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Letter to Editor

Increased Mortality in Male Recipients of Red Cells from ever Pregnant Female Donors: mHAGs on Red Cells to Blame?

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Dear Editor,

It was already shown that plasma from pregnant female patients could cause transfusion-associated lung injury (TRALI)[1] so, increasingly plasma obtained from female donors with a history of pregnancy is no-longer used for routine plasma transfusion. In addition, TRALI associated with red blood cell transfusion by a multiparous woman, as reported in a later paper of this Journal[2], has also been described. Recent evidence as obtained from one extensive study showed that red cell concentrates cause a significant increase in mortality in the male patients who received red cells from ever pregnant female donors.[3] This study conforms to a previous research done at a smaller scale,[4] although other studies,[5,6] not distinguishing ever-pregnant from nulliparous women, could not show a similar effect. The hazard ratio for mortality in hospitalized male recipients of red cells from ever pregnant female donor was from 1.08-1.23 depending on whether it is a single transfusion or multiple transfusion and age group of the recipient. The scenario as described by the authors makes us suspect an immunological cause for such an effect as is seen in sex-mismatched bone marrow transplantation where cells from an ever-pregnant female donor to a male recipient has a higher risk of acute GVHD.[7] This phenomenon has been linked to various minor histocompatibility antigen (mHAG) sensitization in the pregnant female donor.

However, the cause of higher mortality in the case of unisex ever-pregnant female red cell transfusion to a male recipient is not so readily apparent. First, all the recipients received prestorage leucocyte filtered blood. Knowing that modern-day filters are highly efficient, the cells which could have incited a transfusion-associated (TA) GVHD type reaction would be mostly absent ($<1x10^6$) even if not entirely so in such a transfusion. Furthermore, the TA-GVHD type reaction is exceptionally improbable if the dead patients received irradiated red cells. Though the details of death in the recipients were not noted it could be assumed that it was not due to TA GVHD. However, in the animal model, minor histocompatibility antigens on transfused leukoreduced units of red blood cells did cause bone marrow transplant rejection[8], and this was elegantly demonstrated through the development of cytotoxic CD8 lymphocytes against recombinant red cell mHAG in mouse red-cells. In the present scenario, this mHAG then needs to be sex-linked. The only Sex-linked MHAG antigen we know is Xg antigen, and it is likely that female donors were mosaic for such an antigen and in most of such unisex transfusion, there will be Xg antigen mismatch. Could this be the cause of immunological sensitization in those dead patients described in the paper? The small amount of plasma which might have been present in red cell concentrates could have the antibodies against many HLA and other antigens but is unlikely that such a small amount of plasma even if contained substantial antibody could have primed the immune effector cells to cause final catastrophe. Before we go any further, the results of current findings need to be repeated prospectively with details of the cause of death in the recipient of such unisex transfusion. Another curious datum was that the increased mortality was restricted to

recipients of less than 50 years of age. This finding remains unexplainable at present. The present study has raised more questions than answers.

However, if this were proved in a prospective study and mHAGs on red cells be confirmed to be the culprit then transfusion science has to get ready for a big surprise, and some more overhauling red cell transfusion policy had needed to be undertaken.

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