Adv Gen Pract Med, 2025, 6(1): 120-133
DOI: 10.25082/AGPM.2024.01.003

RESEARCH ARTICLE

Breast Density and Volume Changes During the Menstrual Cycle

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Received: April 14, 2025;
Accepted: June 19, 2025;
Published: June 24, 2025.

Citation: Dillard T, Jones J, Bernard B, et al. Breast Density and Volume Changes During the Menstrual Cycle. *Adv Gen Pract Med*, 2025, **6**(1): 120-133. https://doi.org/10.25082/AGPM.2024.01.003

Abstract: This paper explores the dynamic changes in breast moisture content in relation to hormonal fluctuations throughout the menstrual cycle, emphasizing the role of estrogen and progesterone in influencing breast physiology. The menstrual cycle is divided into four phases: menstrual, follicular, ovulatory, and luteal, each of which elicits measurable variations in breast volume, density, and moisture due to hormone-driven tissue remodeling and fluid retention. Estrogen predominates in the follicular phase, promoting ductal proliferation and mild fluid accumulation, while the luteal phase is characterized by a significant rise in progesterone, resulting in marked stromal edema, increased glandular development, and heightened fluid retention. These hormonal changes are mediated through the renin-angiotensin-aldosterone system (RAAS) and vasopressin pathways, which contribute to systemic and localized water retention, especially within breast tissue. The paper synthesizes hormonal biochemistry, breast anatomy, and biomechanical modeling to examine how these cyclic changes impact breast density and volume, with clinical implications for breast tenderness, mammographic sensitivity, and cancer screening. Imaging data and statistical analyses reveal a consistent pattern of increased breast density and volume during the luteal phase. Understanding these cyclical changes enhances the ability to anticipate breast-related symptoms, improve diagnostic timing, and personalize care, particularly for women with dense breast tissue or hormone-sensitive conditions.

Keywords: breast density changes, breast volume, breast development, estrogen during menstrual cycle, progesterone and menstrual cycle

1 Introduction

The breasts are a vital and intricate part of a woman's body serving as a source of nourishment and a symbol of confidence. However, they often require varied levels of support, particularly based on overall size and strain on the body. Breasts vary in size, shape, and position, and they can also change over time. Factors such as weight fluctuations, the menstrual cycle, pregnancy, and aging can all influence their size and shape. It is important to know the makeup of the breasts in order to understand how different cells, hormones, and biological processes affect the physical and mechanical function of the breasts.

Water comprises approximately 50-70% of the breast tissue and plays an essential role due to the spatial arrangement of the water molecules and the impact of metabolism within the tissue [1]. In addition to water, glandular epithelial tissue combined with other epithelial layers forms the foundation of breast composition. For most individuals, the breast composition is 70% adipose tissue and 30% glandular tissue [2]. Figure 1 highlights this anatomic composition in more detail.

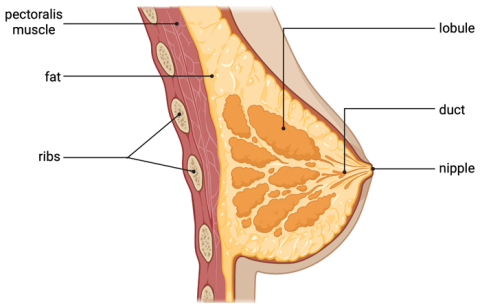

Figure 1 The anatomy of the breast [21]

These components enable the breast size to fluctuate in response to the cyclical hormonal changes that occur during a woman's menstrual cycle, particularly those involving estrogen and progesterone. These hormones play multiple roles, including regulating the stimulation and inhibition of luteinizing hormone (LH) and follicle stimulating hormone (FSH), essential gonadotropins that drive various changes throughout the menstrual cycle. To fully comprehend the variations in breast size over time, it is important to examine how these hormones relate to the cyclical changes in breast volume and density that occur at specific stages of the menstrual cycle.

2 Menstrual Cycle

2.1 Follicular Phase

The menstrual cycle is divided into two phases: the follicular phase and the luteal phase. The follicular phase encompasses the first half of the menstrual cycle and ends with ovulation, with its length varying based on the individual—typically 14 days for a 28-day cycle or 18 days for a 32-day cycle.

Estrogen is secreted by the ovarian follicles during the follicular phase of the menstrual cycle. Inhibin, a hormone produced by granulosa cells within the ovaries, is released continuously, with peaks occurring during the mid-cycle and mid-luteal phases. Both estrogen and inhibin exert negative feedback on the hypothalamic-pituitary-ovarian (HPO) axis, specifically reducing the secretion of FSH and LH from the anterior pituitary gland.

FSH stimulates follicular growth in the ovaries, while LH promotes hormone production and plays a crucial role in triggering ovulation. The secretion of FSH and LH is regulated by gonadotropin-releasing hormone (GnRH), a hormone released in pulses from the hypothalamus. GnRH acts on the anterior pituitary to stimulate the synthesis and release of FSH and LH.

As estrogen levels gradually rise during the follicular phase, they initially continue to suppress FSH and LH via negative feedback. However, once estrogen reaches a critical threshold, it switches to a positive feedback mechanism. This shift increases the pituitary's sensitivity to GnRH, resulting in a surge of LH which triggers ovulation. Ovulation marks the release of a mature oocyte from the dominant follicle, making it available for fertilization. Figure 2 highlights the overall mechanism of these hormones on the menstrual cycle, displaying the shift from negative to positive feedback. The follicular phase encompasses the first half of the menstrual cycle and ends with ovulation, initiated by this LH surge [3, 4].

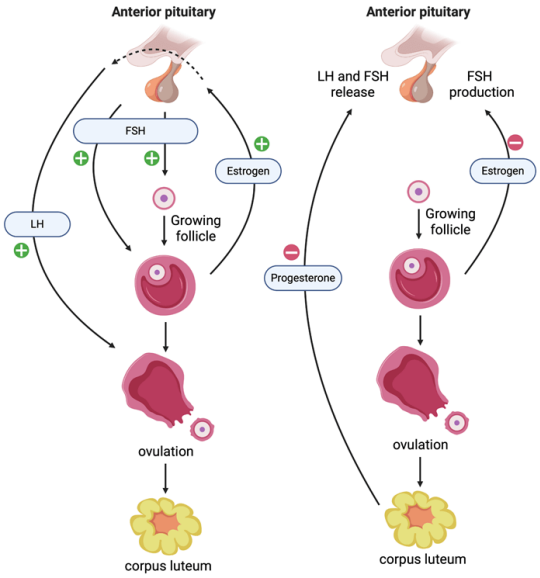

Figure 2 Hormones involved in regulating the menstrual cycle [5]

2.2 Luteal Phase

The luteal phase, however, is fixed at 14 days, starting at ovulation and ending the day before the next menstruation, regardless of the total cycle length. Unlike estrogen, progesterone levels

rise during the luteal phase of the menstrual cycle. Midway through the luteal phase, there is an increase in mitotic activity that is said to be associated with progesterone [2]. Rising progesterone levels inhibit the pulsatile release of GnRH from the hypothalamus leading to increased LH secretion. This mechanism prevents the positive feedback triggered by elevated estrogen levels during the follicular phase [3]. Figure 3 highlights this increase in progesterone in the luteal phase, comparing it to the rest of the ovarian hormones and how they impact folliculogenesis throughout a 28 day menstrual cycle. Additionally, during the luteal phase, there is pronounced stromal edema present, extensive basal cell vacuolization, enlargement of the ductal lumen, and active glandular secretion and venous congestion [6]. During this time, there may be higher background tissue enhancement on imaging and increased parenchymal volume [7].

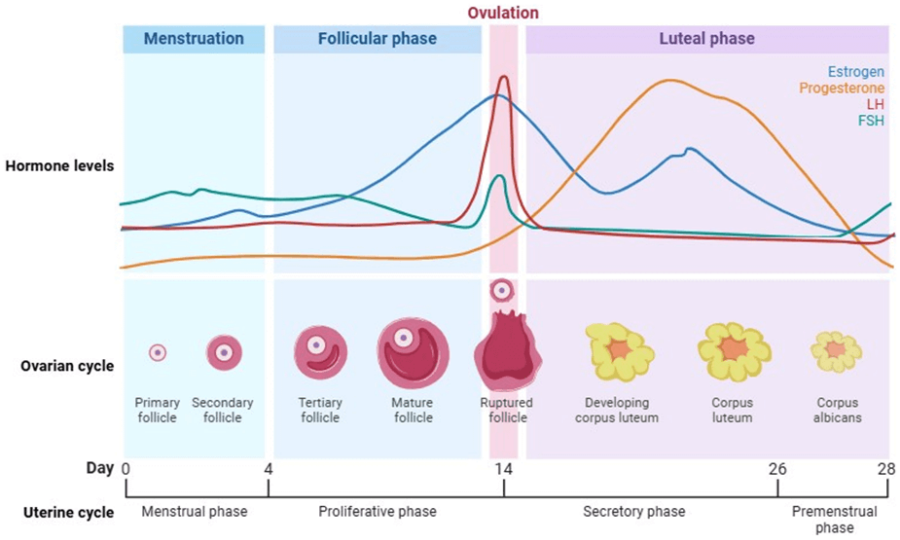

Figure 3 Ovarian Hormones and Folliculogenesis Through the Menstrual Cycle [8]

2.3 Stages of Menstrual Cycle

The menstrual cycle can be divided into four stages across its two phases, each characterized by distinct molecular and histological differences. Stages 1 and 2 fall within the follicular phase. Stage 1 (early follicular phase, Days 0–5) features minimal differentiation between epithelial and myoepithelial layers, round nuclei, sharp luminal borders, and eosinophilic intraluminal secretions, with little edema or stromal infiltrate. During this time, both estrogen and progesterone levels are low, resulting in minimal water retention characterized by minimal distinction between the epithelial layers. Stage 2 (late follicular phase, Days 6–15) is marked by increased distinction between epithelial and myoepithelial layers, basal vacuolation, and well-formed double-layered acini. Estrogen levels rise, promoting water retention via its role in the RAAS system.

Stages 3 and 4 are part of the luteal phase. Stage 3 (early luteal phase, Days 16–24) displays large lobules with distinct terminal duct units, significant basal vacuolations, and intralobular stroma showing increased edema and inflammatory infiltrate. While estrogen-driven water retention persists, progesterone begins to rise, counteracting aldosterone and gradually reducing water retention. Stage 4 (late luteal phase, Days 25–28) is characterized by extensive vacuolation, prominent nuclei, frequent mitotic figures, increased apoptosis, and pronounced stromal edema. High circulating progesterone levels during this stage induce tissue regression via apoptosis, resulting in cellular lysis and the release of intracellular contents, contributing to the observed edema and inflammation [4, 9]. These morphological changes in breast tissue at stages 1-4 are seen in Figure 4.

3 Hormones Impacting Menstrual Cycle

3.1 Estrogen

Estrogen and progesterone work collectively to contribute to cyclical changes in breast volume, density, and functionality. Estrogens are critical hormones in the female body, playing a

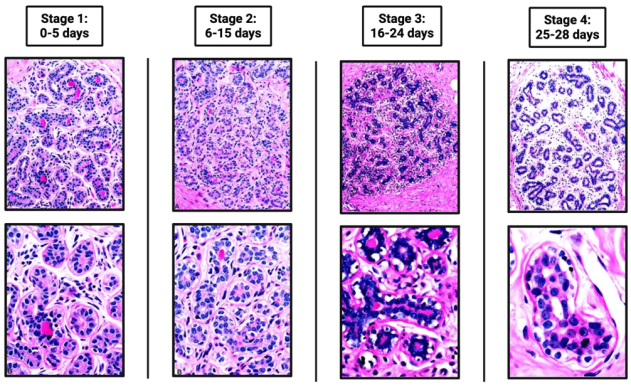

Figure 4 Morphological changes in Breast Tissue [9]

key role in regulating essential physiological processes, including the menstrual cycle. Estrogen has a significant impact on energy metabolism, regulating glucose and lipid metabolism and influencing fat distribution. Estrogen enhances insulin sensitivity and promotes fat storage in subcutaneous tissues. The body naturally produces three types of estrogen: estradiol, estrone, and estriol. The molecular structure of each type of estrogen are seen in Figure 5, 6, and 7, respectively. Estrogens are steroid hormones synthesized from cholesterol, characterized by a cyclopentane-perhydro-phenanthrene backbone consisting of four interconnected rings one cyclohexene ring, two cyclohexane rings, and one cyclopentane ring and 17 carbon atoms [10, 11].

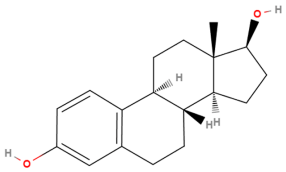

Figure 5 Molecular structure of Estradiol

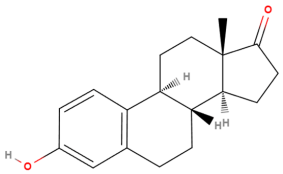

Figure 6 Molecular structure of Estrone

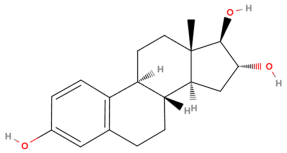

Figure 7 Molecular structure of Estriol

This unique molecular structure contributes to their classification as lipophilic, or fat-soluble, molecules. Biophysical membranes, which are primarily composed of carbon-containing phospholipids, share a similar chemical composition with estrogens. This similarity enhances membrane permeability to estrogens, allowing these small, lipophilic hormones to diffuse efficiently across the lipid bilayer. Once inside the cell, estrogens bind to specific intracellular receptors—either estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ)—located in the cytoplasm. This binding initiates the formation of an activated estrogen-estrogen receptor complex, which undergoes a conformational change. The complex then translocates into the cell's nucleus, where it interacts with specific DNA sequences known as estrogen response elements (EREs). By binding to EREs, the complex regulates the transcription of target genes, thereby influencing a wide range of physiological processes, including cell proliferation, differentiation, and maintenance of reproductive and secondary sexual characteristics [10]. This cellular pathway is depicted in Figure 8.

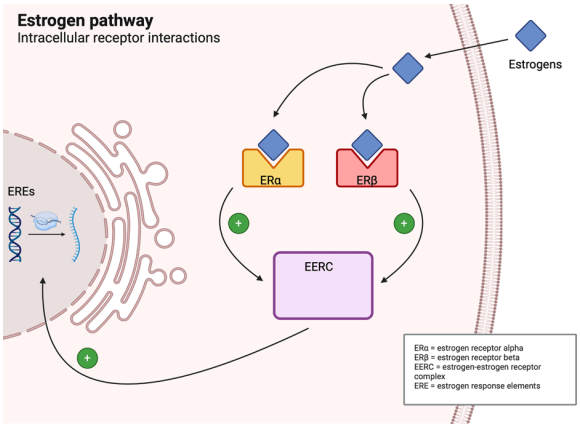

Figure 8 Estrogen Pathway [10]

The widespread distribution of estrogen receptors throughout the body allows estrogens to exert diverse and multifaceted effects on numerous tissues and organ systems. This extensive receptor presence enables estrogens to play a vital role in maintaining physiological homeostasis and regulating essential biological functions.

In pre-menopausal women, estradiol is the most potent estrogen, as it is synthesized directly from the ovaries. It is estimated that circulating estrogen levels tend to fluctuate from 40 to 200 – 400 mcg across the menstrual cycle, with the highest daily production occurring during the follicular phase [11]. Estrone is less potent than estradiol and is produced by peripheral conversion of androgens in peripheral tissues. Estriol, the third type of estrogen, is a peripheral metabolite of estradiol and is primarily significant during pregnancy. However, it is also present in smaller amounts in non-pregnant individuals.

The production of each estrogen is largely influenced by follicular stimulating hormone (FSH), which upregulates the synthesis and activities of steroidogenic enzymes that cleave sex hormones into their biologically active products. Studies show that during the follicular phase, when serum levels of FSH peak, there is also a peak daily production of the two more potent estrogens: estrone and estradiol. Estrone is produced at a rate of 350 mcg per day, while estradiol is produced at a rate of 380 mcg per day. During the late follicular phase, there is an increase in testosterone production at approximately 171 mcg per day, which is converted to estrogen in peripheral tissues via aromatase [4]. The molecular structure and detailed mechanism of the conversion from testosterone to estrogen in shown in Figure 9 and 10, respectively. Figure 11 displays this conversion from a metabolism perspective, depicting the reactions that occur between androgens at each site in the follicle.

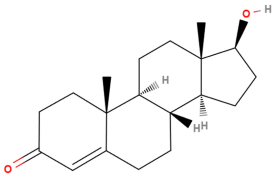

Figure 9 Molecular structure of Testosterone

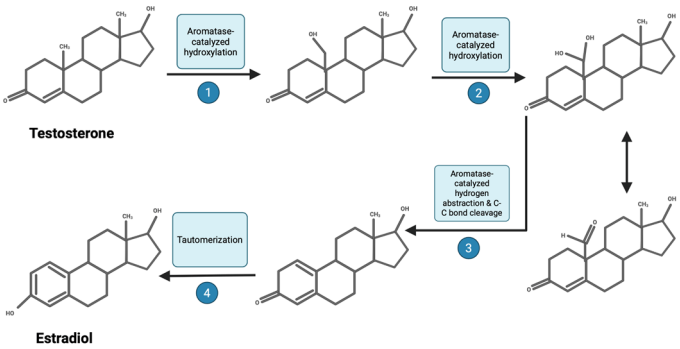

Figure 10 Conversion from testosterone to estradiol

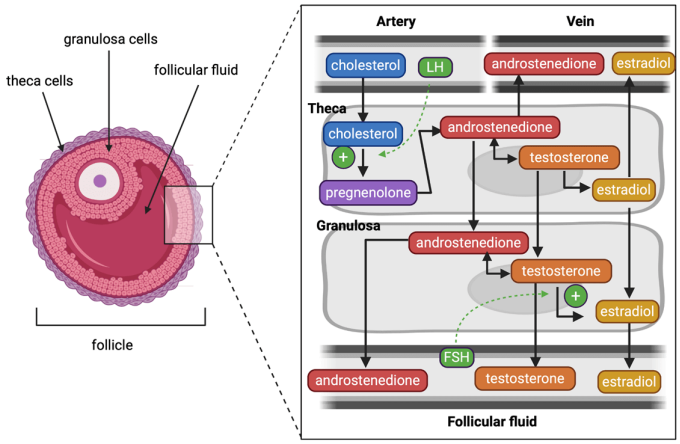

Figure 11 Androgen and estrogen metabolism in the follicle. LH, luteinizing hormone; FSH, follicle-stimulating hormone [38]

3.2 Progesterone

Progesterone is a steroid hormone produced primarily by the corpus luteum in the ovaries during the luteal phase. Like other steroid hormones, progesterone functions by binding to specific intracellular receptors to regulate gene expression and exert its physiological effects. Similar to estrogen, it is synthesized from cholesterol, characterized by a cyclopentane-perhydrophenanthrene backbone. Its chemical formula is $C_{21}H_{30}O_2$, and its molecular structure is displayed in Figure 12.

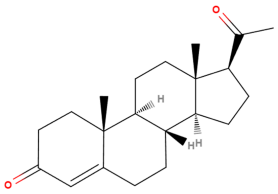

Figure 12 Molecular Structure of Progesterone [20]

Upon entering the cell, progesterone binds to cytoplasmic progesterone receptors (PRs), which then undergo a conformational change. This is followed by receptor dimerization and subsequent translocation of the receptor complex into the nucleus. Once inside the nucleus, the receptor complex binds to specific DNA sequences inducing transcription of target genes.

Progesterone receptors are widely distributed throughout the body and exist in three distinct isoforms: PR-A, PR-B, and PR-C. PR-A and PR-B are the primary functional isoforms. PR-B is the predominant isoform required for mammary gland development while PR-A is mainly associated with uterine development [13]. Notably, studies have demonstrated an antagonistic relationship between PR-A and PR-B. PR-A can inhibit DNA transcription mediated by PR-B and also suppress the activity of estrogen receptors. Upregulation of these receptors within the breast tissue can increase cell proliferation in the mammary gland which in turn increases the number of breast cells in the G2/M phase resulting in an elevated risk of developing breast cancer [13]. Figure 13 characterizes the physiology of different progesterone receptors in the mammary gland.

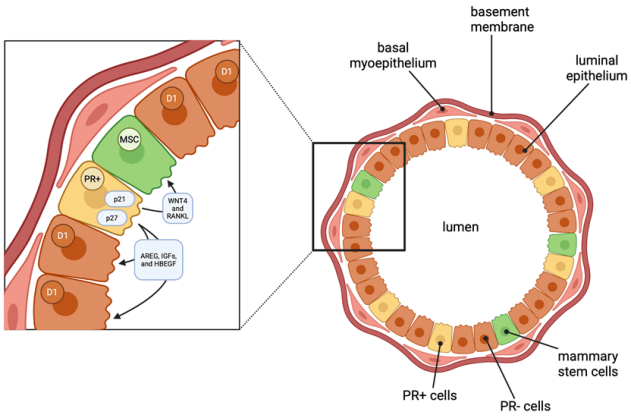

Figure 13 Progesterone Receptors [23]

In reproductive tissues, progesterone plays a critical role in regulating the menstrual cycle, maintaining pregnancy, and preparing the endometrium for implantation. During the luteal phase of the menstrual cycle, progesterone helps transform the endometrium into a secretory state, optimizing conditions for the implantation of a fertilized egg. If pregnancy occurs, progesterone levels remain elevated to support the developing embryo, prevent uterine contractions, and maintain the structural integrity of the endometrium throughout gestation.

Its serum levels fluctuate across the phases of the menstrual cycle, reflecting its dynamic role in reproduction. During the follicular phase, serum progesterone levels remain relatively low, typically below 1.5 ng/mL. After ovulation, progesterone levels rise significantly, peaking at approximately 10–15 ng/mL during the mid-luteal phase, when the hormone is most active in supporting potential implantation and early pregnancy [12]. Unlike estrogen, which is primarily regulated by FSH, progesterone production is largely influenced by LH. After ovulation, LH stimulates the corpus luteum, a temporary endocrine structure formed from the ruptured follicle, to secrete progesterone. During the mid-luteal phase, studies estimate that progesterone is

produced at a daily rate of approximately 25 mg. This production is essential for preparing the endometrium and maintaining early pregnancy should fertilization occur. Progesterone's diverse roles in both reproductive and non-reproductive systems highlight its significance as a key regulator of physiological homeostasis and changes to breast volume, mass and density.

This framework enhances the understanding of hormonal fluctuations at the molecular level and their impact on breast tissue dynamics. Additionally, examining the biomechanical properties, such as mass and volume changes, provides a more comprehensive perspective on the topic.

4 Biomechanical Changes to Breast

4.1 Breast Density

The biomechanics of breast tissue in relation to the menstrual cycle is a complex and intriguing aspect of female physiology, intricately tied to hormonal fluctuations. The breast is composed of three primary types of tissue: glandular tissue, connective tissue, and adipose tissue. These components not only determine the structure and function of the breast but also exhibit dynamic changes throughout the menstrual cycle in response to varying levels of estrogen and progesterone.

Breast density refers to the relative proportion of glandular and connective tissue compared to adipose tissue within the breast [13]. Breast density is typically categorized into four categories: fatty, scattered fibroglandular, heterogeneously dense, and extremely dense. Each category increases the ratio of glandular tissue to fatty tissue with extremely dense breasts having the highest proportion of glandular tissue and the least amount of fatty tissue. High breast density is characterized by a large volume of fibro-glandular tissue relative to breast volume [14].

Women with higher breast density have a greater proportion of glandular and connective tissue, which can affect the biomechanical properties of the breast, including its firmness, elasticity, and overall structure. Hormonal changes during the menstrual cycle significantly influence breast density and associated mechanical properties [13].

4.2 Breast Density and Mammogram

Breast density is typically assessed through mammograms and/or X-rays. The USPTF recommends that all women get screened for breast cancer every other year, starting at age 40 and continuing through age 74 [15]. Recent Food and Drug Administration protocols mandate that all mammogram reports provided to patients must include a breast density assessment. This requirement underscores the significance of breast density as both a diagnostic factor and a potential cancer risk. Younger women generally have more dense breast tissue, which can further reduce the sensitivity of mammograms.

Research has shown that body mass index (BMI) is strongly correlated with breast density. In fact, 53% of women in the lowest BMI quartile had extremely dense breasts, compared to just 5% in the highest BMI quartile [16]. Even after adjusting for BMI, the menstrual cycle phase was found to influence breast density. Among leaner women (BMI below the median), the luteal phase was associated with significantly higher proportions of extremely dense breasts (46% in week 3 and 45% in week 4) compared to the follicular phase (40% in week 1 and 35% in week 2) ($P < 0.01$) [16].

Mammographic sensitivity was found to be higher during the follicular phase (60%) compared to the luteal phase (49%), though the difference did not reach statistical significance [17]. However, the risk of a false-negative result was significantly higher for women undergoing mammograms during the luteal phase, with an adjusted odds ratio of 1.47 ($P = 0.05$) [17].

A smaller proportion of women were found to have "extremely dense" breasts during the follicular phase (24% in week 1 and 23% in week 2) compared to the luteal phase (28% in both weeks 3 and 4) ($P = .04$). This relationship was particularly pronounced in women with a BMI at or below the median, who tend to have the highest breast density ($P < 0.01$) [16]. These images below in Figure 14 to 16 highlight differences in breast glandular volume pre menstruation and during menstruation showing.

4.3 Breast Volume

Breast volume refers to the overall size or mass of the breast, encompassing glandular, connective, and adipose tissues, along with any fluid content. Unlike breast density, which

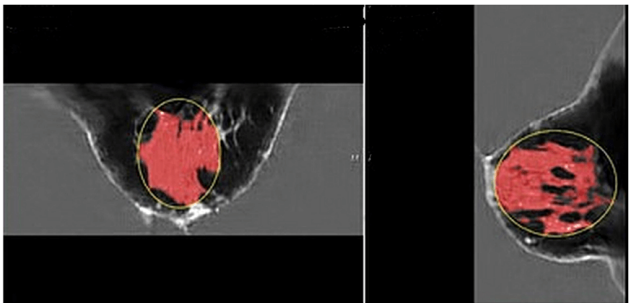

Figure 14 Image taken shows pre-menstrual follicular gland volume in the axial (cranial-caudal; (left)) and sagittal (lateral; (right)) views. The red area is the segmented fibroglandular tissue [18]

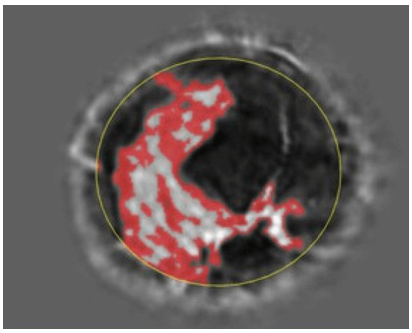

Figure 15 Glandular segmentation before menstruation. The red area is segmented glandular tissue. The lighter the grayscale, the higher the speed of sound. Ductal tissue is shown in light grayscale outside of the red region [18]

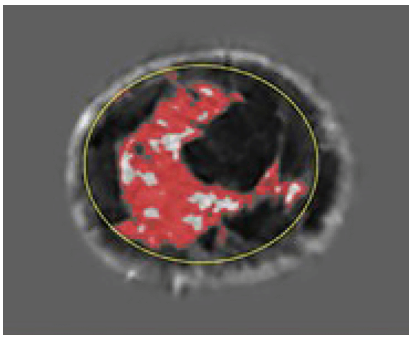

Figure 16 Glandular segmentation on day 1 of menstruation in the same breast as in Figure 4.2.2 showing an increase in glandular volume. The red area is segmented glandular tissue only. The darker region shows fat [18]

is determined by the proportion of different tissue types, breast volume is more significantly influenced by fluid retention and hormonal fluctuations during the menstrual cycle, making it a dynamic measurement. Relative water content showed a strong positive correlation with percent density (Pearson correlation coefficient rp = 0.79, $P < 0.0001$) [19].

Although breast volume is not commonly measured in routine clinical practice, several methods are available to assess it. These include: Archimedes Principle: A water displacement method, Anthropometry: Measurement of external dimensions, Imaging: Techniques like MRI, CT, and 3D ultrasound, Grossman-Roudner Device Method: A volumetric approach using a device to measure the contour and projection of the breast., Casting: Calculating volume from plasters, and Biostereometrics: A three-dimensional scanning method.

Among these methods, imaging techniques, particularly mammography, are regarded as the most accurate for determining breast volume because they provide precise, reproducible, and detailed measurements of internal breast structures. Furthermore, mammograms are widely used as a regular screening tool for breast health, typically initiated at the age of 45, unlike other breast volume measurement methods, which are generally used for specific research or clinical purposes [20].

4.4 Breast Density and Volume throughout the Menstrual Cycle

The menstrual cycle is divided into four main phases: menstruation, the follicular phase, ovulation, and the luteal phase. Each phase influences breast volume and density differently due to fluctuating hormone levels, which impact the structure and composition of breast tissue. Figure 17 highlights the breast density and volume changes throughout the menstrual cycle, emphasizing the importance of hormonal fluctuation.

4.4.1 Menstruation

Breast Volume: During menstruation, breast volume typically remains at baseline or may slightly decrease. This is because hormone levels, including estrogen and progesterone, are at

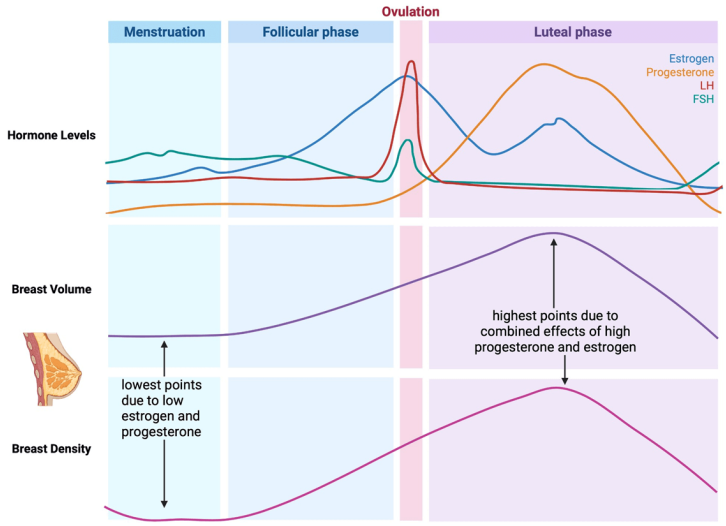

Figure 17 Breast Density and Volume Changes Throughout the Menstrual Cycle [21, 22]

their lowest during this phase, leading to a reduction in fluid retention and minimal stimulation of breast tissue.

Breast Density: Breast density may also be lower during menstruation. The breast tissue is composed of a higher proportion of fatty tissue relative to glandular and connective tissues during this phase, as glandular activity is at its minimum.

4.4.2 Follicular Phase

Breast Volume: As the follicular phase progresses, estrogen levels gradually rise, stimulating the growth and elongation of mammary gland ducts. This hormonal activity leads to an increase in breast volume, and the breasts may feel fuller and slightly tender. The rise in estrogen also promotes an increase in the amount of fluid within the breast tissue. The breast volume is the lowest in the follicular phase where estrogen levels are the highest and breast density is increased [21].

Breast Density: Early in the follicular phase, breast density remains relatively low due to a higher proportion of fatty tissue. However, as estrogen levels increase, breast density begins to rise due to the development of glandular tissue. As ovulation approaches, the surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) enhances glandular activity. During this stage, the breasts may become more sensitive, and their elasticity improves, allowing the tissue to adapt to changes in structure and fluid content.

4.4.3 Ovulation

Breast Volume: Around the time of ovulation, estrogen levels reach their peak, resulting in a further increase in breast volume. The breasts are often at their largest and most tender during this phase, as the heightened estrogen levels stimulate glandular and vascular activity.

Breast Density: Breast density continues to increase during ovulation, primarily due to the influence of high estrogen levels, which promote the expansion of glandular tissue. This phase represents a period of heightened structural and functional activity in the breast.

4.4.4 Luteal Phase

Breast Volume: During the luteal phase, both estrogen and progesterone levels are elevated. Progesterone plays a key role in stimulating the growth of lobular-alveolar structures within the breast. Additionally, progesterone promotes fluid retention, further increasing breast volume. As a result, the breasts feel fuller, heavier, and firmer during this phase, with increased sensitivity and tenderness being common.

Breast Density: Breast density reaches its highest point during the luteal phase due to the combined effects of estrogen and progesterone. The development of glandular tissue is at its peak, and fluid retention contributes to the increase in density. This phase represents the most hormonally active period for breast tissue, as it prepares for potential pregnancy.

Further research has determined that the mean (SD) percent breast density was 35.8% (21.3) in the follicular phase and 36.7% (21.3) in the luteal phase, displayed in Table 1 [22]. The

volume of each breast varies by an average of 76 ml during the menstrual cycle [23]. The cyclic changes in hormone levels lead to increased blood flow and vascular congestion in the breasts, causing them to feel engorged and more sensitive. Studies have demonstrated a positive linear correlation between breast volume and the maximum range of breast volumetric variation, as determined by Pearson's correlation analysis ($r = 0.45$, $p = 0.021$) [23]. On average, breast volume during ovulation is 5.5% lower than the volume measured during menses. Additionally, pre-menses breast volume is, on average, 8.1% greater than the volume recorded during menses [21].

Table 1 The difference in breast density between follicular and luteal phase [22]

	Follicular Phase	Luteal Phase
Density (%)	35.8	36.7

Table 2 highlights this difference in volume and mass in concordance with the changes in estrogen and progesterone throughout both the follicular and luteal phase of the menstrual cycle. In females aged 25 to 45, there is a consistent decline in glandular volume by approximately 25 cc, corresponding to a decrease of 5 cc per every 5-year interval. Concurrently, there is a noticeable increase in breast volume among women within this age range. The relationship between breast density and glandular volume is direct, while the relationship between breast density and breast volume is inverse, given the significant expansion of breast volume during this period. Breast density experiences a reduction from approximately 55% at the age of 25 to around 35% as women reach the age of 45 [14].

Table 2 The numerical differences in volume and mass between progesterone and estrogen during the follicular and luteal phases [22]

	Follicular Phase		Luteal Phase	
	Estrogen	Progesterone	Estrogen	Progesterone
Volume (mcg)	36	1000	250	25000
Mass (mcg)	12.88	358	91.75	9175

Hormonal fluctuations throughout the menstrual cycle lead to dynamic changes in breast volume and density. Estrogen primarily drives increases in breast volume and density during the follicular phase and ovulation, while progesterone adds to these effects during the luteal phase by promoting tissue growth and fluid retention. These changes are temporary and cycle-dependent, reflecting the breast tissue's physiological responsiveness to hormonal signaling. Understanding these dynamics can help individuals better comprehend and manage breast-related discomfort or changes throughout their menstrual cycle. These fluctuations are depicted in Table 3.

Table 3 The median estrogen and progesterone levels throughout each phase of the menstrual cycle [37]

Menstrual Phase	Estrogen (pmol/L)	Progesterone (pmol/L)
Early Follicular	125	380
Intermediate Follicular	172	210
Late Follicular	464	188
Early Luteal	390	22,600
Intermediate Luteal	505	39,200
Late Luteal	396	18,200

5 Sex Hormones and Fluid Retention

The biomechanical changes in breast tissue during the menstrual cycle are not only influenced by hormones but also by water retention. Female sex hormones have a profound influence on fluid metabolism via its effects on the renin-angiotensin-aldosterone-system (RAAS). Studies have shown that estradiol in particular, upregulates RAAS, promoting its water retaining effects [24]. Estradiol is released by the ovaries, which stimulates the liver to synthesize the renin substrate, angiotensinogen. Once this substrate binds to renin, angiotensin I is converted to angiotensin II via the angiotensin converting enzyme (ACE). Angiotensin II is the major vasoconstricting hormone in RAAS that works on the cardiovascular system to increase blood pressure, and stimulates the adrenal glands to release aldosterone which has additional fluid retentive effects. In contrast, progesterone is thought to antagonize RAAS by directly competing

with aldosterone receptors and blunting its effects on the cardiovascular system. Progesterone and aldosterone are steroidal agents that have very similar biomolecular structures that allow them to bind the same mineralocorticoid receptors during the luteal phase [24]. Despite this antagonizing effect, aldosterone levels have been reported to increase during the luteal phase through an unclear mechanism. The molecular structure of aldosterone is depicted in Figure 18.

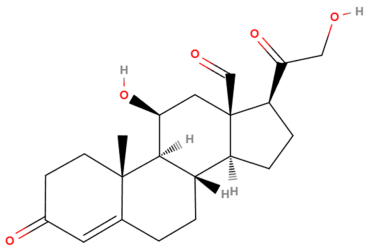

Figure 18 Molecular Structure of Aldosterone [20]

It has been proposed that the increased progesterone production during the luteal phase likely leads to the compensatory activation of the RAAS, thus increasing the overall production of aldosterone [25]. Interestingly, however, the upregulation of RAAS in the setting of elevated serum progesterone is still heavily reliant upon salt intake. Studies have demonstrated that there is a significant increase in serum and urine aldosterone levels in response to angiotensin II in the luteal phase, compared to the follicular phase, among women in high sodium balance [26]. Additionally, an in vitro investigation from the same study was able to show that progesterone, when added to isolated rat ZG cells, caused a 2.8-fold increase in aldosterone production.

Although the exact mechanism remains unclear, some research has been able to pinpoint slight differences in the tubular responses to sodium that occur in the two different phases of the menstrual cycle. A randomized control trial of thirty-five normotensive women prospectively assessed the changes in segmental renal sodium handling that occurs during the menstrual cycle in response to changes in salt intake. Their results showed that in the follicular phase, when estrogen is the highest, an increase in salt intake was not associated with a significant change in renal hemodynamics, an increased fractional excretion of lithium (FELI), and decreased fractional distal reabsorption of sodium (FDRNa) [27]. This data suggests that during the follicular phase, there is a reduction of sodium reabsorption in both the proximal and the distal tubules. In contrast, the luteal phase was associated with a more significant renal response to salt in the distal nephron, though sodium reabsorption by the proximal nephron was unchanged. This study adds more complexity to the nuanced discussion of reproductive hormones and their influence on fluid retention, suggesting that progesterone may play an even more significant role than estrogen on RAAS activation. It is worthwhile to examine how they both influence yet another key component of fluid balance, vasopressin (AVP) release [32].

Despite the limited data available, the increase in estrogenic hormones during the luteal phase is thought to lower the osmotic threshold in which AVP is released [28]. AVP is a nonapeptide hormone that is synthesized in the hypothalamus and secreted from the posterior pituitary gland in response to high plasma osmolarity under normal physiologic conditions. This hormonal response serves to aid the kidneys in their ability to reabsorb water. ADH does this by inducing the expression of aquaporins, which are water transport proteins that work in the distal convoluted tubule (DCT) and the collecting duct of the nephron, in response to osmotic stimuli [32]. Since the luteal phase of the menstrual cycle is thought to require less of an osmotic stimulus to activate the release of AVP, it is reasonable to theorize that serum levels of AVP would be higher during this time, contributing to increased water retention. Further, AVP shares chemical similarities with another vital hormone that is thought to be elevated during the luteal phase, oxytocin. Given its structural similarities, it is likely that this hormone enacts the same physiologic effects on plasma osmolarity as AVP.

6 Discussion

The intricate relationship between breast physiology and the menstrual cycle exemplifies the complexity and adaptability of the female body. Understanding this dynamic interplay not only provides valuable insights into underlying biological processes but also underscores the critical role of hormones in maintaining overall health and functionality. The breast, composed of glandular, connective, and adipose tissues with water comprising 50–70% of its mass, undergoes significant structural and functional changes throughout the menstrual cycle. These changes are driven primarily by the influence of hormones, particularly estrogen and progesterone, which

play pivotal roles in regulating both the menstrual cycle and breast physiology.

Glandular epithelial tissue, which is highly responsive to hormonal signals, enables the breast to undergo cyclical variations in size and shape. During the follicular phase, rising estrogen levels stimulate the growth and elongation of mammary gland ducts, resulting in increased breast volume and density. In contrast, the luteal phase is characterized by elevated levels of both estrogen and progesterone, with progesterone contributing to fluid retention and further development of breast tissue. Notably, studies indicate that breast density peaks during the luteal phase, with an average increase from 35.8% to 36.7%, and an average volumetric increase of 76 mL compared to earlier phases [22, 23]. Estrogen levels increase by approximately sevenfold, while progesterone levels rise by up to twenty-five fold compared to the follicular phase. These hormonal fluctuations are key drivers of the observed changes in breast physiology.

Furthermore, knowledge of fluid retention and hormonal balance during the menstrual cycle can assist in managing symptoms such as breast tenderness, swelling, and discomfort, thereby improving quality of life. Individual variations in breast composition and hormonal responses highlight the importance of personalized approaches to medical care. Tailored treatments and interventions, informed by an individual's unique hormonal profile, can optimize therapeutic outcomes and minimize adverse effects. The molecular and biomechanical aspects of breast physiology provide fertile ground for innovation in medical imaging, diagnostics, and therapeutic techniques. Advancements in imaging technologies, for example, could improve the precision of detecting and characterizing changes in breast tissue associated with both normal physiology and pathology.

Understanding these cyclical patterns carries significant implications for imaging and cancer detection. Mammographic sensitivity is approximately 11% higher during the follicular phase than in the luteal phase, and the likelihood of a false-negative result is significantly greater during the luteal phase, with an adjusted odds ratio of 1.47 (P = 0.05) [17]. These variations reflect not only the influence of hormonal fluctuations but also reinforce the need for menstrual phase aware screening protocols to optimize diagnostic accuracy.

The impact of race on breast composition and hormonal responses represents a critical area for future research, with the potential to address health disparities and improve personalized healthcare approaches. Racial differences in breast density, hormonal levels, and responses to hormonal fluctuations may provide valuable insights into disease risk and tailored interventions. For example, after adjusting for confounders, African Americans have been found to have a higher likelihood of extremely dense breasts [30]. Increased breast density not only poses a significant risk factor for breast cancer but also complicates the ability to accurately detect and rule out true malignancies during mammogram screenings. Therefore, the observed association between density and breast cancer diagnosis may not reflect the relationship between density and disease risk [33]. At an average age of 57 years old, African American women had 32% to 65% higher odds of high breast density when compared to that of white women of the same age group [34]. But when compared to white women, black women had a higher risk of breast cancer death for all tumor subtypes [35].

Early studies from the 1970s reported inferior survival rates among African American and Hispanic women with breast cancer compared to non-Hispanic white women, despite a lower overall incidence of breast cancer among non-white women. Notably, black race has remained an independent predictor of adverse outcomes even after adjusting for other variables [36]. These findings highlight the urgent need for research into racial disparities in breast composition and hormonal influences, which could inform targeted screening programs and preventative measures. Future research focusing on these racial differences is essential to deepen our understanding of breast health and hormonal influences, paving the way for more effective and inclusive healthcare solutions.

Ultimately, the integration of menstrual cycle biology, hormonal profiling, and sociocultural context allows for a more comprehensive approach to breast health. By embracing the complexity of hormonal rhythms and acknowledging population-level differences, clinicians and researchers can better predict risk, tailor screening strategies, and enhance outcomes for diverse patient populations. Continued interdisciplinary research in this domain holds the promise of driving innovation in breast cancer prevention, diagnosis, and care.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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