



Immunophenotype and immunogenetic profiles in females with reproductive failure.

Snezhina Mihailova Kandilarova

¹Clinic of Clinical Immunology with Stem cell Bank, University Hospital Alexandrovska, Sofia, Bulgaria

"Fetus - Semiallogeneic Graft" – an immunological paradox

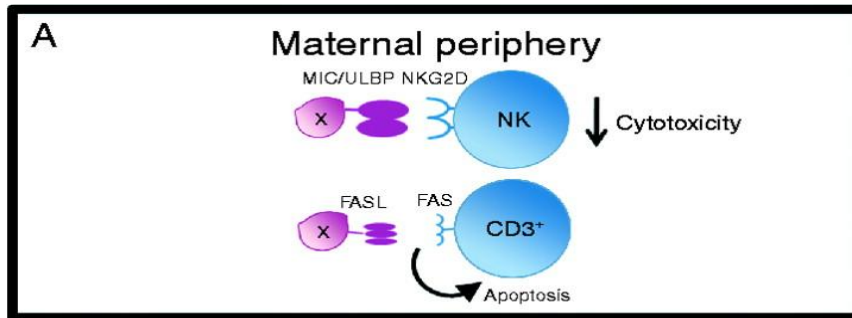


The close relationship between mother and fetus in placental mammals creates the potential problem of co-existence **of two genetically different individuals**

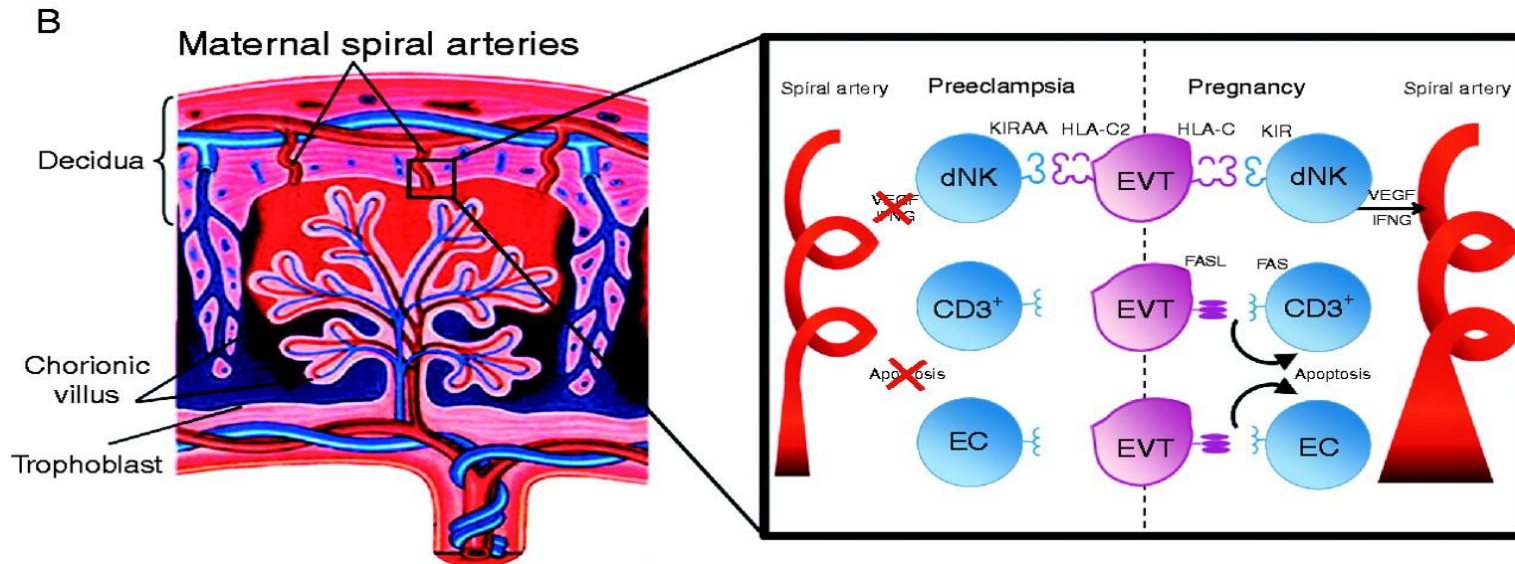
Mother's immune system must tolerate **the presence of paternal alloantigens** (non-self Ags) from the fetus and/or the placenta.

In this context, the pregnancy is a unique immunological challenge and is compared with tissue and organ transplantation from a donor that is tolerated by the recipient (mother) and not rejected. **This is the paradox of the fetal allograft (transplant).**

Trophoblast stimulates vascular remodeling and maternal tolerance, both locally at the maternal-fetal interphase and in the periphery



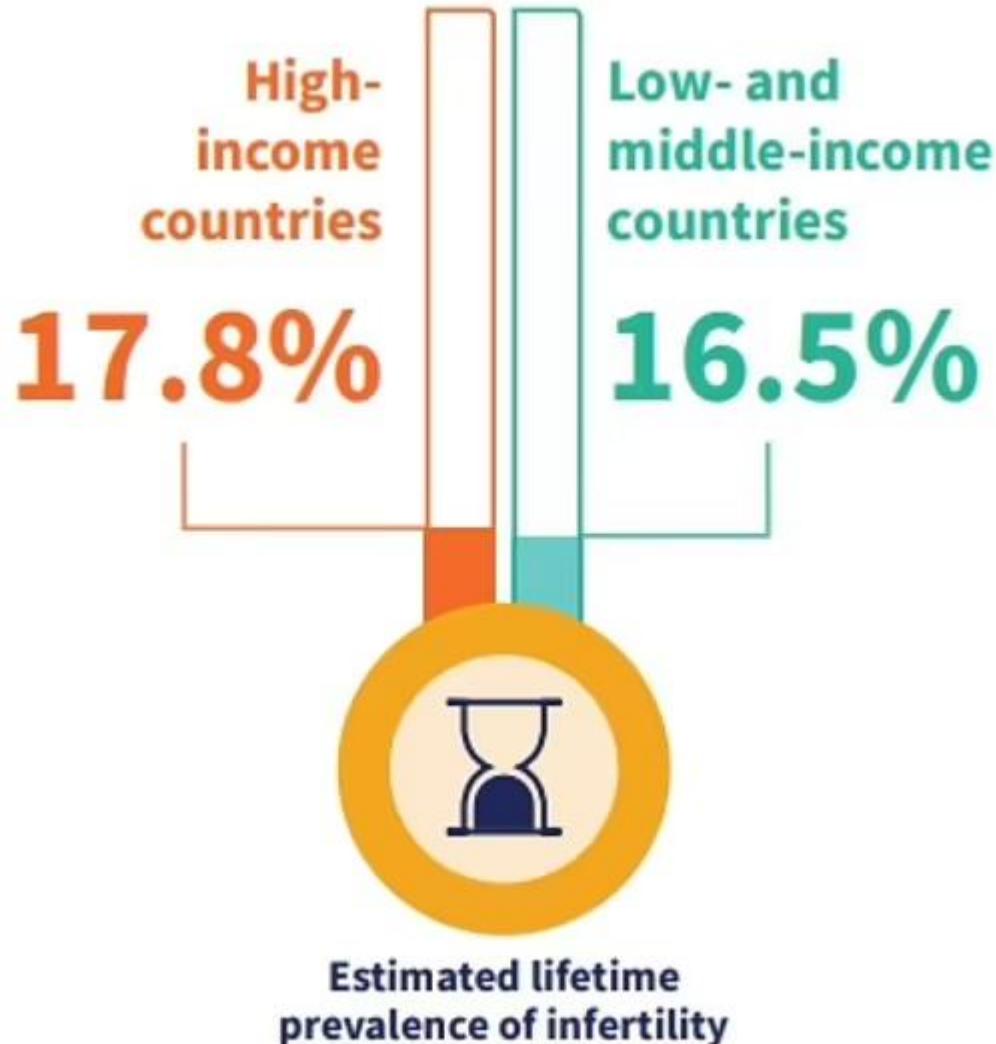
A. Trophoblast shed microparticles such as exosomes (x) resulting in systemic paternal antigen exposure, driving Treg proliferation. Exosomes express MIC and ULBP, both ligands for the NK receptor NKG2D, inhibiting maternal NK cytotoxicity when bound. Exosomes also express FASL, promoting apoptosis of peripheral activated maternal lymphocytes.



B. Extravillous trophoblast (EVT) invades uterine spiral arteries and replaces endothelium, aiding vascular remodeling critical for sufficient blood supply to the fetus. EVT expresses HLA-C. Upon binding the NK receptor, KIR, HLA-C inhibits cytotoxicity, and stimulates secretion of angiogenic and growth factors. This facilitates spiral artery remodeling and promotes trophoblast invasion. In preeclampsia, the combination of maternal KIRAA and fetal HLA-C2 is more common, inhibiting the production of angiogenic factors. EVT expresses FASL, promoting apoptosis of FAS-bearing activated CD3⁺T cells and endothelial cells (EC), protecting against maternal immune activation, while enabling placental invasion and spiral artery remodeling. The expression of FASL on EVT may be reduced in preeclampsia.

Infertility

- Inability to achieve pregnancy after one year (or more) of unprotected intercourse
- About 1 in 6 couples worldwide
- Over 200 million people affected



Infertility-Types-Definitions

Recurrent miscarriage

Two or more consecutive pregnancy losses before 20 weeks of gestation. (ASRM: three or more losses as the threshold).

Recurrent Implantation Failure (RIF)

Failure to achieve a clinical pregnancy after the transfer of at least 3 good-quality embryos in a minimum of 2 or 3 IVF cycles in women under the age of 40.

Unexplained infertility

Couples who have not been able to conceive after 12 months of regular, unprotected intercourse (or 6 months if the woman is over 35), despite all standard fertility tests showing no abnormalities

Infertility

- In about 10-30% of infertile couples, no cause is identified.



Age



Alcohol consumption



Smoking



Obesity



Tubal Infection



Radiation Therapy



Endometriosis



Diet



Mental Stress



Ovulation Disorders



Submucosal Fibroids



Immune disorders

20-50%



Immune mechanisms associated with infertility

❑ Alloimmune

HLA compatibility of parents (absence of blocking antibodies)

Anti-HLA antibodies

HLA G interactions

KIR/KIRL interaction between mother and fetus

❑ Autoimmune

Humoral-mediated

Autoantibodies: aPL, anti- β 2 GP1, ATA, anti-ovarian antibodies, anti-sperm antibodies, antibodies associated with gluten enteropathy

Cell-mediated

Cytotoxic NK cells and T lymphocytes

❑ Immune dysregulation

Th17, Treg, NK cells, cytokine dysregulation

“Shared HLA” phenomenon

- It is suggested that RMs are associated with an increased rate of HLA sharing: with higher frequencies of identical HLA-A and HLA-B alleles?
- Increased HLA sharing with paternal counterparts may suppress the production of blocking antibodies (masking paternal antigens and “forbidding” their recognition by the maternal immune system.)
- The absence of these antibodies compromises the maintenance of pregnancy.

“Shared HLA” phenomenon

Meta-Analysis > Hum Immunol. 2015 May;76(5):362-73. doi: 10.1016/j.humimm.2015.02.004.

Epub 2015 Feb 17.

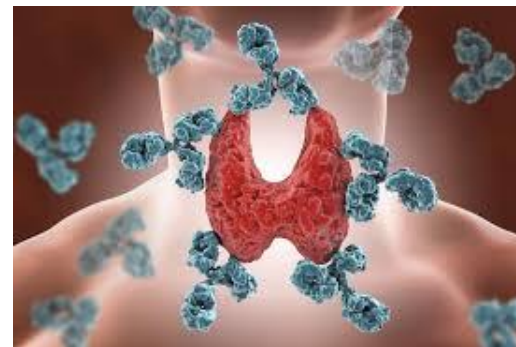
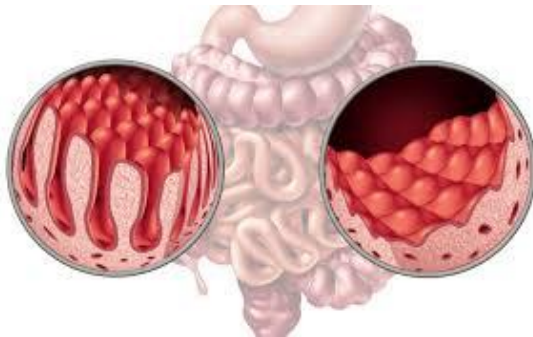
40 studies

RM risk	HLA alleles	Pooled odds ratio (OR)
Increased risk	HLA-DRB1*04 HLA-DRB1*15 HLA-E*01:01 HLA-B sharing HLA-DR sharing	OR 1.41, 95% CI 1.05-1.90 OR 1.57, 95% CI 1.15-2.14 OR 1.47, 95% CI 0.20-1.81 OR 1.39, 95% CI 1.11-1.75 OR 1.57, 95% CI 1.10-1.25
Decreased risk	HLA-DRB1*13 HLA-DRB1*14	OR 0.63, 95% CI 0.45-0.89 OR 0.54, 95% CI 0.31-0.94

HLA polymorphisms, associated with infertility

HLA-DQ

- **HLA-DQ2/DQ8**- increased risk of RM
- Autoimmunity!
- The same genotype is associated with celiac disease, anticardiolipin antibodies and antibodies against thyroid peroxidase



HLA polymorphisms, associated with infertility

HLA DR

HLA-DRB1*07 -RM

HLA-DR3, DR4

Autoimmunity!

Associated with **autoimmune thyroid disease**, **Type 1 diabetes**, and **lupus**, all of which can affect fertility and pregnancy.

Immune mechanisms associated with infertility

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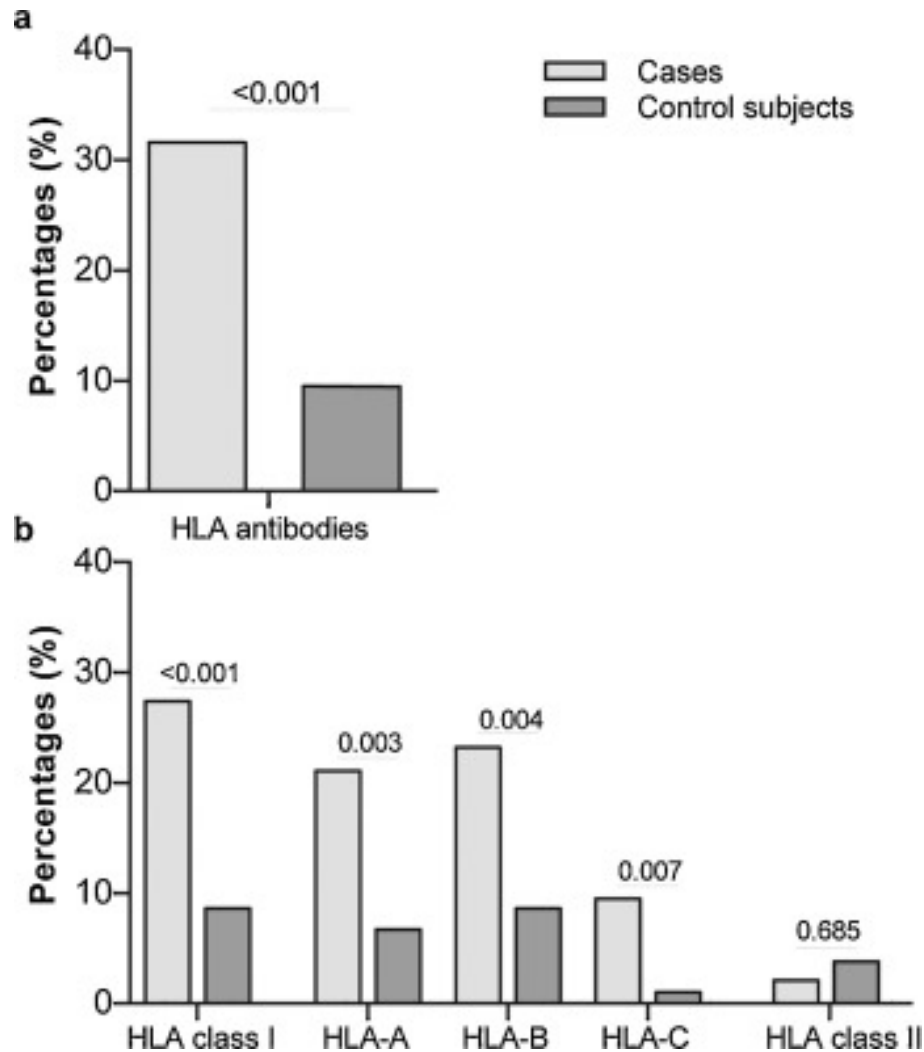
❑ Immune dysregulation

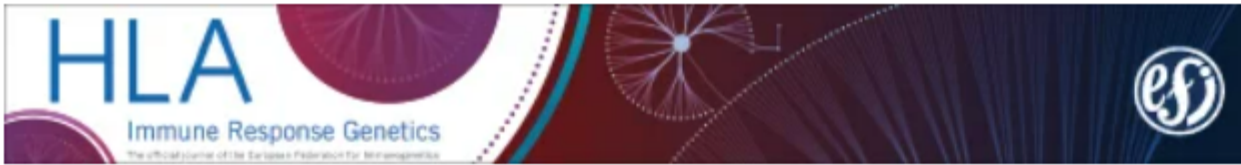
Th17, Treg, NK cells, cytokine dysregulation

Alloimmunization and pregnancy

- SABs tests show that **50% to 75%** of women have detectable anti-HLA antibodies at the time of delivery.
- By about 2 years postpartum, anti-HLA antibodies disappear in 50% of women.
- Barrier to access to transplantation.
- **Higher frequency of HLA antibodies in women with RM** (especially if the first pregnancy with a male fetus).
- The majority of HLA-C antibodies in RM are **complement-fixing**.

Presence of HLA antibodies (a) and specific HLA antibodies (b) in RM and controls.





ORIGINAL ARTICLE

Paternal HLA-Derived Epitopes and Live Birth in Secondary Recurrent Pregnancy Loss: New Insights From a Clinical Trial

Maria Christine Krog, Emma T. M. Peereboom, Kirsten Geneugelijk, Benedict M. Matern, Astrid Marie Kolte, Ole Bjarne Christiansen, Rudi Steffensen, Henriette Svarre Nielsen✉, Eric Spierings

First published: 17 October 2024 | <https://doi.org/10.1111/tan.15723> | Citations: 1

Among IVIg untreated women, those with an anti-HLA antibody response + higher PIRCHE-II had better chances of live birth than those who didn't.

Suggests that in some settings, anti-HLA antibodies *may not be purely harmful and may indicate an immune adaptation* or acceptable response.

IVIg treatment appeared to modulate this.

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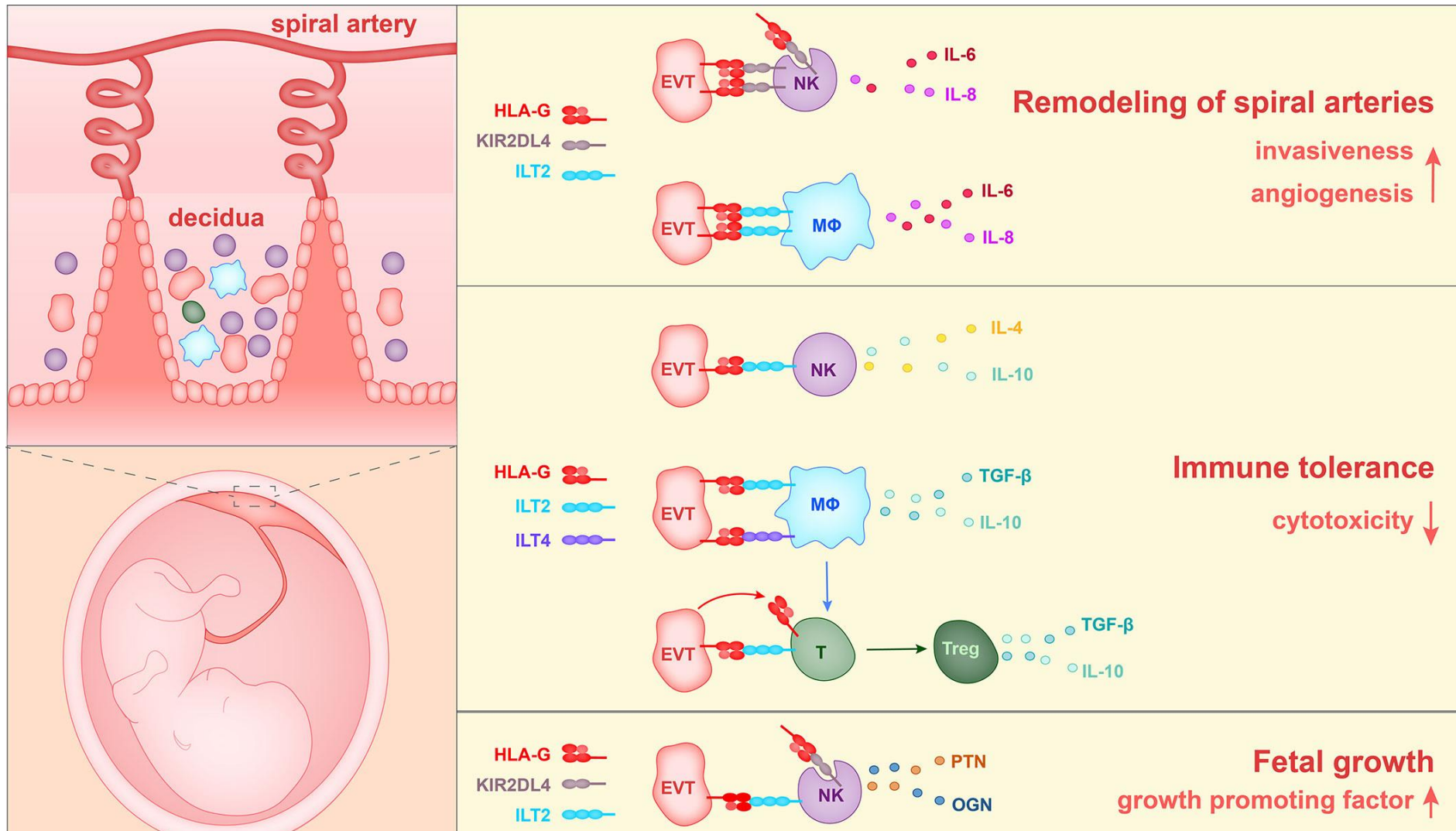
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The role of HLA-G

Expression on extravillous cytotrophoblast cells.

sHLA-G5 -in placenta, chorionic membrane, maternal blood and decidua.



The role of HLA-G

- Limited polymorphism – 157 alleles; 48 proteins
- Reduced sHLA-G concentration in women with reproductive problems.
- 4 bp insertion/deletion in the 3' UTR of HLA-G - increased risk of RM.
- SNPs –1179G > A, –725C > G/T and –486A > C increased risk of RM (incl. carrier status in partner)
- Impaired methylation of the HLA-G gene - with dysregulation in pathological pregnancy
- Reduced expression of KIR2DL4 on NK cells in the placenta

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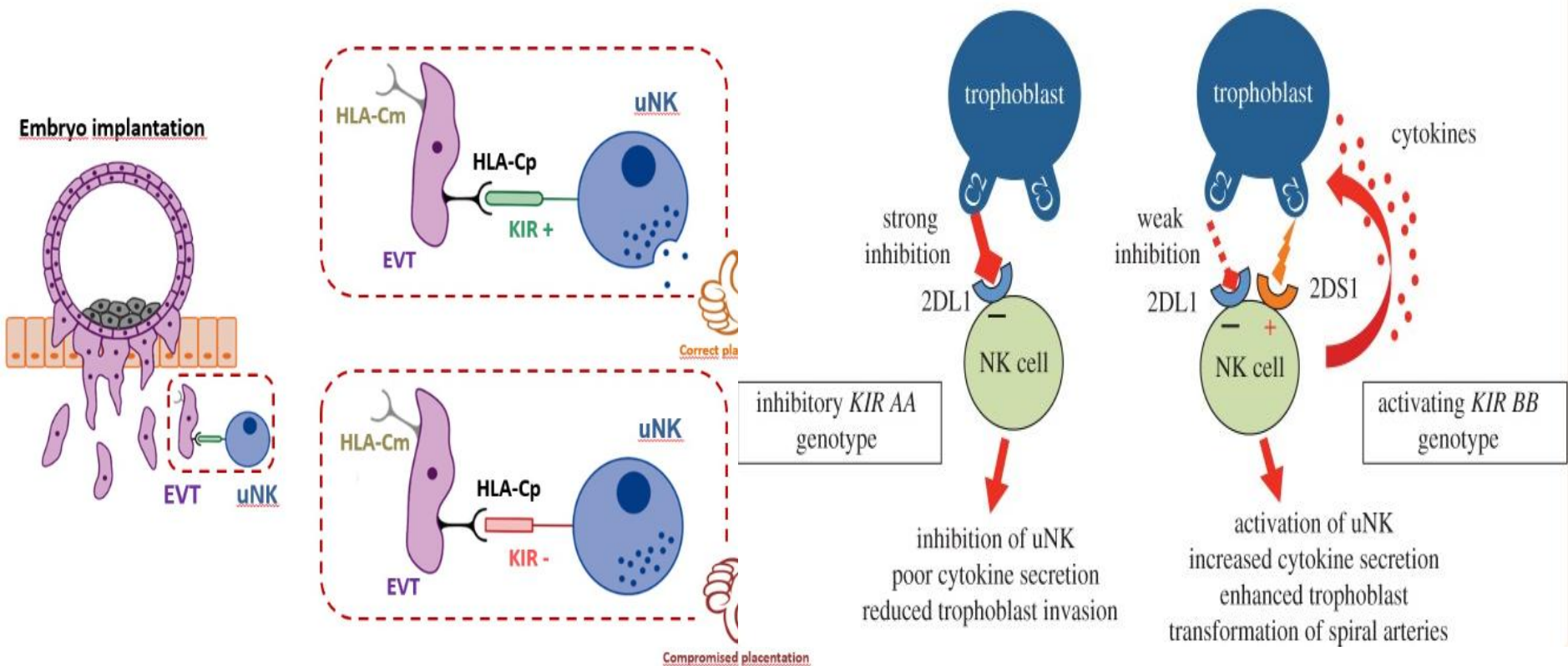
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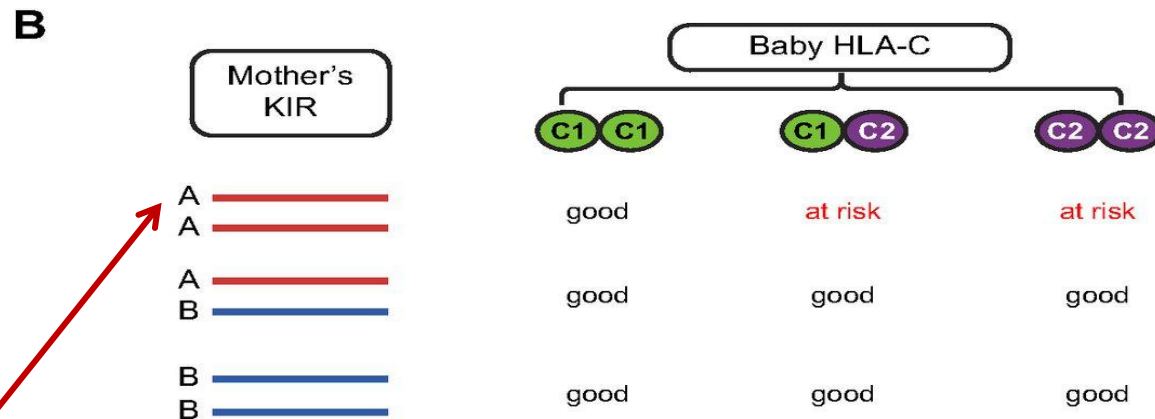
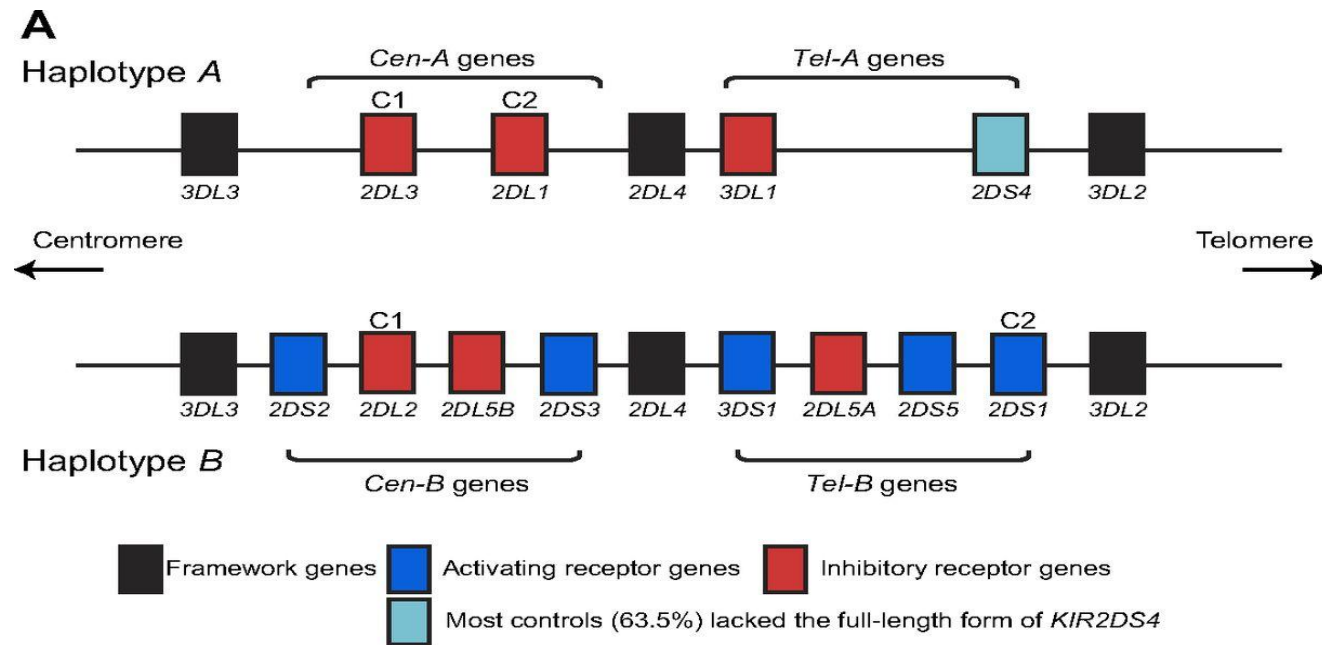
❑ Immune dysregulation

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KIR/HLA-C interactions during early pregnancy



Proposed effect of KIR genotype / HLA-C ligands interactions



Up to date KIR/KIRL

Key Study / Review	Year / Population	KIR / KIR-HLA Findings
Human Reproduction “Association of maternal KIR and parental HLA-C genotypes with recurrent miscarriage” (Hiby et al.)	2008; Caucasian women with RM vs parous controls	Increased frequency of maternal KIR AA genotype in RM; lower for KIR genes on B haplotype (activating ones), e.g. KIR2DS1 protective. Higher frequencies of HLA-C2 in both female & male partners correlated with increased RM
Alecsandru et al. , <i>Maternal KIR haplotype influences live birth rate after double embryo transfer in IVF cycles in patients with recurrent miscarriages and implantation failure</i>	2014; cohort of 291 women with RM or RIF (1304 IVF cycles)	Maternal KIR AA haplotype associated with higher early miscarriage rate when using own oocytes (DET), and decreased live birth rate when using donated oocytes; AB and BB haplotypes showed lower miscarriage & higher live birth in those settings.
Maftai et al., “Single Embryo Transfer in IVF in RPL & RIF”	2023; 108 pregnant women (78 RIF, 30 RPL)	KIR AA haplotype: greater miscarriage risk in IVF vs spontaneously conceived; BB haplotype had lower miscarriage and higher live birth; AB intermediate

Up to date KIR/KIRL

Key Study / Review	Year / Population	KIR / KIR-HLA Findings
Garmendia J et al. Exploring the Immunological Aspects and Treatments of Recurrent Pregnancy Loss and Recurrent Implantation Failure,2025	Broad (various studies / ethnicities))	KIR2DS2 and KIR2DS3 often risk for RPL; inhibitory KIR3DL1 protective; high frequency of maternal KIR AA in RPL; maternal KIR AA + fetal or maternal HLA-C2C2 associated with worse outcomes (RPL, RIF, preeclampsia)
<i>Review: Recurrent Abortion... KIR, NK, etc.</i> (MDPI review on RSA – recurrent spontaneous abortion)	2022 / mixed studies	Confirms accumulating evidence that imbalance toward inhibitory KIRs (i.e. AA haplotype), lower activating KIRs; disturbances in NK cell function; interactions with HLA-C ligands (especially C2) are key; also cytokine / T-cell / regulatory T cell dysfunction.
<i>Immunological Aspects of Infertility—The Role of KIR Receptors and HLA-C Antigen</i> (MDPI review)	2022 / mixed human studies	Women with KIR AA (especially telomeric AA) + HLA- C2C2 have higher risk; B-haplotype seems more favorable for implantation. The AA genotype is disadvantageous because of strong inhibitory signaling and low activation, reducing NK cell secretion of growth/cytokine factors necessary for trophoblast/placentation.

Up to date KIR/KIRL

Key Studies & Reviews

Title / Authors	Journal / Year	Sample / Population	Key Findings Related to KIR / HLA / RIF / Miscarriage
<i>Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage</i> (Hiby et al.)	<i>Human Reproduction</i> , 2008	95 women with ≥ 3 spontaneous miscarriages & their partners; controls	Increased frequency of KIR AA genotype in women with recurrent miscarriage; also increased HLA-C2 in both partners. Suggests maternal KIR AA + fetal HLA-C2 combination raises risk. PubMed
<i>Evaluation of KIR genes in recurrent miscarriage</i>	PubMed, 2012	40 women with unexplained recurrent miscarriage vs 90 controls	Women with miscarriage had higher frequency of Bx genotypes (more activating KIRs) and lower frequency of AA genotype. Suggests imbalance towards activation may contribute. PubMed
<i>Recurrent miscarriage is associated with a decline of decidual NK cells expressing KIR specific for HLA-C</i>	<i>Journal of Obstetrics and Gynaecology Research</i> , 2014	Women with RM vs controls, samples from decidua	Lower expression of KIR2DL1/S1 and KIR2DL2/S2/L3 in decidual NK cells in RM; especially in gestational days ~50-70. Suggests reduced inhibitory and activating KIRs locally. PubMed
<i>KIR, LILRB and their ligands' Genes as Potential Biomarkers in Recurrent Implantation Failure</i>	<i>Archivum Immunologiae et Therapiae Experimentalis</i> , 2016 	Review	Summarizes evidence for KIR (and LILRB) gene variants, KIR/HLA ligand combinations, immunological contributions to RIF. Notes that KIR-AA genotype and lack of activating KIRs may be risk. SpringerLink

Up to date KIR/KIRL

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Title / Authors	Journal / Year	Sample / Population	Key Findings Related to KIR / HLA / RIF / Miscarriage
<i>ERAP/HLA-C and KIR Genetic Profile in Couples with Recurrent Implantation Failure</i>	Piekarska et al., 2021	~491 IVF couples vs 322 fertile couples	Women positive for KIR genes in the Tel AA region + HLA-C2C2 were more prevalent in RIF. Also, certain ERAP1/2 polymorphisms (rs26653, rs26618) were linked with RIF when combined with certain HLA-C2 profiles. PubMed +1
<i>Maternal KIR haplotype influences live birth rate after double embryo transfer in IVF cycles in patients with recurrent miscarriages and implantation failure</i>	Fertility / Reprod Medicine, 2015	291 women (RM or RIF) over 1304 cycles	Mothers with KIR AA haplotype had increased early miscarriage rate when using own oocytes, and reduced live birth rate when using donated oocytes. Suggests AA haplotype has less favourable outcomes. PubMed
<i>The Influence of Maternal KIR Haplotype on the Reproductive Outcomes after Single Embryo Transfer in IVF Cycles in Patients with RPL and RIF</i>	J Clin Med, 2023	Prospective cohort, IVF patients with RPL/RIF	KIR AA haplotype significantly associated with miscarriage risk after IV compared to spontaneous conception. PubMed
<i>Recurrent Spontaneous Abortion (RSA) and Maternal KIR Genes: A Comprehensive Meta-Analysis</i>	JBRA Assist Reprod, 2020	Meta-analysis of many genetic association studies	Found KIR3DL1 (an inhibitory KIR) to be protective; activating KIRs KIR2DS2 and KIR2DS3 as risk factors. Data for KIR2DS1 had heterogeneity. PubMed

Up to date KIR/KIRL

Recent Publications

Year	Title / Authors	Key Findings Relevant to KIR / HLA / Implantation or Miscarriage 
2024	<i>Specific KIR gene profiles and recurrent implantation failure</i> (P. Andreeva et al., Human Reproduction) OUP Academic	In women with RIF, those with the KIR AA1 genotype (a subtype of the KIR AA haplotype) that also express the full-length KIR2DS4 (KIR2DS4-norm) show significantly higher rates of RIF compared to other genotypes. OUP Academic
2024	<i>ERAP/HLA-C and KIR Genetic Profile in Couples with Recurrent Implantation Failure</i> (Piekarska et al.) PubMed	In IVF couples, certain combinations of female ERAP1 polymorphisms + male (partner) HLA-C ligand types are associated with protection vs risk of RIF. E.g., rs27044 in ERAP1 protects in some female/male HLA-C1 combinations; rs30187 increases risk in other combinations. Highlights interplay of KIR ligands & antigen processing. PubMed
2023–2024	<i>The Influence of Maternal KIR Haplotype on the Reproductive Outcomes after Single Embryo Transfer in IVF Cycles in Patients with Recurrent Pregnancy Loss and Implantation Failure — A Single Center Experience</i> (Romania) PubMed	Women with KIR AA haplotype had higher odds of miscarriage when undergoing IVF than those achieving spontaneous pregnancy. Also, the AA haplotype seemed to increase chance of pregnancy in IVF (though outcomes varied). Suggests maternal KIR haplotype may inform risk/management. PubMed

KIR/KIRL

Summary of the data

- **KIR AA haplotype** (i.e. more inhibitory KIRs, fewer activating ones) tends to be associated with:
 - Higher miscarriage risk
 - Higher failure of implantation (RIF)
 - Lower live birth rates under some conditions
- The nature of the *partner's / donor's HLA-C type* matters: e.g. HLA-C2 heavy combinations seem riskier when matched with KIR AA.
- Genetic polymorphisms in ERAP1/2 influence the functional interaction of HLA-C with KIR, affecting implantation success. Thus not only “which KIR/HLA-C” but also how well antigen presentation works.
- Fine granularity matters: not all KIR AA haplotypes are equal; specific subtypes (e.g. presence of functional activating KIRs like KIR2DS4 full-length) may modulate risk.

Gaps/Challenges

- **Heterogeneity in Findings:** some studies find contradictory results, especially for some activating KIRs. Sample size often small.
- **Focus More on RM than RIF.**
- **Population Differences:** Ethnic/population variation in frequencies of KIR and HLA-C ligands.
- **Functional mechanisms not fully understood:** while associations exist, the exact functional immunological mechanisms (which NK cells, what level of expression the interaction with other NK receptors etc.) are still being elucidated.

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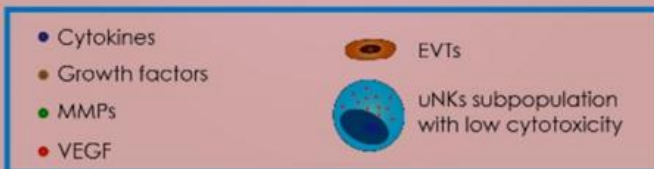
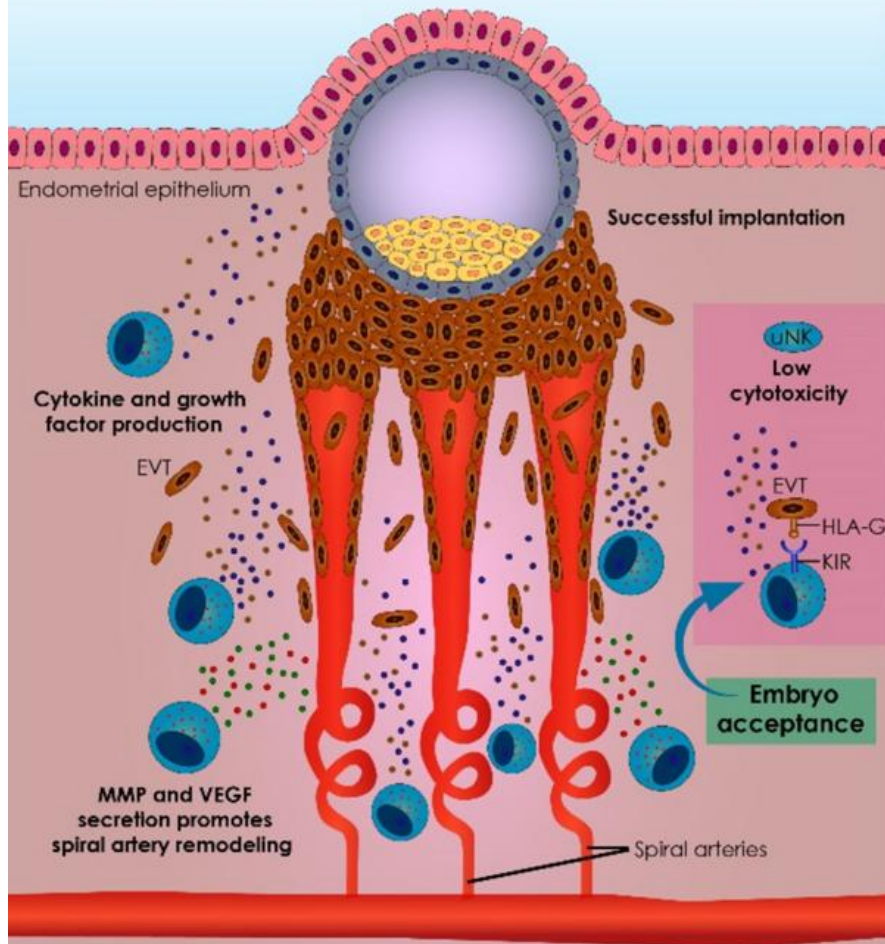
Th17, Treg, **NK cells**, cytokine dysregulation

NK cells

- NK cells – up to 70% in the uterus mucosa during the implantation and early pregnancy:
- Secretion of immunoregulatory cytokines
- NK differentiation depends on hormones and Th2 response (IL-4, 5, 10)
- **Decidua** – 2 types of NK cells
 - CD3-CD16-C56+ (**CD56brightCD16+ NK**) (up to 99%) with Th2 cytokine profile; support the implantation and suppress the mother's immune response against fetus;
 - CD3-CD16+C56+ (**CD56dimCD16-NK**) (up to 1% normally); secrete TNF- α , IFN- γ (Th1)
- **Peripheral blood**
 - >12 % (in PB) CD3-CD16+C56+ NK cells – high risk of spontaneous abortion and impossibility for implantation.
 - Up to 10% of NK cells are **CD56brightCD16-NK** cells. They produce cytokines, express only one MHC class I-specific inhibitory receptor (NKG2A), show low cytotoxic potential

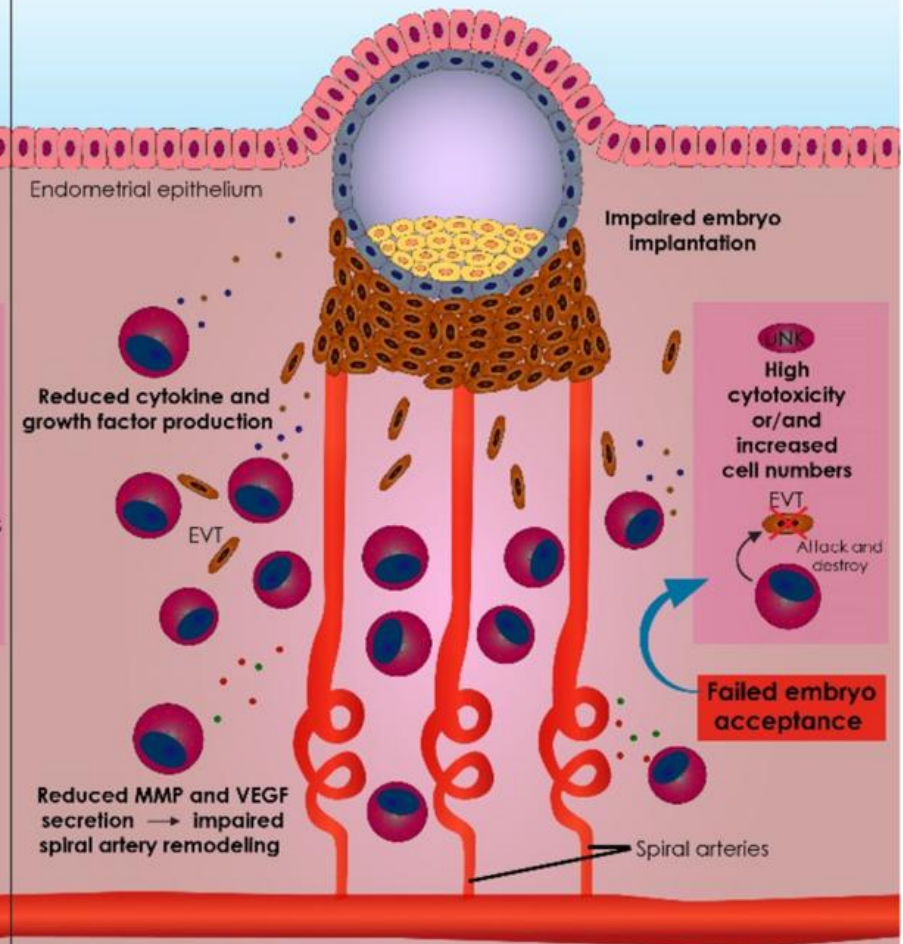
The role of NK cells

A. Successful implantation and pregnancy maintenance



B. RIF and RM

Konstantinos Sfakianoudis,
Biomedicines 2021,



Up to date NK cells

Key Recent Meta-Analyses / Systematic Reviews

Title	Year / Date	Populations Covered (RM, RIF, Infertility)	NK Cell Type / Measurement	Key Findings
<i>Peripheral blood natural killer cell cytotoxicity in recurrent miscarriage: a systematic review and meta-analysis</i>	2023	Women with recurrent miscarriage vs controls; nonpregnant and pregnant phases	Peripheral blood NK cytotoxicity	Higher pNK cytotoxicity in RM vs controls, both when nonpregnant and during pregnancy.
<i>The Effect of Immunotherapy on Natural Killer Cells Level/Activity in Recurrent Pregnancy Loss (RPL) Patients</i>	2024 / up to Sept 2023	RPL patients	Peripheral NK levels/activity; Also therapy with IVIG, intralipid, LIT etc.	Some immunotherapies (IVIG, intralipid, lymphocyte immunotherapy (LIT)) reduce NK level or activity; possibly improve live birth in RPL patients with elevated NK. Evidence is mixed and quality is variable.
<i>Number and function of uterine natural killer cells in recurrent miscarriage and implantation failure: a systematic review and meta-analysis</i>	Published ~2022-2023	Women with RM or RIF vs controls	Uterine NK (uNK) number/function; comparison to peripheral NK, correlation etc.	uNK levels/function differ in RM/RIF vs controls; shows uNK is more relevant (because pNK and uNK differ), but studies still heterogeneous
<i>Immunotherapy to improve pregnancy outcome in women with abnormal natural killer cell levels/activity and recurrent miscarriage or implantation failure: A SR & MA</i>	2020	Women selected for abnormal NK cell level/activity + RM or RIF	Different immunotherapies: IVIG, prednisolone, etanercept, intralipid	In non-RCT studies, IVIG showed increased live birth (RR ~2.57). Some RCTs for intralipid & etanercept showed positive effect; but heterogeneity is high, evidence moderate to low quality. Recommended more high-quality trials.

NK cells

Recent Consensus / Overall Picture

- Elevated peripheral NK cytotoxicity and elevated NK numbers are more consistently associated with **recurrent miscarriage** than with recurrent implantation failure.
- Immunotherapy (IVIg, intralipid, possibly others) *may* help RPL in selected patients with elevated NK activity or levels, but evidence is not definitive;
- For RIF, the evidence is weaker; would need more studies selecting for NK abnormalities and using standardized definitions / outcomes.
- Uterine NK might be more directly relevant, but difficult to use in standard diagnostics; sampling/timing, markers, functional assays need more standardization.

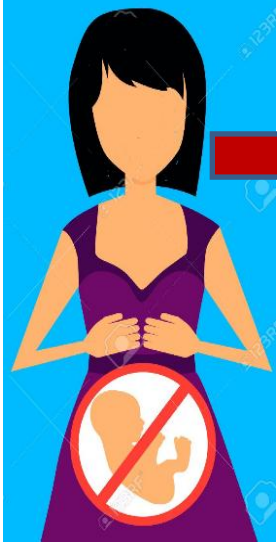
AIM

- To investigate the association between KIR gene polymorphisms and pbNK cell subsets in Bulgarian females with reproductive failure (RM and RIF).

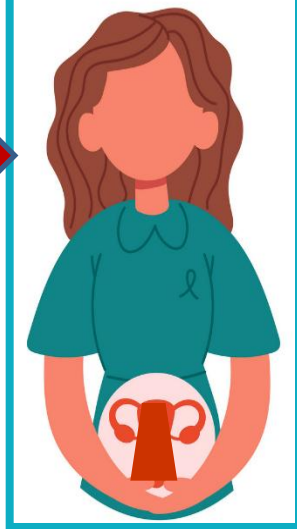
Material and methods:

Individuals studied

RF n=471



RM n=145



IVF/RIF n=152



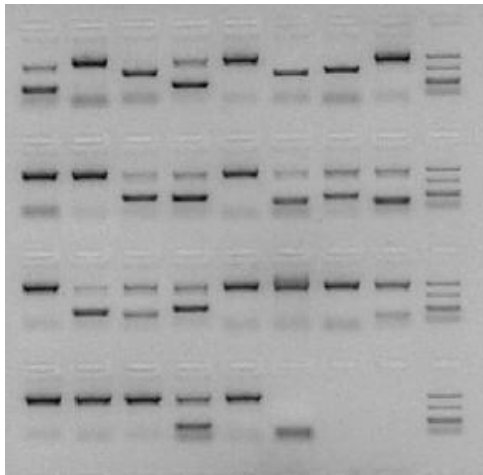
mean age of 37.2 ± 5.8 y
(SD 5.8)

CONTROLS n=126*

Material and methods:

KIR genotyping

- PCR-SSP Olerup SSP® “KIR genotyping kit”
- www.allelefrequencies.net



 **Allele Frequency Net Database**

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Home Populations HLA **KIR** Other polymorphisms HLA-ADR KDDB

KIR » Genotype Reference List

KIR Genotypes

[Click here to select particular population\(s\)](#)

[Clear](#)

Haplotype Group: Genotype ID: Country: Times found in pops.: Source of dataset:

Region: Ethnic Origin: Type of Study: Sort by:

Genotype: 3DL1 2DL1 2DL3 2DS4 2DL2 2DL5 3DS1 2DS1 2DS2 2DS3 2DS5 2DL4 3DL2 3DL3 2DP1 3DP1

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

[1=Positive, 0=negative, n=not tested, leave blank for not known]

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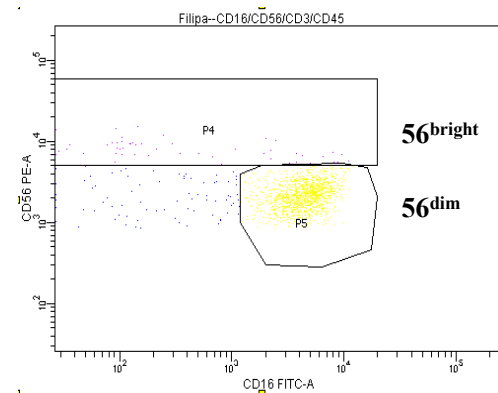
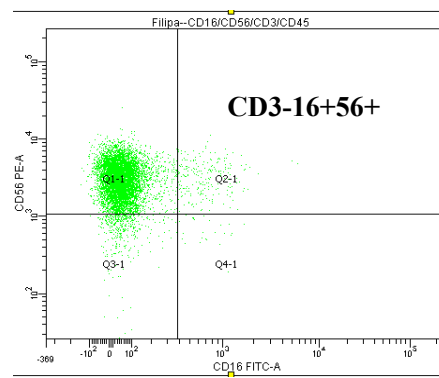
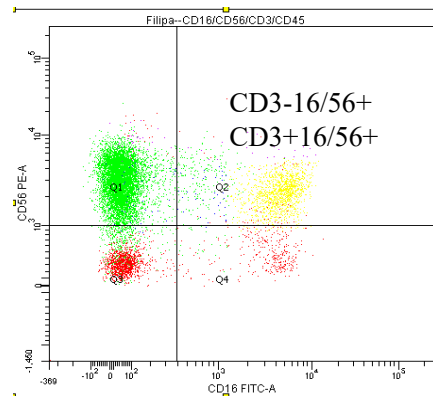
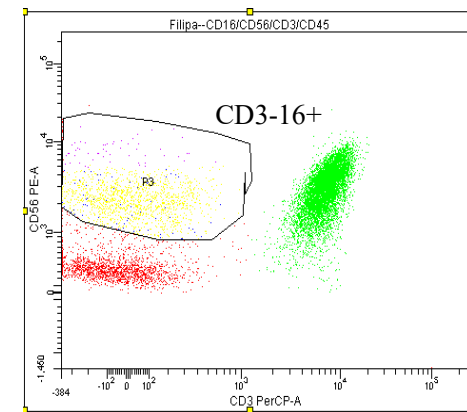
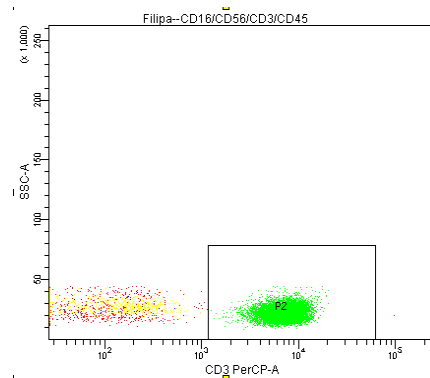
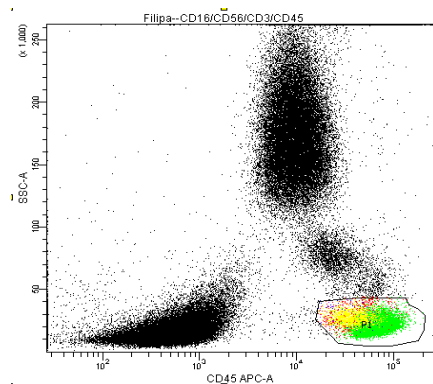
Hapl Group	Genotype ID ¹	3DL1	2DL1	2DL3	2DS4	2DL2	2DL5	3DS1	2DS1	2DS2	2DS3	2DS5	2DL4	3DL2	3DL3	2DP1	3DP1	Populations	Individuals	Population on which the unique genotype was found ²
Bx	10																	56	93	

Listing 1 genotype(s).

¹ Genotype ID - ID assigned by the Allele Frequency Net Database. Please use this number for citations.

² Unique population in which the genotype has been found.

Material and methods: NK cell subsets



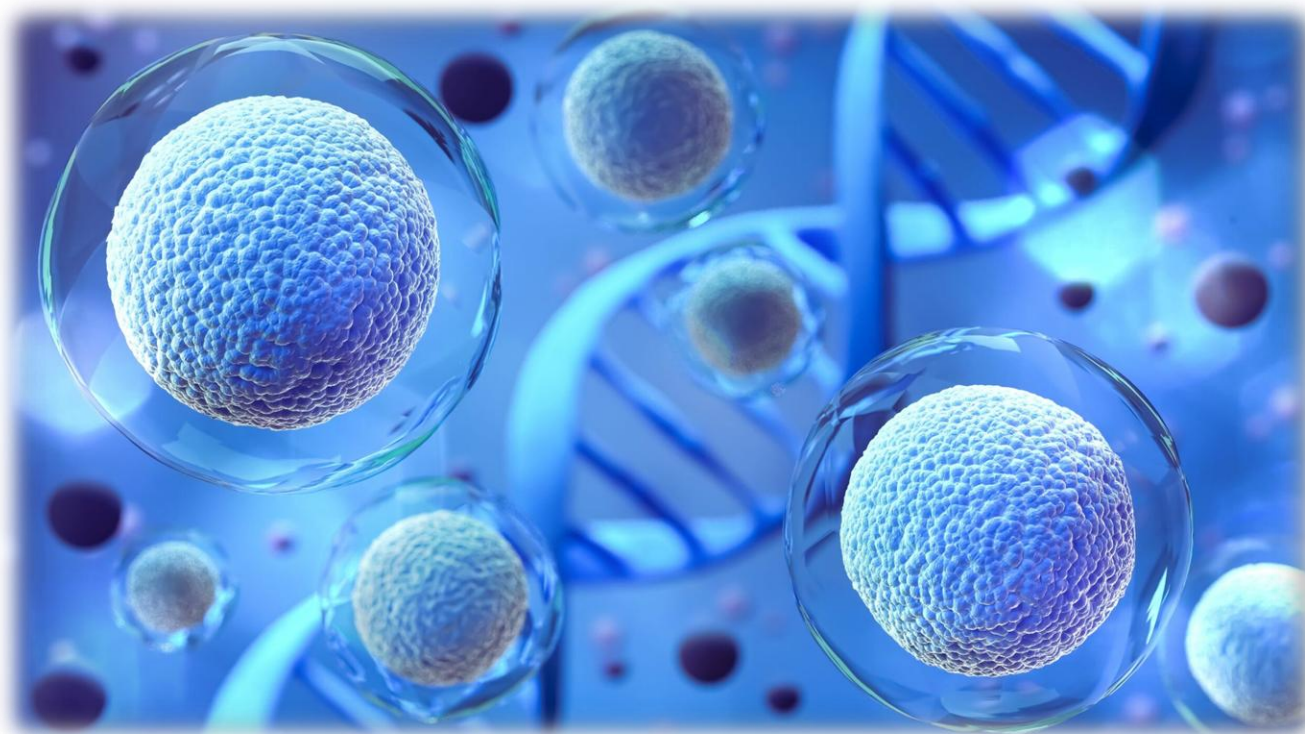
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Materials and methods

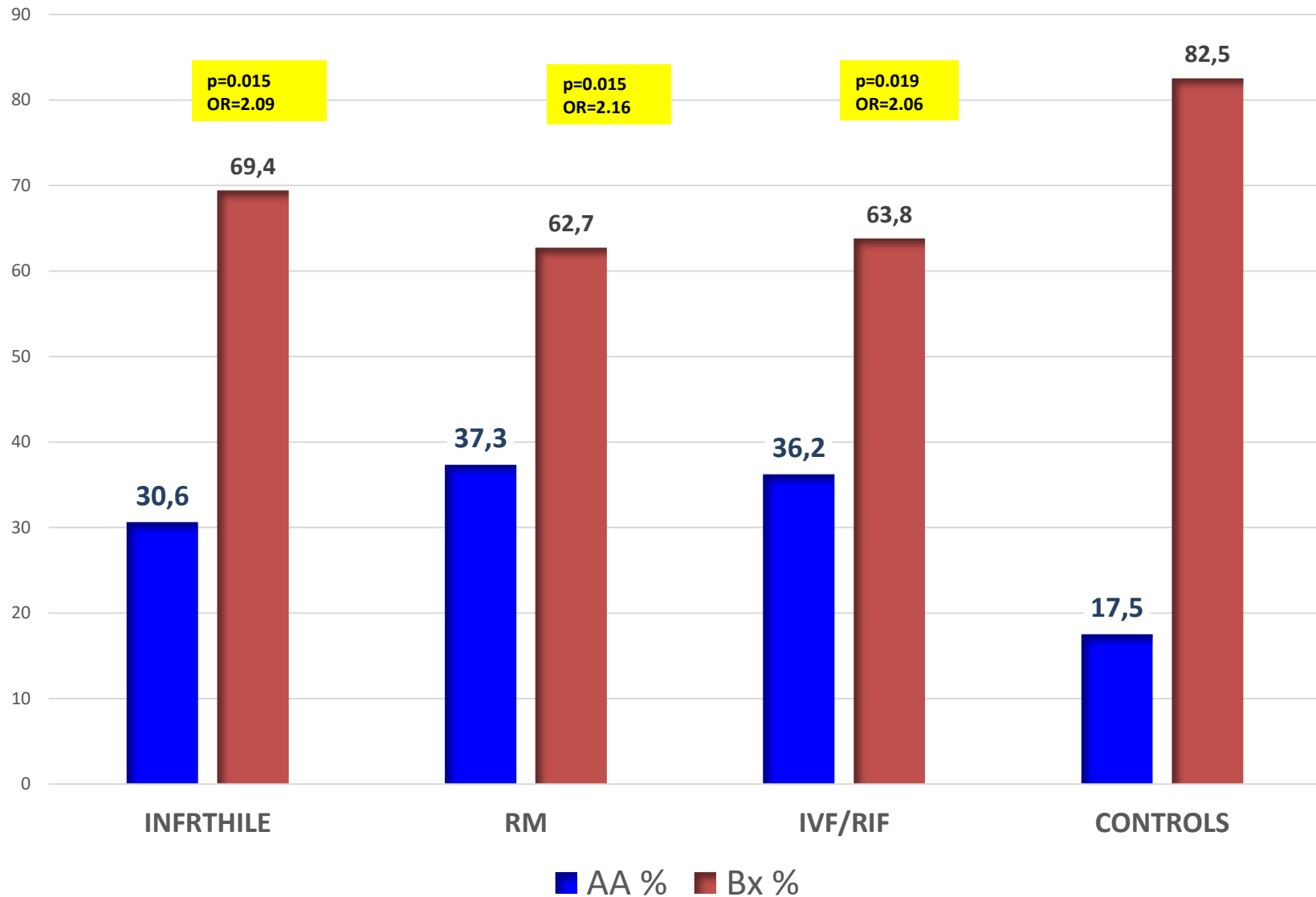
Statistical analysis

- *Descriptive Statistics* to summarize and understand the dataset's characteristics and to investigate the distribution of variables.
- *Mann-Whitney* test to assess differences in continuous data between two independent groups.
- *Kruskal-Wallis* test to evaluate differences in continuous data among multiple independent groups.
- *Chi-Square* test to examine associations between categorical variables.
- *Fisher's Exact* test to assess associations between categorical variables with small sample sizes.
- *Software: SPSS v26* (IBM)
- P-values below 0,05 are considered as statistically significant.

Results



KIR genotype frequencies in RF females compared to controls in %.



Bx haplotypes distribution in RF females and controls in %



УНИВЕРСИТЕТСКА БОЛНИЦА
АЛЕКСАНДРОВСКА

2DL1	2DL2	2DL3	2DL4	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	3DL1	3DL2	3DL3	2DL5A	2DL5B	2DP1	3DP1	ID	INFERTILE	CONTROLS
/2DP1													*001/005					n=124	n=126
																	ID2 *	7 (5,6%)	17 (13.5%)
																	ID3	6 (4,8%)	6 (4.76%)
																	ID4	13 (10,5%)	14 (11.1%)
																	ID5	14 (11,0%)	17 (13.5%)
																	ID6	7 (5,6%)	6 (4.76%)
																	ID7	5 (4,03%)	4 (3.2%)
																	ID70	4 (3,22%)	2 (1.58%)
																	ID71	7 (5,6%)	5 (3.97%)
																	ID73	3 (2,4%)	1 (0.79%)

*

P=0.059; OR=0.38

KIR gene frequencies in women with reproductive failure (RF) and controls in %

%	2DL1	2DL2	2DL3	2DL4	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	3DL1	2DL5A* 001/005	2DL5B	2DP1
RM	97.8	57.8	89	98.9	35.2	59.3	44	97.8	28.6	29.7*	96.7	32.2	56.7	97.8
RIF/IVF	97.2	56.9	91.7	99.1	35.8	59.6	34.9	94.5	33	39.4	94.5	38.5	47.7	97.2
Controls	96.8	60.3	85.7	99.2	45.2	65.1	38.1	92.1	38.1	47.6	90.5	34.7	45.5	96.8

*p=0.012

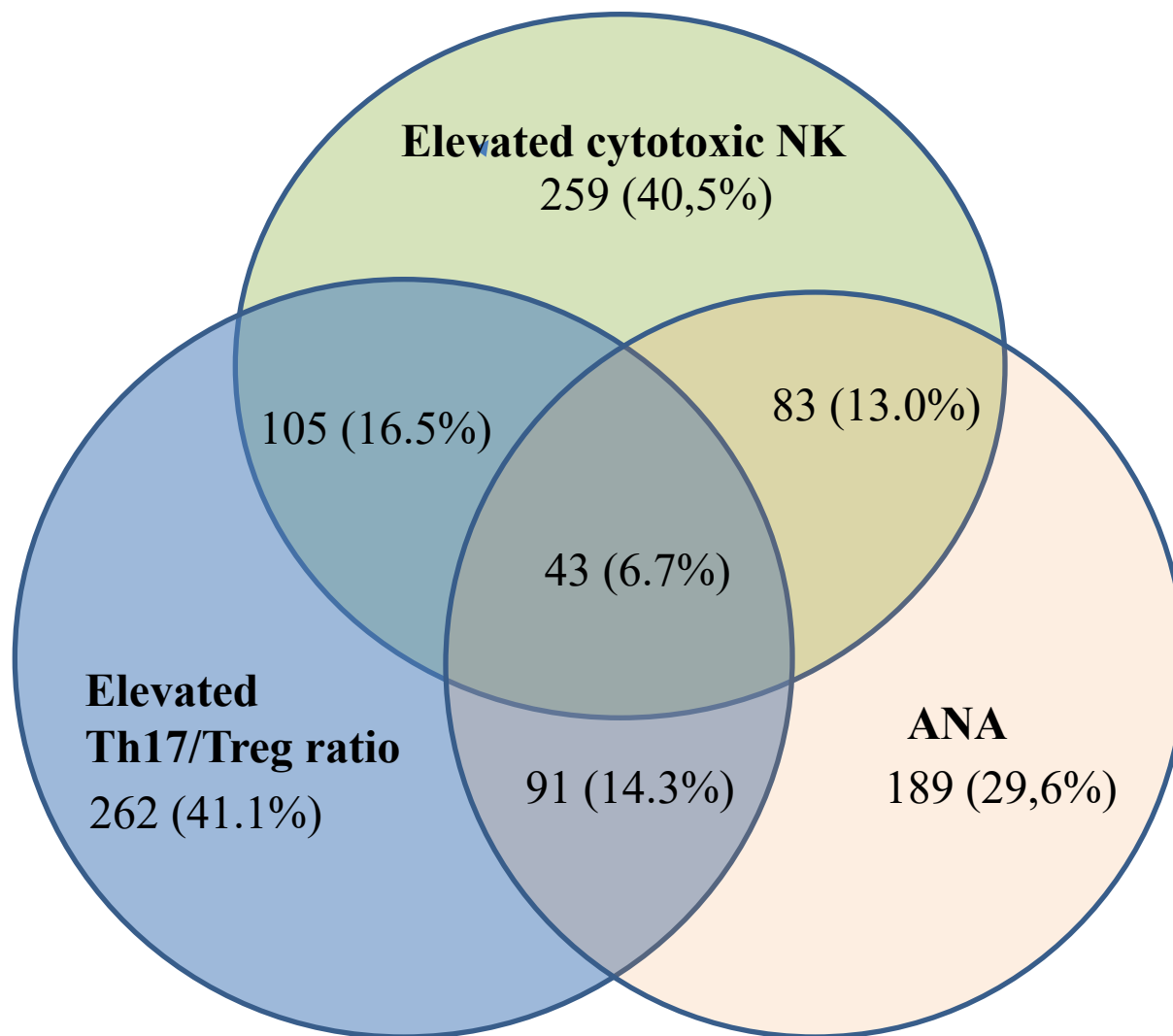
*3DS1-HLA-Bw4-I80 , HLA-F?HLA-G? Selected HLA-C
Protective-HIV, HPV, Pemphigus; Risk- psoriasis, AS, RM?*

*2DS1-HLAC2 supports the development of pregnancy and placentation.
Protective: preeclampsia, RM, LBW*

2DS5-HLAC2

Protective: preeclampsia, endometriosis. Risk: atopic dermatitis

Immune phenotypes in pb, associated with RM/RIF



pbNK cell subsets in females with RIF in %

One-Sample Kolmogorov-Smirnov Normal Test

RIF	Mean	SD	Reference ranges	One-Sample Wilcoxon Signed Rank Test***	One-Sample Kolmogorov-Smirnov Normal Test****
NK cells (CD3-CD16&56+)	17.5	6.9	8÷24	0.042	>0,0001
NKT cells (CD3+CD16&56+)	9.7	6.8	2÷10	>0,0001	>0,0001
CD3- CD16+CD56+	12.0	5.9	0÷12	>0,0001	>0,0001
CD3-CD56dim mature	83.4	9.4	65÷90	>0,0001	>0,0001
CD3-CD56bright imature	6.1	3.7	5÷10	>0,0001	>0,0001

CD3-CD56bright

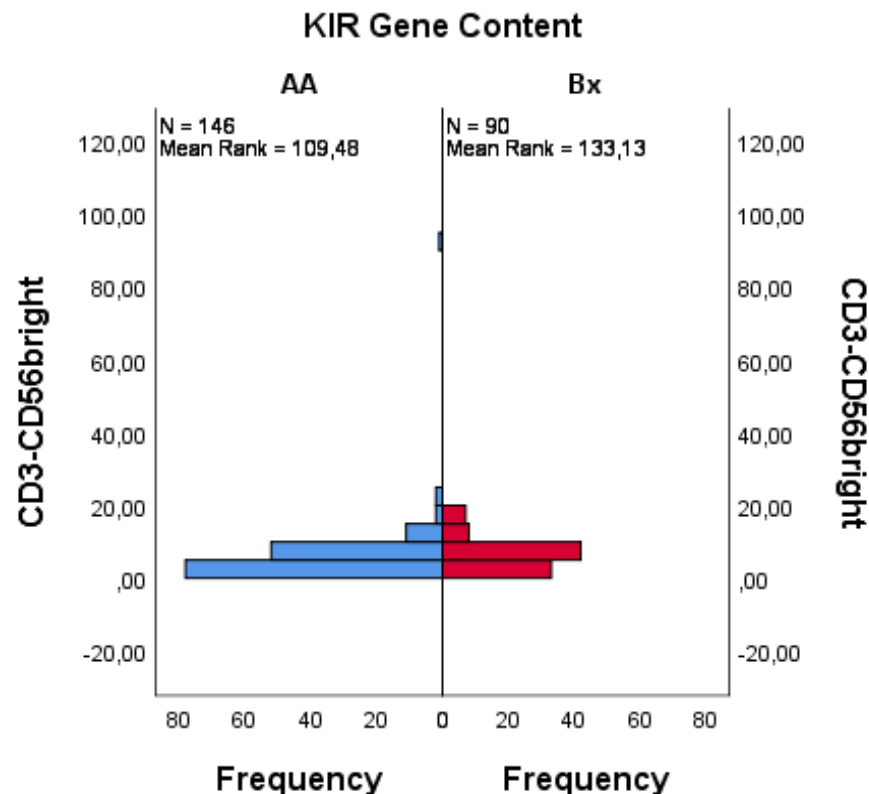
pbNK cell subsets in females with RM in %

RM	Mean	SD	Reference ranges	One-Sample Wilcoxon Signed Rank Test***	One-Sample Kolmogorov-Smirnov Normal Test****
NK cells (CD3-CD16&56+)	17.3	7.1	8÷24	0.154	>0,0001
NKT cells (CD3+CD16&56+)	9.2	5.9	2÷10	>0,0001	>0,0001
CD3- CD16+CD56+	12.2	6.1	0÷12	>0,0001	>0,0001
CD3-CD56dim mature	82.8	9.5	65÷90	>0,0001	>0,0001
CD3-CD56bright imature	6.5	3.8	5÷10	>0,0001	>0,0001

CD3-CD16+CD56+ CD3-CD56dim CD3-CD56bright

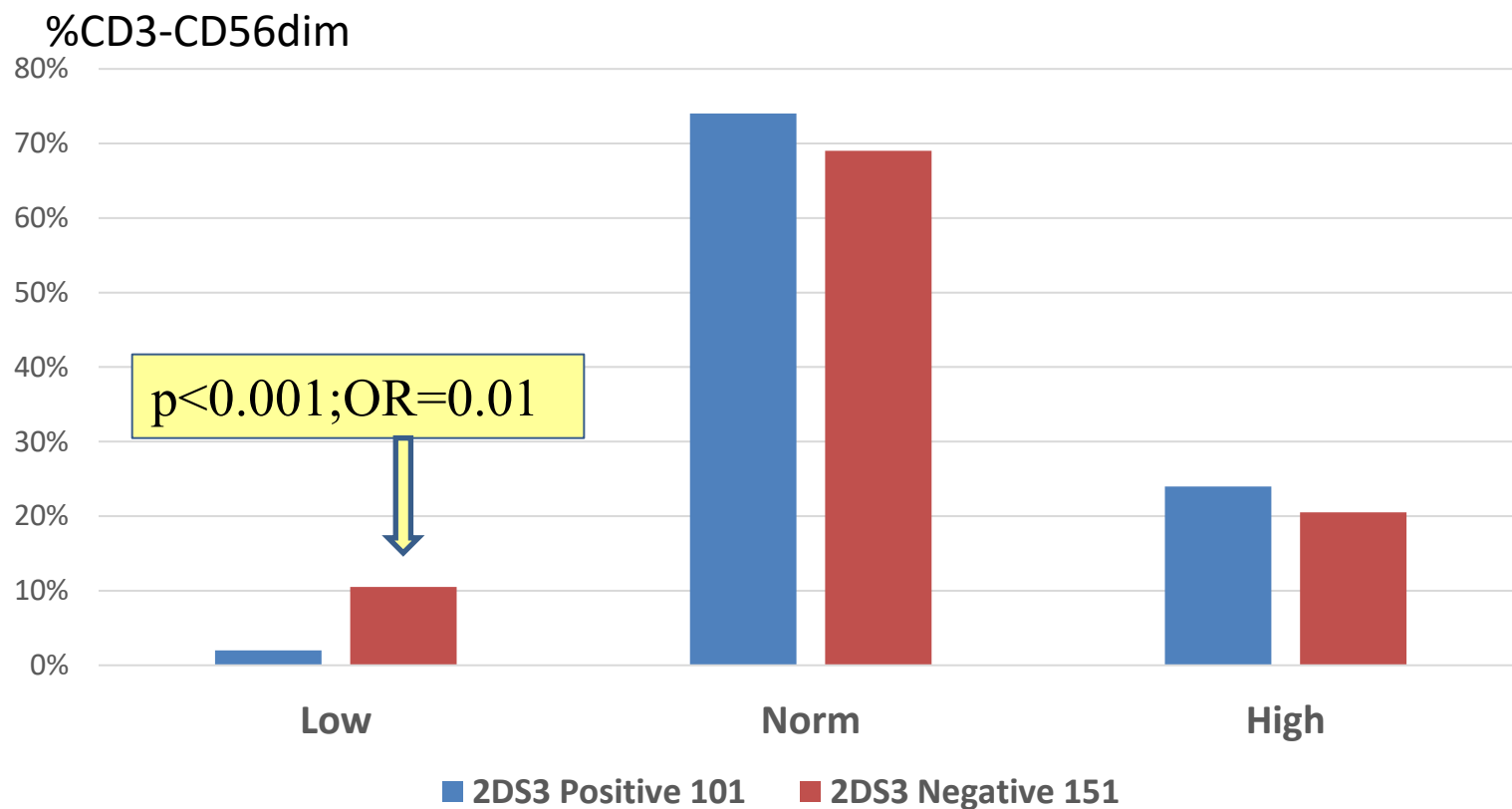
KIR genotypes and pbNK cells associations

In KIR AA females with RF, higher number of immature pbNK cells ($p=0.01$) were observed –
KIR genes can modulate NK cells education? possible compensatory mechanism?

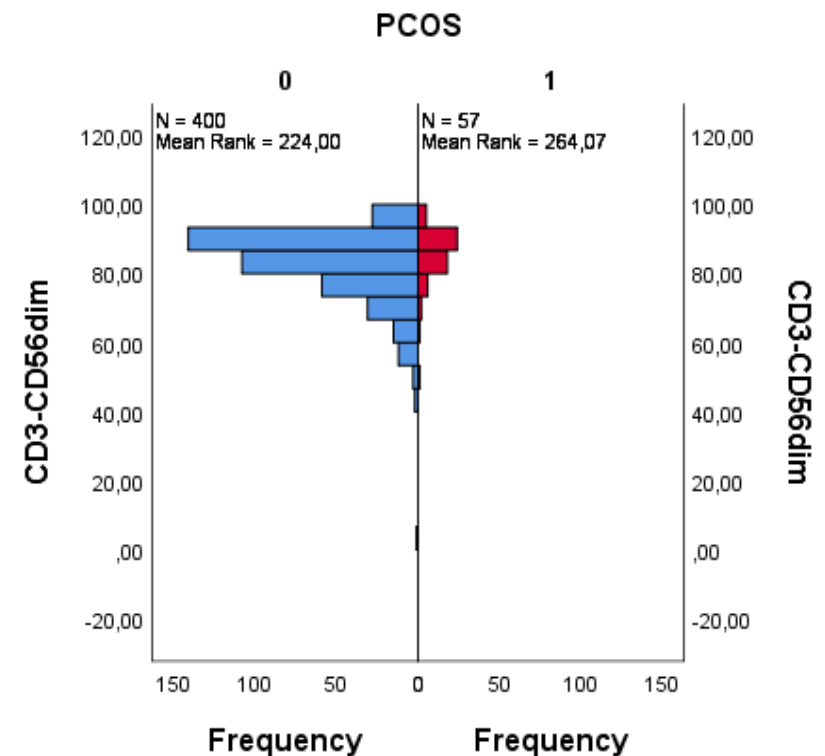
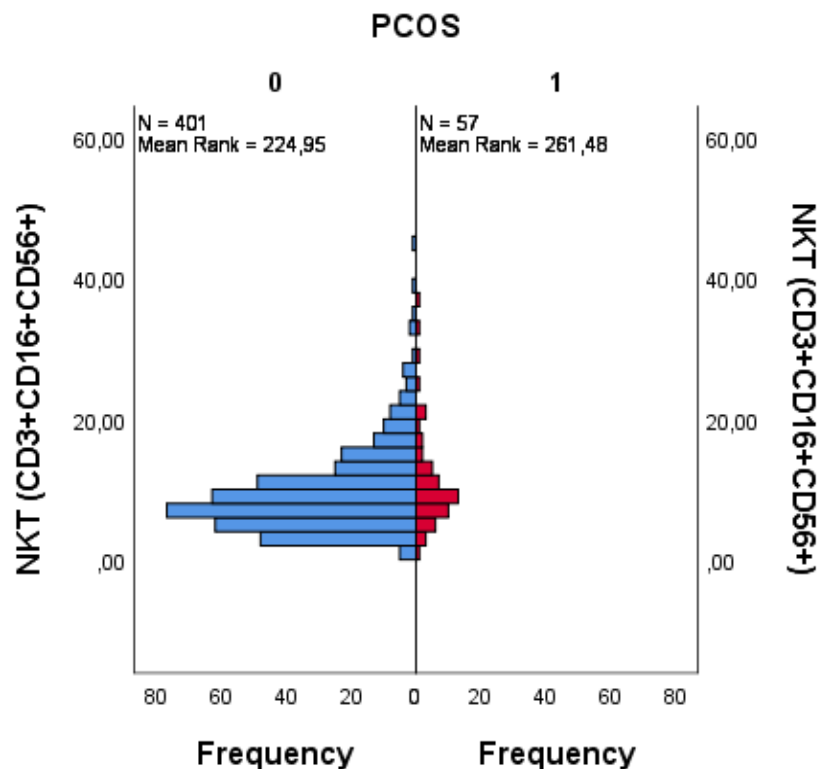


KIR genotypes and NK cell associations

Females with RF without 2DS3 gene had lower % of CD3-16+56^{dim} cells



Patients with PCOS have significantly reduced levels of NKT (p=0.051) and mature cytotoxic pbNK (p=0.032) cells



In summary

- Statistically significant associations of certain KIR genes and genotypes with reproductive failures have been found.
- *Routine KIR profiling can be used as a potential biomarker for predicting adverse reproductive history*
- pbNK cells show a statistically significant association with reproductive failures
- Analysis of the association between particular KIR genes/haplotypes and pNK cells could reveal additional mechanisms related to implantation process.
- *Could be useful as a predictive tool for RF and for the development of immunotherapeutic strategies.*

Acknowledgments



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N. Gesheva, MD



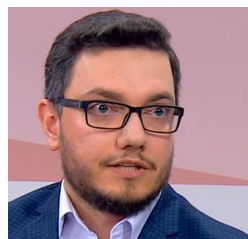
A. Kalchev, MD



A. Nedyalkova



Prof. A. Mihaylova



Ts. Lukanov



L. Teicelkova



I. Todorova



**Prof. E. Naumova,
MD**