

Chapter

1

Physiology of the Menstrual Cycle and Changes in the Perimenopause

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The menopause marks the permanent cessation of menstruation and heralds the transition in a woman's life from a reproductive state to a non-reproductive one. Whilst the average age of this landmark varies slightly across the world, the menopause generally occurs in the early fifties and is only truly affected by factors such as smoking and medical and surgical induction of the menopausal state. However, clinical symptoms may precede this, and the physiological changes which occur with the menopausal transition may begin several years prior to the onset of any manifestations. The basis of the clinical and biochemical changes associated with the perimenopausal period is the depletion of ovarian follicles to a critical level.

Although the physiology of the normal menstrual cycle has been studied extensively, an understanding of the physiological changes of the menopause and their relationship to menopausal symptoms has only begun to make significant advances in the last 2 decades. The development of a validated staging system has been immensely beneficial in standardizing nomenclature surrounding the menopause as well as characterizing the changes at each stage in the transition. Despite these developments, there remain considerable gaps in the literature which require further investigation [1–11]. This chapter outlines current knowledge surrounding the staging and physiology of reproductive aging and its relationship to the troublesome symptoms experienced by the majority of women at this challenging stage of their lives. Before discussing this, however, it is important to have a firm grasp of the concepts surrounding the normal menstrual cycle.

Premenopausal Hormonal Regulation of Ovarian Function

The menstrual cycle is controlled by the hypothalamic–pituitary–ovarian axis, which, apart from its mid-cycle gonadotropin surge, acts as a negative feedback system, whereby peptide gonadotropins stimulate steroid hormone production in the ovaries, which in turn inhibits gonadotropin secretion, thus allowing cycles to occur [1–3].

The hypothalamus secretes gonadotropin-releasing hormone (GnRH). This acts on the pituitary gland in a pulsatile manner, which leads to the secretion of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [1, 2]. It is the frequency and amplitude of these pulses which determine the quantity of each hormone ultimately secreted. Slower frequencies appear to precipitate FSH secretion, whereas LH secretion has a predilection for higher frequencies of GnRH stimulation [2].

At the start of the menstrual cycle, the ovary contains several antral follicles. These follicles consist of an oocyte separated from a fluid-filled sac called the antrum, both of

which are surrounded by a layer of granulosa cells (cumulus cells and mural cells). These cells are surrounded by a basal membrane, around which lies another layer of theca cells. Theca cells develop LH receptors if they are part of the dominant follicle and produce androgens (progesterone or testosterone) from cholesterol. Conversely, granulosa cells have FSH receptors; androgens are absorbed by these cells and aromatized to estradiol (E2). Granulosa cells also produce the glycoprotein hormone inhibin, which includes two isoforms, A and B [1, 2].

In the late luteal phase (prior to menstruation) and the early follicular phase, levels of circulating FSH rise. This in turn stimulates follicular development and leads to selection of a dominant follicle. Whilst it is not known exactly how a dominant follicle is selected, it is thought that through varying follicular sensitivity, the most sensitive follicle goes on to mature, whilst the other follicles undergo atresia (degeneration). With its development, the dominant follicle secretes increasing levels of E2; this acts on the endometrium to stimulate proliferation. At the hypothalamus and pituitary gland, rising levels of E2 and inhibin B act to reduce FSH secretion through a negative feedback mechanism [1–3].

During the early and mid-follicular phases, E2 also exerts negative feedback on LH secretion, which ensures basal levels during this period. However, about 36 hours prior to ovulation (i.e. in the late follicular phase), E2 reaches levels in the circulation which switch this negative feedback effect to a positive feedback effect. This leads to a surge in LH (which is accompanied by a smaller surge in FSH) over a 24-hour period in the 24 hours prior to ovulation. This LH surge leads to rupture of the dominant follicular wall and release of the oocyte [2, 3].

Following ovulation, there is an abrupt fall in E2 production from the ruptured follicle. The follicle undergoes a series of changes which convert it into an endocrine structure called the corpus luteum ('yellow body'). This produces E2 and progesterone, which act on the endometrium to promote implantation. LH maintains the corpus luteum in the week following ovulation, but if pregnancy does not occur, then this begins to degenerate, leading to a gradual reduction in the production of steroid hormones. With falling E2 and progesterone levels, the loss of negative feedback leads to a subsequent rise in FSH, heralding the start of a new menstrual cycle. A summary of these processes is shown in Figure 1.1 [1, 2].

Definitions and Staging in Reproductive Aging

In order to understand the context in which the physiological changes of the menopausal transition are happening, it is necessary to consider the definitions and stages associated with reproductive aging.

The premenopause is typically defined as the phase of a woman's life from the menarche (onset of menstruation) until the beginning of the perimenopausal stage. The perimenopause comprises the time from a woman's mature reproductive state at the point when she begins to experience variability in the length of her cycle or characteristic symptoms of the menopausal transition to the year following her final menstrual period (FMP). It is only following this 12-month period of amenorrhea that a diagnosis of *menopause* can be made. The term *menopausal transition* also refers to the time when a woman's cycle changes or she experiences clinical symptoms, but ends with the FMP. The terms *menopause* and *postmenopause* are often used interchangeably to describe the phase of a woman's life from the FMP [1–11].

Menstrual cycle regulation

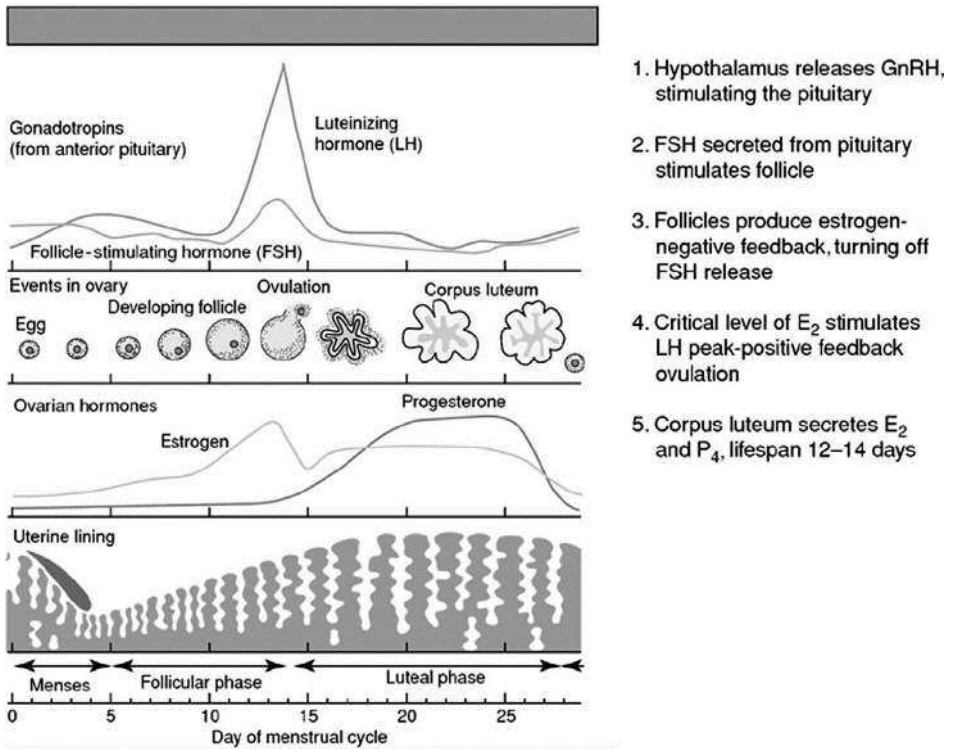


Figure 1.1 Endocrine changes during the menstrual cycle.

In 2001, the Stages of Reproductive Ageing Workshop (STRAW) met to propose criteria for defining the stages of reproductive life. They generated a staging system which provided guidance on ovarian aging in women. Prior to this, there was no generally accepted staging system. The aim of this was to improve research in women transitioning from a reproductive to a non-reproductive state by standardizing nomenclature and outlining the characteristic changes of each stage to aid consistency across studies. In a clinical context, the STRAW staging system provides health care providers and women with a guide to assessing fertility and contraceptive requirements. In 2006, the ReSTAGE collaboration assessed the validity and reliability of STRAW's criteria and made several recommendations. Ten years later, this collaboration and a greater understanding of ovarian aging have led to a revision of the STRAW staging system. The STRAW + 10 staging system is shown in Tables 1.1 and 1.2 [4].

The STRAW + 10 staging system is divided into three phases: the reproductive phase, the menopausal transition and the postmenopausal phase. The reproductive phase is subdivided into three stages (–5 to –3). The early reproductive stage (–5) refers to the period immediately following the menarche, before menstrual cycles become regular. During the peak reproductive stage (–4), menstrual cycles are regular. The late reproductive stage (–3) marks the time when fertility begins to go into decline and is

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Table 1.1 The reproductive phase as outlined in the STRAW + 10 classification

Stage	−5	−4	−3b	−3a
Terminology	Reproductive phase			
	Early	Peak		Late
Duration			Variable	
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in cycle length/flow
FSH			Normal	Variable ^a
AMH			Low	Low
Inhibin B			Low	Low
AFC (2–10 mm)			Low	Low

Note. FSH = follicle-stimulating hormone; AMH = anti-Müllerian hormone; AFC = antral follicle count.

^a Based on blood samples taken at days 2–5 of cycle.

subdivided into two stages. During stage −3b, menstrual cycles are regular, but anti-Müllerian hormone (AMH) levels continue to fall (a process which starts from the menarche) as a result of a gradual depletion in the antral follicle count (AFC) [1, 4, 6]. Stage −3a is characterized by subtle changes in menstrual cycle length and flow. Cycles tend to become shorter and periods heavier [1, 3, 7]. FSH levels rise with increasing variability, whilst AFC, AMH and inhibin B are low [4].

From the onset of the early menopausal transition, also known as the perimenopause (−2), cycle variability increases with a persistent difference of 7 days or more in the length of consecutive cycles. Anatomical and biochemical changes are similar to those of stage −3a, but with increasing variability in FSH levels. The late menopausal transition (−1) is characterized by an interval of amenorrhea lasting at least 60 days [4]. There is an increased prevalence of anovulation and further variability in cycle length and hormonal levels [4, 7, 8]. Indeed, during this stage, FSH levels are typically defined as being greater than 25 IU/L and are often associated with high E2 levels. However, E2 does start to fall [3, 4, 6, 8]. This stage is expected to last between 1 and 3 years, and it is during this time that menopausal symptoms, and in particular vasomotor symptoms (VMS), usually arise [4].

The late menopausal transition concludes with the final menstrual period (FMP) (0) and gives way to the postmenopausal phase (+1 to +2). Stage +1 is defined as the early postmenopausal stage and is subdivided into three stages. Stage +1a lasts 1 year following the FMP, and the end of this stage is defined as the menopause (a period of amenorrhea lasting 12 months). The end of this stage marks the end of the perimenopause, and 1 year into the postmenopausal phase, although this diagnosis can only be made retrospectively [4]. During stages +1a and +1b (which also lasts 1 year), FSH levels continue to rise, whilst E2 levels continue to fall [3, 4, 6, 8]. Thereafter, stabilization of these hormones occurs. Menopausal symptoms, and particularly VMS, are most likely to occur during these stages. Stage +1c marks a period of stabilization in levels of FSH and E2 which lasts between 3 and 6 years. The late postmenopausal stage (+2) lasts for the remaining

Table 1.2 The menopausal transition and postmenopausal phase as outlined in the STRAW + 10 classification

Stage	-2	-1	0	+1a
Terminology	Menopausal transition		FMP	
	Early	Late		
Perimenopause				
Duration	Variable	1–3 years		2 years (1+)
Menstrual cycle	Persistent ≥ 7 day difference in length of consecutive cycles	Interval of amenorrhea of ≥ 60 days		
FSH	\uparrow variable ¹	$\uparrow > 25$ IU/L ^b		\uparrow variable ^a
AMH	Low	Low		Low
Inhibin B	Low	Low		Low
AFC	Low	Low		Very low
Symptoms		Vasomotor symptoms likely		Vasomotor symptoms likely

Note. FSH = follicle-stimulating hormone; AMH = anti-Müllerian hormone; AFC = antral follicle count; \uparrow = elevated.

^a Based on blood samples taken at days 2–5 of cycle.

^b Based on assays using current international pituitary standard.

lifespan of a woman, during which FSH levels tend to fall gradually. Generalized somatic aging processes rather than reproductive aging characterize this period. The prevalence of urogenital symptoms increases at this time [4].

Whilst the STRAW + 10 system is regarded as the gold standard of reproductive aging given its broad applicability to women regardless of age, ethnicity, BMI and smoking status, there remain three key areas where the model cannot be applied. The first is women who are either using hormonal contraception, have had endometrial ablation or have had a hysterectomy. In these instances we must rely on hormonal and clinical criteria alone. The second is women with polycystic ovarian syndrome (PCOS), who have oligomenorrhoea as well as a higher AFC and AMH. The final example is those with chronic illness, such as those undergoing chemotherapy for cancer or those living with HIV [4, 10].

Physiological Changes in the Menopausal Transition

At the root of the physiological changes taking place in the menopausal transition is a gradual reduction in the number and quality of ovarian follicles to critical levels [1–11]. During fetal development, oocyte production occurs until approximately 20 weeks of gestation, at which levels reach between 6 million and 7 million [1, 2]. Thereafter, there is no further oocyte production, and levels begin to decline through a combination of follicular atresia and oocyte release. Fewer than 100 follicles remain in each ovary at the onset of the perimenopause [1, 2, 7, 8, 11]. In addition, the oocyte and its surrounding layer of granulosa cells are thought to become increasingly incompetent with age [2, 3].

With the declining antral follicle count in the late reproductive stage and early menopausal transition, there is a reduced amount of inhibin B production by the granulosa cells. As discussed earlier, inhibin B normally acts on the pituitary gland in a negative feedback mechanism to reduce rising levels of FSH. Lower levels of inhibin B fail to keep this mechanism in check, which leads to higher levels of FSH during the early follicular phase [3, 7–9].

This in turn leads to increased activity of a single dominant follicle, or the recruitment of multiple dominant follicles, and thus higher levels of E2 production [1, 7]. As E2 levels rise to a critical level at an earlier stage, the LH surge occurs earlier and the follicular phase is shortened, which in turn reduces the overall cycle length [1, 3]. It should be noted that the luteal phase does not change in duration until later in the transition [1]. This shortened menstrual cycle length does not occur in all women entering the perimenopause.

As women move into the late menopausal transition, menstrual cycles become progressively longer in duration. The proportion of cycles which are anovulatory also increases. This may be due to a variety of reasons. Concerning the hypothalamic–pituitary–ovarian axis, there appears to be progressive deregulation of positive and negative feedback mechanisms. Indeed, high levels of E2, which would normally elicit an LH surge during the middle of the cycle, have been found to fail in this, whilst a fall in E2 in the luteal phase has failed to lower levels of circulating LH. Thus there may be an element of hypothalamic or pituitary insensitivity. In the ovary, response to FSH may be reduced. In about one-third of women in the menopausal transition, there is higher luteal phase E2, leading to a very early second ovulation. This is called a luteal-out-of-phase (LOOP) event. Whilst data are sparse, progesterone levels appear to fall steadily throughout the menopausal transition. This may be in part due to reduced progesterone

production by the corpus luteum as well as an increase in the frequency of anovulatory cycles [3, 5, 7, 8].

Levels of E2 only appear to fall in the 2 years preceding the FMP (this has been noted in prolonged ovulatory cycles), whilst levels of FSH continue to rise [3, 6, 8]. Only following the 12-month period of amenorrhea which is defined as the menopause are E2 levels persistently low [1, 7]. In postmenopausal women, it is estrone (E1) which predominates in the circulation. This is generated through the aromatization of androgens (secreted by the adrenal glands and postmenopausal ovaries) predominantly in the adipose tissue, but also the ovaries and other extragonadal sites [1].

In the early years after the FMP, levels of FSH are 15-fold higher, and levels of LH are 10-fold higher. This is in part due to low levels of inhibitory ovarian hormone production but also to a longer half-life of FSH and LH following alterations in isoform composition in the absence of E2. However, following the menopause, these levels fall slowly due to reduced GnRH pulse frequency and age-related changes in the pituitary reducing GnRH response [11].

Whilst there is little change in circulating testosterone concentrations across the transition, levels of sex hormone binding globulin fall, leading to an increased proportion of free testosterone. Yet following the menopause, testosterone production decreases by 25 per cent [3, 9].

Anti-Müllerian hormone is a glycoprotein produced by primary, preantral and antral follicles which differs from the other hormones of the menstrual cycle, as it does not appear to be directly involved in feedback mechanisms (gonadotropin independent). Interestingly, the number of antral follicles appears to reflect the size of the primordial pool [2, 7]. Thus, its levels are high at the menarche and decline thereafter [1, 7]. It is for this reason that AMH is of interest as a potential biomarker of reproductive aging and fecundity [2, 6–8]. However, in order to be used in this context, it would require further validation, as well as the development of more sensitive assays, as it is almost undetectable in the 5 years preceding the menopause [6]. This is discussed in more detail in Chapter 3.

Menopausal Symptoms

The menopausal transition and postmenopausal period are characterized by a broad range of physical and psychological symptoms, which can prove extremely debilitating to women undergoing the physiological changes of this period. Physical symptoms comprise vasomotor symptoms, urogenital symptoms, headaches, palpitations, breast tenderness, menorrhagia, musculoskeletal pain, restless leg syndrome, sleep disturbance and fatigue. Psychological symptoms include depression, irritability, poor concentration and memory loss. Sexual dysfunction appears to have somatic and psychogenic origins. Of these symptoms, vasomotor and urogenital symptoms appear to have the most profound effect on quality of life, and it is for these symptoms that women generally seek medical assistance [1, 5, 7, 9].

Physical Symptoms

Vasomotor Symptoms

Vasomotor symptoms are the most common manifestation of the menopausal transition and postmenopausal period, occurring in approximately three-quarters of women, and present as either hot flashes or night sweats. According to the STRAW + 10 staging

system, VMS generally arise in the late menopausal transition and are worst in the early postmenopausal period, and whilst symptoms generally last up to 5 years after the FMP, they can last as long as 15 years [1, 4, 9].

The exact physiology of VMS is not fully understood, but it is thought that the central thermoregulatory zone (where a person can maintain their body temperature without vasodilatation or sweating) becomes narrowed towards the end of the menopausal transition, so that vasodilatation and sweating are triggered at a lower temperature. This is supported by findings of VMS in those with pituitary insufficiency and following hypophysectomy (removal of the pituitary gland). There appears to be an association with low E2. Indeed, the increased prevalence of symptoms in the late menopausal transition and early postmenopausal period when E2 levels are falling, and the improvement of these symptoms with estrogen therapy, provides support to this notion. Supplementary progestogens have also been shown to have a beneficial effect on VMS [1, 5, 9].

A hot flash or night sweat is typically characterized by vasodilatation and sweating of the head, neck and chest. Other cardiovascular changes include an increase in heart rate and baseline electrocardiographic changes. Whilst the skin temperature rises by several degrees Celsius, the core body temperature appears to fall. They can be triggered by high temperatures, stress and hot food and drink. Symptoms generally last up to 5 min but can last up to an hour, and several episodes occur each day [1, 9]. There also appears to be a predilection for night-time symptoms, which in turn leads to insomnia and psychological symptoms including depression, irritability, poor concentration and memory loss [1, 5, 7, 9].

Several factors affect the frequency and severity of VMS. African American women experience VMS more frequently than their white counterparts. Women who have undergone a sudden-onset medically or surgically induced menopause experience significantly worse symptoms than those who have undergone a natural menopause [1, 9]. VMS symptoms are also discussed in Chapter 2.

Urogenital Symptoms

Whilst VMS occur in the late menopausal transition and early postmenopausal period, as outlined in the STRAW + 10 staging system, urogenital symptoms appear to be a predominating issue in the late postmenopause and worsen in severity over time. Approximately 50 per cent of women are affected. These symptoms are now collectively referred to as genitourinary syndrome of the menopause (GSM). At the root of this are estrogen and progesterone receptors which line the urogenital tract. With deficiencies in E2 and progesterone, a number of physiological changes take place [1, 4, 5].

In the vaginal tract, a loss of elasticity leads to shortening and narrowing. There is a reduction in epithelial cover, lubrication, musculature and vascularity. The vaginal rugae are lost. The vulva and vagina become paler, and there is a reduction in pubic hair as well as an increase in adiposity. Symptoms that arise from these changes include dryness, irritation, dyspareunia and traumatic bleeding. Moreover, fewer acid-producing bacilli in the vaginal tract make the pH more alkaline (>5) in postmenopausal women, and this can lead to a heightened susceptibility to infections. In the urological tract, the onset of the postmenopausal period can lead to urinary frequency, urgency, nocturia and incontinence. Women are also at an increased risk of urinary tract infections [1, 5]. Pelvic

organ prolapse is also a predominating feature of the postmenopausal period. These symptoms are discussed in more detail in Chapters 4, 6 and 7.

Other Physical Symptoms

Little is known about the physiological mechanisms which give rise to other physical symptoms characteristic of the menopausal transition. Concerning headaches, migraines can be a problematic feature of the perimenopause; this may be due to fluctuating E2 levels. Palpitations are a common occurrence in perimenopausal women, and are thought to be related to increased sympathetic activity. During the early menopausal transition, women commonly report breast tenderness, although symptom frequency and severity falls with advancing age. High levels of exogenous estrogen or progesterone have both been found to induce breast tenderness [1]. With progressive ovarian follicular depletion and an increase in anovulatory cycles, women often report menorrhagia. This is thought to result from high E2 levels, although progesterone deficiency may also play a contributing factor [1, 7]. Back pain and joint stiffness are common debilitating features of the perimenopausal period [1]. Many women also report sleep disturbance. This can be attributed to physical symptoms including VMS and restless leg syndrome, but it may also be the result of psychological symptoms and external factors. Disturbed sleep patterns can lead to weakness and tiredness [1, 9].

Psychological Symptoms

Psychological symptoms are a common feature of the menopausal transition and include depression, irritability, poor concentration and memory loss. Estrogen, progesterone and testosterone receptors have all been located in several brain centres, whilst estrogen has been shown to have an effect on several neurotransmitters, so it is possible that changes in these hormones may influence psychological symptoms [1]. To date, there is limited evidence that the endocrine changes of the perimenopausal period are responsible for these symptoms, and external factors may play a significant role [1, 9]. Despite this, hormone replacement therapy (HRT) does appear to improve symptoms of depression in the menopausal transition [1]. This is discussed in more detail in Chapters 8 and 9.

Sexuality

Ascertaining the cause of changes in sexuality during the menopausal transition and postmenopause is extremely challenging due to the complex interplay of physical and psychological factors. Many women report a loss of libido, as well as changes in sensitivity during this period. This may be directly due to hormone deficiency. Complications associated with aging may play a role; with advancing age, people are increasingly prone to chronic disease processes which may impede their ability to have sexual intercourse, and they may be on medications which may adversely affect their libido. Women can also experience a change in self-image at the time of the menopausal transition; the loss of reproductive capacity, age-related changes and surgical processes such as mastectomies may affect a woman's confidence. Most likely, a combination of these factors attributes to an increased prevalence of diminished sexual activity in the menopausal transition and postmenopausal phase [1]. Further information on this can be found in Chapter 10.

Other Physiological Consequences of the Menopausal Transition

Metabolic Syndrome and Cardiovascular Disease

Presently, the effect of the menopausal transition on a woman's risk of subsequent metabolic syndrome and cardiovascular disease (CVD) is not fully understood. Postmenopausal women have a significantly increased risk of metabolic syndrome, which is defined as a group of clinical disorders including hypertension, insulin resistance, glucose intolerance, dyslipidemia and obesity. Premenopausal women rarely have CVD, but its incidence is equal across the sexes by the eighth decade [7, 9].

It is known that estrogen can impact on blood pressure, lipid metabolism and insulin action. Concerning blood pressure, estrogen is a potent vasodilator which downregulates the renin angiotensin system and prevents angiotensin II formation (a potent vasoconstrictor), and activates endothelial nitric oxide synthase. With falling estrogen levels following the menopausal transition, these protective mechanisms are lost [7, 9]. Further information can be found in Chapter 15.

Weight gain is a common feature of the menopause. Estrogen deficiency appears to be associated with weight gain, whilst treatment with estrogen therapy can reduce the degree of weight gain or lead to weight loss. With the menopausal transition, the distribution of fat also appears to change. This can in part be explained by estrogen, which has a predilection to promote gluteofemoral adipose tissue accumulation. With the loss of estrogen at the time of the menopause, women start to store their fat abdominally, and this can lead to increased insulin resistance [7, 9].

Loss of Bone Mineral Density

Although osteoporosis and increased fracture risk are common features in postmenopausal women, it appears that rapid bone loss occurs during the menopausal transition through uncoupling of bone remodelling which leads to excess bone resorption. This in turn appears to result from a downward swing in estrogen levels [7]. Indeed, estrogen therapy leads to an improvement in bone mass and a reduction in the risk of vertebral and hip fractures, whilst its cessation causes a reversal of these changes [9]. Falling progesterone levels appear to reduce the rate of bone formation [7]. This is discussed in more detail in Chapter 14.

Breast and Endometrial Cancer

The menopausal transition has been identified as a time of increased risk for the development of both breast and endometrial cancer. Indeed, perimenopausal women (in their forties) are more likely to develop breast cancer than their menopausal counterparts (in their fifties). In this period, higher levels of endogenous E2 and lower levels of progesterone are a common finding [7].

Conclusion

In this chapter, we have provided grounding in the physiology of the normal menstrual cycle, and its dynamic changes through the late reproductive stage, menopausal