
Reproductive Changes in the Female Lifespan

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Abstract

During the lifespan of women, there are dramatic and life-changing transitions associated with the beginning and cessation of reproductive function. These transitions, puberty and menopause, result in dramatic changes in the anatomy, physiology, and cognitive function of females and are caused by fluctuating levels of estrogen and progesterone. Regular menstruation is the result of cyclic release of reproductive hormones and is a sign that all is going well. When a woman approaches menopause, menstruation usually becomes more irregular and eventually ceases because hormones from the ovary are too low to stimulate the lining of the uterus. Because the life expectancy for women is now approaching 80 years and menopause occurs at about 50 years of age, the average female will live approximately 30 years after her ovaries have ceased to produce estrogen. This has serious physical and mental health implications in the aging population, which will increase dramatically in the next few decades. Hormone replacement therapy relieves some of the uncomfortable aspects of menopause, such as hot flashes and sleep disturbances, and protects against osteoporosis. However, recent evidence suggests there may be an increased risk of certain cancers and stroke with hormone therapy. Additional research is needed to unravel the complex actions of hormone replacement formulations so that women can have a healthier life after menopause.

Keywords

Puberty • Menarche • Menstruation • Osteoporosis • Menopause
• Hormone replacement therapy • Alzheimer's

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FEMALE LIFESPAN

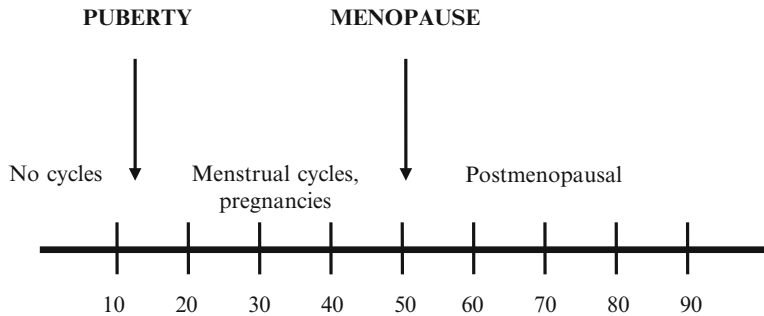


Fig. 2.1 Graphic depiction of the female reproductive capabilities across the lifespan of the average woman

2.1 Learning Objectives

After completing this chapter, you should have an understanding of:

- The major transitions during a woman's life
- How reproductive hormones change throughout the lifespan of a woman
- The terminology used to describe changes in reproductive capabilities
- The impact of menopause on health measures

2.2 Introduction

When considering reproductive competence in the human female, the average lifespan can be divided into three phases. The first of these is childhood where, except in rare instances of precocious puberty, the reproductive system is quiescent and secondary sexual characteristics are absent. Puberty is the transition between childhood and sexual maturity, and menarche or first menstruation is an important sign of this transition. During this second stage of sexual maturity, which in the United States lasts from about 13 years to 51 years of age, menstrual cycles occur about once a month except when interrupted by pregnancy or by synthetic steroids used as birth control. Even when hormonal birth control is used, there is usually an attempt to maintain monthly cyclic menstruation. In modern societies, menstrual cycles can be suppressed by stressful

life events or by lack of nutritional resources, the latter usually due to dieting or exercise. Most women stop having menstrual cycles in their late forties or early fifties and enter the postmenopausal stage. This transition between the fertile period and postmenopausal or infertile phase is called menopause (Fig. 2.1). In the past century, the time spent in the postmenopausal state has become extended because the average lifespan has increased from 50 to over 80 years. The health concerns of postmenopausal women have become a real concern in the past 50 years. The transitions between these two stages, puberty and menopause, are accompanied by dramatic changes in levels of the most important female hormones, estrogen and progesterone.

2.3 Research Findings

2.3.1 Hormonal Changes During Childhood

From shortly after birth until the beginning of sexual maturation, reproductive hormone levels are low, and available energy is largely committed to growth and development. Before puberty, boys and girls have similar lean body mass and the same amount of body fat. Body mass index in girls is generally between 15 and 18 and does not change much during the childhood years. Growth rates are similar for boys and girls before the pubertal growth spurt and, in the absence of

serious illness or genetic abnormality, 12 year-old girls and boys are the same height and weight on average.

Physicians routinely monitor height, weight, chronological age, bone age, and growth during the previous year to evaluate how pubertal development is progressing. Since Title IX legislation, which prohibits sex discrimination in any educational program or activity in institutions from elementary school through college that received federal funding, was passed in 1972, female participation in school athletic programs has increased dramatically. Of the total participants in high school athletics in 1971, less than 10 % were female. Today, the proportion of male and female athletes is nearly equal. While exercise is largely beneficial, excessive exercise can utilize energy needed for growth and development and can significantly impact these processes if energy intake is limited by dietary restrictions. This is important because in some competitive sports, and particularly in elite athletes, rigorous training begins before puberty and can potentially influence sexual development.

2.3.2 What Happens at Puberty?

Although puberty in human females is generally defined as the process of sexual maturation, and it is certainly that because the changes are primarily driven by the increased activity of the ovaries, a more inclusive definition would also encompass the accompanying physiological and behavioral changes that occur during this transition. This process of sexual maturation requires several years, and the ages of 8–14 years are considered the average range of when this process normally occurs. The defining event, menarche (first menstrual period), occurs at an average of 12.5 years in the United States, but there are differences among ethnic groups and between the United States and other countries. Menarche is a sign that the ovaries are sufficiently functional to support growth and development of the uterine lining. The diagnosis of *primary amenorrhea* is made when menarche does not occur by about age 16. Several years before sexual maturation,

increased secretion of steroid hormones from the adrenal gland and ovaries initiates widespread physiologic changes in the body. One of these changes is the adolescent growth spurt. This acceleration in growth lasts for a year or so then slows, and growth is eventually terminated by fusion of the epiphyseal regions of the long bones where growth occurs. Estrogen is responsible for epiphyseal fusion in both males and females. During this pubertal transition in females, there is an increase in percentage of body fat which does not occur in males. Secondary sexual characteristics, such as breast and genital development, are directed by ovarian estrogens, but axillary (underarm) and pubic hair are controlled by androgens from both the ovary and adrenal. The appearance of the female body becomes very different from that of males, and it is primarily the hormones, estrogen and progesterone, from the ovary that drive this change. A major question that has not been answered is the following: Why does the secretion of these ovarian steroid hormones increase at this time in life? In other words, what event initiates the process of sexual maturation?

What we do know is that the process of sexual maturation is driven by increased release of a small peptide (a small molecule composed of ten amino acids) called gonadotropin-releasing hormone or GnRH; what we do not know is why it occurs at this specific time. Recent evidence implicates an obligatory role for a peptide called kisspeptin which directly stimulates GnRH release from the hypothalamus [1]. The prevailing hypothesis is that puberty is initiated at some point when the brain and/or body is sufficiently mature to support successful reproduction. When this occurs, pulses of GnRH are released at 1–2 h intervals into the pituitary portal system and travel a short distance from the base of the brain (hypothalamus) to the pituitary and stimulate the release of two protein hormones (large hormones also composed of amino acids) called luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The LH and FSH travel through the circulation to the ovary where they cause growth and development of follicles containing ova (eggs) and, at the same time, stimulate the secretion of the ovarian hormones (Fig. 2.2).

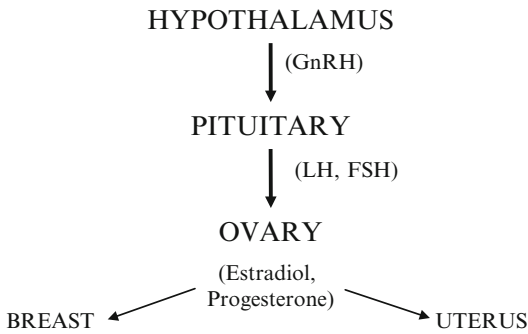


Fig. 2.2 This figure shows the primary components of the female reproductive system and the hormones that communicate between the various organs. The hormones produced by each gland are shown in parenthesis

This process begins slowly at first, with LH pulses released only at night. Because the LH (and FSH) levels are not maintained at adult levels throughout the day and night, stimulation of the ovarian follicles is not sufficient to result in ovulation. As puberty progresses, the time when LH pulses are released gradually expands to the daytime, and in the adult, these pulses are observed throughout the day as well as at night. In response to FSH and LH, estrogen release from the stimulated follicles results in changes in the body including growth of the breasts and hips primarily due to the deposition of fat. Late in the pubertal process, ovulation occurs when the LH and FSH levels are maintained at a level to provide consistent support for the developing follicle. Menarche usually occurs late in the sequence of events defining puberty.

2.3.3 Sexual Maturity: The Reproductive Years

The ability to reproduce is one of the hallmarks of sexual maturity. Sexually mature women who are not taking birth control pills have regular menstrual cycles that average 26–35 days in length and that are (can be) occasionally interrupted by pregnancy and lactation. Menarche signals the beginning of the ability to reproduce although it is possible to become pregnant before the first menstrual period because ovulation can occur during this time.

Menopause marks the end of the reproductive lifespan which lasts nearly 40 years from about 13 years (menarche) to 51 years (menopause). Menstruation occurs at the end of an ovarian cycle as the lining of the uterus dies and sloughs off when implantation of a fertilized ovum has not occurred. Menstruation is also the beginning of a new cycle, and by convention, the first day of menstrual flow is day 1 of the cycle. This sequence of follicular development, ovulation, and menstruation is repeated at regular intervals until menopause, unless interrupted by pregnancy and lactation. Reproduction can be postponed with birth control pills or other contraceptive methods for an indefinite period of time when women decide to pursue educational or career goals. Even though hormonal birth control pills inhibit follicular development and ovulation, they do not extend the fertile lifespan which peaks in the twenties and declines thereafter.

2.3.4 Menopause: The Climacteric

The average age of menopause (last menstrual period) in the United States is 51, but much like the pubertal transition, menopause is a process that occurs over a period of years. Menopause is recognized when a woman has not had a menstrual period for 12 months. As a woman ages, there is a steady decline in the number of ova (eggs) in her ovaries that can be mustered to develop into follicles with the potential to ovulate. As the number of developing follicles declines, so does the level of estradiol in the circulation. The brain and pituitary, sensing this gradual decline in estrogen, increases the signal (levels of LH and FSH) to the ovary to encourage more follicular development and estrogen production. Thus, as a woman approaches menopause, there is a gradual increase in circulating LH and FSH levels, eventually reaching postmenopausal levels that remain high because there is no feedback signal (estrogen) from the ovary to suppress their release. This feedback relationship will be discussed in more detail in Chap. 4. During this menopausal transition, there is also an adjustment to this new hormonal environment

with many psychological and physiological changes, some of which can be unpleasant and disturbing. Symptoms of menopause that most women complain about are vasomotor changes (hot flashes), sleep disruption, mood changes, and urogenital problems. Hot flashes are experienced by about 75 % of menopausal women and typically last for about 3.8 years [2]. Intense heat, sweating, flushing, chills, and clamminess are all symptoms experienced during a hot flash. Once thought to be a figment of the menopausal imagination, hot flashes reflect a real increase in core body temperature and in skin temperature in the digits, cheek, forehead, upper arm, chest, abdomen, back, calf, and thigh [3]. It is interesting that menopausal hot flashes occur at the same time pulses of LH are released from the pituitary [4, 5]. This suggests that the abrupt increases in body temperature are linked to the same central nervous system event that causes the intermittent release of GnRH that stimulates LH release. The current opinion is that since estrogen regulates norepinephrine activity in the brain, and norepinephrine release influences both LH release and body temperature, it is changes in norepinephrine activity due to estrogen withdrawal that causes the hot flashes [3]. Long-term effects of decreased estrogen levels including increased cardiovascular disease, osteoporosis, and decreased mental function are far more debilitating than the transitional changes that occur at menopause.

2.3.5 Postmenopause: Life Without Estrogen

At the beginning of the twentieth century, the average age at menopause was 50 years, and this age was also the approximate life expectancy for women at that time (1900). Because the life expectancy at the present time for women has increased to over 80 years, most women will live more than a third of their life after menopause and without estrogen from their ovaries. This extended postmenopausal is a relatively recent phenomenon, and therefore, some of the health-related issues caused by aging are poorly understood and not well documented. Although the

increase of 30 years in life expectancy in past 100 years is substantial, the gain in healthy, functional years is less impressive. Many women experience physical and mental impairment in these later years that restricts their social function and isolates them from their friends and family. What is even more disturbing is that because of a variety of environmental influences, many young women have menstrual cycle disturbances that result in the hormonal levels that approximate those seen in menopause. If menstrual cycle disruption is prolonged and particularly if there is amenorrhea during the reproductive years, this can result in some of the same consequences at age 30 or 40 that are usually experienced by women in their seventies and eighties.

2.3.5.1 Osteoporosis

Of all the consequences of aging in women, osteoporosis is the most debilitating and affects the most women. The risk of a lumbar or hip fracture, particularly after the ages of 65, approaches 50 % in white women. There are effective treatments for this condition including hormone replacement therapy (HRT) and bisphosphonates. The HRT, specifically estrogen therapy, reduces bone turnover and improves calcium homeostasis. However, there are drawbacks to HRT and the risks of breast and uterine cancer in individuals with a family history of these diseases must be considered when decisions regarding the treatment of osteoporosis are made.

2.3.5.2 Alzheimer's Disease

A significant percentage of older women have some form of dementia (deterioration of cognitive function), and estrogen may protect against this deterioration [6]. Although, compared with previous studies, the recent results of the Women's Health Initiative (WHI) suggest that there is an increased risk of ischemic stroke with estrogen (Premarin) either with or without progesterone (Prempro), this trial used HRT on older menopausal women with obesity as a complicating factor [7–10]. Well-controlled studies with the native estrogen, estradiol-17 β , are needed before a rational, effective treatment regimen for menopausal/postmenopausal women can be

safely proscribed. There are studies suggesting that estrogen replacement therapy, if begun at menopause and continued for a few years, is effective in reducing both the risk for osteoporosis and dementia.

2.3.5.3 Coronary Artery Disease and Stroke

The overwhelming evidence from observational studies indicates that estrogen has a protective effect against coronary artery disease [11]. This effect of estrogen appears to be limited to prevention of cardiovascular disease and does not ameliorate the progression of coronary disease that is established [12]. However, two recent trials, HERS (Heart and Estrogen/progestin Replacement Study) and WHI (Women's Health Initiative), have brought these observational data into question. These two large trials with 2,763 women (HERS) and 16,608 women (WHI) found no net benefit (HERS) or an increased risk (WHI) of coronary artery disease with HRT [13].

2.3.5.4 Breast and Endometrial Cancer

One of the main concerns in women who take HRT for menopausal symptoms is the increased risk of breast and endometrial cancer. The analysis of some 50 studies clearly indicates an increased risk for breast cancer in women taking estrogen alone [14]. The risk is increased substantially when women are on combined treatment of estrogen and progesterone [15]. Conversely, progesterone has a protective effect against the increased incidence of endometrial cancer in postmenopausal women taking estrogen therapy alone [16].

2.4 Current Understanding of the Issues

Because of the dramatic increase in life expectancy in the past century, many women are living 30 or 40 years or more after menopause. Several studies have compared various health outcomes between groups of women who have and have not taken hormone replacement therapy (HRT) after menopause. Because the widely publicized

results of these studies suggested increased risk of certain diseases with HRT, physicians and their patients are reluctant to use HRT, which may actually increase postmenopausal health problems unnecessarily. However, the studies have used different hormone formulations and different routes of administration, concentrations, and hormone sequence, given to women of different ages, and therefore are not directly comparable [18]. At the present time, there are data suggesting that brain and bone health benefit from HRT, but the effects on cardiovascular disease and breast and uterine cancer are not clear. What has emerged in the past two decades is that there are at least two forms of the estrogen receptor mediating the actions of this hormone on estrogen-sensitive tissues (bone, brain, breast, uterus, and heart) as well as adipose tissue and the immune system [18]. Furthermore, many factors including the age, health status, genetic background, previous hormone environment of the patient, and route and sequence of administration of HR may all influence the outcome of HRT [17, 18].

2.5 Future Directions

The HRT has primarily been used to treat the menopausal symptoms that cause the most discomfort: hot flashes, vaginal dryness, and disturbed sleep. However, evidence from large clinical trials has revealed that our knowledge of the constellation of effects of HRT on cardiovascular health, cognition, and reproductive organs is very limited. Additional studies examining both basic and clinical aspects of the effects of HRT on hormone responsive systems are needed before rational replacement therapies can be effectively used to improve health outcomes in postmenopausal women.

2.6 Conclusion

During the lifespan of women, there are dramatic and life-changing transitions associated with the beginning and cessation of reproductive functions.

These transitions, puberty and menopause, result in dramatic changes in the anatomy, physiology, and cognitive function of females and are caused by fluctuating levels of estrogen and progesterone. Because the life expectancy for women is now approaching 80 years and menopause occurs at about 50 years of age, the average female will live approximately 30 years after her ovaries have ceased to produce estrogen. This has serious physical and mental health implications in the aging population, which will increase dramatically in the next few decades. Additional research is needed to unravel the complex actions of hormone replacement formulations so that women can have a healthier life after menopause.

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