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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

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Authors: Jakub Wyroba, Magdalena Imiolek, Andzelika Krol-Mika, Kamil Kiecka, Teresa Wojtowicz, Katarzyna Kostarczyk, Joanna Kochan

DOI: 10.5603/gpl.112176

Article type: Review paper

Submitted: 2026-04-15

Accepted: 2026-05-13

Published online: 2026-07-30

REVIEW PAPER / OBSTETRICS

Diminished ovarian reserve (DOR) — a step-by-step overview of the IVF procedure based on current knowledge

Jakub Wyroba[1, 2] https://orcid.org/0000-0001-6221-8089, **Magdalena Imiolek, Andzelika Krol-Mika**[3], **Kamil Kiecka**[3], **Teresa Wojtowicz**[3] https://orcid.org/0009-0009-8606-9327, **Katarzyna Kostarczyk**[4] https://orcid.org/0009-0009-8606-9327, **Joanna Kochan**[1, 4] https://orcid.org/0000-0003-4296-6471

[1]*Malopolski Institute of Fertility Diagnostics and Treatment — KrakOvi, Cracow, Poland*

[2]*Fertility Disorders Clinic, Andrzej Frycz Modrzewski Cracow University, Cracow, Poland*

[3]*Angelius Medical Center, Katowice, Poland*

[4]*Department of Animal Reproduction, Anatomy and Genomics, University of Agriculture in Cracow, Poland*

Corresponding author:

Joanna Kochan

Malopolski Institute of Fertility Diagnostics and Treatment – KrakOvi, 14/6 Leona Wyczołkowskiego St., 30–118 Cracow, Poland and Department of Animal Reproduction, Anatomy and Genomics, Faculty of Animal Science, University of Agriculture in Cracow, 24/28 Adam Mickiewicz Avenue, 30–059 Cracow, Poland

e-mail: kochanjoanna@wp.pl

ABSTRACT

Review of current knowledge of the *in vitro* fertilization (IVF) procedure in patients with diminished ovarian reserve (DOR). Patients with DOR who undergo IVF require special care and an individualized approach due to the poor prognosis. The IVF procedure is multi-stage, and each step should be carefully planned, with treatments tailored to DOR patients.

The review article was prepared based on an analysis of the latest research findings and ESHRE recommendations for all stages of *in vitro* fertilization in patients with DOR. The article discusses the results of 32 articles published over the last 5 years, including 23 articles published in 2024–2026. Clinical stages such as prediction of ovarian reserve, hormonal

stimulation of the ovaries, and embryo transfer, and laboratory stages such as the quality and quantity of obtained oocytes and embryos, results of preimplantation genetic testing (PGT-A), and finally implantation potential and live birth rate in DOR patients were discussed.

Keywords: diminished ovarian reserve (DOR); *in vitro* fertilisation (IVF); low ovarian response

INTRODUCTION

Diminished ovarian reserve (DOR) is one of the most common challenges in contemporary clinical reproductive medicine. According to the Society for Assisted Reproductive Technology National Summary, DOR is the second most common indication for ART (Assisted Reproductive Techniques) and accounts for one-third of ART cycles [1]. Ovarian reserve refers to the number of primordial follicles stored in the ovary that can be recruited to the preantral and antral stages and are competent for ovulation. Ovarian reserve can be influenced by many factors, including age, environment, diseases, and medications. The main factor in DOR is advanced maternal age. It has been shown that ovarian reserve decreases with age, but some patients have pathological DOR that is inappropriate for age. The estimated prevalence of DOR is 6.3% in patients ≤ 35 years of age [2]. In developed countries, there is a trend toward postponing pregnancy, leading to decreased ovarian reserve and posing a major challenge for assisted reproductive centers. Diminished ovarian reserve is directly related to poor ovarian stimulation response (POR) to hormonal stimulation, a low number of oocytes and embryos obtained, a high cycle cancellation rate, and a decline in pregnancy rate during the *in vitro* fertilization (IVF) procedure [3, 4]. Therefore, patients with DOR and consequently with POR are among the most difficult groups of IVF patients to manage, and standardization of reproductive medical treatment remains a priority. Optimal standards of treatment management for IVF patients with diminished ovarian reserve have been sought for many years. The aim of this study is to present the current state of knowledge regarding the subsequent stages of the *in vitro* fertilization procedure in patients with DOR.

Anti-Müllerian hormone (AMH) — the main ovarian reserve marker

Anti-Müllerian hormone is considered the most precise marker of ovarian reserve and is used to predict the remaining oocyte pool [5]. Anti-Müllerian hormone belongs to the transforming growth factor-β family and is produced by granulosa cells of the ovarian pre-

antral follicles. Anti-Müllerian hormone regulates the biochemical environment of growing follicles. It influences the ovary by inhibiting the cyclic recruitment of primordial follicles and the growth of small follicles. This prevents multiple follicles from maturing simultaneously, protecting the ovarian reserve. Primordial follicles that are not exposed to AMH continue to recruit and grow, developing into dominant follicles, ovulating, and contributing to the formation of the corpus luteum [6, 5]. Interpretation of AMH levels directly impacts infertility treatment management. AMH provides key information for specialists in choosing the appropriate hormonal stimulation strategy, which can significantly influence treatment effectiveness, as AMH levels can indicate a patient's response to ovarian stimulation and help protect patients from hyperstimulation [3]. According to published studies, an AMH cut-off between 0.7 and 1.2 ng/mL can be considered for predicting poor ovarian response [7]. Significantly more oocytes are obtained during ovum pick-up (OPU) and more embryos develop to the blastocyst stage suitable for embryo transfer (ET) from patients with AMH > 1.2 ng/mL than from those with reduced AMH, confirming the efficacy of AMH as an ovarian reserve marker. It is well established that ovarian reserve decreases with age, but there is also a group of younger patients with unexpected DOR/POR inappropriate for age [8, 9]. Anti-Müllerian hormone production ceases immediately after menopause [10]. Among patients with low AMH levels (< 1.2 ng/mL), regardless of age, there is a group of unexpected, good responders to hormonal stimulation. More oocytes are obtained from these patients, increasing the chances of IVF/ICSI success. However, despite an unexpectedly good response to stimulation and a satisfactory number of oocytes, more oocytes remain immature [8]. Therefore, it can be concluded that DOR affects both the number and quality of oocytes, as well as their ability to mature. On the other hand, there are also patients with higher AMH and an unexpectedly poor ovarian response to stimulation. A recent study has shown that a decreased ovarian reserve doesn't always influence the conception rate and clearly shows that the old paradigm regarding AMH, meaning that AMH was believed to be a good predictor of the ovarian response and oocyte number, should not be used as an absolute discriminator in IVF clinics to classify a patient as a poor or good responder [11, 12]. Therefore, despite AMH's significant role as a marker of ovarian reserve, evaluating the expected ovarian response based solely on AMH is insufficient. Apart from AMH, valuable tools for assessment of ovarian reserve are AFC (antral follicle count) and FSH. Antral follicle count refers to the number of small follicles (2–10 mm in diameter) visible on an ultrasound examination of the ovaries. This measure estimates the size of the remaining pool of potentially functional follicles, reflecting the ovarian reserve. The third indirect marker of ovarian reserve is follicle-

stimulating hormone (FSH), and its higher concentration on day 3 of the menstrual cycle indicates a reduced reserve. When the ovarian reserve is low, the ovaries produce less estrogen and inhibin B, which leads to the pituitary gland releasing more FSH to stimulate the ovaries. Although FSH is a useful indicator, its levels can fluctuate and should be used alongside AMH and AFC results [13].

By analyzing all markers of ovarian reserve and the patient's age, physicians should develop a holistic, patient-specific therapeutic strategy and prepare her mentally for the likely outcome of the procedure. The starting point is to determine whether a patient will likely have a normal, poor, or excessive response and to select the ideal treatment protocol tailored to these predictions.

Ovarian stimulation

One of the main factors determining IVF success is ovarian response to stimulation and the attainment of a sufficient number of oocytes, which enables the development of euploid blastocysts and subsequent pregnancy and live birth. Before selecting the optimal stimulation strategy tailored as individually as possible to a patient with DOR, the clinical characteristics and medical history of each patient (age, body mass index [BMI], reproductive history, previous stimulation results, comorbidities, *etc.*) should be carefully analyzed. The choice of stimulation strategy should be based on biomarker analysis, including AMH, AFC, basal FSH, LH, estradiol, progesterone, and inhibin B. According to the latest literature reports and European Society of Human Reproduction and Embryology (ESHRE) recommendations (2025), AMH or AFC have the highest predictive value for ovarian response categories, even as single markers [14, 15]. However, as mentioned in the above chapter, despite the high predictive value of AMH, there are ovarian responses to stimulation that are inadequate (unexpected poor, unexpected high) for the AMH level [8]. Prediction of ovarian response based on other markers (FSH, LH, estradiol, progesterone, inhibin B) is sufficiently reliable and should be treated as adjunctive markers to AMH and AFC [16, 17].

For many years, protocols, treatments, and drugs to maximize the number of oocytes obtained from patients with DOR have been sought. For patients with DOR, various protocols (modified natural cycle, GnRH agonist protocols, GnRH antagonist protocols, progestin protocols), different doses of gonadotropins, adjunctive therapies (growth hormone (GH), testosterone, dehydroepiandrosterone (DHEA), aspirin, sildenafil, antioxidants (myo-inositol), glucocorticoids, CoenzymeQ10), and even nonconventional treatments like acupuncture have been analyzed and compared [18–21].

Based on the latest literature and ESHRE (2025) recommendations, the GnRH antagonist protocol is preferred over the GnRH agonist protocols because of comparable efficacy and greater safety across all patient populations, including those with DOR [21].

The use of GnRH antagonist protocols has improved the safety of stimulation and overcome the significant undesirable effects of the GnRH agonist protocols. There are reports that antagonist protocols may be associated with impaired coagulation at the implantation site and thus contribute to lower pregnancy rates in some patient groups [22]. For many years, there was no clear answer regarding the effectiveness of both protocols. However, over the last decade, large meta-analyses have shown comparable live birth rates for both protocols, with an indication of higher safety with the GnRH antagonist protocol [23, 21].

However, if a GnRH agonist protocol is chosen, the long GnRH agonist protocol is recommended over the short or ultrashort GnRH agonist protocol [20]. The long GnRH agonist protocol has proven highly effective at preventing LH surge and has been associated with fewer cycle cancellations, a greater number of oocytes retrieved, and higher pregnancy rates. Progestogen-based protocols have also been tested in patients with DOR, but they did not improve stimulation outcomes compared with the GnRH antagonist protocol [24, 25].

Over the years, as stimulation protocols have been refined, the question of increasing gonadotropin doses for DOR patients has arisen. Many reports indicate that conventional gonadotropin dosing (150–225 IU per day) is sufficient for DOR patients, and there is no evidence that higher doses (> 300 IU) improve live birth rates [26].

Also, adjunctive therapies such as testosterone, DHEA, aspirin, sildenafil, and myo-inositol, used before or during stimulation, did not yield satisfactory results and are not recommended for low responders [18, 19].

In recent years, Platelet-Rich Plasma (PRP), an autologous regenerative agent, has offered a chance to improve stimulation outcomes in patients with DOR. Most recent clinical studies have shown that intraovarian PRP injection can facilitate ovarian tissue repair, enhance follicle activation, and improve both the number and quality of oocytes, thereby increasing reproductive potential [27–29]. Studies have shown a clear two-phase response to PRP injections. Biochemical improvement in ovarian reserve markers became detectable 4 weeks after the intervention and reached peak effectiveness when assessed after 3 months. The treatment benefit on elevated AMH levels gradually waned starting at 4–5 months, returning to baseline levels by 6 months. Therefore, PRP seems to be a real chance to increase the number of oocytes from DOR patients with an expected low ovarian response.

In summary, despite many years of efforts to improve stimulation methods for DOR/low-responder patients, there remains no gold standard or ideal stimulation protocol. The most important factors are the gynecologist's experience, a comprehensive analysis of the patient's clinical condition and treatment history, and the selection of individualized therapy based on this analysis. Artificial intelligence (AI) can be helpful by analyzing large datasets from previous cycles, clinical parameters, and biomarkers. AI models, primarily machine learning and deep learning, enable step-by-step personalization of IVF procedures, predict outcomes at each stage, and ultimately improve overall IVF success rates [30].

Quantity and quality of oocytes and embryos

It is generally assumed that the optimal number of oocytes after ovarian stimulation is 10-15 [31]. The main problem in patients with DOR is a poor ovarian response to stimulation, resulting in a low number of oocytes. According to many reports, patients with DOR yield an average of 2–6 oocytes per cycle, compared with 11–17 oocytes from patients with normal ovarian reserve (NOR) [32, 33]. However, some patients with DOR respond unexpectedly well to hormonal stimulation, and more than 8 oocytes can be obtained [8]. Most authors do not find any differences in the maturation rate of oocytes obtained from patients with DOR and those with normal reserve. However, there are contradictory reports regarding the relationship between ovarian reserve (based on AMH level) and oocyte quality. Some reports show a correlation between oocyte quality and AMH levels [34, 35], while others, on the contrary, show no relationship [36, 37]. This is probably due to an indirect relationship between age, declining reserve, and oocyte aging. Age significantly impacts quality, with older DOR patients experiencing poorer outcomes due to age-related declines in oocyte quality. In young patients with DOR, this relationship will not be noted because their oocytes are also young.

The consequence of fertilizing a small number of oocytes is a small number of embryos. In addition to the small number of embryos, many authors report reduced developmental potential and morphological quality. According to the literature, the blastocyst rate decreases by approximately 5% in DOR patients [38]. However, because only a small number of oocytes are fertilized, an average of 1–2 blastocysts are obtained per cycle from DOR patients, compared with approximately 3–5 from women with normal reserve [8]. But very often we do not even know the quantity and quality of the blastocysts because cleavage-stage embryos are transferred on day 3. Therefore, access to full data on the developmental

potential and morphology of blastocysts from DOR patients is limited. Embryo quality, as well as oocyte quality, is directly related to the patient's age and indirectly to the decreasing reserve due to ovarian aging.

Reproductive aging leads to increased aneuploidy, oxidative stress, and cellular dysfunction, including mitochondrial dysfunction. Despite the association of embryo quality with age, also reduction of embryo quality on day 3 in young DOR patients compared with embryos from young patients with normal ovarian reserve has been observed [39]. Only approximately 25% of cleavage-stage embryos on day 3 from DOR were top-quality (grade A), compared with 41% from NOR [39]. Embryo quality and developmental potential are determined by both female and male factors. In couples where a woman has DOR and a man has severe oligozoospermia, embryo development parameters are dramatically reduced compared with couples where DOR is the only problem. The already small number of blastocysts from DOR women is further reduced by half if the partner has severe oligozoospermia [40].

A fundamental problem for DOR patients is cycle cancellation due to a lack of oocytes or embryos suitable for transfer. Over 30% of cycle cancellations occur in DOR patients under 35 years of age, and over 40% in those over 35 years of age. In comparison, in non-DOR patients, cycle cancellation occurs in only 9% of cases [39, 41–43]. This leads to higher costs associated with initiating subsequent IVF cycles and psychological distress for patients who lose hope of conceiving a child and motivation to make further attempts. Therefore, patients should be informed by their physician about the consequences of DOR and the reduced prognosis, so they are not surprised by a small number or lack of oocytes.

Embryo transfer strategy

Important clinical stages of IVF, apart from ovarian stimulation and oocyte retrieval, is the transfer of the embryo to the uterus (ET-embryo transfer). This stage of the IVF procedure and waiting for the ET result is also one of the most stressful moments for the patients [44]. For patients with DOR, deciding whether to transfer on day 3 or day 5 is especially important, since we obtain several oocytes and just one or two embryos. Very often, DOR patients have no opportunity for a second transfer using vitrificated embryos (FET) which creates an additional mental burden. Therefore, specific communication between the physician and the patients is particularly important. Patients should be prepared for the possibility of ET on either day 3 or day 5 and not be surprised by a seemingly spontaneous decision by the physician and embryologist [39].

The success of embryo transfer largely depends on selecting the appropriate embryo, a challenge in patients with DOR. These patients are often offered cleavage-stage embryo transfer on day 3 or even day 2. *In vitro* embryo culture conditions do not perfectly reflect those in the uterus; therefore, shortening the *in vitro* culture time before ET can positively impact embryo development. This strategy is used when very few embryos are obtained and the likelihood of obtaining a blastocyst is low. ET on day 3 reduces the risk of cycle cancellation due to a lack of transferable embryos, thereby positively impacting patients' psychological well-being. However, shortening the *in vitro* culture time and ET on day 3 make accurate embryo evaluation and selection impossible. On day 3, much less information about embryo quality is available, as only the number and symmetry of blastomeres and the degree of cytoplasmic fragmentation can be assessed [39, 45]. Therefore, even poor-quality embryos are transferred, reducing the effectiveness of ET. Another strategy proposed for DOR patients is ET on day 5. On day 5, more morphometric parameters of the embryos can be assessed, such as blastocyst expansion and the quality of the inner cell mass and trophoectoderm cells. Furthermore, embryo biopsy is possible for PGT-A (preimplantation genetic testing for aneuploidy), allowing selection of only euploid embryos for transfer. Although the embryo transfer strategy on day 5 allows for better embryo selection before ET, it is typically used for larger numbers of oocytes and embryos [46]. Extending embryo culture to day 5 in the case of a small number of oocytes may result in no blastocysts being obtained, necessitating cancellation of the embryo transfer. If the chances of obtaining additional blastocysts are low, ET on day 3 seems optimal [47, 39]. Some also propose a "freeze-all" strategy [41, 48]. The FET (frozen embryo transfer) strategy assumes the assessment of embryo ploidy through PGT-A and is proposed for older patients (> 35 years), but in patients with DOR, it is often not possible to obtain the appropriate number and developmental stage of embryos, so this method carries the risk of having to cancel the cycle. An interesting proposition is a sequential (two-step) day 3/day 5 frozen-thawed embryo transfer in POR patients, which has been shown to be associated with a higher live birth rate compared with the traditional double cleavage-stage ET (44.2% vs 34.3%), but this strategy requires even more careful evaluation [49]. Although there are a number of embryo transfer strategies for POR patients, ET on cycle day 3 remains the most popular [39, 50, 51].

Preimplantation genetic testing (PGT-A)

For over a decade, preimplantation genetic testing for aneuploidy (PGT-A) has become an irreplaceable tool for a tool for selecting healthy, euploid embryos with the correct number of chromosomes [52]. This method is particularly important for patients of advanced maternal age, in whom the risk of chromosomal defects of embryos increases with age [53]. The biggest problem for patients with DOR/POR is the requirement to have at least one good-quality blastocyst for PGT-A. If we maintain single embryos in culture until day 5, we risk cycle cancellation due to the lack of a blastocyst, which causes the couple great mental burden and giving up further IVF cycles. Therefore, there is a dilemma about whether to offer DOR patients PGT-A and risk a cycle cancellation due to lack of blastocyst, or to transfer an untested embryo on day 3.

According to the latest research, approximately 30% of patients < 35Y and over 70% of patients ≥ 35Y plan to undergo PGT-A testing. Patients with DOR were as likely as NOR patients to undergo PGT-A testing, even though their cycles had a high probability of cancellation due to a lack of oocytes or embryos [54].

There is no clear consensus on the relationship between ovarian reserve and the euploidy rate of embryos from DOR patients. Studies from 2016 and 2021 show that diminished ovarian reserve is associated with reduced euploid rates, independent of age [48, 55]. However, the latest reports from 2025 suggest no relationship between ovarian reserve and euploidy rate [56, 57].

Implantation potential and live birth rate

It is well recognized that embryo morphology is a significant predictor of implantation rate [58]. As described above, in POR patients, there is often no opportunity to select the best-quality embryo because only one embryo is available, so even poor-quality embryos are transferred to the uterus. A meta-analysis found that the cumulative live birth rate (LBR) per IVF/ICSI cycle is on average 50% lower in DOR patients who are poor responders than in normal responders [43, 59]. However, with a single euploid embryo transfer, the implantation rate is similar between DOR and NOR (normal ovarian reserve) patients and often exceeds 50–60% [60, 61]. Patient age and the number of good-quality embryos remain two key predictors of the live birth rate (LBR), regardless of whether the patient has diminished or normal ovarian reserve.

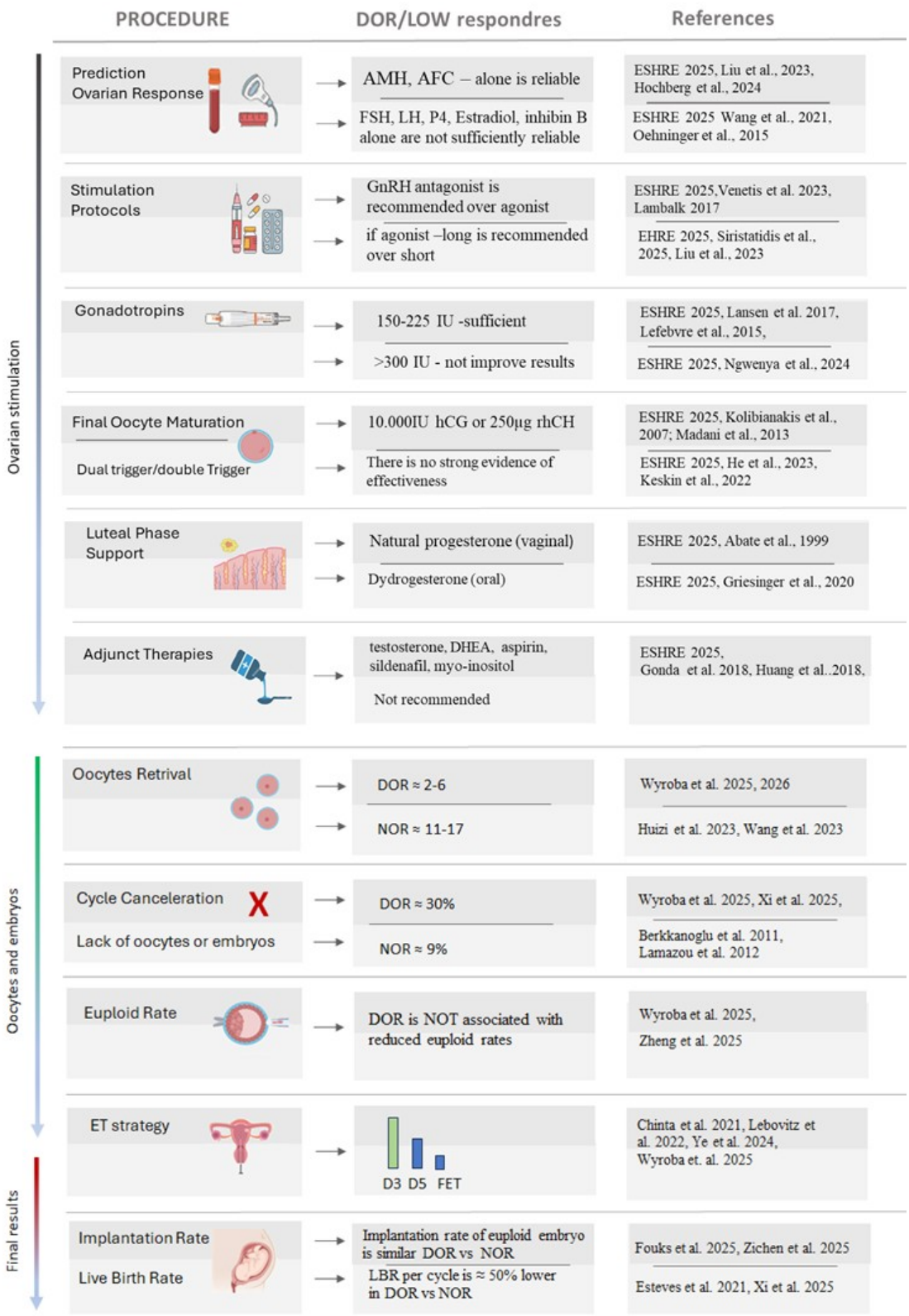

Figure 1. Current state of knowledge on each stage of the *in vitro* fertilization (IVF) procedure in diminished ovarian reserve (DOR) patients; AMH — Anti-Müllerian Hormone; AFC — antral follicle count; DHEA — Dehydroepiandrosterone; FET — frozen embryo transfer; FSH — follicle-stimulating hormone; LH — luteinizing hormone; NOR — normal

ovarian response; ET — embryo transfer; LBR — live birth rate [8, 14, 15, 18, 19, 21, 23, 33, 39, 40, 42, 43, 47, 50, 51, 56, 59–61]

Article information and declarations

Author contributions

JW — the conception, supervison, review of the latest version and final approval; MI, AK-M — writing 2 chapters; KKi, TW — writing 2 chapters and graphics preparation; KKo — references selection and editing of the manuscript; JK — draft of manuscript, supervison, manuscript submission.

Funding

None.

Acknowledgments

None.

Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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