Module 4 - Menstrual cyclicity

Learning objectives:

At the end of this module you should be able to:

1. Have an understanding of the physiology of the menstrual cycle
2. List key fertility hormones and understand how they impact fertility
3. Describe key factors that affect ovulation
4. Summarise the impact of diet on ovulation

The menstrual cycle

The menstrual cycle consists of the hormonal and physical changes that allow for the production of oocytes and preparation of the uterus for pregnancy. The average length of the menstrual cycle is 28-29 days (but may range from 26-35 days).[1] The menstrual cycle consists for four phases:[2]

Phase	Days (approx.)	What happens
Menstrual (part of follicular phase)	1–5	Estrogen and progesterone are low. The lining of the uterus, called the endometrium, is shed, causing bleeding.
Follicular	6–14	The follicular phase starts on the first day of menstruation and ends with ovulation. Prompted by the hypothalamus, the pituitary gland releases follicle stimulating hormone (FSH). This hormone stimulates the ovary to produce around five to 20 follicles (tiny nodules or cysts), which bead on the surface. The growth of the follicles stimulates the lining of the uterus to thicken in preparation for possible pregnancy. The developing follicle causes a rise in the level of oestrogen and progesterone.
Ovulatory	15–17	Rising levels of estrogen trigger a release of Gonadotropin-releasing Hormone (GnRH) which then prompts the pituitary gland to release Leutenizing Hormone (LH) and FSH. These hormones trigger ovulation.
Luteal	18–28	During ovulation, the egg bursts from its follicle, but the ruptured follicle stays on the surface of the ovary. For the next two weeks or so, the follicle transforms into a structure known as the corpus luteum. This structure starts releasing progesterone, along with small amounts of oestrogen. This combination of hormones maintains the thickened lining of the uterus, waiting for a fertilised egg to implant.

		If a fertilised egg implants in the lining of the uterus, it produces the hormones that are necessary to maintain the corpus luteum. This includes human chorionic gonadotrophin (HCG), the hormone that is detected in a urine test for pregnancy. The corpus luteum keeps producing the raised levels of progesterone that are needed to maintain the thickened lining of the uterus. If pregnancy does not occur, the corpus luteum withers and dies, usually around day 22 in a 28-day cycle. The drop in progesterone levels causes the lining of the uterus to fall away (menstruation). The cycle then repeats.

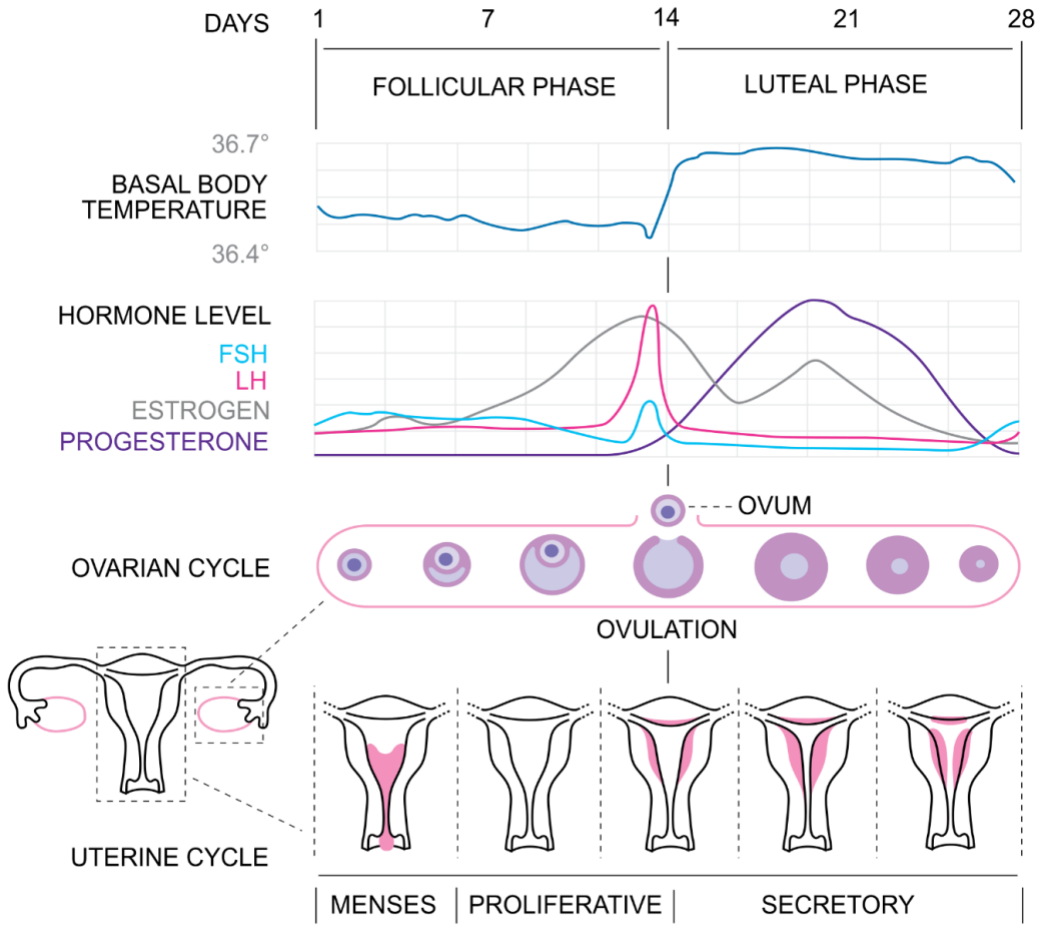

Figure 1: Hormonal, endometrial, ovarian and basal body temperature fluctuations during a normal menstrual cycle [3]

Overview of fertility hormones

The process of fertility is a complex interplay between a range of hormones that affect a woman's fertility. The female reproductive system is primarily regulated by five key hormones including

estrogen, progesterone, gonadotropin releasing hormone, follicle stimulating hormone, and luteinizing hormone. These hormones play a role in one or more stages of development and function of the female reproductive system.

Follicle Stimulation Hormone (FSH)

FSH is produced by the pituitary gland during the first half of the menstrual cycle. Its key role is in the stimulation and development of the maturing ovarian follicle.

Leutenizing hormone (LH)

LH is also produced by the pituitary gland. Its main roles are the stimulation of the ovaries to produce oestrogen and progesterone, triggering the process of ovulation, and promotion of the development of the corpus luteum.

Gonadotropin-releasing hormone (GnRH)

The monthly hormonal changes and development of a mature egg that occur with the monthly cycle are initiated in the brain by secretion of gonadotropin releasing hormone (GnRH). GnRH is made by hypothalamus where it is released into the blood and is involved in the release of FSH and LH.

Estrogen

Estrogen promotes the maturation and release of an ovum during the menstrual cycle. At the end of pregnancy, high levels of estrogen induce the ovaries to produce oxytocin which stimulates uterine contractions.

Progesterone

Progesterone is produced by the corpus luteum in the ovary where its function is to prepare the endometrium for the reception and development of the fertilised ovum. It also suppresses the production of oestrogen after ovulation has occurred.

Ovulatory dysfunction

Ovulatory dysfunction is one of the leading causes of infertility accounting for approximately 30% of cases.[4] It is when ovulation fails to occur (anovulation) or occurs on an infrequent or irregular basis (oligo-ovulation).

Factors affecting ovulation

Some of the key factors involved in healthy ovulation are:

Age

As women age, they may experience irregular ovulation characterised by irregular menstrual cycles. A cohort study concluded that the probabilities of pregnancy declined with age for women from the late 20s onward,[5] with probabilities of pregnancy twice as high for women aged 19–26 years compared with women aged 35–39 years.

Alcohol

Alcohol consumption has been reported to decrease fertility, although the level of consumption associated with this risk is not clear.[6] The mechanisms by which alcohol could impair conception are

unclear but may include an alcohol-induced rise in estrogen, which reduces secretion of FSH suppressing follicle development and ovulation. It may also have a direct effect on the maturation of the ovum, ovulation, blastocyst development and implantation.

Hormones

The five key reproductive hormones covered prior are all important in ovulation and conception and each of these must be present at the right time, and in the right quantity, to ensure that the process goes smoothly. This delicate balance of hormones can be thrown out if the levels of other hormones not involved in ovulation are too high.

One obvious example is PCOS which is a common cause of infertility.[7] PCOS is marked by the presence of elevated androgens such as testosterone which can impair the ovulation process.

In hypothyroidism, thyrotropin-releasing hormone may stimulate prolactin secretion in addition to thyrotropin-releasing hormone.[8] Correction of the hypothyroidism with thyroxine replacement allows thyroid stimulating hormone and prolactin levels to return to normal, releasing the suppression to gonadotrophin secretion and ovulation.

Obesity

Excess body fat is one of the most common causes of an ovulatory dysfunction.[9] In addition to the ovaries, adipose tissue also produces estrogen. Consequently, women (and men) with excess adipose tissue often have a higher estrogen production. Hyperestrogenism can also cause lowered levels of FSH and/or LH (due to suppression of the hypothalamic-pituitary-gonadal axis by estrogen), and lowered levels of androgen hormones.

During menstruation, estrogen levels are at their lowest. This signals the brain to produce FSH to begin maturing more eggs for ovulation. If a woman's estrogen is chronically high, hormone production becomes out of balance, weakening the signal for the body to commence maturation of eggs and thereby affecting her ability to ovulate. As such, women who are overweight or obese are up to three times more likely to experience irregular periods and less regular ovulation, making it much more difficult to conceive. [8] [10] It is recommended that women achieve a BMI of < 29 prior to commencement of ART.

Low BMI

Regardless of the underlying cause (eating disorder, excessive exercise, stress, genetics etc) of the low BMI (<20) [3] the concentrations of luteinising hormone, follicle stimulating hormone, and estradiol (a form of estrogen) will be low. Low levels of these fertility hormones often result in ovulatory dysfunction.

The 'female athlete triad' is a condition seen in physically active female athletes, consisting of low energy availability, low bone mineral density and anovulation (leading to oligomenorrhea followed by amenorrhea).[11] Low estradiol concentrations due to low body fat levels decrease bone mineral density. Energy availability is defined as daily dietary energy intake minus daily exercise energy expenditure corrected for fat-free mass. Energy availability <30 kcal/kg fat free mass per day disrupts menstrual function and bone mineralization.[12]

Weight gain using a high kilojoule, nutrient-rich diet can help recalibrate fertility hormones to recommence ovulation. Optimal energy availability has been identified to be 45 kcal/kg fat-free mass

per day in female adults but may be even higher in adolescents who are still growing and developing. Because the assessment of energy availability can be challenging, other goals of treatment can include the reversal of recent weight loss (if present), return to a body weight associated with normal menses, attainment of BMI ≥20 or >85% expected weight, and a minimum daily energy intake of 2000 kcal. A gradual increase of 200 to 600 kcal/day and a reduction in training volume of 1 day per week are usually sufficient to attain the needed improvements in weight and energy availability.[13] It is important to recognize that the resumption of ovulation may take up to one year or longer after restoration of appropriate energy availability. A written treatment plan (contract) signed by the providers and athlete/parent(s) can be a useful tool to outline and define the treatment plan and expectations on the part of the athlete, parent(s), and medical providers.

Impact of diet

Dietary modifications have been shown to improve ovulatory disorders affecting fertility. A large prospective study of 17,544 healthy women without a history of infertility, found increasing adherence to a healthy 'fertility diet' eating pattern was associated with a lower risk of ovulatory dysfunction.[14] A combination of five or more lifestyle factors was associated with a 69% lower risk of ovulatory disorder infertility. Healthy fertility eating patterns included:

Substituting animal-based proteins with plant-based proteins

One additional serving of meat (red meats, chicken, turkey, processed meats) per day, while holding calories constant, was associated with a 32% (95% CI 8, 62%) increase in the risk of ovulatory infertility.[15] Further, consuming 5% of total energy intake as vegetable protein rather than as animal protein was associated with a more than 50% lower risk of ovulatory infertility.

A large prospective study of 18,555 women found that consumption of red meats and chicken/turkey was associated with a greater rate of ovulatory disorder infertility while consumption of foods rich in vegetable protein showed a decreased risk of ovulatory disorder infertility. [14] This points to the merits of a predominantly plant-based diet in maintaining ovulation health.

Low glycemic index carbohydrates

Greater carbohydrate intake and dietary glycemic load were associated with an increased risk of infertility due to anovulation in a cohort of apparently healthy women.[16] Furthermore, dietary glycemic index was positively related to ovulatory infertility only among nulliparous women. These associations were independent of other characteristics of diet previously found to be associated with fertility and insulin sensitivity.

Higher consumption of monounsaturated fats

Research suggests that trans fatty acids may promote greater insulin resistance which could adversely affect ovulatory function.[17] However intakes of saturated fatty acids, monounsaturated fatty acids, total Polyunsaturated Fatty Acids (PUFAs), omega 3 PUFAs, and omega 6 PUFAS were not associated with ovulatory infertility. [16]

Full fat dairy

No relation was found between total intake of dairy foods and risk of ovulatory infertility (aRR=1.12 [95% CI 0.69,1.82] comparing ≥4 vs. <1 serving per day) yet this overall null finding was due to the fact that full-fat dairy foods were associated with lower risk of ovulatory infertility (aRR=0.73 [95% CI

0.52, 1.01] comparing ≥1 serving per day vs. ≤1 servings per week) while low-fat dairy foods were associated with higher risk of ovulatory infertility (aRR=1.85 [95% CI 1.24, 2.77] comparing ≥2 servings per day vs. ≤1 servings per week).[18]

Folic acid

Folic acid is an important pre-conception supplement as its role in reducing rates of Neural Tube Defects is well documented. However, emerging evidence suggests that it may play an important role in ovulation as well. Among women participating in the Nurses' Health Study II cohort, women who consumed ≥6 multivitamin tablets per week had a 41% (95% CI 25, 54%) lower risk of ovulatory infertility compared to non-consumers with folic acid appearing to explain most of this association.[19] Moreover, it was estimated that 20% (95% CI 11, 28%) of the ovulatory infertility cases could be avoided if women consumed 3 or more multivitamins per week. Consistent with this finding, folate intake was related to a lower frequency of sporadic anovulation and increased progesterone levels in a prospective cohort of young healthy women (adjusted odds ratio=0.36 [95% CI 0.14, 0.92] comparing women in highest to lowest tertile of folic acid).[20]

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