Killer Immunoglobulin-Like Receptor Haplotypes, Fetal HLA-C2 Exposure, and Immune Dysregulation in Recurrent Pregnancy Loss Patients Undergoing Comprehensive Reproductive and Immunologic Evaluation

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BACKGROUND

- Recurrent pregnancy loss (RPL) affects up to 10–20% of IVF patients.
- Immune-genetic factors, including killer immunoglobulin-like receptors (KIR), HLA-C, and immune dysregulation, may contribute to implantation failure and pregnancy loss.
- Maternal KIR–fetal HLA-C interactions play a critical role in trophoblast invasion and placental development.

OBJECTIVES

- To evaluate reproductive outcomes and immune-genetic factors associated with implantation failure and pregnancy loss in RPL patients undergoing comprehensive reproductive immunologic assessment using the Immunologic Reproductive Multifactor Assessment (IRMA).

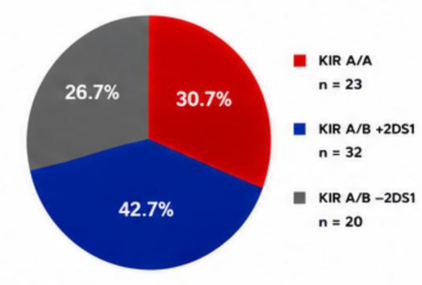
METHODS

- Retrospective cohort of 75 RPL-IVF patients evaluated across 116 embryo transfers.
- IRMA included KIR genotyping, maternal and paternal HLA-C typing , HY immunity assessment and HLA antibody, Th1/Th2 ratio, NK cell activity and Regulatory T-cell analysis.
- Immune therapies were individualized based on laboratory findings and included corticosteroids, G-CSF, IVIG, or combination therapy.

RESULTS

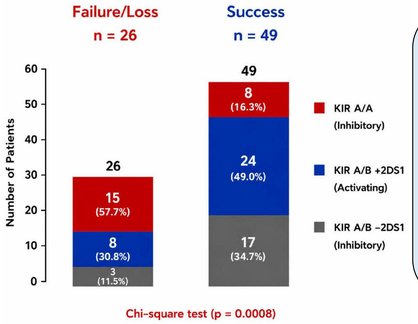
Maternal KIR haplotype appears to be a key determinant of reproductive outcome, with KIR A/A remaining the highest-risk subgroup despite immune-guided therapy.

A. KIR HAPLOTYPE DISTRIBUTION (RPL PATIENTS)



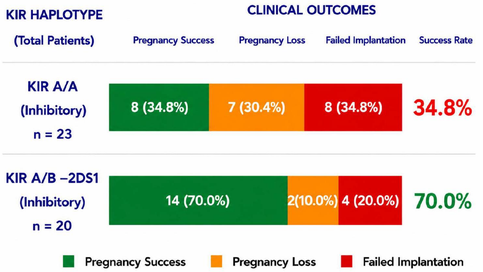
KIR haplotypes were similarly distributed across the RPL population, with no significant enrichment of any haplotype (χ^2, p = 0.22)

B.KIR HAPLOTYPE DISTRIBUTION BY OUTCOME AFTER IMMUNE-GUIDED THERAPY



KIR A/A was associated with poorer reproductive outcomes despite immune-guided therapy, whereas KIR B haplotypes—particularly KIR A/B –2DS1—were associated with improved outcomes.

C. CLINICAL OUTCOMES BY KIR HAPLOTYPE AFTER IMMUNE-GUIDED THERAPY



KIR A/B –2DS1 carriers were more likely to achieve pregnancy success than KIR A/A carriers following immune-guided therapy (70.0% vs 34.8%; OR ≈ 4.4).

D. IMMUNE FINDINGS ASSOCIATED WITH FAILURES

Immune Marker	Failure/Loss (n=26)	Success (n=49)	p-value
HY Allele Burden	1.38 (1.00–1.78)	1.00 (0.00–1.00)	0.04
Treg Cells (%)	4.55 (3.00–10.26)	2.70 (2.20–3.90)	0.0025

At baseline, higher Treg levels and increased HY allele burden were associated with implantation failure and pregnancy loss.

RPL PATIENTS

PATIENTS	EMBRYO TRANSFERS	MEDIAN AGE (years)	PRIOR PREGNANCY LOSSES	MEDIAN BMI (kg/m²)
75	116	35	2	25.3
Total cohort	Total transfers	IQR 31–38	IQR 2–3	IQR 23.1–29.6

CLINICAL OUTCOMES AFTER IMMUNE –GUIDED MANAGEMENT

Implantation Rate	Success Rate per Transfer	Success Rate per Patient	Secondary RPL Success	Primary RPL Success
54.3%	42.2%	65.3%	84.0%	56.0%
(per transfer)	*(n = 116 transfers)*	*(n = 75 patients)*	*(n = 25 patients)*	*(n = 50 patients)*

CONCLUSIONS

- Maternal KIR genotype alone did not influence susceptibility to RPL, as KIR haplotypes were similarly distributed across the cohort.
- Following immune-guided therapy, **KIR A/B –2DS1 carriers achieved significantly higher pregnancy success rates** than KIR A/A carriers (70.0% vs. 34.8%).
- **KIR A/A remained the highest-risk subgroup** despite treatment.
- Higher HY allele burden and baseline Treg levels were associated with reproductive failure.
- **Maternal KIR–fetal HLA-C interactions** appear to be important determinants of reproductive outcome in RPL patients.