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Abstract title:

Treatment strategies to increase the live birth rate in patients with KIR-HLA-C mismatch: a retrospective cohort study

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Study question:

Does the selection of HLA-C1C1 oocyte donor or the administration of granulocyte colony-stimulating factor (G-CSF) improve the live birth rate/cycle in couples with KIR-HLA-C mismatch?

Summary answer:
The selection of HLA-C1C1 oocyte donors improves live birth rate (LBR) compared to random HLA-C donors or to G-CSF administration in couples with KIR-HLA-C mismatch.

What is known already:
Increased risk of recurrent miscarriage (RM), preeclampsia, and fetal growth restriction has described in KIR AA mothers when the fetus has more HLA-C2 genes than the mother, and this HLA-C2 are paternally or egg donor inherited. In ART oocyte donor cycles, oocyte HLA-C behaves as the paternal HLA-C and KIR-HLA-C combination is not currently taken into consideration on donors' selection. KIRAA women have lower live birth rates (LBR) after double embryo transfer (DET) in egg-donation ART cycles especially when the embryo carries HLA-C2. G-CSF administration seems to improve the LBR in patients with recurrent miscarriages lacking activating KIR.

Study design, size, duration:
Between January 2017 and December 2018, we performed a retrospective study that included 72 women whose RM/RIF were of unknown etiology and 261 embryo transfers (ET). All couples had KIR-HLA-C mismatch: maternal KIR AA and paternal HLA-C2. All the patients underwent egg donation. Forty-five couples (group 1) had 135 ETs (70% SET and 30% DET) and 27 couples (group 2) had 126 ETs (83% SET and 27% DET).

Participants/materials, setting, methods:
All the patients were selected from IVI RMA Clinics. Group 1 had 90 ETs with random HLA-C egg donor and 45 SET with HLA-C1C1 egg donor. Group 2 had 99 ETs with random HLA-C egg donor and 27 SET with HLA-C1C2/C2C2 egg donors and G-CSF administration. We performed genetic typing for maternal KIR and paternal and oocyte donors HLA-C. Pregnancy, miscarriage and LBR/transfer have studied by groups and cycles. Fisher test has used.

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, all women had KIR AA and their partners HLA-C2.

A higher LBR/cycle was observed in group 1 when their HLA-C1C1 egg donor cycle (48.89%) was compared to the previous random HLA-C egg donor cycles (5.77%) (OR 42.82).

A higher LBR/cycle was observed in the group 2 when compared the cycles using G-CSF administration (14.81%) and their previous random HLA-C egg donor cycles (6.38%) (OR 6.86).

Higher LBR/cycle was observed in HLA-C1C1 egg donor cycles - group 1 (48.89%) when compared to

HLA-C1C2/C2C2 egg donors and G-CSF administration cycles -group 2 (14.29%) (OR 6.82, p<0.002).

A higher pregnancy rate was observed in group 1 when compared their HLA-C1C1 egg donor cycles (80%) to HLA-C1C2/C2C2 egg donors and G-CSF administration cycles -group 2 (24.44%) (OR 3.8, p<0.01).

We did not observe any differences on miscarriage rates between both groups (C1C1 egg donor 13.33% and G-CSF 17.86%).

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 or C-GSF administration in KIR AA mothers with embryos HLA-C2 and egg donation. However, apart from statistical significance, the association strength was noticeably high, which confers our findings more confidence.

Wider implications of the findings:
We speculate that completing a normal pregnancy is posible only for those KIR AA mothers who carry a baby with a least one non-self HLA-C1. Therefore, selecting HLA-C1C1 amongst oocyte donors for KIR-HLA-C mismatch couples could improve the LBR compared to random HLA-C egg donors or the G-CSF administration.

Trial registration number:
1812-MAD-101-DA

Keywords:
killer cell immunoglobulin-like receptor (KIR)
HLA-C
granulocyte colony-stimulating factor (G-CSF)
egg donation
live birth rate (LBR)