The Science Behind Thymosin Alpha in Successful Implantation and Pregnancy: An Expert Group Consensus

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Abstract:

Recurrent implantation failure (RIF) is the inability to achieve pregnancy after multiple transfers of good-quality embryos, often due to embryo or uterine factors.[1] Immunomodulatory therapies improve implantation success in recurrent implantation failure (RIF) by correcting immune dysregulation at the maternal-foetal interface. They modulate the balance between pro-inflammatory (Th1) and anti-inflammatory (Th2) immune responses crucial for implantation. [2,3]

This source presents an expert group consensus on the potential use of Thymosin alpha 1 (Tα1) for Recurrent Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL) conditions affecting many couples undergoing IVF. The consensus, developed by seven Indian infertility specialists, suggests Tα1 as a promising immunomodulator to address immune imbalances often seen in RIF/RPL, such as elevated Th1 dominance and reduced regulatory T cells. The document discusses clinical experiences, dosing protocols, monitoring strategies and efficacy measures for Tα1, highlighting its role in shifting the uterine immune environment towards a Th2-dominant response crucial for pregnancy. While acknowledging the promising potential of Tα1, the authors emphasize need for standardized immunological tests, evaluation of teratogenic potential in the first trimester, and randomized controlled trials to solidify its effectiveness. While promising, further rigorous research is needed, alongside efforts to enhance education among healthcare professionals and the public. This will solidify its clinical application and address limitations in resource-limited settings.

Understanding RIF and RPL:

Recurrent implantation failure (RIF) refers to the failure to achieve clinical pregnancy after transfer of at least four good-quality embryos across a minimum of three fresh or frozen IVF cycles in women under 40 years. [4] While the definition of RIF varies widely and depends upon maternal age, embryo quality, the presence or absence of aneuploidy screening and the number of embryos transferred, recurrent Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL) are complex conditions affecting approximately 10% of couples undergoing in vitro fertilization and embryo transfer. Up to 50% of patients are reported to have unexplained RIF (uRIF) even after undergoing extensive investigation. A retrospective cohort review article having a sample size of 118 women <39 years with uRIF, the probability of live birth per embryo transferred was 12% compared to the 25–35% reported for unselected women <40 years undergoing IVF. [2]

There is often not a single cause, but rather multiple contributing factors, making diagnosis and treatment challenging. While embryo aneuploidy explains a large proportion of RIF, endometrial factors cannot be ignored especially for patients with recurrent euploid blastocyst transfer failures or young patients with multiple good-quality blastocyst transfer failures. uRIF is associated with substantial physical, emotional, and financial distress as well as high health-care resource utilization and there are no clearly effective therapies to improve conception rates. [2]

Endocrine disorders are a significant factor, especially in early gestation and immune imbalances are also crucial, disrupting the delicate interplay required for embryo implantation.

Because the immune system is thought to be intricately involved in mediating endometrial receptivity and facilitating implantation, a dysfunctional immune response during the window of implantation (WOI) has long been suspected to explain RIF in certain patients. Both insufficient and overactive endometrial inflammatory response are hypothesized to lead to implantation failure through various mechanisms.[2]

These imbalances can involve dysregulation of inflammatory responses, cellular immunity and antibody activity, often presenting as elevated Th1 dominance (high TNF-α, IFN-), reduced Th2 activity (low IL-4, IL-10), and elevated levels of peripheral Natural Killer (NK) cells with lower uterine NK (uNK) cell counts. In RIF/RPL, there is often a decrease in regulatory T cells (Treg) and an increase in Th17 cells. [5,6,7]

Thymosin Alpha 1 (Tα1) is emerging as a promising immunomodulator for addressing RIF and RPL.

Methods:

The consensus was developed by an expert group comprising 7 infertility specialists from all four zones of India. All working group members had given a declaration of their individual conflicts of interest as per the rules of the International Committee of Medical Journal Editors (ICMJE). The draft recommendations were sent to the consensus group via email in the first DELPHI round from March to May 2025. We received a strong consensus (agreement of >90%) for 80% of the recommendations and a consensus (agreement of 80-90%) for 20% recommendations. Recommendations having an agreement lower than 90% were again deliberated. The chairperson of the consensus development group guided the discussion and ensured that all the experts presented their opinions. In case of disagreements, the chairperson summarized the differing viewpoints and asked the members to clarify their reasoning. After the voting, all the selected recommendations were discussed, modifications were incorporated, and a consensus greater than 90% was reached. There was more than 80% agreement on all the proposals.

Clinical Experience and Outcomes:

- RIF/RPL Spectrum: Dr. RG noted RIF and RPL as an "extended version of spectrum," with a 30% miscarriage rate at his centre. In RIF/RPL, "cytokine storm" leads to "lesser action on the receptor," impacting endometrial function. Dr. RJ explained that "Any inflammatory marker is a receptor blocker and this receptor blockage leads to inaction of the hormones which are working on the receptor," particularly affecting FSH, LH, Oestrogen, and Progesterone. Tα1 aims to counteract these inflammatory effects.
- Pilot Data: Dr. VH presented data on 65 patients, showing "60% had positive biochemical pregnancies in RIF group while 25% had miscarriage" and a "46% clinical pregnancy rate."
- TPO Levels: Patients with "High TPO levels were prescribed thymosin" in Dr. RG's experience, though "no difference in implantation" was observed in 60 such patients.
- Immunological Testing: Immunological testing is typically initiated after the "3rd transfer failure" in Dr. VH's centre. Preliminary prerequisite blood tests include "CD 3/4, CD 15/56 blood," with TNF alpha testing increasing the cost.
- Indications for Tα1 Use: Patients with RIF/RPL, particularly where immune imbalances are suspected. Conditions where "B cell dominance is conducive for pregnancy" (Dr. RJ).

- Contraindications: "autoimmune ds" (autoimmune disorders) were identified as conditions "where Not to prescribe thymosin."
- Dosing Protocol: While a "Consensus following the dose determination trial" was discussed, the "daily dosing protocol is better than the alternate day with the compliance of the patients."
- Duration: Instead of "limiting the dosing to 13 injections, better to change the dosing protocol from the endometrial priming to the embryo transfer."
- Cycle Type: "Thymosin can be also prescribed both in fresh and frozen cycles."
- Monitoring: Immunological tests "should be done pre and post cycle before the initiation of progesterone so as to find the thymosin response."
- Efficacy Measures: Improved "oocyte quality and quantity" compared to previous cycles could be a parameter for comparison.

Recommendations and statements:

The polypeptide Tα1 is produced readily in the thymus gland and regulates the immune system by interacting with toll-like receptors. Clinical trials involving thymosin alpha 1 have shown promising results in treating hepatitis B and C, melanoma, HIV, DiGeorge syndrome, hepatic carcinoma, and non-small cell lung cancer, COVID-19 and sepsis.[8]

An increase in activated T helper (Th) cells (CD4 T cells) and a shift toward the Th1 subclass is caused by the presence of Tα1. Activated Th1 cells and DCs work together to fight viral, bacterial, or fungal infections as well as tumour cells. Additionally, they help certain B cells change into plasma cells, which make antibodies. Moreover, Tα1 triggers the NF-kappa B and p38 MAPK pathways, necessary for DC maturation and antigen presentation. It has been demonstrated to activate monocytes by upregulating the human leukocyte antigen (HLA)-DR, stimulate macrophages, encourage the production of interleukin (IL)-1ß, and boost T-cell proliferation.[9,10,11,12]

Tα1 shows promise for use in reproductive medicine, especially in the management of RPL and RIF. A study suggests that its immunomodulatory qualities could be utilized to enhance immunological tolerance in the uterus, thereby improving the environment for embryo implantation and pregnancy maintenance.

Tα1 significantly affects T and NK cells in the endometrium. Tα1 may be able to regulate NK cell activity, lessening the vulnerability of the embryo to immune assaults.[13] It may aid in altering the uterine immune milieu, promoting the successful implantation and the advancement of pregnancy by affecting the ratio of pro-inflammatory Th1 cells to anti-inflammatory Th2 cells and increasing the activity of regulatory T-cells (Tregs). It also impacts Th1, Th2, Th17, and Treg T-cell subsets. Crucially, it facilitates a shift towards "a Th2-dominant response and "Increased Treg activity," both "necessary for immune tolerance during pregnancy." This helps alter the uterine immune milieu, promoting the successful implantation and the advancement of pregnancy. [14,15,16]

Through its effects on TLR9 and indolamidedioxigenase (IDO), Tα1 is also involved in the development of immunologic tolerance. Moreover, it has been demonstrated that Toll-like receptor 9 (TLR9)-dependent pathways allow Tα to activate regulatory T-cells (Tregs). [17,18,19]

Future Considerations:

There is a "need to standardise the immunological tests for the subject population. Dr. AK highlighted a "need for the teratogenic potential of thymosin to promote it in the first trimester. Further studies

such as randomized controlled trials are warranted to determine the effectiveness of Thymosin alpha 1 for RIF and RPL.

Conclusion:

The discussions highlight exploring novel immunomodulatory therapies like Thymosin Alpha 1 to address challenging conditions such as RIF and RPL. Tα1 shows promising potential for improving pregnancy outcomes by modulating the uterine immune environment, although further rigorous research is needed to solidify its role and refine its clinical application.

Limitations:

Implementing these recommendations in rural or resource-limited settings in India has some challenges. One key issue is the need for better education among both healthcare professionals and the general public for the role of immunomodulation in RIF and RPL. Further research should be carried out to overcome these limitations.

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Dr. Ameet Patki conceived the idea and the first draft was prepared by Dr. Samvveda Sameel. All authors contributed equally to the refinement of the manuscript.

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Conflicts of interest

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