Case Report

Live Birth after Rescue *In vitro* Maturation–intracytoplasmic Sperm Injection in Type 1 Diabetes, Polycystic Ovary Syndrome Patient Using Clomiphene–antagonist Protocol

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Abstract

Infertility in patients with polycystic ovary syndrome (PCOS) associated with diabetes leads to challenging situations seeking alternative treatments. *In vitro* maturation (IVM) followed by intracytoplasmic sperm injection (ICSI) could overcome the challenges with promising pregnancies in such patients. In the treatment of a 32-year-old diabetic woman who also had PCOS, single immature oocyte was retrieved. Rescue IVM followed by ICSI yielded a grade 1 day 3 embryo which on transferring resulted in pregnancy and a healthy infant was delivered. Rescue IVM–ICSI could help in achieving pregnancy and live birth. Stimulation involving clomiphene and gonadotropin-releasing hormone antagonist is an effective and patient-friendly protocol for women with PCOS and diabetes and also for poor responders.

Keywords: *Clomiphene, diabetes, in vitro fertilization, in vitro maturation, polycystic ovary syndrome*

Introduction

Infertility is an increasing problem in both developed and developing countries, with up to one in six couples requiring treatments.[1] Polycystic ovary syndrome (PCOS) is present in almost one of every four women with type 1 diabetes.[2] The major risk factors for infertility related to diabetes mellitus are hyperandrogenism and PCOS in women.

Conventional stimulation protocol in spite of its higher pregnancy rates increases the risk of ovarian hyperstimulation syndrome (OHSS), multiple gestations, etc., The need for simpler protocols with low risks, low cost, and maximum singleton pregnancies could be achieved by modifying stimulation protocols.

The present case highlights the successful treatment for infertility of type 1 diabetic PCOS patient using clomiphene–antagonist protocol followed by rescue *in vitro* maturation (IVM)–intracytoplasmic sperm injection (ICSI) procedures.

Case Report

A 32-year-old woman and her 35-year-old husband presented in 2016 with a 5-year history of primary infertility and two failed attempts of conventional *in vitro* fertilization (IVF)/ICSI. The female was a type 1 diabetic patient and the existence of bilateral polycystic ovaries was discovered by ultrasound examination. The findings of hysteroscopy were normal and the hormonal parameters were as expected (follicle-stimulating hormone [FSH]: 7.40 mIU/ml, luteinizing hormone: 9.89 mIU/ml, and prolactin: 15.84 ng/ml). The semen analysis showed normal semen parameters. The chromosomal analysis showed normal male and female karyotypes.

The female started an IVF program in which she was given clomiphene tablets orally for the first 5 days, and from day 7 to 13, 150 IU of recombinant FSH was administered subcutaneously. From day 8 to 14, 150 IU of menotropin and from day 10 to 14, 0.25 mg of cetrorelix were administered subcutaneously. The patient was evaluated continuously, and when leading follicle of 20 mm (only follicle) on day 15 was observed,

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How to cite this article: Sankari S, Elanchezhian M, Selvamani D, Nagarajan M, Gopikrishnan D. Live birth after rescue *in vitro* maturation–intracytoplasmic sperm injection in type 1 diabetes, polycystic ovary syndrome patient using clomiphene–antagonist protocol. J Hum Reprod Sci 2018;11:75-8.

Access this article online

Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/jhrs.JHRS_65_17

250 μg recombinant human chorionic gonadotropin-alpha was administered subcutaneously for triggering. After 36 h, one oocyte was collected which was found to be immature [Figure 1] (germinal vesicle stage) when denuded. The denuded oocyte was subjected to rescue IVM for 25 h (until the extrusion of the first polar body) in culture medium (Vitrolife®, Goteborg, Sweden). The matured oocyte [Figure 2] (metaphase II) was injected with the husband sperm after processing the semen by swim-up method. Two pronuclei [Figure 3] were seen 18 h post-ICSI and a grade 1 embryo [Figure 4] was generated on day 3. A successful pregnancy was achieved. Fetal cardiac activity was noted from 6 weeks' gestational age. The patient developed gestational hypertension which along with the diabetes was managed optimally with antihypertensives and insulin, respectively. As the patient developed preeclampsia at 32 weeks, pregnancy was terminated by a safe cesarean section and a healthy male infant (birth weight 2200 mg) was delivered.

Discussion

Diabetes mellitus in female is associated with disturbed ovarian function, but strict metabolic control may encourage the resumption of ovulation and allow ovarian stimulation for assisted reproductive technology.[3] The protocol involving clomiphene citrate (CC), human menopausal gonadotropin (hMG), and cetrorelix helps women with PCOS as the incidences of moderate and severe OHSS are reduced.[4] It is evident that CC/hMG protocol has resulted in a significantly lower incidence of severe OHSS when compared to GnRA long protocol.[5] Moreover, it was also suggested that protocol involving gonadotropin-releasing hormone (GnRH) antagonist plus mild doses of exogenous gonadotropins and oral compounds such as CC or aromatase inhibitors was more patient friendly.[6] Similarly, a chronic low-dose regiment of gonadotropins in PCOS patients has completely eliminated the troublesome complications of OHSS and also reduced the multiple pregnancy rates to a reasonable minimum.[3,7] Therefore, modifications in stimulation

Figure 1: Obtained germinal vesicle oocyte after denudation

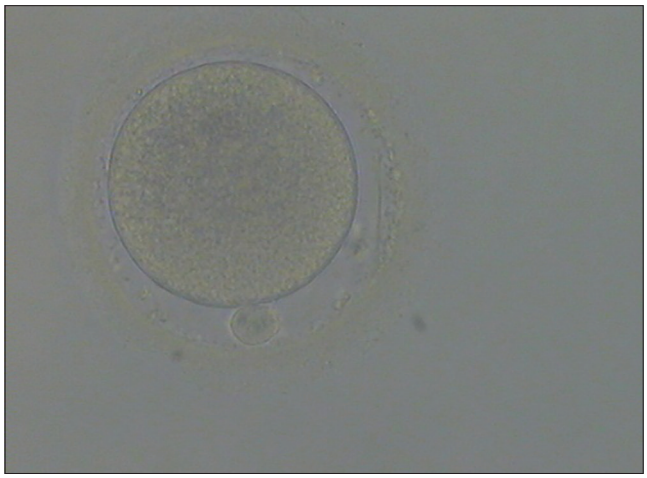

Figure 2: MII oocyte after *in vitro* maturation

Figure 3: Two pronuclei stage

Figure 4: Transferred day 3 embryo

protocol for patients with PCOS can overcome the risks of OHSS, and the side effects are less as the medication is administered only for a few days.

A pregnancy using immature oocytes in nonstimulated cycles was achieved, in 1994, where the IVM period was 43–54 h.[8] In another study, oocytes retrieved using nonstimulated cycles were *in vitro* maturated for 24–48 h.[9] Hence, IVM requires the maturation of oocytes in the laboratory for ≥24 h before insemination, and there is a need for monitoring maturity of immature oocytes periodically during the maturation time.[10,11]

Characteristic features of PCOS such as hyperandrogenism, obesity, insulin resistance, and metabolic abnormalities may contribute to the increased risks of obstetrical and neonatal complications, and those patients are prone to pregnancy-induced hypertension, preeclampsia, and preterm birth suggesting cesarean section.[12,13]

There are many reports on successful live births using IVM–IVF procedures that have ~ 50% maturation rates and ~ 60% fertilization rates, but the number of live births was comparatively low.[14-18] A pregnancy rate of 27.1% was achieved after IVM–IVF by transferring 6.3 embryos per patient.[19]

Conclusion

Rescue IVM–ICSI is an important tool at certain circumstances in the treatment of women with PCOS and diabetes which can result in pregnancy and live birth. It is also acceptable that the modified approach involving GnRH antagonist, CC, and hMG is an effective ovarian stimulation protocol which also holds good with poor responder women and serves as a patient-friendly protocol as duration of gonadotropin injection is shorter.[20]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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