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REVIEW

Endocrine factors associated with infertility in women: an updated review

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ABSTRACT

Introduction: Infertility is defined as the inability to conceive after unprotected sexual intercourse for at least 12 consecutive months. Our objective is to present an updated narrative review on the endocrine causes of infertility in women.

Areas covered: A comprehensive review was conducted using Scielo, Scopus, and EMBASE databases, comprising 245 articles. The pathophysiology of infertility in women was described, including endocrinopathies such as hypothalamic amenorrhea, hyperprolactinemia, polycystic ovary syndrome, primary ovarian insufficiency, obesity, thyroid dysfunction, and adrenal disorders. The diagnostic approach was outlined, emphasizing the necessity of hormonal studies and ovarian response assessments. Additionally, the treatment plan was presented, commencing with non-pharmacological interventions, encompassing the adoption of a Mediterranean diet, vitamin supplementation, moderate exercise, and maintaining a healthy weight. Subsequently, pharmacological treatment was discussed, focusing on the management of associated endocrine disorders and ovulatory dysfunction.

Expert opinion: This comprehensive review highlights the impact of endocrine disorders on fertility in women, providing diagnostic and therapeutic algorithms. Despite remaining knowledge gaps that hinder more effective treatments, ongoing research and advancements show promise for improved fertility success rates within the next five years. Enhanced comprehension of the pathophysiology behind endocrine causes and the progress in genetic research will facilitate the delivery of personalized treatments, thus enhancing fertility rates.

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Fertility; female infertility; anovulation; reproductive health; ovarian reserve; hormones

1. Introduction

Infertility is a medical disease characterized by the inability to conceive after engaging in regular unprotected sexual intercourse for at least 12 consecutive months [1]. It is recognized as a significant public health issue, as it affects approximately one-sixth of the adult population [2]. In the United States, the prevalence of infertility in women ranges from 7.3% to 9.1% among women aged 15 to 34 years, 25% among women aged 35 to 39 years, and 30% among women aged 40 to 44 years [3].

Approximately 50% of infertility cases are attributed to female factors [4], among which the most common causes include ovulatory disorders (32%), endometriosis (25%), pelvic adhesions (11%), and tubal blockage (11%) [5,6]. Endocrine disorders also play a significant role in the etiology of infertility in women [7], involving non-reproductive endocrine organs such as the thyroid, adipose tissue, adrenal glands, and pancreas [8].

The objective of this study is to provide an updated narrative review on the endocrine causes of infertility in women, addressing aspects related to their pathophysiology, diagnosis, and treatment.

Systematic reviews, narrative reviews, meta-analysis, clinical trials, practice guidelines, retrospective studies, and cross-sectional studies that were pertinent to the research objective, were included. Case reports, correspondence, congress summaries and conference abstracts were excluded. The bibliographic research was conducted in the PubMed/Medline, EMBASE and Scielo databases focusing on the Medical Subject Heading terms 'female infertility', 'endocrine glands', 'prolactin', 'thyroid', 'adrenal', 'acromegaly' and 'polycystic ovarian syndrome' including 245 articles.

2. Physiology of fertility in women

Gonadotrophin-releasing hormone (GnRH) is produced in the medial preoptic area and the arcuate nucleus of the hypothalamus, and is released in a pulsatile manner, stimulating the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [9,10]. Kisspeptin, produced in the arcuate

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Article highlights

- Correcting underlying hormonal abnormalities enhances fertility in most patients.
- Polycystic ovary syndrome is a common cause of anovulation.
- Hormonal evaluation is crucial within the assessment of female infertility causes.
- Ovarian reserve should be evaluated using antimüllerian hormone and imaging.
- Healthy lifestyles contribute to improving fertility.

and anteroventral periventricular nuclei (a caudal extension of the preoptic area), enhances the production of GnRH [10–12]. Neurokinin B stimulates kisspeptin-producing neurons, while dynorphin inhibits them. Both are produced in the arcuate nucleus [13].

FSH stimulates the development of ovarian follicles, whose granulosa cells produce estrogens and inhibin B. These hormones inhibit FSH secretion through a negative feedback mechanism [5,14–16]. Decreased levels of FSH lead to the atresia of adjacent tertiary follicles, while a dominant follicle is selected due to its greater biological capacity to continue growing and maintain estrogen production [5,16].

Persistent elevation of estrogens induces the sudden release of LH, triggering ovulation. After ovulation, the dominant follicle transforms into a corpus luteum that produces estrogen and progesterone. If fertilization does not occur, the corpus luteum degenerates, initiating the menstrual cycle [5,14,16]. (Figure 1)

3. Patophysiology

The causes of infertility in women can be related to the fallopian tubes and uterus in 68% of cases, and to ovulation in 32% of cases [5,6]. The latter are mainly due to hormonal abnormalities in the hypothalamic-pituitary-ovarian (HPO) axis but can also be associated with dysfunction of other endocrine glands such as the thyroid, adrenal glands, and pancreas [8].

3.1. Hormonal abnormalities of the HPO axis

In 1973, the World Health Organization (WHO) developed a classification of anovulation based on gonadotropin and estrogen levels [17]. This classification has been used and modified by various authors since then, without additional scientific discussion or consensus development. Over the past five decades, this classification has been referenced in various gynecology, infertility, and reproductive endocrinology texts, often incorrectly citing a document on contraception [18]. The United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines on infertility research and management, first published in 2004, also refer to this document and describe the three groups that most authors currently refer to. This classification stands out for its simplicity and usefulness in clinical practice, has been widely used and applied to date [18–21], and divides anovulatory disorders into three classes:

3.1.1. Class 1: Anovulation with hypogonadotrophic hypogonadism (*Figure 2a*)

It is characterized by decreased secretion or pituitary resistance to GnRH, resulting in low levels of FSH and estrogens. The main disorders in this class are hypothalamic amenorrhea and hyperprolactinemia [22].

3.1.1.1. Hypothalamic amenorrhea. It is caused by a decrease in pulsatile secretion of GnRH or its complete inhibition, leading to reduced production of FSH and LH and suppression of ovarian hormonal function. It affects 3–5% of

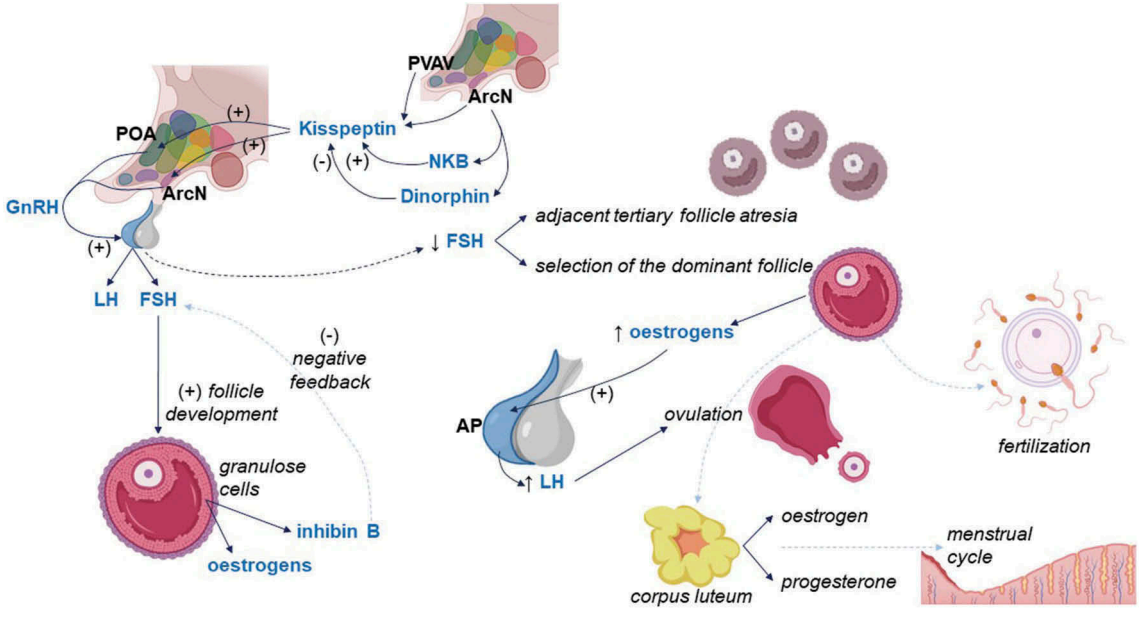

Figure 1. Neuroendocrine regulation of reproductive function. AP: anterior pituitary; ArcN: arcuate nucleus; FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone; LH: luteinizing hormone; NKB: neurokinin B; POA: preoptic area; PVAV: periventricular anteroventral nucleus; (+): stimulation; (-): inhibition.

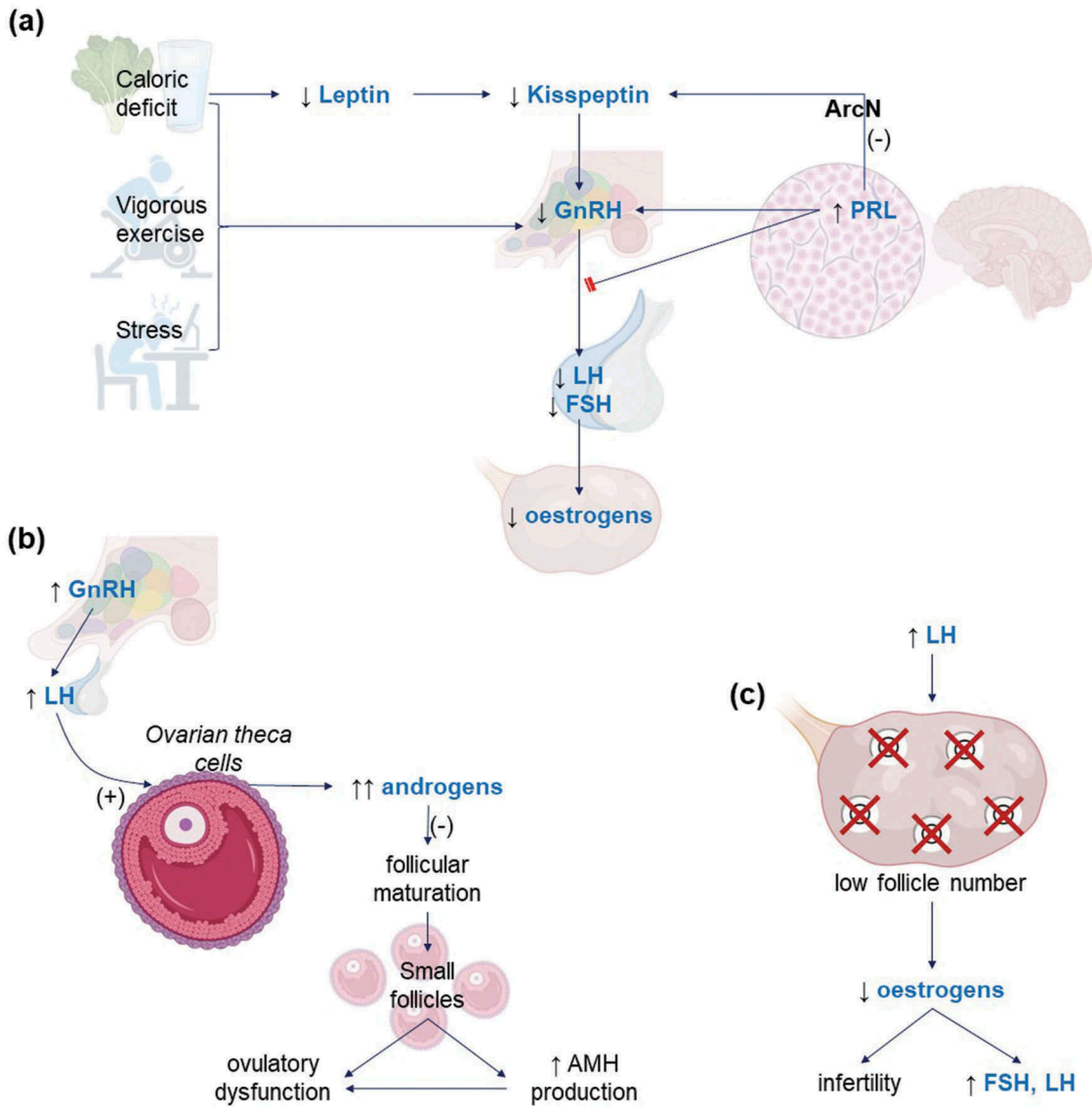

Figure 2. Pathophysiology of anovulation according to the affected level of the hypothalamic-pituitary-ovarian axis. (a) Functional hypothalamic amenorrhea and hyperprolactinemia. (b) Polycystic ovary syndrome. (c) Primary ovarian insufficiency. ArcN: arcuate nucleus; FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone; AMH: Anti-Müllerian hormone; LH: luteinizing hormone; PRL: Prolactin; (+): stimulation; (-): inhibition; red lines: blockage.

women of reproductive age and 25–35% of women with secondary amenorrhea [9,23,24]. It can be caused by structural lesions but these are rare conditions [25].

Functional hypothalamic amenorrhea occurs without a structural damage, and it is a diagnosis of exclusion, after other disorders have been ruled out [26]. It is mainly associated with stress, excessive exercise, and caloric deficit [25]. These factors can lead to alterations in hypothalamic neuronal nuclei with decreased secretion of kisspeptin, resulting in decreased GnRH secretion [27]. Genetic predisposition to hypothalamic amenorrhea has been suggested, with mutations in genes regulating GnRH and increasing susceptibility to stress factors [28]. Rarely, it can be associated with chronic disease, malabsorptive illnesses and hypermetabolic states such as severe burns or hyperthyroidism [25].

In addition to its effects on appetite regulation, body weight, and energy balance, leptin increases the expression of kisspeptin in the hypothalamus, which enhances GnRH expression and plays an important role in the regulation of reproduction [29]. Acute and chronic caloric deprivation decrease leptin levels, leading to hypothalamic amenorrhea and infertility [29,30].

3.1.1.2. Hyperprolactinemia. It is caused by increased secretion of lactotroph cells and affects approximately 4% of women of reproductive age and between 9% and 17% of women with infertility [31]. Hyperprolactinemia inhibits kisspeptin-expressing neurons in the arcuate nucleus, decreasing GnRH production [32], and blocks its effect in the anterior pituitary, suppressing the production of LH and FSH, which ultimately reduces ovarian estrogen production [33]. It manifests with galactorrhea and amenorrhea [34]. Its main causes are psychological stress, vigorous physical exercise, hypothyroidism, polycystic ovarian syndrome, liver cirrhosis, chronic

kidney failure, prolactinoma, and certain drugs, such as antipsychotics, antidepressants, metoclopramide, estrogens, among others. Less frequent causes include craniopharyngioma, empty sella, irradiation, trauma, and infections [35].

Craniopharyngioma is an infrequent and benign embryonic malformation that originates from the residual epithelial cells of Rathke's pouch (the tissue from which the anterior pituitary develops) [36,37]. It has the potential to induce hypopituitarism, amenorrhea, and infertility [38].

Empty sella refers to a radiological observation of a flattened pituitary gland within a sellar space that is occupied by cerebrospinal fluid (CSF), and it can be related to postpartum hemorrhage, head trauma, central nervous system stroke, hormonally active pituitary microadenoma, radiation therapy, or surgical interventions. The elevated CSF pressure in the pituitary stalk causes hyperprolactinemia in roughly 10% of patients [39]. It can cause headaches, visual disturbances, and hypopituitarism [40].

3.1.1.3. Other disorders. Sheehan's syndrome typically includes a history of severe postpartum bleeding, lactation failure after childbirth, various degrees of pituitary insufficiency, inability to resume menses following delivery, and an observed empty sella on images. This condition can result in premature aging, osteoporosis, genital atrophy and profound weakness [41].

Kallmann syndrome is a cause of congenital hypogonadism [42], characterized by a deficiency of GnRH production, which leads to primary amenorrhea and impaired olfaction [43].

Other less common etiologies of hypogonadotrophic hypogonadism include tumors, infiltrative disorders, infections, radiation exposure, trauma, specific medications, and other endocrinopathies [44].

3.1.2. Class 2: Anovulation with normoestrogenic normogonadotrophic status (*Figure 2b*)

It is characterized by adequate secretion of gonadotrophins and estrogens, although FSH levels decrease during the follicular phase [45]. The representative disorder of this class is polycystic ovary syndrome (PCOS) [46]. -

3.1.2.1. Polycystic ovary syndrome. It is the most common endocrinopathy and the leading cause of anovulation. It affects 10% of women of reproductive age and 70% of women with anovulation [46]. The frequency of GnRH pulses is increased, which elevates LH production, subsequently leading to increased androgen production in the ovarian theca cells [9,23,47]. This inhibits the maturation of ovarian follicles, resulting in multiple small antral follicles and ovulatory dysfunction [48].

3.1.3. Class 3: anovulation with hypergonadotrophic hypogonadism (*Figure 2c*)

Its cause is ovarian failure and occurs in approximately 5% of women with infertility.

3.1.3.1. Primary ovarian insufficiency. This condition is traditionally defined as the total cessation of ovarian function prior to the age of 40. However, in the majority of affected women, antral follicles are still present, albeit in reduced quantities [49,50]. It affects 1% of women over 30 years of age and 0.1% of women under 30 years of age [51]. The pathophysiology of this condition is still not fully understood [51,52]. However, contrary to the previously believed notion that the down-regulation of FSH receptors is the main problem in follicle dysfunction, it is now postulated that the more probable mechanism involved is the inappropriate luteinization of follicles [49,50,53]. There are mutations that cause a loss of function in the FSH receptor, resulting in impaired functionality and inhibiting follicle development [54–58]. Up to 5% of primary ovarian insufficiency cases are caused by autoimmune oophoritis, wherein the autoimmune destruction selectively targets the theca cells, resulting in an initial preservation of granulosa cells and elevated levels of inhibin B. This characteristic distinguishes it from the classic forms of primary ovarian insufficiency [59]. Biochemically, it is characterized by low estrogen levels and elevated gonadotrophins due to reduced number of ovarian follicles, resulting in amenorrhea and infertility [60]. Most of the cases are attributed to non-genetic and epigenetic causes, which may be related to autoimmune factors, exposure to environmental toxins and chemicals [51,61,62].

There is a growing body of evidence linking chemotherapy and abdominopelvic and cranial radiotherapy to gonadal toxicity. This can lead to primary ovarian insufficiency in up to 30% of patients treated with these agents [63,64]. There is a limited amount of information available regarding the impact of targeted therapy and immunotherapy on fertility outcomes in women [64].

Ovarian surgery may lead to the loss of the follicular pool and result in ovarian insufficiency, especially when using the stripping technique during cystectomy [65].

3.2. Hormonal alterations of other endocrine glands

3.2.1. Primary hypothyroidism (*Figure 3a*)

In women of reproductive age, its prevalence is 2 to 4%, primarily caused by autoimmunity [66,67]. Hypothyroidism reduces the elimination of androstenedione and testosterone, leading to increased peripheral aromatization toward estrone and estradiol (E2). Additionally, it decreases the level of sex hormone-binding globulin (SHBG) and reduces the concentration of testosterone and E2 (although their free fractions increase) [68]. It is also associated with hyperprolactinemia due to increased thyrotropin-releasing hormone (TRH) secretion, which decreases the production of LH, FSH, and ovarian estrogens, resulting in ovulatory dysfunction [69,70].

3.2.2. Hyperthyroidism (*Figure 3b*)

Its prevalence in women of reproductive age is approximately 1%, with the primary cause being Graves' disease due to the presence of antibodies against the TSH receptor [71]. It has been reported that 5.8% of patients with hyperthyroidism have primary infertility [72]. Thyrotoxicosis reduces the elimination of E2 and increases its formation from testosterone, thereby increasing the total concentration of E2 while decreasing its free fraction. Additionally, it increases the level of SHBG

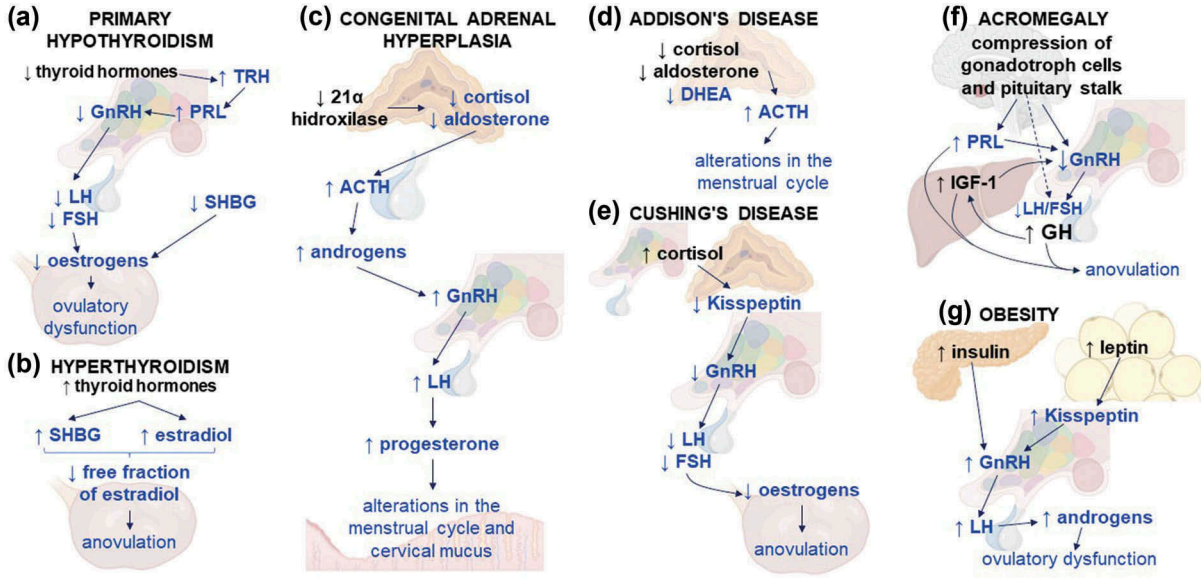

Figure 3. Pathophysiology of infertility in women caused by other endocrine disorders. (a) Primary hypothyroidism. (b) Hyperthyroidism. (c) Congenital adrenal hyperplasia. (d) Addison's disease. (e) Cushing's syndrome. (f) Acromegaly. (g) Obesity. ACTH: adrenocorticotropic hormone; DHEA: Dehydroepiandrosterone; FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone; AMH: Anti-Müllerian hormone; LH: luteinizing hormone; PRL: Prolactin; SHBG: sex hormone-binding globulin; TPOAb: thyroid peroxidase antibodies; TRH: thyrotropin-releasing hormone.* both primary hypothyroidism and Addison's disease can be associated with primary ovarian insufficiency.

[73,74]. All these factors contribute to anovulation and disruption of menstrual cycles [14].

3.2.3. Congenital adrenal hyperplasia (*Figure 3c*)

It is a group of autosomal recessive genetic disorders that affect the steroidogenesis of the adrenal cortex. The most common form is due to 21α-hydroxylase deficiency, which reduces cortisol and aldosterone levels and increases adrenocorticotropic hormone (ACTH) production [75]. Excess ACTH and the subsequent adrenal overproduction of androgenic hormones lead to hyperandrogenism [76], which is associated with early puberty, acne, hirsutism, menstrual disturbances, and infertility [77]. It is believed that hyperandrogenism has a direct effect on pulsatile GnRH secretion, increasing LH and progesterone production [78]. The increase in adrenal-derived progesterone disrupts menstrual cyclicity and cervical mucus [77]. Furthermore, the accumulation of 17-hydroxyprogesterone is associated with alterations in endometrial maturation and possibly implantation [79]. The classic, more severe form is associated with a greater degree of ovarian dysfunction and infertility [80]. It can be associated with PCOS [14]. The non-classical form is more common, occurring in 1 in 1000 live births, and is associated with hyperandrogenism but does not cause the classic virilization of the external genitalia in girls at birth. It may even be asymptomatic and diagnosed in adulthood during infertility evaluation [81].

3.2.4. Addison's disease (*Figure 3d*)

Primary adrenal insufficiency results in deficiency of cortisol, aldosterone, and adrenal androgen precursors such as dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) [82]. In 10–20% of cases, it is associated with primary ovarian insufficiency, leading to infertility [83]. Additionally, it is an important component of autoimmune polyendocrine syndromes type 1 and type 2. The prevalence of infertility can reach 50–70% in women with autoimmune polyendocrine syndrome type 1 [84]. Anti-steroid cell antibodies predict the risk of primary ovarian insufficiency in patients with Addison's disease, with antibodies against the side-chain cleavage enzyme showing the highest accuracy and positive association with 21α-hydroxylase antibodies [85,86].

3.2.5. Cushing's syndrome (*Figure 3e*)

Hypercortisolism inhibits the release of GnRH and suppresses the production of LH and FSH, causing anovulation and infertility. It appears that hypercortisolism decreases the expression of kisspeptin, although the exact pathophysiology is not fully understood [87]. Less than 200 pregnancies have been reported in women with Cushing's syndrome [88].

3.2.6. Acromegaly (*Figure 3f*)

It is caused by excessive production of growth hormone (GH) from a somatotroph adenoma in the pituitary gland, resulting in excessive secretion of insulin-like growth factor 1 (IGF-1) [89]. A retrospective study found that all women with acromegaly were infertile, but after disease control, 73.3% of them achieved at least one conception [90]. Acromegaly is associated with hyperprolactinemia in one-third of cases, and in addition to the effects of prolactin (PRL), it can cause compression of gonadotrophin cells and the pituitary stalk, leading to reduced production of GnRH, LH, and FSH, resulting in dysfunction of the HPO axis and ultimately anovulation [91,92].

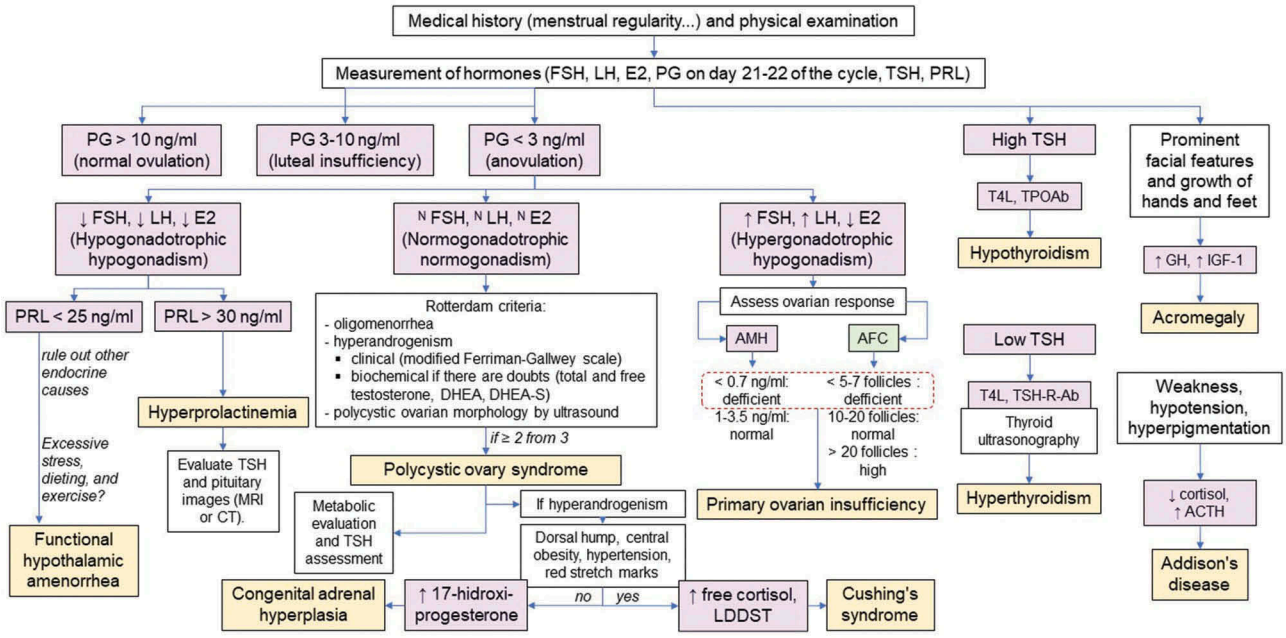

Figure 4. Hormonal assessment of infertility in women. ACTH: adrenocorticotropic hormone; AFC: antral follicle count; DHEA: Dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate; E2: Estradiol; FSH: follicle-stimulating hormone; GH: growth hormone; GnRH: gonadotrophin-releasing hormone; AMH: Anti-Müllerian hormone; IGF-1: insulin-like growth factor 1; LNSC: late-night salivary cortisol; UFC: urinary free cortisol; LDDST: low-dose dexamethasone suppression test; LH: luteinizing hormone; PG: Progesterone; PRL: Prolactin; MRI: magnetic resonance imaging; FT4: free thyroxine; CT: computed tomography; TPOAb: Anti-thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone; TSH-R-Ab: Anti-TSH-receptor antibodies. * one-third of women with regular menstrual cycles experience anovulation.

Moreover, the excess of GH and IGF-1 could directly inhibit the action of GnRH and ovarian function [93].

3.2.7. Obesity (*Figure 3g*)

Obesity is associated with menstrual irregularity and anovulation, similar to the PCOS [94]. Insulin resistance, present in over 70% of women with obesity and PCOS, is the underlying pathophysiological alteration linking both conditions [95]. Obesity increases insulin levels, stimulating its receptors in GnRH-producing neurons and accelerating its pulsatile secretion [23]. Moreover, hyperinsulinemia enhances ovarian androgen production [96], which aromatizes to estrogens peripherally due to increased adipose tissue, negatively feedback on the HPO axis, reducing gonadotrophin production, and disrupting ovulation [97]. Hyperlipidemia also contributes to decreased gonadotrophin secretion [98].

Leptin, which is elevated in obesity, has been found to have cerebral resistance to its effects [99], and negatively impacts the reproductive axis, leading to decreased levels of estrogen and progesterone, as well as ovulation disturbances [100].

4. Diagnosis

The diagnosis of infertility in women should be a systematic process that begins with a thorough medical history and physical examination in order to guide the hormonal and imaging tests that should be performed [5].

4.1. Medical history and physical examination

Firstly, infertility should be confirmed by inquiring about the duration of the patient's attempts to conceive. The patient's age is an important prognostic factor [101]. It is important to obtain information about the age of menarche, menstrual patterns, sexual history, previous pregnancies, duration of infertility, and previous treatments, as well as the use of medications that may affect the HHO axis, including hormonal contraceptives [5]. Anovulation is suspected when menstrual cycles are persistently irregular, i.e. less than 21 days or more than 35 days in duration, presence of abnormal uterine bleeding, a history of amenorrhea, or fewer than 8 menstrual cycles per year [5,14,102,103]. Lifestyle factors, dietary habits, stress, physical activity, smoking, alcohol consumption, and use of addictive substances should also be investigated [104]. Occupation and exposure to endocrine disruptors such as pesticides, fertilizers, industrial products, and heavy metals can affect hormonal axes [105]. General symptoms such as weight changes, mood alterations, fatigue, gastrointestinal symptoms, palpitations, sweating, tremors, cold or heat intolerance, galactorrhea, and other symptoms based on clinical suspicion should be inquired about [5].

The physical examination should include anthropometric measurements (weight, height, abdominal circumference, and waist-to-hip ratio), assessment of vital functions, Tanner staging inspection, evaluation of breast secretion, palpation of the thyroid gland, search for phenotypic features of Turner syndrome, search of signs of insulin resistance such as acanthosis nigricans and acrochordons, signs of

hyperandrogenism such as acne, and hirsutism, and signs of Cushing syndrome such as purple-colored violaceous striae greater than 1 cm, easy bruising and dorsocervical fat pad [5,14,102].

glicemia

4.2. Hormonal studies (*Figure 4*)

4.2.1. Evaluation of ovulation

The biochemical evaluation of infertility should include measurement of hormones of the HHO axis, such as gonadotrophins and estrogen levels, to establish the differential diagnosis between hypogonadotrophic and hypergonadotrophic causes and normoestrogenic causes. The traditional classification of the WHO, which has been applied up to the present, has demonstrated usefulness; however, there have been significant advancements in understanding ovulation control, the pathophysiology of ovulatory disorders, and improvements in technology and genomics. For this reason, the International Federation of Gynecology and Obstetrics (FIGO) has proposed a new classification that groups the causes of ovulatory disorders anatomically, based on HHO axis levels, recognizing PCOS as a separate entity as it does not reside in a single anatomical location [19]. (Table 1)

Generally, women with regular menstrual cycles are likely to have normal ovulation. However, up to one-third of them may experience anovulation [106], which can be confirmed by measuring progesterone levels on day 21–22 of the cycle (luteal phase). This retrospective evaluation allows determining if ovulation has occurred. A progesterone level above 10 ng/mL is considered indicative of adequate ovulation [107], while levels below 3 ng/mL indicate anovulation [106]. Progesterone levels between 3 and 10 ng/mL may be associated with luteal insufficiency or ovulation occurring on a different day than expected [16].

It is important to recognize that transvaginal ultrasonography is the standard reference examination for detecting ovulation. In this context, the time of ovulation can be determined as the point between the maximum follicular diameter and follicular collapse [16]. Furthermore, it is useful in detecting a wide variety of uterine and adnexal pathologies [108].

Regarding hyperprolactinemia, it has been observed that a mild elevation of PRL levels between 30–50 ng/mL may be associated with a shortened luteal phase and infertility. On the other hand, a moderate elevation between 51 and 75 ng/mL is related to oligomenorrhea, and levels above 100 ng/mL are associated with galactorrhea, hypogonadism, and amenorrhea [109]. Chronic kidney and liver diseases can cause mild to moderate hyperprolactinemia [110]. Patients with PCOS may also present moderate elevations in PRL [111].

In the evaluation of PCOS, other endocrine pathologies such as hypothyroidism and non-classical congenital adrenal hyperplasia should be ruled out [112]. The diagnosis is established, according to consensus, by the presence of at least 2 out of the following 3 Rotterdam criteria: oligomenorrhea, hyperandrogenism (either clinical or biochemical), and

Table 1. Comparison between the traditional classification of anovulation by the WHO and the FIGO. FIGO: International Federation of Gynecology and Obstetrics; PCOS: polycystic ovary syndrome; WHO: World Health Organization.

	WHO	FIGO
Authors	WHO Scientific Group on Agents Stimulating Gonadal Function in the Human	FIGO Ovulatory Disorders Steering Committee
Year of creation	1973 [17]	2022 [19]
Basis of the classification	Levels of gonadotrophins and estrogens.	Anatomical location of the condition.
Groups	Group I: Low endogenous estrogen activity and decreased gonadotrophins. Group II: 'Distinct' estrogen activity (urinary estrogens < 10 mcg/24 h), with normal gonadotrophins. Group III: Primary ovarian failure (primary ovarian insufficiency), associated with low endogenous estrogen activity and pathologically elevated gonadotrophins.	Acronym 'HyPO-P' Type I: Hypothalamic Type II: Pituitary Type III: Ovarian Type IV: PCOS
Subgroups	No further subclassification.	Acronym 'GAIN-FIT-PIE' Type I: • Genetic • Autoimmune • Iatrogenic • Neoplasm Type II: • Functional • Infectious or Inflammatory • Trauma & Vascular Type III: • Physiological • Idiopathic • Endocrine Type IV: No subclassification

polycystic ovary morphology on ultrasound [113]. In cases of anovulation and biochemical hyperandrogenism, ovarian ultrasonography may not be indispensable; however, it may be useful to assess other pathologies [108]. Polycystic ovarian morphology is characterized by the presence of more than 20 follicles per ovary measuring 2–9 mm each, and/or an ovarian volume of 10 mL or greater, as detected using a transducer with a frequency equal to or greater than 8 MHz. In the case of older equipment, it suffices to observe an ovarian volume of 10 mL or greater. Within the initial 8 years following menarche, there can be a heightened prevalence of polycystic ovaries, thus ultrasound is not recommended for diagnostic purposes of PCOS [114]. On the other hand, the clinical diagnosis of hyperandrogenism focuses on evaluating hirsutism using the modified Ferriman-Gallwey scale, and biochemical diagnosis is reserved when there are doubts in the clinical diagnosis by measuring free and total testosterone, DHEA, and DHEA-S [112]. Additionally, the evaluation of insulin resistance is performed by performing an oral glucose tolerance test, measuring basal insulin, and determining the homeostatic model assessment of insulin resistance (HOMA-IR) index [115,116].

Thyroid function evaluation is also important, by measuring thyroid-stimulating hormone (TSH) and, if necessary, free thyroxine. Subclinical hypothyroidism, with a TSH level > 4 mIU/L, is associated with a higher frequency of infertility [117]. The American Thyroid Association (ATA) recommends measuring TSH in women with infertility [118]. In some cases, it may be useful to perform tests to detect the presence of antithyroid peroxidase antibodies (TPOAb), antithyroglobulin antibodies, and antibodies against the TSH receptor, based on clinical suspicion, although the evidence is limited. Thyroid antibodies have been found in ovarian follicles, which has been associated with impaired development [119]

4.2.2. Evaluation of ovarian response

Ovarian reserve is defined as the number of primordial follicles present in the ovaries at any given point in life [120], serving as an indicator of reproductive age [121]. However, there are currently no direct tests available in routine practice to accurately assess the true ovarian reserve [122]. On the other hand, ovarian response refers to the endocrine and follicular reaction of the ovaries in response to a stimulus [121]. This can be assessed through hormonal assay methods or imaging studies.

4.2.2.1. Anti-Müllerian Hormone (AMH). Previously, tests such as FSH and estradiol measurements, clomiphene citrate stimulation test, and inhibin B measurement were performed. However, currently, the focus is on measuring AMH, which has emerged as the standard for evaluating ovarian response, rendering the previously described tests obsolete [123–126].

AMH is produced by the granulosa cells of early follicles [46], and its role in assessing ovarian response has been known for about 20 years [7,127]. Its function is to inhibit the recruitment of primordial follicles from the resting oocyte pool and the recruitment of small antral follicles by decreasing their sensitivity to FSH [128–130], thereby preventing premature follicle depletion [130].

AMH expression begins when primordial follicles are recruited to grow, reaches its peak in preantral and small antral follicles measuring 2–4 mm [131], continues until they reach approximately 8 mm in diameter, and is absent in larger antral follicles, which grow under the influence of FSH [124,128,132]. It is also not produced in corpus luteum or atretic follicles [133].

The level of AMH reflects the size of the follicle pool and is the preferred hormonal marker for evaluating ovarian response [127]. As described earlier, AMH levels decrease with age [132,133], starting at approximately 35 years old and accelerating after 40 years old [127,134,135].

Unlike other hormonal markers, its secretion is independent of GnRH, and it can be measured at any time during the menstrual cycle [123,135,136]. The normal range varies between 1.0 and 3.5 ng/mL [137]. An AMH value below 0.7 ng/mL is associated with a significant reduction in fertility [138].

Since women with PCOS have a higher number of preantral and small antral follicles, AMH levels increase 2 to 3 times [46]. AMH level is related to the severity of PCOS and infertility [139]. Furthermore, by suppressing FSH action, it contributes to ovulatory disorders [128]. An AMH value above 3.8–5 ng/mL is a useful diagnostic tool for PCOS [140], potentially replacing the criterion of polycystic morphology when transvaginal ultrasound is not feasible [141].

However, young women with low AMH did not exhibit reduced fecundability, whereas those with high AMH showed reduced fecundability even after accounting for covariates [142]. Besides, AMH is a weak independent predictor of live birth following ART, specifically in the context of both fresh and frozen embryo transfer, be it single or multiple transfers [143].

Diminished ovarian reserve (DOR) can be defined as the decrease in the number and quality of oocytes, diminished AMH levels, and elevated FSH levels. It is commonly associated with advanced age (over 35 years old). Despite using assisted reproductive techniques, DOR leads to reduced fertility and unfavorable fertility outcomes [144].

4.2.2.2. Imaging studies. Ovarian response can also be assessed through imaging studies. During the early follicular phase, antral follicles can be observed, which have a diameter of 2 to 10 mm and can be recruited for use in assisted reproduction techniques (ART). During menstruation, ovarian follicles measure 4 to 9 mm, and before ovulation, the dominant follicle reaches a diameter of 20 to 25 mm, indicating that ovulation has occurred [127,145,146]. The antral follicle count (AFC) in a woman with normal ovulation during reproductive years ranges from 10 to 20 [147]. An AFC below 5–7 is associated with a reduced pregnancy rate, while an AFC equal to or greater than 20 is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) [122]. Similar to AMH, the number of antral follicles decreases with age, approximately 4.8% per year before 37 years old and 11.7% per year after 37 years old [148].

The use of ART has demonstrated that the AFC through transvaginal ultrasound is one of the best predictors of a good response during controlled ovarian hyperstimulation [127,146,149].

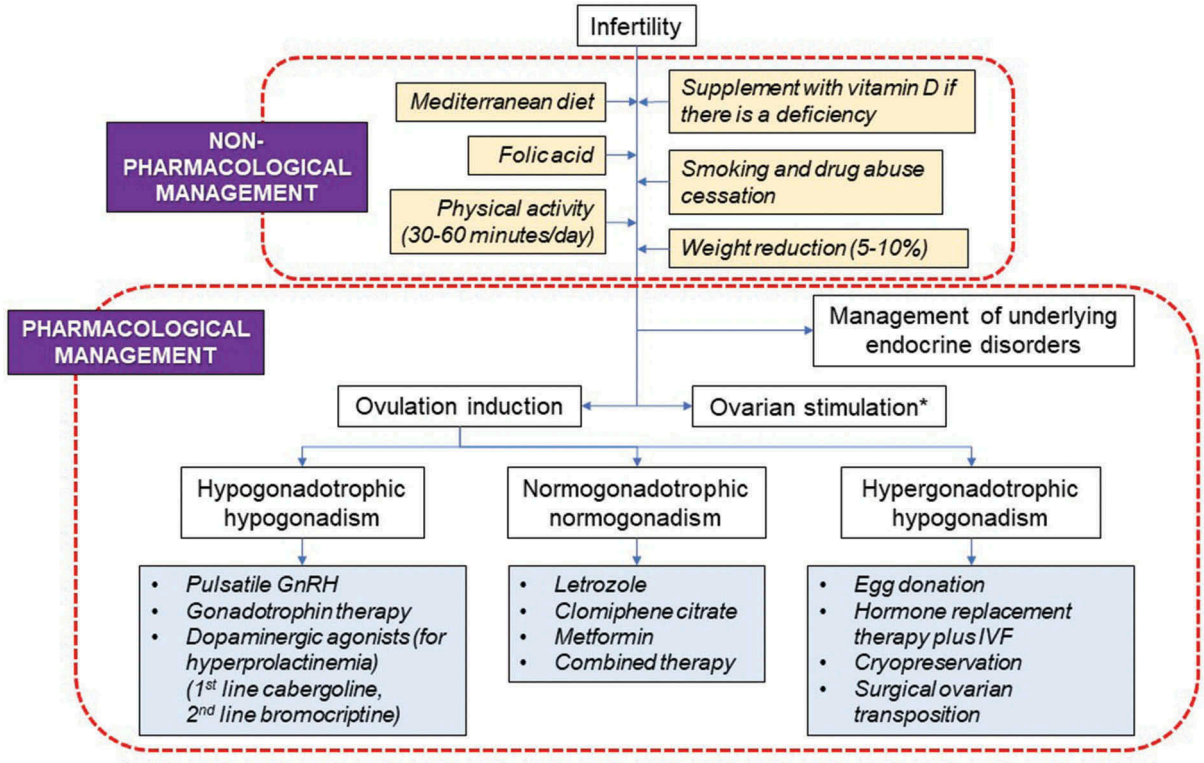

Figure 5. Medical treatment of infertility in women. IVF: in vitro fertilization; GnRH: gonadotrophin-releasing hormone. * IVF or select cases of IUI.

5. Treatment (Figure 5)

5.1. Non-pharmacological interventions

Numerous studies have demonstrated the relevance of lifestyle factors in infertility in women.

5.1.1. Mediterranean diet

The Western dietary pattern has a negative impact on fertility, while the Mediterranean diet has a positive impact [150–158]. Among these, the study by Karayiannis revealed that women following a Mediterranean diet had a higher pregnancy rate (50% vs 29.1%, $p = 0.01$) and a higher number of live births (48.8% vs 26.6%, $p = 0.01$) compared to those who did not follow it [159]. Specifically, whole grains and dietary fiber have been shown to improve implantation rates, clinical pregnancies, and live births [160–162].

5.1.2. Omega-3 and omega-6 fatty acids

The benefits on fertility are controversial. The discrepancies are due to the heterogeneity of the studies [160,163–167].

5.1.3. Coffee

High caffeine consumption has been associated with increased time to achieve pregnancy, as well as an increased incidence of miscarriage, low birth weight, and intrauterine growth retardation, in a dose-dependent relationship [168]. However, a systematic review found no association between caffeine consumption and natural fertility, nor in the outcomes of assisted reproductive treatments [169].

5.1.4. Alcohol consumption

A clear relationship between alcohol consumption and natural fertility has not been established; however, a negative effect on assisted reproduction has been observed [170]

5.1.5. Tobacco

It can increase the thickness of the zona pellucida, hindering sperm penetration, and advance menopause by up to 4 years [170] Additionally, it may increase oxidative stress. Smoking cessation could improve fertility in female smokers [171]

5.1.6. Drug abuse

Opioids cause amenorrhea and decrease E2 and LH levels [172]. Marijuana is associated with menstrual disturbances, reduction in the number of oocytes, and an increased risk of preterm birth. A specific period of drug abstinence for fertility restoration has not been established [173,174].

5.1.7. Exercise

Vigorous exercise of 30 to 60 minutes daily decreases the risk of anovulatory infertility. However, very strenuous exercises exceeding 60 minutes daily increase the risk of anovulation. Additionally, in women with PCOS and obesity or overweight, exercise accompanied or not by diet can restore ovulation [175]. Possible mechanisms include the regulation of the HPO axis and the reduction of insulin and free androgen levels [176].

5.2. Pharmacological treatment

Pharmacological treatment of infertility in women includes managing associated endocrine disorders, ovulation induction, and ovarian stimulation [177–179]. Ovulation induction ensures the release of at least one egg, which can be used for natural fertilization or intrauterine insemination (IUI) [180]. Ovarian stimulation produces multiple eggs to select the highest-quality one for use in in vitro fertilization (IVF), although in selected cases, it could also be combined with IUI [180]. The recommended drugs for ovulatory disorders are grouped according to the traditional classification of the WHO described in the diagnostic section [18].

5.2.1. Group I: hypogonadotrophic hypogonadism

Correction of energy imbalance is imperative to enhance the functioning of the HPO axis in women with functional hypothalamic amenorrhea. This can be attained by diminishing the intensity of exercise and augmenting caloric intake. The precise extent of weight gain requisite for this purpose remains unclear; however, it is advisable to target a weight equal to that at which menstruation ceased. Relying solely on oral contraceptives for reestablishing menstrual cycles proves insufficient as it does not adequately address lingering bone complications. For adult women desiring conception, initial treatment involving pulsatile GnRH is recommended, followed by gonadotropin therapy and induction of ovulation in cases where GnRH is not viable. Ovulation induction is advised exclusively for individuals with a BMI of 18.5 kg/m^2 or higher and after endeavors to reinstate energy equilibrium [26].

5.2.2. Pulsatile GnRH

Its administration restores the physiological stimulation of FSH and LH to induce follicular maturation and ovulation. The frequency of pulses is adjusted to mimic the physiological variation in GnRH pulse variability [181]. It is recommended as a first-line treatment for inducing ovulation in this group [26]. Pulsatile GnRH administration can induce ovulation in over 90% of cycles, with pregnancy rates ranging from 18 to 32% per cycle [182]. It is generally well-tolerated and presents a lower risk of OHSS or multiple pregnancies compared to exogenous gonadotrophin treatment [183,184].

5.2.2.1. Gonadotrophin Therapy. The use of injectable gonadotrophin preparations is an alternative method to induce folliculogenesis when pulsatile GnRH administration is ineffective [9]. In women with hypogonadotrophic hypogonadism and intrinsic ovulatory dysfunction, the use of exogenous ovulatory inducers is required [182,183]. This therapy presents a cumulative live birth rate of 33% over 4 cycles when combined with IUI [185]. In the case of IVF with autologous oocytes, the live birth rate can exceed 65% per cycle [185].

5.2.2.2. Dopaminergic Agonists. In women, normal PRL levels range from 15 to 25 ng/mL [186]. Normalization of PRL levels is recommended before attempting conception [187]. Dopaminergic agonists are the first-line treatment for ovulatory disorders secondary to hyperprolactinemia [188], as they are effective in resolving amenorrhea and achieving pregnancy [189,190] in over 85% of cases after correcting hyperprolactinemia [191]. Cabergoline is recommended over bromocriptine due to its better tolerance and effectiveness in restoring fertility in women, according to comparative studies [192]. For women using antipsychotics associated with hyperprolactinemia, it is recommended to contemplate dose reduction and, if possible, shifting to alternative medications while carefully assessing the risk/benefit for both the patient and her offspring [33,193]

5.2.3. Group II: normoestrogenic normogonadotrophic state

5.2.3.1. Letrozole. It is an aromatase inhibitor that blocks the conversion of testosterone to E2, reduces the concentration of the latter, decreases negative feedback in the hypothalamus, and stimulates gonadotrophin production [194]. It has been shown to be superior to clomiphene citrate in terms of live birth rates [194–196]. A Cochrane systematic review comparing letrozole versus clomiphene citrate reached a similar conclusion [197]. The international evidence-based guideline for the assessment and management of polycystic ovary syndrome also recommend letrozole as the first option treatment [112]. However, currently, the use of letrozole for ovulation induction is not approved by the US Food and Drug Administration or the European Medicines Agency [198].

5.2.3.2. Clomiphene citrate. It is a selective modulator of the E2 receptor that blocks the negative feedback exerted by circulating estradiol, increasing the frequency of GnRH pulses, FSH secretion, and promoting folliculogenesis [199]. The rates of ovulation and pregnancy with its use are 73% and 36% per cycle, respectively [199,200]. Clomiphene citrate remains recommended as first-line treatment for anovulatory PCOS by multiple consensuses and guidelines [45,200].

5.2.3.3. Metformin. It is used to decrease insulin resistance and hyperinsulinemia in PCOS [201]. On its own, it can induce ovulation with an odds ratio (OR) of 3.88 (95% CI: 2.25 to 6.69) [202]. When combined with clomiphene citrate, ovulation rates improve compared to monotherapy with clomiphene citrate, with an OR of 4.41 (95% CI: 2.37 to 8.22) [202].

5.2.4. Group III: hypergonadotrophic hypergonadism

In women with primary ovarian insufficiency, to date, oocyte donation is an option for treating infertility [203]. Treatment remains challenging and generally involves hormonal replacement therapy and IVF [204]. However, considering that follicle luteinization could be the primary factor contributing to follicle dysfunction, it is suggested that reducing LH levels could lead to improvements in ovulation and conception rates [49]. The physiological hormone replacement therapy was studied by the National Institutes of Health in 2010, focusing on women with overt primary ovarian insufficiency [49]. Suppressed LH levels prevent follicle luteinization, restored follicle function, promoted ovulation, and increased the chances of achieving pregnancy in approximately one-half of

these women [50,205]. Besides, it improved their bone health [206]. Physiological estradiol replacement treatment is currently recommended as the treatment for women with overt primary ovarian insufficiency should be maintained until reaching the average age of natural menopause [207].

In women who underwent chemotherapy or radiotherapy, fertility preservation is recommended, including cryopreservation of oocytes, embryos, and ovarian tissue. The use of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy has shown to reduce chemotherapy-induced ovarian insufficiency. Additionally, prior to pelvic radiotherapy, surgical ovarian transposition can be performed as an attempt to prevent primary ovarian failure [63].

Women with premature ovarian insufficiency perceive that the evaluation of their medical condition is aggressive [208], and they experience a lack of social support, leading to lower self-esteem [209]. Moreover, considering the emotional impact of this diagnosis and its implications, it is essential to provide them with improved information about their condition, alleviate feelings of stigmatization related to the disorder, and support them in formulating alternative goals concerning family planning and other aspirations [210].

5.3. Management of other endocrine disorders

5.3.1. Thyroid disorders

ATA recommends that women with subclinical hypothyroidism undergoing IVF should receive levothyroxine treatment to maintain TSH below 2.5 mIU/L [118]. On the other hand, the American Society for Reproductive Medicine recommends considering the use of levothyroxine in women with subfertility if TSH exceeds the upper limit of normal (4–4.5 mIU/L). If the TSH value is between 2.5 and 4 mIU/L, the presence of thyroid antibodies should be evaluated, and if present, initiating levothyroxine treatment at an initial dose of 25–50 µg/day is also recommended [211].

In euthyroid women, despite the association between thyroid antibodies, infertility [212] and low ovarian response [213], to date, there is no evidence to justify the systematic use of levothyroxine or corticosteroids [214].

In cases of thyroid autoimmunity, the European Thyroid Association recommends using the intracytoplasmic sperm injection (ICSI) technique instead of IVF as TPOAb in the follicular fluid could bind to the zona pellucida, and this can be avoided by using the ICSI method. Additionally, it recommends evaluating TSH levels after ovarian stimulation (in case of pregnancy, on the day of the second confirmatory human chorionic gonadotrophin [hCG] administration) [215].

5.3.2. Adrenal insufficiency

Continuous evaluation and endocrine counseling are recommended before conception, as well as guidance on steroid dose regulation during pregnancy and childbirth [216].

5.3.3. Congenital adrenal hyperplasia

It is suggested to maintain progesterone levels below 2 nmol/L during the follicular phase, although achieving this value may require the administration of supraphysiological steroid doses [217]. Administration of hydrocortisone has been observed to regulate menstrual cycles, reduce androgen and progesterone levels, and decrease time to achieve conception [218].

5.3.4. Obesity

NHANES study found that the relationship between body mass index (BMI) and fertility has a turning point at a value of 19.5 kg/m^2, representing the point of highest fertility. In women with a BMI below 19.5 kg/m^2, each unit reduction below 19.5 kg/m^2 increases the risk of infertility by 33%, and each unit increase above 19.5 kg/m^2 increases it by 3%. It is suggested to maintain a body mass index close to 19.5 kg/m^2 [219].

Significant clinical benefits can be achieved in women with overweight and obesity even with moderate weight loss (5–10% of initial body weight) and lifestyle changes [220]. There are limited studies comparing the effects of anti-obesity medications on fertility in women [221]. These drugs are not safe for use during pregnancy, so contraceptive methods should be used during treatment and discontinued in case of pregnancy [222].

Bariatric surgery significantly improves the conception rate in nulliparous women with obesity, even within a time frame of less than 18 months after the operation. However, a reduction in AMH levels has been observed, indicating potential impairment of ovarian function, regardless of the type of procedure performed. Regarding outcomes in ART, improvements have been observed after surgery, such as a decrease in the required gonadotrophin units, an increase in the number of follicles, improvement in embryo quality, and higher pregnancy rates [223,224].

5.4. Other pharmacological treatments

5.4.1. Folic acid

There is evidence that high doses of folic acid improve fertility outcomes [225–227]. Regarding the effect of folic acid on ovarian response, supplementation with 400–800 µg/day of folic acid has been observed to have a positive impact on AFC [228]. In women undergoing ART, supplementation with doses higher than 800 µg/day of folic acid improves implantation rate and clinical pregnancies [227].

5.4.2. Vitamin D

The results of studies investigating the association between serum vitamin D levels and markers of ovarian response in human female populations are heterogeneous [229–233]. However, a study conducted by Naderi evaluated the effect of weekly administration of 50,000 IU of 25-hydroxy vitamin D on AMH levels in 30 women with infertility and low levels of 25-hydroxy vitamin D and AMH, and found a significant correlation between serum levels of 25-hydroxy vitamin D and AMH after three months [234]. Patients with low vitamin D concentrations should receive supplementation with doses of 1500–2000 IU/day [168,235].

5.4.3. Antioxidants

Studies have not demonstrated a positive impact on fertility [225,236]. A systematic review by Cochrane examined the use of antioxidants such as N-acetylcysteine, melatonin, arginine,

inositol, carnitine, selenium, vitamin E, vitamin C, and calcium, but found no positive effects on fertility in women due to the low quality of evidence and high heterogeneity among studies [237].

5.4.4. Probiotics

Based on current evidence, there is insufficient data to support their use in improving fertility in women [238].

5.5. Assisted reproductive technologies

In patients with unexplained infertility, IUI in combination with ovarian stimulation is recommended [239]. This stimulation can be performed using clomiphene citrate, aromatase inhibitors, gonadotrophins, or a combination of these medications at doses similar to those used for ovulation induction [239,240].

IVF is an effective tool for achieving conception [205] and should be considered in couples with unexplained infertility who have been unable to conceive after 2 years [185], cases of untreated bilateral tubal factor infertility, severe male factor infertility, or when preimplantation genetic testing will be used. In women over 38 to 40 years old, immediate IVF may be considered [241]. A typical IVF cycle involves stimulation with gonadotrophins to stimulate folliculogenesis, followed by aspiration of multiple ovarian follicles. In current IVF protocols, oocyte maturation is triggered using hCG or gonadotrophin-releasing hormone agonists (GnRHa) [242]. It is noteworthy that despite appropriate correction, the presence of the endocrine disorder could still have a detrimental impact on the pregnancy rate during IVF treatment [243].

OHSS is a potentially severe and life-threatening iatrogenic complication, characterized by ovarian enlargement, third-space extravasation, and multiorgan failure. The use of hCG as a drug (included in over 75% of IVF cycles) [244] is the main cause of OHSS due to its long half-life, high LH receptor activity, and prolonged duration of intracellular effects. Therefore, special care must be taken in populations at high risk of OHSS, such as women with PCOS [245]. As for GnRHa, used as single agents or in combination with hCG in dual trigger protocols, they provide greater safety in terms of OHSS risk, as they generate a short-duration LH secretion [242,244,245].

6. Expert opinion

Infertility in women is an area under constant investigation within the field of reproductive medicine. It affects millions of women globally and involves various interconnected factors, including endocrine disorders. Understanding the complex endocrine causes is crucial. The most frequent endocrine diseases associated with infertility are obesity, polycystic ovary syndrome, type 2 diabetes and thyroid disorders, however they are not the only ones, so it is important to carefully evaluate the root causes, since in this way healthcare professionals can create personalized treatments that target the core problem, increasing the chances of successful pregnancies.

In our manuscript, we thoroughly explore the endocrine disorders that negatively impact fertility in women. We have developed diagnostic and therapeutic algorithms to help healthcare professionals systematically address endocrine-related infertility in women. These detailed algorithms guide accurate diagnosis and effective treatment decisions, empowering clinicians and researchers in their respective fields, whether endocrinologists or gynecologists, and promoting standardized approaches to patient management.

Despite the progress made in our review, certain knowledge gaps remain in the pathophysiology of many endocrine disorders contributing to infertility in women. Currently, the scientific community is actively involved in numerous studies, working diligently to bridge the complex knowledge gaps and deepen our understanding of the elusive biological and genetic mechanisms that contribute to infertility in women. Researchers aim to identify innovative therapeutic targets that could transform infertility treatments, providing personalized interventions tailored to the specific needs of each patient.

Furthermore, there is a concerted effort to identify reliable biomarkers that can predict treatment response and the potential success of assisted reproductive procedures. The discovery of such predictive indicators represents a significant advancement, enabling clinicians to make well-informed decisions, optimize treatment options, and improve overall patient outcomes.

A promising horizon awaits, offering a more refined diagnostic and therapeutic approach to address endocrine-related infertility. Persistent research endeavors will equip clinicians with finely tuned diagnostic tools, enabling precise identification of the underlying causes of infertility. These advances will be complemented by cutting-edge therapeutic interventions, designed to address each patient's unique challenges and enhance the effectiveness of treatment strategies. The cumulative result will lead to improved fertility outcomes.

Furthermore, significant advancements are expected in the treatment of infertility in women. Innovations in ovulation-inducing medications are poised to surpass existing pharmaceutical options, potentially leading to higher rates of implantation success. This promising shift will particularly benefit women facing infertility due to anovulation.

In addition, gene and cellular therapies are on the cusp of revolutionizing the landscape of infertility treatment in women. By harnessing the power of genetic manipulations and cellular reprogramming, scientists aim to address infertility at the molecular level, opening up new possibilities for intervention. Concurrently, developments in fertility preservation techniques will safeguard the aspirations of parenthood.

The pursuit of excellence in assisted reproductive techniques will persist, fueled by groundbreaking innovations promising superior outcomes. This transformative progress aims to reduce the risk of complications, relegating the

specter of ovarian hyperstimulation syndrome to the past. As these novel techniques mature, they will pave the way for patient-centric care.

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JEQA and MJCZ designed the outline of this article review. JEQA, JCA, MCDV, ERGO, JSR, SPIN and LPRR were the main writers and performed the literature review. MJCZ and JPI were reviewers and prepared the manuscript. All authors have read and approved the final manuscript.

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