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ANSWERS

1. The hormones of the anterior pituitary include
2. Adrenocorticotropic hormone (ACTH): ACTH stimulates the adrenal glands to produce hormones. After ACTH is made in the pituitary gland, ACTH is released into the bloodstream and travels around the body. Production of ACTH is regulated by corticotrophin-releasing hormone (CRH) from the hypothalamus and cortisol from the adrenal gland. If ACTH levels are low, the hypothalamus releases CRH which is key to the stress hormone system and acts on many areas of the brain such as appetite and memory. Once the CRH is discharged, it triggers the pituitary gland to secrete ACTH. If too much ACTH is produced, this can lead to high levels of cortisol in the body, also known as Cushing syndrome.
3. Follicle-stimulating hormone (FSH): FSH works with LH to ensure normal functioning of the ovaries and testes. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are called gonadotropins because stimulate the gonads. In males, the testes, and in females, the ovaries. In women, this hormone stimulates the growth of ovarian follicles in the ovary before the release of an egg from one follicle at ovulation. It also increases oestradiol production. In men, follicle stimulating hormone acts on the Sertoli cells of the testes to stimulate sperm production (spermatogenesis).
4. Growth hormone (GH): GH is essential in early years to maintaining a healthy body composition and for growth in children. In adults, it aids healthy bone and muscle mass and affects fat distribution. Growth hormone release is not continuous, it is released in a number of ‘bursts’ or pulses every three to five hours. This release is controlled by two other hormones that are released from the hypothalamus (a part of the brain), growth hormone-releasing hormone, which stimulates the pituitary to release growth hormone, and somatostatin, which inhibits that release. Under normal conditions, more GH is produced at night than during the day. GH acts on many tissues throughout the body. In children and adolescents, it stimulates the growth of bone and cartilage. In people of all ages, GH boosts protein production, promotes the utilization of fat, interferes with the action of insulin, and raises blood sugar levels. GH also raises levels of insulin-like growth factor-1 (IGF-1).
5. Luteinizing hormone (LH): LH works with FSH to ensure normal functioning of the ovaries and testes. In women, LH stimulates estrogen and progesterone production from the ovary. A surge of LH in the midmenstrual cycle is responsible for ovulation, and continued LH secretion subsequently stimulates the corpus luteum to produce progesterone. Development of the ovarian follicle is largely under FSH control, and the secretion of estrogen from this follicle is dependent on FSH and LH. The granulosa cells of the ovary secrete inhibin, which plays a role in cellular differentiation. In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells). FSH stimulates testicular growth and enhances the production of an androgen-binding protein by the Sertoli cells, which are a component of the testicular tubule necessary for sustaining the maturing sperm cell.
6. Prolactin: Prolactin stimulates breast milk production. Prolactin is a hormone and its function is to promote milk production (lactation) in mammals in response to the suckling of young after birth. Lactotroph cells in the pituitary gland produce prolactin, where it is stored and then released into the bloodstream. Human prolactin is also produced in the uterus, immune cells, brain, breasts, prostate, skin and adipose tissue. Dopamine restrains prolactin production, the more dopamine there is, the less prolactin is released. Prolactin itself enhances the secretion of dopamine, so this creates a negative feedback loop. High levels of prolactin in the blood also cause difficulty in getting an erection for men, as well as breast tenderness and enlargement.
7. Thyroid-stimulating hormone (TSH): TSH stimulates the thyroid gland to produce hormones. It controls production of the thyroid hormones, thyroxine and triiodothyronine, by the thyroid gland by binding to receptors located on cells in the thyroid gland. Thyroxine and triiodothyronine are essential to maintaining the body’s metabolic rate, heart and digestive functions, muscle control, brain development and maintenance of bones. When thyroid stimulating hormone binds to the receptor on the thyroid cells, this causes these cells to produce thyroxine and triiodothyronine and release them into the bloodstream. These hormones have a negative effect on the pituitary gland and stop the production of thyroid stimulating hormone if the levels of thyroxine and triiodothyronine are too high. They also switch off production of a hormone called thyrotropin-releasing hormone. This hormone is produced by the hypothalamus and it also stimulates the pituitary gland to make thyroid stimulating hormone.
8. Melanocyte-stimulating hormone: Melanocyte-stimulating hormone is a collective name for a group of peptide hormones produced by the skin, pituitary gland and hypothalamus. In response to ultraviolet (UV) radiation its production by the skin and pituitary is enhanced, and this plays a key role in producing coloured pigmentation found in the skin, hair and eyes. It does this by inducing specialised skin cells called melanocytes to produce a pigment called melanin; melanin protects cells from DNA-(1)'>DNA damage, which can lead to skin cancer (melanoma).Melanocyte-stimulating hormone is produced from the same precursor molecule as adrenocorticotropic hormone called pro-opiomelanocortin (POMC). melanocyte-stimulating hormone produced in the hypothalamus can also suppress appetite by acting on receptors in the hypothalamus in the brain. This effect is enhanced by leptin, a hormone released from fat cells.

1b) Principle of Letrozole

Letrozole is a drug that stops androgens in the body from converting into estrogen. When estrogen is blocked, the pituitary gland gets a message that it needs to produce follicle-stimulating hormone (FSH), which stimulates the ovary to produce an egg. Some women on letrozole actually release more than one egg because they produce more FSH while on letrozole than a woman produces when ovulating naturally. Letrozole is an aromatase inhibitor used in the treatment of breast cancer. Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens by a process called aromatization. As breast tissue is stimulated by estrogens, decreasing their production is a way of suppressing recurrence of the breast tumor tissue. It is also used to treat certain types of breast cancer (such as hormone-receptor-positive breast cancer) in women after menopause. Letrozole is also used to help prevent the cancer from returning. Some breast cancers are made to grow faster by a natural hormone called estrogen.

Principle of Clomifene

Clomifene has both estrogenic and anti-estrogenic properties, but its precise mechanism of action has not been determined. Clomifene appears to stimulate the release of gonadotropins, follicle-stimulating hormone (FSH), and leuteinizing hormone (LH), which leads to the development and maturation of ovarian follicle, ovulation, and subsequent development and function of the corpus luteum, thus resulting in pregnancy. Gonadotropin release may result from direct stimulation of the hypothalamic-pituitary axis or from a decreased inhibitory influence of estrogens on the hypothalamic-pituitary axis by competing with the endogenous estrogens of the uterus, pituitary, or hypothalamus. Clomifene has no apparent progestational, androgenic, or antrandrogenic effects and does not appear to interfere with pituitary-adrenal or pituitary-thyroid function. Used mainly in female infertility due to anovulation (e.g. due to polycystic ovary syndrome) to induce ovulation. Clomiphene citrate is considered as the drug of choice for first line treatment of anovulatory dysfunction.

Menotropin / Gonadotrophins : Being a combination drug, Menotropins bind to the follicle stimulating hormone receptor (FSH), which results in ovulation in the absence of sufficient endogenous luteinizing hormone (LH). It also binds the LH receptor, thereby stimulating proper hormone release. The drug contains both FSH and LH, therefore, it induces ovarian follicular growth and development as well as gonadal steroid production in women who do not have ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and is involved in the physiological events leading to development of a competent pre-ovulatory follicle. It is used to treat female infertility, Menotropins stimulates late follicular maturation and resumption of oocyte meiosis, and initiates rupture of the pre-ovulatory ovarian follicle. Menotropins bind to the LH/hCG/FSH receptor of the granulosa and theca cells of the ovary to effect these changes in the absence of an endogenous LH surge.

1. Amenorrhea

Amenorrhea refers to the absence of menstrual periods, it may be either primary (meaning a woman never developed menstrual periods) or secondary (absence of menstrual periods in a woman who was previously menstruating or the absence of menstrual periods for three consecutive cycles or a time period of more than six months in a woman who was previously menstruating.). Amenorrhea may result from disorders of the ovaries, pituitary gland, hypothalamus, or uterus. Intensive exercising, extreme weight loss, physical illness, and stress can all result in amenorrhea.

Laboratory findings

1. History

Patients would be asked about age, eating and exercise patterns, changes in weight, previous menses (if any), medication use, chronic illness, presence of galactorrhea, and symptoms of androgen excess, abnormal thyroid function, or vasomotor instability. Taking a sexual history can help corroborate the results of, but not replace, the pregnancy test. Family history should include age at menarche and presence of chronic disease. Although it is normal for menses to be irregular in the first few years after menarche, the menstrual interval is not usually longer than 45 days.

1. Physical examination

The physician should measure the patient's height, weight, and body mass index, and perform thyroid palpation and Tanner staging. Breast development is an excellent marker for ovarian estrogen production. Acne, virilization, or hirsutism may suggest hyperandrogenemia. Genital examination may reveal virilization, evidence of an outflow tract obstruction, or a missing or malformed organ. Thin vaginal mucosa is suggestive of low estrogen. Dysmorphic features such as a webbed neck or low hairline may suggest Turner syndrome.

1. Pregnancy test

If a woman with amenorrhea is sexually active, it is worthwhile to conduct a pregnancy test. Pregnancy is a common cause amenorrhea and should always be considered in sexually active women, even if they use contraceptive methods. If abdominal pain is present, ectopic pregnancy should be considered. Patients should be questioned about contraceptive use, because extended-cycle combined OCs, injectable medroxyprogesterone acetate (Depo-Provera), implantable etonogestrel (Implanon), and levonorgestrel-releasing intrauterine devices (Mirena) may cause amenorrhea.

1. Urine microscopy, culture and sensitivity

The urine culture test is performed to grow and identify organisms, mainly bacteria and fungi that may cause a Urinary Tract Infection (UTI). While in the bladder, urine is normally sterile and free from any organisms. Urinary tract infections are common in females and children than in adult males.

1. Detection of anatomic abnormalities

Mullerian agenesis, a condition characterized by a congenital malformation of the genital tract, may present with normal breast development without menarche, and may be associated with urinary tract defects and fused vertebrae. Other congenital abnormalities that may cause amenorrhea include imperforate hymen and transverse vaginal septum. In these conditions, products of menstruation accumulate behind the defect and can lead to cyclic or acute pelvic pain. Physical examination, as well as ultrasonography or MRI, is key to diagnosis, and surgical correction is usually warranted. Rare causes of amenorrhea include complete androgen insensitivity syndrome, which is characterized by normal breast development, sparse or absent pubic and axillary hair, and a blind vaginal pouch; and 5-alpha reductase deficiency, which is characterized by partially virilized genitalia. In these conditions, serum testosterone levels will be in the same range as those found in males of the same age. The karyotype will be 46, XY, and testicular tissue should be removed to avoid malignant transformation.

1. Hormonal assessment

Thyroid-stimulating hormone (TSH), b-HCG, prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) measurements are always the first line of testing this is because they are all involved in reproductive processes. Abnormal thyroid function can alter levels of sex hormone-binding globulin, prolactin, and gonadotropin-releasing hormone, contributing to menstrual dysfunction. Low LH and oestradiol suggests a hypothalamic cause for amenorrhoea (e.g. weight loss, excessive exercise or stress). Elevated FSH suggests reduced ovarian reserve and the possibility of impending premature ovarian failure.

1. Clomid stimulation test: The Clomid Challenge Test (CCCT) is a sensitive means to measure ovarian reserve and is often conducted if a woman's FSH level is 10-15 mIU/mL or the estradiol level is greater than 65 pg/mL. The Clomid Challenge Test is routinely performed at HRC in women aged 38 years or older regardless of how the cycle day 3 levels look. This will identify patients with ovarian dysfunction. It is also done in women of any age with otherwise unexplained infertility, as approximately 30 percent will show abnormalities that adversely impact their prognosis with fertility treatment.

2b) Menopause is defined as the absence of menstrual periods for 12 months. It is the time in a woman's life when the function of the ovaries ceases. The average age of menopause is 51 years old, but menopause may occur as early as the 30s or as late as the 60s. There is no reliable lab test to predict when a woman will experience menopause. In females, the combined action of FSH and LH stimulates growth of ovarian follicles and steroidogenesis, with the production of androgens, which are then converted to oestrogens by the action of the enzyme aromatase. A mid-cycle surge in LH also triggers ovulation. FSH levels usually increase during menopause, because the ovaries become less responsive to FSH, which causes the pituitary gland to increase FSH production. However, fluctuating ovarian activity, especially early in perimenopause, means that FSH and oestradiol levels are not reliable predictors of menopause, as they are sometimes at pre-menopausal levels.

1. Infertility

Infertility is defined as not being able to get pregnant despite having frequent, unprotected sex for at least a year for most couples without contraception. Infertility may result from an issue with either of the partners, or a combination of factors that prevent pregnancy. Infertility affects both women and men. A woman is considered infertile if she has tried for 1 year to get pregnant and hasn’t used birth control. A man is considered infertile if he has too few sperm or his sperm are too unhealthy to combine with a woman’s egg.

Laboratory investigation of infertility

1. History: This is a review of age, past medical history, prior surgeries and medications used. A discussion of family history of infertility or birth defects, a careful review of social history and occupational hazards to evaluate potential exposure to hazardous substances that could impact fertility. For females Menstrual history, including age of menarche, cycle length and characteristics, and presence/severity of dysmenorrhea, should be queried.
2. Physical Exam

A thorough physical examination should identify thyroid enlargement, nodules, or tenderness suggestive of thyroid dysfunction, breast secretions due to hyperprolactinemia, and virilizing effects of androgen excess (hirsutism, acne, hair thinning, male pattern baldness), due to adrenal disorder or polycystic ovary syndrome. For males, a thorough physical examination is done to evaluate the pelvic organs such as the penis, testes, prostate and scrotum. For females Pelvic examination is done to assess vaginal/cervical anatomical abnormalities or discharge. Size, shape position, and mobility of uterus has to be documented to exclude leiomyomas, endometriosis, or uterine adhesive disease. The ovaries and uterus may be examined by ultrasound, and a specific X-ray test can check the uterus and fallopian tubes.

1. Urine microscopy, culture and sensivity:

These can indicate the presence of an infection.

1. Semen Evaluation

The evaluation assesses sperm motility or movement, the shape and maturity of the sperm, the volume of the ejaculate, the actual sperm count and the liquidity of the ejaculate. A semen analysis is necessary even if the male partner has fathered a child before.

1. Hormonal Tests

Hormonal tests evaluate levels of testosterone and FSH (follicle-stimulating hormone) to determine the overall balance of the hormonal system and specific state of sperm production. Serum LH and prolactin are other hormonal tests that may be done if initial testing indicates the need for them. Thyroid-stimulating hormone (TSH) and prolactin levels are useful to identify thyroid disorders and hyperprolactinemia, which may cause problems with fertility, menstrual irregularities, and repeated miscarriages.

1. Laparoscopy: This is a surgical procedure in which a lighted telescope-like instrument (laparoscope) is inserted through the wall of the abdomen into the pelvic cavity. Laparoscopy is useful to evaluate the pelvic cavity for endometriosis, pelvic adhesions, and other abnormalities.
2. Ovarian Reserve Testing: When attempting to test for a woman’s ovarian reserve, the clinician is trying to predict whether she can produce an egg or eggs of good quality and how well her ovaries are responding to the hormonal signals from her brain. The most common test to evaluate ovarian reserve is a blood test for follicle stimulating hormone (FSH) drawn on cycle day 3. In addition to the FSH level, the physician may recommend other blood tests, such as estradiol, antimüllerian hormone (AMH), and/or inhibin-B, as well as a transvaginal ultrasound to do an antral follicle count (the number of follicles or egg sacs seen during the early part of a menstrual cycle).

3b) To support couples in achieving conception, the following can be advised-

1. Understanding when a lady is ovulating and having sex regularly five days before and on the day of ovulation can improve the odds of conceiving.
2. Maintain a normal weight because Overweight and underweight women are at increased risk of ovulation disorders.
3. Lifestyle changes : These include

Improving diet/exercise habits, eliminating alcohol, quit smoking, if either of them smoke and to cut back on caffeine.

1. Antibiotics to treat infections in the reproductive organs.
2. Medications and counseling to treat problems with erections or ejaculation.
3. Hormone treatments if the problem is a low or high level of certain hormones.
4. Fertility drugs and hormones to help the woman ovulate or restore levels of hormone
5. Surgery to remove tissue that is blocking fertility (such as endometriosis) or to open blocked fallopian tubes if the cause is a varicoele (widening of the veins in the scrotum) or a blockage in the vas deferens, tubes that carry sperm.

Infertility in men and woman can also be treated with assisted reproductive technology, or ART. There are several types of ART:

1. IUI (intrauterine insemination): Sperm is collected and the placed directly inside the woman's uterus while she is ovulating.
2. IVF (in vitro fertilization): The sperm and egg are collected and brought together in a lab. The fertilized egg grows for 3 to 5 days days. Then the embryo is placed in the woman's uterus.
3. GIFT (gamete intrafallopian transfer) and ZIFT (zygote intrafallopian transfer): The sperm and egg are collected and quickly placed in a fallopian tube. With GIFT, the both sperm and eggs are placed into the fallopian tube. With ZIFT, the sperm and eggs are brought together in a lab and then a fertilized egg is placed into the tube at 24 hours.