

Live birth rate after oocyte donation is influenced by donor HLA-C: one step beyond conventional markers of success

Study question: Do maternal KIR have an impact on pregnancy, miscarriage and live birth rates (LBR)/cycle in donor oocytes –ART by paternal and oocyte donor HLA-C?

Summary answer: The maternal KIR and parental donor HLA-C combination could predict which couple can benefit for donor selection by HLA-C in order to increase LBR.

What is known already: Increased risk of recurrent miscarriage (RM), preeclampsia, fetal growth restriction has been described in KIR AA mothers when the fetus has more HLA-C2 genes than the mother. Pregnancy disorders are predicted to reduce the frequency of KIR A/HLA-C2, and this selection is thought to have originated during human evolution. In ART oocyte donor cycles, oocyte HLA-C behaves as the paternal HLA-C and KIR-HLA-C combination is not presently taken into account during donors' selection. KIRAA women have lower live birth rates (LBR) after double embryo transfer (DET) in egg-donation ART cycles.

Study design, size, duration: Between April 2014 and September 2016, we performed a prospective study that included 201 women whose recurrent reproductive failure was of unknown etiology: recurrent implantation failure (RIF) (N = 113) and RM (N = 89), who had 138 oocyte donor-assisted reproductive (ART) transfers and 63 own oocyte transfers.

Participants/materials, setting, methods: All the patients were selected from IVI Clinics, and had normal karyotype, thrombophilic, and immunological results. They had 201 embryo transfers (ET)(1 transfer/patient), of which 138 were with oocyte donation (57 DET, 81 SET). We performed genetic typing for maternal KIR and HLA-C, and for the HLA-C of their partners, oocyte and sperm donors, babies and product of conception after miscarriage. Pregnancy, miscarriage and LBR/transfer were studied by the maternal KIR haplotype and embryo HLA-C. Main results and the role of chance: The median age of our patients was 40 years, and 25 years for oocyte donors.

In our cohort, 36.3% of women had KIR AA, 41.3% KIR AB and 22.4% KIR BB had the BB genotype. Higher miscarriage rate/transfer after DET-oocyte donation was observed in KIRAA women (47.6%) compared with KIR AB (4.5%) and KIR BB (7.7%) ($p < 0.01$). Lower LBR/transfer was observed after DET-oocyte donation in KIR AA women (4.8%) compared with AB (22.7%) or BB (46.2%) ($p < 0.03$).

The study of LBR/transfer by maternal KIR and HLA-C and their embryos HLA-C revealed that LBR significantly lowered from 100% after transferring embryo HLA-C1 (N = 2) to 0% after transferring DET and HLA-C2 embryos (N = 11) in KIR AA women ($p < 0.000$). This trend was not observed in the KIR AB or BB patients.

LBR lowered in KIR AA patients as differences between embryo and mother HLA-C2 increased. When comparing both groups, i.e., Embryo HLA-C2 \leq Mother HLA-C2 (group 1) and Embryo HLA-C2 $>$ Mother HLA-C2 (group 2), a significantly higher LBR per transfer was noted in group 1 (57.1%) vs. group 2 (25%) ($p > 0.01$) in the KIR AA women.

Limitations, reasons for caution: Our sample was small and this is the first report to observe differences in LBR by oocyte donor/embryo HLA-C in KIR AA mothers. However, apart from statistical significance, the association strength was noticeably high, which confers the findings more confidence.

Wider implications of the findings: We speculate that completing normal pregnancy is possible only for those KIR AA mothers who carry a baby with a least one non-self HLA-C1. Therefore, selecting HLA-C1 amongst oocyte and/or sperm donors for KIR AA patients who undergo egg donation could be more efficient and safer. Trial registration number: not applicable since no intervention was made.