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ORIGINAL ARTICLE

Flow Cytometric Detection of NK Cell KIR Receptors: a Novel Tool for Functional Profiling in Reproductive Failure

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ABSTRACT

Background: **Reproductive failures, including recurrent implantation failures (RIF), recurrent pregnancy losses (RPL), and adverse pregnancy outcomes (APO), are increasingly linked to immunological factors at the maternal-fetal interface. Killer immunoglobulin-like receptors (KIRs) on natural killer (NK) cells play a key role in regulating maternal immune responses to trophoblast HLA-C antigens.**
Methods: **In this study, we present a novel flow cytometric protocol to phenotypically characterize the expression of three KIR receptors (KIR2DL1, KIR2DL3, KIR2DS1) on peripheral blood NK cells in 144 women with reproductive failure. KIR phenotyping results were compared with PCR-based genotyping in a subset of 62 patients, revealing a 98.4% concordance.**
Results: **The KIR AA phenotype, defined by the presence of inhibitory receptors and absence of the activating KIR2DS1, was identified in 45% of patients and was significantly associated with RIF. Multivariate logistic regression further demonstrated that both maternal KIR AA phenotype and higher paternal HLA-C2 allele count were independent predictors of RIF ($p = 0.013$ and $p = 0.030$, respectively). Exploratory analysis in RPL and APO subgroups revealed nonrandom patterns suggestive of similar immunogenetic influences, although statistical significance was not reached.**
Conclusions: **These findings support the hypothesis that maternal KIR AA profiles may predispose to poor reproductive outcomes, particularly in the presence of paternal HLA-C2 alleles. Flow cytometric KIR profiling represents a reliable and clinically informative tool that may facilitate personalized immune-based diagnostics and therapeutic decision-making in reproductive medicine.**
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INTRODUCTION

Recurrent pregnancy losses (RPL), repeated implantation failures (RIF), and adverse pregnancy outcome (APO) remain significant challenges in reproductive medicine, often occurring in the absence of identifiable

anatomical, hormonal, immunological, or chromosomal abnormalities. Emerging evidence suggests that immune dysregulation at the maternal-fetal interface may play a crucial role in these reproductive failures. Natural killer (NK) cells, particularly those residing in the uterus, are known to influence implantation and early placental development through their interactions with trophoblast cells. These interactions are mediated by killer immunoglobulin-like receptors (KIRs), which recognize specific HLA class I molecules, notably HLA-C, expressed on the fetal side [1].

The diversity of KIR genes and their haplotypes - particularly the presence or absence of activating versus inhibitory receptors - has been implicated in pregnancy outcomes [2]. Women homozygous for the inhibitory KIR A haplotype (KIR AA) may be at increased risk for complications when carrying a fetus with HLA-C2 alleles, due to a lack of activating KIRs such as KIR2DS1 [3]. Until now, the identification of KIR genotypes has relied on PCR-based molecular methods [4].

In this study, we present a novel flow cytometric method to detect the surface expression of key KIR receptors - KIR2DL1, KIR2DL3, and KIR2DS1- on peripheral blood NK cells. Our method allows for direct phenotypic characterization of KIR expression and thus offers complementary insight into the functional immunological landscape of women with reproductive failure. We applied this approach to a cohort of women with RPL, RIF, or APO and compared the flow cytometric phenotyping with conventional PCR genotyping.

The primary aim of this study was twofold: first, to validate the utility and reliability of flow cytometry in detecting specific KIR receptor expression; and second, to explore the prevalence and potential clinical significance of the KIR AA phenotype of NK cell receptors in women with RPL, RIF, and APO. We hypothesize that this cytometric-based approach can identify immune risk profiles faster and simpler and pave the way for more individualized immunological diagnostics and therapeutic strategies in reproductive medicine.

MATERIALS AND METHODS

Patients

A total of 144 women from a single tertiary-care *in vitro* fertilization (IVF) center were enrolled in this study. All participants were of reproductive age and were referred for immunological evaluation due to reproductive failure. Inclusion criteria required 1) a history of either RIF or RPL, whereas RIF [5] and/or RPL [6] were defined according to Guidelines of European Society of Human Reproduction and Embryology (ESHRE), and/or 2) at least one APO defined as fetal loss ≥ 20 weeks of gestation, severe preeclampsia < 36 weeks, or severe intrauterine growth restriction defined as birth weight < 10th percentile for gestational age [7]. All patients provided written informed consent prior to participation, and the study was conducted in accordance with institutional ethical guidelines. A retrospective observational study assessing the KIR phenotype of NK cell receptors and clinical reproductive history in this cohort was performed.

Sample collection

Peripheral blood samples were collected from all participants via venipuncture into EDTA 4 mL tubes (Vacuette K3EDTA). Samples were processed within 12 hours of collection.

Flow cytometric detection of KIR receptors

Flow cytometry was used to determine the surface expression of three KIR receptors: KIR2DL1, KIR2DL3, and KIR2DS1 on $CD3^{-}CD56^{+}$ NK cells.

In the first step, the peripheral blood samples were stained with the following antibodies: Anti-Human CD3 Pacific Blue (Exbio, Prague, Czech Republic), Conjugated Antibody CD56-PC7 (Beckman Coulter, Brea, CA, United States), FITC Mouse Anti-Human CD158a, clone HP-3E4 (BD Biosciences, San Jose, CA, United States), Human CD158b2 APC monoclonal antibody (Bio-Techne, Minneapolis, MN, United States), and Human CD158h PE monoclonal antibody (Bio-Techne, Minneapolis, MN, United States). The samples were then incubated for 20 minutes.

Following incubation, erythrocyte lysis was performed using Excellyse I lysing solution (Exbio, Prague, Czech Republic) in combination with distilled water. Lysis of erythrocytes was carried out for 10 minutes, after which the samples were analyzed using the Navios EX flow cytometer (Beckman Coulter, Brea, CA, United States). For each sample, a minimum of 2,000 NK cells were acquired.

Data analysis was conducted using Kaluza Analysis Software, version 2.2.1 (Beckman Coulter, Brea, CA, United States). A lymphocyte population was gated on the FS vs. SS dot plot. From this region, NK cells were further identified and gated as $CD3^{-}CD56^{+}$. Within the NK cell population, the expression of individual receptors was analyzed. The $CD3^{-}CD56^{+}$ population was visualized in CD158b2 vs. CD158a, CD158a vs. CD158b2, and CD158h vs. CD158a dot plots. Each receptor was also represented in separate histograms displaying peaks of negative and positive populations. The positive population indicates the surface expression of the respective receptor on NK cells.

Expression was reported as percentage of NK cells expressing each individual receptor. Phenotypic KIRAA profile was defined by the expression of KIR2DL1 and KIR2DL3 in the absence of KIR2DS1 on the NK cell surface.

Molecular genotyping of KIR genes

KIR genotyping was performed using the KIR Typing SSP Kit (Inno-train Diagnostik GmbH, Germany), which employs sequence-specific primer polymerase chain reaction (SSP-PCR) to detect the presence or absence of 15 functional KIR genes. Genomic DNA was

extracted from peripheral blood using standard protocols. PCR reactions were prepared with gene-specific primers, Taq polymerase, and reaction buffer were amplified under the following thermal cycling conditions: initial denaturation at 96°C for 2 minutes; 10 cycles of 96°C for 15 seconds, 65°C for 1 minute, 30 cycles of 96°C for 15 seconds, 61°C for 50 seconds, and 72°C for 30 seconds, and final hold at 4°C. Amplified products were separated on a 1,5% agarose gel stained with GelRed and visualized under UV light. The presence or absence of specific bands corresponding to expected product sizes indicated the presence or absence of each KIR gene. The kit detects both inhibitory (e.g., KIR-2DL1, 2DL2, 2DL3, 3DL1) and activating (e.g., KIR-2DS1, 2DS2, 3DS1) KIR genes, as well as pseudogenes (KIR2DP1, KIR3DP1) for haplotype analysis. The resulting KIR gene profile is interpreted according to the manufacturer's guidelines to classify the individual's KIR genotype into the A or B haplotype group.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software (version 23.1.7, MedCalc Software Ltd., Ostend, Belgium). Data distribution was assessed using the Shapiro-Wilk test and was found to be non-Gaussian. Therefore, non-parametric statistical tests were used throughout. The concordance between flow cytometric and PCR-based KIR detection was evaluated using Pearson's chi-squared test. Differences in the frequency of phenotypic KIR profiles between groups were analyzed using Fischer's exact test. Continuous variables were compared using the Mann-Whitney U test. Multivariate associations between reproductive outcomes (RIF, RPL, APO) and laboratory predictors (KIR phenotype, parental HLA-C status, and their interactions) were evaluated using multinomial logistic regression. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Patient details

The main descriptive characteristics of the analyzed cohort are summarized in Table 1.

Out of 144 women included in the study, NK cell receptor flow cytometric phenotyping was performed in all cases.

Gating strategy

The aim was to determine the surface expression of three killer immunoglobulin-like receptors (KIRs) on $CD3^{-}CD56^{+}$ natural killer (NK) cells: KIR2DL1 (CD-158a), KIR2DL3 (CD158b2), and KIR2DS1 (CD158h), so that peripheral blood samples were stained with monoclonal antibodies targeting CD3, CD56, and the three selected KIR receptors. Lymphocytes were initially gated based on forward and side scatter (FS vs. SS; Figure 1A).

From this population, NK cells were identified as $CD3^{-}CD56^{+}$ (Figure 1B).

Within this gate, the expression of KIR2DL1, KIR-2DL3, and KIR2DS1 was assessed using bivariate dot plots (e.g., CD158b2 vs. CD158a, CD158h vs. CD-158b2, and CD158h vs. CD158a; see Figure 2A - C.

Each receptor was also individually displayed in single-parameter histograms to differentiate between positive and negative populations (Figure 3A - C).

KIR phenotype and genotype correlation

Based on the combination of KIRs detected on the NK cell surface, individuals were classified according to phenotypic KIR profiles. The KIR AA phenotype was defined as co-expression of KIR2DL1 and KIR2DL3 in the absence of KIR2DS1. In total, 65 women (45%) displayed a KIR AA phenotype, while 79 women (55%) showed expression patterns consistent with Bx or AB profiles.

These data were further correlated with genotypic findings in a subset of 62 patients.

Among these 62 individuals, the NK receptor phenotype results corresponded to the genotype in 61 cases (98.4%). In one case, however, a discrepancy was observed: the phenotype indicated a KIR AA profile, while the genotyping revealed a Bx genotype. This single patient was retested using two independently collected blood samples to rule out the possibility of sample misidentification; however, both analyses yielded identical results.

Statistical analysis using Pearson's chi-squared test confirmed a highly significant correlation between phenotype and genotype in n = 62 cohort ($\chi^2 = 54.31$, $p = 1.7 \times 10^{-13}$), supporting the robustness of phenotypic inference in the majority of cases.

KIR AA phenotype of NK cell receptors and clinical reproductive history

Women with the KIR AA phenotype of NK cell receptors had undergone a slightly higher number of prior IVF stimulations; however, the difference between the KIR AA and KIR Bx groups did not reach statistical significance ($p = 0.071$). In contrast, recurrent pregnancy loss (RPL) was significantly more frequent in the KIR AA group ($p = 0.050$) and in recurrent implantation failure (RIF) with gametes from own oocytes ($p = 0.021$). Due to the limited number of cases involving donor oocyte transfers, statistical analysis using the Mann-Whitney U test could not be performed for these cases. In the subgroup of patients with APO, the KIR AA phenotype was also significantly more prevalent ($p = 0.050$) compared to KIR Bx.

Female KIR AA phenotype, parental HLA-C genotypes, and clinical reproductive history

It is well established that the inhibitory KIR AA receptor phenotype is at risk of incompatibility with HLA-C2, particularly in situations where the number of HLA-C2 alleles in the embryo exceeds that of the mother, and

Table 1. Descriptive characteristics of the analyzed patient cohort.

Parameter	
Age, years, median (IQR)	37 (33 - 40)
Previous IVF stimulations for own oocyte puncture, n, median (IQR), mean (min-max)	2 (0.75 - 3) 2.3 (0 - 11)
Previous failed embryo transfers with own oocyte, n, median (IQR), mean (min-max)	3 (0 - 5) 3.2 (0 - 15)
Previous failed embryo transfers with donor's oocyte, n, median (IQR), mean (min-max)	0.0 (0 - 0) 0.65 (0 - 8)
Miscarriages before week 20 of pregnancy, n, median (IQR), mean (min-max)	0.0 (0 - 2) 1.18 (0 - 7)
Adverse pregnancy outcome after week 20 of pregnancy, n, median (IQR), mean (min-max)	0.0 (0 - 0) 0.31 (0 - 4)

IQR: interquartile range, IVF: *in vitro* fertilization.

Table 2. The multivariate regression analysis examining associations between parental KIR/HLA-C characteristics and recurrent implantation failures.

Predictor	Coefficient (β)	p-value	Significant
Maternal KIR AA phenotype	4.73	0.013	yes
Paternal HLA-C2 allele count	3.43	0.03	yes
Risk combination maternal KIR AA + paternal C2 > maternal C2	-1.71	0.378	no
KIR AA x paternal C2 interaction	-1.95	0.203	no
Maternal HLA-C2 allele count	1.21	0.448	no
C2 interaction (mother x father)	-1.67	0.105	trend

Table 3. Exploratory observations of maternal KIR phenotype and parental HLA-C genotype across diagnostic subgroups in a total of n = 60 patients.

Diagnosis	KIR AA overrepresentation	Paternal HLA-C2 effect	Maternal HLA-C2 effect	KIR x C2 interaction
RIF n = 38	yes (p = 0.013)	yes (p = 0.030)	not significant	suggestive (p = 0.203)
RPL n = 9	suggestive (model unstable)	possible trend (β ~ 0.2)	inverse trend (β < 0)	not evaluable
APO n = 13	non-significant, but trend present	present in cluster of APO cases	not significant	not significant

The following table summarizes exploratory findings across all three diagnostic subgroups of RIF, RPL, and APO. While only the RIF subgroup yielded statistically robust associations, observed trends in RPL and APO groups suggest biologically meaningful patterns that merit further investigation.

when the embryonic HLA-C2 allele is of paternal origin [8]. To investigate the clinical relevance of maternal KIR AA phenotype and parental HLA-C genotypes in our cohort, we performed a multivariate analysis of 60 women. The risk combination was defined as presence of KIR AA phenotype in the mother, combined with a risk of the higher number of HLA-C2 alleles in the embryo compared to the mother, specifically when the paternal genome contributed to HLA-C2 allele.

Multinomial logistic regression revealed that the KIR AA genotype was significantly associated with RIF (β = 4.73, p = 0.013). Similarly, a higher paternal HLA-C2

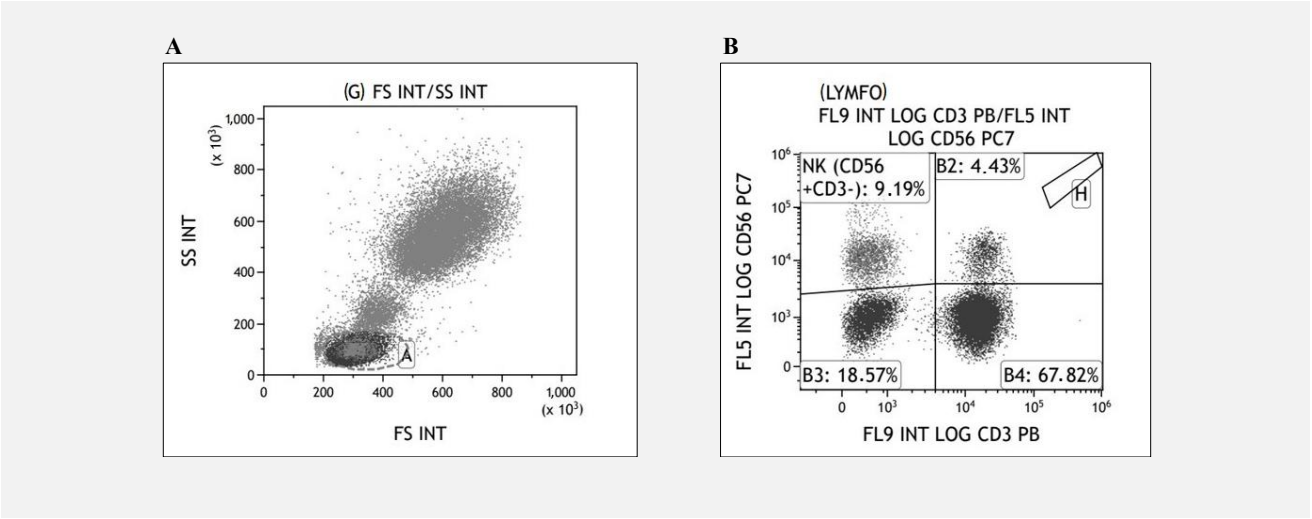

Figure 1. Identification of NK cells in peripheral blood samples.

A: Lymphocyte population gated on forward scatter (FSC) vs. side scatter (SSC) plot, B: From the lymphocyte gate, NK cells were identified as $CD3^{-}CD56^{+}$ in a bivariate plot of CD3 Pacific Blue vs. CD56-PC7.

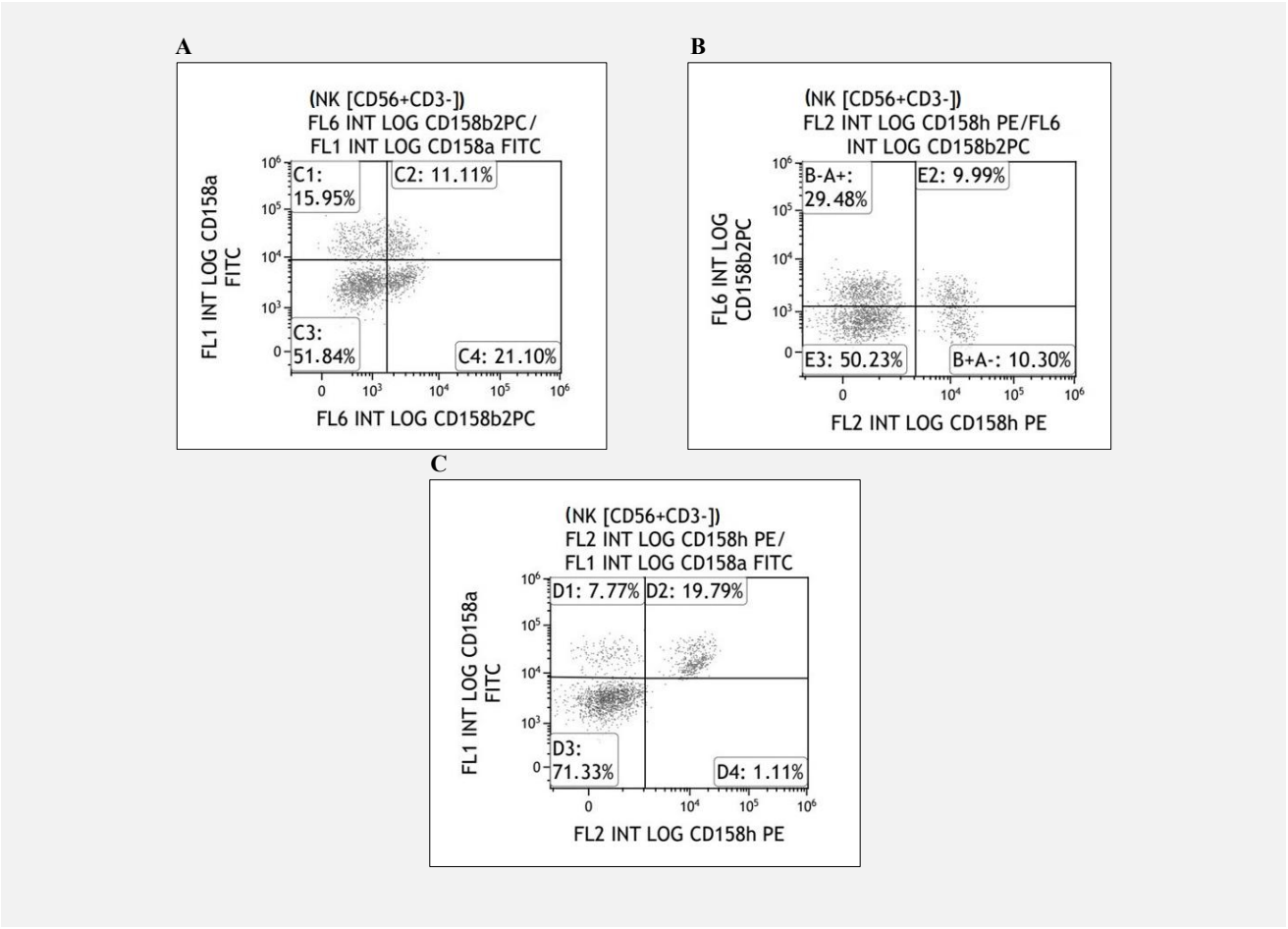

Figure 2. Surface co-expression of KIR receptors on $CD3^{-}CD56^{+}$ NK cells.

A: Dot plot showing KIR2DL3 (CD158b2-APC) vs. KIR2DL1 (CD158a-FITC), B: Dot plot of KIR2DS1 (CD158h-PE) vs. KIR2DL3 (CD158b2-APC), C: Dot plot of KIR2DS1 (CD158h-PE) vs. KIR2DL1 (CD158a-FITC).

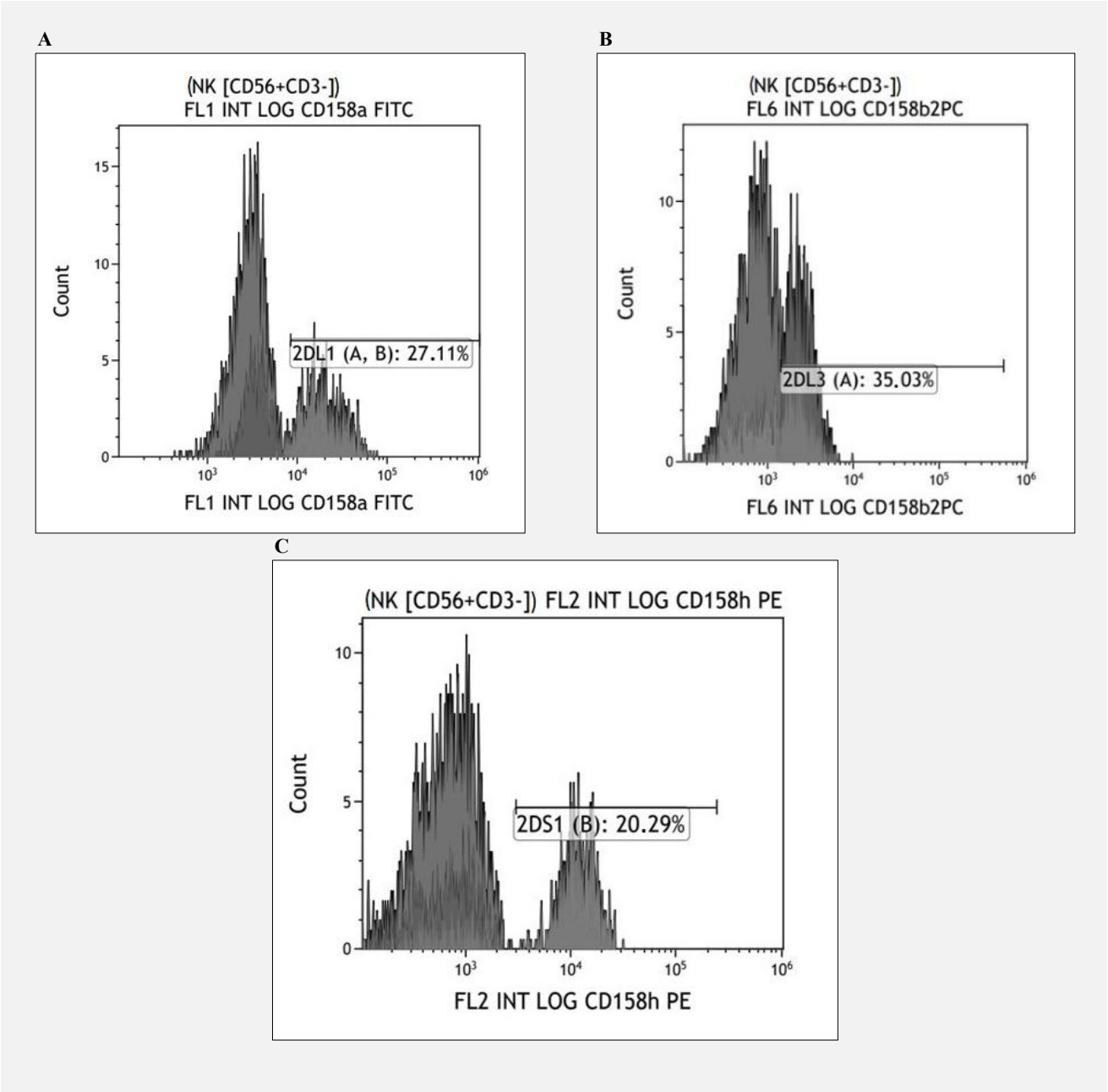

Figure 3. Histograms of individual KIR receptor expression on NK cells.

A: Histogram of KIR2DL1 (CD158a-FITC) expression, B: Histogram of KIR2DL3 (CD158b2-APC) expression, C: Histogram of KIR2DS1 (CD158h-PE) expression.
Each histogram shows a clear separation between negative (left peak) and positive (right peak) NK cell subpopulations. Receptor expression is reported as the percentage of NK cells falling into the positive gate.

allele count emerged as a statistically significant independent predictor of RIF ($\beta = 3.43$, $p = 0.030$). The overall model demonstrated good explanatory power (pseudo $R^2 = 0.269$, likelihood ratio test p-value = 0.003), supporting a clinically relevant relationship between female KIR AA genotype, paternal HLA-C2 status, and the occurrence of implantation failure, see Table 2.

Exploratory analysis suggested notable trends in patients with RPL and APO. While the regression model for RPL did not converge reliably, likely due to the limited subgroup size and potential collinearity, preliminary coefficients indicated a pattern consistent with the proposed hypothesis, specifically, an overrepresentation

of KIR AA genotype and an inverse relationship with maternal HLA-C2 allele load. In the APO subgroup, no single variable reached statistical significance; however, a nonrandom distribution of KIR AA phenotypes and higher paternal HLA-C2 frequency was observed. These patterns may reflect subtle immunogenetic dynamics underlying inadequate placentation or abnormal trophoblast invasion, particularly in pregnancies where the maternal NK cell profile exhibits inhibitory bias. See Table 3.

DISCUSSION

Our study presents a novel approach to characterizing KIR receptor expression in women with reproductive failure, using flow cytometry as a practical tool to identify functionally relevant receptor phenotypes. The high concordance between KIR phenotyping and genotyping (98.4%) supports the clinical utility of this method as a rapid, cost-effective alternative to molecular typing. This technical validation lays the foundation for functional immunogenetic profiling in reproductive medicine.

The observed discordance between KIR AA phenotype and Bx genotype in one individual assessed may reflect several potential sources of variability. First, limitations in flow cytometric detection of KIR expression can arise due to low surface density or altered epitope accessibility of specific KIR receptors, particularly in the case of allelic variants with reduced expression [9]. Second, technical variability in sample handling or antibody performance may affect staining reliability. Third, post-transcriptional regulation or monoallelic expression patterns may lead to underrepresentation of certain KIRs at the protein level, even when the corresponding genes are present [10]. Finally, rare cases of somatic mosaicism or gene conversion could also contribute to discrepancies between genotype and immunophenotype [11].

The frequency of the KIR AA phenotype in our study cohort was 45%, which appears notably higher than the prevalence reported in the general Czech population, estimated at around 30% [12]. This elevated frequency among women with reproductive failure suggests a potential enrichment of the inhibitory KIR AA receptors in clinically affected individuals. The overrepresentation of KIR AA in this cohort aligns with its hypothesized role as a genetic risk factor in the absence of activating KIR receptors such as KIR2DS1. In particular, when combined with paternal HLA-C2 alleles, the lack of activating signaling through maternal NK cells may lead to insufficient immune support for embryo implantation or early placental development.

Our data demonstrates a statistically significant association between the KIR AA phenotype and recurrent implantation failures (RIF). Furthermore, a higher number of paternal HLA-C2 alleles emerged as an independent predictor of RIF, suggesting that excessive fetal HLA-C2 signals, particularly in the absence of activating KIRs, may provoke an inadequate uterine immune environment [13]. These findings are consistent with the previously described concept of KIR/HLA-C incompatibility [14], in which inhibitory signaling predominates at the maternal-fetal interface, potentially impairing trophoblast invasion and spiral artery remodeling. The strength of this association is further supported by the multivariate regression model, which demonstrated both statistical significance and solid explanatory power. While the interaction between KIR AA and paternal C2 did not reach statistical significance, the observed trend suggests a complex, possibly nonlinear relationship that warrants further study. Our results are supported by a recent Polish review [1] that further emphasizes the detrimental impact of the maternal KIR AA genotype in combination with fetal HLA-C2 alleles on reproductive success. Wasilewska's group highlights the increased risk of recurrent implantation failure and pregnancy complications in women with this genetic combination, which aligns with our observations, and draws attention to the protective role of the activating KIR2DS1 receptor in women, particularly when the fetus expresses the HLA-C2 allele - a finding that supports the hypothesis of KIR2DS1-mediated facilitation of proper trophoblast invasion and placentation. Uniquely, they also report data from male infertility studies, suggesting that, contrary to women, the KIR AA genotype may be more common in fertile men, while activating KIR profiles are overrepresented among men with impaired fertility. This sex-specific divergence raises the possibility of differential immunogenetic mechanisms influencing male and female reproductive outcomes.

In addition to the RIF subgroup, exploratory analyses revealed suggestive trends in women with recurrent pregnancy loss (RPL) and adverse pregnancy outcome (APO). Although the regression model did not reliably converge for RPL (likely due to limited subgroup size), an overrepresentation of the KIR AA phenotype and an inverse trend for maternal HLA-C2 were observed, aligning with the proposed immunological model. These findings raise the possibility that maternal immune tolerance may also be compromised in early gestation in women lacking activating KIRs. Similarly, in the APO subgroup, we identified nonrandom clustering of the KIR AA phenotype and increased paternal HLA-C2 frequencies, suggesting an immunogenetic background that may predispose to abnormal placental development. While not statistically significant in this sample, such patterns underscore the importance of maternal-fetal immunogenetic interplay in shaping implantation and placentation outcomes. Our findings align with the pioneering work of Moffett's study group in several aspects [15]. Both studies emphasize the detrimental impact of maternal KIR AA genotype in combination with fetal HLA-C2 alleles on reproductive success. Consistent with Moffett's conclusions, we observed that the absence of activating KIR receptors in moth-

ers carrying fetuses with paternal HLA-C2 alleles is associated with an increased risk of reproductive failure, particularly recurrent implantation failure (RIF). While Moffett's research focused predominantly on pre-eclampsia, our data extends this concept to encompass earlier stages of reproduction, such as implantation and early pregnancy maintenance. However, there are also notable differences. Moffett group's work primarily highlighted the maternal KIR AA and fetal HLA-C2 combination as a risk factor for preeclampsia, with less focus on implantation outcomes. In contrast, our study suggests that this risk combination exerts significant influence even before placental insufficiency becomes clinically evident, as reflected in our RIF and RPL cohorts.

One of the key strengths of our study is the introduction and validation of a flow cytometry-based protocol for direct KIR receptor phenotyping, which offers a practical, rapid, and functionally informative alternative to traditional genotyping. The high level of concordance between phenotypic and genotypic data underscores the robustness of our approach. Additionally, the inclusion of HLA-C genotypes from both partners allowed us to assess clinically relevant maternal-paternal immunogenetic interactions, going beyond maternal immune profiling alone. Another strength lies in the clearly defined patient cohort, which included well-characterized diagnostic categories - RIF, RPL, and APO - allowing for subgroup-specific analyses within a real-world clinical population. Nonetheless, several limitations should be acknowledged. First, although the overall cohort was relatively large, subgroup analyses were constrained by limited sample sizes, which may have reduced the statistical power and stability of multivariate models. Second, while our cytometric method enables surface-level receptor profiling, it does not capture allelic variation or post-transcriptional regulatory effects that may influence receptor function. Finally, the retrospective and observational nature of the study limits causal inference, and prospective validation in independent cohorts will be necessary to confirm the clinical utility of our findings.

In conclusion, our findings support the integration of functional NK cell phenotyping into clinical reproductive diagnostics and emphasize the need for personalized immune-based strategies in infertility care. Further prospective and mechanistic studies are warranted to validate these observations and to elucidate the complex interactions at the maternal-fetal interface.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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