Adv Gen Pract Med, 2022, 4(1): 54-66
DOI: 10.25082/AGPM.2022.01.004

REVIEW

Etiology of breast development and asymmetry

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Received: June 7, 2022;
Accepted: July 10, 2022;
Published: July 14, 2022.

Citation: Adkins EN, Anderson S, McKoy T, *et al*. Etiology of breast development and asymmetry. *Adv Gen Pract Med*, 2022, **4**(1): 54-66. https://doi.org/10.25082/AGPM.2022.01.004

Abstract: Etiology of breast development and asymmetry is a fascinating research topic physiologically as well as pathophysiology from a certain condition. The shape, contour, and size of the breast are unique to each female. These factors are influenced by genetics, weight, exercise, menstruation cycles, pregnancy, menopause status, and age. An attempt was made to research the breast development at fetal development and transitioning into adulthood and menopause. Additionally, we compare breast development in males to the developments in females. Although breast asymmetry is experienced by all women, it ranges from grossly undetectable to the need for surgical intervention. It is thought that breast asymmetry has intrinsic and extrinsic factors that determine the type and the extent of asymmetry observed. Hormones at play and their effect on breast asymmetry throughout breast development has been charted. Breast asymmetry is most often secondary to benign breast disorders and unassociated with a risk for malignancy. As the perception of one's body image is an integral part of self-confidence, breast asymmetry has the potential to affect every woman's quality of life, regardless of the degree of asymmetry. Throughout this effort, our aim was to analyze and understand breast development in males and females, breast changes from the prepubertal to post-menopausal period, benign pathological changes, summarizing the etiologies of breast asymmetry, and their effects on quality of life.

Keywords: breast asymmetry etiology, quality of life, prenatal breast development, Men's Health, Gynecomastia

1 Introduction

Breasts develop at the same rate until a certain point in life. The way in which the breast develops from gastrulation into puberty into pregnancy/adulthood determines how the breast present overtime. In order to fully understand breast development, one must start at the very beginning: the point of conception. As time goes on, there should be focus on the molecular aspect of development along with the hormonal aspects. Although the focus may be on females, looking at male breast development and how it compares to female breast development is essential and conducted in this paper.

Additionally, almost everyone experiences breast asymmetry in their life. This asymmetry can be mild, moderate, or severe. Breast Asymmetry can also be further divided into subsets with many intrinsic and extrinsic factors leading to the asymmetry. Breast asymmetry can be benign or metastatic, both of which will be discussed in this paper. Ultimately, quality of life is a major factor to keep in mind when it comes to breast development and asymmetry. How someone values their life, based on their appearance, can have mental, psychological, and physicals effects. All of which are necessary to understand in order to purpose solutions and interventions to improve one's quality of life.

2 Breast development

2.1 Prenatal breast development

Prenatal breast development encompasses two tasks: the creation of the primary mammary bud and the development of the mammary gland [1]. This development is largely regulated by the interaction between the epithelium and surrounding mesenchyme [2]. It's unclear whether the mesenchyme or the epithelium induce breast development first; however, these interactions are vital to ensure proper development of the functional units of mammary tissue [2].

2.1.1 First trimester: 0 – 14+6 weeks

Within the first six weeks of gestation, breast development begins [1]. Epithelial cells of the thoracic region proliferate, and extend between the axilla and inguinal region, forming mammary crest or milk lines by day 35 [1]. Eventually, only the mammary crest along the fourth intercostal space should remain, with all other mammary crest atrophying [3]. Failure of mammary crest atrophy will lead to supernumerary nipples anywhere along the axilla to the inguinal line [3]. (see Figure 1)

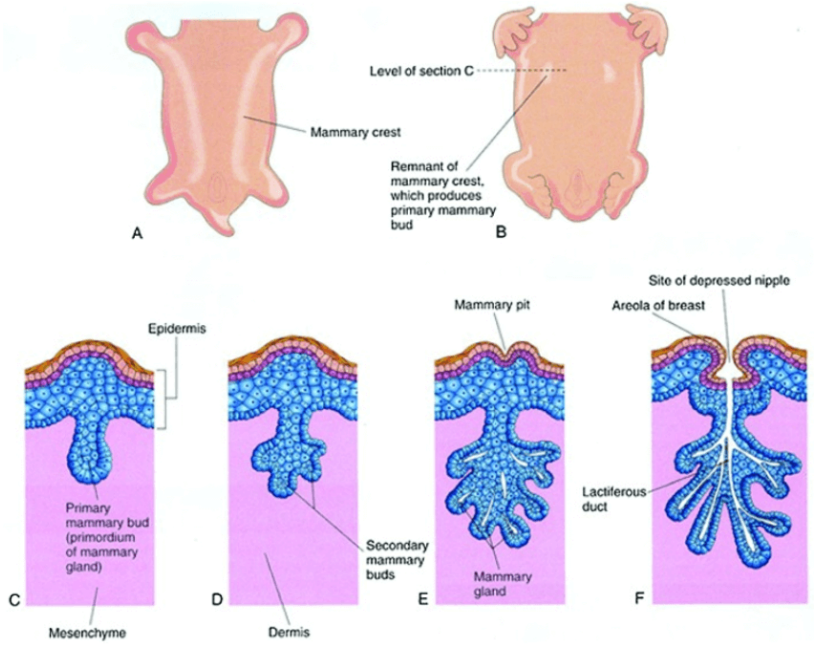


Figure 1 Primary buds form throughout first trimester. Secondary buds fully formed by completion of second trimester. Mammary pit formed throughout third trimester [4]

As the primary bud grows, the underlying mesenchyme secretes regulatory factors which induce downward growth of the primary bud [2]. Indentation's form along the basolateral margin of the primary bud, which will later become secondary mammary outgrowths [5]. Collagenous mesenchyme continues to surround the primary mammary bud throughout this time [1].

By fourteen weeks gestation, a defined mammary bud will penetrate the upper dermis, and the epithelium is divided into the central and basal cells [5]. Mesenchymal cells are now differentiated into the functional cells of the mammary bud – fibroblast, smooth muscle cells, capillary endothelial cells, and adipocytes [5].

2.1.2 Second trimester: 15 – 27+6 weeks

As secondary mammary buds continue to form along the basolateral membrane of the primary mammary bud, they form channels and coalesce together to create lactiferous ducts. These ducts will produce milk during lactation or become blocked with keratin plugs when females are not lactating to prevent bacteria colonization. Epithelial cells lining the lactiferous ducts will arrange into the luminal and basal layers. The luminal layer will later have secretory functions, while the basal layer becomes myoepithelial cells. By the sixth month of gestation, mammary glands have formed with tubular architecture and dense fibroconnective tissue. Breast tissue will be apparent in both sexes [1] (see Figure 2).

2.1.3 3rd Trimester: 28 weeks – delivery

Throughout the third trimester, secondary mammary buds continue to subdivide and canalize [1, 5]. The epidermis in the region of the future nipple depresses, forming the mammary pit [7]. The mammary pit will be the site where the lactiferous ducts converge after draining into the retro-ampullae space [8] (see Figure 2).

The nipple is also formed by mesoderm proliferation. The areola, which was created by ectoderm proliferation during the 5th gestational month surrounds the nipple. Furthermore, stroma fibroconnective tissue increases in vascularity [1, 7].

By thirty-nine weeks gestation, there are 15- 20 glandular tissue lobes with lactiferous ducts which open on the breast surface through the mammary pit [1].

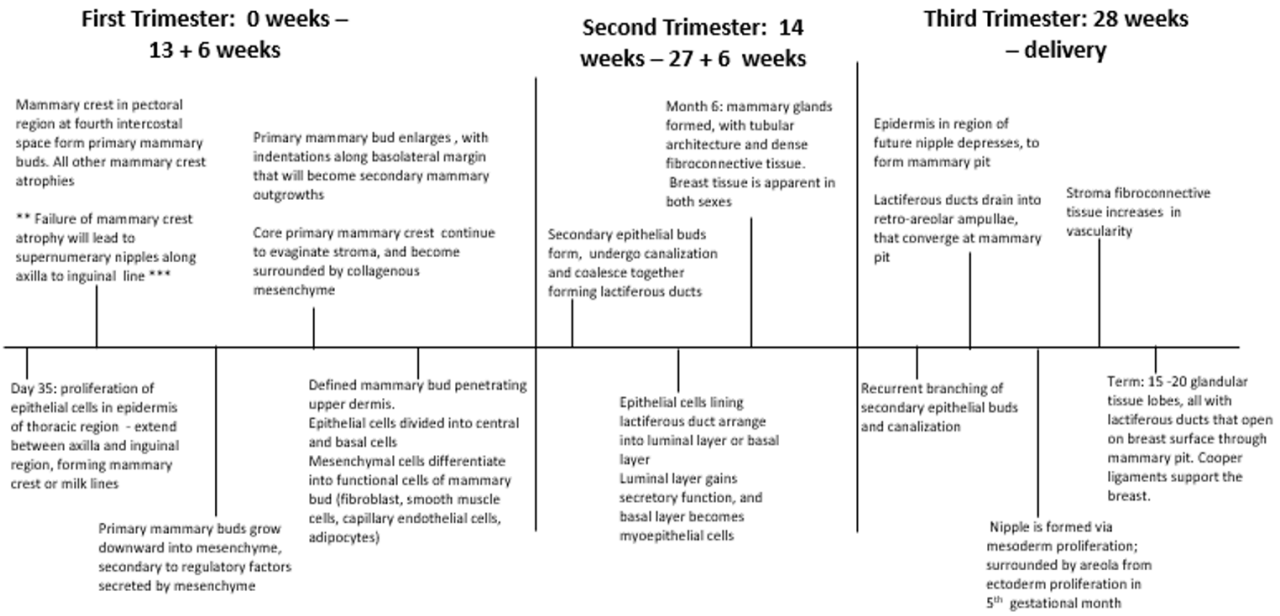


Figure 2 Timeline of prenatal breast development [4]

2.2 Birth to 10 years of age

When looking at breast development from birth to before puberty, there few to no differences between males and females [8]. At this stage of development there are three types of ductal systems and five stages of functional development seen.

Focusing on the ductal systems, Type 1 consists of a rudimentary ductal system. Type 2 consists of branching ductal system. Lastly, Type 3 consists of a branching ductal system like Type 2, but also includes terminal lobules [8].

On the other hand, the functional development is characterized a little differently. During stage 1 there is mild dilation, and the breast ductal system is lined with luminal epithelial cells. Stage 2 consists of ducts and alveoli with cystic dilation and metaplastic changes of the secretory epithelial cells. Stage 3 is similar to that of stage 2, but there is complete cystic dilation of all of the ductal system in addition to apical metaplasia of the luminal epithelium. Stage 4 marks a gradual transition into involution dilated ducts and alveoli. Stage 5 is that of the involuting gland and the lobules are lined by an outer layer of myoepithelial cell and an inner layer of epithelial cells [8]. Myoepithelial cells have both muscle and epithelial cell functioning [5]. While epithelial cells contain tight junctions and all three germ cell types. Epithelial cell functions include protection, secretion, and excretion. Lubrication, sensory reception, and much more [9]. There is slight overlap in the different ages and progression through the stages, as growth and development have variability from person-to-person [8].

2.2.1 Birth to 3 months

There is evidence of milk proteins that allow for milk secretion in newborns. In addition to this, the breast nodules are palpable in both males and females. Once the baby reaches about 3 months of age, the breast nodule tends to disappear [8]. Also, the baby has ductal system of types 1, 2, and 3 along with functional stage development progression from stage 1 to stage 4.

When looking at the hormonal side of development, newborns go through an instant withdrawal of hormones administered through the placenta, leading to the release of the hypothalamic-pituitary-gonadal (HPG) axis, thus causing a large increase in the gonadotropins and sex hormones of the newborn. The effects of the specific sex hormones are specific to both males and females. For male newborns, the LH concentration is comparable to the LH concentrations of a male in puberty for the first couple of weeks of life. These LH concentrations tend to peak between the 1^{st} and 3^{rd} month of life. In females, FSH usually peaks between the 2^{nd} and 4^{th} month. This peak is indicative of puberty-like levels as seen in the menstrual hormonal cycle of females.

2.2.2 4 – 7 Months

Breast glands involute a few months after birth. This is similarly seen in post-menopausal women [8]. Babies in this age range can be seen with characteristics of Stage 3, 4, and 5 of

functional development [8]. Additionally, babies of this age and above demonstrate types 1, 2, and 3 of rudimentary development.

On the hormonal side, the LH and testosterone concentrations in males slowly decrease to reach the pre-pubertal concentration levels around 4 to 6 months of life [10].

2.2.3 8 Months – 2.5 Years

Babies are seen with characteristics of Stage 5 of functional development [8]. Around the 12-month, FSH levels in females slowly decrease to the appropriate pre-pubertal levels [10].

2.2.4 2 Years – Puberty

The breast glands have no activity from about 2 years of age until puberty [10]. This shows slight overlap with 8 months to 2.5 years category. (see Figure 3)

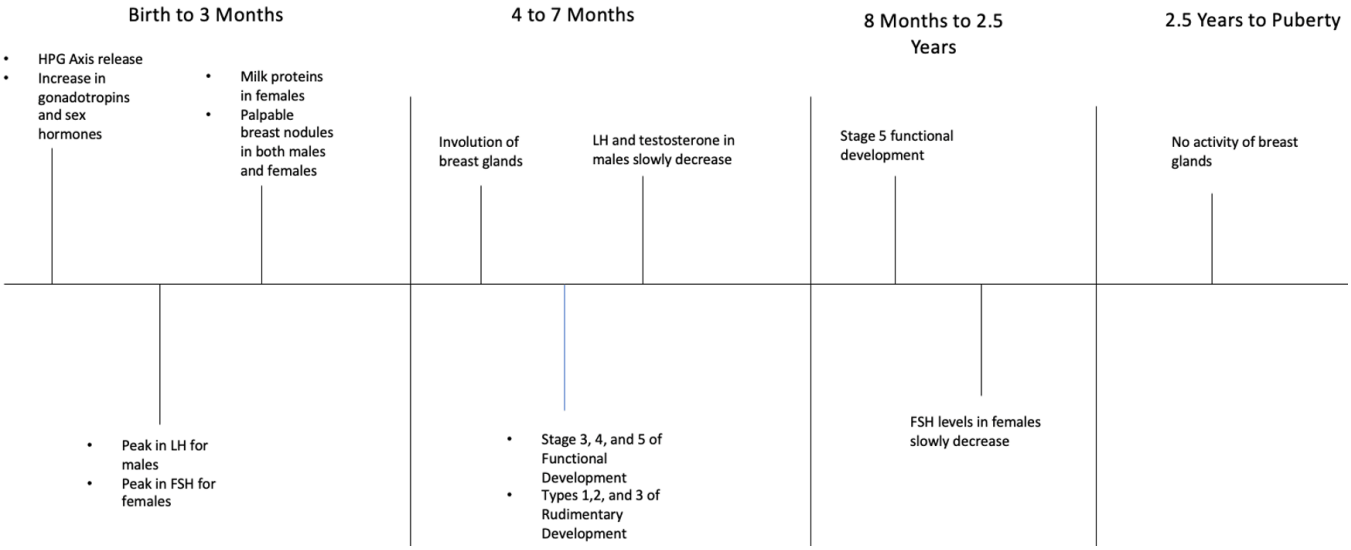


Figure 3 Changes throughout Prepuberty

2.3 Puberty and breast changes

During puberty, breast changes are regulated by the reproductive hormones, estrogen and progesterone. The secretion of these hormones are regulated by the hypothalamus-pituitary-ovarian axis [11, 12]. The hypothalamus secretes gonadotropin releasing hormone (GnRH), inducing the anterior pituitary gland to secrete follicular stimulating hormone (FSH) and luteinizing hormone (LH) [11, 12]. In females, FSH and LH stimulate estrogen and progesterone production, respectively. Estrogen determines the appearance of the breast through stromal tissue development, ductal system extension and fat deposition [12]. Progesterone controls ductal proliferation and development of the functional units of the breast [12] (see Figure 4).

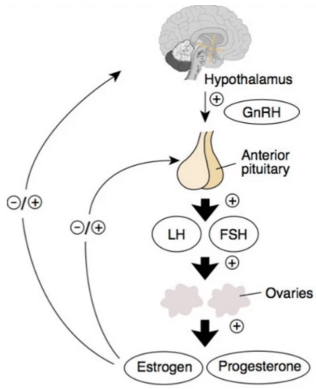


Figure 4 Hypothalamus-pituitary – ovarian axis [10]

First, the epithelium forms into a branching, bilayer ductal structure. The outer layer is composed of basal myoepithelium, and the inner luminal layer divides into the ductal luminal layer and alveolar luminal cells. With each menstrual cycle more alveoli form, which will be used to secrete milk into the ductal lumen [1].

Next, estrogen stimulates lactiferous duct elongation and branching at the terminal end bud. Progesterone then stimulates ductal proliferation. Primary ducts reach the nipple from subsidiary ducts. Subsidiary ducts branch into segmental and subsegmental ducts. Subsegmental ducts form terminal ducts which will divide into terminal ductules or acini. The functional unit of the breast, the terminal duct lobular units, are now formed. It is a collection of acini with surrounding intralobular stroma [1, 14].

Terminal duct lobules can be four types [7]. Type 1 lobules are short terminal ducts that terminate at alveoli [7]. Type 2,3, and 4 lobule terminal ducts branches into ductules with multiple alveoli [14]. Type 4 lobules are only in parous females who lactated [15]. Ducts will continue to elongate while the remaining space is filled with adipose tissue, blood vessels, lymphatic channels, immune cells, and fibroblasts [16]. Nulliparous breasts complete ductal and stromal proliferation by 18 to 20 years old, with type 1 lobules [1]. Mammary glands are now mature but will be inactive until pregnancy [1, 7].

These changes mark the first stage of puberty, thelarche, which will begin between 8–13 years [11]. If by fourteen years of age a female does not experience thelarche, it warrants further investigation for genetic or hormonal abnormalities. (see Figure 5)

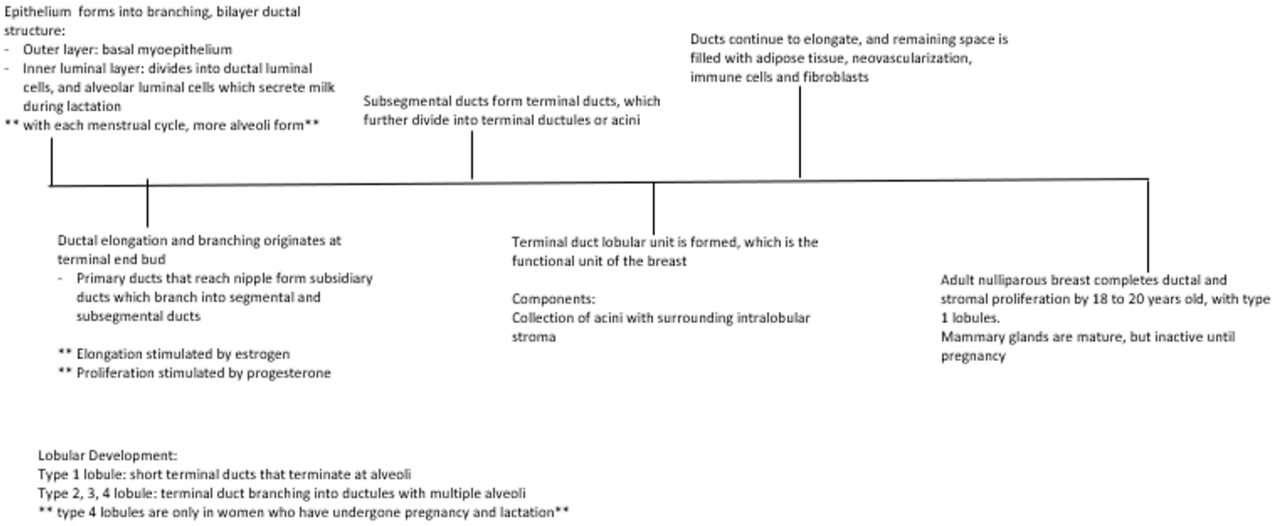


Figure 5 Cellular Changes throughout puberty

2.4 Menstruation, pregnancy and menopause

Throughout menstruation, estrogen and progesterone levels vary in concentration. Estrogen levels are elevated during the first fourteen cycle days, although this time-period is specific to each female. Progesterone then dominates the last fourteen cycle days, which is consistent in all females. Breast pain and enlargement experienced during the menstrual cycle is due to estrogen induced tissue stimulation [11, 12].

Throughout pregnancy, the breast prepares for milk production and lactation. During the first ten weeks, the corpus luteum secretes estrogen and progesterone. Adipose tissue decreases and the ductal system proliferates in response to estrogen [17]. After week ten, the corpus luteum involutes, and the placenta continues hormone production until delivery. Estrogen causes breast enlargement and lobular branching. Progesterone causes further ductal elongation and proliferation. The anterior pituitary also increases the number and size of lactotrophs in response to estrogen [17, 18]. Lactotrophs are responsible for prolactin secretion, which stimulates lactation within the lobular alveolar cells. After birth, progesterone levels rapidly decline, and milk production and secretion are facilitated by prolactin and oxytocin [17, 18]. Breastfeeding is physical manipulation to the breast tissue and may resort in permanent distortion following cessation.

After thirty years, breast epithelial tissue and lobule volumes steadily decrease, regardless of previous pregnancies or initial tissue mass [19]. Once menopause occurs, progesterone and estrogen levels decline, primarily affecting the terminal ductal lobular units. The intralobular stroma becomes collagenous and the acinar basement membrane thickens [20]. This may occur in a heterogeneous manner, with varying amounts of fat and stroma [20]. Overall, the breast tissue composition will transition from predominantly fibromuscular to adipose tissue, increasing the likelihood of breast asymmetry. Below is a chart of absolute breast volume (BV) asymmetry in women up to 70+ years old.

3 Breast asymmetry

3.1 Pathophysiology

Breast asymmetry is a difference in fibroglandular tissue density seen on only 1 of 2 mammographic views (craniocaudal or mediolateral). It is categorized as either fluctuating, focal, global, or developmental. *Fluctuating asymmetry* is random and caused by intrinsic (genetics, pregnancy, environmental and demographic features) or extrinsic factors (weight, diet, age, environmental and demographic features). *Focal asymmetry* is small asymmetry of fibroglandular tissue seen on minimum of two different mammographic projections without convex-outward contours or masses. *Global asymmetry* is greater than 30% of fibroglandular tissue in at least one breast quadrant without microcalcifications, masses or architectural distortion when comparing it to the other breast at the same location. *Developing asymmetry* is focal asymmetry that is new, or old but increasing in size, or denser in comparison to previous examinations [21].

3.1.1 Fluctuating asymmetry

Errors in growth and development leads to breast asymmetry. The most common seen is very rapid growth during development, especially puberty [22]. Rapid growth during puberty can lead to breast asymmetry. Thus, asymmetry of the breast results after growth. These different deviations from perfect breast symmetry are termed fluctuating asymmetry (FA).

FA measures the developmental stability of the breast [22, 23]. Additionally, FA is random and caused by both intrinsic and extrinsic factors. Intrinsic factors include genetics, pregnancy, environmental, and demographic features, while extrinsic factors include weight, diet, and age [21]. Estrogen is a key factor in breast development and an increase in estrogen could be due to an increase in a female's body fat. Since estrogen has properties that can cause it to be immunocompetent, it leads to breast asymmetry causing it to be positively related to FA of the breast.

The extrinsic factors, weight and diet are mentioned. Women with larger breast have smaller FAs [22]. An increase in weight (fat deposition) of a female can lead to an increase in estrogen thus leading to an increase in breast size. So, breast asymmetry is, in turn, related to breast size. The larger someone's breast are, the less FA seen compared to females with smaller breast. Would weight loss cause an increase in FA seen? What about dieting? These questions should be investigated. It is important to understand the extent to which weight is related to increased estrogen leading to increased breast size. Additionally, is it only the increase in fat deposition that leads to increased weight size? Would the same effects be seen with someone who has an increase in weight due to muscle mass? We believe that since estrogen is more related to the increased breast size due to fat deposition, an increase in weight due to muscle mass would not have the same effects. The other extrinsic factor to look at is age. Sometimes in a woman's life where they experience weight gain is during puberty, as they age, and pregnancy. An increase in age influences the hormones at play considering as we age, we gain more weight.

The intrinsic factors, it is important to look at genetics, pregnancy, menstrual cycle (MC), environmental, and demographic features. Some genetic features leading to breast asymmetry are Adolescent Idiopathic Scoliosis (AIS) and Poland Syndrome. AIS is an example of breast asymmetry as both an intrinsic and extrinsic factor [24]. AIS is axial rotation and lateral curvature of the spine with a measurement greater than 10 degrees. This because of the curving of the spine leads to the breast asymmetry, and this can be pseudosymmetry or actual asymmetry. Not only does the curvature of the spine displace the breast in such a way that they are perceived as asymmetric, but it can also affect the volume of the breast. The implications this could have on quality of life are important to think about and will be discussed further in the paper. Poland Syndrome can also cause breast asymmetry. Compared to AIS, Poland Syndrome is congenital, and affects the chest wall and shoulder along with other upper limb parts. Poland Syndrome is a congenital disease that ultimately affects the chest wall [25]. Something both AIS and Poland syndrome have in common is the effect of chest wall positioning. If there is a defect or malformation of the chest wall, the breast is more likely to be or appear asymmetrical. These types of asymmetries would be considered position asymmetry.

Pregnancy has a large effect on the volume and size of a woman's breast. During pregnancy, breast volume increases with every trimester as seen in Figure 7 [26]. As the pregnancy advances, the mother's body is going through many changes that involves aspects of all major organ systems and processes. During pregnancy, different reasons cause breast asymmetry in pregnant women including breast tissue components, exaggeration of a previous asymmetry, and milk production [26]. It appears that the main indicator of breast asymmetry is the milk production. Milk can fill the spaces in a women's breast leading them to become enlarged, and ultimately leading to some asymmetry. This asymmetry can become aggravated for mothers

who breastfeed, especially depending on which breast they feed their newborn from and/or whether they pump. Another aspect of pregnancy is the weight gain, women can experience going through the process. Weight gain, specifically fat deposition, can lead to greater increases in estrogen. Estrogen is needed for breast development and growth, so it can lead to increased breast size. These processes are presented in Figure 6.

The menstrual cycle can be broken up into 4 phases. Phase 1 consists of an undistinguishable difference between the epithelial and myoepithelial cell layers. This phase runs from day 0 – 5 of the menstrual cycle. Phase 2 consists of an increase in the distinction between the epithelial and myoepithelial cell layers of the acini within the breast an endometrium. This phase runs from Day 6 – 15 of the menstrual cycle. Phase 3 consist of the basal layer having with visible vacuolations that have nuclei centrally or apically along with a clear cytoplasm. This phase runs from day 16 -24 of the menstrual cycle. Lastly, phase 4 consists of extensive vacuolation and the epithelial cells have very large nuclei. This phase runs from days 25 -28 of the menstrual cycle [28]. Myoepithelial cells relate to functional asymmetry seen in the breast and the menstrual cycle relates to the increase or decrease in the hormones estrogen and progesterone, two special factors in breast development. The presence of myoepithelial cells, as described above, is linked to stage 5 of functional asymmetry.

Phase 2 of the menstrual cycle, we can say that there will be some functional asymmetry of the breast due to the distinct observance of myoepithelial cells. Additionally, during phase 2 there is a spike in estrogen levels and a slow increase in progesterone levels of the menstrual cycle (Figure 6). If there is a large increase in estrogen during phase 2 of the menstrual cycle, then, at this time, the breast would be expanding through the ductal system and fat deposition. Increased estrogen is also associated with increased breast density, so this will also be seen during phase 2 of the menstrual cycle [29]. Additionally, if there is a slow increase in progesterone, then this marks the start of ductal proliferation within the breasts with the peak of this proliferation during phase 3 where there is the largest increase in progesterone. All of this is in congruence with the functional asymmetry due to the myoepithelial cells seen in phase 2 of the MC. Outside of phases 2 and 3 of the MC there is phase 1 and 4. Phase 1 consists of low levels of estrogen and progesterone along with no distinction between epithelial and myoepithelial cells [28]. With this being the case, there would be no observable breast density, ductal expansion/proliferation, or fat deposition within the breasts. None of the markers are present during phase 1 of the MC. During phase 4 of the MC there is a decline in the estrogen and progesterone phases. During this phase, there is an increase in mitotic figures and apoptosis [28]. The increase in apoptosis is linked to regression of breast enlargement due to the hormonal changed during phase 2 and 3 [28].

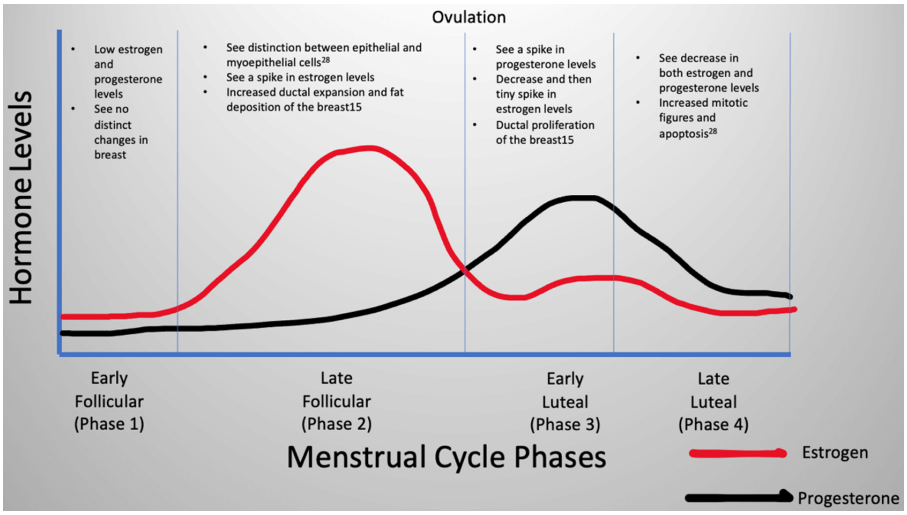


Figure 6 Menstrual Cycle Phases and Hormonal Changes on Breast Development [28, 30]

Various factors of FA allow us to predict whether FA is more likely to happen. In general, if we know that rapid growth during puberty can lead to FA, then we can predict that a young female child who undergoes an expedited puberty will most likely have FA. Additionally, if a female is diagnosed with AIS or Poland Syndrome, it is most likely that she will experience FA. Same for women who get pregnant.

Figure 7 lists various stages of asymmetry development. First signs of observable breast development are during adolescence due to estrogen stimulation. Then, during puberty further elongation of the ductal and glandular system. A large increase in breast size occurs during

pregnancy. Lastly during menopause a decrease in female hormones. More specifically, a decrease in estrogen can cause a reduction in the glandular tissue leading to a display of breast asymmetry. There are endogenous options to combat this decrease in estrogen levels that could lead to breast cancer [31].

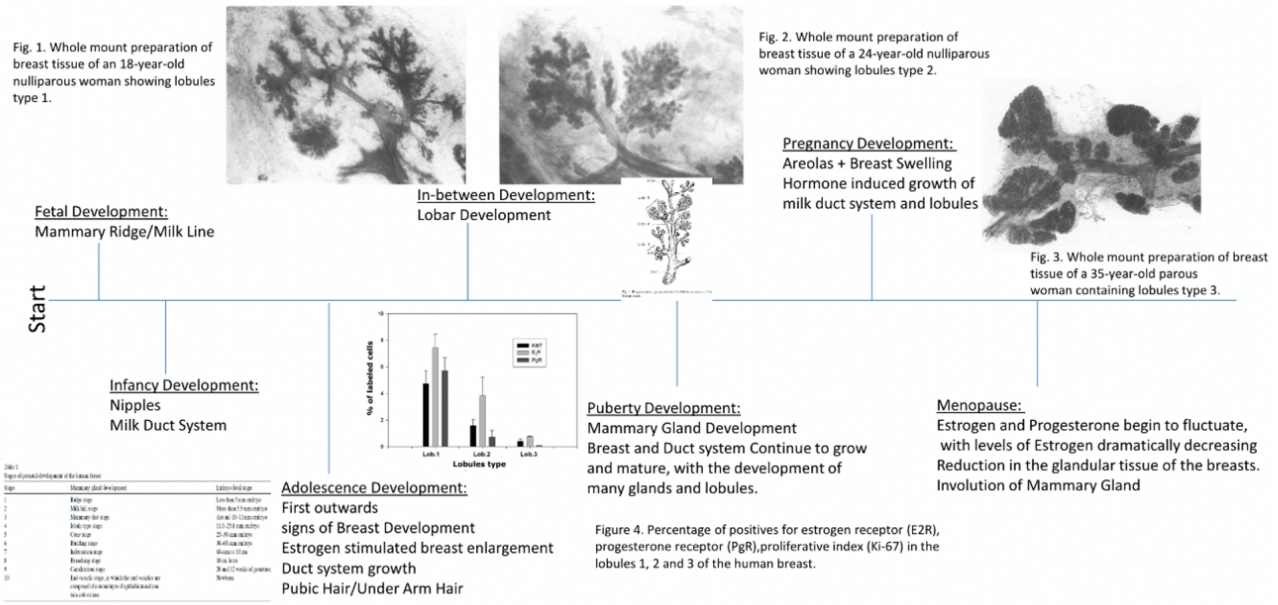


Figure 7 Breast Development through different stages of life

3.2 Benign breast asymmetry etiologies

In pubescent females, breast asymmetry can be caused by amastia, hypomastia, tuberous breast, polymastia or breast hypertrophy. Amastia or hypomastia is due to a congenital absence of breast glandular tissue possibly due to the obliteration of the milk line during embryogenesis. Tuberous breasts are a variant of breast development where the breast base is limited in size, with nipple and areola underdevelop [29]. Polymastia and polythelia are supernumerary breast tissue and accessory nipples, respectively, which occurs during embryogenesis [29]. Breast hypertrophy is caused by idiopathic uncontrolled enlargement of the breast, secondary to hypersensitivity to estrogen and progesterone, without the risk of malignancy [32].

Post-pubescent benign breast asymmetry most commonly arise from breast composition changes such as fibrocystic changes and benign breast cysts. Additional causes include benign neoplasms, breast trauma, pregnancy, and menopause. Fibrocystic changes are due to an exaggerated response to estrogen leading to simple or proliferative changes [33]. Fibrocystic breast disease is one the most common types of breast disease and it can lead to breast asymmetry. The time in which a woman is more susceptible to these fibrocystic changes is in times of great hormonal fluctuations [27]. The growth and development of woman, during puberty, pregnancy, and menopause; there is a surge in the different female hormones due to the starting of the menstrual cycle during puberty. During pregnancy, a female undergoes great hormonal changes to better support the fetus. Finally, during menopause there is a stop or limit so some of the important hormones, thus causing a large fluctuation to what the body is used to. Fibrocystic asymmetry is common in women between the ages of 30 and 50 years old with the most common form being fibroadenomas. Fibroadenomas consist of localized proliferation of breasts ducts and stroma [27]. Proliferative changes lead to endometrial hyperplasia, with an increased risk for malignancy [33]. Benign breast cysts are fluid-filled widenings of the terminal duct lobular units associated with the cyclical nature of reproductive hormone levels throughout the menstrual cycle [32]. Benign neoplasms include fibroadenoma, phyllodes tumor, or intraductal papilloma. Fibroadenomas are unilateral masses resulting from proliferation within the intralobular stroma [33]. Although fibroadenomas are responsive to estrogen, their exact cause is undetermined. Benign phyllodes tumors are caused by periductal intralobular stroma proliferation, without interlobular stromal hypercellularity [30]. Intraductal papilloma derive from the lactiferous ducts, presenting as subareolar masses with bloody or serous nipple discharge, with risk of malignancy [33]. Traumatic fat necrosis is caused by breast trauma, leading to calcification, fat necrosis, and cholesterol clefts within the breast. Fluctuating levels of estrogen and progesterone throughout a female's life cycle, affects breast composition contributing to benign breast asymmetry [16, 34].

3.3 Malignant breast asymmetry etiologies

Breast cancer is a major malignant breast asymmetry etiology. The way in which breast asymmetry can be related to breast cancer is through the different amounts of estrogen in the body. The times in which estrogen levels increase are when a woman is overweight or obese, pregnant, menstruating, or using post-menopausal hormone treatments [31]. Overweight and obese individuals have an increased in estrogen to the increase in fat tissue deposition. Post-menopausal, and obesity increases the estrogen further. While pregnant, estrogen levels can increase within a woman thus leading to a possibility of dormant cancer cells to grow. If the woman gives birth before 32 weeks or has an induced abortion there will be increased exposure to estrogen [31]. During the menstrual cycle, there is a spike in estrogen just before an egg is released for ovulation. On the other hand, women who use estrogen creams post-menopause experience a surge in estrogen levels within the body. Estrogen can cause breast cancer through increasing cell division causing mutations can act as a carcinogen causing direct DNA damage leading to cancer cells to form [31].

3.4 Observation of breast asymmetry

A more concrete way to observe breast asymmetry is through a system called BFACE [34]. BFACE is used as a way to pre-assess the breasts before a breast operation. If plastic surgeons can use this method, then this method can be the basis for understanding more structural aspects of breast asymmetry. BFACE stands for bones, footprint, areola, conus, and envelope. Bones refer to the part of the bony skeleton that is involved with the structure of the breasts. Some of these structures include the shoulders, sternum, spine, and ribs [34]. Any deviation from the normal structure's presentation can affect the symmetry. Footprint consists of the shape of the outline of the breasts [34]. Footprint is confined by its natural anatomical position on the body. No augmentation to the breasts will raise or lower the footprint. Areola refers to the nipple-areola complex. According to Maryann and Nadia, the visual characteristics for the nipple-areola complex include size, position, projection, vector, state of contraction, and symmetry with the contralateral side. The areola tends to grow larger with age, weight gain, and pregnancy. Smaller areolas are typically seen on those with smaller breasts [34]. Something to take note of is that about 95% of women undergoing breast augmentation presented with areola location asymmetry [34]. Could this be due to a lower quality of life because of breast asymmetry? Although it is subjective and varies from culture to culture, it has to be proportional to the body. Lastly, the envelope is the skin that encompasses the breasts, and it can be evaluated qualitatively and quantitatively. The envelope is evaluated qualitatively through visual examination and quantitatively through measurement [33]. Some of the envelope factors that can affect the symmetry of the breasts include striae (representing loss of skin elasticity), scarring, and excessive skin. These represent ways in which we can observe breast asymmetry.

4 Male breast development

Male breast development is termed gynecomastia and is the most common clinical and pathologic abnormality of the male breast. It results from hypertrophy of breast tissue [35]. Numerous conditions have been associated with gynecomastia, but the pathophysiological bases are due to an imbalance of reproductive hormones and the tissue responsiveness to them [34]. A few examples of corresponding endocrine deficiencies may include but are not limited to: adrenal adenocarcinoma, hypergonadism, hypogonadism and steroid use [36]. Gynecomastia usually occurs at different phases of life: infancy, puberty, and older age. After a male and female baby are born, the mother produces high levels of estradiol and progesterone leading to breast tissue stimulation in the newborn.

Gynecomastia during puberty is often asymmetrical even though it is mostly bilateral. Gynecomastia at this stage is seen in up to 60% of young males and usually resolves within 3 years of its onset [37]. During male puberty, estrogen levels rise throughout the day, and it is noted that for males with pubertal gynecomastia there is a decrease in the androgen to estrogen ratio. Additionally, within the skin fibroblast of pubescent males with gynecomastia, there is an increase in aromatase activity in the skin [37]. Aromatase is an enzyme that catalyzes the conversion of androgens to estrogen. This is greatly seen in boys and men with gynecomastia, especially those with androgen insensitivity syndromes. An excessive amount of androgen can aromatize into estrogen by aromatase which can result in gynecomastia and other phenotypic female appearances. Androgens alone may not lead to male breast development, but they can if they aromatize to estrogen.

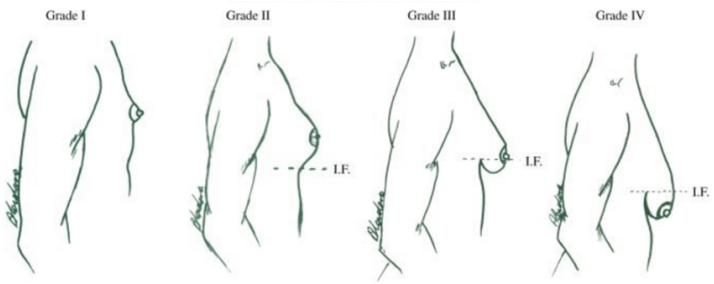
The final phase of life where gynecomastia is mostly present is that of older age, more than 60 years of age or older. The exact mechanisms are unknown, but there is evidence that suggests

the increased peripheral aromatase activity due to the increased total body fat plays a role along with elevated LH concentrations and decreased serum testosterone concentrations that are in male aging. The increased aromatase activity seen in aging due to the increase total body fat is similar to what is seen in obesity patients at a smaller scale, but gynecomastia is, ultimately, a byproduct of this due to initiating the cascade of breast development [36].

4.1 Hormones seen with gynecomastia

The hormones with relations to gynecomastia include estrogen, Growth hormone (GH), IGF-1, Luteinizing hormone (LH), aromatase, androgens, and testosterone. For breast development, there is a requirement for estrogen, GH, and IGF-1. Estrogen levels alone or estrogen with progesterone is not enough to aid in breast development. GH and IGF-1 along with estrogen and/or progesterone cause breast development. Specifically with pubertal gynecomastia, there is an elevation in the IGF-1 levels compared to males in puberty without gynecomastia [37]. This increase in IGF-1 levels is enough along with the estrogen for a male to start showing signs of breast development. In addition to these hormones, examiners have found there to be LH/human chorionic gonadotropin receptors in male (and female) breast tissues [37].

An excessive amount of androgens can aromatize into estrogen by aromatase which can result in gynecomastia and other phenotypic female appearances. Estrogen is a requirement for breast development and androgens oppose the effects of estrogen [37]. Therefore, a decrease in androgens inadvertently leads to an increase in estrogen. Increased estrogen levels can cause direct stimulation of glandular tissue leading to suppression of LH, thus decreasing testosterone secretion and further increasing the estrogen to androgen ratio (or in the way stated above further decreased the androgen to estrogen ratio). Decreased testosterone can cause an elevation in the estrogen to androgen ratio producing gynecomastia. This gynecomastia is the combined result of decreased androgen responsiveness at the breast level and increased estrogen levels as a result of elevated androgen precursors of estradiol and estrone. So, it is a result of increased estradiol levels that arise due to unopposed androgen unresponsiveness [37]. A gain-of function mutation in chromosome [12], polymorphism of aromatase cytochrome P45019 (CYP19), and hyperthyroidism. Since these increase aromatase activity, may lead to developing breasts in males. (see Figure 8)



- Grade I, increase in diameter and protrusion limited to the areolar region;
- Grade II, hypertrophy of all the structural components of the breast. The nipple-areola complex is above the inframammary fold;
- Grade III, hypertrophy of all the structural components, nipple-areola complex at the same height as or about 1 cm below the inframammary fold; in this group we can also include male tuberous breast;
- Grade IV, hypertrophy of all the structural components, nipple-areola complex more than 1 cm below the inframammary fold.

Figure 8 Classification of gynecomastia

5 Comparison of female to male breast development

Up until about puberty, few days after birth, males and females go through similar processes for breast development. The process of breast development embryologically is the same. Where one of the initial differences happen is right after birth with the surge in gonadotropins and sex hormones due to the instant stop in the placental hormones that were once provided by the mother [10].

Another place in which the development of breast in females and males differ is that of puberty. The two major hormones involved in breast development are estrogen and progesterone. Estrogen controls the appearance of the breast and progesterone is involved with the proliferation of the functional unit of the breast [12].

6 Breast asymmetry and its effects on quality of life

Breast asymmetry is a descriptive term encompassing common and abnormal conditions. Breast asymmetry is common amongst all females and has the potential to affect each female's

quality of life in varying capacities. While very few women have perfectly symmetrical breasts, severe developmental breast asymmetry can be a severe psychological and aesthetic handicap [35].

If breast asymmetry may lead to breast reconstruction surgery. Severe distortions of breast size and shape can lead to adverse effects in quality of life resulting in social discomfort or psychological distress. In one study by Laura Nuzzi et. al, self-esteem and self-perceived happiness of women with noticeable breast asymmetry were measured [38]. These measurements were collected using the Rosenberg self-esteem scale. The Rosenberg scale is a 10-item scale that measures global self-worth by measuring both positive and negative feelings about the self. These surveys were chosen for their reliability and validity and have been used in other studies to assess the physical and emotional well-being of adolescents and adults with other breast conditions. These women completed the survey independently, either in the clinic or at home. Women with more severe and noticeable breast asymmetry tended to score lower on the Rosenberg scale. The lower scores were shown to be associated with more detriments in mental health, social functioning, and mood congruency. Results yielded a significant correlation between self-esteem and perceived self-image to the level of happiness and psychosocial quality of life [38]. Women who went through with breast reconstruction due to asymmetrical breast had an overall increase in quality of life [39].

7 Interventions

Mild to moderate differences in breast shape, size, and position in the developing adolescent may resolve or be managed by reassurance. However, those with substantial breast differences that persist through puberty may require more intensive medical intervention. Specifically, more invasive medical management through reduction mammography and breast reconstruction has been used. In comparison, less invasive measures such as cognitive behavioral therapy have also been used as a form of treatment [40]. Both forms of medical intervention have their benefits and shortcomings that will be discussed further.

Conservative management with cognitive behavioral therapy has aimed to appropriate the individual's perception of self-image and lessen the psychosocial burden of their respective deformity. This form of intervention is less invasive and, in some instances, less expensive due to the role of insurance companies' willingness to aid financially. However, as suggested, this management does not correct the underlying deformity. The improvement observed using cognitive behavioral development has shown to yield greater results in those with milder asymmetry [40]. In addition, consultation with behavioral therapy can be used as the primary treatment or as an adjunct therapy for patients either prior to or after operative intervention.

Invasive intervention such as reduction mammoplasty and breast reconstruction are more definitive modes of treatment of breast deformity. However, surprisingly, such treatment can improve or destroy body image. Although, prior studies suggested an improved post-surgical body image in patients who undergo breast reconstruction [40].

8 Conclusion

From utero to death, the breast undergoes numerous changes increasing the likelihood of asymmetry. Breast development starts within the first 6 weeks in utero and continues well into a woman's life. During puberty is when the large surge in hormones happen and persist until menopause. There are many categorizations of breast asymmetry, but fluctuating asymmetry is of particular focus. FA is random and occurs through intrinsic and extrinsic factors. It is thought that FA can occur as early as puberty due to rapid growth during development. Some of the extrinsic factors involved with FA include weight gain due to fat deposition and duet. Some of the intrinsic factors include genetics, pregnancy, environmental and demographic features. These FA allow us to cast predictions about whether someone is more likely to experience breast asymmetry. Observations about asymmetry can be discovered through the BFACE system. Although most are commonly benign, this asymmetry may negatively impact a female's self-perception. So much so that most literature about an improvement in quality of life after breast reconstruction surgery. Interventions range from conversative management to invasive intervention. Breast development is not isolated to just women, it can occur in men through a process caused gynecomastia. There are three main phases in life that gynecomastia can occur. In every case, it deals with an increase in the hormone estrogen.

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