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Successful pregnancy after administration of thymosin alpha-1 in a woman with recurrent implantation failure

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Abstract
Recurrent Implantation Failure (RIF) poses a significant challenge in the management of infertility. We report a novel approach using Thymosin alpha 1 (TA 1) in a 32-year-old female with unexplained RIF. Despite previous failed IVF attempts and various interventions, including endometriosis treatment, ovarian platelet rich plasma therapy and Oocyte Donor (OD)-ICSI cycles along with other adjuvant therapies such as intralipids, steroids, low molecular weight heparin (LMWH), Hydroxychloroquine (HCQ), still pregnancy remained elusive. Immuno-profiling revealed Type 1 T helper cells (TH1) dominance, leading to TA 1 therapy alongside Hormone Replacement Therapy (HRT). TA 1, known for immune modulation, was administered as 13 injections before embryo transfer. Patient achieved a successful pregnancy, indicating TA 1 potential in immune-mediated RIF cases. Thymosin alpha's safety and efficacy in pregnancy warrants further investigation through prospective trials for broader validation.

Keywords: Recurrent implantation failure (RIF), thymosin alpha 1 (TA1), Immune modulation, IVF failure

Introduction
According to the ESHRE good practice recommendations, Recurrent Implantation Failure (RIF) describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions [1]. Various factors contribute to RIF, including uterine abnormalities, sperm factors, genetic, hormonal, metabolic, thrombophilia, Immune dysregulation, endometrial receptivity, and embryo factors [2]. But almost 30% of RIF remains unexplained [3]. This paper discusses a pioneering case of RIF treated with Thymosin alpha 1 (TA 1), revealing immune modulation's potential in RIF.

Case Report
The patient, a 32-year female, has a history of primary infertility for 8 years and has undergone multiple unsuccessful IVF cycles despite various interventions for RIF. Her treatment history includes a diagnostic hysterolaparoscopy (DHL) procedure, endo-cystectomy, and adhesiolysis, followed by her first Ovum Pick-Up (OPU) procedure, which yielded 3 oocytes and 3 embryos formed on day 3. However, embryo development arrested by day 5, resulting in a failed cycle. In 2019, she underwent repeat DHL procedure with bilateral salpingectomy, and right oophorectomy due to endometriosis. Subsequent OPU procedure elsewhere failed to yield embryos. In 2022, she received left Ovarian Platelet-Rich Plasma (PRP) treatment elsewhere before undergoing a third OPU cycle and fresh embryo transfer (ET), resulting in a negative pregnancy test. Additionally, she underwent two frozen ET cycles with Oocyte Donor (OD)-ICSI, both unsuccessful. Endometrial Receptivity Array (ERA) testing elsewhere indicated post receptive status at 148 hours.
After these failed attempts, she sought treatment at our hospital. Comprehensive testing for APLA, immunological screening tests - Anti-thyroid peroxidase (TPO), Anti-thyroglobulin (TG), Endometrial CD 138 and couple karyotyping returned normal.

Our plan included OD-ICSI with Preimplantation Genetic testing for Aneuploidies (PGT A) to enhance success rates. We obtained 4 embryos - two euploid embryos, one with low DNA and the other non-biopsied. A fourth transfer was performed at our hospital with 2 day-5 embryos following ERA, with PRP administered twice and various adjuvants such as LMWH, intralipids, HCQ, Prednisolone, and G-CSF. Despite these efforts, the cycle failed. Immunological analysis of cytokines indicated elevated levels of Tumour Necrosis Factor (TNF) alpha and Interferon gamma, along with reduced levels of Interleukin 10 and Transforming Growth Factor-β (TGF-β), indicating a predominance of Type 1 T helper cell (TH1) activity. Consequently, we decided to implement TA 1 therapy. Subsequently, in a second cycle of OD-ICSI, we obtained 6 embryos and sent it for PGT-A. TA 1 treatment commenced concurrently with Hormone Replacement Therapy (HRT). We prescribed 3.2 mg of TA 1 on alternate days, amounting to 13 injections, and administered a final dose of 1.6 mg 48 hours prior to embryo transfer, considering TA 1's half-life and the thickness of the endometrium [4, 5]. subsequently, two euploid embryos were transferred during the 6th Frozen ET cycle. The patient achieved conception, evidenced by a positive serum beta hCG test, currently progressing with a single ongoing pregnancy at 15 weeks.

Discussion

In cases of RIF, the primary focus revolves around selecting euploid embryos for transfer and ensuring the transfer occurs during the implantation window with optimal endometrial thickness. However, there exists a significant cohort of patients experiencing unexplained RIF, which presents a perplexing challenge. The process of implantation, which involves guiding the blastocyst to attach to the endometrial lining, trophoblast cell invasion, and the repair of damaged endometrial tissue, is governed by proinflammatory cytokines (TH1 dominance) [6]. Yet, for sustaining pregnancy beyond the initial stages, creating an anti-inflammatory environment (TH2 dominance) becomes imperative [7, 8]. This shift is possibly associated with reduced Treg cell activity, potentially contributing to implantation difficulties and unexplained infertility. Thymosin alpha 1 (TA 1) has the potential to increase the Treg cells, making it beneficial in promoting a positive TH balance [9].

Diagnosing immune dysregulation in women experiencing RIF can redirect attention toward immune modulation, aiding in the attainment of a healthy pregnancy. Additionally, the altered peripheral and endometrial immune status observed in women with endometriosis might contribute to infertility, early pregnancy loss, and disrupted tissue homeostasis [10]. We identified TH1 dominance through immunoprofiling instead of TH2 dominance. Consequently, she received treatment with TA 1, which aids in immune modulation. TA 1 is a 28-amino acid peptide naturally found in the thymus, known for its ability to modify, enhance, and restore immune function. Research suggests that TA 1 could potentially improve outcomes in severely ill COVID-19 patients by repairing damage caused by lymphocytic immunity over activation and preventing excessive T cell activation. TA 1 therapy helps in modulating and partially normalizing T-lymphocyte numbers and function [11]. Women experiencing unexplained recurrent failed IVF treatments often exhibit a TH1 bias, which intensifies after hormonal manipulations during IVF. Comparing IFN-γ: IL-4 and TNF-α: IL-4 ratios pre-treatment with those at oocyte retrieval can provide valuable clinical insights, particularly considering that these ratios often increase in women experiencing recurrent IVF failure. [12]. The safety and effectiveness of Thymosin alpha 1 (TA 1) during pregnancy in cases of Recurrent Implantation Failure (RIF) are under investigation, with several ongoing trials. Existing literature confirms elevated maternal serum levels of TA 1 in viable pregnancies compared to lower levels in non-viable pregnancies [13].

As TA 1 is a naturally occurring hormone in pregnant women, external supplementation is not anticipated to result in adverse effects or fetal anomalies. However, it's worth noting that the last administered dose was 1.6mg, given 48 hours before FET, which exceeds 5 times the half-life of TA 1. [11].

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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