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REVIEW

Menopause is not a disease – grasping the hormonal changes that induce menopause requires a prior understanding of the physiology of the menstrual cycle

P de Valdoleiros

Private practice, Cape Town, South Africa
Corresponding author, email: *paulodevaldoleiros@gmail.com*

This is the first of a number of articles on menopause and the primary purpose of this series is to place questions in your mind and lead you to ponder about long-held suppositions and the extent of their validity, so that you may serve patients in a more meaningful way. As we set out, it is evident that the volume constraints imposed by this manner of communication place limitations on how deep and wide one may go. I will not answer every question that arises as you read – that would require a semester course. I will endeavour to set out the basics, engage your curiosity and desire for understanding, and hence, set you on your way to follow the evidence to wherever it may lead you. Let the adventure begin.

Menopause is generally defined in medical dictionaries as the cessation of menstruation. In other words, the physiological processes that previously resulted in pregnancy or menstruation have undergone certain modifications leading to the termination of a function of the female reproductive system. I propose that we begin by investigating the exquisite hormonal dances performed primarily by the hypothalamus, the pituitary gland, the adrenal glands, and the ovaries, that regulate the menstrual cycle.

It is of crucial importance to review the hormonal effects and fluctuations that occur during the cycle, and to pay particular attention to the effect of progesterone as it will become the unsuspecting main protagonist when we eventually consider menopause. Take courage! Surely you did not think that there was nothing else to learn. This understanding is essential for grasping the hormonal environment of menopause. One could say that menstruation is the 'aetiology' of menopause.

The reproductive purpose of the menstrual cycle is the preparation of a uterine environment conducive to the implantation of a fertilised oocyte and the subsequent initial maintenance of a viable pregnancy. Everything begins in the deep recesses of the mysterious hypothalamus. Here, gonadotropin-releasing hormone (GnRH) is secreted in an increased and pulsatile manner once puberty starts. GnRH travels to the anterior pituitary, providing a signal for the secretion of stimulating follicle hormone (FSH) and luteinising hormone (LH), which, in turn, are transported to the ovaries. The ovarian follicle contains two cell types responsible for hormonal production known as theca cells and granulosa cells. LH stimulates theca cells to produce progesterone and androstenedione. The latter diffuses to the granulosa cells, where FSH from the pituitary stimulates these cells to convert androstenedione to testosterone first, and then to 17-β-estradiol. As the levels of progesterone and 17-β-estradiol fluctuate during the cycle, there is negative/positive feedback to the anterior pituitary to regulate its production of FSH and LH.[1-4] If you listen to classical music, you will identify the events so far as the first of the four movements. This initiating control system is setting the tempo and the rhythm of a beautiful symphony that has been replayed countless times in women over the ages, and which was the sound that facilitated your conception in your mother's womb. Yes, this is personal. On that note, let us set the platform by strolling through the different stages of the menstrual cycle.

The so-called first phase of the menstrual cycle is the follicular or proliferative phase. Based on an average cycle duration of 28 days, this phase occurs from day 1 to day 14. It is this phase that is responsible for the variable lengths of the menstrual cycle experienced by different women. The chief hormonal player during this phase is 17-β-estradiol, which acts upon the endometrial layer of the uterus, increasing its growth and thickness, as well as the amount of stroma and glands and the depth of the spiral arteries which feed it. The environment is being prepared for the implantation of a fertilised oocyte. Under the action of 17-β-estradiol, channels are created within the cervix allowing for sperm entry. In the meanwhile, back at the ovaries, a primordial follicle begins to mature into a Graafian follicle, while the surrounding follicles degenerate.[1,3,4] Whereas the first movement was brisk and lively, the second movement of the symphony of reproduction is slower and more lyrical. But do I hear a drum roll coming?

The mature Graafian follicle is set up. The levels of LH surge and the mature follicle breaks, releasing an oocyte for the journey of a lifetime – an epic voyage through a fallopian tube in the longing hope of meeting its soulmate. This is ovulation and it always happens 14 days before menses. The LH surge stimulates luteinisation of the granulosa cells and induces the synthesis of progesterone responsible for the midcycle FSH surge. Elevated FSH levels at this time are thought to free the oocyte

from follicular attachments, stimulate plasminogen activator, and increase granulosa cell LH receptors. The cervical changes that began during the follicular phase take on a new turn allowing for increased, waterier cervical mucous for improved accommodation of possible sperm.[1,4]

Significantly the levels of 17-β-estradiol drop precipitously at the end of ovulation, immediately prior to the LH peak. This is due to LH downregulation of its own receptor and to the direct inhibition of estradiol synthesis by progesterone. LH levels decline due to the loss of the positive feedback effect of oestrogen, the increasing inhibitory feedback effect of progesterone, and a depletion of the LH content of the pituitary from downregulation of GnRH receptors.[1,4] The oocyte is on its way in the third movement of our symphony in the form of an energetic dance down (or up!) the highway of conception.

Known as phase 2, the final phase of the menstrual cycle is called the luteal or secretory phase, and it occurs over the last 14 days of the cycle. Progesterone is the dominant hormone during this phase and its two main functions are the preparation of both the corpus luteum and the endometrium for a possible fertilised ovum implantation. The corpus luteum is a transient endocrine organ formed in the ovary at the site of the Graafian follicle rupture, predominantly secreting progesterone to prepare the endometrium for implantation by slowing down endometrial infiltration, decrease lining thickness, develop more complex glands, accumulate energy sources in the form of glycogen, and provide more surface area within the spiral arteries. This is the fourth and final movement. Our symphony is coming to an end. A rollicking finale! The conductor has a choice of two possible endings.

If pregnancy occurs, a fertilised ovum is implanted within the endometrium, and the corpus luteum will persist and maintain the progesterone levels until the placenta takes over progesterone production at about twelve weeks of gestation. However, if fertilisation has not occurred, the corpus luteum regresses, the levels of all hormonal players decrease rapidly, and the endometrial layer cannot be maintained, resulting in the typical blood flow lasting an average of approximately five days. This is called menses, and this period is considered the beginning of the next menstrual cycle. Bravo! Take a bow! What a performance! This beautiful symphony is performed an average of 400–450 times throughout a woman's lifetime.

Grasping the hormonal interplays during the menstrual cycle is the only way of understanding the transition into menopause. In our next article, we will consider whether menopause is an oestrogen deficiency-induced condition and realise that, as we have seen today, the steroid hormone system is an orchestra, not a single guitarist on a street corner.

Right now, make a cup of tea (or coffee!), find a comfortable sofa, listen to Symphony No 6 by Ludwig van Beethoven, and let your mind wonder about the real meaning of both the highly complex hormonal physiology of reproduction, and the human ability to compose and appreciate music. Some things cannot be measured empirically…

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