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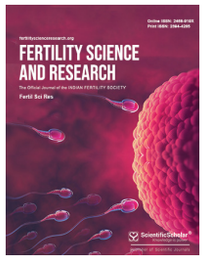

Case Report

Ectopic Pregnancy in In-Vitro Fertilisation - Embryo Transfer in a Patient with Natural Killer Cell Imbalance and Endometriosis

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ABSTRACT

The incidence of ectopic pregnancy (EP) worldwide is 1–2% of all pregnancies. Endometriosis poses an additional risk for EP; the odds ratio has been reported as 2.66 (95% confidence interval [CI] = 1.14–6.21, p = .02). However, the mechanisms are not fully understood. Natural killer cells (NK cells) have also been proposed to play a role in ectopic implantation. Here we present a case of a 32-year-old female who presented with a history of primary infertility and three failed IVF cycles in the past. The patient had an incidental ovarian endometrioma of 3 x 4 cm and a high level of serum NK cells. Alpha-thymosin therapy for 2 weeks was given in view of recurrent implantation failure. Subsequently, the patient underwent two cycles of frozen embryo transfer. In both the cycles, the patient tested positive. The first resulted in a blighted ovum and the second in ectopic conception. The ectopic conception was managed medically. In this article, we discuss the possible role of ovarian endometrioma and serum NK cells.

Keywords: Ectopic pregnancy in IVF, Endometriosis, Infertility, In-vitro fertilization, NK-cells and infertility, Recurrent Implantation failure

INTRODUCTION

Ectopic pregnancy is a major cause of morbidity and mortality throughout the world. It affects 1–2% of all pregnant women.[1] In the general population, there is an increased risk of ectopic pregnancy in patients with endometriosis. The increased risk of ectopic has been supported by a recent meta-analysis, which reported an increased association with endometriosis in an ectopic pregnancy with an odds ratio of 2.16–2.66.[2] ACOG in 2019 also reported an increased incidence of ectopic pregnancy in endometriosis with a relative risk of 1.46 and an absolute risk of 1.8% in women with endometriosis vs. 0.8% in patients without endometriosis (more than twice).[3]

The pathophysiology behind the increased risk is not yet fully understood. This increased incidence is owed to multiple factors. These include altered relations between tubes and ovaries, either due to adhesions or ovarian endometriomas, endometriotic deposits on the tube changing its physiology, and altered endometrial receptivity. The endometriotic deposits affect the cilia and hamper their movements to propel the embryo towards the endometrial cavity. Another possibility is conflicting signals from the uterine and fallopian tube epithelium. There is competition between the signals from the endometrium and the fallopian tube. The blastocyst

receives stronger signals (secondary to enhanced release of cytokines and chemokines) from the fallopian tube and thus gets implanted in the fallopian tube.[1]

The endometrial tissue fragments that reflux into the fallopian tubes and the abdominal cavity form endometrial deposits on the abdominal organs. The refluxed endometrial tissue can get arrested in the fallopian tube and start to generate endometrial tissue in the area. Such a segment of endometrial tissue responds normally and proliferates under the effect of oestrogen and progesterone. The ovum or embryo, due to its size, may not be able to travel through and get arrested in the fallopian tube. The embryo may also perceive this ectopic endometrium as fertile ground for implantation and hence get implanted in the same area, leading to ectopic pregnancy.[4]

Adrenomedullin (ADM) is responsible for the proper transport of the embryo through the tube. ADM also has anti-inflammatory properties. In patients with endometriosis, there is a decrease in the level of ADM, thus affecting the proper transport of the embryo and excessive inflammation leading to ectopic pregnancy.[1]

It has also been seen that at the site of implantation in the fallopian tube in patients with endometriosis, there is an increase in pro-inflammatory cytokines like TNF-alpha, interleukins-6 and 8, beta-catenin, and B-cell activation factor (BAFF). There also occurs an increase in the expression of PROK receptors at the site of implantation. This increase in an inflammatory environment favours blastocyst adhesion and invasion into the tube.[1]

Immune cells have a significant role in endometrial receptivity and implantation as they promote the attachment of the embryo to the endometrium, improve uterine vascular adaptation, modulate trophoblast invasion, regulate the maturation of decidual cells, and suppress response to paternally derived antigens.

NK cells occur both in the periphery and in the endometrium. These two differ in their cytotoxic potential, the peripheral NK cells being more cytotoxic. Decidual natural killer cells (NK cells) increase in the endometrium during implantation and the first trimester, potentiating the interaction between the embryo and the endometrium. However, they also interact with the trophoblast cells during implantation, preventing their deeper invasion by exerting their cytotoxic potential. In cases of recurrent implantation failure (RIF) or recurrent pregnancy loss (RPL), these may acquire cytotoxicity as that of peripheral NK cells, thus leading to failure of implantation or pregnancy losses. These uterine NK cells differ from those in the peripheral blood; therefore, performing an endometrial biopsy is justified compared to peripheral blood sampling.[5]

Implantation in humans is a pro-inflammatory mechanism. During the window of implantation, the uterine NK (uNK) cells increase in the endometrium and comprise 70–80% of the total leukocytes early into pregnancy as well. uNK cells also determine the fate of the embryo. A poor-quality embryo does not get implanted, and this is regulated by the uNK cells. Hence, the role of uNK cells is pivotal around the time of implantation and in early pregnancy.[6]

An imbalance in the NK cells alters the endometrial receptivity for the embryo. There occurs a change in the predominant NK cells locally in the endometrium, which in turn increases the cytotoxic behaviour of these cells and hampers implantation. This association, however, has not been studied in detail.In patients with endometriosis, the immature and cytotoxic NK cells are increased significantly in the endometrium, leading to failure of implantation. Hence, these patients may present with recurrent pregnancy loss or infertility.[6]

May-Tal *et al*. compared the clinical effect of endometrial NK cells and Tregs (regulatory T cells) on clinical pregnancy rate. It was observed that higher levels of endometrial Tregs and lower levels of $CD16^+$ NK cells (higher cytotoxic potential) are positive prognostic markers in frozen embryo transfer cycles.[6] Another study performed by Emma Guiliani *et al*. concluded that a higher proportion of $CD16^+$ NK cells, with or without endometriosis, are at greater risk of subfertility due to endometrial asynchrony for implantation.[7]

CASE REPORT

A 32-year-old female, married for 5 years, had been keen to conceive for 5 years. Two years after marriage in 2021, the couple sought treatment in Chicago, where they underwent preliminary tests that identified the primary cause to be male-factor infertility. Given this, IVF was planned for the couple. Upon further follow-up, an incidental endometrioma of 3 × 4 cm was identified on ultrasound, for which the patient did not receive any treatment as the patient was asymptomatic. Subsequently, the first IVF cycle was performed. 24 COCs were retrieved. Out of these, 14 fertilised and 8 embryos reached the day 5 blastocyst stage. Upon PGT analysis, 5 tested to be normal. Following this, 2 frozen embryo transfers (2 embryos transferred in each transfer; 1 remaining cryopreserved) were performed in 2021 and 2022, which failed. The couple was reviewed again, and the woman was diagnosed with high levels of serum NK cells (2130 cells/µl; normal range—78–470 cells/µl). For the same, the patient received treatment with intralipid infusion, methyl folate, and hydroxychloroquine. A second IVF cycle was performed when killer cells were reduced to normal. 18 COCs were retrieved, 8 embryos formed, and 5 tested normal

for PGT analysis. One frozen embryo transfer (2 embryos) was performed in 2022, which failed. The balance from the first and second embryo transfers was cryopreserved at the same centre.In 2023, the couple visited our clinic. Given recurrent implantation failure, the patient was administered alpha-thymosin therapy for 2 weeks. Following that, a third IVF cycle was performed, and 7 COCs were retrieved. 5 embryos reached day 5. The first embryo transfer was done in February 2024 with 2 day-5 blastocysts of 4AB and 3AB quality. It was successful; however, it ended in a blighted ovum. The second embryo transfer was a frozen cycle, which was performed after 2 months in April 2024. The embryos transferred were on day 5 with 4AA and 2AB quality. This time the patient had an ectopic pregnancy, which was diagnosed on TVS. The ectopic pregnancy was managed medically with methotrexate and followed by serum beta-HCG levels. Both cycles were frozen embryo transfers.

In both cycles, the technique was implantation at the site of MIP (maximum implantation potential) under transabdominal ultrasound guidance.

DISCUSSION

ART techniques carry a risk of ectopic pregnancy higher than the general population owing to variable factors. The primary factor to consider so that the risk of ectopic pregnancy is balanced is the predisposing factor in the patient. Secondly, we need to be wary about the technical factors that may play a role, like embryonic factors, the volume within the catheter, and the pressure with which transfer was performed. The secondary factors are nullified in the hands of an experienced clinician.

In the case discussed above, IVF was chosen as the treatment plan given long-standing infertility with endometriosis. The basal ultrasound scan was normal with no apparent uterine or tubal pathology that required treatment. The embryo transfers at our centre resulted in positive conception; hence, we believe it was the underlying deranged endometrial milieu that may have been the underlying cause of the occurrence of RIF and ectopic pregnancy. No other uterine or tubal factor could be attributed as a cause of ectopic. The role of NK cells cannot be commented upon clearly as the test was performed on serum and was reported to be normal prior to treatment at our centre. However, with the growing role of immune imbalance as contributory factors to RIF, diagnostic modalities, and immunomodulatory therapies, the testing for NK cells may be considered in selected groups of patients, especially RIF, as was the case here.

CONCLUSION

Endometriosis affects the endometrium or causes an immunological imbalance of the natural killer cells. When these factors are at play, intrauterine implantation may not be favoured leading to recurrent implantation failure. Since the NK cell testing was performed in peripheral blood and testing for uterine NK cells was not performed in the case discussed, its role is controversial.

Author contribution

AC: Details of the patient and review of literature; RB: Treating clinician and provision patient treatment.

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REFERENCES

1. Załęcka J, Pankiewicz K, Issat T, Laudański P. Molecular Mechanisms Underlying the Association Between Endometriosis and ectopic Pregnancy. Int J Mol Sci 2022;23:3490.
2. Yong PJ, Matwani S, Brace C, Quaiattini A, Bedaiwy MA, Albert A, *et al*. Endometriosis and Ectopic Pregnancy: A Meta-Analysis. J Minimally Invasive Gynecol 2020;27:352–61.
3. Farland LV, Prescott J, Sasamoto N, Tobias DK, Gaskins AJ, Stuart JJ, *et al*. Endometriosis and Risk of Adverse Pregnancy Outcomes. Obstet Gynecol 2019;134:527–36.
4. Hunter RH. Tubal Ectopic Pregnancy: A Patho-Physiological Explanation Involving Endometriosis. Hum Reprod 2002;17: 1688–91.
5. Zhang X, Wei H. Role of Decidual Natural Killer Cells in Human Pregnancy and Related Pregnancy Complications. Front Immunol 2021;12:728291.
6. Sauerbrun-Cutler MT, Huber WJ, Krueger PM, Sung CJ, Has P, Sharma S. Do Endometrial Natural Killer and Regulatory T Cells Differ in Infertile and clinical pregnancy patients? an analysis in Patients Undergoing Frozen Embryo Transfer Cycles. Am J Reprod Immunol 2021;85:e13393.
7. Giuliani E, Parkin KL, Lessey BA, Young SL, Fazleabas AT. Characterization of Uterine NK Cells in Women With Infertility or Recurrent Pregnancy Loss and Associated Endometriosis. Am J Reprod Immunol 2014;72:262–9.

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