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Case Series

Overcoming poor ovarian reserve: a case report series of spontaneous conception after failed intracytoplasmic sperm injection

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ABSTRACT

This case report addresses the possibility of spontaneous conception in women with diminished poor ovarian reserve (POR) after multiple failure of assisted reproductive technology (ART) cycles, including intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI). Four cases were analyzed, including patients aged 31 to 41 years, each with a unique clinical profile for POR. These patients were infertile for durations of 5 to 12 years, as well as with other conditions like hypothyroidism and raised BMI. Recombinant FSH was used in all cases for ovarian stimulation, but the outcome was suboptimal with poor oocyte retrieval rates and fertilization failure. The cumulative follicle-stimulating hormone (FSH) dose used in patients ranged from 1875 IU to 3000 IU. This strategy produced a low yield of oocytes, most of which were immature or failed to fertilize. Remarkably, all four patients subsequently conceived spontaneously and gave birth to healthy babies without additional ART treatments, despite the difficulty encountered in the ART cycles. The observation that spontaneous conception was successful in these complicated cases underscores the need for further studies into the mechanisms underlying such events to occur, especially in patients who have had multiple failure with ART. This case report underscores the merit of individualized treatment strategies and continued investigation into the determinants influencing fertility in women with POR.

Keywords: Poor ovarian reserve, Infertility, Ovarian stimulation, Assisted reproductive treatment, Spontaneous conception

INTRODUCTION

Infertility remains an imperative condition in reproductive medicine, especially among patients with POR. The success of harvesting mature oocytes and achieving fertilization is usually thwarted by restricted ovarian response to stimulation protocols.

The introduction of ART has significantly offered varied treatment modalities; however, in POR patients, the outcome remains suboptimal despite intense gonadotropin stimulation. POR is attributed to a range of causative factors such as advanced maternal age, metabolic disorders, and endocrine dysfunctions, making the treatment modalities more complex.[1,2]

The conventional method in ART to maximize oocyte production is through purposeful ovarian stimulation (COS) with recombinant FSH (rFSH). Poor ovarian responders tend to have a suboptimal gonadotropin response, with reduced oocyte retrieval rates and reduced likelihood of successful fertilization.[3,4] Even with ongoing studies on various methodologies and adjunctive medications to maximize outcomes and stimulate ovaries, treatment of POR remains difficult. ART results in patients with POR remain substantially lower compared to those with normal ovarian reserve, even when using high-dose stimulation protocols.[5]

This series of cases describes four patients who underwent COS with rFSH and have variable degrees of POR. The cases illustrate a variety of presentations, including co-

morbid medical conditions like hypothyroidism, history of previous failed ART cycles, and BMI (Table 1). Notably, all four patients conceived spontaneously, challenging traditional assumptions regarding infertility prognosis, in spite of their suboptimal ovarian response and history of previous ART failure. This phenomenon provokes thoughtful questions regarding the limitations of ART and the potential for spontaneous conception in women who have been previously categorized as poor responders.

CASE SERIES

Case 1

A 31-year-old female patient (BMI: 41) presented with a five-year history of primary infertility, which had arisen despite normal menstrual cycles. Initial evaluation found hypothyroidism (TSH: 16.42 µIU/mL), which was treated successfully, along with a profoundly depleted ovarian reserve (AMH: 0.2 ng/mL, AFC: 2). After a failed attempt at IUI, the patient underwent ovarian stimulation with recombinant FSH (rFSH; cumulative dose: 2175 IU). Although four follicles were observed to mature, ovulation was induced using Decapeptyl 0.2 mg and Ovitrelle 250 µg; however, no mature oocytes were observed, necessitating cycle cancellation. The patient was then started on a course of dehydroepiandrosterone (DHEA) and multivitamin supplements for purpose of enhancing ovarian function. Interestingly, she conceived spontaneously within 1 month. The pregnancy course was uneventful, ultimately culminating in a full-term live birth.

Case 2

A 38-year-old female (BMI: 30.51) had a history of secondary infertility for 12 years and spontaneous abortion. Her menstrual cycles were regular but had low ovarian reserve (AMH: 0.7 ng/mL, AFC: 6). Six follicles grew on stimulation with 2250 IU of rFSH. Ovulation was induced by Decapeptyl 0.2 mg and Ovitrelle 250 µg, and four oocytes were retrieved, three of them being mature (MII) and successfully fertilized. One high-quality embryo (4 BB) was cryopreserved on day 5. The follow-up frozen embryo transfer (FET) was unsuccessful. She continued DHEA and coenzyme Q10 supplementation. However, she became pregnant spontaneously 2 months later. Pregnancy was uneventful and led to a healthy live birth.

Case 3

This case was a 41-year-old female (BMI: 23.76) with primary infertility of five years and normal menstrual cycles. She had a history of hypothyroidism and was found to have severely depleted ovarian reserve (AMH: 0.43 ng/mL, AFC: 5). After two failed IUI cycles and two failed ICSI cycles, she underwent another stimulation cycle with 1875 IU rFSH. This led to the development of ten follicles, five of which yielded oocytes; two reached MII stage. Only one embryo fertilized and was cryopreserved on day 5 (4AA), but embryo transfer did not result in pregnancy. She was on adjunctive therapy with DHEA and coenzyme Q10. She conceived spontaneously later and the pregnancy continued uneventfully to term, resulting in a healthy live birth.

Case 4

A 31-year-old woman (BMI: 43.81) had a nine-year history of infertility and a history of seven cycles of failed IUI. She had normal menstrual cycles, low ovarian reserve (AMH: 0.3 ng/mL, AFC: 5), and an endometrial polyp, which was treated by hysteroscopic resection to enhance uterine receptivity. She was then undergoing COS with a total of 3000 IU of rFSH. Three follicles developed, and ovulation was induced with Decapeptyl 0.2 mg along with Ovitrelle 250 µg. Ultimately, only one oocyte was retrieved, which achieved maturation (MII) but was unable to accomplish fertilization. After multiple ART failures, she became pregnant spontaneously. The pregnancy was normal and culminated in a full-term live birth.

Table 1: Clinical characteristics and ART outcomes of presented cases.

Parameters	Case 1	Case 2	Case 3	Case 4
Age (in years)	31	38	41	31
BMI (kg/m²)	41	30.51	23.76	43.81
Infertility duration (in years)	5	12	5	9
Type of infertility	Primary	Secondary	Primary	Primary
Menstrual cycle	Regular	Regular	Regular	Regular
AMH (ng/ml)	0.2	0.7	0.43	0.3
Antral follicle count (AFC)	2	6	5	5
Associated conditions	Hypothyroidism	None	Hypothyroidism	Endometrial polyp
Previous ART failures	1 IUI	1 FET	2 IUI, 2 ICSI	7 IUIs, multiple ART cycles
Total rFSH dose (IU)	2175	2250	1875	3000
Number of follicles developed	4	6	10	3
Triggering agents	Decapeptyl 0.2 mg + Ovitrelle 250 mcg	Decapeptyl 0.2 mg + Ovitrelle 250 mcg	Decapeptyl 0.2 mg	Decapeptyl 0.2 mg + Ovitrelle 250 mcg

Continued.

Parameters	Case 1	Case 2	Case 3	Case 4
Oocytes retrieved	0	4	5	1
Mature (MII) oocytes	0	3	2	1
Fertilized oocytes	0	3	1	0
Embryo development	None	1 blastocyst (4 BB)	1 blastocyst (4 AA)	None
Embryo transfer outcome	-	Failed FET	Failed FET	-
Adjuvant therapies	DHEA, multivitamins	DHEA, CoQ10	DHEA, CoQ10	DHEA, CoQ10
Spontaneous conception	Yes	Yes		Yes
Pregnancy outcome	Term live birth, no complications	Term live birth, no complications	Term live birth, no complications	Term live birth, no complications

DISCUSSION

The cases presented demonstrates the clinical challenges with treating patients with POR undergoing ART. Despite varied stimulation protocols and significant amounts of rFSH, outcomes in the cases were still poor with respect to oocyte retrieval, maturation, and fertilization highlighting the capricious nature of ovarian physiology among patients with POR. In case 1, the patient, who was the youngest at 31 years, had a highly elevated BMI which has been associated with changed endocrine function, lowered follicular responsiveness to gonadotropins and untreated hypothyroidism at baseline both of which are known adverse factors affecting ovarian stimulation outcomes.[6] The very low AMH level (0.2 ng/mL) further worsened the case, pointing to a lower follicular reserve. Despite a cumulative dose of 2175 IU of rFSH and appropriate ovulatory triggering, no mature oocytes were achieved, consistent with available literature. Interestingly, the patient subsequently achieved spontaneous conception, suggesting the existence of residual reproductive potential not fully captured under the pharmacological regime of ART.

Case 2 was a 38-year-old female with 12 years of secondary infertility, moderately elevated BMI and relatively better AFC with low AMH. Following stimulation, four oocytes were retrieved, three of which matured and fertilized well. Although the day 5 (4 BB) blastocyst did not result in pregnancy on frozen embryo transfer, the ability to form a viable embryo proves that oocyte quality is not always directly correlated with ovarian reserve markers. Her subsequent natural conception also supports the hypothesis that some patients possess latent fertility potential even after long-standing infertility and ART failure.

Case 3 illustrates the significant effect of advanced maternal age on ART success. Remarkably, despite an AFC of 5 and successful folliculogenesis, only five oocytes were retrieved, of which only two made it to the MII stage. The one 4AA blastocyst formed did not result in a successful pregnancy. The outcome in this case is in agreement with published literature indicating that maternal age has a strong correlation with reduced oocyte quality, chromosomal abnormalities, and reduced embryonic competency, even with sophisticated techniques such as ICSI.[7] This illustrates that despite ovarian stimulation that can produce follicles, the inherent quality of oocytes tends to dictate ART failure in older women.

Case 4 was a young patient but with severe obesity and long-standing infertility with seven unsuccessful IUI attempts. Following hysteroscopic polypectomy and a vigorous stimulation regimen, only a single MII oocyte was recovered, which failed to fertilize. Severe obesity was likely central to this case and caused endocrine dysregulation, oxidative stress, and altered mitochondrial function, all of which are detrimental to oocyte competence and endometrial receptivity.[8] This shows that young age alone is not a safeguard against ART failure in the presence of severe metabolic and reproductive pathology.

A particularly compelling and consistent observation across all four cases is the occurrence of spontaneous conception culminating in successful term pregnancies following failed ART cycles. This paradoxical-appearing outcome challenges closer scrutiny of possible underlying mechanisms. First, it is progressively clear that the supraphysiological hormonal milieu created by COS carries the unforeseen risk of compromising competence of the oocyte and receptivity of the endometrium, disrupting the intricate molecular and temporal synchrony required for optimal implantation of the embryo. This iatrogenic disruption of the per-implantation milieu may actually thwart, rather than facilitate, the likelihood of conceiving in some patients. Second, the psychophysiological effect of failed ART tends to cause individuals to make lifestyle modifications, including better nutrition, lower stress levels, and compliance with medical therapies, factors that synergistically may reinstate a more favorable endocrine and metabolic profile conducive to natural conception. Third, therapeutic procedures performed during the course of ART cycles, such as hysteroscopic correction of intrauterine pathologies, optimization of thyroid status, and subtle priming of the ovaries, may have aggregate effects that extend beyond the treatment interval. These treatments

may reset the reproductive axis or condition the uterine environment, facilitating spontaneous conception in a subsequent natural cycle. All of these observations collectively highlight the importance of taking a holistic and individualized treatment approach to infertility management, one that respects the interplay among iatrogenic effects, global health, and the inherent potential for reproductive recovery.

CONCLUSION

These cases contradict the conventional paradigm that ART is the sole route to motherhood for women with POR. In the presence of suboptimal COS response and serial failure of ART, all the patients ultimately experienced spontaneous conceptions with live term births. These cases bear witness to the inherent, though uninterpretable, reproductive potential that still exists in some women in spite of highly compromised ovarian reserve and adverse clinical predictors. Moreover, these cases reaffirm the necessity for future prospective studies to illuminate the biological, hormonal, and environmental factors controlling spontaneous conception after ART. Not only might this knowledge optimize patient selection and prediction, but it also might direct the development of more physiologically responsive stimulation protocols with minimal iatrogenic interference in oocyte and endometrial quality.

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