopozal kadınlarda HRT'nin uterin arter doppler akımları üzerine etkisi

Çalışmalar	Östrojen	Progesteron	n	PI	RI
Tanawattanacharoen ve arkadaşları	0.625 mg konjuge östrojen	2,5 mg MPA	38	-	istatistiksel anlamlı değişiklik yok
Battaglia ve arkadaşları	50 mikrogram transdermal östradiol	2,5 mg MPA	57	istatistiksel anlamlı değişiklik yok	-
Exacoustos ve arkadaşları	50 mikrogram transdermal östradiol	10 mg didrogesteron	40	istatistiksel anlamlı değişiklik yok	istatistiksel anlamlı değişiklik yok
Jarvela ve arkadaşları	50 mikrogram transdermal östradiol	20 mikrogram levonorgestrel intrauterin sistem	13	istatistiksel anlamlı değişiklik yok	-
Doren ve arkadaşları	2 mg östradiol + 1 mg östriol	1 mg norethisteron asetat (NETA)	33	istatistiksel anlamlı azalma (p<0.05)	istatistiksel anlamlı azalma (p<0.05)

Kaynak: Altındağ T. Leiomyomu bulunan postmenopozal kadınlarda hormon replasman tedavisinin leiomyom üzerine etkileri. Uzmanlık tezi. Dokuz Eylül Üniversitesi; 2004.

Tablo 5. Postmenopozal leiomyomu olan kadınlarda HRT'nin leiomyom üzerine etkisi

Çalışmalar	n (total)	Tedavi süresi	Tedavi	Leimiyom boyutunda artış	Uterus boyutunda artış
Colacurci ve arkadaşları	60	12 ay	50 mikrogram transdermal 17 beta östradiol + 5 mg nomegestrol asetat	yok	yok
Frigo ve arkadaşları	50	12 ay	4 mg östradiol valerat + 20 mg progesteron enantat	yok	yok
Şener ve arkadaşları	40	12 ay	50 mikrogram transdermal östradiol + 5 mg oral MPA (n=22)	var	yok
Şener ve arkadaşları			0.625 mg konjuge östrojen + 2.5 mg MPA (n=18)	yok	yok
Gregoriou ve arkadaşları	40	12 ay	2.5 mg tibolon (n=20)	yok	yok
Gregoriou ve arkadaşları			HRT verilmeyen (n=20)	yok	yok
Fedele ve arkadaşları	38	12 ay	50 mikrogram transdermal	var	var

			östradiol + 10 mg oral MPA		
Fedele ve arkadaşları			2.5 mg tibolon	yok	yok
Polatti ve arkadaşları	160	24 ay	2 mg östradiol valerat + 1 mg siproteron asetat	yok	yok
Polatti ve arkadaşları			50 mikrogram transdermal östradiol + 10 mg oral MPA	var	yok
Palomba ve arkadaşları	27	12 ay	2 mg mikronize östradiol + 2.5 mg MPA	yok	yok
Palomba ve arkadaşları			2 mg mikronize östradiol + 5 mg MPA	var	yok
Şimşek ve arkadaşları	46	6 ay	2.5 mg tibolon	yok	yok
Şimşek ve arkadaşları			transdermal HRT:0.05 mg östradiol + 0.25 mg noretisteron asetat	yok	yok

Kaynak: Altındağ T. Leiomyomu bulunan postmenopozal kadınlarda hormon replasman tedavisinin leiomyom üzerine etkileri. Uzmanlık tezi. Dokuz Eylül Üniversitesi; 2004.

TARTIŞMA

Bu prospektif çalışma aşağıdaki sonuçları ortaya koymaktadır:

Postmenopozal leiomyomlu hastalarda hormon replasman tedavisi mutlak kontrendikasyon değildir.

Düşük doz rejimlerde leiomyom büyümesi minimaldir.

Standart doz rejimlerde hafif artış olabilir; ancak çoğu klinik olarak önemsizdir.

Uterin arter akımı hormonal etkilerden etkilenebilir.

Düzenli ultrasonografik takip çoğu hasta için yeterlidir.

Özellikle semptomatik menopoz hastalarında tedavisiz bırakmanın yaşam kalitesi üzerine olumsuz etkisi, leiomyom büyüme riskinden daha belirgin olabilir.

PRATİK KLİNİK YAKLAŞIM

Hormon replasman tedavisi aşağıdaki hastalarda düşünülebilir:

Küçük (<5 cm) stabil leiomyom

Semptomsuz hasta

Normal endometrium

Malignite şüphesi bulunmaması

Yakın takip gerektiren durumlar ise şunlardır:

Çoklu leiomyom

Hızlı büyüme öyküsü

Postmenopozal kanama

Pelvik ağrı

Kontrol Şeması

Başlangıç transvajinal ultrasonografi

6 ay kontrolü

12 ay kontrolü

Sonrasında yıllık takip

SONUÇ

Postmenopozal uterin leiomyomlu hastalarda hormon replasman tedavisi, uygun hasta seçimi ile güvenle uygulanabilir. Bu prospektif randomize çalışma verilerine göre hem düşük doz hem standart doz rejimlerde leiomyom hacminde anlamlı büyüme

saptanmamıştır. Özellikle düşük doz rejimler daha avantajlı görünmektedir.

Leiomyom varlığı tek başına hormon replasman tedavisine engel değildir; esas olan bireyselleştirilmiş klinik yaklaşımdır.

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BÖLÜM 6

ANNE-BEBEK SAĞLIĞI PARAMETRELERİNDE DİJİTAL DÖNÜŞÜM: DEMOGRAFİK VERİLERİN MAKİNE ÖĞRENMESİ İLE ANALİZ YAKLAŞIMLARI

1. Büşra CESUR¹

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Giriş

İçinde bulunduğumuz yüzyılda dünya genelinde, toplumsal yapıların temelini sarsan ve literatürde "demografik durgunluk" olarak nitelendirilen kritik bir eşikten geçilmektedir. Dünya Bankası (2026) ile Birleşmiş Milletler (2024) tarafından sunulan küresel raporlar doğum eğilimlerinde aşağı yönlü bir ivme olduğu, Türkiye ise çok daha keskin ve hızlı bir kırılmayla kendini göstererek, nüfusun ikame seviyesinin altına gerilediğini göstermektedir. Temelinde kadınların eğitim sürelerinin uzaması, ilk evlilik yaşının geciktirilmesi ve makro-ekonomik endişeler gibi çok boyutlu sosyo-ekonomik gerekçelerin yattığı bu tablo (TÜİK, 2025), klinik ebelik uygulamaları ve toplum sağlığı disiplini için sadece niceliksel bir azalmayı ifade etmemektedir. Bu noktada anne ve bebek sağlığının geleceğini şekillendiren temel parametrelerin klinik ve demografik boyutu hayati bir önem

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taşımaktadır. Toplam doğurganlık hızı, kaba doğum hızı, perinatal ve maternal mortalite (anne ve bebek ölüm) oranları, gebelik izlem sıklığı, anne yaşı, gestasyonel yaş ve canlı doğum istatistikleri gibi göstergeler, sadece birer istatistiki veri değil; bir toplumun refah seviyesini, sağlık altyapısının gücünü ve koruyucu sağlık hizmetlerinin etkinliğini doğrudan gösteren en temel parametrelerdir. Özellikle doğurganlık hızının düşmesiyle birlikte anne yaşının ilerlemesi ve kronik hastalık öyküsü gibi biyolojik değişkenler, gebelik süreçlerindeki riskleri artırmaktadır. İşte bu geleneksel anne-bebek sağlığı parametrelerinin her biri, modern dijital sistemlerde birer stratejik yol haritası görevi görmektedir. Bu hayati parametrelerin doğru analizi; sahada çalışan ebelerin riskli gebeleri henüz klinik komplikasyonlar gelişmeden ayırt edebilmesine, ziyaret sıklıklarını optimize etmesine ve anne-bebek ölümleri gibi "önlenebilir" ölümleri henüz ortaya çıkmadan engelleyebilmesine olanak tanımaktadır. Dolayısıyla bu parametrelerin derinlemesine kavranması ve takibi, halk sağlığı ebelerinin tahminleyici bir yapıya bürünmesindeki en büyük klinik güçlerden biridir.

Yaşanan bu dönüşüm, anne-bebek sağlığı hizmetlerinde geleneksel yaklaşımların ötesine geçilmesini zorunlu kılmaktadır. Dijital sağlık devrimiyle birlikte ebelerinin hizmetleri, geçmiş verileri raporlayan tanımlayıcı (descriptive) bir yapıdan, "gelecekte ne olabileceğini" öngören tahminleyici (predictive) bir paradigmaya evrilmiştir. Bu teknolojik geçişin en önemli basamağı ise veriden doğrudan öğrenerek doğruluğunu zamanla artıran modeller sunan Makine Öğrenmesi (ML) algoritmalarıdır.

Bu kitap bölümü, anne-bebek sağlığı parametrelerindeki dijital dönüşümü küresel ve ulusal veriler doğrultusunda inceleyerek, makine öğrenmesi yaklaşımlarının sahada nasıl stratejik bir karar destek mekanizmasına dönüştürülebileceğini ele almaktadır. Bu doğrultuda çalışma boyunca Demografik Dönüşüm ve Dijital Sağlık, Ebelerinde Büyük Veri Kaynakları, Halk Sağlığı ve Ebelerinin Hizmetlerinde Uygulama Alanları, Etik, Veri Gizliliği ve Algoritmik Yanlılık, Hibrit Model (Makine ve İnsan), Geleceğe Yönelik Sonuç ve Öneriler'e yer verilmiştir.

Demografik Dönüşüm ve Dijital Sağlık

21.yüzyılda küresel ölçeekte "demografik durgunluk" olarak adlandırılan bir dönem yaşanmaktadır. Dünya Bankası ve Birleşmiş Milletler verilerine göre, küresel Toplam Doğurganlık Hızı, 2000 yılında 2.7 iken 2023 yılı itibarıyla 2.2 seviyelerine gerilemiş; ülkelerin üçte ikisinden fazlası nüfus ikame düzeyi olan 2.1'in altında kalmıştır (World Bank, 2026; UN, 2024). Doğum oranlarındaki bu azalma, Türkiye genelinde daha radikal bir seyir izleyerek ikame düzeyinin altına inmiştir. TÜİK (2025) verilerine göre, 2001 yılında 2.38 olan Toplam Doğurganlık hızı değeri, 2024 yılı itibarıyla 1.48'e kadar gerileyerek Türkiye tarihinin en düşük seviyesine ulaşmıştır. Bu düşüş; ekonomik kaygılar, kadınların eğitim düzeyinin artması ve evlenme yaşının ertelenmesi gibi çok katmanlı sosyo-ekonomik faktörlerle açıklanmaktadır. Ebelik mesleği açısından bu durum sadece doğum sayısının azalması değil, aynı zamanda ileri yaş gebelikleri ve beraberinde gelen yüksek riskli doğumların yönetilmesi zorunluluğunu getirmektedir.

Dijital sağlık devrimiyle birlikte ebelik hizmetleri, tanımlayıcı (descriptive) yaklaşımdan, "gelecekte ne olabileceği"ni öngören tahminleyici (predictive) bir paradigmaya evrilmektedir. Makine Öğrenmesi (ML), bu geçişin en önemli basamağıdır. Makine öğrenmesi algoritmaları, veriden doğrudan öğrenerek doğruluğunu zamanla artıran modeller sunmaktadır. Son yapılan sistematik derlemeler; ML tabanlı sistemlerin obstetrik risk değerlendirmesi, fetal izlem tahmininde doğruluk oranlarına ulaştığını göstermektedir (Takeuchi, 2025: 3). Bu teknoloji, ebeyi sadece bir "bakım verici" değil, aynı zamanda veriye dayalı stratejiler geliştiren bir "karar verici" konumuna taşımaktadır (Dailah, 2024:2 ; Hu, 2025: 5).

Ebelikte Büyük Veri Kaynakları

Ebelik disiplini, gebelik öncesinden başlayarak doğum sonu döneme kadar uzanan süreçte, yapılandırılmış ve yapılandırılmamış büyük veriler üretmektedir. Makine öğrenmesi (ML) modellerinin başarısı, bu verilerin kalitesine ve nasıl işlendiğine doğrudan bağlı olmaktadır (Çitil & Çitil 2022:1 ; Dlugatch, 2024:5).

Ebelik temelli bir ML modeli oluşturulurken kullanılabilecek temel dijital sistemler şunlardır:

- Sağlık Bilgi Sistemleri (SBS) ve Elektronik Sağlık Kayıtları (EHR): Hastanelerde tutulan protokol numaraları, laboratuvar sonuçları, ultrason verileri ve ebe izlem notları, modelin hafızasını oluşturur. Özellikle e-Nabız gibi entegre sistemler veri takibi için birer kaynaktır (Badem & Ünal, 2025:1).
- MERNİS ve Nüfus Kayıt Sistemleri: Doğum oranlarının makro düzeyde analizi için MERNİS verileri; doğum yerleri, nüfus hareketliliği ve demografik yoğunluk gibi stratejik bilgileri sağlar. Bu veriler, halk sağlığı ebelik hizmetlerinin lokasyon bazlı planlanmasında kritik öneme sahiptir.
- Ebelik İzlem Kayıtları ve Saha Verileri: Birinci basamak sağlık hizmetlerinde ebelerin tuttuğu gebe izlem formları (aşılar, kilo takibi, tansiyon ölçümleri), klinik durumun gidişatını öngörmek için veriler sunar.

Ham verinin bir ML modeline "girdi" (feature) olarak tanıtılması süreci, modelin performansını belirleyen en teknik aşamadır. Ebelik alanında bu parametreler şu kategorilerde sınıflandırılabilir:

- Biyolojik ve Klinik Değişkenler: Anne yaşı, vücut kitle indeksi (VKİ), gestasyonel yaş, önceki doğum şekli (sezaryen/vajinal) ve kronik hastalık öyküsü. Yaş değişkeni, özellikle 35 yaş üstü gebeliklerin artışıyla birlikte ML modellerinde "yüksek risk" sınıflandırıcısı olarak merkezi bir rol oynar.
- Sosyo-Ekonomik ve Eğitimsel Girdiler: Annenin eğitim durumu, hanedeki gelir düzeyi ve çalışma statüsü, sağlık okuryazarlığı ve prenatal bakıma erişim ile doğrudan ilişkilidir. ML modelleri, bu parametreleri kullanarak "bakıma erişim bariyerlerini" tahmin edebilmektedir.

- Coğrafi ve Çevresel Parametreler: İkamet edilen bölgenin iklim koşulları hava kalitesi ve en yakın sağlık kuruluşuna olan mesafe, lojistik risklerin hesaplanmasında kullanılır (Arnaout, 2018: 7, Borycka, 2025:3).

Halk Sağlığı ve Ebelik Hizmetlerinde Uygulama: Veriden Eyleme

Makine öğrenmesi modellerinden elde edilen öngörüler, sadece teorik birer çıktı değil, halk sağlığı ebelik hizmetlerini yeniden yapılandıran stratejik birer araçtır. Geleneksel sağlık yönetimi, genellikle "geçmiş veriye" dayalı statik bir planlama yapar. Makine öğrenmesi ise "gelecek öngörüsüne" dayalı dinamik bir kaynak yönetimi (Resource Optimization) sunar.

Erken Uyarı Sistemleri (EWS) ve Koruyucu Ebelik

Makine öğrenmesinin ebelik mesleğine kattığı en büyük değer, "proaktif" koruyucu rollerin güçlendirilmesidir:

- Anomali Saptama: Doğum oranlarındaki ani düşüşler veya belirli bir bölgede kümelenen (clustering) olumsuz sağlık çıktıları (örn: ölü doğum artışı), ML tabanlı erken uyarı sistemleri tarafından anında fark edilir. Bu durum, halk sağlığı ebelerinin bölgeye hızlıca müdahale etmesini, çevresel veya sosyal risk faktörlerini (örn: su kirliliği, beslenme yetersizliği) yerinde incelemesini sağlar.
- Kişiselleştirilmiş Risk İzlemi: Algoritmalar, gebe izlem verilerini analiz ederek "komplikasyon gelişme olasılığı yüksek" olan gebeleri otomatik olarak işaretler (flagging). Ebe, bu uyarı sayesinde söz konusu gebeye yönelik ziyaret sıklığını artırabilir, eğitimlerini özelleştirebilir ve "önlenebilir" komplikasyonları henüz oluşmadan engelleyebilir (McGaughey, 2021:6).

Toplum Temelli Karar Destek Mekanizmaları

Ebelik hizmetlerinde ML uygulamaları, veriyi sınıflandırarak sahadaki ebelik uygulamalarını güçlendirir.

Tabletler üzerinden erişilen karar destek sistemleri, ebelere takip ettikleri popülasyonun "sağlık karnesini" sunar. Bu durum, ebelik bakımının standartlaştırılmasını sağlarken, en ücra köylerdeki gebelerin dahi merkezdeki akademik veriye dayalı bir risk değerlendirmesinden geçmesine imkan tanır (Ward & ark., 2025: 5).

Tartışma: Etik, Veri Gizliliği ve İnsan Faktörü

Makine öğrenmesinin ebelik ve halk sağlığına entegrasyonu, sadece teknik bir başarı değil, aynı zamanda derin etik sorumluluklar gerektiren bir dönüşümdür. Algoritmaların klinik karar verme süreçlerine dahil edilmesi, veri güvenliğinden insani dokunuşun korunmasına kadar bir dizi kritik tartışmayı beraberinde getirmektedir.

- Bölgesel ve Etnik Yanlılık: Örneğin, kısıtlı sağlık imkanlarına sahip kırsal bölgelerden gelen veriler, modelin bu bölgelerdeki gebeler için sistematik olarak daha düşük sağlık çıktıları öngörmesine neden olabilir.
- Temsil Sorunu: Azınlık grupların veya dezavantajlı popülasyonların veri setlerinde yeterince temsil edilmemesi, modelin bu gruplar üzerinde hatalı sonuçlar vermesine yol açabilir. Bu durum, "algoritmik ayrımcılık" riskini doğurarak halk sağlığı adaletini zedeleyebilir.
- Sağlık verileri, kişisel mahremiyetin en hassas katmanını oluşturur. Gebelik izlemeleri, genetik bilgiler ve yaşam tarzı verilerinin ML modellerinde işlenmesi, siber güvenlik protokollerinin en üst düzeyde uygulanmasını zorunlu kılar.
- Diferansiyel Gizlilik (Differential Privacy): Modern ML yaklaşımlarında, bireysel verilerin ifşa edilmesini önlemek için veriye stratejik "gürültü" ekleyen diferansiyel gizlilik teknikleri kullanılmaktadır.

- Anonimleştirme vs. Sözde Anonimleştirme: Verilerin isimden arındırılması yeterli değildir; büyük veri analitiği ile anonim verilerin tekrar kimliklendirilebilme (re-identification) riski mevcuttur. Bu nedenle, KVKK ve GDPR gibi yasal çerçevelere uyum, akademik çalışmaların temel etik zeminini oluşturmalıdır (Asıl, 2025:8).

Son Söz: Makinenin Tahmini mi, Ebenin Sezgisi mi?

Ebelik, tarih boyunca sadece bir teknik uygulama değil, aynı zamanda "yanında olma" sanatı ve derin bir klinik sezgi olarak tanımlanmıştır. Makine öğrenmesi tartışmalarının en can alıcı noktası, bu insani unsurun dijitalleşme karşısındaki konumudur.

- Hibrit Model Savunusu: Geleceğin ebelik vizyonu, makine ile insanı karşı karşıya getiren bir rekabet değil; her ikisinin de güçlü yönlerini birleştiren bir "artırılmış zeka" modelidir. Algoritmalar, binlerce veriyi saniyeler içinde işleyerek ebeye "analitik bir öngörü" sunarken; ebe, bu veriyi hastanın kültürel değerleri, korkuları ve fiziksel tepkileriyle birleştirerek "nihai insani kararı" verir.
- Ebenin Rolü: Teknoloji ne kadar gelişirse gelişsin, bir gebenin elini tutmak, onun kaygısını anlamak ve doğumun kutsallığına eşlik etmek algoritmaların sınırları dışındadır. Makine öğrenmesi, ebenin üzerindeki veri işleme yükünü alarak, onun asli görevi olan "insan odaklı bakıma" daha fazla zaman ayırmasına imkan tanımaktadır (Barbounaki & Vivilaki 2021: 7).

Sonuç ve Öneriler

Makine öğrenmesi, doğum oranlarındaki dramatik düşüş ve artan riskli gebelik profilleri karşısında ebelere sadece bir teknolojik araç değil, aynı zamanda stratejik bir karar destek mekanizması sunmaktadır. Veriye dayalı bu yeni yaklaşım, halk sağlığı göstergelerini iyileştirme potansiyeline sahiptir.

Bu dönüşümün sağlıklı bir şekilde gerçekleştirilebilmesi için şu öneriler sunulabilir:

- Müfredat Güncellemesi: Ebelik lisans ve lisansüstü eğitim programlarına "Sağlıkta Veri Okuryazarlığı" ve "Dijital Sağlık Teknolojileri" dersleri entegre edilebilir. Geleceğin ebeleri, algoritmaların çıktılarını yorumlayabilecek ve bu verileri klinik sezgileriyle harmanlayabilecek yetkinlikte yetiştirilmelidir.
- Multidisipliner Çalışmalar: Ebelik araştırmacıları; veri bilimciler, yazılım mühendisleri ve biyoistatistikçiler ile ortak projeler geliştirerek, klinik saha bilgisini algoritma geliştirme süreçlerine doğrudan aktarılabilir.
- Veri Standartizasyonu: Türkiye genelindeki ebelik kayıtlarının (izlem formları, saha notları vb.) makine öğrenmesi algoritmaları tarafından işlenebilir, yüksek kaliteli ve standart bir formatta dijitalleştirilmesi teşvik edilmelidir.
- Etik Çerçeve Oluşturulması: Sağlıkta yapay zeka kullanımıyla ilgili ulusal etik rehberlerde, ebelik gibi "insan dokunuşu"nun merkezde olduğu meslekler için özel maddeler geliştirilmeli; algoritmanın önerisi ile ebenin kararı arasındaki seçim mekanizması netleştirilmelidir.
- Şeffaflık ve Güven: Kullanılan modellerin "kara kutu" olmaktan çıkarılarak, ebelere kararın arkasındaki gerekçeleri sunan "Açıklanabilir Yapay Zeka" (XAI) yöntemleriyle sunulması, teknolojinin sahada kabul görmesini kolaylaştıracaktır.

Sonuç olarak; dijitalleşen dünyada ebelik, veriler ile ebelerin şefkatli dokunuşuyla birleştirerek, anne ve bebek sağlığı için daha güvenli, öngörülebilir ve insan odaklı bir gelecek inşa etme gücüne sahiptir.

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İNTRAHEPATİK KOLESTAZİSİNİN GEBELİKTEKİ YERİ BÖLÜM 7 İNTRAHEPATİK KOLESTAZİSİNİN GEBELİKTEKİ YERİ DİAGNOSİS VE YÖNETİMİNE GÖRE ULUSLARARASI KILAVUZLAR

Ashhan KURT¹

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the most common pregnancy-specific liver disorder characterized by maternal pruritus and elevated serum bile acid concentrations developing during pregnancy and resolving spontaneously after delivery (1,2). The prevalence varies significantly according to geographic and ethnic differences, ranging from approximately 0.7% to 5% worldwide (2,3). Higher incidence rates have been reported in South American and Scandinavian populations, whereas lower prevalence has been observed in North America and parts of Europe, suggesting important interactions between genetic predisposition and environmental influences (2,3). Although maternal prognosis is generally favorable, ICP is associated with substantial fetal morbidity and mortality, including spontaneous preterm birth, meconium-stained amniotic fluid, respiratory distress syndrome, fetal distress, neonatal intensive care unit admission, and sudden intrauterine fetal death (1,4). Importantly, fetal death may occur suddenly and unpredictably despite reassuring fetal surveillance findings, indicating that conventional fetal monitoring methods such as cardiotocography and biophysical profile assessment have limited predictive value in preventing adverse outcomes (4,5). Consequently, timely diagnosis and appropriate delivery planning remain the cornerstones of clinical management.

The pathogenesis of ICP is multifactorial and incompletely understood. Genetic susceptibility plays an important role, with mutations involving hepatobiliary transport proteins such as ABCB4, ABCB11, and ATP8B1 identified in affected patients (2,6). These mutations impair bile acid transport across the canalicular membrane of hepatocytes, leading to intrahepatic bile acid accumulation and cholestasis. Familial clustering and the high recurrence rate in subsequent pregnancies further support the contribution of hereditary factors to disease development (2,6). Hormonal influences also contribute substantially, as elevated estrogen and progesterone levels impair bile acid transport and hepatocellular excretion during pregnancy (2,7). Estrogen metabolites reduce the activity of bile salt export pumps, while progesterone sulfates further inhibit bile flow and hepatobiliary transport mechanisms. The tendency for ICP symptoms to peak during the third trimester, when maternal hormone concentrations are highest, strongly supports the role of pregnancy-related hormonal changes in disease pathogenesis (2,7). Environmental factors may additionally modulate disease expression. Seasonal variation has been consistently reported, with increased incidence during winter months, particularly in temperate climates (8). Environmental factors including seasonal variation, selenium deficiency, reduced vitamin D levels, and dietary influences have been proposed as potential contributors to ICP pathogenesis, particularly in genetically susceptible women (8). These observations further support the multifactorial nature of the disorder. Physiological alterations during pregnancy also contribute to cholestatic predisposition. Under normal conditions, progesterone-mediated smooth muscle relaxation causes delayed gallbladder emptying and reduced bile flow, thereby promoting biliary stasis (7). In susceptible individuals, these physiological adaptations may progress to clinically significant cholestasis with accumulation of maternal serum bile acids. Elevated maternal bile acids cross the placenta

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and accumulate within the fetal circulation, where they may disrupt fetal cardiomyocyte calcium homeostasis and induce arrhythmogenic effects (5). Experimental studies suggest that toxic bile acids impair myocardial conduction and may trigger sudden fetal arrhythmias leading to intrauterine fetal demise (5). This mechanism is believed to explain the unpredictable nature of fetal death observed in severe ICP cases. Maternal pruritus remains the hallmark clinical manifestation and usually develops after 30 weeks of gestation (2). The itching predominantly affects the palms and soles and worsens at night, often significantly impairing maternal quality of life and sleep patterns. Importantly, symptoms may precede biochemical abnormalities by several weeks; therefore, repeated laboratory testing is recommended in symptomatic patients with initially normal bile acid levels (3,9). Primary skin lesions are absent, although secondary excoriations due to scratching are frequently observed. Total serum bile acid concentration is currently considered the most sensitive diagnostic marker for ICP and plays a central role in disease severity classification and risk stratification (1,3). Recent evidence demonstrates that adverse perinatal outcomes correlate closely with increasing bile acid concentrations, particularly when levels exceed 100 $\mu\text{mol/L}$ (1). Accordingly, current international guidelines increasingly emphasize individualized management strategies based on serum bile acid levels and gestational age.

Ursodeoxycholic acid (UDCA) remains the most commonly used pharmacological treatment for ICP because of its beneficial effects on maternal symptoms and liver biochemistry (3). Several studies suggest that UDCA may improve placental bile acid transport and reduce fetal exposure to toxic bile acids, although evidence regarding improvement in perinatal outcomes remains controversial (10). Therefore, despite ongoing debate regarding medical therapy, most international guidelines agree that optimal timing of delivery remains the most effective strategy for reducing the risk of stillbirth in pregnancies complicated by ICP (1,3,4).

Epidemiology

The prevalence of intrahepatic cholestasis of pregnancy (ICP) demonstrates considerable geographic and ethnic variability worldwide. Reported incidence rates range from approximately 0.1% to 15%, depending on the studied population and diagnostic criteria used (11,12). The highest prevalence has been reported in South American countries, particularly Chile and Bolivia, as well as in Scandinavian populations, whereas lower rates are generally observed in North America and most European countries (11,12). Seasonal variation has also been described, with increased incidence during winter months, suggesting potential environmental and nutritional influences, including selenium deficiency (13). Several maternal characteristics are associated with an increased risk of ICP, including advanced maternal age, multiple gestation, assisted reproductive technologies, hepatitis C infection, and a personal or family history of cholestatic disorders (14,15). The incidence is also increased in pregnancies associated with elevated estrogen levels, further supporting the hormonal contribution to disease pathogenesis (15).

Familial clustering and high recurrence rates in subsequent pregnancies strongly support a genetic predisposition. The recurrence risk has been reported to range between 60% and 70% in future pregnancies (12). Variants involving hepatobiliary transport proteins, particularly ABCB4, ABCB11, and ATP8B1, have been implicated in disease susceptibility and severity (16). In addition to pregnancy-related complications, women with a history of ICP may have an increased long-term risk of hepatobiliary disease later in life. Previous studies have demonstrated higher rates of gallstone disease, chronic hepatitis, cirrhosis, and hepatobiliary malignancies among affected women compared with the general population (17,18).

Furthermore, emerging evidence suggests a possible association between ICP and future metabolic and cardiovascular disorders, although additional longitudinal studies are needed to clarify these relationships (19).

Pathophysiology

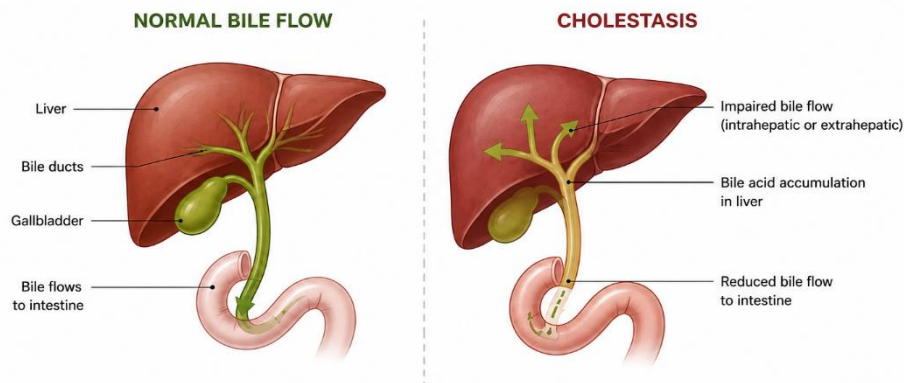
The pathophysiology of intrahepatic cholestasis of pregnancy (ICP) is multifactorial and incompletely understood, involving a complex interaction between genetic susceptibility, hormonal influences, environmental factors, and altered hepatocellular bile acid transport mechanisms (11,16). The hallmark of the disease is impaired bile acid secretion from hepatocytes, resulting in cholestasis and accumulation of potentially toxic bile acids within the maternal circulation (11,12).

Under physiological conditions, bile acids are synthesized in hepatocytes and secreted into bile canaliculi through specialized transport proteins, including the bile salt export pump (ABCB11/BSEP) and multidrug resistance protein 3 (ABCB4/MDR3) (16). Dysfunction or reduced expression of these transporters impairs biliary excretion and promotes intrahepatic bile acid accumulation. Genetic mutations involving ABCB4, ABCB11, ATP8B1, and related hepatobiliary transport genes have been identified in affected women and may contribute to both disease susceptibility and severity (16,20). Hormonal changes during pregnancy play a central role in disease development. Rising estrogen and progesterone levels during the second and third trimesters impair hepatocellular bile acid transport and reduce biliary flow (15,21). Estrogen metabolites may directly inhibit bile acid export pumps, whereas sulfated progesterone metabolites interfere with nuclear receptors involved in hepatic bile acid homeostasis (21). During normal pregnancy, progesterone-mediated smooth muscle relaxation contributes to delayed gallbladder emptying and biliary stasis (15). In genetically susceptible women, these physiological changes may progress to clinically significant cholestasis.

Accumulated maternal bile acids can cross the placenta and enter the fetal circulation, where fetal clearance mechanisms remain immature (22). Elevated fetal bile acid concentrations have been implicated in placental vasoconstriction, cardiomyocyte dysfunction, arrhythmogenesis, and meconium passage, potentially explaining the increased risk of fetal distress, spontaneous preterm birth, and sudden intrauterine fetal death associated with ICP (22,23). Environmental and metabolic factors may also contribute to disease expression. Seasonal variation, selenium deficiency, altered gut microbiota, and inflammatory pathways have all been proposed as possible contributors to ICP pathogenesis, although their precise roles remain incompletely understood (13,24).

Figure-1 : Intrahepatic Cholestasis

CHOLESTASIS



Genetic Factors

Mutations in genes encoding bile acid transport proteins impair hepatocellular bile secretion and contribute to disease development. Variants in ABCB4, ABCB11, and ATP8B1 are among the most commonly implicated genetic abnormalities (6).

Hormonal Factors

Estrogen metabolites inhibit bile acid transport proteins and impair hepatocellular excretion, while progesterone sulfates further reduce bile flow (2,7). The increased incidence during the third trimester supports the role of hormonal mechanisms.

Environmental Factors

Seasonal variation has been consistently reported, with increased incidence during winter months (8). Selenium deficiency and reduced vitamin D levels have been proposed as contributing environmental factors.

Clinical Presentation

Pruritus is the cardinal symptom of ICP and typically begins after 30 weeks of gestation (2). The itching is generalized but predominantly affects the palms and soles and tends to worsen during nighttime. Primary skin lesions are absent, although excoriations secondary to scratching are common. Additional symptoms may include:

- Mild jaundice
- Dark urine
- Steatorrhea
- Nausea
- Anorexia

Importantly, pruritus may develop weeks before laboratory abnormalities become detectable (9). Therefore, repeat testing is essential when clinical suspicion persists.

Laboratory Findings and Diagnosis

Total serum bile acid concentration is currently considered the most sensitive diagnostic marker for ICP (1,3).

Diagnostic thresholds differ slightly among international guidelines:

Guideline	Diagnostic Threshold
------------------	-----------------------------

- | | |
|---------------|---------------------------|
| • SMFM / ACOG | $\geq 10 \mu\text{mol/L}$ |
| • RCOG | $\geq 19 \mu\text{mol/L}$ |

Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are observed in approximately 60–85% of patients (2). ALT elevation is generally more pronounced. Gamma-glutamyl transferase (GGT) is usually normal or mildly elevated, whereas alkaline phosphatase is less useful because placental production physiologically increases during pregnancy.

Recent studies suggest that non-fasting bile acid measurements may be more clinically informative than fasting measurements because fasting samples may underestimate disease severity (9).

Maternal Complications

Although maternal outcomes are generally favorable, ICP has been associated with increased risks of:

- Gestational diabetes mellitus
- Preeclampsia
- Postpartum hemorrhage secondary to vitamin K deficiency
- Operative delivery

Fat malabsorption resulting from impaired bile acid secretion may lead to deficiencies of fat-soluble vitamins, particularly vitamin K (3).

Fetal and Neonatal Complications

Fetal complications represent the most clinically significant aspect of ICP. These complications include:

- Spontaneous preterm birth
- Fetal distress
- Meconium-stained amniotic fluid
- Respiratory distress syndrome

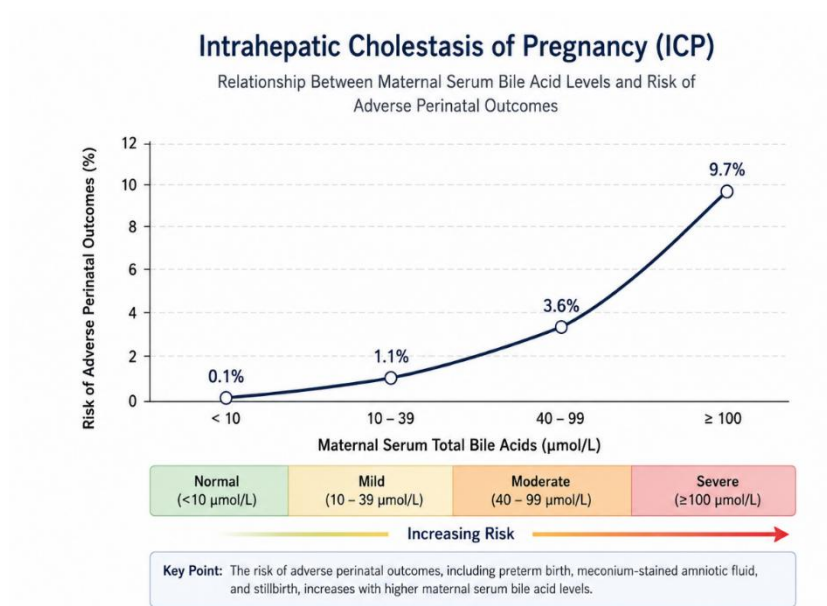
- Neonatal intensive care admission
- Sudden intrauterine fetal death

The risk of adverse outcomes correlates strongly with maternal bile acid concentration (1).

<u>Total Bile Acids</u>	<u>Clinical Severity</u>
• <40 $\mu\text{mol/L}$	Mild disease
• 40–99 $\mu\text{mol/L}$	Severe disease
• ≥ 100 $\mu\text{mol/L}$	Very severe disease

Ovadia et al. demonstrated that stillbirth risk increases substantially when bile acid concentrations exceed 100 $\mu\text{mol/L}$ (1). Importantly, fetal death in ICP is often sudden and may not be predicted by conventional fetal surveillance methods such as NST or biophysical profile assessment (4,5).

Figure-2: Relationship Between Maternal Serum Bile Acid Levels and Risk of Adverse Perinatal Outcomes



Differential Diagnosis

The differential diagnosis of ICP includes:

- Viral hepatitis
- HELLP syndrome
- Acute fatty liver of pregnancy
- Cholelithiasis
- Dermatological disorders of pregnancy

The absence of primary skin lesions and elevated serum bile acid levels help distinguish ICP from other pruritic disorders of pregnancy.

Medical Management

Ursodeoxycholic Acid (UDCA)

UDCA remains the first-line pharmacological therapy for ICP (3).

Recommended dosage:

- Initial dose: 10–15 mg/kg/day
- Maximum dose: up to 21 mg/kg/day

UDCA improves bile acid transport, reduces maternal pruritus, and improves liver function parameters (25). Several studies suggest that UDCA may improve placental bile acid transport and reduce fetal exposure to toxic bile acids (14). However, the PITCHES trial demonstrated no significant improvement in adverse perinatal outcomes despite modest symptomatic improvement (8). Consequently:

- SMFM and ACOG continue recommending UDCA for symptomatic relief
- RCOG no longer routinely recommends UDCA for fetal benefit

Additional Therapies

Rifampicin

Rifampicin may be considered in refractory cases not responding adequately to UDCA (3).

Cholestyramine

Cholestyramine reduces pruritus by binding bile acids but may worsen vitamin K deficiency and should therefore be used cautiously.

Antihistamines

Antihistamines may improve sleep quality but have limited effect on cholestatic pruritus.

Antenatal Surveillance

Current guidelines recommend regular monitoring of:

- Serum bile acid levels
- Liver function tests
- Maternal symptoms

Weekly monitoring is generally recommended in severe disease (3,4).

Although fetal surveillance with NST and biophysical profile assessment is commonly performed, evidence suggests that these methods do not reliably predict sudden fetal demise in ICP (4,5).

Timing of Delivery

Delivery timing should be individualized according to bile acid concentration and disease severity.

Total Bile Acids	SMFM / ACOG	RCOG
• <40 $\mu\text{mol/L}$	36–39 weeks	40 weeks
• 40–99 $\mu\text{mol/L}$	Early part of 36–39 weeks	38–39 weeks
• ≥ 100 $\mu\text{mol/L}$	36 weeks	35–36 weeks

The primary goal is balancing the risks of prematurity against the increasing risk of stillbirth with advancing gestation (1,3,4). Continuous intrapartum fetal monitoring is recommended during labor.

Postpartum Management

Symptoms generally improve rapidly after delivery, with pruritus resolving within 48 hours and biochemical abnormalities normalizing within 2–8 weeks (3). Repeat liver function and bile acid testing should be performed 6–8 weeks postpartum. Persistent abnormalities require evaluation for underlying liver disease (8).

Women should also receive counseling regarding:

- High recurrence risk in future pregnancies
- Long-term hepatobiliary disease risk
- Contraceptive counseling

Non-hormonal contraceptive methods may be preferable in women with prior severe ICP.

Conclusion

Intrahepatic cholestasis of pregnancy (ICP) is a significant pregnancy-specific liver disorder characterized by maternal pruritus, elevated serum bile acid concentrations, and an increased risk of adverse perinatal outcomes. Although maternal prognosis is generally favorable and symptoms typically resolve rapidly after delivery, ICP remains clinically important because of its association with spontaneous preterm birth, meconium-stained amniotic fluid, fetal distress, neonatal respiratory complications, and sudden intrauterine fetal death. Serum total bile acid concentration remains the cornerstone of diagnosis, disease monitoring, and fetal risk stratification. Increasing evidence demonstrates that adverse perinatal outcomes correlate closely with the severity of maternal hypercholanemia, particularly when bile acid levels exceed 100 $\mu\text{mol/L}$. Consequently, accurate biochemical assessment and close antenatal surveillance are essential components of clinical management.

Ursodeoxycholic acid (UDCA) remains the most widely used pharmacological treatment and has been shown to improve maternal pruritus and liver function parameters in many affected women. However, evidence regarding its ability to reduce stillbirth and severe

perinatal morbidity remains inconclusive. Therefore, optimal timing of delivery continues to represent the most effective strategy for minimizing fetal complications, particularly in women with severe disease and markedly elevated bile acid concentrations.

Current international guidelines from organizations such as International Society of Ultrasound in Obstetrics and Gynecology, Society for Maternal-Fetal Medicine, and Royal College of Obstetricians and Gynaecologists differ slightly regarding diagnostic thresholds, fetal surveillance protocols, and recommended timing of delivery. Nevertheless, all emphasize individualized management based on gestational age, disease severity, maternal symptoms, and serum bile acid concentrations.

Future research should focus on improving understanding of the molecular mechanisms underlying ICP, identifying more reliable predictors of adverse fetal outcomes, and developing targeted therapeutic strategies capable of reducing perinatal morbidity and mortality. Further prospective multicenter studies are also needed to optimize delivery timing and establish standardized evidence-based management protocols across different clinical settings.

BÖLÜM 8

COVID-19 ENFEKSİYONLU GEBELERDE GEBELİK SONUÇLARININ DEĞERLENDİRİLMESİ

İSMAİL YILMAZ¹

Giriş

ABSTRACT

Objective: This study investigates the impact of COVID-19 on pregnancy, fetuses, and newborns by comparing outcomes between infected and uninfected pregnant women.

Method: Electronic hospital records from March 2020 to October 2021 were analyzed. A total of 320 COVID-19-positive and 438 COVID-19-negative pregnant women were included. Data on infection timing, delivery method, gestational age, fetal condition, newborn weight, and test results were examined.

Results: First-time pregnancies made up 39.7% of the sample; 40.5% delivered via cesarean section. The average gestational age was 38.03 ± 1.73 weeks, and the mean birth weight

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was $3,228.67 \pm 511.86$ grams. Differences were found in maternal age, parity, and infection timing during pregnancy between groups.

Conclusion: Although obstetric characteristics varied between infected and uninfected women, pregnancy, fetal, and neonatal outcomes were similar. While COVID-19 may pose risks for mothers and infants, further clinical research is needed to clarify its full impact.

Keywords: COVID-19, Fetal, Neonatal, Newborn, Pregnancy.

ÖZ

Amaç: Bu çalışma, COVID-19'un gebelik, fetüs ve yenidoğan üzerindeki etkisini, enfekte ve enfekte olmayan gebe kadınlar arasındaki sonuçları karşılaştırarak incelemeyi amaçlamaktadır.

Yöntem: Mart 2020 ile Ekim 2021 tarihleri arasındaki elektronik hastane kayıtları geriye dönük olarak analiz edilmiştir. Toplam 320 COVID-19 pozitif ve 438 COVID-19 negatif gebe dahil edilmiştir. Enfeksiyon zamanlaması, doğum şekli, gebelik haftası, fetal durum, yenidoğan ağırlığı ve test sonuçlarına ilişkin veriler incelenmiştir.

Bulgular: Örneklemin %39,7'si ilk gebeliğini yaşıyordu; %40,5'i sezaryenle doğum yaptı. Ortalama doğum haftası $38,03 \pm 1,73$, ortalama doğum ağırlığı $3.228,67 \pm 511,86$ gram olarak saptandı. Gruplar arasında anne yaşı, parite ve gebelik sırasındaki enfeksiyon zamanlaması açısından farklılıklar tespit edildi.

Sonuç: Enfekte ve enfekte olmayan kadınlar arasında obstetrik özellikler farklılık gösterse de gebelik, fetal ve neonatal sonuçlar benzer bulunmuştur. COVID-19 anne ve bebek için risk oluşturabilmekle birlikte, tam etkisini ortaya koymak için ileri klinik araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Fetal, Neonatal, Yenidoğan, Gebelik.

GİRİŞ

COVID-19 virüsünün 31 Aralık 2019'da Çin'in Wuhan şehrinde tanımlanmasının ardından enfeksiyon küresel ölçekte yayılmıştır (Rasmussen ve ark., 2020). Amerika Birleşik Devletleri Hastalık Kontrol ve Önleme Merkezleri'nin (CDC) verilerine göre Temmuz 2022 itibarıyla 220.673 gebe COVID-19'a yakalanmıştır (CDC, 2022). Koronavirüsler, Coronaviridae ailesi ve Nidovirales takımından, insanlarda ve memelilerde yaygın olarak görülen, zarflı nonsegmente ribonükleik asit virüsleridir. İnsan koronavirüs enfeksiyonlarının büyük çoğunluğu hafif semptomlarla seyretmekle birlikte, önceki iki beta-koronavirüs salgınında —şiddetli akut solunum sendromu koronavirüsü ve Orta Doğu solunum sendromu koronavirüsü— 10.000'i aşkın kümülatif vaka saptanmış; mortalite oranları sırasıyla %10 ve %37 olarak bildirilmiştir (Huang ve ark., 2020).

Gebeler, fetüsler ve yenidoğanlar, ağır akut enfeksiyonlara karşı savunmasız popülasyonlar arasında yer almakta; bu virüslerin maternal ve perinatal sonuçlar üzerindeki olumsuz etkilerine ilişkin ciddi kaygılar bulunmaktadır (Allotey ve ark., 2020). Önceki salgınlar önemli sonuçlar doğurmuştur: Zika virüsü ağır fetal etkilere yol açarken, 2009 H1N1 influenza pandemisi gebe kadınları ve fetüsleri derinden etkilemiştir (Rasmussen ve ark., 2020). COVID-19 pnömonisi şiddetli akut solunum sendromunu tetiklemektedir (Chan ve ark., 2020). Dünya genelinde 64.000'den fazla gebede şüpheli veya doğrulanmış COVID-19 enfeksiyonu bildirilmiştir. Amerikalı gebe kadınları kapsayan bir kohort çalışmasında en sık görülen başlangıç semptomları öksürük (%20), boğaz ağrısı (%16), miyalji (%12) ve ateş (%12) olarak belirlenmiştir (Afshar ve ark., 2020). Bir başka araştırmada ise öne çıkan semptomlar arasında

öksürük (%50,3), baş ağrısı (%42,7), kas ağrısı (%36,7), ateş (%32,0), boğaz ağrısı (%28,4) ve nefes darlığı (%25,9) sayılmıştır (Vásconez-González ve ark., 2023). Gebelerde ateş ve miyalji, gebe olmayan bireylere kıyasla daha az sıklıkla gözlemlenmektedir (Allotey ve ark., 2020; Schwartz, 2020).

Enfekte annelerden doğan tüm bebekler COVID-19 açısından test edilmelidir. Anne-bebek bağlanması doğum sonrası izolasyon protokollerine uygun şekilde sürdürülmelidir. Mevcut veriler anne sütünde virüs saptanmadığını göstermekte olup, doğrudan anne-bebek temasını önlemek amacıyla maske ve koruyucu ekipman kullanılarak emzirmeye devam edilmelidir (Desdicioğlu ve Yavuz, 2020; Çağlar ve Oskay, 2020).

Gebelikte COVID-19 konusunda önemli bilgi açıkları mevcuttur. Bağışıklık fonksiyonu, solunum kapasitesi, koagülasyon ve kardiyovasküler performansı etkileyen gebeliğe özgü fizyolojik değişiklikler, COVID-19 enfeksiyonu sırasında ve sonrasında gözlemlenmiştir (Wastnedge ve ark., 2021). Dikey geçiş olasılığı hâlâ netlik kazanmamış olup neonatal enfeksiyonun önlenmesi ve yönetimine ilişkin yeterli kanıt bulunmamaktadır (Zhu ve ark., 2020). Bu araştırma, COVID-19'un maternal, fetal ve neonatal etkilerini belirlemek amacıyla yürütülmüştür.

HASTALAR VE YÖNTEM

Bu çalışma geriye dönük olarak tasarlanmıştır. Düzce Atatürk Devlet Hastanesi'nin elektronik kayıtlarından Mart 2020 ile Ekim 2021 tarihleri arasında lohusa dönemindeki kadınlar tespit edilmiştir. Gebelik süresince COVID-19 testi yapılan kadınlar çalışmaya alınmış; negatif ve pozitif sonuç gruplarına ayrılmıştır. Her grup için anne yaşı, gebelik sayısı, düşük öyküsü, doğumdaki gebelik haftası, doğum ağırlığı, önceki ve mevcut doğum şekli ile fetal durum (canlı/ölü doğum) kaydedilmiştir. COVID-19 testi

pozitif 320 gebe ile negatif 438 gebe tanımlanmıştır. Tüm veriler üç kez doğrulamadan geçirilmiştir.

Dahil Etme Kriterleri

Mart 2020 ile Ekim 2021 tarihleri arasında gebeliğin herhangi bir döneminde COVID-19 testi yapılmış, sonucu pozitif veya negatif olarak kayıt altına alınmış, tekil gebeliği olan kadınlar çalışmaya dahil edilmiştir.

Dışlama Kriterleri

Çoğul gebeliği olan kadınlar ile rutin preoperatif COVID-19 testi sonucu negatif çıkan asemptomatik gebeler çalışma dışı bırakılmıştır.

İstatistiksel Analiz

Veriler, Windows için Statistical Package for Social Sciences (Sürüm 20.0) kullanılarak analiz edilmiştir. Sürekli değişkenler ortalama ve standart sapma, kategorik değişkenler ise frekans ve yüzde olarak sunulmuştur. Normal dağılım Kolmogorov-Smirnov testi ile doğrulanmıştır. İkili grup karşılaştırmalarında bağımsız örneklem T testi, kategorik değişkenler arasındaki ilişkilerde ki-kare testi kullanılmıştır. Doğum ağırlığı ile anne yaşı, önceki ve mevcut doğum şekli, COVID-19 durumu, doğumdaki gebelik haftası, gebelik sayısı ve düşük öyküsü arasındaki ilişkileri incelemek için doğrusal regresyon analizi uygulanmıştır. İstatistiksel anlamlılık $p < 0,05$ olarak tanımlanmıştır.

BULGULAR

Mart 2020 ile Ekim 2021 tarihleri arasında COVID-19 testi uygulanan 791 gebe incelenmiştir. İkiz gebeliği bulunan kadınlar ($n=8$) ile rutin preoperatif testi negatif çıkanlar ($n=25$) dışlandıktan sonra nihai çalışma popülasyonu 758 gebeden oluşmuştur: 320'si COVID-19 test pozitif, 438'i negatif sonuçludur.

Tablo I, gebelerin obstetrik özelliklerini sunmaktadır. Ortalama anne yaşı $29,14 \pm 5,46$ yıl, ortalama gebelik sayısı $1,96 \pm 0,92$ 'dir. Ortalama doğum haftası $38,03 \pm 1,73$, ortalama doğum ağırlığı $3.228,67 \pm 511,86$ gramdır. Kadınların %39,7'si için bu ilk gebeliklerini temsil etmekte olup %19,8'i vajinal yolla doğum yapmıştır. Ölü doğum oranı %0,4 (n=3) olarak kaydedilmiştir (Tablo I).

Tablo I. Gebelerin obstetrik özellikleri

Özellikler		Ortalama $\pm$ SS	Min-Maks (Medyan)
Yaş		$29,14 \pm 5,46$	18-47 (29)
Gebelik sayısı		$1,96 \pm 0,92$	1-6 (2)
Doğum sayısı		$1,82 \pm 0,82$	1-5 (2)
Düşük sayısı		$0,13 \pm 0,38$	0-3 (0)
Doğum haftası		$38,03 \pm 1,73$	22-41 (38)
Doğum ağırlığı (g)		$3.228,67 \pm 511,86$	560-5.060 (3.257,50)
Önceki doğum şekli	İlk gebelik	301	%39,7
	Normal vajinal doğum	150	%19,8
	Sezaryen	307	%40,5
Doğum şekli	Sezaryen	514	%67,8
	Normal vajinal doğum	244	%32,2
Ölü/canlı doğum	Ölü doğum	3	%0,4
	Canlı doğum	755	%99,6

Tablo II, COVID-19 pozitif ve negatif gruplar arasında yaş ve obstetrik özelliklerin karşılaştırmasını göstermektedir. Analiz, anne yaşı, gebelik sayısı, doğum sayısı ve COVID-19 tanısının konulduğu gebelik haftası açısından istatistiksel olarak anlamlı farklılıklar ortaya koymuştur (Tablo II).

Tablo II. Gebelerin yaş ve obstetrik özelliklerinin COVID-19 test sonucuna göre karşılaştırılması

Özellikler	COVID-19 Sonucu	n	Ortalama $\pm$ SS	Test ist.*	p
Yaş	Negatif	438	28,70 $\pm$ 5,45	-2,636	0,009
	Pozitif	320	29,75 $\pm$ 5,43		
Gebelik sayısı	Negatif	438	1,88 $\pm$ 0,89	-2,564	0,010
	Pozitif	320	2,06 $\pm$ 0,96		
Doğum sayısı	Negatif	438	1,76 $\pm$ 0,80	-2,461	0,014
	Pozitif	320	1,91 $\pm$ 0,84		
COVID testi haftası	Negatif	438	20,36 $\pm$ 10,72	-3,909	0,000
	Pozitif	320	23,37 $\pm$ 10,28		
Doğum haftası	Negatif	438	38,09 $\pm$ 1,62	1,108	0,268
	Pozitif	320	37,95 $\pm$ 1,89		
Doğum ağırlığı (g)	Negatif	438	3.231,84 $\pm$ 526,28	0,199	0,842
	Pozitif	320	3.224,33 $\pm$ 492,22		

*Bağımsız örneklem T testi

COVID-19 pozitifliği ile doğum şekli arasında istatistiksel olarak anlamlı bir fark saptanmamıştır (Tablo III).

Tablo III. COVID-19 test sonucu ile doğum şekli arasındaki ilişki

		COVID-19 Negatif	COVID-19 Pozitif	χ^2 / p
Doğum şekli	Sezaryen	303	211	0,890 / 0,346
	Normal vajinal doğum	135	109	
Toplam		438	320	

Doğrusal regresyon modeli, yenidoğan doğum ağırlığı ile anne yaşı, önceki ve mevcut doğum şekli, COVID-19 durumu, gebelik haftası, gebelik sayısı ve düşük öyküsü arasındaki ilişkileri incelemiştir. Model istatistiksel olarak anlamlı bulunmuştur ($F=35,809$; $p<0,001$). Doğum haftası ile doğum ağırlığı arasında anlamlı bir ilişki saptanmıştır ($p=0,000$). Her ek gebelik haftası, yenidoğan ağırlığında 0,58 katlık artışla ilişkili bulunmuştur (Tablo IV).

Tablo IV. Doğum ağırlığını etkileyen faktörlere ilişkin regresyon analizi sonuçları

Değişken	B0 (95%GA)	B1	SH	Test ist.	p	r1	r2
(Sabit)	-3.438,46 (- 4.187,8 – - 2.689,13)		381,70	-9,01	0,00		
Yaş	4,58 (-1,42– 10,58)	0,05	3,06	1,50	0,13	0,01	0,06
Doğum haftası	171,84 (153,53– 190,15)	0,58	9,33	18,42	0,00	0,56	0,56
Pozitif COVID-19 testi	6,01 (-56,39– 68,4)	0,01	31,78	0,19	0,85	-0,01	0,01

$F=35,809$; $p<0,001$; $R^2=0,324$. B0: Standartlaştırılmamış katsayı, B1: Standartlaştırılmış katsayı, r1: Basit korelasyon, r2: Kısmi korelasyon, SH: Standart Hata, NVD: Normal vajinal doğum.

TARTIŞMA

Gebeler, deęiřmiř fizioloji, artan enfeksiyona yatkınlık ve bozulmuř mekanik ile imm nolojik iřlevler nedeniyle bulařıcı hastalık salgınlarında savunmasız bir pop lasyonu temsil etmektedir (Dashraath ve ark., 2020). COVID-19 enfeksiyonunun ř pheli ya da doęrulanmıř olduęu durumlarda anne bakımı ve doęum y netimi g  leřmektedir (Elshafeey ve ark., 2020; Yang ve ark., 2022). Pandemi s recinde, ř pheli veya doęrulanmıř COVID-19’u olan t m gebeler i in standart kabul prosed rleri ve tarama uygulamaları hayata ge irilmelidir. Doęum  ncesi muayene birimlerinin yerel, federal ve uluslararası rehberlere uyması; y ksek riskli durumların y netiminde bu protokolleri hızla devreye sokması gerekmektedir (Yang ve ark., 2022).  alıřmamız, COVID-19’un gebelik ve doęum s re leri  zerindeki etkilerini bu  er evede incelemiřtir.

 alıřmamızda COVID-19’lu gebelerin ortalama yařı 29 olup ortalama iki gebelik ve iki doęum  yk s  bulunmakta; enfeksiyon tanısı aęırlıklı olarak ikinci trimesterde konulmaktadır. Obstetrik  zellikler a ısından (anne yařı, gebelik sayısı, doęum sayısı ve COVID-19 tanısının konulduęu gebelik haftası) anlamlı farklılıklar saptanmıřtır. Zhu ve ark., enfekte dokuz gebenin analizinde ortalama yařı 30 olarak bildirmiř; yedi sezaryen ve iki vajinal doęum ger ekleřtięini, ortalama gebelik haftasının 35, ortalama doęum aęırlıęının ise 2.400 gram olduęunu raporlamıřtır (Zhu ve ark., 2020). Chen ve ark. ise COVID-19 pozitif dokuz gebenin incelendięi  alıřmalarında bir olguda influenza, birinde preeklampsi, birinde gestasyonel hipertansiyon saptamıřtır (Chen ve ark., 2020).

Gebelikte viral enfeksiyonlar fetal saęlıęı olumsuz etkilemektedir (Wastnedge ve ark., 2021; Dor lien, 2019). Ulusal kayıt verilerini kullanan bir ABD  alıřması, gebelikte mevsimsel influenzanın erken doęum ve bebek mortalitesi ile anlamlı bi imde iliřkili olduęunu g stermiřtir (Dor lien, 2019). Benzer řekilde, bir Birleřik Krallık kohort  alıřması H1N1 enfeksiyonunu artmıř preterm doęum ve perinatal mortalite oranlarıyla iliřkilendirmiřtir

(Mosby ve ark., 2011). Elshafeey ve ark., COVID-19’lu gebelerin gebe olmayan yetişkinlerle benzer klinik özellikler sergilediğini ve kötü perinatal sonuçlarla ilişki saptanmadığını bildirmiştir (Elshafeey ve ark., 2020). COVID-19 pozitif dokuz gebenin gebelik sonuçlarını inceleyen başka bir çalışmada ise beş olguda fetal distres ve yedisinde erken membran rüptürü raporlanmıştır (Chen ve ark., 2020). Abbas-Hanif ve ark., COVID-19’lu gebelerin yaşla eşleştirilmiş gebe olmayan kadınlara kıyasla ciddi komplikasyonlar açısından belirgin biçimde daha yüksek risk taşıdığını göstermiştir (Abbas-Hanif ve ark., 2022). Çalışmamızda enfeksiyon ağırlıklı olarak ikinci trimesterde ortaya çıkmış; preterm doğum veya düşük doğum ağırlığı riskinde anlamlı bir artış gözlemlenmemiştir.

Gebelik ilerledikçe uterusun büyümesi akciğer kapasitesini azaltabilmektedir. Bu nedenle COVID-19 enfeksiyonu, ileri gebelik döneminde daha hızlı klinik kötüleşmeye ve olumsuz gebelik sonuçlarına yol açabilir (Cai ve ark., 2021). Erken gebelikte (ilk 12 hafta) COVID-19’un etkileri konusundaki kanıtlar sınırlıdır. Geç gebelikte (24. haftadan sonra) COVID-19 enfeksiyonunun intrauterin büyüme kısıtlaması, erken doğum eylemi ve perinatal mortalite gibi olumsuz sonuçlarla ilişkili olduğu bilinmektedir (Wastnedge ve ark., 2021). Preterm doğum, COVID-19 pozitif gebelerde daha sık görülmektedir (Allotey ve ark., 2020; Mullins ve ark., 2021). Çalışmamızda ortalama doğum 37. gebelik haftasında gerçekleşmiş olup enfekte ve enfekte olmayan gruplar arasında gebelik haftası açısından anlamlı bir farklılık saptanmamıştır.

COVID-19 pozitif gebelerde doğum şekli ve neonatal geçiş riski konusundaki bilgiler hâlâ yetersizdir. Geçiş en aza indirmek için en uygun doğum yaklaşımı bilinmemektedir (Dashraath ve ark., 2020; Chen ve ark., 2020). COVID-19 pozitif gebeler düşük, orta ve yüksek riskli olarak sınıflandırılarak klinik aciliyet belirlenmektedir. COVID-19 varlığında vajinal doğum kontrendike değilken, acil doğum gerektiğinde sezaryen uygundur (Dashraath ve ark., 2020).

COVID-19 pozitif dokuz gebenin incelendiği bir çalışmada tüm olgular sezaryenle doğurmuştur (Chen ve ark., 2020). Cai ve ark.'nın gerekli doğum yöntemlerini değerlendiren meta-analizine göre sezaryen ile vajinal doğum sonuçları arasında farklılık bulunmamaktadır (Cai ve ark., 2021). Çalışmamızda da gruplar arasında doğum şekli açısından anlamlı bir farklılık saptanmamıştır.

SONUÇ

COVID-19 enfeksiyonu olan ve olmayan gebeler karşılaştırıldığında, obstetrik özellikler (anne yaşı, gebelik sayısı, doğum sayısı ve enfeksiyon zamanlaması) açısından anlamlı farklılıklar saptanmıştır. Bununla birlikte, gebelik sonuçları (düşük oranları, bebek durumu) ile fetal ve neonatal sonuçlar (gebelik haftası, doğum ağırlığı, doğum şekli) gruplar arasında benzer bulunmuştur. Gebelik ve doğum sürecinin etkin yönetimi; uygun izolasyon uygulamalarını, yakın maternal-fetal izlemi, gerektiğinde mekanik solunum desteğini, doğum planlamasını ve doğum sonrası anne-bebek ilişkisinin optimizasyonunu gerektirmektedir. Gebelik bağışıklık işlevini ve fiziksel durumu değiştirmekte; bu durum COVID-19 enfeksiyonu sırasında daha büyük güçlükler doğurabilmektedir. COVID-19'un gebelik sürecindeki klinik seyri ve sonuçlarına ilişkin mevcut anlayış sınırlı kalmaya devam etmekte olup, gebelik ve perinatal boyutlara ilişkin ek araştırmalara ihtiyaç duyulmaktadır.

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BÖLÜM 9

THE EFFECTS OF PREECLAMPSIA ON MATERNAL AND FETAL OUTCOMES AND CURRENT TREATMENT APPROACHES

REMZİ KARASUNGUR¹

Introduction and Definitions

Hypertensive disorders of pregnancy constitute a broad spectrum of clinical conditions that pose significant risks to both the mother and the fetus, including chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and HELLP syndrome (Fisher et al., 2018; Spiro & Scemons, 2018; Holm et al., 2019). These disorders may lead to life-threatening maternal complications such as stroke, myocardial infarction, heart failure, and chronic kidney disease. Currently, hypertensive disorders of pregnancy represent the second leading cause of maternal mortality in developed countries, while preeclampsia and eclampsia account for approximately 10–15% of maternal deaths in low- and middle-income countries (Uslu Yuvaci, 2018). In addition to their adverse effects on maternal health, these conditions have profound consequences for fetal well-being. They are among the leading causes of preventable perinatal morbidity and mortality, primarily due to preterm birth. Hypertensive disorders during pregnancy are classified according to the timing of onset and the presence of systemic involvement. Hypertension diagnosed before the 20th week of gestation is defined as chronic hypertension, whereas

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gestational hypertension refers to new-onset hypertension occurring after 20 weeks of gestation, characterized by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in the absence of proteinuria or other systemic manifestations (Hauspurg & Jeyabalan, 2022). Preeclampsia, in contrast, is a more severe clinical condition characterized by the development of arterial hypertension after the 20th week of gestation accompanied by multisystem organ dysfunction. These manifestations may include renal involvement characterized by proteinuria and oliguria, hematological abnormalities such as thrombocytopenia and hemolysis, hepatic injury associated with elevated liver transaminases, neurological complications ranging from severe symptoms to stroke and eclamptic seizures, and fetal complications such as intrauterine growth restriction (Fowosere, 2024). Accordingly, the primary aim of this study is to review current therapeutic approaches aimed at minimizing the adverse effects of preeclampsia on maternal and fetal morbidity and mortality and to provide healthcare professionals with evidence-based information regarding its management.

Epidemiology and Risk Factors

The lack of standardized diagnostic criteria used in population-based databases makes it difficult to accurately determine the true incidence of preeclampsia. According to current epidemiological data, preeclampsia complicates approximately 3% of pregnancies in the United States (Hutcheon et al., 2011). Hypertensive disorders during pregnancy are a significant global health concern, affecting an estimated 10–15% of pregnancies worldwide. The incidence of preeclampsia ranges from 2% to 7% among healthy nulliparous women (Chourdakis et al., 2021), increasing to 14% in twin pregnancies and up to 18% among women with a history of preeclampsia in previous pregnancies (Sibai, 2003). While the overall rate of progression to eclampsia

among pregnant women with hypertensive disorders is approximately 0.8%, this rate may reach 2% in cases of severe and poorly controlled preeclampsia (Overton et al., 2022). In recent years, the increasing incidence of preeclampsia has been accompanied by corresponding increases in maternal and fetal morbidity and mortality. Marked ethnic and regional disparities have also been observed. For example, in the United States, African American women experience both a higher incidence of preeclampsia and a maternal mortality rate approximately three times greater than that of White women (Magley & Hinson, 2022). In Türkiye, preeclampsia and eclampsia are important causes of maternal mortality, being responsible for nearly 17% of maternal deaths and constituting the second most common cause of maternal mortality (Maternal Mortality, 2014).

According to the 2019 guidelines of the National Institute for Health and Care Excellence (NICE), women are considered to be at high risk of developing preeclampsia if they have a history of chronic kidney disease, hypertensive disorders in a previous pregnancy, autoimmune diseases, diabetes mellitus, or chronic hypertension. Moderate-risk factors include nulliparity, a body mass index (BMI) ≥ 35 kg/m², maternal age over 40 years, multiple pregnancy, a family history of preeclampsia, and an interpregnancy interval exceeding 10 years. Women with one high-risk factor or two or more moderate-risk factors should receive aspirin prophylaxis before 16 weeks of gestation to reduce the risk of developing preeclampsia. The pathogenesis of preeclampsia is complex and multifactorial, with a wide range of risk factors reported in the literature. These include elevated mean arterial blood pressure before 15 weeks of gestation, respiratory disorders such as obstructive sleep apnea, polycystic ovary syndrome, periodontal disease, urinary tract infections, and microbial agents such as *Helicobacter pylori*, all of which have been associated with

an increased susceptibility to preeclampsia. Furthermore, certain obstetric and reproductive factors, including vaginal bleeding lasting at least five days during pregnancy, oocyte donation, and the use of assisted reproductive technologies such as in vitro fertilization (IVF), have been linked to an elevated risk of preeclampsia (Fox et al., 2019).

To facilitate early diagnosis and risk stratification, considerable research has focused on biochemical and ultrasonographic markers. In this context, maternal genotypes and fetal molecular markers detected in maternal blood, particularly cell-free fetal deoxyribonucleic acid (cfDNA), have emerged as promising indicators for predicting the risk of preeclampsia development (McGinnis et al., 2017).

Pathophysiology of Preeclampsia

Preeclampsia can be classified into two major subtypes that differ in their etiological and phenotypic characteristics: early-onset (placental) preeclampsia and late-onset (maternal) preeclampsia (Nirupama et al., 2021). Early-onset preeclampsia is primarily associated with defective placentation. Histopathological examination of preeclamptic placental tissue reveals placental hypoperfusion resulting from inadequate trophoblastic invasion, accompanied by extensive placental infarctions, arterial sclerosis, and placental ischemia (Goswami, et al., 2006). In contrast, maternal (late-onset) preeclampsia develops despite the presence of a structurally normal placenta and is largely attributed to the interaction of maternal susceptibility factors that promote microvascular injury. Maternal endothelial dysfunction plays a central role in this mechanism. Because minimal or no abnormalities are observed in the spiral artery remodeling process, placental perfusion is generally preserved in late-onset disease.

This relatively maintained uteroplacental circulation allows the implementation of expectant (conservative) management strategies until 37 weeks of gestation in appropriately selected patients (Dionisio & Favero, 2024).

Maternal Effects of Preeclampsia

Early maternal complications of hypertensive disorders of pregnancy include cerebrovascular events such as intracerebral hemorrhage and seizures, as well as cardiovascular and renal complications. Women with pre-existing chronic hypertension who develop end-organ damage during pregnancy are at increased risk of pulmonary edema, hypertensive encephalopathy, retinopathy, cerebral hemorrhage, and acute kidney injury. The major acute maternal complications associated with hypertensive disorders of pregnancy are summarized in Table 1.

Table 1. Acute Maternal Complications of Hypertensive Disorders of Pregnancy

Organ Sistemi	Klinik Belirti ve Semptomları
Cardiovascular	Hypertension, pulmonary edema, reduced cardiac output
Renal	Decreased glomerular filtration rate, proteinuria, cortical necrosis
Hepatic (HELLP syndrome)	Elevated liver enzymes, hepatic dysfunction, subcapsular hematoma, hepatic rupture
Central Nervous System	Cerebral hemorrhage, headache/blurred vision, scotoma, cortical blindness, Posterior Reversible Encephalopathy Syndrome (PRES), seizures

References: (Kattah & Garovic, 2013).

It is inaccurate to regard preeclampsia as a disease that is completely cured following delivery. Substantial evidence indicates that women with a history of preeclampsia remain at increased risk for long-term adverse health outcomes, even years after pregnancy. Whether these long-term sequelae result from persistent endothelial injury caused by preeclampsia itself or from shared pre-existing risk factors that predispose women to future organ damage remains a subject of ongoing debate. Nevertheless, experimental animal studies have demonstrated that preeclampsia may induce the expression of specific proteins associated with vascular disease, atherosclerosis, and persistent inflammatory responses in the postpartum period. These findings suggest that preeclampsia is not merely a condition that unmasks underlying chronic susceptibility, but rather an independent pathological process capable of causing lasting vascular injury (Bajpai, 2020).

Effects of Preeclampsia on the Fetus and Newborn

Preeclampsia substantially increases the risk of both short- and long-term perinatal and neonatal complications, particularly neonatal mortality (Table 2). These adverse outcomes are largely influenced by birth weight and gestational age at delivery. Consequently, the majority of these complications are considered to be primarily associated with the placental dysfunction and prematurity characteristic of early-onset preeclampsia.

Table 2. Short-Term and Long-Term Perinatal and Neonatal Complications Associated with Preeclampsia

Short-Term Complications	Long-Term Complications
Fetal growth restriction	Hypertension
Preterm birth	Diabetes mellitus
Intrauterine fetal death	Hearing impairment

Requirement for neonatal intensive care unit (NICU) admission	Coronary artery disease
Non-reassuring fetal heart rate patterns during labor	Insulin resistance
Oligohydramnios	Reduced intelligence quotient (IQ)
Low Apgar score	Visual impairment and cerebral palsy

References: (Poon et al., 2019).

The increased risk of adverse neonatal outcomes in pregnancies complicated by preeclampsia is primarily attributable to placental insufficiency, chronic fetal hypoxia, and the need for medically indicated preterm delivery. Neonates born to affected mothers frequently require intensive care support and are more likely to experience respiratory, neurological, and metabolic complications during the early postnatal period. Furthermore, accumulating evidence suggests that exposure to an adverse intrauterine environment may have lasting consequences on cardiovascular, metabolic, and neurodevelopmental health, extending well into childhood and adulthood.

Diagnosis and Monitoring of Preeclampsia

Contemporary approaches to the diagnosis of preeclampsia extend beyond conventional blood pressure measurements and urinalysis, focusing increasingly on specific blood biomarkers and Doppler ultrasonographic assessments that facilitate the early detection of organ dysfunction (Sharma et al., 2024).

Current diagnostic criteria classify preeclampsia into preeclampsia without severe features and preeclampsia with severe features, thereby enabling more effective clinical management. Preeclampsia without severe features is characterized by the onset of hypertension after 20 weeks of gestation, defined as blood

pressure $\geq 140/90$ mmHg on at least two measurements obtained at least four hours apart, accompanied by edema ($>1+$) and proteinuria exceeding 0.3 g in a 24-hour urine collection. Severe preeclampsia is indicated by blood pressure $\geq 160/110$ mmHg on two measurements at least four hours apart and proteinuria exceeding 5 g per 24 hours. Additionally, severe preeclampsia may be diagnosed in the presence of one or more of the following findings: serum creatinine >1.2 mg/dL, intrauterine growth restriction, oligohydramnios, elevated liver enzyme levels, persistent headache, visual disturbances, epigastric pain, retinal hemorrhage or papilledema, pulmonary edema, and oliguria (Doğan Yüksekol & Başer, 2019). The diagnostic criteria for preeclampsia established by the American College of Obstetricians and Gynecologists (ACOG) are summarized in Table 3.

Table 3. ACOG Diagnostic Criteria for Preeclampsia

Hypertension	Preeclampsia	Preeclampsia with Severe Features
	New-onset systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg after 20 weeks of gestation in a previously normotensive woman, confirmed on two measurements at least four hours apart	SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on two measurements at least four hours apart (in the absence of antihypertensive treatment)
And		
Proteinuria	≥ 300 mg protein in a 24-hour urine collection, or protein/creatinine ratio ≥ 0.3 mg/dL, or urine dipstick reading of $\geq 1+^*$	—

Or, in the absence of proteinuria, new-onset hypertension accompanied by one of the following:		
Thrombocytopenia	Platelet count <100,000/ μ L	
Renal insufficiency	Serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration in the absence of other renal disease	
Impaired liver function	Elevated liver transaminases (ALT, AST) to at least twice the upper limit of normal	Persistent severe right upper quadrant pain or treatment-resistant epigastric pain, with or without elevated liver enzymes
Neurological and visual disturbances		New-onset cerebral or visual symptoms
*Urine dipstick testing should be used only when other quantitative methods are unavailable.		

References (ACOG, 2013).

In modern obstetric practice, several advanced screening tools have been developed to improve the early identification of women at risk for preeclampsia (Sharma et al., 2024). Commonly utilized screening methods include uterine artery Doppler ultrasonography, assessment of angiogenic biomarkers through the soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio, and integrated screening models endorsed by international organizations such as the Fetal Medicine Foundation and the International Federation of Gynecology and Obstetrics. Uterine artery Doppler ultrasonography is a completely non-invasive imaging technique that evaluates placental perfusion by measuring uteroplacental blood flow. In normal pregnancies, uterine arteries undergo physiological remodeling, resulting in

decreased vascular resistance. In contrast, pregnancies complicated by preeclampsia exhibit impaired vascular remodeling, leading to increased resistance indices, elevated pulsatility index (PI) and resistance index (RI) values, and the presence of characteristic early diastolic notching. During the first trimester (11–13+6 weeks of gestation), combining uterine artery pulsatility index (UtA-PI) measurements with maternal mean arterial pressure can identify approximately 75% of cases destined to develop preterm preeclampsia. Furthermore, high-resistance flow patterns detected during the second trimester (18–24 weeks) have been reported to predict early-onset preeclampsia with a sensitivity approaching 96%. Another important diagnostic tool is the sFlt-1/PlGF ratio, which reflects the angiogenic imbalance characteristic of preeclampsia. Reduced circulating levels of PlGF, a proangiogenic factor, together with elevated levels of the antiangiogenic factor sFlt-1, are strongly associated with disease development. This biomarker assay is especially valuable in cases where preeclampsia is suspected but clinical findings are not definitive, by improving diagnostic accuracy, this approach may also contribute to reducing unnecessary hospital admissions. Currently, screening strategies based on combined prediction models are considered the most effective method for risk assessment.. Rather than relying on a single test, these algorithms integrate maternal demographic characteristics and medical history, mean arterial pressure, uterine artery Doppler measurements, and biochemical markers into a comprehensive risk assessment. The Fetal Medicine Foundation (FMF) screening model has demonstrated the ability to predict preterm preeclampsia with an accuracy approaching 90% during early pregnancy, making it one of the most powerful tools available for early risk stratification and preventive intervention (What Is Preeclampsia, 2026).

Current Treatment and Management Approaches for Preeclampsia

Non-Pharmacological Management of Preeclampsia;The management of preeclampsia can be broadly divided into non-pharmacological and pharmacological approaches. Although non-pharmacological interventions alone cannot treat preeclampsia, they play a supportive role in blood pressure control, risk reduction, and the preservation of maternal and fetal health. These preventive and supportive strategies should be implemented through a holistic approach beginning before conception, continuing throughout pregnancy, and extending after the diagnosis of preeclampsia has been established (Widiasih, et al., 2024). From a nutritional perspective, dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet have been associated with a reduced risk of preeclampsia. To optimize antioxidant and dietary fiber intake, pregnant women are encouraged to consume at least 400 g of fresh fruits and vegetables daily, incorporate green leafy vegetables into their diet, and prioritize healthy fat sources such as olive oil, nuts, and avocados. In addition, consumption of omega-3-rich fish, including salmon, at least twice weekly is recommended. Conversely, processed foods, packaged industrial products, and foods high in sodium and saturated fats should be avoided due to their potential adverse effects on cardiovascular and metabolic health (What Is Preeclampsia and Why Is It Important, 2025).

Maternal obesity and elevated body mass index (BMI) are recognized as independent risk factors for the development of preeclampsia. Therefore, attaining and maintaining a healthy body weight prior to pregnancy is considered an important preventive measure. During pregnancy, provided that no medical contraindications such as threatened preterm labor or vaginal bleeding are present, regular physical activity—including walking

and prenatal yoga—may improve uteroplacental blood flow and reduce systemic inflammation. Furthermore, studies have demonstrated that regular stretching exercises may contribute to reductions in arterial blood pressure (Perry et al., 2022). Psychological well-being and stress management may also influence the pathophysiological processes associated with preeclampsia. Accordingly, relaxation techniques such as progressive muscle relaxation, deep-breathing exercises, autogenic training, and meditation are frequently recommended to help reduce stress and anxiety levels during pregnancy (Widiasih, et al., 2024). Maternal positioning represents another supportive measure. During periods of rest or sleep, the left lateral position is generally recommended because it minimizes uterine compression of the inferior vena cava, thereby enhancing blood flow to the kidneys, placenta, and fetus. Improved venous return and uteroplacental perfusion may contribute to reductions in edema and blood pressure levels (Nadeem et al., 2025). In addition, harmful lifestyle habits such as tobacco smoking and alcohol consumption should be completely avoided throughout pregnancy. Both smoking and alcohol exposure are associated with endothelial dysfunction, impaired placental perfusion, and an increased risk of adverse maternal and fetal outcomes (Nadeem et al., 2025). It is important to emphasize that these non-pharmacological interventions should not be considered substitutes for medical treatment. Rather, they serve as complementary measures that support overall disease management. Consequently, pregnant women should be encouraged to perform regular home blood pressure monitoring and seek immediate medical attention if warning signs of severe preeclampsia develop, including severe headache, visual disturbances, epigastric or right upper quadrant pain, or other symptoms suggestive of disease progression.

Pharmacological Treatment of Preeclampsia; The only definitive treatment for preeclampsia is delivery of the placenta, that is, termination of the pregnancy through childbirth. Contemporary management strategies focus on balancing maternal safety with fetal maturity by controlling maternal symptoms and determining the optimal timing of delivery. Preventive interventions are particularly important in women at high risk of developing preeclampsia. Evidence suggests that administering low-dose aspirin (up to 150 mg/day) between 12 and 16 weeks of gestation can significantly decrease both the risk and severity of preeclampsia. In addition, daily calcium supplementation is recommended, particularly for women with inadequate dietary calcium intake (Sharma et al., 2024).

Antihypertensive Therapy; Current guidelines for the management of hypertension in preeclampsia recommend methyldopa as a preferred first-line agent, administered orally at a dose of 0.5–3 g/day. Methyldopa acts centrally on alpha-adrenergic receptors, reducing sympathetic outflow through inhibition of norepinephrine release. An important alternative is labetalol, which is administered orally in divided doses ranging from 200 mg to 1.2 g/day. Labetalol blocks both alpha- and beta-adrenergic receptors and generally produces a more rapid antihypertensive effect than methyldopa. Extended-release nifedipine is another commonly used antihypertensive agent and is typically administered orally at doses of 10–30 mg/day. As a calcium channel blocker, nifedipine is preferred in its sustained-release formulation because short-acting preparations may adversely affect uteroplacental blood flow. Hydralazine, a potent direct vasodilator, is generally reserved for hypertensive emergencies or refractory hypertension and may be administered intravenously as a 5 mg dose infused slowly over 1–2 minutes, with subsequent dosing adjusted according to clinical response. Second-line antihypertensive agents include clonidine

(0.1–0.6 mg/day orally), hydrochlorothiazide (12.5–25 mg/day orally), nicardipine (3–9 mg/hour intravenously), and sodium nitroprusside (0.25–5 µg/kg/min intravenously) (Odigboegwu et al., 2018; Podymow & August, 2008). Alternative pharmacological options include verapamil, diazoxide, prazosin, and oxprenolol.

Because of their well-established teratogenic and fetotoxic effects, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists such as spironolactone should not be used during pregnancy (30). The National High Blood Pressure Education Program (NHBPEP) additionally recognizes sustained-release nifedipine, beta-blockers (excluding atenolol), and selected diuretics as acceptable therapeutic alternatives (Brown & Garovic, 2014).

Magnesium Sulfate Therapy in Severe Preeclampsia; Eclampsia is one of the most serious complications of preeclampsia, and antihypertensive medications alone are insufficient to prevent seizure development. For this reason, magnesium sulfate (MgSO_4) is administered because of its well-established neuroprotective and anticonvulsant properties. Although magnesium sulfate is not primarily considered an antihypertensive agent, it remains the standard of care for seizure prophylaxis in women with severe preeclampsia and for the treatment of eclamptic seizures. The American College of Obstetricians and Gynecologists (ACOG) recommends magnesium sulfate primarily for women with preeclampsia accompanied by severe features. These include severe hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on two occasions at least four hours apart), thrombocytopenia, impaired liver function, pulmonary edema, persistent headache unresponsive to medication, and new-onset visual disturbances. Magnesium sulfate exerts its therapeutic effects through multiple

mechanisms within the central nervous system, including modulation of acetylcholine receptors, N-methyl-D-aspartate (NMDA) receptors, and calcium channels. Furthermore, it contributes to stabilization of the blood–brain barrier, reduces cerebral edema, and promotes vasodilation within both cerebral and peripheral vascular beds (Chappell et al., 2019). Numerous studies have demonstrated its superiority over alternative anticonvulsants such as phenytoin, diazepam, and nimodipine in preventing recurrent seizures.

Standard magnesium sulfate therapy begins with a loading dose of 4–6 g administered intravenously over 20–30 minutes using an infusion pump. This is followed by a continuous maintenance infusion of 1–2 g/hour, which is typically continued until 24 hours postpartum. Throughout treatment, close bedside monitoring is essential because of the risk of magnesium toxicity. Clinical signs of hypermagnesemia correlate with serum magnesium concentrations. Loss of the patellar reflex generally occurs at concentrations of approximately 8–10 mEq/L, while respiratory paralysis may develop when levels exceed 13 mEq/L. At excessively elevated concentrations, the risk of cardiac arrest increases, potentially resulting in a life-threatening outcome (Chappell et al., 2019).

Emerging and Experimental Therapies; In addition to conventional treatment strategies, several experimental therapies are currently being investigated with the aim of modifying the underlying pathophysiology of preeclampsia. These novel approaches focus on restoring angiogenic balance, improving endothelial function, and reducing oxidative stress and inflammation. Investigational therapies include modulation of angiogenic pathways, nitric oxide donors, regulation of carbon monoxide-mediated protective mechanisms, hydrogen sulfide (H₂S) donors, and statins, which have demonstrated potential

endothelial-protective effects in preclinical and early clinical studies (Dickerson et al., 2025). Although these approaches remain experimental, they represent promising avenues for future targeted therapies in the management of preeclampsia.

Timing and Mode of Delivery in Preeclampsia

The only definitive treatment for preeclampsia is termination of pregnancy through induction of labor or cesarean delivery. According to current clinical guidelines, delivery at 37 weeks of gestation is generally recommended for women with preeclampsia who do not exhibit severe features. According to the American College of Obstetricians and Gynecologists (ACOG), management strategies should be individualized based on gestational age, disease severity, maternal condition, and fetal well-being (32). For pregnancies complicated by preeclampsia before 34 weeks of gestation, expectant management may be considered in carefully selected patients. While prolongation of pregnancy may provide significant fetal benefits by improving fetal maturity and reducing complications associated with prematurity, this approach must be balanced against the increased maternal risks associated with severe disease progression. Therefore, decisions regarding the timing of delivery should be based on a comprehensive assessment of maternal and fetal status and the presence of factors that may necessitate immediate delivery (Chappell et al., 2019;Euser & Cipolla, 2009).

Once the decision to deliver has been made, determining the optimal mode of delivery becomes another important consideration. One of the principal factors influencing this decision is cervical favorability, commonly assessed using the Bishop score. Studies have demonstrated that induction of labor in women with an unfavorable cervix is associated with higher rates of failed induction, prolonged labor, and conversion to cesarean delivery

(Chappell et al., 2019). When maternal condition remains stable, the cervix is favorable, and fetal growth and well-being are reassuring, labor induction represents an appropriate and often preferred option. In carefully selected women with severe preeclampsia at or before 34 weeks of gestation, induction of labor may represent a suitable alternative, as successful vaginal delivery is often achievable. The Bishop score at hospital admission has consistently been identified as one of the strongest predictors of successful vaginal delivery. Furthermore, the likelihood of successful labor induction generally increases with advancing gestational age (Griffin & Shennan, 2014). Evidence suggests that planned delivery, rather than prolonged expectant management, may reduce maternal complications and decrease the incidence of severe hypertension. However, planned delivery is also associated with increased rates of neonatal intensive care unit (NICU) admission due to prematurity. Importantly, available data do not indicate that this increase in NICU admissions results in higher rates of long-term neonatal morbidity or permanent adverse health outcomes.

Nursing Care and Patient Education; The primary goal of nursing care in women diagnosed with preeclampsia is to prevent progression to eclampsia, reduce the risk of maternal and fetal mortality, and facilitate early recognition of clinical deterioration. In addition to close clinical monitoring, patient education constitutes a fundamental component of comprehensive nursing management. Pregnant women should be thoroughly educated about the signs and symptoms that may indicate disease progression, including severe headache, visual changes, epigastric or right upper abdominal pain, sudden onset edema, reduced fetal movements, and manifestations of severe hypertension. Education should also emphasize the importance of self-monitoring, adherence to prescribed treatment plans, and attendance at

scheduled prenatal visits. Promoting patient awareness and encouraging timely medical evaluation when warning signs occur are essential strategies for improving maternal and neonatal outcomes in pregnancies complicated by preeclampsia (Doğan Yüksekol & Başer, 2019).

Conclusion

Preeclampsia remains one of the most complex pregnancy-specific disorders, exerting profound multisystem effects on both the mother and the fetus through mechanisms involving endothelial dysfunction and placental insufficiency. From a maternal perspective, the disease is associated not only with life-threatening acute complications such as eclampsia, HELLP syndrome, stroke, and acute kidney injury, but also with an increased long-term risk of cardiovascular and metabolic disorders. These findings highlight that preeclampsia should not be regarded merely as a pregnancy complication but rather as a condition with lasting implications for women's health. For the fetus, reduced uteroplacental perfusion is directly associated with fetal growth restriction, oligohydramnios, placental abruption, and adverse outcomes related to medically indicated preterm delivery. Consequently, preeclampsia remains a major contributor to perinatal morbidity and mortality worldwide. Despite considerable advances in obstetric care, delivery of the fetus and placenta remains the only definitive cure for preeclampsia. Nevertheless, contemporary obstetric practice increasingly focuses on early prediction, risk stratification, and preventive interventions. Early identification of high-risk pregnancies through first-trimester screening programs and the initiation of low-dose aspirin prophylaxis before 16 weeks of gestation represent the most effective evidence-based strategies currently available for reducing the incidence of preeclampsia. Current clinical management aims to stabilize maternal hemodynamics through antihypertensive therapy, prevent seizures

and provide neuroprotection through magnesium sulfate administration, and promote fetal lung maturation with antenatal corticosteroids when preterm delivery is anticipated. The fundamental objective is to maintain an optimal balance between maternal and fetal well-being while determining the most appropriate timing of delivery. Accordingly, delivery is generally recommended at 37 weeks of gestation for women with preeclampsia without severe features, at or beyond 34 weeks for those with severe disease, and immediately regardless of gestational age when maternal or fetal life is threatened. Ultimately, successful management of preeclampsia depends on early risk assessment, continuous maternal and fetal surveillance, multidisciplinary collaboration, and adherence to current evidence-based clinical guidelines.

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