The pathophysiology of menopausal symptoms

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Abstract

Increasing life expectancy means that most Western women will experience the menopausal transition. This phase of reproductive life involves a biopsychosocial process where the majority of women experience physiological changes, influenced by a wide range of ethnic, psychological, social and cultural factors. With relatively similar endocrine changes, symptom reporting should be generalised, yet more women in Western cultures report vasomotor symptoms (hot flushes and night sweats) compared to women in Asian cultures. Different approaches to menopause based on biological, medical, psychological or psychosocial premises result in different treatments for women who have troublesome symptoms.

Hormone Replacement Therapy (HRT) is widely used in the management of symptoms associated with oestrogen withdrawal such as hot flushes, night sweats, sleep disturbance, vaginal dryness and dyspareunia, but has no known role in the treatment of midlife depression or arthritis. HRT prevents menopausal bone loss and osteoporotic fracture, though long-term use remains controversial because of the increased risk of breast cancer, myocardial infarction and stroke, as reported by the Women's Health Initiative. An understanding of the pathophysiology of menopausal symptoms and the risks and benefits of both hormonal and non-hormonal treatments assists in the individual management of patients.

Keywords endocrinology; hormone replacement therapy; menopausal transition; nomenclature; perimenopause; risks and benefits; symptoms

Introduction

The menopausal transition is generally defined as the time between onset of menstrual irregularity and the menopause. This phase of reproductive life involves a biopsychosocial process where the majority of women experience some physiological changes, which may be influenced by a wide range of ethnic, psychological, social and cultural factors. There is increasing evidence that such factors as lifestyle (smoking, diet, exercise and reproductive history), socio-economic status, body mass index, mood, climate and cognitions (including attributions of symptoms to the menopause, beliefs and attitudes towards menopause) might explain cultural variations in reports of menopausal symptoms. This review will focus on the pathophysiology of the common symptoms associated with the menopausal transition. The Stages of Reproductive Ageing Workshop (STRAW) staging system will be used when referring to various stages of reproductive ageing.

Hormone Replacement therapy (HRT) is widely used in the management of symptoms associated with oestrogen withdrawal (hot flushes, night sweats, sleep disturbance, vaginal dryness and dyspareunia). However, since the first results of the Women's Health Initiative (WHI) were published in 2002, the use of HRT has reduced significantly, due to a combination of fear (particularly of breast cancer) amongst women themselves and a more conservative approach to management by their physicians. In fact, the evidence suggests that treatment should be individualised, taking into consideration the risk/benefit ratio for each woman.

Definitions

There has been some confusion with the terms used to describe reproductive ageing in women. The menopause marks the end of reproductive life and occurs after 12 consecutive months of amenorrhoea, for which no other pathological or physiological cause can be established. The menopausal transition is the time before the final menstrual period (FMP) associated with irregular cycles, hormonal instability and symptoms. In the UK, the average age of menopause is 51.

Reproductive ageing occurs with loss of follicular activity within a wide age range (42–58 years). As chronological age is an unreliable indicator, guidelines for the classification of reproductive ageing were proposed at the 2001 Stages of Reproductive Ageing Workshop (STRAW). Previous attempts by the World Health Organisation (WHO) and the Council of Affiliated Menopause Societies (CAMS) to define the terminology resulted in terms such as premenopause, perimenopause, menopausal transition and climacteric that overlap. The STRAW staging system is the internationally recognised standard for characterising and classifying reproductive ageing through the menopausal transition. This system defines seven stages; five before and two following the FMP. Stages −5 to −3 includes the Reproductive period; −2 to −1 the Menopausal transition; and +1 to +2 the Postmenopause. In September 2011, the STRAW+10 was convened and further refined the definition of the reproductive stages in a woman's life and provides a comprehensive basis for assessing reproductive ageing. The recommendations from the STRAW+10 workshop appear in Figure 1 below, showing that Stage −3 (late reproductive age) is now divided into −3b and −3a, and Stage +1 is divided into +1a, +1b and +1c.

STRAW+10 criteria should not be use in women under 40 years with suspected premature ovarian failure (due to variable reproductive ageing). These criteria are not reliable in women with a history of hysterectomy or ablation, PCOS, chemotherapy or chronic disease.

The menopausal transition is defined by menstrual cycle and endocrine changes, beginning with a variation in menstrual cycle

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The 2011 Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women

	Menarche					FMP (0)				
Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ length	*Variable length* Persistent ≥7-day difference in consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very low Very low		
Antral follicle count			Low	Low	Low	Low	Very low	Very low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most likely*			*Increasing* symptoms of urogenital atrophy

*Blood draw on cycle days 2–5 ↑ = elevated
**Approximate expected level based on assays using current international pituitary standard

Figure 1 The 2011 Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. (Reproduced with permission from Harlow et al. Copyright Elsevier Science Inc).

length in a woman who has a monotropic follicle stimulating hormone (FSH) rise and ends with the FMP. According to the original STRAW criteria (unchanged in STRAW+10), the menopausal transition is divided into early and late stages. Stage −2 is characterized by variable cycle length, a minimum of seven days different from normal. The late menopausal transition is defined as two skipped cycles and an interval of amenorrhoea of at least 60 days.

The menopausal transition — endocrine changes

The endocrinology of the menopausal transition is complex and varies considerably from woman to woman. The decline in numbers of ovarian follicles (from atresia or ovulation) is the basis for reproductive ageing and occurs throughout life. The intricate feedback between the ovary and the hypothalamic −pituitary axis remains a challenge to understanding the endocrinology of reproductive ageing (Figure 2). Gonadotrophins regulate the secretion of ovarian steroid (oestradiol [E2], progesterone and testosterone) and peptide hormones (inhibins A and B). Anti-Mullerian hormone (AMH) is produced by ovarian granulosa cells independently of the gonadotrophins. Levels of inhibin B parallel the number of developing ovarian follicles.

During the early menopausal transition, the decline in follicle numbers reaches a critical level. Follicular phase inhibin B concentrations fall and FSH rises. The rise in FSH has been attributed to a fall in antral follicle production of inhibin B. This disruption to the feedback system is complex and involves a change from predominantly normal ovulatory cycles to predominantly abnormal ovulatory or anovulatory cycles until the FMP. Despite the overall diminishing follicle numbers during the menopausal transition, increased FSH stimulates residual ovarian follicles and continues to preserve normal levels of serum E2 until the late menopausal transition (Figure 3). The changes in pituitary gonadotrophin levels and AMH may result in intermittent ovulation and variability in cycle length — characteristics of the menopausal transition. Indeed, the only clinical sign of the menopausal transition is cycle length. Testosterone levels show little change in relation to the menopausal transition, whereas dehydroepiandrosterone sulphate (DHEAS) continues to fall with age.

Symptoms of the menopausal transition

Symptoms associated with the menopausal transition occur in up to 85% women and include vasomotor, vaginal dryness,