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Review

Insights from clinical experience in treating IVF poor responders

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KEY MESSAGE
This review discusses the characteristics and needs common to many poor responders and provides guidance on how these patients can be managed using a holistic approach that includes the synchronization of early follicle development and the use of tailored IVF protocols and techniques to manage patient distress and anxiety.

A B S T R A C T

'Poor responders' is a term used to describe a subpopulation of IVF patients who do not respond well to ovarian stimulation with gonadotrophins. While there is no standard definition of a poor responder, these patients tend to be of advanced maternal age (≥40 years), have a history of poor ovarian response with conventional stimulation protocols, and/or have low ovarian reserve. Despite the heterogeneity of this patient group, there are characteristics and needs common to many poor responders that can be addressed through a holistic approach. Stimulation during the earlier stages of follicle maturation may help synchronize follicle development for improved response to later gonadotrophin stimulation, and supplementation with dehydroepiandrosterone or human growth hormone may promote early follicle development in poor responders. IVF protocols should be specifically tailored to poor responders to complement the patient's natural cycle. Because poor responders tend to have high levels of stress and anxiety, patients should receive psychological counselling and support, both prior to and during IVF cycles, to ensure optimal outcomes and improve patients' experience. It is important to set realistic expectations with poor responders and their partners to help patients make informed decisions and better manage their distress and anxiety.

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Introduction

In the field of IVF, the term 'poor responder' refers to a subpopulation of patients, typically with diminished ovarian reserve, that experience heightened problems in conceiving with IVF. The identification of poor responders is important to help determine the patient's appropriateness for IVF, guide selection of protocols to maximize ovarian response, and identify patients who may particularly need counselling to set expectations and minimize distress during IVF; however, there is no standard definition of a 'poor responder' (Ferraretti et al., 2011). The Bologna criteria suggest that classification as a poor responder requires two of the following features: (i) advanced maternal age (≥40 years) or other risk factors for poor ovarian response, (ii) a previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol), and (iii) an abnormal ovarian response test (antral follicle count <5–7 or anti-Müllerian hormone <0.5–1.1 ng/ml [< 3.6–7.9 nmol/l]) (Ferraretti et al., 2011). However, published studies suggest a variety of alternative or additional criteria to define poor responders. It is therefore important to consider each patient's IVF history and clinical characteristics.

Despite the heterogeneity of this patient group, there are some characteristics and needs that are common to many poor responders, such as synchronization of early follicular development, IVF protocols tailored to poor responders, guidelines for the use of alternative medicine and nutritional supplements, and suggestions for the successful management of patient distress and anxiety. Addressing these needs through a holistic approach may help to improve the overall management of poor responders.

Synchronizing early follicle development

Ovarian follicles mature over a period of approximately 2–4 months (McGee and Hsueh, 2000). Ovarian stimulation in IVF cycles has traditionally focused on the stimulation of antral follicles, which develop during the last 2 weeks of this maturation process, to increase the number of mature follicles for oocyte retrieval. However, successful ovarian stimulation with gonadotrophins is limited by the requirement of the presence of multiple antral follicles (Amer, 2007). The stimulation and synchronization of earlier follicles prior to traditional ovarian stimulation may thus further improve IVF outcomes, particularly for poor responders (McGee and Hsueh, 2000).

Recent animal studies have demonstrated that androgens are engaged in follicle stimulation at pre-antral and antral stages, primarily affecting granulosa cells (**Figure 1**) (Gleicher and Barad, 2011; Gleicher et al., 2011). There is also evidence to suggest that androgen signalling interacts synergistically with FSH activity in granulosa cells during the early stages of follicle maturation (Gleicher and Barad, 2011; Gleicher et al., 2011). It is postulated that, in some patients, diminished ovarian reserve may essentially be an androgen deficiency state and, in these women, androgen supplementation via testosterone or dehydroepiandrosterone (DHEA) may help stimulate early follicle development and improve functional ovarian reserve (Gleicher and Barad, 2011; Gleicher et al., 2011, 2013). A summary of the reported reproductive outcomes of DHEA supplementation are provided in **Table 1**. Notably, DHEA supplementation has been associated with lower miscarriage rates (Gleicher et al., 2009) and higher pregnancy and live birth rates (Wiser et al., 2010) in some studies. However, it is important to note that the use of DHEA supplementation is still considered experimental and is contested by some clinicians (Triantafyllidou et al., 2017). Further prospective, randomized studies are needed to clarify the potential benefits of DHEA in poor responders. Patients offered DHEA supplements should be informed of the potential negative side effects associated with DHEA, such as acne, oily skin, deepening of the voice, hirsutism and hair loss (Barad et al., 2007; Gleicher and Barad, 2011; Sciard et al., 2016; Xu et al., 2014).

DHEA administration is increasingly becoming the preferred method of androgen supplementation over testosterone because it is taken up and metabolized by organs as needed, whereas

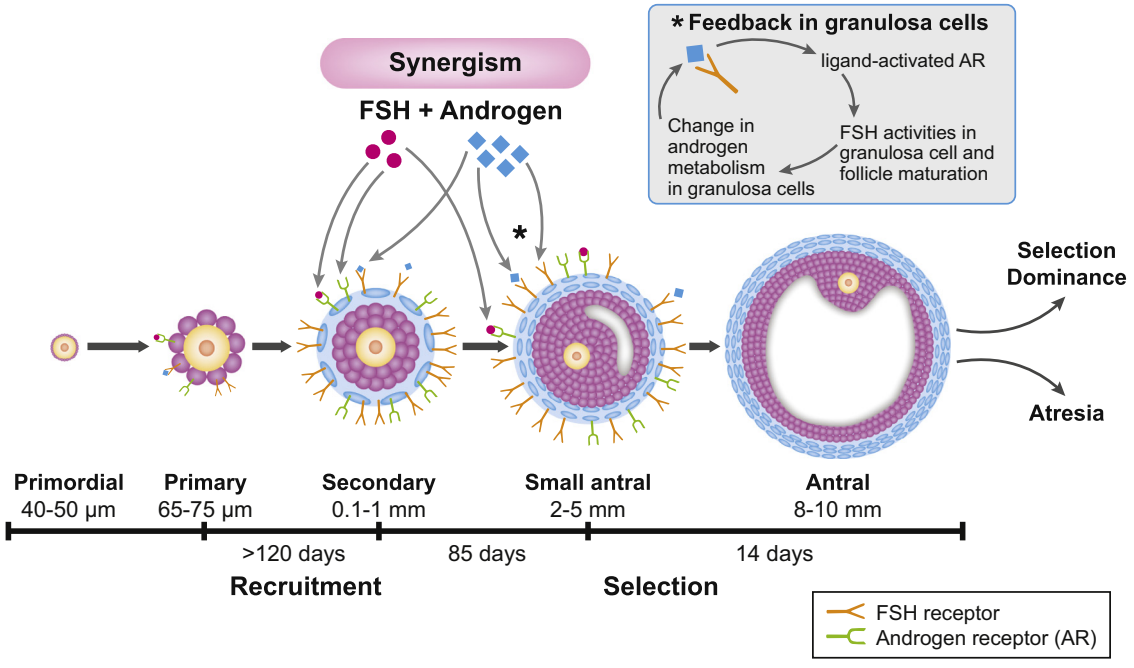

Figure 1 – Potential synergism of androgens and FSH during early folliculogenesis.

Table 1 – Reported outcomes of DHEA and HGH supplementation for fertility.

DHEA	HGH
Positive outcomes	
Improved hormone levels (Barad and Gleicher, 2005, 2006; Casson et al., 2000; Gleicher et al., 2010b)	Greater number of overall and MII oocytes (Bassiouny et al., 2016; Eftekhar et al., 2013; Lattes et al., 2015)
Greater egg and embryo numbers (Barad and Gleicher, 2005, 2006)	Higher fertilization rates (Bassiouny et al., 2016; Bergh et al., 1994)
Higher fertilization rates (Barad and Gleicher, 2006)	Increased number of embryos (Eftekhar et al., 2013; Lattes et al., 2015)
Improved embryo quality (Barad and Gleicher, 2006; Gleicher et al., 2010a)	Increased number of top-quality embryos (Lattes et al., 2015)
Lower rate of cycle cancellations (Barad and Gleicher, 2006; Barad et al., 2007)	May improve embryo quality (Bosch et al., 2016)
Lower rate of miscarriage (Gleicher et al., 2009)	Increased number of cryopreserved embryos (Lattes et al., 2015)
Higher clinical and cumulative pregnancy rates (Barad et al., 2007; Wiser et al., 2010)	
Neutral outcomes	
No improvement in ovarian response to stimulation (Sciard et al., 2016; Vlahos et al., 2015; Yeung et al., 2014)	No difference in the number of overall and MII oocytes (Dunne et al., 2015; Norman et al., 2016; Tesarik et al., 2005)
No increase in the number of embryos available (Sciard et al., 2016; Vlahos et al., 2015; Xu et al., 2014)	No improvement in embryo quality (Norman et al., 2016; Tesarik et al., 2005)
No increase in fertilization rates (Xu et al., 2014)	No difference in clinical pregnancy rates (Bassiouny et al., 2016; Dunne et al., 2015; Eftekhar et al., 2013; Kucuk et al., 2008; Norman et al., 2016)
No reduction in miscarriage rates (Sciard et al., 2016; Yeung et al., 2014)	No difference in live birth outcomes (Bassiouny et al., 2016; Norman et al., 2016)
No difference in clinical or ongoing pregnancy rates (Kara et al., 2014; Vlahos et al., 2015; Yeung et al., 2014)	
No difference in live birth outcomes (Vlahos et al., 2015; Yeung et al., 2014)	

DHEA, dehydroepiandrosterone; HGH, human growth hormone; MII, metaphase II.

testosterone floods the body with a steady amount across organs (Shohat-Tal et al., 2015). Micronized DHEA formulations from a trusted manufacturer with good quality controls are recommended; however, a small percentage of patients do not respond to DHEA and instead require testosterone administration (Shohat-Tal et al., 2015). The follicles require about 6–8 weeks after the initiation of androgen supplementation to achieve synchronization and become mature enough to respond to ovarian stimulation with gonadotrophins (Gleicher and Barad, 2011; Gleicher et al., 2011). Based on this, many patients could potentially benefit from androgen supplementation beginning weeks or months prior to starting their IVF cycle.

Human growth hormone (HGH), either directly or indirectly via insulin-like growth factor 1 (IGF-1), also regulates oocyte maturation by increasing the sensitivity of the ovaries to gonadotrophins and promoting early follicle development (Magon et al., 2011; Zhou et al., 2013). The effects of FSH on Cyp19 and AKT in granulosa cells depend on IGF-1 expression and signalling, and FSH and IGF-1 act synergistically to stimulate steroid production (Zhou et al., 2013). Clinical studies have demonstrated positive effects of HGH on oocyte- and embryo-related outcomes, including indications of improved embryo quality; however, other studies have not shown a difference in pregnancy or live birth outcomes with HGH supplementation (**Table 1**). A Cochrane Review demonstrated improved clinical pregnancy (odds ratio [OR] = 3.28 [95% confidence interval (CI), 1.74–6.20]) and live birth rates (OR = 5.39 [95% CI, 1.89–15.35]) in poor IVF responders who received HGH supplementation (Duffy et al., 2010). Minimal side effects, such as peripheral oedema and joint pain, have been reported in women taking HGH supplements (Blackman et al., 2002; Dunne et al., 2015; Lattes et al., 2015).

IVF protocols for poor responders

Follicle development is a complex process that involves the regulated expression and interaction of multiple reproductive hormones at different stages of the development timeline (Filicori et al., 2002; Fleming et al., 1996; Hillier, 1994). As noted previously, poor responders may benefit from the synchronization of basal antral follicles with DHEA supplementation for a few weeks or months prior to initiating their IVF cycle. We recommend that subsequent ovarian stimulation protocols for poor responders should try to mimic and enhance the natural developmental process of single follicle growth, but in a multi-follicle approach. In general, we believe it is important to refrain from overriding the patient's natural cycle with the use of high-dose exogenous gonadotrophins, which can be associated with side effects and safety concerns, often without an improvement in response. However, stimulation dosages may be individualized, with special attention paid to the fact that higher gonadotrophin dosages can increase transferable embryo numbers and, therefore, cumulative pregnancy chances. Any form of suppressive therapy on the ovaries, including luteal phase (long) gonadotrophin-releasing hormone (GnRH) agonists, GnRH antagonists and oral contraceptives, should, if possible, be avoided in poor responders.

Each patient's clinical characteristics (e.g. basal antral follicle number, luteal synchronization), treatment history and past stimulation outcomes should be carefully considered when selecting stimulation protocols for poor responders (Oehninger, 2011). For example, premature luteinization occurs frequently in older patients (e.g. aged ≥43 years) and some other poor responders. In these patients, earlier ovulation trigger (i.e. when the leading follicle is 16 mm) may improve the number and quality of embryos, as well as clinical pregnancy rates (Wu et al., 2015). Often the optimal treatment approach is not clear until the patient visits on Day 2 to 3 of her cycle and all relevant baseline bloodwork/testing has been performed. Examples of protocols recommended for poor responders include a low-dose gonadotrophin protocol, low-dose clomiphene/gonadotrophin protocol and augmented natural cycle protocol.

Although controversial, some authorities advocate low-dose (or 'mild') stimulation in poor responders. The low-dose gonadotrophin protocol involves initiating highly purified human menopausal gonadotrophin (HP-HMG) 150 IU/day and recombinant follicle-stimulating

hormone (rFSH) 150 IU/day on Day 2 for 9 days; inclusion of HP-HMG is important to provide some LH activity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, followed by ovulation trigger with leuprolide or human chorionic gonadotrophin (HCG) 10,000 IU when the lead follicle is 16–17 mm.

The low-dose clomiphene/gonadotrophin protocol involves administration of clomiphene citrate 100 mg/day for 5 days beginning on Day 2 to obtain pituitary output. A low dose of HP-HMG (150 IU/day) is given on Days 2, 4 and 6, followed by daily dosing until the follicle reaches maturity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, which is intentionally a little early to help avoid breakthrough ovulation; if the patient's LH level begins to rise, the GnRH antagonist can be given twice a day. Ovulation is triggered with HCG 10,000 IU or leuprolide when the lead follicle is approximately 18–19 mm. Low-dose clomiphene/gonadotrophin protocols may be a good treatment strategy for patients who have previously responded to clomiphene, but did not have a successful cycle due to other factors. A clinical study in 31 poor responders compared a low-dose clomiphene/gonadotrophin protocol with a full stimulation protocol (FSH 300 IU/day and HMG 150 IU/day SC starting cycle Day 3 + ganirelix acetate 0.25 mg/day SC starting on cycle Day 8 for an average of five doses) (Zarek and Muasher, 2011). Patients who received the full stimulation protocol used significantly more vials of gonadotrophins and had a higher number of mature oocytes retrieved (3.8 versus 2.4 with the minimal protocol), but the clinical pregnancy rates per cycle (36% versus 38%) and per transfer (47% versus 42%) were similar between groups and the low-dose protocol had fewer patient cancellations (Zarek and Muasher, 2011).

Augmented natural cycle protocols are designed to provide continued gentle cycle support for women who have slow follicle development. In our experience, the timeline is not as important as observing the important developmental milestones in natural cycle protocols. Patients are monitored for oestradiol production >20 pg/ml and/or the presence of 3- to 4-mm sized basal antral follicles; in these patients it may take 7–10 days for these characteristics to be observed. Once the follicles are present, ovarian stimulation is initiated with a low-dose combination of HP-HMG and rFSH 75 (e.g. 75 IU/day of each) and continued for approximately 6 days, depending on continued follicle development; a GnRH antagonist is added when the lead follicle reaches ≥12 mm. Ovulation is triggered with HCG 10,000 IU or leuprolide. This protocol may particularly benefit patients who have not had a positive response (no mature follicles) to past stimulation protocols. A 2005 prospective study demonstrated that augmented natural cycle protocols may benefit some patients: the cycle cancellation rate was 17.7%; embryo transfer occurred in 42.5% of cycles with oocyte retrieval, and clinical pregnancy was achieved in 28.3% of cycles with oocyte retrieval (Castelo et al., 2005). The cumulative rate of clinical pregnancy per patient after three cycles was 35.2% (19/54) (Castelo et al., 2005). Because the number of transferable embryos, after female age, is the most important predictor of pregnancy and live birth chances with IVF (Gleicher et al., 2016), the utility of mild stimulation protocols in poor responders has been questioned (Gleicher et al., 2012).

Objectively determined optimal stimulation protocols for poor responders do not exist in the literature. A Cochrane Review published in 2010 identified four comparison groups for modified ovarian stimulation in poor responders, but each was represented by only one trial and no significant differences between protocols were seen for clinical pregnancy and/or live birth rates (Pandian et al., 2010). The authors concluded that 'There is insufficient evidence to support the routine use of any particular intervention. . .in the management of poor responders to controlled ovarian stimulation in IVF' (Pandian et al., 2010).

Debate remains about whether Day 3 or Day 5/6 embryo transfers provide the best IVF outcomes, with the relative benefit possibly due to patients' clinical characteristics. A randomized controlled trial found no overall difference in implantation and pregnancy rates between Day 3 and Day 5 embryo transfers (Coskun et al., 2000). However, the study also showed that patients without good-quality embryos on Day 3 still benefited from proceeding with embryo transfer on Day 3 (pregnancy rate of 33%), but were unlikely to become pregnant with a Day 5 transfer (Coskun et al., 2000). Some embryos do not persist in culture to Day 5/6, so patients with very low embryo counts may also benefit from Day 3 transfer to ensure they have an embryo(s) to transfer. Conversely, in some cases it is predicted that a patient's uterus will be in better condition on Day 5, and for these patients it may be better to plan for a Day 5/6 embryo transfer.

Segmentation of the IVF cycle through embryo cryopreservation and deferred (i.e. cryopreserved) embryo transfer has been proposed as a possible strategy to accumulate greater numbers of embryos over several stimulation cycles in poor responders (Cobo et al., 2012; Rienzi et al., 2017). This segmentation of the IVF cycle is thought to improve clinical outcomes in poor responders by allowing for the selection of only high-quality embryos for transfer and ensuring that the embryos are transferred to a more receptive endometrium (Rienzi et al., 2017). A study of over 700 poor responders reported a cumulative live birth rate per patient of 36.4% in patients who underwent cycle segmentation versus 23.7% in those who underwent fresh transfer (Cobo et al., 2012). Segmented treatment cycles were associated with lower dropout rates compared with fresh cycles and resulted in comparable cumulative success rates to those seen in normal responders (Cobo et al., 2012).

Preimplantation genetic screening (PGS) can screen for chromosomal abnormalities and diagnose the presence of known gene mutations to assist in the selection of good-quality embryos for transfer (American Society for Reproductive Medicine, 2014). However, mosaicism (chromosomal abnormalities in some of the embryo's cells) can affect the reliability of PGS because the analysis reflects the chromosomes and genes of only the biopsied cells (Capalbo et al., 2013; Fragouli et al., 2011; Northrop et al., 2010). In some instances, embryos are seen to 'self-correct' abnormalities as they develop (Northrop et al., 2010). Thus, undesirable PGS results may sometimes lead to the unnecessary discarding of embryos, which is particularly problematic among poor responders. In our experience, the additional embryo handling required for embryo biopsy for PGS may also be a concern for poor responders with few available embryos.

As in normal responders, progesterone supplementation during the luteal phase improves cycle outcomes in poor responders (Aboulghar, 2009; Tolunay, 2017). There is some evidence to suggest that the addition of oestradiol to progesterone for luteal phase support may improve implantation rates in women undergoing IVF (Pritts and Atwood, 2002); however, this approach has not been shown to improve pregnancy outcomes in poor responders (Aghahosseini et al., 2011).

Use of alternative medicine and nutritional supplements

Many IVF patients turn to alternative medicine and/or nutritional supplements as methods to manage their anxiety and distress, improve

their overall health and optimize their IVF outcome. Anecdotal evidence suggests that alternative medicine practices can be beneficial for some IVF patients, but some practices can also be problematic. A recent randomized controlled study found that the use of transcutaneous electrical acupoint stimulation improved the clinical pregnancy rate among patients with diminished ovarian reserve (Zheng et al., 2015), but good-quality studies on acupuncture and other forms of alternative medicine are generally lacking. Additionally, in some instances, medical advice from alternative medicine practitioners interferes with or directly contradicts the care and instructions given to patients by their IVF healthcare team. The use of some nutritional supplements has been associated with a variety of beneficial effects (improve their chances of conception, more 'natural' or holistic approach, helps patients feel more involved and in control (Kienle et al., 2011; Rayner et al., 2009, 2011)). However, supplements are not regulated as drugs and are thus not required to prove their efficacy, and the quality of supplements can vary greatly between manufacturers (US Food and Drug Administration, 2008). Some supplements have been shown to interact with drugs and other supplements, potentially causing harmful effects (Tsai et al., 2012), while for others the full scope of potential health impacts is not yet known. Some supplements and alternative medicine practices can impact the interpretation of test results (e.g. DHEA impacts the measurement of progesterone (Franasiak et al., 2016)) that are used to inform treatment decisions, leading to misinterpretation of medical tests and outcomes in the IVF centre and, thus, suboptimal treatment. Finally, the costs associated with alternative practices and supplement use may significantly increase costs, which could limit a patient's ability to afford future IVF cycles.

In our experience, many patients do not fully disclose all of the medications and supplements they are taking, including DHEA, to their nurses and doctor. Because of the impact that alternative medicine practices and supplement use can have on treatment decisions and outcomes, we recommend that nurses strongly encourage patients to disclose all alternative medicine practices, additional medications and supplement use. Nurses can also help to guide patients toward treatments that best fit their life goals and are generally considered safe and complementary to IVF therapy. If using supplements, we suggest that patients be counselled to make their purchases from reputable locations and websites, such as those accredited by the Verified Internet Pharmacy Practice Site (VIPPS), a program that establishes criteria and standards for quality online pharmacies. Patients should also be encouraged to select supplements that have been evaluated for safety and quality by a certifying organization such as ConsumerLab.com, NSF International or The United States Pharmacopeial Convention (USP) (Akabas et al., 2016).

Managing patient distress and anxiety

Patients seeking treatment for infertility tend to experience higher rates of psychological stress compared with fertile patients (De Berardis et al., 2014; Pasch et al., 2016; Volgsten et al., 2008). A recent study of 352 women undergoing infertility treatment found that 57% of patients scored in the clinical range for depression and 76% scored in the clinical range for anxiety (Pasch et al., 2016). A separate study of 106 women receiving treatment at an infertility/IVF clinic reported a 9.4% incidence of suicidal ideation or suicidal attempts; women who experienced these emotions were more likely to have fewer or no children and to exhibit higher levels of depressive symptoms (Shani et al., 2016). A recent survey of 324 insured patients undergoing IVF found that the emotional burden of infertility treatment is the main reason for treatment discontinuation, with 40% of patients indicating that further treatment was too stressful (Domar et al., 2016).

While there have been studies on the mental health effects of infertility in the overall population of infertile patients, there is little to no published research on the psychological impact of poor IVF response or the efficacy of interventions aimed at increasing coping skills in patients diagnosed as poor responders. Most infertility healthcare professionals agree that poor responders often have a high level of anxiety, distress and depression. A diagnosis of diminished ovarian reserve is associated with other health concerns as well, including low bone mass, sexual dissatisfaction and disturbed sleep (Pal et al., 2008), which may further increase the patient's anxiety, distress and depression.

To mitigate distress, we recommend that poor responders be counselled prior to and throughout their IVF cycle. One study at the Instituto Bernabeu in Spain, which has a special unit for poor responders with personalized counselling provided both prior to starting IVF treatment and as a follow-up during ovarian stimulation, found that counselling was effective in helping poor responders handle the stress of an IVF cycle (Gosalbez et al., 2014). In fact, the researchers determined that the distress level of the counselled poor responders was no higher than that of normal responders (Gosalbez et al., 2014). Ideally, we suggest that all IVF patients attend an initial counselling visit prior to starting their first IVF cycle, to help prepare patients and their partners and set reasonable expectations. These visits can also help overcome obstacles associated with later counselling. Larger IVF centres, which are more likely to see poor responders with multiple failed cycles, may find it cost effective to keep a mental health professional on staff. Furthermore, during each patient's IVF cycle, nurses can use each blood test and ultrasound as a mini-counselling session to help alleviate the extreme anxiety and fear of cancellation that often accompanies these procedures in poor responders. In addition to improving patient experience, research suggests that decreasing patient distress also helps to increase pregnancy rates (Frederiksen et al., 2015).

Although nurses are an important source of support, they cannot be expected to adequately address all of the needs of their patients. Therefore, the clinic should consider providing patients with a variety of suggested resources for external support (outside of the IVF clinic) and interventions that can help mitigate their anxiety and distress (e.g. lifestyle modifications, group or individual counselling, psychotherapy, pharmacotherapy, stress reduction kits). Mind–body therapy, which involves aspects of cognitive behavioural therapy, social support and skills training, can help patients feel more in control by giving them something that they can do proactively or reactively (Domar et al., 2011). The IVF centre can develop stress reduction kits to provide to patients as a convenient resource to use at home. In a recent study of 166 women about to undergo their first IVF cycle, randomization to receive a stress reduction kit was associated with significant improvements in psychological status and a reduced dropout rate (5% versus 15% in the control group) (Domar et al., 2015).

In some instances, we find that the high levels of anxiety, distress and frustration experienced by poor responders may lead to episodes of agitation or confrontational behaviour. Because nurses and technicians spend a substantial amount of time with patients, they are frequently the targets of such behaviour. We recommend that each

Table 2 – Key recommendations for poor ovarian responders.

Set expectations: set expectations with patients and their partners prior to beginning IVF
Luteal phase synchronization: initiate DHEA supplementation in the weeks to months before starting an IVF cycle
Managing distress/anxiety: provide patients with external resources (counselling, support groups, mind–body therapy, yoga classes, take-home stress reduction kits) to help patients cope and feel more in control; warn about the potential dangers of alternative medicine practices and supplement use during IVF
Stimulation protocol: consider the patient's clinical characteristics and cycle history and select a protocol that complements her natural cycle; avoid high-dose gonadotrophins and suppressive treatments (e.g. GnRH agonists and oral contraceptive pills)
Ongoing counselling: continue counselling (formal or informal) throughout the IVF cycle
Embryo handling: limit the use of PGS in patients with very few available embryos; consider Day 3 embryo transfer to limit the culture time

IVF centre has standard procedures in place to ensure confrontations do not escalate, to protect the centre's staff, and to limit undue stress for other patients. For example, the staff can temporarily disengage from a patient in response to aggressive behaviour, encouraging the patient to call back once she is calmer. Nurses can also help patients develop a 'plan B' for their future, such as a different medication protocol, some time off from IVF, or consideration of donor egg or adoption options.

Conclusions

Poor responders are a heterogeneous population of IVF patients with unique needs. Holistic management of poor responders can help to improve the patient experience and may improve egg yields and clinical pregnancy rates. Key recommendations for poor ovarian responders are provided in **Table 2**. Stimulation during the earlier stages of follicle maturation may help to synchronize the follicles for improved response to later gonadotrophin ovarian stimulation. We recommend that IVF protocols for poor responders should complement the patient's natural cycles, rather than override them with high doses of exogenous gonadotrophins, and avoid suppressive hormonal treatments. Because of the heterogeneous nature of the poor responder population, protocol selection should consider the patient's clinical characteristics, treatment history and goals. Counselling and support, both prior to and during IVF cycles, can help to ensure optimal outcomes for poor responders and manage associated distress and anxiety. Research on the optimal management of poor responders is extremely limited, highlighting the need for robust studies to support evidence-based clinical recommendations.

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