Female Fertility Assessment

Fertility challenges impact millions of couples in the United States and around the globe. Approximately 10% of US women ages 15-44 have difficulty getting or staying pregnant.[1] Infertility is defined as the inability to get pregnant after one year of trying (or six months in a woman 35 years or older) through unprotected sex.[2] In addition to age and coital frequency,[3] hormonal health has a major physiological influence on fertility.

In women, ovulation depends on a regular menstrual cycle, a 28-day symphony of the hypothalamic-pituitary-gonadal (HPG) axis involving specific fluctuations in estrogen and progesterone levels, shown in the Figures in this assessment.[4,5] The pituitary gland sends pulses of follicle-stimulating hormone (FSH) in the follicular phase (days 1-14), triggering the rise of estrogen, which stimulates the hypothalamic release of gonadotropin-releasing hormone (GnRH), causing the pituitary secretion of luteinizing hormone (LH).[4,5] FSH and LH surges result in egg release from the follicle, with egg maturation and potential fertilization (i.e., if sperm are present) occurring in the ovulatory phase (day 14).[4,5] This is followed by the luteal phase (days 14-28), in which FSH and LH levels decrease and the corpus luteum secretes progesterone.[4,5] In the absence of fertilization, corpus luteum disintegration results in a progesterone drop and menstrual bleeding from endometrial lining shedding.[4,5]

Outlined in the Assessment section below, disruption of this hormonal pattern and other factors can negatively impact female hormonal homeostasis and fertility; these facets may include: infectious agents, inadequate nutritional status, thyroid dysfunction, key genetic variants, chronic stress, and insulin resistance. Let's explore the latter two, chronic stress and insulin resistance, further.

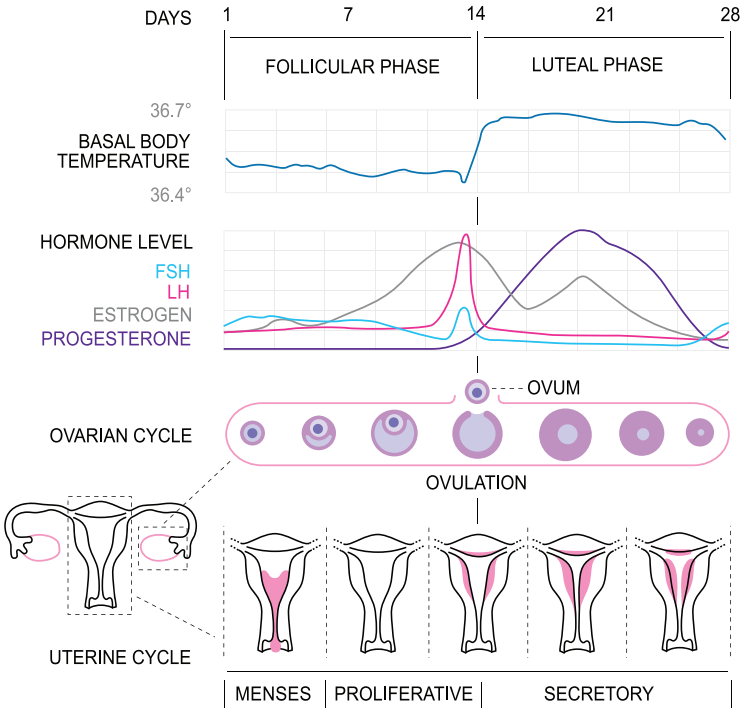
In a biochemical path often referred to as the "pregnenolone" or "cortisol steal," chronic stress can monopolize the production of cortisol,[6] thereby shunting pregnenolone (an endogenous steroid made from cholesterol, major precursor in the biosynthesis of stress and sex hormones)[7] toward stress hormone synthesis and away from sex hormone synthesis. This shift can reduce the availability of estrogen precursors like dehydroepiandrosterone (DHEA) and result in reduced levels of pregnenolone and progesterone, whereby the estrogen:progesterone (E:P) ratio is altered and can negatively impact menstrual regularity and fertility.[8,9]

Cardiometabolic factors, like blood glucose control and insulin sensitivity, can also impact sex hormones and fertility.[10] Insulin resistance can decrease sex hormone-binding globulin (SHBG),[11] resulting in excess free estrogen, testosterone, and dihydrotestosterone (DHT). Excess free estrogens further imbalance the E:P ratio, affecting ovulation, and excess free testosterone can impact FSH/LH pulsing, which can lead to polycystic ovary syndrome (PCOS) and androgen imbalance in women.[12]

Medical conditions that impact the function of a woman's ovaries, fallopian tubes, or uterus can contribute to female infertility. Anovulation causes can include underweight, overweight/obesity, PCOS, endometriosis, diminished ovarian reserve (e.g., due to age), functional hypothalamic amenorrhea (FHA), dysfunction of the hypothalamus or pituitary gland, premature ovarian insufficiency, and menopause.[2,13]

Reproductive endocrinologists specialize in infertility and also support women who have experienced recurrent pregnancy loss; however, a multidisciplinary clinical team approach addressing hormonal, lifestyle, social support, and other factors is ideal. While this clinical tool focuses on female fertility, it is important to point out that approximately 40% of fertility cases involve a male factor (e.g., low sperm count or quality).[3] Thus, a couple's approach to fertility assessment is prudent to uncover and address underlying root causes preventing conception.

Figure 1: Menstrual cycle[5]



Assessment

In addition to the screening labs described in the following table, a medical and sexual history, tubal evaluation, and ovarian reserve testing may be utilized.[2] Imaging assessments and procedures may include an ultrasound exam, hysterosalpingography, sonohysterography, hysteroscopy, and laparoscopy.[6] Basal body temperature (BBT) may also be tracked at home.[6]

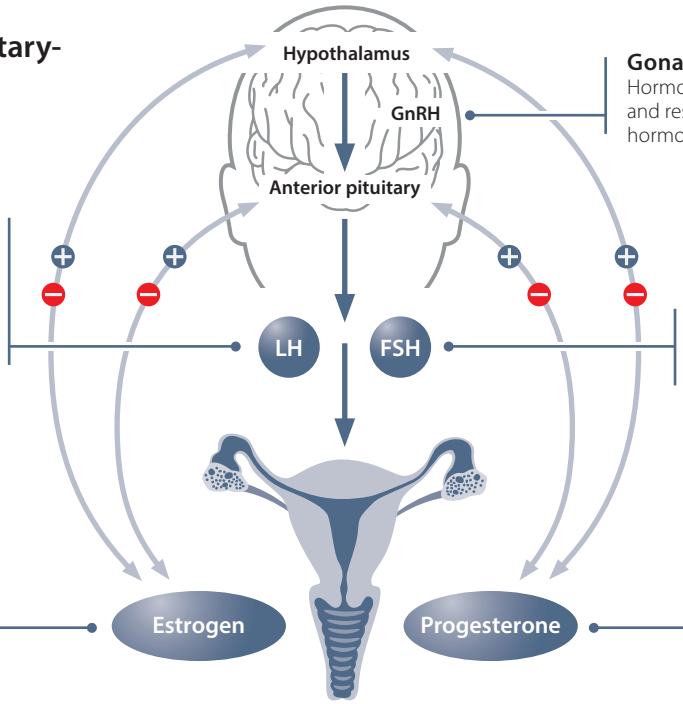
Screening labs

Routine	• CMP (assurance of inclusion to fasting glucose) • CBC with platelets • 25-hydroxyvitamin D (increasing benefit from top 2 quartiles) • Omega-3 index (particularly associated to assisted/IV fertilization and healthy conception overall) • Homocysteine (particularly associated to history of miscarriage/pregnancy loss) • Zinc

Known infertility	• Insulin (associated with impaired fasting glucose) and/or:
	  • Oral glucose tolerance test with insulin
	  • HbA1c
	• Hormone panel (FSH, LH, estrogen, progesterone, prolactin, testosterone, DHEA, cortisol/serial, multiple testing)
	• Iron sufficiency (serum iron and ferritin, transferrin, TIBC)
	• Thyroid panel (TSH/FT3/FT4/TPO antibodies)
	• AMH (antimüllerian hormone—PCOS, ovarian reserve)

Infectious	• HBsAg • RPR • GC/CT • TB • Zika
Additional	• Carnitine (acyl, free, total) • CoQ10 • ESR/CRP • Lupus anticoagulant • Anticardiolipin antibody
Genetics	• MTHFR C677T (methylenetetrahydrofolate reductase) • MTHFR A1298C (methylenetetrahydrofolate reductase) • COMT V158M (catechol-O-methyltransferase) • BMP15 (bone morphogenetic protein 15) • VDR (vitamin D receptor)

Figure 2: Hypothalamic-pituitary-gonadal (HPG) axis[4,14]



Gonadotropin-releasing hormone (GnRH)
Hormone released through the anterior pituitary and responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Luteinizing hormone (LH)
Works with follicle-stimulating hormone (FSH) to stimulate the release of the egg from the ovary (ovulation). LH is controlled by the hypothalamus and pituitary gland.

Follicle-stimulating hormone (FSH)
Acts in conjunction with luteinizing hormone (LH) to stimulate release of eggs by ovaries (ovulation). It is controlled by the hypothalamus and pituitary gland.

Estrogen
The female sex hormone produced by ovarian follicles. Helps breast development during puberty, regulates menstruation, builds uterine lining to prepare for pregnancy, and maintains bone health.

Progesterone
Secreted by the corpus luteum in the female body after ovulation during the second half of the menstrual cycle. Prepares the endometrium for the potential pregnancy after ovulation, counterbalances estrogen by helping regulate uterine lining, emotions, and sleep.

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