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Original Research Article

Efficacy of thymosin alpha-1 as an immunomodulatory adjuvant in patients with recurrent implantation failure: a real-world retrospective analysis

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ABSTRACT

Background: Recurrent implantation failure (RIF) remains a major challenge in assisted reproductive technology (ART), affecting approximately 10–15% of couples undergoing treatment. Immune dysregulation is considered an important contributor to implantation failure. Thymosin Alpha-1, an immunomodulatory agent, has shown promising results in difficult-to-treat infertility cases. This study evaluated the real-world effectiveness of Thymosin Alpha-1 as an adjuvant therapy in patients with RIF in an Indian clinical setting.

Methods: This retrospective, observational study was conducted at a private infertility center in India. Medical records of adult women aged over 30 years diagnosed with RIF over a one-year period were analyzed. All included patients received Thymosin alpha-1 (1.6 or 3.2 mg daily or on an alternate-day regimen) for a minimum of 118 days. Demographic characteristics, comorbidities, infertility-related conditions including polycystic ovary syndrome (PCOS), endometrial features, immunological parameters, treatment regimens and outcomes were evaluated.

Results: Most patients were aged 31–35 years (41.1%), followed by 36–40 years (25.6%). Thyroid disorders (5.6%) and diabetes (2.2%) were uncommon, while 82.2% had no comorbidities; latent tuberculosis was present in 13.3%. Anovulatory cycles were observed in 17.8% of patients and 71.1% had a thin endometrium. Immunological parameters showed marked variability, including mean CD16+56 natural killer cell counts of 175±103 cells/µl and mean TNF-α levels of 18.4±41.2 pg/ml. PCOS was identified in a subset of patients. All patients with RIF (n=90) who received thymosin alpha-1 therapy for at least 118 days demonstrated positive reproductive outcomes, regardless of dosing regimen.

Conclusions: Thymosin alpha-1 therapy was associated with encouraging outcomes in patients with RIF, supporting its role as an effective immunomodulatory adjuvant.

Keywords: Immunomodulatory, Infertility, Recurrent implantation failure, Thymosin alpha-1

INTRODUCTION

Advances in ART have enabled many couples with infertility to achieve successful pregnancies and have simultaneously enhanced the ability to detect early pregnancy loss. Despite these significant improvements in reproductive outcomes, a new clinical challenge has emerged: RIF.[1] RIF is a condition specific to patients undergoing ART. Despite its significant clinical relevance, no universally accepted definition of RIF currently exists. In general, the term is used to describe women who experience three consecutive unsuccessful in vitro

fertilization (IVF) cycles despite the transfer of good-quality embryos.[1,2] As per ESHRE working group on recurrent implantation failure, it is a clinical scenario in which repeated transfer of embryos deemed viable fails to result in a positive pregnancy test with sufficient frequency in a given patient to justify further diagnostic evaluation and/or therapeutic intervention.[3] The reported incidence of RIF varies widely, ranging from approximately 10-15% of couples undergoing ART.[1,2]

The exact cause of RIF is still unknown, but RIF is influenced by multiple factors, including uterine abnormalities, sperm quality, genetic and hormonal imbalances, metabolic disorders, thrombophilia, immune dysregulation, impaired endometrial receptivity and embryo-related factors.[4-6] Successful implantation depends on maternal-foetal immune tolerance, mediated by complex molecular and cellular interactions.[6] Trophoblast invasion triggers maternal immune recognition of foetal antigens, activating endometrial immune cells that regulate decidualization, vascular remodelling, epithelial attachment and immune responses. Immune populations such as innate lymphocytes, T cells, dendritic cells and macrophages are also associated with adverse pregnancy outcomes, including RIF.[6]

Given the growing evidence supporting an immunological basis for RIF, immunomodulatory therapies have been increasingly explored as adjunctive treatments in ART. [6,7] One such agent is Thymosin alpha-1, a naturally occurring thymic peptide known for its immunoregulatory properties. Thymosin alpha-1 is involved in the maturation and differentiation of T lymphocytes, enhancement of immune tolerance and modulation of cytokine production. Through these mechanisms, it is hypothesized to improve the immunological environment of the endometrium and facilitate successful embryo implantation.[6-8] Although the exact mechanism through which thymosin alpha-1 influences implantation remains incompletely understood, several clinical studies have suggested that immunomodulatory therapies may enhance implantation and pregnancy rates in women with RIF.[6,7]

These therapies are believed to restore immune balance at the maternal–fetal interface, thereby promoting endometrial receptivity and embryo survival. Immunomodulatory therapies have been shown to improve implantation outcomes in women with RIF, with some studies reporting significantly higher pregnancy rates.[6-9] However, the available evidence remains limited and heterogeneous and data regarding the effectiveness of thymosin alpha-1 in different populations are still evolving.[6-9]

In particular, evidence from the Indian population remains scarce and real-world clinical data evaluating its role as an adjunct therapy in ART are limited. Considering the increasing use of immunomodulatory approaches in reproductive medicine, further evaluation of their effectiveness in routine clinical practice is warranted. Therefore, this study was therefore undertaken to provide real-world evidence on thymosin alpha (Guficin alfa) as an immunomodulatory adjuvant in patients with RIF and its potential to improve implantation outcomes.

METHODS

This retrospective, observational study was conducted at a private infertility center (OURIVFANGELS, Nashik) in India. Records of patients treated for RIF from April 2024 to October 2025 were analyzed. The study evaluated the outcomes of Thymosin (Guficin alfa) as an immunomodulatory adjuvant in patients who had undergone ART.

Records of Adult women diagnosed with RIF, defined as failure to achieve a clinical pregnancy after at least three IVF/ICSI cycles with good-quality embryos, were eligible. Patients included were aged >30 years, had received Thymosin therapy (1.6 or 3.2 mg daily or on an alternate-day regimen) for at least 118 days and had complete medical records. Patients were excluded if they did not meet RIF criteria, received concurrent immunomodulatory therapies other than Thymosin, had incomplete therapy or had incomplete medical records. Data were collected retrospectively from medical records and included demographic details, clinical history, duration of infertility, prior IVF/ICSI cycles, associated pathologies, treatment details and clinical outcomes.

Data were summarized using descriptive statistics. Continuous variables were reported as means±standard deviations and categorical variables as frequencies and percentages. Associations between categorical variables were assessed using the Chi-square test. A p value<0.05 was considered statistically significant.

RESULTS

Records of 103 patients with RIF were initially extracted. Of these, 90 patients met the inclusion criteria and were analysed, while the remaining 13 were excluded due to incomplete medical records or incomplete therapy.

Baseline characteristics of the Recurrent implantation failure patients

A total of 90 patients meeting the study criteria were included. The mean age was 34.7±5.5 years. The mean body weight was 59.1±10.2 kg and the mean height was 156.4±5.5 cm, resulting in a mean body mass index (BMI) of 24.0±3.5 kg/m². The mean duration of infertility was 10.7±5.0 years (Table 1).

BMI, 26.7% were overweight and 4.4% were obese, while 2.2% were underweight. The duration of infertility varied, with 13.3% having ≤5 years, 40.0% having 6–10 years, 33.3% having 11–15 years and 13.3% experiencing infertility for more than 15 years (Table 2).

Association of age with infertility duration

In this study, we found that the Age was significantly correlated with infertility duration (χ^2=50.111, p<0.001), with increasing age associated with longer periods of infertility (Table 3).

Clinical characteristics

In this study, 5.6% had thyroid disorders and 2.2% had diabetes, while the majority (82.2%) had no comorbidities. Latent tuberculosis was present in 13.3% of patients. Anovulatory cycles were observed in 17.8% of the cohort. Endometrial evaluation revealed a thin endometrium in 71.1% of patients, with 28.9% having normal endometrial thickness (Table 2).

Immunological parameters

Baseline immunological profiles were assessed in subsets of the study population. The mean total leucocyte count was 9,443±10,633 cells/µl and the mean absolute lymphocyte count was 2,189±1,001 cells/µl. T-cell subsets showed a mean CD3 count of 1,690±709 cells/µl and a mean CD16+56 (natural killer cells) count of 175±103 cells/µl. Pro-inflammatory cytokine TNF-α levels averaged 18.4±41.2 pg/ml (Table 3).

In this study, the majority of patients (41.1%) were in the 31–35-year age group followed by 25.6% were 36–40 years, reflecting that RIF predominantly affected women in their early to mid-30s in this cohort, followed by 25.6% were in 36–40 years age group. Around 66% had normal

Diagnosis for the cause of infertility in Recurrent implantation failure

Around 44% had no definitive diagnosis established. Infertility without other specified conditions accounted for 26.7% of cases. Additional diagnoses included ovarian cysts (10.0%), endometrial cysts (6.7%), polycystic ovary syndrome (PCOS) (4.4%), infertility concomitant with PCOS (3.3%), fallopian tube obstruction (2.2%), endometrial fibroids (1.1%) and cervical cysts (1.1%) (Figure 1).

Thymosin therapy and outcomes

Thymosin Alpha-1 was administered at doses of 1.6 mg or 3.2 mg, either daily or on an alternate-day regimen, for a minimum duration of 118 days. Among the patients treated with Thymosin, 66.7% received daily dosing, 26.7% were administered the therapy on alternate days and 6.7% followed a regimen of daily dosing followed by alternate-day administration (Figure 2). All patients with recurrent implantation failure (n=90) who received thymosin alpha-1 therapy for at least 118 days achieved a positive outcome, resulting in a 100% pregnancy rate (Figure 3).

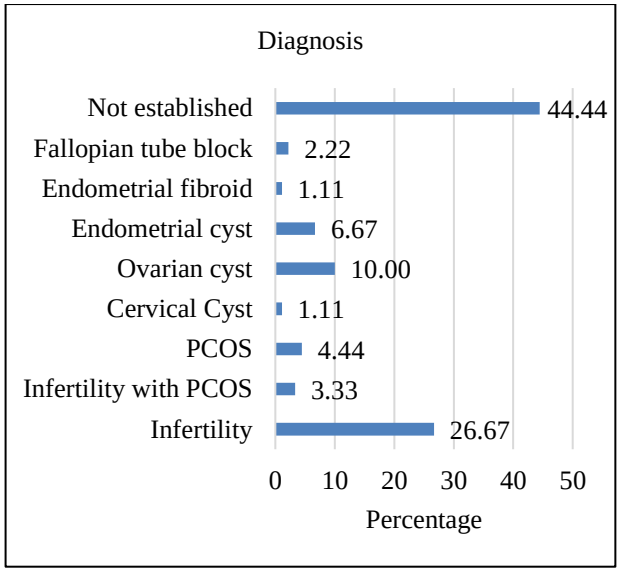

Figure 1: Diagnosis of the recurrent implantation failure patients.

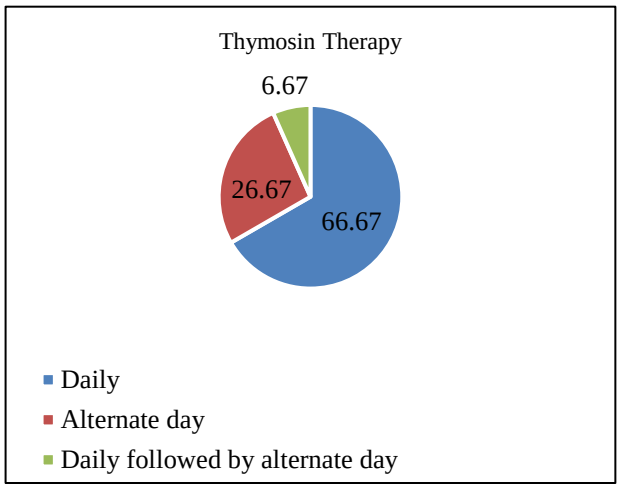

Figure 2: Details of thymosin therapy.

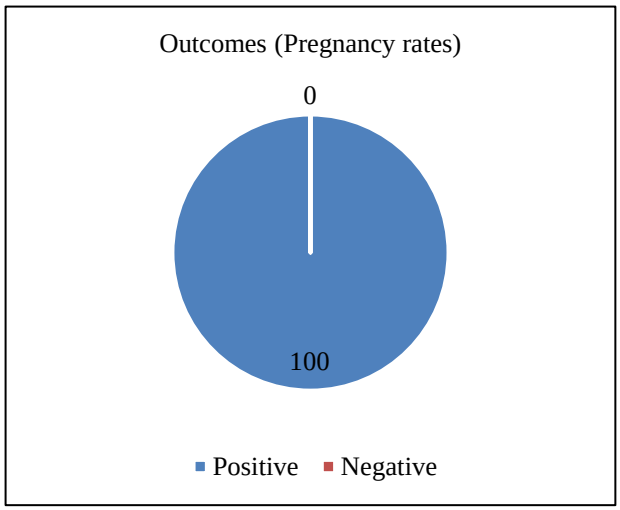

Figure 3: Outcomes (pregnancy rates) after thymosin administration.

Table 1: Baseline characteristics of the RIF patients.

Parameters	Mean	Std. deviation
Age (in years)	34.73	5.49
Weight (in Kg)	59.05	10.15
Height (in cm)	156.43	5.52
BMI	24.01	3.53
Duration of marriage (in years)	10.72	5.03

Table 2: Baseline and clinical characteristics of the recurrent implantation failure patients.

Parameters		N	%
Age group (in years)	≤30	17	18.89
	31- 35	37	41.11
	36 - 40	23	25.56
	40 above	13	14.44
BMI groups	Underweight	2	2.22
	Normal	60	66.67
	Overweight	24	26.67
	Obese	4	4.44
Duration infertility groups	≤5 years	12	13.33
	6 to 10 years	36	40.00
	11 to 15 years	30	33.33
	15 above years	12	13.33
Co-morbidity status	Thyroid disorder	14	15.56
	Diabetes	2	2.22
	No comorbidities	74	82.22
Latent TB status	Present	12	13.33
	Absent	78	86.67
Anovulatory cycle status	Present	16	17.78
	Absent	74	82.22
Endometrium status	Thin	64	71.11
	Normal	26	28.89

Table 3: Association of age groups with duration of infertility.

Parameter		Duration of infertility group (years)				Total	chi value	P value
		≤5	**6 -10**	**11 -15**	**15 above**			
Age group (in years)	<30	6	7	4	0	17	50.111	<0.001
	31-35	5	23	8	1	37		
	36-40	0	4	15	4	23		
	40 above	1	2	3	7	13		
Total		12	36	30	12	90		

Table 4: Immune profiling values of the recurrent implantation failure patients.

Parameters	Mean	Std. deviation
Total leucocyte count	9443.42	10633.09
Absolute lymphocyte	2188.52	1000.79
CD3	1690.36	708.57
CD (16+56)	175.47	103.47
TNF Alpha	18.41	41.15

DISCUSSION

The findings of this real-world observational study demonstrated encouraging outcomes, suggesting Thymosin alpha (Guficin alfa) as an effective immunomodulatory adjuvant in patients with RIF. Advances in ART have enabled many infertile couples to achieve successful pregnancies. Despite these improvements, RIF has emerged as a significant clinical challenge, affecting around 10-15% of couples undergoing ART.[1,2] The findings of this real-world observational study demonstrated encouraging outcomes, suggesting thymosin alpha-1 as an effective immunomodulatory adjuvant in

patients with RIF. Recently, thymosin alpha-1 has emerged as a novel immunomodulatory therapy and has shown promising clinical results, supporting its use in difficult-to-treat patient populations.[6-9] This real-world retrospective study was conducted to explore the effectiveness of thymosin alpha-1 in patients with RIF in the Indian clinical setting. In this analysis, the majority of patients (41.1%) were aged 31–35 years, followed by 25.6% aged 36–40 years, indicating that RIF predominantly affected women in their early to mid-30s. Most patients had a normal body mass index (BMI), suggesting that extreme weight-related risk factors were uncommon, although over a quarter were overweight, which may have contributed to implantation challenges in this subgroup.

Regarding underlying diagnoses, 44% of patients had no definitive diagnosis, while infertility without other specified conditions accounted for 26.7% of cases. Established diagnoses included ovarian cysts (10.0%), endometrial cysts (6.7%), polycystic ovary syndrome (PCOS) (4.4%), infertility with PCOS (3.3%), fallopian tube obstruction (2.2%), endometrial fibroids (1.1%) and cervical cysts (1.1%). These findings highlight the heterogeneous aetiologies contributing to RIF, underscoring the complexity of this patient population. Comorbid conditions were relatively uncommon, with 5.6% of patients having thyroid disorders and 2.2% having diabetes, while the majority (82.2%) had no comorbidities. Latent tuberculosis was observed in 13.3% of patients. Anovulatory cycles were present in 17.8% of the cohort and endometrial evaluation revealed a thin endometrium in 71.1% of patients, whereas 28.9% had normal endometrial thickness. These structural and metabolic factors, in addition to immunological contributors, may influence implantation outcomes in patients with RIF.

Immunomodulatory therapies have been shown to improve implantation outcomes in women with RIF, with several studies reporting significantly higher pregnancy rates.[6-8] In this analysis, all patients with recurrent implantation failure (RIF) who received Thymosin Alpha-1 therapy for at least 118 days (n=90) demonstrated positive reproductive outcome, resulting in a 100% pregnancy rate, regardless of whether dosing was daily or on alternate days. Among treated patients, 66.7% received daily dosing, 26.7% received therapy on alternate days and 6.7% followed a regimen of daily dosing followed by alternate-day administration. These findings support flexible, individualized dosing regimens based on patient needs and clinical judgment. Emerging evidence in Indian context also highlights the effectiveness of thymosin alpha 1 as an immunomodulatory therapy in patients with recurrent implantation failure (RIF). In a real-world observational study by Hirachan et al, treatment with alpha thymosin resulted in a positive β hCG response in 64.3% of patients, with the majority of these achieving confirmed foetal cardiac activity, demonstrating its potential to enhance implantation success.[6] Similarly, a case report by Rajan et al, described a successful pregnancy in a woman with unexplained RIF following administration of thymosin alpha 1, suggesting that immune modulation at the maternal-foetal interface can directly facilitate implantation.[8] These findings, together with our own cohort results showing positive outcomes in all patients treated for at least 118 days, reinforce the therapeutic potential of thymosin alpha 1 in improving reproductive outcomes in women with RIF. Thymosin Alpha-1 is an endogenous thymic peptide with strong immunomodulatory effects that may enhance embryo implantation through several complementary mechanisms.[6-8,10,11]

Restoration of immune homeostasis (regulates the Th1/Th2 immune balance by attenuating excessive pro-inflammatory Th1 activity and fosters the immune tolerance required for successful embryo implantation). Modulation of natural killer (NK) cell function (decreases pathological uterine NK cell cytotoxicity and promotes a receptive and supportive endometrial immune milieu). Augmentation of regulatory T cells (Tregs) (enhances maternal immune tolerance toward the developing embryo). Reduction of chronic endometrial inflammation (normalizes inflammatory cytokine expression and improves endometrial receptivity and optimizes the implantation window). Optimization of maternal–embryo communication (facilitates early placentation and contributes to implantation stability)

Overall, the study emphasizes the multifactorial nature of RIF and reinforces the potential role of thymosin alpha-1 as an adjunctive immunomodulatory therapy. Structural, metabolic and immunological factors contribute to implantation failure and targeted immunomodulation with thymosin alpha-1 may improve reproductive outcomes (pregnancy rates) in this challenging patient population However, despite the positive outcomes, several limitations should be considered. The lack of a control group and the retrospective study design limit the ability to draw definite conclusions about causality and different underlying causes. Therefore, further prospective, randomized controlled trials are warranted to validate the effectiveness of thymosin alpha 1 and to establish optimal dosing and treatment protocols in patients with RIF.

CONCLUSION

Thymosin alpha-1 therapy was associated with encouraging outcomes in patients with RIF, supporting its role as an effective immunomodulatory adjuvant.

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