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Successful twin live birth following a two-step embryo transfer in a patient with poor ovarian reserve: a case report

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Abstract

Globally, the prevalence of infertility ranges from 8 - 12%, but in Sub-Saharan Africa, it is 20 - 32%. The advent of assisted reproductive technology brought hope and has become a huge solution to the social and public health challenge of infertility. However, infertile women with poor ovarian reserve remain a frustrating dilemma to fertility experts worldwide. We report the case of a 32-year-old poor ovarian responder who was successfully treated with in-vitro fertilisation followed by two-step cleavage-stage and then blastocyst-stage embryo transfers in Ghana that resulted in twin live birth.

Keywords: in-vitro, fertilisation, poor, ovarian, response, consecutive, embryo-transfer, twins, Ghana

INTRODUCTION

Globally, the prevalence of infertility ranges from 8 to 12%. It affects over 180 million couples in developing countries, with a prevalence of 20 − 32% in Sub-Saharan Africa (SSA) [1]. The social stigma associated with childlessness in Africa gives rise to significant psycho-emotional problems and, in some cases, social isolation [1]. The advent of assisted reproductive technology brought hope and has remained a great solution to this global social and public health challenge of infertility. Since the birth of the first in vitro fertilisation baby in 1978, the practice has spread worldwide [2]. Unfortunately, areas of the world with the highest rates of infertility often have poor access to assisted reproductive techniques (ARTs) [3]. In vitro fertilisation (IVF) treatment has been performed in Ghana for nearly three decades, but there is limited data on the use of two-step consecutive embryo transfer in our setting. Poor ovarian response refers to the situation where less than 3 − 5 dominant follicles develop by the time of human chorionic gonadotropic (HCG) trigger injection or retrieving below 3 − 5 oocytes following standard ovarian stimulation [1]. This case report presents the success story of this uncommon practice and reviews existing literature on this potentially viable option for women with a poor ovarian reserve and few embryos.

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Case Report

A 30-year-old para 1+1 with 4-year secondary infertility presented at a fertility centre on 17th June 2019. The patient had been treated the previous year for hyperprolactinaemia with cabergoline. She attained menarche at 15 years and had regular monthly cycles during which she bled for five days. Her clinical examination findings were unremarkable, and she had a normal body mass index. She had a normal-sized, anteverted uterus with two tiny anterior intramural fibroid nodules. Her baseline hormonal assay was normal to save a low serum anti-mullerian hormone (0.41 nanogram/millilitre). A saline infusion sonohysterogram revealed a normal endometrial cavity and bilateral patent tubes. Her 40-year-old husband had a 24 million/ml sperm concentration with 10% active linear movement and 4.0% normal morphology. She had a long protocol treatment cycle involving down-regulation with 3.6 mg of goserelin. This was followed by 15 days of daily follicle-stimulating hormone (FSH) injections that yielded three follicles measuring 16 -20 mm at the time of trigger of HCG 10,000 international units, followed 36 hours later by an ultrasound-guided oocyte retrieval (17th December 2019)

at which two oocytes were obtained. Intracytoplasmic sperm injection (ICSI) was done, both were fertilised, and one blastocyst resulted on day 5, which was vitrified. Antioxidant and multivitamin supplementation was administered for three months, and the treatment cycle was repeated.

This second cycle followed a similar treatment protocol, yielded four (4) follicles measuring 16 – 20.6 mm after 15 days of FSH had a trigger HCG, and oocyte retrieval yielded three (3) oocytes. Luteal support was provided with twice daily vaginal progesterone 400 mg. One day post-ICSI, two oocytes got fertilised, and one embryo cleaved the next day. A day-2 single cleavage-stage embryo transfer (ET) was done under ultrasound guidance. The embryo was placed close to the fundus. Three days later, the frozen blastocyst from the first cycle was thawed, and a hatching blastocyst (Grade 5AA) transfer was done sequentially by placing the embryo approximately 1-2 cm distal to the fundus on 8th June 2020. She was continued on luteal phase support, and a 154 test performed on day 14 post the first ET was 1,600 iu/l. Her first transvaginal ultrasound scan on 9th July 2020 revealed intrauterine viable triplet gestation with cardiac activities and crown-ramp lengths (CRL) of 7 weeks 0 days, 6 weeks 6 days, and 6 weeks 2 days. Fetal nuchal translucency (NT) measurements at 12 weeks were 1.2 mm, 1.2 mm and 1.3 mm, respectively, with all triplets having confirmed nasal bones. Placentation was tri-amniotic dichorionic, cervical length was 45 mm, and no fetal chromosomal soft markers were detected. The first trimester was occasioned with severe nausea and vomiting, for which she was admitted on two occasions for rehydration and parenteral anti-emetic therapy. She had a prophylactic cervical cerclage stitching done at 13 weeks.

A fetal anomaly scan at 21 week of pregnancy showed triplet-1 had grossly normal anatomy, triplet-2 appeared grossly smaller, measuring bi-parietal diameter (BPD) at 18 weeks, femur length (FL) 17 weeks 6 days, abdominal circumference (AC) 17 weeks 3 days, while triplet-3 showed an enlarged right atrium, abnormal implantation of tricuspid valves and some nuchal edema suggestive of Ebstein anomaly with a possible Turner syndrome. The couple was counselled on the findings, and the pregnancy continued with regular antenatal monitoring. She subsequently received regular antenatal follow-up care with routine prenatal multivitamins, iron and calcium supplements. At 27 weeks, there was the demise of the triplet-3, which was managed conservatively with two-weekly ultrasound scans that monitored the growth and well-being of the other fetuses. The remaining two carried on till 34 weeks 3 days when there was a spontaneous rupture of membranes. The intramuscular steroid was administered, and an emergency caesarean section on account of prolonged secondary infertility and successful IVF twin pregnancy delivered two live neonates (both male) with birth weights of 1.73 kg and 1.49 kg, respectively. Both neonates were admitted to the neonatal intensive care unit for six days for triplet-1 on account of prematurity and 11 days for triplet-2, who were managed for respiratory distress syndrome and neonatal sepsis. Both babies are currently well and attaining expected developmental milestones.

DISCUSSION

Globally, despite significant progress in advancing the effectiveness and success of IVF treatments, management of poor ovarian response has remained a challenge that frustrates both patients and fertility experts. Approximately 25% of patients undergoing ovarian stimulation have been found to be poor ovarian responders (PORs) [4]. Following standard ovarian stimulation, recruiting below 3-5 dominant follicles on the day of HCG injection or retrieving fewer than 3-5 oocytes constitute a ‘poor response’ [1]. This resulted in cycle cancellation and was associated with a significantly diminished probability of pregnancy. Currently, ovarian reserve tests, including basal FSH, estradiol, anti-mullerian hormone (AMH), inhibin-B, antral follicular count (AFC), ovarian volume, ovarian vascular flow, ovarian biopsy and multivariate prediction models, have little clinical value in predicting ovarian response [1]. This evidence suggests that AMH and AFC are the most reliable predictors [5]. The patient, in our case, had a low serum AMH and subsequently poor ovarian response in both cycles.

European Society of Human Reproduction and Embryology (ESHRE) defines poor response in IVF as a minimum of two of the three criteria: (i) advanced maternal age or any other risk factor for a poor ovarian response, (ii) previous POR, (iii) abnormal ovarian reserve test (ORT). Two episodes of POR after maximal stimulation categorise a patient below 35 years as a poor responder [6]. Our patient was below 32 years but responded poorly in both cycles. Increasing evidence demonstrates a significant association between oocyte number and cumulative live birth rates [7]. Various strategies have therefore been suggested to manage poor responders, including dual-stimulation in one ovarian cycle, oocyte-pooling, and the use of donor oocytes. The concept of consecutive cleavage-stage transfer followed by blastocyst transfer in the same cycle has also been experimented on. However, a consensus on the most acceptable, beneficial and cost-effective approach remains unreached [7]. Our patient was treated with the consecutive transfer of cleavage and blastocyst-stage embryos successfully. Ashkenazi et al. [8] found no difference in implantation or pregnancy rates and concluded that the double (consecutive) transfer of early embryos and blastocyst(s) showed no advantage over the traditional early transfer, as the second transfer may interfere with implantation [8]. Another study examined outcomes when a two-step (consecutive) embryo transfer procedure in which a single cleavage-stage embryo was transferred on day 2, followed by a single blastocyst

transfer on day 5. Their results showed that pregnancy and implantation rates in the two-step group were significantly higher than in the control group. They concluded that the two-step embryo transfer might be an effective option for patients with insufficient embryos [9], as was in our case. Similarly, Yazbeck et al. [10] also found that the live birth rate was significantly higher in the two-step embryo transfer group than in the single day-2/3 transfer group. It also prevented cycle cancellation when embryos failed to reach the blastocyst stage [10]. While there is an increasing shift toward blastocyst transfer, proponents of day-2/3 embryo transfer argue that it minimises embryo wastage and cycle cancellation from failure to reach the blastocyst stage [11]. A lower cumulative live birth rate following blastocyst transfer may result from embryos not attaining the blastocyst stage, leading to cycle cancellation [11]. In our case, only one of the two embryos formed a blastocyst, it was frozen, and the fresh (second) cycle resulted in a single day-2 embryo that was transferred and both implanted successfully. Blastocyst transfer is thought to provide an enhanced embryo-endometrium synchronisation which closely mimics the natural conception process, thereby increasing the chances of implantation [13].

Available evidence suggests that blastocyst transfer improves the odds of transferring a viable embryo without necessarily guaranteeing euploidy of blastocysts [14]. Our second step of embryo transfer was a blastocyst, and this was implanted successfully, indicating that it was viable. Human embryonic genome activation occurs on Day 3, without which the embryo is unlikely to survive or implant. Prolonging the duration of embryo culture to the blastocyst stage may therefore enable the identification of embryos with genomic activation. However, insisting on the blastocyst stage, embryo transfer risks losing embryos that might not survive extended culture but could survive in-vivo if transferred earlier. The success in our case presented may have been derived from the cumulative advantages of both stages of embryo transfer. Our patient had a preterm delivery of low birth weight (growth-restricted) twins at 34 weeks. This is consistent with reports from numerous studies and a meta-analysis that singletons and twins born after IVF are associated with an increased incidence of low birth weight and preterm birth [16].

Conclusion

Our success story of two-step consecutive embryo transfer indicates that poor responders could potentially benefit from this strategy to optimise assisted reproductive technology (IVF/ICSI) treatment outcomes and offer hope of live births in this patient population.

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Consent to publish

All authors agreed to the content of the final paper.

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Competing Interests

No potential conflict of interest was reported by the authors.

Author contributions

All authors contributed in developing the concept, drafting and reviewing the manuscript all through till final submission.

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Availability of data

Data is available upon request to the corresponding author.

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