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Female infertility of endocrine origin

Infertilidade feminina de origem endócrina

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ABSTRACT

Infertility is defined as the failure to conceive, with no contraception, after one year of regular intercourse in women < 35 years and after 6 months in women > 35 years. A review on causes, management and treatment of endocrine causes of female infertility was performed. Epidemiological data suggest that around 10% to 15% of couples are infertile. Anovulatory problems are responsible from 25% to 50% of causes of female infertility. Advanced age, obesity, and drugs, have a negative effect on fertility. Different hypothalamic, pituitary, thyroid, adrenal, and ovarian disorders may affect fertility as well. Infertility is a growing phenomenon in developed societies. We here provide information about how to identify endocrine patients with ovulatory dysfunction. Women must be advised about limiting factors to be avoided, in order to protect their fertility. Arq Bras Endocrinol Metab. 2014;58(2):144-52

Keywords
Infertility; infertility causes; infertility propaedeutics; anovulation; ovarian factor

RESUMO

A infertilidade é definida como uma falha na concepção, sem anticoncepcionais, após um ano de relações sexuais regulares em mulheres com menos de 35 anos e após seis meses em mulheres com mais de 35 anos. Foi feita uma revisão das causas, manejo e tratamento das causas endócrinas causadoras de infertilidade feminina. Os dados epidemiológicos sugerem que cerca de 10% a 15% dos casais são inférteis. Os problemas de anovulação são responsáveis por 25% a 50% das causas de infertilidade feminina. A idade avançada, a obesidade e as drogas têm um efeito negativo na fertilidade. Diferentes transtornos hipotalâmicos, pituitários, tireoideanos, adrenais e ovarianos também podem afetar a fertilidade. A infertilidade é um fenômeno cada vez mais comum nas sociedades desenvolvidas. Fornecemos aqui informações sobre como identificar pacientes endocrinológicos com disfunções ovulatórias. As mulheres devem ser aconselhadas a evitar fatores limitadores de forma a proteger sua fertilidade. Arq Bras Endocrinol Metab. 2014;58(2):144-52

Descritores
Infertilidade; causas de infertilidade; propedêutica da infertilidade; anovulação; fator ovariano

INTRODUCTION

Infertility is defined as the failure to conceive after one year of regular intercourse in women < 35 years not using contraception and after six months in women > 35 years (1). Epidemiological data suggest that about 10% to 15% of all couples will experience difficulties to conceive (primary infertility) or to conceive the number of children they wanted (secondary infertility).

Based on a survey performed in developed countries, the World Health Organization (WHO) estimates that female infertility accounts for 37% of causes in infertile couples, male infertility for 8% and both – male and female infertility – for 35%. Five percent of couples have unexplained infertility and 15% became pregnant during the study. The most common identifiable factors that accounted for female infertility, were ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (11%), tubal blockage (11%), other tubal abnormalities (11 %), and hyperprolactinemia (7%). Other reports describe ovulatory disorders as responsible for more than half of the causes of female infertility (2).

INVESTIGATION

Albeit anovulation accounts for 25% to 50% of the causes of female infertility (2,3), even in women in whom it is highly suspected, like those with irregular cycles, it is important to check tubal patency (usually by means of hysterossalpingography) and endometrial cavity status (by transvaginal ultrassound ou hysteroscopy), as these two are common causes of female infertility. Male

factors should be promptly investigated by means of at least one spermogram. Assessment of multiple causes is especially important in women of more advanced age, in which investigation should be shortened in order not to delay treatment. The main factors to be addressed in the infertile couple are presented in figure 1.

Ovarian fators comprise (i) anovulation, (ii) ovulation with luteal insufficiency, when progesterone secretion by the corpus luteum is not enough to maintain endometrial stability until HCG production is settled (4); and (iii) luteinized non-ruptured follicule syndrome (LUF), when the follicle develops to its maturity, but remains in the ovary without rupture, and there it undergoes luteinization, being able to produce progesterone. In this situation, secretory changes occur in the mucus, and vaginal cytology; and progesterone levels are consistent with ovulation. Effectively, however, no oocyte is released to the tubes. All these three modalities will be here referred to as ovulatory dysfunctions.

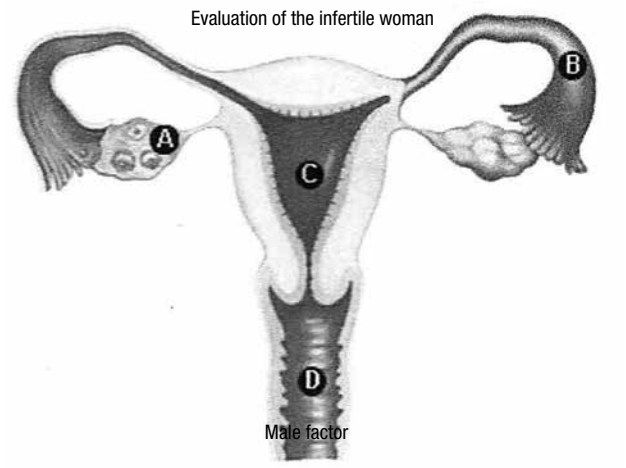

Figura 1. Infertility causes and evaluation. Female causes: (**A**) Ovarian fator; (**B**) Tubo-peritoneal fator; (**C**) Uterine fator; (**D**) Cervical fator.

OVULATION PROPAEDEUTICS

History and physical exam

Regular cycles, low abdominal pain in the middle of the cycle for a few hours and abundant mucus, all suggest ovulation. However, up to 10% of women with these features turn out to be anovulatory (5), or to have luteal insufficiency. Complete anamnesis, comprising menarchal age, menstrual pattern since the first two years after menarche, contraceptive use, previous pregnancies and outcomes, hirsutism, acne, galactorrhea, weight changes and hot flashes should be considered. Physical exam should include polycystic ovary syndrome (PCOS) stigmata, as well as goiter or Turner syndrome features. Breast and genital examination ensure normal sexual development, and may provide an estimation of estrogenic status.

One or more of the methods below are employed to detect ovulation (6):

Cervical mucus

Women with ovulatory cycles show clear, smooth, slippery mucus of increasing volume when getting closer to the mid-cycle (oestrogenic mucus), in parallel to estrogen rise and the ovulatory peak. After ovulation, viscosity increases and mucus becomes sticky, grainy, and tacky (gestagenic mucus). During the genital exam, it is possible to collect a sample of the mucus and let it dry on a slide to be examined in a microscope at low magnification: a typical pattern, resembling fern leaves can be observed in estrogenic mucus.

Hypoestrogenic women show little or no mucus during the genital exam, together with a pale mucosa. Anovulatory PCOS patients, on the contrary, show the same pattern of estrogenic mucus all over their cycle.

Nowadays, personal devices, which are in fact mini microscopes, using saliva instead of cervical mucus, may act like monitors of the ovulation period. Women seeking pregnancy put saliva samples on the device across their cycle. Samples dry and are magnified by the lens, showing the same ferning pattern present in cervical mucus when estrogen levels are high, allowing women to detect their possible period of ovulation.

Limiting factors for mucus analysis in detecting ovulation are genital infecctions and LUF, among others.

Hormonal cytology

A vaginal Papanicolau stained smear show flat, scattered, and eosinophilic cells in the follicular phase. When ovulation occurs, cells become closer to each other and basophilic. LUF is also a limitation for this method.

Basal body temperature

Progesterone secretion during luteal phase increases body temperature in 0.3 a 0.5 degrees Celsius. However, infections and even stress can alter body temperature as well, making this indirect method also limited for ovulation confirmation nowadays.

Hormonal dosages

Blood and urinary dosages may be performed in order to assess ovulation, in two or more moments of the cycle:

- Early follicular phase (2^{nd}-5^{th} day): FSH and inhibin B levels may show the likelihood of ovulation, especially in older women candidates for *in vitro* fertilization (IVF). FSH levels > 10 IU/L are considered predictive of poor pregnancy outcome, and >18 IU/L were reported as resulting in no live births (7), the same happening with inhibin B levels < 45 pg/mL (8).
- Mid cycle: LH peaks before ovulation, achieving two to fourfold above baseline levels. Ovulation usually occurs 28-36 hours after the beginning of LH rise, and 8-20 hours after the LH peak. Estrogen levels, as well as those of FSH and progesterone, rise steadly from the follicular phase and reach an ovulatory peak. For monitoring purposes, LH peak can be measured in the blood, together with estrogen levels in assisted reproduction cycles of low complexity. LH surge can also be identified by the patient with the help of ovulation prediction urinary test kits, which come with five to seven sticks sensible to LH surge detection. Typically, the patient places the stick into urine flow once a day, and when LH increases, the stick changes its colour, just like pregnancy urinary tests. Positive predictive values for follicular collapse within 24 or 48 hours after a positive urine LH test were first described as 73 and 92%, respectively (9). When different LH kits were compared, the lowest level detected as positive ranged from 25.5 mIU/mL to 48.7 mIU/mL. Follicular collapse occurred within 24 hours of the urinary LH peak in 80% and by 48 hours in 20% of the women analyzed (10).
- Luteal phase: progesterone levels in the mid-luteal phase (7 days before the next menstrual period, or 8 days after ovulation) < 3 ng/mL imply in anovulation, and > 10 ng/mL imply in proper ovulation. Values between 3 and 10 ng/mL suggest luteal insufficiency but can also be caused by ovulation in a different day than originally presumed, if the cycle is not being monitored.

Like the other methods described before, LH detection kits and progesterone luteal levels are not able to identify anovulation in the LUF syndrome.

Serial transvaginal ultrassound (US)

This is the gold standard, most precise method for the evaluation of ovulation, where direct visualization of follicular development is possible. It is usually performed from the 9-10^{th} day of the cycle up to ovular rupture. It is also the only method able to detect LUF syndrome. The addition of dopplerfluxometry elicits corpus luteum evaluation (11). The association between hormonal dosages and US monitoring confers even more accuracy in analyzing anatomical and functional ovulation parameters. Serial US should be performed by a doctor experienced in ovulation monitoring, and ideally by the same person, because follicule measures can vary from observer to observer. In general, follicles grow 1-2 mm per day and are mature, prone to rupture when measuring 18-24 mm. Cumulus oophorus visualization may further predict ovulation (12), as well as a endometrial thickness around 10 mm, and a three-fold ovulatory pattern.

The methods for monitoring ovulation, which can be employed in association, are shown in table 1.

CAUSES OF OVULATORY DYSFUNCTION

Genetic factors

Genetic factors contribute to risk of many common diseases affecting reproduction and fertility, including endometriosis, uterine fibroids, age at menarche, and age at menopause (13).

Modifiable factors

Knowledge about the effects of modifiable factors that affect fertility, such as age, obesity, smoking, and time of intercourse was questioned among women aged 18 to 45 years who wished to have a child or another child now or in the future. The majority of the respondents underestimated, by about 10 years, the age at which male and female fertility starts to decline. Female fertility starts to decline before age 35, and male fertility starts to decline before age 45. Most women were aware that obesity and smoking affect fertility. They clearly presented an inadequate knowledge of when, during the menstrual cycle, a woman is most likely to conceive (14,15).

Factors that modify the risk of infertility can be prevented with awareness of these important issues. The proportion of women who are intentionally delaying

Table 1. Methods of assessing ovulation

Phase of the cycle and days*	Method	Results suggesting ovulation
Early follicular phase (2^{nd}-5^{th} day)	FSH and inhibin B levels	FSH < 10 IU/L and inhibin B levels > 45 pg/mL
	Analysis of cervical mucus or saliva	Clear, smooth, and slippery mucus of increasing volume with ferning pattern closer to ovulation 
Follicular phase – ovulation (9^{th} day – up to expected result)	Hormonal cytology	Flat, scattered and eosinophilic cells in the follicular phase become closer to each other and basophilic near ovulation
	Basal body temperature	Increases in 0.3 a 0.5ºC body temperature after progesterone secretion upon ovulation
	Serial transvaginal ultrassound (US)	Follicles grow 1-2 mm per day and are mature when measuring 18-24 mm. Visualization of follicular disappearance is mandatory
Ovulatory phase (12^{th}-15^{th} day)	Urinary test kits for LH peak detection	Ovulation usually occurs 8-20 hours after LH peak
Mid-luteal phase (8 days after ovulation)	Progesterone levels	Progesterone levels > 10 ng/mL imply proper ovulation

pregnancy beyond the age of 35 years has increased greatly in the past decades because of the clash between the optimal biological period for women to have children with obtaining additional education and building a career. Delayed childbearing is rarely a conscious choice, and women are unaware that, at present, with the exception of oocyte cryopreservation and egg donation, assisted reproductive technology has no answer yet to age-related decline in female fertility (15).

Obesity has grown to epidemic proportions. Currently, nearly half of the reproductive-age women are overweight or obese. There seems to be a strong association between increased body mass index, lower pregnancy and live birth rates and increased rate of miscarriage. Coexisting factors, such as age and PCOS status have also been blamed for these adverse effects. Unfavorable ovarian stimulation characteristics, such as increased gonadotropin consumption, fewer selected follicles, and lower number of retrieved oocytes have been observed in obese women undergoing assisted reproductive technologies. The mechanisms underlying those adverse outcomes, whether ovarian or endometrial, remain to be clarified (16).

Active smoking is associated with reduced ovarian reserve, as reflected by decreased antral follicle count (AFC) and serum anti-Müllerian hormone (AMH) levels, and leads to poor prognosis in IVF cycles, whatever stimulation protocol used. Passive smoking results in the development of embryos of poorer quality. Among women in reproductive age, an active campaign should be carried out against nicotine on behalf of their fertility and future maternity (17).

Endocrine disorders

Many endocrine conditions lead to ovulatory dysfunction and infertility:

Hypothalamic amenorrhea

Hypothalamic amenorrhea results from a change in the normal pattern of episodic secretion of the GnRH pulse generator, with ovulation failure and amenorrhea. It can be due to congenital GnRH deficiency, hypothalamic lesions, or it may be functional. A practical definition of functional hypothalamic amenorrhea (HA) is the absence of menstrual cycles for more than 6 months without evidence of anatomic or organic abnormalities, thus being a diagnosis of exclusion. Three main types have been recognized: stress, weight loss, and exercise. Underweight is not a prerequisite for diagnosis (18-20).

Leptin appears to play an important role in regulating hypothalamic function, as leptin administration has been shown to induce GnRH pulsatility and menstruation. Rare genetic mutations (FGFR1, PROKR2, GNRHR, and KAL1) may contribute to the varied susceptibility of women to the functional changes in GnRH secretion that characterizes HA (2).

Functional pituitary adenomas

Prolactinomas

Prolactinomas are the most common pituitary tumors, but not the sole cause of hyperprolactinemia. The clinical picture varies from menstrual abnormalities, galactorrhea, or regular cycles with infertility. The secretion

of GnRH is abnormal in these patients. When pulsatilie GnRH is administered, restoration of ovulatory cycles has been described.

It is recommended that serum prolactin is measured twice before sellar imaging is requested, particularly in women with borderline levels (< 50 ng/mL) (21).

Acromegaly

Menstrual dysfunction and decreased fertility are present in 50% of women with acromegaly. The reason may be:

- Pituitary effects, such as destruction or compression of gonadotroph cells; hyperprolactinemia due to mixed GH-Prolactin adenoma; and pituitary stalk compression resulting in hypothalamic-pituitary-ovarian axis dysfunction.
- Polycystic ovary syndrome – direct effect of excessive GH/IGF-I secretion on the ovaries or secondary to GH induced insulin resistance (2,22).

Cushing's disease

Menstrual dysfunction and decreased fertility are common findings in this syndrome. Many features of Cushing syndrome are comparable to those observed in PCOS, such as obesity, low Sex Hormone Binding Protein (SHBG), increased androgens, and hirsutism. Several explanations have been put forward:

- Acyclic conversion of adrenal androgen to estrogen in fat cells together with obesity would lead to inappropriate acyclic feedback to the hypothalamic-pituitary axis.
- Hypercortisolemia can block GnRH release resulting in low estrogen levels.
- High levels of CRH and ACTH may affect the hypothalamic-pituitary secretion of GnRH and LH, as suggested by hypothalamic chronic anovulation (23).

Thyroid disorders

Hiperthyroidism

The prevalence of primary or secondary infertility associated with hyperthyroidim was described to be 5.8% (24). Nowadays, the prevalence of irregular cycles is 21.5% compared with what had been previously described (50%), due to earlier detection and treatment of hyperthyroidism.

Thyrotoxicosis results in increased serum levels of SHBG and estradiol (E2) compared to those in euthyroid women. The high levels of E2 may be explained by:

- Increased levels of SHBG.
- Increased levels of testosterone and androstenedione, as well as its raised conversion rate to E2.

In patients with Graves's disease, it was shown that LH secretion was also increased, and that this feature normalized after using antithyroid drugs.

If a patient is treated with the average dose of radioactive iodine (370 MBq), it is important to point out that no significant damage effect on gonads is expected. It is advised that conception is avoided until 6 months after administration, in order to be sure no hypothyroidism developed after ^{131}I, since the later may impair pregnancy outcome (2,25).

Hypothyroidism

The real prevalence of infertility in hypothyroidism is unknown. Early miscarriages rates are increased, together with fertility difficulties. The main changes explaining infertility in patients with hypothyroidism are (26):

- Altered peripheral estrogen metabolism: decreased clearance of androstenedione and estrone, and increase in peripheral aromatization to testosterone and estradiol. As plasma-binding activity of SHBG is decreased, the result is a decrease in total plasma concentrations of both testosterone and E2, although their unbound fractions are increased. This feature normalizes when euthyroid state is achieved.
- Hyperprolactinemia, due to TRH hypothalamic secretion.
- Defects in hemostasis, resulting in polymenorrhea and menorrhagia, explained by decreased levels of factors VII, VIII, IX, and XI.
- Disturbances in GnRH secretion that result in abnormal pulsatile release of LH, and a blunted or delayed response to GnRH.

Subclinical hypothyroidism

According to the Endocrine Society (27), studies are now focusing on the potential impact of subclinical hypothyroidism and subclinical hyperthyroidism on maternal and fetal health, the association between miscarriage and preterm delivery in euthyroid women positive for anti-thyroperoxidase (TPO) and/or anti-thyroglobulin (Tg) antibodies, and the prevalence and long-term impact of postpartum thyroiditis.

Ten to 20% of all pregnant women in the first trimester of pregnancy are positive for TPO or Tg antibodies, and are euthyroid. Sixteen percent of the women who are euthyroid and positive for TPO or Tg antibodies in the first trimester will develop a TSH that exceeds 4.0 mIU/L by the third trimester, and up to 50% of women who are positive for TPO or Tg antibodies in the first trimester will develop postpartum thyroiditis. The American Thyroid Association (ATA) recommends the following TSH reference ranges during pregnancy (28): first trimester: 0.1–2.5 mIU/L; second trimester: 0.2–3.0 mIU/L; third trimester: 0.3–3.0 mIU/L.

Adrenal disorders

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene. Irregular menses are common in females with CAH, with amenorrhea being more frequent in patients with Salt Wasting (SW) and Simple Virilizing (SV) forms. The number of pregnancies among women with CAH is related to the severity of the mutation.

Women with Non-Classical Congenital Adrenal Hyperplasia (NCAH) often present reduced fertility due to secondary PCOS and hyperandrogenism, which inhibit the normal hormonal cycle resulting in anovulation. Reports in women with classical CAH suggest that elevated progesterone concentrations play an important role in preventing menstrual cyclicity and fecundity. Likewise, persistently elevated levels of progesterone during the follicular phase in women with NCAH may interfere with the quality of cervical mucus, preventing sperm penetration. In addition, elevated levels of 17-OHP and/or progesterone during the preovulary (follicular) phase of the menstrual cycle may result in inadequate endometrial maturation and impaired embryo implantation (2,29).

Addison's disease

Primary adrenal insufficiency (Addison's disease) is characterized by deficiency of cortisol, aldosterone and androgen hormonal precursors, usually caused by an autoimmune reaction towards the adrenal cortex. Even with state-of-the-art replacement therapy with mineralo- and glucocorticoids, patients with Addison's disease consistently show reduced health-related quality of life. The loss of adrenal androgens could possibly influence fertility and increase in spontaneous abortions and has been associated with Addison's disease present in pregnancy, but the prognosis of pregnancies in patients with known Addison's disease has usually been considered good. Concomitant diseases, such as autoimmune thyroid disease and premature ovarian insufficiency (POI) are possible causes of reduced fertility in these patients, as well as inappropriate treatment of adrenal insufficiency and the burden of disease, with loss of energy and vitality required for wanting and planning a pregnancy and to rear children (30).

Ovarian disorders

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is the most frequent endocrinopathy in women, affecting up to 10% of those at reproductive age, characterized by ovulatory dysfunction, hyperandrogenism, and metabolic changes. Furthermore, PCOS presents a lifetime risk of type 2 diabetes, cardiovascular disease, and endometrial cancer (31).

The physiophatology of anovulation is complex. Dysregulated gonadotropin secretion with higher LH pulsatility and perturbed LH-FSH ratios, which likely contribute to the ovarian phenotype, might be indicative of disrupted GnRH secretory activity. Current hypothesis are that the increase of AMH would be responsible for disturbed folliculogenesis detected in PCOS (32), with increased AMH levels inhibiting primordial follicule recruitment, and reducing responsiveness of follicules recruited from FSH, thus preventing selection of the dominant follicule.

Experimental studies have shown that altered production of adipokines plays a main role in development and progression of PCOS. In particular, reduced secretion of adiponectin has a crucial role not only in inducing insulin resistance, but also in determining the clustering of elevated triglycerides and small, dense LDL particles. Increased leptin secretion may be responsible for sympathetic nervous system overactivity and hypertension, while reduced omentin may have an important permissive role in the development of atherogenic processes. Other adipokines (resistin, visfatin) determine and modulate the inflammatory process, which is an essential component of cardiovascular risk. Because obesity is common in PCOS, it is not surprising that these

patients present altered adipokine levels and increased prevalence of metabolic syndrome. However, because of androgen excess, in PCOS, adipokine dysfunction is particularly severe (33).

Useful research and diagnostic criteria arose from an expert meeting in Rotterdam (34), where it was recommended that PCOS should be defined when at least two of the following three features were present, after exclusion of other etiologies: (i) oligo- or anovulation, (ii) clinical and/or biochemical hyperandrogenism, or (iii) polycystic ovary appearance at an ultrasound (ovarian volume 10 ml and/or 12 follicles less than 9 mm in size). These criteria effectively created different phenotypes of PCOS as criticized by the AE-PCOS Society, which recommends the presence of clinical/biochemical hyperandrogenism and one other criterion for diagnosis (35).

When comparing the severe PCOS phenotype (hyperandrogenism, chronic anovulation, and polycystic ovaries: type I classic PCOS) with patients presenting hyperandrogenism and chronic anovulation but normal ovaries (type II PCOS), the patients with polycystic ovaries had a higher luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. Ovulation in type II PCOS was relatively common (28.8% of patients), and milder clinical and endocrine alterations compared to classic PCOS phenotypes were found. The normoandrogenic phenotype was relatively uncommon. These patients had a normal body mass index, insulin sensitivity, and free androgen index, but showed increased levels of LH and LH/FSH ratio (36).

Premature ovarian failure

Premature ovarian failure or insufficiency (POI), is a disorder characterized by amenorrhoea, low estrogen and increased gonadotropin levels in women aged < 40 years. POI is the result of premature exhaustion of the follicular pool, or can be attributed to follicular dysfunction, for example, owing to mutations in the follicle-stimulating hormone receptor or steroidogenic cell autoimmunity (2).

Moreover, advances in cancer therapeutics have led to increasing survival rates for both pediatric and adult malignancies. Given the gonadotoxic effect of many cancer treatments, more women develop POI. A marker that predicts whether women are at risk of POI would, therefore, aid in early diagnosis and fertility counselling. Anti-Müllerian hormone (AMH), a growth factor produced solely by small, growing follicles in the ovary, might constitute such a marker, as serum levels of this hormone correlate strongly with the number of growing follicles. In addition, AMH could potentially help to assess the progression of ovarian senescence, as serum AMH levels are independent of hypothalamic-pituitary-gonadal axis function, and decrease to undetectable levels at menopause. The most established role for AMH measurement is in women about to start IVF treatments, identifying women whose response will be poor, thus tailoring protocols and expectations (37,38).

PRINCIPLES OF TREATMENT

Endocrine disorders should be addressed and body weight normalized. So, hyperprolactinemia should be treated with dopamine agonists, hypothyroidism replaced with L-tyroxine, and so on. Upon correction, if anovulation persists and ovulation stimulation is still needed, specific treatments are cited below. Depending on the type of anovulation, different drugs are employed. Ovulation stimulation should always be monitored by serial transvaginal US, because ovarian cysts and hyperstimulation syndrome can occur even with oral agents in low doses.

Hypogonadotrophic anovulation of hypothalamic origin can be treated with pulsatile gonadotrophin-releasing hormone administration by means of a pump. Pregnancy rates range from 80% to 93% after 6 and 12 months respectively, and are mostly single (39). Ovulation stimulation in pituitary or hypothalamic disorders can be also performed with injectable gonadotropins (purified FSH or a mixture of FSH and LH), starting from days 2 or 3 of the cycle, in step-up or step-down protocols, with dosis ranging from 37.5 to 150 IU/day during 10-14 days. When the dominant follicle reaches 18 mm an HCG injection is provided to simulate the LH surge and cause ovulation. The luteal phase is usually supplemented with progesterone.

Normogonadotropic anovulation, comprising PCOS, represents the largest group of patients. Initial treatment should be performed with clomiphene citrate 50 mg/day during 5 days in the beginning of the cycle. The dose can be increased up to 150 mg/day in case of no response, but clomiphene use should be limited to 6 cycles. Ovulation, pregnancy and live birth rates reach 73%, 36% and 29% per woman, respectively (40), with multiple pregnancies reported in up to 7% to 10% of the pregnancies (41). Resistant women, or those who do not conceive after six months should be offered go-

nadotropins or other treatments. In PCOS patients, conventional dose gonadotropin regimens have higher risk of multiple pregnancies and severe ovarian hyperstimulation syndrome, but low-dose FSH regimens show monofollicular ovulation in 70% of the patients, and a cumulative pregnancy rate of 55% to 70%, with rates of ovarian hyperstimulation syndrome and multiple pregnancy of less than 1% and 6%, respectively.

Metformin may be added to clomiphene in insulin-resistant patients. A recent Cochrane review (42) described that co-treatment with metformin and clomiphene improved ovulation and clinical pregnancy rates, but not livebirth rate compared with clomiphene citrate alone. However, in obese women and in those resistant to clomiphene, metformin association was described to improve live birth rates (43). Although we reported a rare triplet pregnancy after metformin, this drug is usually not associated with ovarian hyperstimulation or multiple pregnancies (44).

When medical treatment fails in PCOS patients, laparoscopic ovarian drilling is the next option (5).

For established hypergonadotropic anovulation, egg donation is the standard procedure. Women at risk for hypergonadotropic hypogonadism should be informed about oocyte or ovarian tissue cryopreservation, an option now available that can help their future pregnancy attempts.

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