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REVIEW

Risk factors for inadequate response to ovarian stimulation in assisted reproduction cycles: systematic review

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Abstract

Purpose Controlled ovarian stimulation is a fundamental part of a successful assisted reproduction treatment, and recognizing patients at risk of a poor response allows the development of targeted research to propose new treatment strategies for this specific group. The objective of this systematic review was to determine risk factors for poor ovarian response (POR) to controlled stimulation in assisted reproduction cycles described in the literature.

Methods The primary databases MEDLINE, Cochrane, LILACS, and SciELO were consulted, using specific terms with a restriction for articles in English or Portuguese published in the last 10 years.

Results and conclusion Our data suggest that environmental endocrine disruptors, tobacco, genetic mutations, endometriomas, ovarian surgery, chemotherapy, and short menstrual cycles are factors that influence stimulation in assisted reproduction cycles. Further studies are necessary for characterizing patients with prior risk factors.

Keywords Poor response · Poor responder · Human reproduction · Assisted reproduction · In vitro fertilization · Bologna criteria · POR · ART

Introduction

A fundamental part of assisted reproduction therapy (ART) is ovarian stimulation through several protocols that allow follicular recruitment and maturation for subsequent oocyte retrieval [1]. However, there are patients who do not respond adequately to stimulation, constituting the poor ovarian response (POR) group.

The first mention in the literature of POR dates to 1983, when a patient with low estradiol levels and diminished follicular response was observed after FSH/HMG stimulation, resulting in few oocytes retrieved and few embryos transferred [2]. Since then, studies on poor responders have been performed, and the incidence of inadequate response to ovarian stimulation is estimated to be between 9 and 24% [3–5].

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In 2011, a consensus of experts from the European Society of Human Reproduction and Embryology (ESHRE) met in Bologna, Italy, to develop diagnostic criteria for POR based on the evidence available at the time [6]. After the disclosure of the criteria in 2011, some studies were made as an attempt at diagnostic validation. The live birth rate after conventional ovarian stimulation was similarly low in the Bologna group in three unrelated studies [7–9], corroborating the validity of the criteria.

Critics of the Bologna criteria refer to the fact that there are several subpopulations with different characteristics among the patients diagnosed as poor responders, with possible differences in prognosis. In the discussion of the original article, the following were cited as risk factors beyond age: tubal infection and chlamydial infection, genetic mutations, endometrioma, ovarian surgery, chemotherapy, and shortening of the menstrual cycles [6].

In addition, remarks have been made regarding the lack of evaluation of oocyte quality, the cut-off values established for age and ovarian response tests, and the absence of discrimination of all risk factors for POR [10–14]. The present study consists of a systematic review of the literature describing the risk factors associated with poor response to ovarian stimulation in assisted reproduction therapy.

Materials and methods

We conducted a systematic review of studies regarding risk factors for POR to controlled ovarian stimulation. This study was conducted in accordance with the recommendations established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) in 2009 [15].

Our research group searched for papers in the databases Medline, Cochrane, LILACS, and SciELO published in the last 10 years using the following descriptors: poor ovarian response, poor responder, poor response, low ovarian response, diminished ovarian reserve, ovarian response, Bologna criteria, and risk factors. We chose keywords that were in accordance with our selected P.I.C.O. ("patient," "intervention," "control," and "outcome"). Studies involving women with risk factors for poor ovarian response (P) who had been submitted to controlled ovarian stimulation for IVF (I) were included in this review. The control group consisted of patients without risk factors (C). The outcome was the number of oocytes retrieved (O). The bibliographic references of the selected articles were reviewed for further selection. The inclusion criteria were time of publishing in the last 10 years, female subjects, English, or Portuguese language. This review includes clinical trials, cohort studies, case-control studies, and meta-analysis. The exclusion criteria were case reports, non-meta-analysis reviews, editorials, animal studies, and repeated papers.

Overall, 76 articles published in the period between the last 10 years were selected. The study selection process and the evaluations of the titles and abstracts obtained through the above searches were conducted in an unbiased manner in strict accordance with the inclusion and exclusion criteria of this study by two researchers (MEBA and DE) skilled in the preparation of systematic reviews. The original articles were subsequently critically evaluated to decide whether they should be included in the review. The search strategy and the process of manuscript retrieval are described in Table 1 and Fig. 1.

Table 1 Databases and search strategies

Medline: Poor ovarian response OR poor responder OR poor response OR low ovarian response OR diminished ovarian reserve OR ovarian response OR Bologna criteria AND risk factors
Cochrane: Poor ovarian response OR poor responder OR poor response OR low ovarian response OR diminished ovarian reserve OR ovarian response OR Bologna criteria AND risk factors
BVS (LILACS/SciELO): Poor ovarian response OR poor responder OR poor response OR low ovarian response OR diminished ovarian reserve OR ovarian response OR Pobre respondedora OR Má respondedora OR Bologna criteria AND risk factors OR fator de risco

The quality of the literature upon each risk factor was rated according to the rating system that follows below.

Classification of evidence levels	
1A	High-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with very low risk of bias
1B	Well-conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with low risk of bias
1C	Meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with high risk of bias
2A	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with very low risk of confounding, bias or chance, and high probability that the relationship is causal
2B	Well-conducted case-control or cohort studies with low risk of confounding, bias or chance, and moderate probability that the relationship is causal
2C	Case-control or cohort studies with high risk of confounding, bias or chance, and significant risk that the relationship is not causal
3	Non-analytical studies, e.g., case reports, case series
4	Expert opinion

Results

Studies searching for an association of the following factors with POR were found: obesity, environmental endocrine disruptors, genetic factors, ABO blood type, thrombophilia, thyroid disease, endometriosis, pelvic surgery, history of chemotherapy or radiotherapy, and shortening of the menstrual interval. *Articles in Portuguese did not meet the selection criteria.*

Each factor will be described in detail.

Obesity

Obesity is known to be associated with changes in reproductive physiology by various mechanisms, such as insulin resistance, hyperandrogenism, and elevated leptin levels [16, 17]. Obese women who undergo in vitro fertilization have lower quality embryos, worse implantation rates, higher miscarriage rates, and lower live birth rates [17–19].

Regarding the influence of obesity on the ovarian response to controlled stimulation, which is the focus of the present review, the evidence is inconsistent. A cohort of 487 patients showed a higher rate of canceled cycles and the need for higher doses of gonadotropins in obese patients [20] (Pinborg et al., 2011). In 2008, Matalliotakis et al. [21] conducted a retrospective study comparing 140 women with BMI > 24 kg/m^2 with a control group of 138 patients that indicated that the number of oocytes obtained and the embryo transfer rate decreased with the

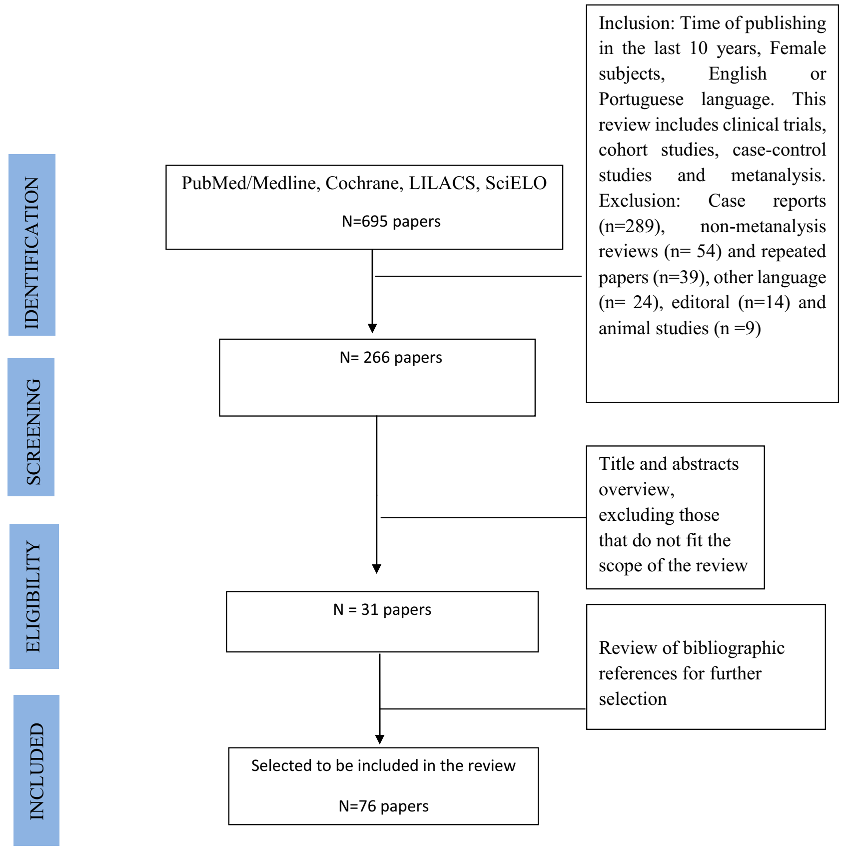

Fig. 1 Selection of studies flow diagram

increase in BMI. Those results are consistent with the findings of a retrospective cohort studied by Muasher et al. in 2016 [22]. That study involved 239,127 fresh IVF cycles from the 2008–2010 Society for Assisted Reproductive Technology registry, which were divided into cohorts according to BMI. The findings were that the mean number of oocytes retrieved was inversely proportional to BMI.

On the other hand, different results are also described in the literature. One example is a retrospective study published in 2010, which designated the oocyte retrieval rate as the primary outcome and contained 1970 patients undergoing ovarian stimulation who were divided by BMI, age, and response to stimulation. When assessing the factors that affect the number of oocytes retrieved in groups of patients who obtained a poor response and an adequate response, no association between obesity and poor response to ovarian stimulation was observed [23]. This finding is consistent with a meta-analysis of 33 articles comprising 47,976 treatment cycles to evaluate the impact of obesity and overweight on the results of assisted reproduction treatment. Specifically, regarding the number of oocytes retrieved, no difference was observed in the group of patients with high BMI [19].

Conclusion Regarding ovarian response to stimulation the evidence on obesity being a risk factor is still inconclusive (Level of evidence: 2C).

History of chemotherapy or radiotherapy

Chemotherapy and radiotherapy for cancer treatment are two known risk factors for poor response to ovarian stimulation and premature ovarian failure, and the preservation of the fertility of these patients is a new and promising field in human reproduction [24].

A study in 2012 compared 71 cancer survivors aged 15–39 years with a control group of 67 women of the same age in a cross-sectional study. Women exposed to alkylating agents had altered ovarian reserve tests, as did the group exposed to pelvic radiotherapy. The impact on the tests was proportional to the dose received [25]. Longitudinal studies with childhood cancer survivors support the hypothesis of ovarian reserve reduction, which remains in adult life [26–28].

The gonadotoxicity of each individual chemotherapeutic agent is difficult to determine. A prospective cross-sectional study in 2015 sought to evaluate the independent impact on the ovarian reserve of each alkylating agent in patients undergoing chemotherapy in childhood. The study compared 105 survivors with 20 controls, observing a greater drop in ovarian reserve in patients who received chemotherapy in high doses, in survivors of Hodgkin lymphoma, and in patients who received procarbazine as an alkylating agent. However, the intersection of the Hodgkin lymphoma group and procarbazine therapy group makes it difficult to discriminate which of these factors independently implies a worse outcome [29]. To determine the duration of the transition between a low ovarian reserve and complete ovarian failure, further longitudinal studies are needed.

Specifically, regarding poor response to ovarian stimulation, a retrospective study in 2011 compared 23 cancer survivor patients submitted to IVF with 70 age-matched women with male factor infertility submitted to the same stimulation protocol and found a lower oocyte retrieval rate in the cancer survivor group [24].

Conclusion Cancer survivor patients submitted to gonadotoxic chemotherapy have a diminished ovarian reserve and increased chance to respond poorly to ovarian stimulation (Level of evidence: 2A).

Short menstrual cycles

A prospective observational study by Brodin et al. in 2012 evaluating 6271 cycles of IVF/ICSI reported an association between short menstrual cycles and increased patient age. The duration of the menstrual cycle had an age-independent association with the ovarian response to stimulation with gonadotrophins [30].

A 2015 retrospective cohort study of 455 patients without ovulatory dysfunction submitted to IVF/ICSI found that shortened menstrual cycles are associated with poor ovarian response to stimulation. The study suggested that the length of the menstrual cycle could be used to discriminate patients with a higher probability of a poor response in the group aged over 40 years or with an AMH count below 1.1 ng/ml (according to the Bologna criteria, patients who meet the latter two criteria are already likely to respond poorly) [31].

In 2014, Vassena R et al. evaluated ovodonation cycles resulting in 3427 transfers and observed an association between shortening of the menstrual cycle and poor ovarian response to stimulation as well as a lower pregnancy rate in the receivers, suggesting that the duration of the menstrual cycle is related to both the number and quality of the oocytes [32].

Conclusion Short menstrual cycles are associated with POR (Level of evidence: 2B).

Genetic factors

Studies evaluating the relationship between ovarian reserve and genetic mutations, genetic polymorphisms, altered gene expression, and chromosomal abnormalities were found, as discussed below.

Chromosomal abnormalities

Abnormalities on the X chromosome constitute an important source of premature ovarian failure. The second X chromosome is required for folliculogenesis, and a low ovarian reserve is often dependent on the type of arrangement [14]. No studies were found regarding the oocyte retrieval rate in patients with Turner syndrome or mosaic Turner syndrome who underwent IVF. The reason might be that the criteria of the present review excluded case reports, which compound the majority of the literature on the subject.

Gene mutations

Among genetic mutations, mutation of the FMRI gene is one of the most studied in the literature. The mutation involves increasing the repetitions of CGG (cytosine, guanine, guanine) nucleotide chains at the 5′ locus of the gene, with up to 54 replicates considered as normal. Increased frequency of repetitions is associated with decreased ovarian reserve, and more than 200 repetitions characterize fragile X syndrome [33]. In an IVF-PGD setting for fragile X syndrome analysis, 27 patients with the FMR1 mutation (5 with full mutation, 22 with premutation) who underwent 79 cycles were compared to 33 controls with other genetic diseases who underwent 108 treatment cycles. FMR1 mutation carriers required significantly higher doses of gonadotropins, which nevertheless yielded significantly fewer numbers of oocytes, indicating poor response and diminished ovarian reserve in FMR1 carriers [34].

A study carried out by Shapiro et al. in 2015 aimed to evaluate the relationship between BRCA gene mutation and poor response to stimulation and concluded that there is no significant association [35].

Attempts to find a genetic marker for poor ovarian response have not yet been successful. A 2012 paper evaluating the relationship of previously described polymorphisms of the FSH receptor with poor ovarian response to controlled stimulation showed that there was no significant difference in the frequency of this alteration between the control group and the poor responders [36].

Conclusion Mutation of the FMRI gene is associated with decreased oocyte retrieval rate in IVF cycles. Nevertheless, an established genetic marker for screening of poor ovarian response is not defined yet. (Level of evidence: 2B).

Thrombophilia

Although there are studies associating thrombophilia with early menopause and failure in ART, only one specific study reported the association between thrombophilia and POR. The study consisted of a prospective cohort of 89 patients undergoing infertility treatment who were divided into groups with POR (three or fewer oocytes retrieved) and normal response, the latter being the control group. Ovarian reserve and thrombophilia panel tests were performed in both groups.

Screening for protein S deficiency, protein C deficiency, acquired resistance to protein C, antithrombin III, anticardiolipin antibodies, lupus anticoagulant, Leiden factor V deficiency, prothrombin G20210 mutation, and methyltetrahydrofolate reductase mutation (MTHFR) were included. No association was found between thrombophilia and POR; however, the findings were not conclusive about the role of thrombophilia in the development of ovarian failure [37].

Conclusion There is no evidence of association of thrombophilia and POR in current literature. (Level of evidence: 2A).

Environmental risks

External factors may either influence the establishment of the ovarian reserve during intrauterine life or reduce the existing reserve in adult women [38]. The environmental factors related to changes in ovarian reserve and ovarian response include endocrine disruptors and recreational drugs, which are described more fully below.

Endocrine disruptors

Endocrine disruptors are chemicals that mimic or disrupt the action of naturally occurring hormones. Many of these substances have estrogenic effects and may affect reproductive outcomes by many pathways, such as by modulating biosynthesis, signaling, and hormonal metabolism or acting as hormone receptor binders. Examples of endocrine disruptors that are commonly associated with POR are bisphenol A and phthalates [39–42].

Bisphenol A (BPA) is a monomer used to make hard, polycarbonated plastics, and some epoxy resins. They are commonly found in hard sport water bottles, infant bottles, medical tubing, and devices. BPA made epoxy resins are used to coat metal products, such as food cans and some dental sealants. The main route of exposure is through diet, since BPA can migrate to food from containers. Significant negative associations between increased urinary BPA concentrations and decreased peak E_2 and oocyte yield on the day of egg retrieval were found in a study by Mok-Lin et al. in 2010 [40]. A study-arm of the EARTH group (a large prospective still ongoing cohort on environmental exposure and reproductive outcomes) also found an inverse relationship between urinary BPA levels and number of oocytes retrieved [42].

Phtalates are another type of plastics that are used in soft, flexible plastics, and polyvinyl chloride (PVC) products. They are found in medical devices, many consumer products, flooring, and a variety of personal care products, such as some shampoos and lotions. They also may be added to drugs and dietary supplements as and excipients. Among women in the EARTH study undergoing assisted reproduction therapy, higher urinary concentrations of metabolites of di-(2-ethylhexyl) phthalate (DEHP) were associated with reduced oocyte yields [39, 42].

Conclusion Endocrine disruptors such as bisphenol A and phtalates are associated with POR, and patients should be advised lifestyle choices in order to minimize exposure. (Level of evidence: 2B).

Alcohol abuse

Regarding the relationship between alcohol consumption and response to controlled ovarian stimulation, we found four cohort studies with divergent results. A prospective cohort of 2545 patients published in 2011 applied standardized questionnaires assessing drink habits near the beginning of the IVF cycle, noting that women who consumed > 50 g of alcohol per week had significantly lower peak estradiol levels and greater odds of failed fertilization. Moreover, women drinking white wine weekly had significantly fewer oocytes retrieved compared with nondrinkers [43]. These results are corroborated by another prospective cohort published in 2017 evaluating 2134 patients that shows that daily drinkers have fewer oocytes retrieved than nondrinkers, although such a relationship is not equally demonstrated for social drinkers [44].

These results contradict that of two other smaller cohorts found in the same subject, which did not observe a relationship between alcohol use and the number of oocytes retrieved [45, 46]. However, in their discussion, an observation made is that the lack of association is not generalizable for heavy drinkers and do not evaluate the temporal relationship between drinking and the beginning of the stimulation cycle. The fact that all studies on the subject are cohorts from self-administered questionnaires further increases the risk of bias in the results obtained.

Conclusion There is insufficient data to associate social drinking with POR, although it is a good practice advice to discourage patients from heavy drinking habits. (Level of evidence: 2C).

Cigarette smoking

Among recreational drugs, cigarette smoking is the most widely studied and associated with ovarian failure with a dose-dependent impact [47, 48]. A study carried out in 2012 by Frèour et al. comparing 80 female smokers with a control group of 197 women found worse results in the ovarian reserve tests of the exposed subjects and related the level of exposure directly with poor response to ovarian stimulation [47].

In 2012, the American Society of Reproductive Medicine, after reviewing the literature, issued guidelines advising patients to cease smoking, noting that the available evidence demonstrates a causal association of smoking with infertility and worse outcomes of assisted reproduction cycles in smokers [49].

Conclusion Cigarette smoking is associated with worse outcomes in assisted reproduction techniques, including poor ovarian response, and should be discouraged. (Level of evidence: 1A).

Thyroid diseases

There have been several studies evaluating the relationship between clinical and subclinical hypothyroidism and negative outcomes, such as infertility, abortion, and adverse maternal-fetal events during pregnancy [50].

In 2011, Michalakis et al. estimated the incidence of TSH values higher than 2.5 mIU/L in patients submitted to ART to be 23%, but there were no significant differences in the number of oocytes retrieved and the gestation rates [51]. A randomized clinical trial conducted in 2011 included 64 patients with subclinical hypothyroidism who were divided into one control group and another group treated with 50 μg of levothyroxine. Although better embryo quality, implantation rates, and live birth rates were observed in the treatment group, no significant difference was observed in the number of oocytes recovered per cycle [52]. Another clinical trial conducted in 2010 evaluated 70 patients with subclinical hypothyroidism and did not observe a difference in the rate of oocytes retrieved in the control versus treatment group [53]. In those studies, subclinical hypothyroidism was defined as TSH greater than or equal to 4 mIU/L and normal T4L.

The role of thyroid autoantibodies in the outcomes of assisted reproduction therapy is also under investigation. A retrospective study in 2015 analyzed 5076 women, and no relation was observed between thyroid autoimmunity and low ovarian reserve [54]. A case-control study conducted in 2016 observed no changes in the number of oocytes retrieved in patients with euthyroidism and positive autoantibodies [55]. A meta-analysis of 12 papers on the impact of thyroid autoimmunity on outcomes in assisted reproduction that was published in 2016 also reached the same conclusion, without observing a significant difference in ovarian response to controlled stimulation [56].

Conclusion Present evidence is insufficient to indicate subclinical hypothyroidism or the presence of autoantibodies as risk factors for POR, and hormonal replacement does not seems to alter oocyte retrieval rate. (level of evidence: 1C).

ABO blood type

Several attempts to associate ABO blood groups with POR were found. The biological basis of this hypothesis relies on the fact that the direct translation product of the ABO blood group gene is glycosyltransferase. FSH and LH receptors are heavily glycosylated proteins, and FSH receptor expression in ovarian granulosa cells functions together with activated LH receptors to promote follicular development. A study by Nejat et al. in 2011 reported that blood types A and AB are more associated with low ovarian reserve [57]. However, such results were not repeated in other subsequent studies, including a meta-analysis on the subject [58–60].

Specifically, regarding POR, a study by Pereira et al. in 2015 sought to evaluate in a group of patients with low ovarian reserve whether there was any difference in response to controlled ovarian stimulation depending on blood type and did not observe a significant association [61]. Other studies also corroborate this finding and do not demonstrate an association between blood type and ovarian response to controlled stimulation [62, 63].

Conclusion Present evidence is insufficient to indicate ABO blood type as a factor related to diminished ovarian reserve (Level of evidence: 2A) of as a risk factor for poor ovarian response (Level of evidence: 2B).

Endometriosis

Endometriosis is a frequent indication for in vitro fertilization and embryo transfer (IVF-ET). Patients with moderate or severe endometriosis may have anatomic distortions of the fallopian tubes and ovaries, which may necessitate the use of IVF [64].

However, even mild stages of endometriosis may have negative effects on oocyte development, embryogenesis, or implantation [65]. Deep infiltrative endometriosis affects the ovarian reserve and the ovarian response to controlled stimulation, and even mild endometriosis (grades I–II) seems to have an influence on the number of oocytes retrieved per cycle, although this effect is lower than that of the most advanced degrees [64–67].

Yang et al. in 2015 performed a meta-analysis of nine studies regarding the association of endometrioma and POR, finding a lower rate of oocytes retrieved in the endometrioma group. Comparisons between ovaries with endometriomas and healthy ovaries of the same individuals were also made. The numbers of oocytes retrieved, MII oocytes retrieved, and total embryos formed were not significantly different between the affected ovaries and the contralateral normal ovaries [68]. Similar results were also found in a 2015 meta-analysis of 33 articles, which found that endometrioma was associated with a higher cancelation rate and a lower oocyte retrieval rate compared to those of a control group, although a similar bad prognosis was found when comparing endometrioma group and peritoneal endometriosis group [69]. Thus, endometriosis and ovarian endometriomas are independent risk factors for a poor response [68–71].

Conclusion Endometriosis and endometriomas are risk factors for POR. (Level of evidence: 2A).

Pelvic surgery

In 2010, a demographic study was conducted analyzing 104 patients who had POR compared to 324 controls. A significant association was observed between pelvic surgery and insufficient ovarian response, and in the POR group, the most common procedure was endometrioma excision [72].

A study by Rustamov et al. in 2016 analyzed the impact of different surgical procedures on ovarian reserve, comparing the effect of salpingectomy, unilateral salpingo-oophorectomy, and cystectomy. The study found that there was no difference in the AMH levels and AFC of women undergoing salpingectomy and cystectomy for causes other than endometrioma. There was an observable decrease in AMH in patients submitted to salpingo-oophorectomy and cystectomy by endometrioma [73]. However, a meta-analysis of 10 articles evaluating 367 patients published in 2016 showed a reduction of AMH in patients undergoing ovarian cystectomy due to nonendometriotic benign causes [74].

The impact of ovarian endometrioma excision on the ovarian reserve remains controversial. Depending on the assessed reserve test, the results of studies assessing AMH or AFC are conflicting. There are criticisms regarding both tests because AMH presents methodological difficulties in the correct storage of samples [75–77], and the antral follicle count may be distorted in patients with endometrioma due to the presence of cysts and local inflammation, leading to difficulty in ultrasonographic evaluation [78]. Studies evaluating AMH demonstrated impairments in the ovarian reserve after surgery [79–85], but a meta-analysis evaluating studies using AFC did not observe a decrease in the reserve based on this parameter [86].

Conclusion Ovarian surgery seems to be a risk factor for diminished ovarian reserve. Given the controversy regarding the tests used to evaluate the ovarian reserve after surgery for endometrioma, the conflicting results and the poor methodological quality of most of the studies used in the meta-analyses (heterogeneous and observational), caution is recommended in the management of patients with endometrioma and reproductive desire when indicating surgery prior to ART, since prior ovarian surgery for endometrioma is potentially a risk factor for POR (Level of evidence: 2C).

Discussion

Individualization of the ovarian stimulation protocol is a current trend in reproductive medicine. Regarding the poor responders, the determination of the risk factors allows a correct orientation of the couple and the search for more adequate protocols for this subgroup. The Bologna criteria emerged in 2011 as an attempt to standardize the definitions of POR. A cohort published in 2015 of women with poor prognosis according to this criteria determined that the live birth rate was proportional to the number of embryos transferred [87]. Because of that, the number of oocytes recruited and retrieved is a very important marker of treatment success.

To distinguish, the low response population should be made with the intention of improving protocols for induction of in vitro fertilization and not as refusal for treatment. Patients who reach the stage of embryo transfer have a moderate rate of live births [87]. Likewise, a diminished ovarian reserve could not be used in isolation as an indicator of infertility in an a priori non-infertile population [88].

In the discussion of the original article, the following were cited as risk factors beyond age: tubal infection and chlamydial infection, genetic mutations, endometrioma, ovarian surgery, chemotherapy, and shortening of the menstrual cycles.

The articles relating poor response with tubal infection or chlamydia infection date from 1987 and 1998 [89, 90], and no more recently published articles have been found in the last 10 years about this relationship. As to the other factors listed in the original article, there is evidence in the literature from the last 10 years of the association of all the factors with POR, although there is still controversy regarding the extent of damage to ovarian reserve and ovarian response caused by the excision of endometriomas.

It should also be mentioned that among the genetic risk factors, although many alterations related to poor response have already been identified, no test has yet been established to be used as a genetic marker for the identification and screening of POR. The original article of 2011 also makes no mention of environmental risks, and occupational screening and counseling to reduce exposure could be performed based on existing evidence of the association of various environmental factors (i.e., smoking, pesticides, plastic packaging) with POR.

As explained in the topics above, the relationship of obesity with ovarian response to stimulation is still unclear, although a higher BMI is already well established as a factor related to poor outcomes in IVF treatment (i.e., lower live birth rates, higher miscarriage rate). This uncertainty regarding obesity as a risk factor to POR may be because of heterogeneity between the populations of the studies, as some of them included patients with polycystic ovarian syndrome in the high-BMI groups and patients in different age groups.

One limitation in our search was that there is no consensus in the POR diagnostic criteria. Many synonyms to the term “poor response” were found, such as the following: low ovarian reserve, low responders, poor ovarian response, and diminished ovarian reserve. Polyzos et al. in 2011 performed a meta-analysis of the studies regarding poor responders. In 47 randomized studies evaluated, 41 different definitions of POR were used. Even different works by the same research group used different definitions. None of the diagnostic criteria used in the studies were repeated in more than 50% of the studies. Therefore, the performance of meta-analyses of existing clinical trials is discouraged due to heterogeneity between definitions, leading to possible biases [91]. Most of the papers included in this review are composed of cohorts or case-control studies in which ovarian response to stimulation is one of the outcomes analyzed, but not always the main outcome. In most of cases, poor response is defined solely based on the number of oocytes retrieved during IVF. When using "strict" criteria, meaning looking only for articles using the Bologna criteria to define poor response, a more accurate or extra analysis as well as new insight cannot be made.

Although the frame set of 10 years determined to be the scope of the review could be a way to see what is the most recent data on a very extensive subject, it is also a weakness of the study. Foundational studies done before those 10 years, if well designed, may not have been repeated and be missing in the analysis. That is also true for older studies on risk factors found to have insufficient evidence of association with POR that might not have been repeated ever since.

Conclusion

Our data suggest that environmental endocrine disruptors, tobacco, genetic mutations, endometriomas, ovarian surgery, chemotherapy, and short menstrual cycles are factors that influence stimulation in assisted reproduction cycles. Some of these risk factors are modifiable, and counseling on lifestyle habits is a way of providing good assistance to the infertile patient.

Further studies are necessary to better characterize patients with prior risk factors, as are well-conducted studies on personalized therapy based on individual risk factors analysis.

References

1. Speroff, Leon; Fritz, Marc A. Clinical gynecologic endocrinology and infertility.7th ed. Philadelphia: Lippincott Williams & Wilkins; c2005.
2. Garcia JE, Jones GS, Acosta AA, Wright G. HMG/hCGfollicular maturation for oocytes aspiration: phase II, 1981. Fertil Steril 1983; 39:174–179.
3. Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. Fertil Steril. 2000;73:667–76.
4. Jenkins JM, Davies DW, Devonport H, Anthony FW, Gadd SC, Watson RH, et al. Comparison of "poor" responders with "good" responders using a standard buserelin/human menopausal gonadotrophin regime for in-vitro fertilization. Hum Reprod. 1991;6:918–21.
5. Ben-Rafael Z, Bider D, Dan U, Zolti M, Levran D, Mashiach S. Combined gonadotropin releasing hormone agonist/human menopausal gonadotropin therapy (GnRH-a/hMG) in normal, high, and poor responders to hMG. J In Vitro Fert Embryo Transf. 1991;8:33–6.
6. Ferraretti AP, La Marca BC, Fauser B, Tarlatzis G, Nargund L, Gianaroli, et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26(7):1616–24.
7. Polyzos NP, Nwoye M, Corona R, Blockeel C, Stoop D, Haentjens P, et al. Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI. Reprod BioMed Online. 2014;28:469–74.
8. Busnelli A, Papaleo E, Del Prato D, La Vecchia I, Iachini E, Paffoni A, et al. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. Hum Reprod. 2015;30:315–22.
9. Marca L, Grisendi V, Giulini S, Sighinolfi G, Tirelli A, Argento C, et al. Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study. J Assist Reprod Genet. 2015;32:931–7.
10. Younis JS. The Bologna criteria for poor ovarian response; has the job been accomplished? Hum Reprod. 2012;27:1874–5.
11. Papathanasiou A. Implementing the ESHRE 'poor responder' criteria in research studies: methodological implications. Hum Reprod. 2014;29:1835–8.
12. Venetis CA. The Bologna criteria for poor ovarian response: the good, the bad and the way forward. Hum Reprod. 2014;29:1839–41.
13. Ferraretti AP, Gianaroli L. The Bologna criteria for the definition of poor ovarian responders: is there a need for revision? Hum Reprod. 2014;29:1842–5.
14. Younis JS, Ben-Ami M, Ben-Shlomo I. The Bologna criteria for poor ovarian response: a contemporary critical appraisal. J Ovarian Res. 2015;8:76.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.
16. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod BioMed Online. 2007;15(5):532–8.
17. Bellver J, Busso C, Pellicer A, Remohí J, Simón C. Obesity and assisted reproductive technology outcomes. Reprod BioMed Online. 2006;12(5):562–8.
18. ASRM, The Practice Committee of the American Society of Reproductive Medicine. Obesity and reproduction: a committee opinion. Fertil Steril. 2015a;104:1116–26.
19. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod BioMed Online. 2011;23(4):421–43.
20. Pinborg A, Gaarslev C, Hougaard CO, Nyboe Andersen A, Andersen PK, Boivin J, et al. Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. Reprod BioMed Online. 2011;23(4):490–9.
21. Matalliotakis I, Cakmak H, Sakkas D, Mahutte N, Koumantakis G, Arici A. Impact of body mass index on IVF and ICSI outcome: a retrospective study. Reprod BioMed Online. 2008;16(6):778–83.
22. Muasher S, et al. Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008–2010 Society for Assisted Reproductive Technology registry. Fertil Steril. 2016;105(3):665–9.
23. Kilic S, Yilmaz N, Zülfikaroglu E, Sarikaya E, Kose K, Topcu O, et al. Obesity alters retrieved oocyte count and clinical pregnancy

rates in high and poor responder women after in vitro fertilization. Arch Gynecol Obstet. 2010;282(1):89–96.
24. Das M, Shehata F, Son WY, Tulandi T, Holzer H. Ovarian reserve and response to IVF and in vitro maturation treatment following chemotherapy. Hum Reprod. 2012;27(8):2509–14.
25. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. Fertil Steril. 2012;97:134–40.
26. Krawczuk-Rybak M, Leszczynska E, Poznanska M, Zelazowska-Rutkowska B, Wysocka J. The progressive reduction in the ovarian reserve in young women after anticancer treatment. Hormone Metab Res. 2013;45:813–9.
27. Lunsford AJ, Whelan K, McCormick K, McLaren JF. Antimüllerian hormone as a measure of reproductive function in female childhood cancer survivors. Fertil Steril. 2014;101:227–31.
28. Nielsen SN, Andersen AN, Schmidt KT, Rechnitzer C, Schmiegelow K, Bentzen JG, et al. A 10-year follow up of reproductive function in women treated for childhood cancer. Reprod BioMed Online. 2013;27(2):192–200.
29. Thomas-Teinturier C, Allodji RS, Svetlova E, Frey MA, Oberlin O, Millischer AE, et al. Ovarian reserve after treatment with alkylating agents during childhood. Hum Reprod. 2015;30(6):1437–46.
30. Brodin T, Bergh T, Berglund L, Hadziosmanovic N, Holte J. Menstrual cycle length is an age-independent marker of female fertility: results from 6271 treatment cycles of in vitro fertilization. Fertil Steril. 2008;90:1656–61.
31. Gizzo S. Et Al. Menstrual cycle length: a surrogate measure of reproductive health capable of improving the accuracy of biochemical/sonographical ovarian reserve test in estimating the reproductive chances of women referred to ART. Reprod Biol Endocrinol 2015; 10;13:28.
32. Vassena R, Vidal R, Coll O, Vernaeve V. Menstrual cycle length in reproductive age women is an indicator of oocyte quality and a candidate marker of ovarian reserve. Eur J Obstet Gynecol Reprod Biol. 2014;177:130–4.
33. Gleicher N, Weghofer A, Oktay K, Barad D. Relevance of triple CGG repeats in the FMR1 gene to ovarian reserve. Reprod BioMed Online. 2009;19(3):385–90.
34. Tsafrir A, Altarescu G, Margalioth E, Brooks B, Renbaum P, Levy-Lahad E, et al. PGD for fragile X syndrome: ovarian function is the main determinant of success. Hum Reprod. 2010;25:2629–36.
35. Shapiro M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, et al. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 2015;104(5):1162–7.
36. Binder H, Strick R, Zaherdoust O, Dittrich R, Hamori M, Beckmann MW, et al. Assessment of FSHR variants and antimullerian hormone in infertility patients with a reduced ovarian response to gonadotropin stimulation. Fertil Steril. 2012;97(5):E1169–75.
37. Younis JS, Ben-Ami M, Izhaki I, Jadaon J, Brenner B, Sarig G. The association between poor ovarian response and thrombophilia in assisted reproduction. Eur J Obstet Gynecol Reprod Biol. 2013;166(1):65–9.
38. Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. Hum Reprod Update. 2014;20(3):353–69.
39. Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S, et al. Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: results from the EARTH study. Environ Health Perspect. 2016;124(6):831–9. https://doi.org/10.1289/ehp.1509760.
40. Mok-Lin E, Ehrlich S, Williams PL. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. Intl J Androl. 2010;33(2):385–93.
41. Ehrlich S, Williams PL, Missmer SA. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Hum Reprod. 2012;27(12):3583–92.
42. Messerlian et al. for the EARTH Study Team. The Environment and Reproductive Health (EARTH) Study: a prospective preconception cohort. Human Reproduction Open, pp. 1–11, 2018.
43. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. Obstet Gynecol. 2011;117(1):136–42.
44. Hacker MR, et al. Women's alcohol consumption and cumulative incidence of live birth following in vitro fertilization. J Assist Reprod Genet. 2017;34:877–83.
45. Gaskins AJ et al for the EARTH Study Team. The association between pre-treatment maternal alcohol and caffeine intake and outcomes of assisted reproduction in a prospectively followed cohort. Hum Reprod, Vol.32, No.9 pp. 1846–1854, 2017.
46. Firns S, Cruzat VF, Keane KN, Joesbury KA, Lee AH, Newsholme P, et al. The effect of cigarette smoking, alcohol consumption and fruit and vegetable consumption on IVF outcomes: a review and presentation of original data. Reprod Biol Endocrinol. 2015;13:134.
47. Fréour T, Masson D, Dessolle L, Allaoua D, Dejoie T, Mirallie S, et al. Ovarian reserve and in vitro fertilization cycles outcome according to women smoking status and stimulation regimen. Archives Genecology Obstet. 2012;285:1177–82.
48. Dólleman M, Verschuren WM, Eijkemans MJ, Dollé ME, Jansen EH, Broekmans FJ, et al. Reproductive and lifestyle determinants of anti-Müllerian hormone in a large population-based study. J Clin Endocrinol Metab. 2013;98:2106–15.
49. ASRM The Practice Committee of the American Society of Reproductive Medicine. Smoking and infertility: a committee opinion. Fertil Steril 2012; 98 1400–1406.
50. ASRM The Practice Committee of the American Society of Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril 2015b; 104 545–553.
51. Michalakis KG, Mesen TB, Brayboy LM, Yu B, Richter KS, Levy M, Widra E, Segars JH.. Subclinical elevations of thyroid-stimulating hormone and assisted reproductive technology outcomes. Fertil Steril 2011 30;95(8):2634–2637.
52. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril. 2011;95:1650–4.
53. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract. 2010;16:792–7.
54. Polyzos NP, Sakkas E, Vaiarelli A, Poppe K, Camus M, Tournaye H. Thyroid autoimmunity, hypothyroidism and ovarian reserve: a cross-sectional study of 5000 women based on age-specific AMH values. Hum Reprod. 2015;30(7):1690–6.
55. Sakar MN, Unal A, Atay AE, Zebitay AG, Verit FF, Demir S, Turfan M, Omer B. Is there an effect of thyroid autoimmunity on the outcomes of assisted reproduction? J Obstet Gynaecol 2016; 36: 213–217.
56. Businelli A, et al. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Hum Reprod Update. 2016;22(6):775–90.
57. Nejat eJ, Jindal S, Berger D, Buyuk E, Lalioti M, Pal L. Implications of blood type for ovarian reserve. Hum Reprod. 2011;26:2513–7.
58. de Mouzon J, Hazout A, Cohen-Bacrie M, Belloc S, Cohen-Bacrie P. Blood type and ovarian reserve. Hum Reprod. 2012;27:1544–5.
59. Timberlake KS, Foley KL, Hurst BS, Matthews ML, Usadi RS, Marshburn PB. Association of blood type and patient characteristics with ovarian reserve. Fertil Steril. 2013;100:1735–9.

60. Deng J, Jia M, Cheng X, Yan Z, Fan D, Tian X. ABO blood group and ovarian reserve: a meta-analysis and systematic review. Oncotarget. 2017;8(15):25628–36. https://doi.org/10.18632/oncotarget.15759.
61. Pereira N, Hutchinson AP, Bender JL, Lekovich JP, Elias RT, Rosenwaks Z, et al. Is ABO blood type associated with ovarian stimulation response in patients with diminished ovarian reserve? J Assist Reprod Genet. 2015;32:985–90.
62. Awartani K. Association of blood groups with ovarian reserve and outcome of in vitro fertilization treatment. Ann Saudi Med. 2016;36(2):116–20.
63. Spitzer D, Corn C, Stadler J, Wirleitner B, Schuff M, Vanderzwalmen P, et al. Implications of blood type for ovarian reserve and infertility -impact on oocyte yield in IVF patients. Geburtshilfe Frauenheilkd. 2014;74:928–32.
64. Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertil Steril. 2007;88(6):1568–72.
65. Coccia ME. Impact of endometriosis on in vitro fertilization and embryo transfer cycles in young women: a stage-dependent interference. Acta Obstet Gynecol Scand. 2011;90(11):1232–8.
66. Papaleo E, Ottolina J, Viganò P, Brigante C, Marsiglio E, De Michele F, et al. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. Acta Obstet Gynecol Scand. 2011;90(8):878–84.
67. Mekaru K, Yagi C, Asato K, Masamoto H, Sakumoto K, Aoki Y.Effects of early endometriosis on IVF-ET outcomes. Front Biosci (Elite Ed) 2013 1;5:720–724, E5.
68. Yang C, Geng Y, Li Y, Chen C, Gao Y. Impact of ovarian endometrioma on ovarian responsiveness and IVF: a systematic review and meta-analysis. Reprod BioMed Online. 2015;31:9–19.
69. Hamdam M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update. 2015;21(6):809–25.
70. Somigliana E, Infantino M, Benedetti F, Arnoldi M, Calanna G, Ragni G. The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. Fertil Steril. 2006;86(1):192–6.
71. Ashrafi M, Fakheri T, Kiani K, Sadeghi M, Akhoond MR. Impact of the endometrioma on ovarian response and pregnancy rate in in vitro fertilization cycles. Int J Fertil Steril. 2014;8(1):29–34.
72. Padhy N, Gupta S, Mahla A, Latha M, Varma T. Demographic characteristics and clinical profile of poor responders in IVF / ICSI: a comparative study. J Human Reprod Sci. 2010;3(2):91–4.
73. Rustamov O, Krishnan M, Roberts SA, Fitzgerald CT. Effect of salpingectomy, ovarian cystectomy and unilateral salpingo-oopherectomy on ovarian reserve. Gynecol Surg. 2016;13:173–17.
74. Mohamed AA, Al-Hussaini TK, Fathalla MM, El Shamy TT, Abdelaal II, Amer SA. The impact of excision of benign nonendometriotic ovarian cysts on ovarian reserve: a systematic review. Am J Obstet Gynecol. 2016;215(2):169–76.
75. Clark CA, Laskin CA, Cadesky K. Mullerian hormone: reality check. Hum Reprod. 2014;29:184–5.
76. Ledger WL. Measurement of antimüllerian hormone: not as straightforward as it seems. Fertil Steril. 2014;101:339.
77. Rustamov O, Smith A, Roberts SA, Yates AP, Fitzgerald C, Krishnan M, et al. The measurement of anti-Mullerian hormone: a critical appraisal. J Clin Endocrinol Metab. 2014;99:723–32.
78. Kitajima M, Defrere S, Dolmans MM, Colette S, Squifflet J, Van Langendonckt A, et al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil Steril. 2011;96:685–91.
79. Salihoğlu KN, Dilbaz B, Cırık DA, Ozelci R, Ozkaya E, Mollamahmutoğlu L. Short-term impact of laparoscopic cystectomy on ovarian reserve tests in bilateral and unilateral endometriotic and nonendometriotic cysts. J Minim Invasive Gynecol. 2016;23(5):719–25.
80. Uncu G, Kasapoglu I, Ozerkan K, Seyhan A, Oral Yilmaztepe A, Ata B. Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve. Hum Reprod. 2013;28(8):2140–5.
81. Chen Y, Pei H, Chang Y, Chen M, Wang H, Xie H, Yao S.The impact of endometrioma and laparoscopic cystectomy on ovarian reserve and the exploration of related factors assessed by serum anti-Mullerian hormone: a prospective cohort study. J Ovarian Reserve 2014 26;7:108.
82. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146–54.
83. Kwon SK, Kim SH, Yun SC, Kim DY, Chae HD, Kim CH, et al. Decline of serum antimullerian hormone levels after laparoscopic ovarian cystectomy in endometrioma and other benign cysts: a prospective cohort study. Fertil Steril. 2014;101:435–41.
84. Alborzi S, Keramati P, Younesi M, Samsami A, Dadras N. The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas. Fertil Steril. 2014;101:427–34.
85. Celik HG, Dogan E, Okyay E, Ulukus C, Saatli B, Uysal S, et al. Effect of laparoscopic excision of endometriomas on ovarian reserve: serial changes in the serum antimullerian hormone levels. Fertil Steril. 2012;97:1472–147.
86. Muzzi L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. Hum Reprod. 2014;29(10):2190–8.
87. Gleicher N, et al. Live-birth rates in very poor prognosis patients, who are defined as poor responders under the Bologna criteria, with nonelective single embryo, two-embryo, and three or more embryos transferred. Fertil and Steril. 104(6):1435–41.
88. Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. JAMA. 2017;318(14):1367–76.
89. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred c Ngu A, Johnston IH. Performance of patients with a 'frozen pelvis' in an in vitro fertilization program. Fertil Steril 1987;47:450–455.
90. Keay SD, Barlow R, Eley A, Masson GM, Anthony FW, Jenkins JM. The relation between immunoglobulin G antibodies to Chlamydia trachomatis and poor ovarian response to gonadotropin stimulation before in vitro fertilization. Fertil Steril. 1998;70:214–8.
91. Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel? Fertil Steril. 2011;96(5):1058–61.