Perinatal and neonatal outcome in poor ovarian responders in assisted reproductive technology (ART) pregnancy

Cătălin Ioan Bosoancă[1,2], Simona Vlădăreanu[1,2], Alina-Gabriela Marin[1,2], Radu Vlădăreanu[1,2]

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. "Elias" University Emergency Hospital, Bucharest, Romania

Corresponding author:
Simona Vlădăreanu
E-mail: simconst69@gmail.com

Abstract

Poor ovarian response in assisted reproductive techniques is defined by an association of clinical features, hormonal markers and ultrasound parameters that have been grouped by ESHRE under the name of Bologna criteria. The incidence of poor ovarian responders among infertile women has been estimated within the range of 9% to 22%. Poor response to controlled ovarian hyperstimulation reflects advanced ovarian aging, which may be associated with early vascular aging. The aim of this research is to identify whether poor perinatal outcomes and pregnancy complications are higher among women with poor ovarian response.

Keywords: *controlled ovarian hyperstimulation, poor responders, pregnancy, perinatal complication*

Rezumat

Răspunsul ovarian scăzut în reproducerea umană asistată este definit printr-o asociere de caracteristici clinice și paraclinice, precum markeri hormonali și parametri imagistici obținuți ecografic, care au fost integrați de ESHRE sub denumirea de criteriile Bologna. Incidența răspunsului ovarian slab în rândul femeilor infertile a fost estimată în intervalul 9-22%. Răspunsul slab la hiperstimularea ovariană controlată reflectă îmbătrânirea ovariană avansată, care poate fi asociată cu îmbătrânirea precoce vasculară. Scopul acestui review este de a identifica dacă rezultatele perinatale slabe și complicațiile din sarcină sunt mai frecvente în rândul femeilor cu un răspuns ovarian scăzut.

Cuvinte-cheie: *hiperstimulare ovariană controlată, răspuns ovarian scăzut, sarcină, complicații perinatale*

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Introduction

In vitro fertilization (IVF) technologies with a controlled ovarian hyperstimulation approach have classified patients into three different groups (high ovarian response group, normal ovarian response group, and poor ovarian response group). The poor ovarian response (POR) is used to define a subgroup of patients who have difficulty in the success of IVF procedures, and in literature it has been observed that it varies in incidence between 9% and 22%[1-3].

Poor responders were described for the first time in 1983, as a group of patients who achieved a peak concentration of oestradiol <300 pg/mL, based on a standard stimulation protocol (with 150 IU of human menopausal gonadotrophin), this particular fact leading to a poor follicle production and to a low number of oocytes retrieved and, therefore, to a smaller number of embryos transferred into the uterus[4].

The reproductive aging process is a gradual decrease in both the quantity and the quality of the oocytes and contributes to the gradual decline in fertility and in the final occurrence of natural sterility. Menopause is the final step in the process referred to as ovarian aging. The identification of women who have severely decreased ovarian reserve for their age is relevant and is done by ovarian reserve tests which can be fairly accurate in predicting the response to ovarian stimulation in the assisted reproductive technology (ART) setting. The capacity to predict the chances for spontaneous pregnancy or pregnancy after ART appears very limited.

Since 2011, additional clinical features, hormonal markers and ultrasound parameters have been used under the name of Bologna criteria and, therefore, the ESHRE working group defined as poor responder the subpopulation that gathers two of the following features:

a) advanced maternal age (age ≥40 years old) or any other risk factors for POR;

b) a previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol);

c) an abnormal ovarian reserve test (ORT) – antral follicle count (AFC) <5-7 or anti-Müllerian hormone (AMH) <0.5-1.1 ng/ml (<3.6-7.9 nmol/l).

Also, poor responders can be subgrouped based on a retrospective definition (if a patient experienced two

episodes of POR after maximal stimulation protocols), or based on a prospective definition as "expected poor responders" (if the patient's age is over 40 and has an abnormal ORT)[5]. The decrease in fertility according to age varies and it is important to note that the chronological age is not always directly proportional to the reproductive potential. Therefore, ORT is a good predictor of ovarian reserve and for the response obtained from controlled ovarian hyperstimulation, but not a predictor of the qualitative characteristics of oocytes (implicitly of the success rate of the treatment, obtaining a healthy newborn), and does not reduce the time to obtain a pregnancy through IVF[6].

The main causes for the decrease of the ovarian reserve are represented by the previous ovarian surgeries (unilateral oophorectomy or cystectomy, for endometrioma)[7-10], congenital absence of an ovary with or without the absence of the adjacent Fallopian tube (rare event), genetic defects, chemotherapy or radiotherapy, autoimmune diseases, chronic smoking, and unexplained[11,12]. Also, there have been taken into account new risk factors incriminated for POR, such as type 1 diabetes mellitus[13], transfusion-dependent beta thalassemia[14], and the embolization of uterine artery performed as treatment for uterine leiomyomas[15,16].

Search procedure

This review was conducted by searching the MEDLINE (PubMed), Cochrane Central and Embase databases from January 2011 until March 2020. The keywords employed and combined for the search strategy were: "*in vitro* fertilization", "IVF", "assisted reproduction", "assisted reproduction techniques", "medical assisted reproduction", "intracytoplasmic sperm injection", "ICSI", "perinatal outcome", "perinatal complication", "neonatal complications", "poor ovarian reserve", "maternal outcome", "obstetrical outcome", "poor ovarian responders".

The original search returned 598 studies from the three databases. Following the removal of duplicate studies (n=115), all records were screened and full-text was sought and obtained for relevant articles. The relevant articles (n=57) were identified following title and abstract screening, employing the flow chart PRISMA. Citation mining was performed where the reference lists of all included articles and relevant reviews and meta-analyses were reviewed to identify other articles of relevance. The search was limited to full-length manuscripts published in English in peer-reviewed journals up to March 2020. A total of 44 studies were included in the present review.

Only studies that were performed following 2011 were included. As evidenced by the majority of literature, IVF from inception until 2011 reported continuous improvements regarding live birth rates[17]. Since 2011, live birth rates have reached a plateau with adjustments reported each year. The population of the study included women undergoing IVF. The primary outcome measure was live birth rate and/or ongoing pregnancy (LB/OP). Both LB and OP were included, as many studies report on different findings and there is a lack of consensus on the desired outcome[18]. The aim of our study was to investigate a possible argument for complications caused by pregnancy in patients with POR in IVF procedures.

Discussion

In the literature, there is growing evidence that subfertile patients who conceived after infertility treatments have an increased risk of pregnancy and perinatal complications, and this is particularly true for patients who conceived after using high-technology infertility treatments. Moreover, high-technology infertility treatments include many concomitant clinical and biological risk factors.

Poor responders after *in vitro* fertilization (IVF) remain a challenging group to treat in infertility practice, even though substantial research has been done and various treatment options, such as androgen supplementation, addition of growth hormone and mild stimulation protocols[1,2], have been explored. The live birth rate in poor responders following IVF varies between 9.9% and 23.8%[7,8]. This wide variation in live birth rate is due to the different criteria for poor responders in different studies[3-6].

In the poor responder group, there have been noticed significantly higher maternal age, FSH serum levels and total gonadotrophin amounts compared to the significantly lower AMH serum levels, number of embryos transferred and blastocyst stage transfers. AMH was confirmed as an excellent predictor for poor responders and it offers a quantitative evaluation with low inter- and intracycle variability of the ovarian follicles that can't be assessed by AFC[19-21]. In spite of being an excellent predictor for poor responders, AMH – alone or in association with AFC – did not lead to an improved rate of prediction of ongoing pregnancy rates[22].

This category of patients is characterized, in an independent way regarding the therapeutic protocol used[17] and also the patient's age[18], by cycle cancellation from insufficient response in follicle recruitment and reduced pregnancy rates in comparison with the other categories (normal and high responders)[19]. Therefore, it is absolutely necessary to optimize the clinical results in this group of patients by choosing the best COH protocol in order to exploit the potential of whole ovarian reserve and to increase the number of oocytes, not only to predict the ovarian reserve, knowing that at least half of the cancelled IVF cycles were due to poor ovarian response[18].

A very important aspect to be emphasized is the possible link between the POR and the specific risks for this category of patients in terms of pregnancy complications.

According to Jirje, the age of the patient is very important, therefore advanced maternal age is associated with increased obstetric and perinatal complications. Jirje noticed that women older than 35 years of age

who undergo IVF procedures have a greater risk for POR compared to the younger counterparts[35]. This fact mostly suggests an ovarian aging and subsequent vascular endothelial dysfunction[36] that determine a greater risk for adverse perinatal outcomes[37].

Romunstad et al. compared pregnancies conceived spontaneously with the ones obtained after subsequent ART but in the same mother, and noticed an increase by three folds in the incidence of *placenta praevia* in the IVF pregnancy group[19]. Also, Deckers et al. noticed a higher incidence of *placenta praevia* in patients diagnosed with endometriosis who conceived with ART when compared to patients without endometriosis[10]. Indeed, compared to pregnancies in the general population, pregnancies obtained by IVF tend to have a 2.7-fold increased risk for preeclampsia, with an incidence of pregnancy-induced hypertension in those obtained by IVF between 6.4% and 21% compared to 4% to 5.2% in the spontaneous conception of pregnancy[23-25]. However, the main cause is the association of advanced female age with low ovarian reserve and a higher cardiovascular risk[26,27]. The failure of uterine vasculature to adapt to the increased hemodynamic demands of pregnancy in women with an adanced age is a proposed explanation.

In their clinical study, Parlakgümüş et al. observed that pregnancy complications in patients with POR did not increase, with approximately two-thirds of them having eventless pregnancies compared to the control group. They also reported that the incidence of pre-eclampsia and gestational diabetes was not increased in patients who had a poor response compared to other pregnant women of the same age[28].

Most studies indicate similar rates for both pregnancy complications such as preeclampsia and gestational diabetes[29], as well as for perinatal complications, such as premature birth or low birth weight[30], among women undergoing IVF procedures, regardless of the type of ovarian response.

In a clinical study, it was observed that pregnancy (23.8% versus 41.6%; p<0.01) and subsequent live birth rates (17% versus 29.3%; p<0.001) were significantly lower in poor responders, as multiple pregnancies were represented in a higher number in normal respondents[31]. The early aging of the vascular system can lead to low ovarian reserve[27,28], through a reduced amount of oocytes (often resulting in a poor response) and low oocyte quality[29-31], being reflected in low pregnancy rates and higher abortion rates (possibly due to higher rates of fetal aneuploidy)[32].

The patient's age is very important, being observed that women over the age of 35 who follow an IVF program have a higher risk of POR[33], suggesting that ovarian aging and vascular endothelial dysfunction[34] can determine a higher risk situation for perinatal outcome[35]. The patient under the age of 35 classified as a poor responder has a higher pregnancy rate when compared to the older women with the same ovarian reserve (23% versus 12%; p<0.0001)[36]; in this case, age offers a better oocyte quality during IVF[37].

In Vasario's study, the finality of twin pregnancies obtained by IVF is comparable to that of spontaneously conceived twin pregnancies, given the same management criteria regarding gestational age at birth, birth weight, perinatal morbidity and mortality, and malformation rate. The rate of caesarean section was slightly but not significantly higher in IVF pregnancies[38].

Compared to spontaneous twin pregnancy, Nasar and co-workers suggest in their study that artificially obtained twins are more prone to caesarean delivery, having a higher incidence when it comes to premature birth and respiratory complications related to prematurity, with a prolongation of admission time in intensive care[39].

In ongoing pregnancies, gestational diabetes, hypertension and placental defects, such as *placenta praevia* and *abruptio placentae*, are more common in older women[40]. In women >35 years of age who follow IVF procedures, the percentage of POR is higher compared to younger women[37]. Therefore, many of the PORs are older women and at high risk of perinatal complications[41]. Compared to spontaneously conceived pregnancy, Robert Ochsenkühn et al. observed in a retrospective clinical study on 322 single pregnancies and 78 twin pregnancies that pregnancy-induced hypertension was a more frequently diagnosed complication in the IVF single pregnancy group[42]. Also, Healy et al. objectified a higher incidence of *placenta praevia* in patients diagnosed with endometriosis who conceived with IVF compared to patients without endometriosis. We must keep in mind that, even in the case of a primiparous, where we do not have a previous uterine scar to explain the mechanism of *placenta praevia*, there is always the possibility of an undiagnosed endometriosis, but also an advanced maternal age[43].

As mentioned before, the patient's age is directly proportional to the quality of the oocyte. As a result, older women develop increased chromosomal senescence of oocyte genetic material, leading to an increase in the rate of early pregnancy loss, as well as an increased abortion rate and fewer ongoing pregnancies[44-50].

It should also be noted that one study showed that there is no difference regarding clinical pregnancy in women older or younger than 40 years old (14.4% versus 13.7%; OR 1.06; CI 95%; 0.63-1.78)[18].

Regarding the mean gestational age (36.35±2.3 versus 36.37±3.04) and the delivery type, these facts appear to have similar rates in both low-response and normal-response patients. Finally, some data highlight the possible role of the Body Mass Index in the reproduction of women, those with poor response and obese having a lower pregnancy rate than those with poor response and normal weight[51,52].

There have been studies in women over the age of 35 who have obtained pregnancies with donated oocytes with excellent results in terms of the risk of perinatal complications. Kenyon et al. compared the pregnancies of women aged >45 years old with pregnancies of those who conceived spontaneously at <36 years old. They reported that mature women over the age of 45 who conceive

largely through IVF with donated oocytes can expect similar results to younger women cared for in the same setting of increased obstetrical risk management[53].

In another study, newborns of surrogate mothers had perinatal complications such as premature birth, growth restriction, preeclampsia, gestational diabetes and *placenta praevia* compared to single-fetal pregnancies conceived spontaneously by the same woman. The data suggest that assisted reproduction procedures may affect the quality of the embryo and that its negative impact cannot be overcome even with a proven uterine environment[54-60].

A prospective study determined the rate of neonatal outcomes, in women who underwent *in vitro* fertilization and who were 40 years of age or older; birth weight <1,500 g was noticed in 17.16% of cases compared with 5.55% in women who had a spontaneous pregnancy, and neonatal intensive care unit admissions included 22.86% newborns and 8.33% newborns from the control group, respectively[61].

Xu Xiao-Yan et al. investigated the survival quality of infants conceived by *in vitro* fertilization and identified the factors that caused birth defects and neonatal complications in IVF infants compared with naturally conceived infants. The results showed no significant differences regarding the incidence of birth defects between the two groups ($p>0.05$); the IVF group had higher incidence rates of low birth weight and neonatal scleroderma ($p<0.05$), with a longer hospital stay ($p<0.01$)[62].

Conclusions

A very important aspect to be emphasized is the possible link between the POR and the specific risks for this category of patients in terms of pregnancy complications. The present review aims to answer the question of whether the complications of pregnancies obtained by *in vitro* fertilization are greater compared to those obtained spontaneously, and this requires a more in-depth study of the causes and effects.

Most of the studies concluded that decreased ovarian reserve and significant ovarian aging lead to an increased incidence of chromosomal abnormalities and subsequent miscarriages. Perinatal complications are mainly due to age (POR patients tending to be a little older), and less to the fact that women resort to assisted human reproduction techniques.

Regarding the increase in the number of comorbidities (hypertension, preeclampsia, gestational diabetes, premature births etc.) occurred in pregnancies obtained by IVF, this is a well-known fact, but this number is also increased in surrogate women who have suffered more frequently from these complications rather than in pregnancies obtained spontaneously in the same women, suggesting that the ovarian aging process would have this impact. There is no significant difference in the incidence of birth defects between IVF and naturally conceived infants, but some neonatal complications are more frequent in pregnancies resulted from IVF.

Older women (>40 years of age) may be at an increased risk for abnormalities in the course of labor, perhaps secondary to the physiology of aging, and this require further investigations, because these women seem to be at an increased risk for perinatal mortality, including stillbirth.

Poor responders are associated with significantly lower live birth rates compared to normal responders. However, the risk of adverse perinatal outcomes is not significantly different in both groups. This piece of information is useful for clinicians and women undergoing IVF who are at risk for poor response. There is also a need to further validate these findings by planning larger studies. ■

Conflict of interests: The authors declare no conflict of interests.

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