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Hypopituitarism

Paola Ascoli · Francesco Cavagnini

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Abstract Hypopituitarism is the partial or complete insufficiency of anterior pituitary hormone secretion and may result from pituitary or hypothalamic disease. The reported incidence (12–42 new cases per million per year) and prevalence (300–455 per million) is probably underestimated if its occurrence after brain injuries (30–70% of cases) is considered. Clinical manifestations depend on the extent of hormone deficiency and may be non specific, such as fatigue, hypotension, cold intolerance, or more indicative such as growth retardation or impotence and infertility in GH and gonadotropin deficiency, respectively.

A number of inflammatory, granulomatous or neoplastic diseases as well as traumatic or radiation injuries involving the hypothalamic-pituitary region can lead to hypopituitarism. Several genetic defects are possible causes of syndromic and non syndromic isolated/multiple pituitary hormone deficiencies. Unexplained gonadal dysfunctions, developmental craniofacial abnormalities, newly discovered empty sella and previous pregnancy-associated hemorrhage or blood pressure changes may be associated with defective anterior pituitary function.

The diagnosis of hypopituitarism relies on the measurement of basal and stimulated secretion of anterior pituitary hormones and of the hormones secreted by pituitary target glands. MR imaging of the hypothalamo-pituitary region may provide essential information. Genetic testing, when indicated, may be diagnostic.

Secondary hypothyroidism is a rare disease. The biochemical diagnosis is suggested by low serum FT4 levels and inappropriately normal or low basal TSH levels that do not rise normally after TRH. L-thyroxine is the treatment of choice. Before starting replacement therapy, concomitant corticotropin deficiency should be excluded in order to avoid acute adrenal insufficiency. Prolactin deficiency is also very rare and generally occurs after global failure of pituitary function. Prolactin deficiency prevents lactation. Hypogonadotropic hypogonadism in males is characterized by low testosterone with low or normal LH and FSH serum concentrations and impaired spermatogenesis. Hyperprolactinemia as well as low sex hormone binding globulin concentrations enter the differential diagnosis. Irregular menses and amenorrhea with low serum estradiol concentration (< 100 pmol/l) and normal or low gonadotropin concentrations are the typical features of hypogonadotropic hypogonadism in females. In post menopausal women, failure to detect high serum gonadotropin values is highly suggestive of the diagnosis. In males, replacement therapy with oral or injectable testosterone results in wide fluctuations of serum hormone levels. More recently developed transdermal testosterone preparations allow stable physiological serum testosterone levels. Pulsatile GnRH administration can be used to stimulate spermatogenesis in men and ovulation in women with GnRH deficiency and normal gonadotropin secretion. Gonadotropin administration is indicated in cases of gonadotropin deficiency or GnRH resistance but is also an option, in alternative to pulsatile GnRH, for patients with defective GnRH secretion.

P. Ascoli · F. Cavagnini (✉)
Chair of Endocrinology, Istituto Auxologico Italiano, University of Milan, Ospedale San Luca,
Milan, Italy
e-mail: francesco.cavagnini@unimi.it

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Hypopituitarism is the partial or complete defect in anterior pituitary hormone secretion and may result from pituitary or hypothalamic disease [1].

The incidence and prevalence of hypopituitarism range from 11.9 to 42.1 per million inhabitants per year and from 300 to 455 per million inhabitants, respectively [2, 3]. These figures might increase significantly if hypopituitarism secondary to brain injury is taken into account, as the latter is largely undiagnosed.

Clinical features

Clinical manifestations of hypopituitarism are variable, often non specific and insidious at onset, and depend on the severity of hormone deficiency (Table 1).

When hypopituitarism is secondary to pituitary tumors, symptoms related to mass effects, e.g., headache, visual impairment, electrolyte alterations, as well as consequences of hypothalamic dysfunction, e.g., disorders of the autonomic nervous system, may also be present. Hyperprolactinemia is a common finding in non prolactin-secreting macroadenomas, due to compression of the pituitary stalk and impairment of dopaminergic inhibitory tone.

Etiology

Many diseases affecting the hypothalamic-pituitary region, both in childhood and adult life, may lead to hypopituitarism (Table 2).

Table 1 Clinical symptoms of hypopituitarism

Corticotroph deficiency
Acute: fatigue, weakness, dizziness, nausea, vomiting, hypotension, hypoglycemia
Chronic: tiredness, pallor, anorexia, weight loss, hypoglycemia
Children: failure to thrive, hypoglycemia
Thyrotropin deficiency
Tiredness, cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, slow mental processes
Gonadotropin deficiency
Children: delayed puberty
Women: amenorrhea, oligomenorrhea, infertility, loss of libido, dyspareunia (short-term); osteoporosis, premature atherosclerosis (long-term)
Men: loss of libido, impaired sexual function, decreased muscle and bone mass, erythropoiesis and hair growth
Growth hormone deficiency
Children: growth retardation
Adults: decreased muscle mass and strength, increased visceral fat mass, fatigue, premature atherosclerosis, decreased quality of life

From van Aken and Lamberts [4].

Table 2 Causes of hypopituitarism

Childhood onset
Genetic disorders, including familial hypopituitarism with isolated or multiple hormone deficiencies
Perinatal damage (abnormal delivery, asphyxia), pituitary hypoplasia or aplasia
Craniopharyngiomas and other parasellar tumours
Craniospinal irradiation
Head trauma
Adult onset
Pituitary tumours, pituitary surgey, irradiation, infarction (apoplexia)
Peripituitary tumors, including meningiomas, gliomas, metastases
Lymphocytic hypophysitis
Postpartum hemorrhage (Sheehan's syndrome)
Internal carotid artery aneurysm, subarachnoid hemorrhage
Trauma, infections, abscesses
Hemochromatosis, granulomatous diseases, histiocytosis X

From Van Aken and Lamberts [4].

Screening for pituitary failure

Assessment of pituitary function should always be performed in presence of pituitary or hypothalamic lesions or after cranial irradiation. Unexplained gonadal dysfunctions, inflammatory disorders, head trauma, skull surgery, brain granulomatous disease, developmental craniofacial abnormalities, newly discovered empty sella and previous pregnancy-associated hemorrhage or blood pressure changes also call for a thorough exploration of anterior pituitary hormone reserve [5].

Diagnosis

The diagnosis require the measurement of basal and stimulated (see below) secretion of anterior pituitary hormones and their target hormones. Clinical and/or biochemical evidence of hypopituitarism calls for imaging of the hypothalamo-pituitary region and MR imaging is currently the first choice modality. Serum and CSF angiotensin converting enzyme activities (neurosarcoid), serum ferritin (hemochromatosis), human chorionic gonadotropin (germ cell tumors), may provide additional etiological information. Genetic testing is particularly helpful in syndromic/non syndromic isolated or multiple pituitary hormone deficiency (Table 3).

Hypopituitarism following traumatic brain injury (TBI) and subarachnoid haemorrhage

Cross-sectional studies have recently shown that anterior pituitary dysfunction after traumatic brain injury (TBI) is more common than previously appreciated, with up to 30–

Table 3 Genetic causes of hypopituitarism

	Gene defect	Hormone deficiences
Combined	PIT-1 (POU1F1, GHF1)	GH, TSH, PRL
	PROP-1	GH, LH/FSH, TSH, ACTH, PRL
	HESX1 (Rpx)	GH, LH/FSH, TSH, ACTH, ADH
	LHX3/LHX4	GH, LH/FSH, TSH, PRL
	PITX2	GH, PRL
Isolated	GH	GH
	GHRH receptor	GH
	HESX1	GH
	KAL	FSH/LH
	GnRH receptor	FSH/LH
	DAX1/AHC	FSH/LH
	TBX19 (TPIT)	ACTH
	TSH-β	TSH
	TRH receptor	TSH

From Jostel A, Lissett CA, Shalet SM [6].

70% prevalence [7, 8]. GH is the first of pituitary hormone to be affected after TBI [8], in 9–40% of patients. Early identification of TBI-induced hypopituitarism is important because it may affect recovery from TBI and replacement therapy may improve rehabilitation outcome and enhance quality of life [9].

Patients with an initial Glasgow Coma Scale score of 13 or less should be monitored closely. Special attention should also be paid to children and adolescents as normal pituitary function is essential for their growth.

Nearly half of patients presenting pituitary defects six months after TBI, resume normal pituitary function after 1 year. On the other hand, some patients with preserved pituitary hormone secretion early after TBI have been shown to become hormone deficiency after 12 months. Early post-traumatic panhypopituitarism generally persists. Thus, re-evaluation of anterior pituitary function and quality of life is advisable 6–12 months after TBI. There is still no consensus as regards the time of early evaluation.

Isolated or multiple pituitary hormone deficiencies may occur after aneurysmal subarachnoid haemorrhage. These patients, therefore, should also be adequately monitored.

Thyrotropin deficiency

Secondary hypothyroidism is considered a rare disease at 50 cases per million inhabitants which, however, is most likely an underestimation. Most patients suffer from additional pituitary hormone deficiencies whose clinical manifestations usually overshadow those of TSH deficiency.

Clinical features

Symptoms include fatigue, weakness, inability to lose weight, constipation and cold intolerance, in keeping with the clinical features of primary hypothyroidism. Symptoms are generally milder because of some residual TSH secretion. Growth retardation is the main clinical problem in children, accompanied by fatigue and gonadal dysfunction.

Etiology

See Table 2.

Biochemical diagnosis

TSH deficiency is suggested by low basal serum free/total thyroxine (T4) with inappropriately normal or low TSH levels. Occasionally, TSH values may be moderately elevated due to the production of inactive hormone. Measurement of serum tri-iodothyronine (T3) is not helpful because it is often within the normal range even in hypopituitary patients with low thyroxine concentrations. The thyrotropin-releasing hormone stimulation test should be interpreted with caution as false negative results (i.e., slight elevations of TSH) may occur [10].

Therapy

L-thyroxine is the treatment of choice. Concomitant corticotropin deficiency should be excluded prior to starting replacement therapy in order to avoid an adrenal crisis, since thyroid hormones are known to increase cortisol clearance. It is advisable to start with low doses of L-thyroxine, 25–50 μg daily, and increase the dosage by 25 μg daily every 2 weeks. Special care should be exercised in the elderly or in patients with ischemic heart disease. Mean replacement doses are 75–100 μg daily (1.6 μg/kg b.w.).

Adequacy of replacement therapy can be established on clinical grounds and by serum free T4 concentrations which should attain the reference range. During pregnancy, thyroid hormone binding globulin levels increase and thyroid hormone replacement needs to be increased in parallel by approximately 30%. Caution should be paid to overtreatment causing iatrogenic hyperthyroidism; this may have adverse effects on the cardiovascular system (atrial fibrillation) and bone mineral density, which can already be compromised in patients with coexisting hypogonadism and growth hormone deficiency [11].

Prolactin deficiency

Prolactin deficiency is very rare and generally occurs after failure of other pituitary hormones. Basal plasma prolactin

levels are low and fail to rise upon iv injection of TRH. Not rarely, however, prolactin levels are increased in patients in whom hypopituitarism is secondary to pituitary mass lesions. Prolactin deficiency prevents lactation.

Growth hormone deficiency (see specific article)

ACTH deficiency (see specific article)

Male hypogonadotropic hypogonadism

Biochemical diagnosis

Hypogonadotropic hypogonadism is characterized by low testosterone with low or normal LH and FSH serum concentrations, and impaired spermatogenesis. Serum testosterone should be measured in the morning given its diurnal rhythmicity. Borderline values (e.g. between 250 and 350 ng/dl) require a second assessment. Semen analysis should be obtained in the hypogonadal patient before starting any form of treatment. The World Health Organization criteria for normal semen analysis include: volume >2 ml, sperm count >20 millions/ml, total sperm count $\geq 40 \times 10^6$ with motility $\geq 50\%$, and normal morphology $\geq 30\%$. Because of the variability in sperm counts, a second analysis should be done if the first is abnormal. Hyperprolactinemia as well as low sex hormone binding globulin concentrations have to be excluded.

Etiology

In addition to general causes of hypopituitarism (Table 2), hypogonatotropic hypogonadism may be due to congenital defects (Table 4) or feature in a variety of syndromes, such as morbid obesity (Prader-Willi), cerebellar ataxia [12], cranial nerves palsies and peripheral neuropathy [13], congenital spherocytosis [14].

Clinical features

Clinical features differ according to whether gonadotropin deficiency occurred before or after puberty. In the former, clinical examination will reveal small penis, small testes, and eunochoid proportions (arm span exceeding height by >5 cm). Micropenis defines a morphologically normal penis, with a length of the stretched penile urethra, measured along the dorsal surface from the pubis to the tip of the glans, of 2.5 SD below the mean value for age. Mean length at birth is 3.5 ± 0.4 cm. A stretched penis length of less than 2.5 cm for a newborn at term is defined micropenis.

Gonadotropin deficiency acquired after puberty is associated with a reduction in testicular size, loss of facial and body hair and thinning of the skin, finely wrinkled facial skin typical of the "aging youth". Other clinical features include loss of libido and impaired sexual function as well as decreased muscle and bone mass.

Table 4 Etiology of congenital hypogonadotropic hypogonadism

Congenital Idiopathic hypogonadism (CIHH)
anosmic (Kallmann syndrome)
non anosmic: normosmic IHH (nIHH)
Fertile eunuch syndrome
Adrenal hypoplasia congenital
Genetic defects of the gonadotropin subunits
FSH-β mutations
LH-β mutations
mutations in leptin and leptin receptor genes
Hypogonadotropic hypogonadism associated with other pituitary
hormone deficiencies
PROP-1 mutations
HERS1 mutations
Complex syndromes which include hypogonadotropic
hypogonadism
Prader-Willi syndrome
congenital spherocytosis
Moebius syndrome
cerebellal ataxia
retinitis pigmentosa

From Winters SJ [15].

Evaluation before starting replacement therapy

Digital rectal examination should be performed and serum prostate-specific antigen (PSA) measured in middle aged or elderly males. If serum PSA is elevated and/or prostate nodules or irregularities are detected, the patient should be referred for urological assessment. The patient should also be advised of the risk of urinary obstruction or excessive libido.

Blood cell count, clotting parametres, liver function tests and lipid profile should be obtained in order to exclude polycithemia, bleeding disorders, impaired liver function and dyslipidemia. Evaluation of bone density by DEXA is recommended. In pre pubertal subjects, bone age has to be determined. Androgens should be administered with caution to patients with cardiac or renal failure or severe hypertension.

Treatment

Infants

Infants with micropenis due to congenital hypopituitarism require testosterone administration to increase the length of the organ. Long-acting esters of testosterone may be used,

e.g. testosterone enanthate 25 mg i.m. every 4 week for 3 times. If a satisfactory increase in penis length (>0.9 cm) has not occurred, another 3 injections can be given [16, 17]. It is not necessary to repeat the treatment during infancy.

Induction of pubertal changes

There is no general consensus on the ideal procedure to induce pubertal development. An acceptable proposal may be to induce pubertal development at 12 years and obtain a slow and progressive increase in serum sex steroids.

Monthly i.m. injections of 25–50 mg testosterone enanthate or cypionate can be used. The dose should be kept as low as possible in order to preserve maximal growth potential. Dosage is increased every 6–12 months and adult replacement dosage (see below) reached in 3–5 years. One disadvantage of androgen therapy is that testicular volume does not increase. When an increase in testicular volume and fertility are desired, therapy with gonadotropins or GnRH can be carried out.

Testosterone replacement therapy in adult males

Injectable preparations testosterone esters (enanthate, cypionate) 250 mg can be administered i.m. every 2–3 weeks. These preparations induce large plasma testosterone oscillations, with supraphysiological levels immediately after injection and levels below the therapeutic range in the days before the subsequent administration. These peaks and troughs of serum testosterone may result in mood swings and acne. In these patients, dosage may be decreased and frequency of the injections increased (e.g. testosterone enanthate 100 mg every 7–10 days).

Oral preparations testosterone undecanoate is most widely used. It is adsorbed via the lymphatic system thus escaping first-pass liver metabolism. Serum testosterone levels, however, fluctuate largely and multiple daily doses are required (160–240 mg/day in 3–4 doses). On balance, testosterone undecanoate is not optimal for long-term treatment [18].

Transdermal preparations these formulations are an attractive and viable alternative to oral preparations. Nonscrotal transdermal patches are small in size and release testosterone at a relatively constant rate. Patches applied daily achieve physiological testosterone levels in more than 90% of males. Skin irritation may occur in up to 60% of subjects and lead to discontinuation of therapy (some 10–15% of subjects) [19]. Most recently, gel preparations for transdermal testosterone delivery have been developed. The daily doses vary between 5 and 10 g, each delivering 5 to 10 mg testosterone. Relatively steady levels of serum testosterone are obtained after a few days [20]. One potential problem is transferal of androgen via close contact.

Subcutaneous implants crystallized testosterone implants (600–800 mg, i.e. 3–4 pellets of 200 mg) induce stable physiological testosterone levels for 4–6 months, but require minor surgery and local anesthesia for implantation on the lateral wall of the abdomen or hip. One caveat of this treatment is the possibility of implant expulsion (5–10% of cases), especially in subjects with scarce adipose tissue or in those who perform vigorous physical activity [21].

Follow-up during androgen therapy

Optimal dosage of testosterone should be established by monitoring serum testosterone concentrations at appropriate times, based on the pharmacokinetics of the specific preparation (e.g. before and 7 days after the injection). Serum estradiol concentrations should also be measured if high serum levels of testosterone are recorded, and the intervals between the injections should be lengthened if estradiol levels are high [22].

Hemoglobin and hematocrit should be monitored 3 months after each dose adjustment, then yearly. Patients with high hemoglobin levels before treatment should be watched more carefully. Liver function tests and lipid profile should be obtained every year. Serum PSA should be measured 1–3 months after initiation of treatment, then yearly according to the common urological practice.

Bone density should be measured in patients receiving testosterone substitution therapy before treatment and then regularly every 2 years. Bone age has to be monitored in prepubertal subjects to avoid premature epiphyseal closure.

Induction of fertility

Pulsatile GnRH therapy can be used to stimulate spermatogenesis in men with GnRH deficiency and normal gonadotropin secretion [23]. GnRH pulses are dispensed via a portable pump, with a subcutaneous butterfly needle inserted in the abdominal wall. Small boluses of GnRH are delivered every 120 min, starting at 4 μg per pulse and increasing by 2 μg every two weeks, up to 20 μg per pulse if serum LH levels do not rise. Serum testosterone generally normalizes in 2 months and testicular volume increases in 3–6 months. The time required for appearance of sperm in the ejaculate is quite variable, ranging from 2 to 22 months [24]. Treatment for up to 2 years is generally necessary to maximize testicular growth and spermatogenesis while longer treatments may be necessary in patients with small testes (volume <3 ml).

When pulsatile GnRH therapy fails, mutation in the GnRH receptor gene or antibodies against GnRH or its receptor should be suspected. In these patients, spermatogenesis may be attempted by gonadotropin administration.

Gonadotropin therapy is effective in achieving fertility in patients with gonadotropin deficiency or GnRH resistance

but it is also an option, in alternative to pulsatile GnRH therapy, for patients with defective GnRH secretion.

Human chorionic gonadotropin (hCG) may be used in patients with adult-onset hypogonadism and residual FSH secretion at 1000–2500 I.U. i.m. or s.c. twice weekly for 8–12 weeks [25]. Dose adjustments are required to achieve normal serum testosterone levels. Gynecomastia may occur due to aromatization of testosterone into estradiol and requires dose reduction. An initial testicular volume greater than 4 ml is a positive predictor for outcome. Treatment has to be continued as long as fertility is desired.

In patients with congenital hypogonadism or not responsive to hCG alone, a combined treatment with hCG and FSH-containing preparations is required [25]. Among the latter, human menopausal Gonadotropin (hMG), purified from urine of menopausal women, or highly purified urinary human FSH (uFSH –HP) can be administered (75–150 IU i.m. or s.c. three times weekly) together with hCG. Full spermatogenesis is generally obtained in 6–9 months in 90% of cases [24]. Recombinant human FSH (r-hFSH), which contains no LH and is superior to urinary preparations in terms of purity and specific activity, is now available. r-hFSH 150 IU s.c three times weekly or 225 IU twice weekly is administered in combination with hCG. If azoospermia persists after 6–9 months, the dose of r-hFSH may be increased to a maximum of 300 UI three times a week [26].

Surveillance during fertility therapy

Testicular size should be evaluated by palpation or ultrasonography every 3–6 months. Increased echodensity is a favorable sign for active spermatogenesis. Serum testosterone should be monitored at the beginning of therapy, then every six months together with estradiol, hemoglobin and hematocrit once the maintenance dosage has been established.

Female hypogonadotropic hypogonadism

Diagnosis

Menstrual disturbances and amenorrhea with low serum estradiol concentration (<100 pmol/l) and normal or low concentrations of gonadotropins are typical features of hypogonadotropic hypogonadism. In postmenopausal women, failure to detect high serum gonadotropin values is highly suggestive of the diagnosis. Hyperprolactinemia must be excluded. Dynamic testing is of limited value and seldom employed.

Etiology

In addition to common causes of hypogonadism (Tables 2 and 4), an exclusively female form of hypogonadotropic hypogonadism is Sheehan syndrome. This disorder results from infarction of the enlarged pituitary gland due to peri- or postpartum hemorrhage and may involve one or more pituitary hormones. Diagnostic criteria include: (a) history of postpartum hemorrhage or inadequate lactation or menstrual disturbances; (b) clinical and/or laboratory evidence of deficiency of at least one pituitary hormone; (c) no evidence of pituitary mass [27].

Clinical features

Clinical features parallel those of male hypogonadism and depend on the pre- or post pubertal onset. In the former, primary amenorrhea and absent breast development will be found. In the adult woman, oligomenorrhea or amenorrhea, infertility, breast atrophy, vaginal dryness and dyspareunia are referred. Pubic and axillary hair become sparse and thin when ACTH is also deficient.

Treatment

Induction of puberty

The proper age to intervene is 11 years using one of the available protocols [28]. Conjugated estrogens (initial dose 0.15 mg daily or 0.3 mg on alternate days), ethynil-estradiol (initial dose 0.05–0.1 μg/kg daily, 2.5–5 μg daily) or 17 β-estradiol (initial dose 5 μg/kg daily) can be administered and the dose increased every 6–12 months over the following 2–3 years, until adult replacement dosage is achieved (0.6–1.25 mg conjugated estrogens, 10–20 μg ethinylestradiol or 1–2 mg 17β-estradiol daily). After 6 months of therapy or in case of spotting or menstrual bleeding, cyclic progestagens (usually medroxyprogesterone 5–10 mg daily or norethisterone 0.7–1.0 mg daily) should be added for 12–14 days every month to protect the uterus and establish monthly menstrual cycles.

In alternative, estrogen-releasing patches can be used. The smallest commercially available patch releases 25 μg 17β-estradiol daily. The patch can be subdivided into six —eight fragments which allows release 0.08–0.12 μg/kg daily. Application of the patch may be limited to the night in order to obtain serum estradiol levels similar to those seen in early puberty and mimic the pattern of estrogen secretion that is predominantly nocturnal during initiation of puberty [29]. The dosage should be increased, every 6–12 months, until adult replacement dosage is reached (50–100 μg/day).

Replacement therapy in the adult female

A detailed description is beyond the scope of this article. According to the current protocols, natural or synthetic estrogens (the former carrying lesser risk of thromboembolism

and arterial hypertension) are administered for approximately three weeks every month and a progestagen added during the third week. Therapy is resumed after one week of drug withdrawal during which menstrual bleeding occurs. In alternative to the oral route, estrogens can be administered transdermally through patches changed two times a week.

Full dosage of estrogens, greater than that used for contraception, can be used if tolerated and ensures maintenance of bone mass. Transdermal estrogen therapy appears preferable to oral administration for women who smoke or who suffer from migraine headaches, hypertrigliceridemia, hepatobiliary disorders, fibrocystic breast disease or thromboembolism [30]. The long-term impact of estrogen replacement therapy on cardiovascular morbidity or development of breast cancer in hypopituitary patients is at present unknown.

Induction of fertility

Pulsatile GnRH is the treatment of choice for ovulation induction in patients with hypothalamic hypogonadotropic hypogonadism and normal gonadotrophs.

Pulses of GnRH are delivered i.v. or s.c. every 60–90 min by a portable pump, starting with 2.5–5 μg/bolus and increasing the dosage up to 10–20 μg/bolus if no response is obtained after 10–15 days of treatment [31]. Once oocyte maturation has occurred, ovulation is achieved by administration of 5000 IU hCG. Corpus luteus is maintained by progesterone or hCG (two-three injections of 1500–2000 IU given at three day intervals) or by continuation of GnRH at the same or slower pulse frequency (120–240 min.).

Vaginal ultrasound is used to assess follicular development. The growing of a single follicle is a favorable response. Multiple follicular responses may lead to cycle cancellation if multiple pregnancy is unadvised. The ovulation rate is 60–80% and the pregnancy rate is around 30% per ovulatory cycle. Multiple pregnancies occur in 5% of cases with an abortion rate of 20–25%.

Gonadotropin therapy is indicated in patients with gonadotropin deficiency or GnRH resistance but can also be used in patients with GnRH defect. According to the conventional protocol the first treatment cycle is initiated with 75 IU daily of a preparation containing only FSH or a combination of FSH and LH (hMG), and the dosage is increased by 37.5 IU or 75 IU after one week up to a final dosage of 150 IU daily, if a good follicular response is not achieved. Plasma estradiol measurements and transvaginal ovarian sonography are performed sequentially until estradiol levels reach 500–1500 pg/ml and the diameter of the largest follicle is 16–18 mm. At this point 5000 IU of hCG are administered to trigger ovulation that is expected to occur in 36–48 h. If estradiol levels are greater than 1500 pg/ml, hCG is not administered given the high risk of ovarian hyperstimulation.

Cycle fecundity ranges between 5% and 15% and cumulative conception rates between 30% and 60% [32]. Multiple pregnancies are more frequent than with the use of pulsatile GnRH, occurring in 15–25% of all pregnancies. Spontaneous miscarriage takes place in about 20–25% of cases.

A step-down protocol for gonadotropin therapy can also be used, starting with 150 IU and gradually decreasing the dosage to 75 IU. This protocol is associated with a higher rate of monofollicular maturation and thus with a lower occurrence of multiple pregnancies.

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