

Fertility Management of Patients with Reduced Ovarian Reserve

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Abstract

Reduced ovarian reserve is a condition characterized by a reduced competence of the ovary to produce oocyte due to advanced age or congenital, medical surgical and idiopathic causes. Age is considered to be the principal factor in determining the reduction of ovarian reserve, especially in woman over 40 years of age, but it's well known that a premature reduction of ovarian reserve can also occur in young patients. Management of patients with diminished ovarian reserve is challenging for fertility experts and frequently the only option to conceive is represented by assisted reproduction technologies. Here we review the aetiology, presentation and diagnosis of reduced ovarian reserve both in advanced and in young age and we discuss recent advances in the management of infertility of these women.

Keywords: Reduced ovarian reserve; Diminished ovarian reserve; Premature ovarian failure

Introduction

Reduced ovarian reserve is a condition of reduced ability of the ovary to produce oocytes due to advanced age or congenital, medical, surgical and idiopathic causes. This condition, also known as Diminished Ovarian Reserve (DOR) is often used to characterize women at risk for poor performance with Assisted Reproductive Technologies (ART) due to egg factor [1-4]. The most extreme phenotype of DOR in young age is represented by Premature Ovarian Failure (POF), a disorder characterized by amenorrhoea, hypooestrogenism and high gonadotrophin levels in young patients under 40 years of age. Spontaneous POF affects the 1% of women under 40 years, 0.1% of patients younger than 30 years and 0.01% of patients under the age of 20 years [5,6]. However, with the increasing of cancer cures in children and in young women the incidence of POF is quickly increasing [7,8]. Analyses performed by the Childhood Cancer Survivor Study show that the 6.3% of women who received cure for cancer suffered of acute ovarian failure [9]. In this manuscript we review the aetiology, presentation and evaluation of old and young woman with reduced ovarian reserve and we discuss recent advances in the management of infertility of these patients.

Aetiology

The reduction of ovarian reserve may be the consequence of various mechanisms.

Age is considered to be the principal factor in determining quality and quantity of ovarian reserve. It's well known that either the quantity and quality of ovarian follicles decrease with age. Different trials showed that biological capability to conceive of a woman, after an acme of competence in the early 20s, decreases in a universal way among all mammalian species [10]. The progressive reduction of fertility increases in the late 30s, ending on average age of 50-51 [11]. The crucial role of the ovary in regulating reproductive aging, it's well known [11], and this is accredited by the evidences that age-related decrease in women fertility can be surmounted by oocyte donation from younger patients [12]. The reduction of ovarian function with aging has been widely defined in term of progressive reduction of ovarian follicles and diminished capability to generate competent oocytes [13,14]. Age is considered to be the main cause of reduced ovarian reserve in woman over 40 years of age, but as it is known, a premature reduction of ovarian reserve can also occur in young age. This condition known as Premature Ovarian Failure (POF) can occur spontaneously, primary POF, or can be a consequence of chemotherapy, radiation or surgery, secondary POF. Primary POF is in 90% of cases idiopathic. Nevertheless, a lot of conditions predisposing to POF have been described. Possible causes

of POF can be principally divided in two main groups: chromosomal and non chromosomal anomalies. In about 50% of women with POF who have primary amenorrhoea, chromosomal anomalies are observed [15], while in women with secondary amenorrhoea these are much less common. Identifying chromosomal anomalies may have a limited effect on women managing, but can be helpful for other family members in programming a family. X chromosome abnormalities such as deletions and translocations within X chromosome, X monosomy and FMR1 gene mutation, are identified most commonly in patients with familiarity for POF. Deletions and translocations within X chromosome that have been related to POF are frequently located in the Xq13-26 region which probably plays an important role in ovarian growth and physiology. Turner syndrome, X monosomy, is connected to the accelerated decline of follicles that starts from birth and leads to POF frequently before menarche.

FMR1 gene is the gene responsible of fragile X syndrome (FXS), the main cause of intellectual deficit. FXS is generally due to an expansion of a repetitive CGG triplet sequence placed in the 5'-untranslated region (5'-UTR) of the *FMR1* gene on the X chromosome (Xq27.3) [16], but rarely it results from point mutations or deletions within the *FMR1* gene [17].

The allele becomes unsteady in the transmissions when the expansion repeat numbers is in order of 50 to 200, premutation [18]. Reports suggest that approximately 13-26% of patients with *FMR1* gene premutation will evolve in POF and a growing number of CGG repeats is a related to younger age at menopause [19]. The relationship between FRAXA premutations and POF is undiscovered, therefore FRAXA screening could be especially helpful in the discovery of families at risk of transmitting fragile X syndrome and so in predicting POF [20].

Galactosemia is an autosomal recessive defect of galactose assimilation pathway due to the lack of the enzyme galactose-1-phosphate uridylyltransferase (GALT). Long-term complications of this disorder, include hypergonadotrophic hypogonadism in 60-70% of patients affected [21]. The mechanism of ovarian toxicity induced by

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galactose is undefined, but probable mechanisms are represented by direct toxicity of galactose and metabolites, defective galactosylation of glycoproteins and glycolipids, oxidative stress and activation of apoptosis [22].

Another syndrome associated with POF is Pseudohypoparathyroidism type Ia (PHP-Ia). This disorder results from heterozygous inactivating mutations of the alpha subunit of the heterotrimeric stimulatory G-protein (Gs), due to mutations of the *GNAS1* gene. Reproductive dysfunction is common in affected women and probably represents partial resistance of theca and granulosa cells of the ovary to gonadotropins due to deficient Gs alpha activity [23].

Additional relevant genetic defects include those coding for enzymes essential to reproduction such as Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH) receptor mutations, 17 α -hydroxylase deficiency and others as Gut-Associated Lymphoid Tissue (GALT), eukaryotic translation initiation factor 2B (EIF2B) and forkhead box protein L2 (FOXL2). A missense mutation in the inhibin α subunit gene, *INHHA G769A*, is related to POF in various populations, nevertheless evidence recommends that this mutation may represent a susceptibility factor that increases the probability to develop POF [24]. Recently, Bonomi et al. studied mtDNA content in blood cells of patients with POF [25]. They proved the correlation between blood and ovarian mtDNA content in peripheral blood cells of patients affected by POF or with anticipated reduction of ovarian reserve and in two control groups constituted by women with normal ovarian reserve and by women in physiological menopause. They noted a significant association between ovarian reserve and blood mtDNA content and observed diminished mtDNA copies number in peripheral blood cells of women with compromised ovarian reserve in comparison to controls. The Italian researchers concluded that among patients affected by POF, blood cells mtDNA depletion is frequently identified. This suggests that a generalized mitochondrial defect, still undefined, may frequently predispose to POF. The measurement of mtDNA content in blood may be an helpful device for POF risk prediction [25].

Non-chromosomal causes of POF can be divided in three different groups: iatrogenic (surgery, chemotherapy and radiations), autoimmune (susceptibility mediated by AIRE gene mutation), infective (herpes virus, cytomegalovirus, mumps) and idiopathic.

It's well established that many patients could evolve in POF after medical therapy. The main causes of iatrogenic POF are represented by chemotherapy, pelvic radiation or surgery for cancer. It has been demonstrated that older age at the moment of treatment, abdominal pelvic and spinal radiotherapy and some chemotherapeutic drugs as alkylating agents, increase the percentage of ovarian failure in women cancer survivors [9,26].

The relationship between POF and autoimmune disorders is well known. POF is commonly observed in the 25% of cases of hypothyroidism, in the 3% of Addison's disease and in the 2.5% of diabetes mellitus [27]. POF it is also associated with autoimmune polyendocrine syndromes, APS types 1 and 2, pernicious anaemia, systemic lupus erythematosus, rheumatoid arthritis and vitiligo. Around 50% of patients with POF have ovarian antibodies, but the clinical relevance of these is undefined because of their high prevalence (31%) in patients with normal ovarian reserve [28].

Some infections such as mumps, malaria, varicella, tuberculosis, cytomegalovirus, herpes simplex and shigella have been associated with POF. It is estimated that the 2-8% of women with mumps oophoritis develop a commonly transitory ovarian failure [29].

The risk of idiopathic POF varies by ethnicity [6]. Luborsky et al. [6] observed that Caucasian, African-American and Hispanic women have a significantly augmented risk of develop this affection in comparison to Japanese women. Chang observed that cigarette smoking was related to an augmented risk of idiopathic POF, while oral contraceptive use reduce the risk of early menopause [30]. Later menarche, irregular menstruation and longer breast feeding, are all factors that cumulatively reduces the risk of premature reduction of ovarian reserve.

Initial Evaluation

For the majority of women, the cessation of periods is asymptomatic [31] and a lot of them have a normal menstrual and fertility history at the time of diagnosis. In some women a frequent symptom is the lack of restarting normal menstrual cycle after a pregnancy or after discontinuation of oral contraceptive. This diagnosis can be, abrupt and stressful, with unsightly symptoms, and worsened by the discovery of infertility [32,33]. Primary POF typically presents with secondary amenorrhoea or oligomenorrhoea in a young woman under 40 years of age, accompanied or not by flushing [27]. In the few women who experience primary amenorrhoea there is frequently an underlying chromosomal abnormality. Various conditions may influence the appearance of different symptoms in these women. Women with a diagnosis of POF before of 20 years old are considerably less inclined to exhibit symptoms of flushing and sweats, depressive mood and vaginal dryness [34], on the contrary patients with iatrogenic POF, due to surgery or cancer therapy are frequently symptomatic. The criteria to make diagnosis of POF are not always standardized [35]. Many clinicians make the diagnosis on the basis of the presence of amenorrhoea for 3–6 months, the finding of FSH values above 40 mIU/ml on at least two different moments at a distance, and low estrogen levels [31]. In order to make a diagnosis, it's important to exclude other causes of amenorrhoea, such as pregnancy and polycystic ovarian syndrome. Evaluation of thyroid function and prolactin levels is also necessary to eliminate the hypothesis of other endocrine disorders. When the diagnosis has been established, further specific investigations are necessary to understand the cause. Karyotype analysis is important in order to exclude genetic causes. If genetic abnormalities are identified, implications for future pregnancies should be discussed. Autoantibody screening for antiovarian, antithyroid and antiadrenal antibodies, is also suggested.

The assessment of Ovarian Reserve (OR) it's critical for the management of infertility in these patients. Total Ovarian Reserve (TOR) comprises of all largely primordial follicles (NGFs) and to a minor extent of maturing Growing Follicles (GFs) after recruitment. So, GFs usually evaluated in clinical practice, and usually referred as OR, in reality reflects only a small portion of the totality of follicles. So, OR represents only a part of total ovarian reserve. Because most GFs are undergoing to degeneration and apoptosis, TOR really consists of only the still not recruited primordial follicles (NGFs) [36,37], but unfortunately a clinical device to evaluate NGFs does not exist.

Age and menstrual pattern are considered the most important clinical markers in determining quality and quantity of OR. Menstrual cycle Length (MCL) is suggested to be mainly due to the proportion and quality of follicular development and to the duration of the follicular phase. Commonly a gradual shortening in cycle length starts in the late 40s, but in some cases may occur in the late 30s. Brodin et al. has demonstrated an association between MCL and the Antral Follicle Count (AFC) during ultrasonographic evaluation [38] and the possibility of pregnancy after assisted reproduction was approximately doubled for women with a MCL less than 34 days compared with

women with a MCL less than 26 days; mean MCL is strictly associated to success rates in assisted reproduction irrespective of age. The age related shortening of MCL is probably linked with the shortened follicular phases and it is in part due to the reduced production of inhibin-B by a little number of antral follicles and to the subsequent premature rise of FSH secretion [39,40]. Day 3 levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the most widely used test for ovarian screening [41]. FSH should be measured various times in order to rule out discontinuous ovarian activity as cause of increased gonadotrophins [42]. On the other hand, it has been described that the rise of FSH values is delayed respect to the events related to ovarian ageing [43]. Hence, if the aim to the assessment of ovarian reserve is the management of infertility, the only increase of FSH is of limited utility as a mark [44]. For what concern oestradiol (E2) values, in women with reduced ovarian reserve, they are generally reduced, with values of 50 pg/ml in patients with poorly functioning follicles [45].

Several studies show that antral follicle count (AFC) and ovarian volume are very effective in estimating the response to ovarian stimulation [46]. Ovarian antral follicles are evaluated by transvaginal ultrasound at the beginning of the follicular phase of menstrual cycle and the total number of 2–10 mm follicles in both the ovaries represents the AFC [47,48]. AFC with diameter larger than 2 mm are described as “recruitable” and they are highly sensitive and responsive to gonadotropins. Another endocrine marker that has been identified as growth index of small antral follicle cohort [49] is represented by inhibin B. Inhibins are glycoprotein hormones produced by by granulosa and theca cells, that belong to the superfamily of transforming growth factors β (TGF- β) [50] and their activities include suppression of FSH production [51,52]. As demonstrated by investigation on infertile patients aged between 24 and 40, there is a significant negative association among basal inhibin-B and FSH, and significant positive association among basal inhibin-B and AFC [53]. When the size of follicular pool decreases, inhibin B values decrease and FSH levels increase. Inhibin B values vary with the menstrual cycle, and they have two principal peaks: one at the beginning of the midfollicular phase and one the time of ovulation [54]. In order to give the highest information, inhibin B values should be measured at the beginning of the follicular phase of menstrual cycle [55]. Although the association between diminished basal serum concentrations of inhibin-B, poor response to ovarian stimulation in ART is well established, several reports, did not recommend the only use of inhibin B as a trustworthy marker of ovarian reserve [56].

Anti-Müllerian Hormone (AMH), is an hormone secreted by growing antral follicles. This hormone, that can be measured anytime in the menstrual cycle, is actually considered to be the most trustworthy marker of diminished ovarian reserve and might be able to predict age at menopause [57]. AMH is secreted by fetal Sertoli cells during testicular differentiation, and promotes the involution of the Müllerian ducts. Lacking of AMH, leads to the development of uterus, fallopian tubes and upper part of vagina from Müllerian ducts [58]. In female AMH is secreted in the ovary by granulosa cells [59,60] and its presence in ovaries has been identified since 36 weeks of pregnancy [61], becomes scarcely measurable at birth and increases after puberty [61,62]. AMH expression decreases with the advancing of age and becomes unmeasurable again at menopause [63].

The correlation between AMH levels and AFC evaluated by ultrasound, it's well known [64–66]. AMH is now considered to be the best marker of the progressive decline in reproductive capacity in women [67,68] and an accurate predictor of the occurrence of poor response to ovarian stimulation in IVF [65,69–71].

AMH and AFC are nowadays considered two markers with similar diagnostic performance in the assessment of ovarian reserve [72,73].

Management of Infertility

Management of women with compromised ovarian reserve is challenging for fertility experts and generally the only option to conceive is represented by Assisted Reproduction Technologies (ART). Women with reduced ovarian reserve retrieve less oocytes, have less embryos for transfer and their chances of pregnancy are obviously lower. Frequently, their cycles have to be cancelled because of the absence of follicular development, the lack of oocytes retrieved or the failure to develop embryos [74–77]. In accordance with ESHRE consensus [77] patients with reduced ovarian reserve should be defined as “expected poor responder” to ovarian stimulation during ART cycles. These patients can be treated in various ways and the different protocols used include both the stimulation protocols with high doses of gonadotropins with the addition of various dosages and timing of GnRH analogs or antagonists, IVF in a natural cycle and IVF with minimal stimulation. Several studies finally suggest the benefit of the supplementation of some hormones like dehydroepiandrosterone, growth hormone, estradiol and androgens. Oocyte cryopreservation provides a potential tool to preserve fertility in patients at high risk to develop POF who are not trying to get pregnant [78]. In women with a greatly reduced ovarian reserve, the strategy that provides the greatest chance of pregnancy is represents by egg donation [79].

IVF Stimulation Protocols

Gonadotropins

The most commonly used approach to enhance oocyte production in patients with compromised ovarian reserve includes an augmented daily intake of gonadotropins, from 300 to 450 IU per day, associated with GnRH agonist with long, stop or microdose flare protocols or GnRH antagonist protocols.

Several years ago, it was reported that the administration of high doses of gonadotropins, more than 300 IU per day, in poor responders could potentially enhance follicular growth and minimize cycle cancellation rates [80,81], however further reports did not approve this scheme because to the high costs and side effects of treatment [82]. The starting dose that seem to be universally accepted ranges from 300 IU per day, up to a maximal dosage of 450 IU per day [83].

The administration of high purified hMG in aged women and in those with poor ovarian response, give a better performance than rFSH. This is probably due to the action of exogenous LH and/or to greater acidic isoforms of FSH protein secreted when estrogens are low [84].

Some authors suggest that LH supplementation may confer a benefit in poor ovarian responders [85,86], however other authors observed that this is real only for young patients, because in older poor responder patients recombinant LH (rLH) supplementation provides no further benefit [87].

Natural cycle IVF

The first report that investigated the natural cycle as a first strategy in women with low prognosis related to age and diminished ovarian reserve was performed by Papaleo et al. Papaleo et al. found a similar pregnancy rate to that of conventional IVF in older women and not, reduced by a single embryo transferred [88]. Schimberni et al. evaluated 500 Intracytoplasmic Sperm Injection (ICSI) natural cycles in poor responders women. He observed that natural cycle IVF is an efficacious protocol for poor responder patients, especially in younger women [89].

Natural cycles IVF is a relatively easy procedure, especially for patients, that minimizes physical and emotional stress, the costs of treatment and laboratory tests [90]. Natural cycle IVF allows an oocytes natural selection, an improved embryo quality [91] and an higher endometrium receptivity [92]. However the use of natural cycles presents some disadvantages mainly due to the frequent spontaneous luteinizing hormone surge (LH), the resulting high cancellation rate (up to 30%), the difficulties in programming oocytes retrievals, the high incidence of failure to recover oocytes during oocyte pick-up (16.7–71.4%) and low pregnancy rate per embryo transfer (ET) cycle (0–23.5%) [93]. Hence, natural cycles could not be used as first choice in IVF, but should be regarded as an option after repeated ovarian response failures with classical protocols of stimulation [94].

Modified natural cycle/mild stimulation with Gonadotropin Releasing Hormone (GnRH) antagonist Cycle IVF

Modified natural protocol means GnRH antagonist administration when a follicle of 13 mm is viewed on ultrasound, and the daily addition of Follicle Stimulation Hormone (FSH) or Human Menopausal Gonadotropin (hMG), during antagonist administration so as to support the additional follicular growth. Mild ovarian stimulation is a patient-friendly procedure that decreases the incidence of ovarian hyperstimulation syndrome, minimizes unessential patients discomfort and as using low doses of gonadotropin, decreases treatment costs [95]. Recently Yoo et al. compared IVF outcomes of mild ovarian stimulation with conventional ovarian stimulation in poor responders; they observed an higher pregnancy rate in women over 37 years old and they recommended the use of mild ovarian stimulation protocol in poor responders women over 37 years old [96]. The literature is lacking of studies that compare natural cycles and minimal stimulation in poor responder; as a consequence no conclusions can be drawn about the cost-effectiveness of the two approach.

GnRH Agonist versus Antagonist

The underlying mechanism of Gonadotropin Releasing Hormone (GnRH) agonist/antagonist is to inhibit pituitary gonadotrophins production and then to increase follicular development by administration of exogenous gonadotrophins, facilitating cycle control.

The combination of exogenous gonadotropin plus GnRH agonist (GnRH-a) for the suppression of pituitary FSH and LH secretion, is associated with higher pregnancy rates in IVF-ET as compared to protocols without GnRH-a. However, two prospective randomized trials which compared the use of flare protocol and the traditional long GnRH agonist protocol in poor responders, did not observe any significant differences in pregnancy rate [97,98]. Nevertheless, Weissman et al. observed a favorable trend for a better result in the long GnRH agonist protocol group [99]. The use of long GnRH agonist protocol was related to a lower cancellation rate even if not related to better overall outcomes, even when pregnancy rates are calculated for embryo transfer, probably because of the overall poor embryo quality in these women [100]. The logic principle for the administration of a flare up protocol in poor responders is the ideal improvement of follicular development which may experience with the flare effect that occurs with the start of GnRH agonist. The drawback is that there may occur an early LH surge which causes cycle cancellation [101].

In these patients, the protocol with GnRH antagonist can control the premature LH surge without causing any suppression in the early follicular phase [102].

Some reports showed that the use of GnRH antagonist may reduce the duration of stimulation, reduce the total gonadotropin necessity,

decrease patient's expense, lower cycle cancellation, and give to greater ongoing pregnancy and delivery rate [103,104].

Two meta analyses [105,106] and several studies [107,108] that compared GnRH antagonist protocol to GnRH agonist flare protocol with long GnRH agonist protocol reported no variation in pregnancy rate. Recently a randomized controlled trial performed by Prapas et al., compared the efficacy of the long GnRH agonist and the fixed GnRH antagonist protocols in IVF poor responders; even if they observed similar pregnancy rates using the two protocols, the occurrence of higher cancellation rate in the antagonist group, gives them to suggests the long GnRH agonist protocol as the first choice for ovarian stimulation in poor responder patients [109].

Other Strategies

Dhea supplementation

Dehydroepiandrosterone (DHEA) is a steroid hormone produced by the adrenal glands, theca cells of the ovarian follicle, and central nervous system. In the ovarian follicle DHEA is converted to androstenedione and estrone, the source of testosterone and estradiol in accordance to the two-cell theory.

The clinical advantage of DHEA supplementation in women with reduced ovarian reserve was firstly described by Casson et al. [110] and now about one third of all IVF centers all over the world use DHEA supplementation in women with reduced ovarian reserve. Recent trial reported that DHEA promotes ovarian function, enhances pregnancy possibilities and, by decreasing aneuploidy, decreases the percentage of miscarriage. DHEA supplementation seems objectively enhances ovarian reserve [111]. The beneficial effects are maximized after two to four month of administration of 75 mg of micronized DHEA per day [112]. Our recent study shows that Dehydroepiandrosterone-sulfate (DHEAS) administration for three months in poor responders patients improve both the follicular microenvironment and oxygen levels in follicular fluid that is crucial to the development of oocytes and embryo of good quality. The best reproductive outcomes after DHEA supplementation in poor responders are probably due to the effect that this prohormone exerts on follicular microenvironment [113].

Growth Hormone (GH) supplementation

The positive correlation between growth hormone supplementation and exogenous gonadotropins administration in facilitating ovulation it's well known [114]. GH modulates the activity of FSH on granulosa cells through adjustment of the local synthesis of insulin-like growth factor-I (IGF-I) that magnifies gonadotropin activity on both the granulosa and theca cells [115]. Actually, data about GH supplementation come from limited studies in various patient subgroups [116] and as such remains outside routine clinical application. Kolibianakis in a systematic review and meta-analysis showed that GH addition increases the possibility of pregnancy and live birth [117]. Yovich and Stanger [118] has evaluated in a sequential crossover report of IVF performed from 2002 to 2006, the effect of GH administration in poor-prognosis patients, evaluated on the basis of previous failure to conceive (mean 3.05 cycles) due to poor response to ovarian stimulation (<3 metaphase II oocytes) or poor-quality embryos.

Yovich and Stanger [118] reported that GH supplementation significantly improved the clinical pregnancy rate both per fresh transfer ($P<0.001$) and per frozen-thawed embryo ($P<0.05$) with a greatly significant productivity rate ($P<0.001$). The effect was relievable in all age groups, in particular in younger patients, and was not related to stimulation protocol or number of transfers [118]. However, before

recommending GH supplementation in IVF, further studies are needed to completely characterize its role [119].

Estradiol (E2)

Estradiol administration in the luteal phase prior to IVF hyperstimulation it's a new option for the treatment of poor responder; estradiol in fact may inhibit FSH in the early luteal phase and result in more coordinated cohort of follicles responding to the hormonal stimulation. Even if some studies reports that E2 supplementation in the luteal phase could enhance embryo quality and pregnancy rates [120,121], recently some authors observed that adding E2 as luteal support did not increase the clinical pregnancy rate or reduce the miscarriage rate and that the routine use of a combination of E2 and progesterone as luteal support in GnRH α long protocol IVF/ICSI cycles is not recommended [122,123].

Androgens and androgen modulating agents

It is well known that testosterone enhances follicular FSH receptor expression in granulosa cells [124], facilitates the initial development of primordial follicle and increases the number of developing pre-antral and small antral follicles [125]. Fabregues et al. reports that transdermal testosterone supplementation could enhance FSH ovarian sensitivity and follicular response to exogenous gonadotrophin in previous poor responder patients and that strategy leads to a better follicular response compared with an high-dose gonadotrophin and minidose GnRH agonist protocol [126].

Oocyte cryopreservation

Oocyte cryopreservation allows to preserve fertility in patients with an high risk to develop ovarian failure that require chemotherapy or radiotherapy. This technique should no longer be considered experimental and should be recommended with appropriate counseling [78].

In women at high risk of POF for family history of early menopause or for genetic disorders associated with POF [127], oocyte cryopreservation provides a potential tool to preserve fertility if they have no partner or they do not try to become pregnant at the time of the diagnosis.

Oocyte donation

Despite the enormous progress in ART for many older women or young women with POF, in countries in which is allowed, the only option its egg donation [128].

Psychological and psychosexual support

The psychological distress of women with infertility has been well-documented in the literature. The inability to conceive creates a profound psychological distress in women and this condition affects their self-esteem and relationships with others [33]. Patients with POF have an elevated incidence of anxiety, depression, somatization and decreased self-esteem and comprehensive satisfaction with life in comparison to control groups [32,129,130]. Loss of reproductive capacity appears to be a dominant disconcerting factor, and this does not seems to be related to the fact that women have or not already children. Psychological support therefore play a crucial role in the management of these patients.

Sexual disturbances, with diminished sexual well-being, decreased arousal, lower frequency of sexual intercourse and augmented pain, are other common problems in women with POF [129]. Psychosexual counseling and estrogen and potentially androgen supplementation represent a strategy in the management of sexual dysfunction.

Conclusion

The management of patients with reduced ovarian reserve should ideally be multidisciplinary [131] and include professionals from various specialties in order to provide proper treatment and to comply the various necessity of these patients. Management of infertility is a challenge for IVF experts and these patients must be approached as "expected poor responder" for ovarian stimulation. Current evidence suggests that DHEA administration appears to objectively improve ovarian reserve. Oocyte cryopreservation is a device that allows women at high risk of developing premature ovarian failure to preserve their reproductive potential. Despite the enormous advances in IVF protocol for many women the only option it's represented by egg donation. In patients with compromised ovarian reserve it's also recommended an adequate counseling and emotional support [35].

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