Social Science & Medicine 132 (2015) 103–112

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Review

Puberty and perimenopause: Reproductive transitions and their implications for women's health

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ARTICLE INFO

Article history:
Available online 14 March 2015

Keywords:
Puberty
Perimenopause
Chronic disease
Women's health
Life course health
HPG axis
HPA axis

ABSTRACT

This scoping review synthesizes existing research on two major transitions in females' lives: puberty and perimenopause. These two periods of vast physiological change demarcate the beginning and the end of the reproductive life cycle and are associated with major neuroendocrine reorganization across two key systems, the hypothalamic-pituitary-gonadal (HPG) axis the hypothalamus-pituitary-adrenal (HPA) axis. Despite growing evidence suggesting that the timing and experience of puberty and perimenopause are related to various physical and mental health outcomes (e.g., mood disorders, metabolism, cardiovascular health, autoimmune conditions, and cancer), these two processes are rarely examined together. In this paper, we bridge these disparate literatures to highlight similarities, isolate inconsistencies, and identify important areas for future research in women's health.

Puberty and perimenopause demarcate the beginning and the end of the female reproductive life cycle and are two major transitions in a woman's life. Despite underlying biological parallels, previous research suggests a weak or non-existent relationship between these reproductive life events (Forman et al., 2013). Growing evidence, however, suggests that the experience and timing of puberty and perimenopause are independently associated with many of the *same* health outcomes. For example, prevalence of mental health conditions, autoimmune diseases, and cardiometabolic risk all appear to increase during both puberty (Patton and Viner, 2007) and perimenopause (Greendale et al., 1999). Similarly, the timing in which these reproductive events occur (i.e., early or late as compared to average) in women's lives is also associated with various disease outcomes and mortality (Forman et al., 2013).

A life course approach to women's health recognizes that biological and social factors act interactively and cumulatively throughout the entire lifespan to shape health outcomes in later life (Kuh and Hardy, 2002). However, distant developmental periods (such as adolescence and middle age) are rarely examined together in an integrative and cohesive way to understand the epidemiology of common disease processes. The aim of this paper was to map a wide range of literature on the association of chronic conditions with puberty and perimenopause in order to identify the similarities and differences across these two key reproductive transitions. We propose that exploring these chronologically distant, yet physiologically connected, reproductive events together will help us understand important issues in women's health.

First, we summarized the neuroendocrine processes that define these two periods of change and development. Next, we conducted a scoping review (Arksey and O'Malley, 2005; Armstrong et al., 2011; Levac et al., 2010) of these fields to examine the relationships between progression and timing of puberty and perimenopause with long-term health and disease risk. We concluded with the implications of these findings and identified important areas for future research.

1. Introduction

Puberty is initiated in late childhood through a cascade of neuroendocrine changes that results in extensive physical growth, sexual maturation, and reproductive capability. Pubertal maturation consists of two associated but independent processes:

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http://dx.doi.org/10.1016/j.socscimed.2015.03.031
0277-9536/

Table 1
Summary of changes in the hypothalamic pituitary gonadal (HPG) axis during puberty and perimenopause.

	Puberty	Perimenopause
Gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and controls the synthesis and secretion of LH and FSH. In the brain, steroids influence GnRH secretion via neuroendocrine feedback loops to determine reproductive status during development.	The onset of puberty is characterized by a gradual increase in the frequency and amplitude of intermittent episodes of GnRH secretion.	GnRH pulse frequency decreases, in particular, during early perimenopause.
Luteinizing hormone (LH), produced by the pituitary gland, stimulates the ovaries to form androgenic precursors of estradiol. During the reproductive lifespan, a mid-cycle surge of LH triggers ovulation.	There are sleep-related increases in the pulsatile release of LH at the beginning of puberty, which eventually persist into the daytime and begin to cycle regularly by menarche.	Few observable changes in LH transpire until late perimenopause, when intermittent elevations in LH concentration and pulse amplitude occur.
Follicle-stimulating hormone (FSH), produced by the pituitary gland, stimulates gonadal growth and the production of gonadal hormones, such as estradiol and progesterone.	Starting at the beginning of puberty, FSH is secreted in parallel with LH, but increases relatively less. LH-to-FSH ratios are typically less than 1 during childhood and greater than 1 during puberty.	Intermittent elevations in FSH concentration occur at the beginning of perimenopause. The rise in FSH accelerates during late perimenopause.
Estradiol is the primary form of estrogen produced in women during her reproductive years. It is mostly released from the ovaries and adrenal glands, which subsequently downregulates secretion of LH and FSH.	Estradiol increases many-fold across pubertal development, and then levels off and begins to cycle regularly approximately one year after menarche.	Estradiol is erratic and elevated throughout early perimenopause. Estradiol decreases and is less erratic towards the end of perimenopause, accompanied by large increases in FSH and LH.
Progesterone is a hormone produced mainly by the ovaries and plays an important role in regulating the menstrual cycle. Production ceases if the egg is not fertilized, upon which menstruation occurs.	Production begins with menarche. Youth tend to have low or variable progesterone levels during the first few years after menarche.	Progesterone decreases gradually but continuously during perimenopause.

adrenarche, the reappearance of adrenal androgen production (around ages 6–8); and gonadarche, the pubertal reactivation of the hypothalamic-pituitary-gonadal (HPG) axis a few years later (Grumbach, 2004). Menarche, the initiation of the menstrual cycle, occurs toward the end of puberty, around the ages of 12–13 in most developed countries (Patton and Viner, 2007).

Perimenopause is defined as the period immediately preceding menopause when endocrinological, biological, and clinical features of approaching menopause commence (Hale and Burger, 2009; Prior, 1998). Women typically begin the shift from a reproductive state to non-reproductive state during their mid-to late 40s, and they remain in this transitory state for approximately 4–5 years before reaching menopause (Burger et al., 2007b; Prior and Hitchcock, 2011). Perimenopause culminates with menopause, when menses have ceased for a period of at least 12 consecutive months (Burger, 2008).

The neuroendocrine system presides over the significant hormonal changes occurring in the HPG axis during puberty and perimenopause (see Table 1 for a summary). In particular, both of these periods are characterized by major changes in the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which together regulate ovarian follicle growth and ovulation, and estradiol, the most abundant form of endogenous estrogen (Albin et al., 2012; Archibald et al., 2003; Burger, 2008; Burger et al., 2007a; Burger et al., 2007b; Nelson, 2008; Prior and Hitchcock, 2011; Prior, 2006). Mean levels of estradiol increase across pubertal development until menarche, when estradiol levels stabilize and then cycle regularly through the menstrual cycle each month. During late perimenopause, concentration of estradiol falls markedly from its elevated levels present during early perimenopause and eventually begins to stabilize (see Fig. 1).

In addition to the HPG axis changes related to puberty and perimenopause, another set of endocrine changes occur in the hypothalamus-pituitary-adrenal (HPA) axis. Levels of cortisol, the major hormonal output of the HPA system, vary throughout the day based on: (1) a strong circadian rhythm (i.e., basal pattern with high morning levels, low evening levels, and a strong negative slope), and (2) experiences of stress or challenge (i.e., cortisol reactivity) (McEwen et al., 1997). A growing body of research suggests that the overall basal activity of the HPA axis increases with sexual maturation in girls (i.e., higher average levels of cortisol across the day) (Adam, 2006; Gunnar et al., 2009; Legro et al., 2003; Netherton et al., 2004; Schiefelbein and Susman, 2006; Shirtcliff et al., 2005; Stroud et al., 2009). Initial research also suggests that girls experience increased cortisol reactivity (i.e., hypercortisolism) to stressful tasks across puberty (Gunnar et al., 2009; Stroud et al., 2009; Stroud et al., 2004).

Although comparatively less is known about the HPA axis changes during perimenopause, some studies have found an increase in cortisol levels as women transition from an early to late menopausal transition stage (Woods et al., 2006; Woods et al., 2009). Other research suggests that estrogen regulates corticotropin-releasing hormone gene expression, resulting in elevated cortisol levels (Vamvakopoulos and Chrousos, 1993). Therefore, as women approach menopause, increasing levels of FSH stimulate ovarian follicles to produce excess estrogen, which may influence cortisol levels (Santoro et al., 1996). There is also some evidence for greater HPA reactivity among postmenopausal women, with older women showing higher cortisol in response to challenge compared to both younger women and similarly-aged males (Seeman et al., 2001). Importantly, HPA activity is involved in regulating many physiological processes relevant to health including cardiovascular activity, blood pressure, and immune and inflammatory functioning (Chrousos and Gold, 1998).

The years surrounding both the initiation and completion of the female reproductive cycle are associated with major neuroendocrine reorganization that is distinct from other periods of the life course. In particular, dramatic changes occur across two key systems: the HPG axis—including fluctuations of LH, FSH, and estradiol— and hyperactivation of the HPA axis. By exploring the shared biological processes and associated health outcomes related to both puberty and perimenopause, we sought to answer: (1) What chronic diseases show a discontinuous increase in prevalence across *both* transitions? (2) Independent of the experience of these transitions, what is the association of pubertal and perimenopausal timing on health and disease?