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FERTILITY

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SUMMARY

Energy balance is crucial to reproductive function, and consequently physical activity may affect fertility. However, the influence of physical activity on reproduction varies, depending on the intensity and type of physical activity and on the kind of population being investigated. There are concerns that excessive activity in female athletes can have adverse effects on fertility. In contrast, regular exercise may improve reproductive function in non-active women who are obese or have disorders of ovulation.

TAKE HOME MESSAGES:

- Diet and exercise comprise the most successful strategy to improve fertility in women who are obese and have disturbed ovulation.
- Strenuous exercise in normal-weight women appears to be associated with reduced fertility.
- Menstrual disturbances of varying degrees, all of which may negatively affect fertility, are common in female athletes.
- Little information exists on the reversibility of menstrual disturbances in female athletes after discontinuing training, or on the long-term impact of athletics on fertility.
- Hypothalamic amenorrhoea is an acquired condition that should be reversible by optimal nutrition in relation to energy needs.
- Polycystic ovary syndrome (PCOS), which requires the interaction of a genetic predisposition and environmental factors, is an alternative cause of menstrual disorders in sportswomen.
- In anovulatory women with PCOS who are of normal weight, induction of ovulation is the first choice for fertility treatment.



FERTILITY AND PHYSICAL ACTIVITY IN NON-ACTIVE WOMEN

Fertility can be described in terms of pregnancy rate, number of children (parity) and infertility rate. Infertility is defined as the inability of a couple to conceive within a year of trying to start a pregnancy. The prevalence of infertility in the general population is estimated at about 10% in developed countries. One-third of infertility cases are ascribed to female reproductive problems, one-third to male fertility problems, and one-third to a combination of female and male fertility problems. Several factors related to lifestyle influence fertility. These factors include body mass index (BMI), smoking, alcohol consumption and psychological stress. However, little is known about the impact of physical activity on female fertility in the general population.

Women in the general population

In a large research study of American nurses, vigorous exercise was associated with reduced risk of female infertility related to ovulatory dysfunction. In contrast, a Norwegian population-based health survey of 3887 women, which was conducted during 1984–1986 with follow-up a decade later, demonstrated that high levels of physical activity (i.e. almost daily) and high-intensity training (i.e. to exhaustion) were associated with an increased risk of fertility problems (3.2-fold and 2.3-fold increases, respectively). After age, parity, smoking and marital status were accounted for, BMI did not influence the results. Furthermore, the same study showed that a high frequency of physical activity was associated with voluntary childlessness. However, lower levels of physical activity and fertility were not directly associated. Similar results were found in a retrospective case-control study that reported a 6.2-fold increased risk of infertility in women who exercised vigorously. It was suggested that, in women of normal weight, strenuous exercise not compensated for by increased energy intake leads to a negative energy balance. In this state of negative balance, the energy requirements for reproductive functions may not be met (see below, *Hypothalamic amenorrhoea*).

Women who are obese or overweight

Obesity (defined as a BMI equal to or greater than 30), particularly the 'abdominal' type of obesity, has a major impact on reproductive function. Women who are obese are three times more likely to suffer from infertility than are women of normal weight. These women are also less likely to benefit from fertility treatment and have a higher risk of complications during pregnancy. Possible ways in which fertility may be reduced in women who are obese include disturbed ovulation, impaired development of oocytes (egg cells) and embryos, defects in implantation of the embryo into the wall of the uterus (womb), and increased pregnancy losses (spontaneous abortions or miscarriages).

The most common cause of disturbed ovulation in women with obesity is polycystic ovary syndrome (PCOS). PCOS is an endocrine (hormonal) disorder that affects approximately 5–10% of women of reproductive age. The clinical features of PCOS include menstrual dysfunction, increased body hair and polycystic ovaries on ultrasound. These signs are related to increased production of testosterone in the ovaries. In addition, PCOS is associated with insulin resistance (often a precursor to diabetes), accumulation of abdominal fat, and obesity. Reduced fertility is one of the major concerns for patients with PCOS, and various therapeutic strategies are employed in an attempt to improve ovulatory function. In women with obesity, a change of lifestyle that results in weight loss is considered the most successful strategy for improving reproductive function. Several studies have demonstrated that even a 5–10% reduction in body weight can restore the menstrual cycles and ovulation in these women.

Both diet and exercise improve reproductive function in women with obesity and ovulatory disorders. A clinical study has demonstrated that diet and exercise are equally effective in improving reproductive function in women with obesity and PCOS, despite the very minor weight loss associated with exercise alone. The underlying mechanism may be related to improved insulin sensitivity (function), because both exercise (independently of weight loss) and diet can improve insulin sensitivity. Factors that regulate insulin sensitivity are also known to play an important role in ovarian function, including follicular¹ growth and ovulation. Although exercise undoubtedly benefits women who are overweight and have ovulatory disorders, a huge clinical challenge is that many patients find making lifestyle changes difficult, and either fail to lose weight or quickly regain weight after an initial weight loss. Structured lifestyle management with long-term support may improve patients' compliance. In patients with severe obesity, bariatric surgery (e.g. 'gastric bypass') seems to be the most effective therapy to lose weight and improve fertility.

If lifestyle management is insufficient or ineffective, inducing ovulation with clomiphene citrate (an oral anti-oestrogen that stimulates the release of gonadotrophins²) is the next step. If the patient does not conceive with this treatment, various forms of assisted reproduction treatments, including in vitro fertilisation (IVF), can be offered.

FERTILITY IN ATHLETES

It is well known that menstrual disorders are common in female athletes, particularly in sports emphasising leanness, such as aesthetic and endurance sports and sports with weight classes (see Chapter 14). Varying degrees of menstrual disturbances have been described in athletes, ranging from luteal phase³ defects with subnormal production of oestrogen and progesterone⁴ but mostly regular bleeding intervals; to irregular bleeding separated by long intervals (oligomenorrhoea); and the total absence of bleeding (amenorrhoea). The exact prevalence of these menstrual disturbances in athletes is unknown but is probably much higher than in non-athletes. Although the underlying mechanisms may vary, all forms of menstrual disturbances can reduce fertility. Therefore, every case of menstrual disturbance in exercising women should be evaluated (see Issue 2.5).

Because female athletes usually do not plan pregnancies during their sports career, they may be more interested in the long-term impact of frequent or high-intensity exercise on fertility. Unfortunately, very little is known about the reversibility of menstrual disturbances in athletes, or about the effect of sports on female fertility.

Hypothalamic amenorrhoea

Today we understand that the most common cause of amenorrhoea in female athletes is the low availability of energy in relation to energy expenditure. This imbalance disrupts a chain of hormonal interactions, which ultimately prevents ovulation and leads to amenorrhoea. Briefly, an area of the brain called the hypothalamus controls the release of hormones (gonadotrophins) from the pituitary gland at the base of the brain. The gonadotrophins, in turn, control the secretion of the hormones oestrogen and progesterone from the ovaries.

1 A developing egg cell surrounded by its special supporting cells is called a follicle.

2 *Gonadotrophins* are hormones that control the function of the ovary.

3 The *luteal phase* of the menstrual cycle is governed by the hormone progesterone, which is secreted by a structure called the *corpus luteum* in the ovary.

4 *Oestrogen* (or oestradiol) and *progesterone* are the two main hormones secreted by the ovary. These hormones control the menstrual cycle.

The energy deficiency suppresses the hormonal release via the hypothalamus, which causes a chain reaction of hormonal suppression that results in reduced levels of oestrogen and progesterone in the ovary. Low levels of these hormones inhibit ovulation and cause amenorrhoea. More details of the hormonal pathway affected are shown in Figure 1.

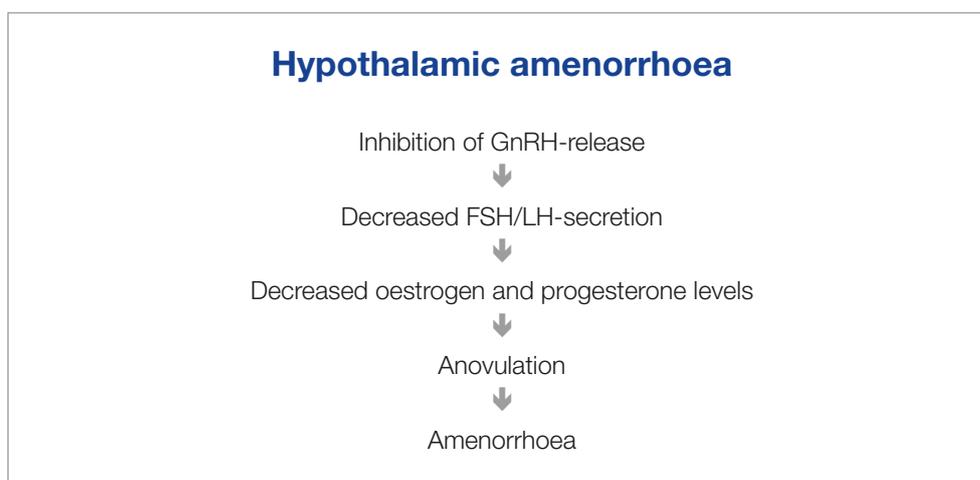


Figure 1. Alterations in the hormonal pathway that lead to hypothalamic amenorrhoea. GnRH = gonadotrophin-releasing hormone; FSH = follicle stimulating hormone; LH = luteinising hormone.

Increasing suppression of the reproductive system is reflected by a gradual progression of clinical signs, from short luteal phases to oligomenorrhoea and finally amenorrhoea. Luteal phase defects are often asymptomatic and only evident from measurements of reproductive hormones in the blood or urine during a menstrual cycle. This condition is associated with subnormal oestrogen levels in the follicular phase of the menstrual cycle, leading to reduced development of the follicles, delayed ovulation and reduced progesterone secretion by the corpus luteum in the ovary during the luteal phase (Figure 2). Insufficient progesterone to support the endometrium (the lining of the uterus) may prevent the successful implantation of a fertilised egg, and consequently result in infertility.

When development of the follicles is so impaired that ovulation does not occur, the menstrual cycle becomes irregular, with long intervals between bleeding. Thus, oligomenorrhoea is a typical sign of anovulation (failure to ovulate). The production of both oestrogen and progesterone is low, but enough oestrogen is produced to stimulate the endometrium to proliferate, and bleeding occurs when the endometrium breaks down. Amenorrhoea is the persistent absence of menses (bleeding), and in this case, oestrogen levels are too low to stimulate development of the follicles and endometrial growth. Consequently, amenorrhoeic women are anovulatory and infertile.

Although hypothalamic amenorrhoea implies infertility, it is important to remember that this disorder is an acquired condition that ought to be reversed by optimal nutrition in relation to energy needs. However, little information exists on the reversibility of menstrual disturbances in female athletes. Only case reports and small follow-up studies suggest that normal menstrual cycles resume after athletes discontinue training. Weight gain and/or a decrease in exercise level may be sufficient to treat hypothalamic amenorrhoea. If this is not the case and pregnancy is desired, ovulation can be induced with clomiphene citrate, gonadotrophins or gonadotrophin-releasing hormone (GnRH).

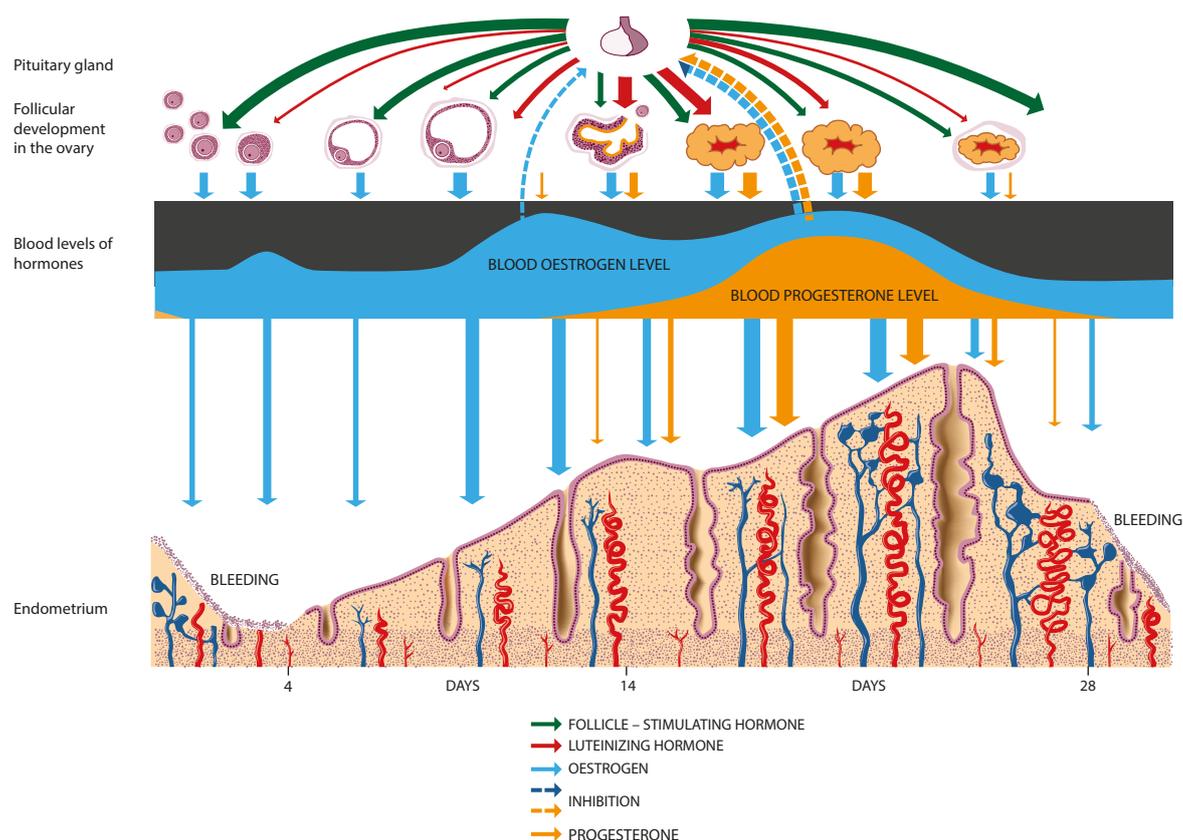


Figure 2. Follicular development, blood levels of reproductive hormones and changes in the endometrium during a normal menstrual cycle. [Source: XX]

Polycystic ovary syndrome

Not all female athletes with menstrual disturbances are in an energy-deficient state, and other mechanisms besides hypothalamic inhibition may therefore be involved. PCOS has been shown to be an alternative cause of menstrual disorders in female athletes, particularly in those with oligomenorrhoea and very muscular bodies (see Issue 2.5). This syndrome, which involves increased production of testosterone (the 'male' hormone) by the ovaries, requires a genetic predisposition, although environmental factors are involved as well. The hormonal profile of women with PCOS may therefore be an advantage for physical performance: androgens (testosterone and other similar hormones) are known to increase muscle strength in a dose-dependent manner (i.e. strength increases as the hormone concentration increases), and to improve physical performance in both men and women. Therefore, some researchers have suggested that PCOS could play a role in the recruitment of women to sports activities.

PCOS is considered the most common cause of anovulatory infertility, accounting for up to 70% of cases. The increased androgen production associated with PCOS inhibits ovulation and has been linked to implantation failure and reduced quality of oocytes and embryos. However, PCOS is also associated with an increased number of follicles, and long-term fertility is usually good because of a prolonged reproductive period.

Fertility in female athletes with PCOS has not been studied. Women who have PCOS and are not athletes are encouraged to be physically active to improve fertility and to counteract the metabolic complications such as insulin resistance, accumulation of abdominal fat and becoming overweight or obese. Athletic training may also be beneficial for these women.

In contrast to female athletes with hypothalamic amenorrhoea, there is no evidence that reduction or discontinuation of training improves reproductive function in athletes with PCOS.

In anovulatory women with PCOS, clomiphene citrate is the first choice of treatment to induce ovulation. If the patient fails to conceive, alternative treatments to induce ovulation, or IVF, can be offered.

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