Editorial

Outcome of red blood cell transfusion: ladies first, but perhaps not in donation

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In efforts investigating mechanisms of the association between blood transfusion and adverse outcome, the research field has increasing attention for the contribution of specific donor characteristics. In particular, there have been reports highlighting the association between increased risks of mortality in (male) recipients of red blood cells derived from female donors (1-3), although this association was not confirmed in a recent large cohort (4).

In the October 2017 issue of *JAMA*, Caram-Deelder and colleagues follow-up on the risk of female red blood cell donations, using observational data derived from a database of a cohort of 42,132 Dutch patients (5). This study presents results indicating an increased risk of mortality in male recipients from red blood cells derived from female donors with a reported history of a previous pregnancy ("ever-pregnant donors"), but not from females that did not report pregnancy ("never-pregnant donors"). This is the first study that has attempted to analyze the impact of a history of pregnancy on recipient outcome following red blood cell transfusion, generating several thought-provoking results.

If the association between donor pregnancy history and mortality indeed reflects a causal relationship, results may have important implications, urging transfusion services to mitigate the risk of red blood cell transfusion; similar to what has been done for plasma transfusion. As from 2007, following the association between transfusion of plasma derived from female donors and the occurrence of transfusion-related acute lung injury (TRALI), a blood bank policy of banning (previously pregnant) female donors from donation of plasma-rich products has been implemented in various countries. This policy resulted in a reduction of the incidence of TRALI with about 60% (6,7). However, maintaining a steady blood supply of red blood cells is likely to be impossible if all females with a history of pregnancy will be deferred from donation. Although there may be alternative options to mitigate the risk of red blood cell transfusion, such as matching of sex between donor and recipient, or improving the blood product by deleting the causative agent (provided that this has been found out), such costly interventions need to be backed up by substantial evidence of a possible benefit on patient outcome. Given the risk of covariate imbalance in observational studies in large databases with complex analyses, such as the present one, possible alternative causes for the observed association need to be identified. Also, results need to be intelligible.

Caram-Deelder and colleagues analyzed the association between donor pregnancy status and outcome in 42,132 patients from 6 Dutch hospitals receiving red blood cell transfusions (the full-cohort). Primary analyses were performed in the sub-cohort of patients who received transfusions exclusively from male donors, or exclusively from never-pregnant donors, or exclusively from ever-pregnant donors (no-mixture cohort, n=31,118). Another analysis was done in the sub-cohort of recipients of a single

red blood cell unit (n=16,959). These analyses in sub-cohorts were done to avoid drowning of any effects from mixing patients who received red blood cell transfusions from both male and female donors. Follow up time was at least 2 years. Cox proportional hazard ratios (HRs) for death were calculated. In the no-mixture cohort, male patients transfused with blood from ever-pregnant donors had an increased mortality risk [HR: 1.13 (95% CI, 1.01–1.26); P=0.03] when compared to male patients receiving blood from male donors. This risk was not observed with blood derived from never-pregnant donors. In female patients, there was no impact of donor sex or pregnancy status. Results were also comparable in the analysis in the single-transfusion cohort, although statistical significance was lost, probably due to smaller numbers. In the full cohort, similar results were found, although risk was slightly lower, with a HR of 1.08 (95% CI, 1.02–1.15). Intriguingly, the association was present in young male recipients, but was not found in those with 50 years of age and older.

When trying to understand these data, what comes to mind is the question of the potential mechanism of this association. In the introduction of the study, the authors explain the rationale for this study by referring to the risk of TRALI as a potential immunological mechanism underlying the association between transfusion of blood from female donors and increased mortality. The association between TRALI and receipt of female donor blood is thought to be due to the presence of antibodies in the donor as a result of repeated pregnancy. Immune-mediated TRALI occurs after transfusion of blood containing these antibodies, resulting in lung injury within 6 hours of transfusion, often requiring admission to the Intensive Care and mechanical ventilation (8). In the present study however, the association between transfusion of female blood and mortality is more apparent after 2 years then immediately following the transfusion. Of note, this long interval between exposure to female blood and mortality has also been found before (1). Also, if TRALI would be the mechanism underlying the observed association, it is not comprehensible that only male recipients and not female recipients have increased mortality, as sex of the recipient is not a known risk-factor for TRALI (9,10). In addition, there does not seem to be an impact of age of the recipient on the incidence of TRALI, as the prevalence appears the same across age groups (11,12), whereas in this study, the association between mortality and female blood was present only in young patients. Thereby, it seems unlikely that antibody-mediated TRALI accounts for the observed increase in mortality of male recipients of blood from ever-pregnant donors in this study.

Given the provided rationale for conducting this study, some of the results can be regarded as unexpected. In the event of unexpected results in studies with an inherent risk of confounding due to the nature of their design, it is important that there is an intelligible mechanism underlying an association. This study is a challenge for the research community to dive deeper and find out.

An intriguing finding that needs further exploration is that besides mismatch in sex between donor and recipient, this study suggests that the age of the recipient also determines outcome, with a higher risk of dying observed in younger male recipients but not in the elderly. Taken together, this study points towards a role for a mechanism that is both sex and age-specific. Given the influence of hormones on erythropoiesis and on red blood cell membrane integrity (13), experimental studies or prospective clinical studies determining the impact of various hormone levels on donor red blood cells may help to strengthen evidence. Also, even though the products in this study were leuco-reduced, immunological explanations other than the presence of antibodies may underlie the age effect found in this study, given that transfusions exert a myriad of immune responses, and given that the ability of the host to generate an immune response highly depends on age (14). Another tempting speculation that comes up when thinking about impact of age of the patient on outcome of transfusion may be that the changes relating to endothelial condition and vasoregulatory ability of the recipient that occur during a lifetime may play a role. The endothelium of younger recipients may interact differently with donor red cells compared to elderly recipients. This area is still largely unexplored.

Alternatively, the observed relation between ever-pregnant donors and increased mortality of male recipients found in this study may not be true, due to methodological issues. In the study, 44% of the female donors could not be classified regarding their pregnancy status. Although authors note that these missing data are due to logistics and are likely to introduce a 'random error', this is still an assumption. Also, analyses were performed in a no-mixture cohort and in a single unit cohort, which is an understandable approach in order to reduce the chance of losing a potential signal related to donor-recipient sex mismatch. However, this method may introduce bias. In particular, censoring the patients that have received blood from both male and female donors may have resulted in losing patients that received more units of blood, which may have reflected increased illness severity with subsequent

increased risk of dying. Also, patient referrals between hospitals may have resulted in censoring of patients due to loss of follow-up data in the participating hospitals. As more sick patients are more likely to be referred, e.g., to an academic hospital, this may also introduce bias. In this study, the majority of the data were derived from records of non-academic hospitals.

Although pregnancy status was not investigated, the present results are not concordant with a study performed in nearly a million Scandinavian patients receiving red blood cells, in which an association between female donor blood and mortality was not detected (4). Results of the study under discussion need to be validated in other cohorts in parts of the world that use the same type of leuco-depleted blood, preferably manufactured in a similar way, and preferably in a prospective setting, with more detailed data on pregnancy status and outcome. Also, exploratory mechanistic studies will surely appear in the time to come, which may underline or refute the observed association between female blood and adverse outcome. Given the absence of a plausible mechanism, the methodological issues and the conflicting results with previous findings, I feel that results do not justify changing current blood donor policies at the present time.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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