Transfusion of ever-pregnant donor red blood cells and mortality of male patients

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Abstract

Previous studies found exposure to red blood cell transfusions from female donors who have been pregnant reduces survival in male patients compared to exposure to male donor products, but evidence is not consistent. We postulate the previously observed association is modified by offspring sex, with an expected increased mortality risk for male patients receiving units from female donors with sons. Here, marginal structural models were used to assess the association between exposure to units from ever-pregnant donors, ever-pregnant donors with sons and ever-pregnant donors with daughters, and mortality. Clinical data were collected on first-ever transfusion recipients in the Netherlands and donor data were supplemented with information about offspring sex and date of birth. In this analysis, 56,825 patients were included, of whom 8,288 died during follow-up. Exposure to red blood cell units from ever-pregnant donors with sons was not associated with increased all-cause mortality risk among male transfusion recipients (hazard ratio [HR]=0.91, 95% confidence interval [CI]: 0.83-1.01). Exposure to ever-pregnant donors, irrespective of offspring sex, was associated with mortality in male patients aged between 18 and 50 years (ever-pregnant donors: HR=1.81, 95% CI: 1.31-2.51) compared to male donor units, but was protective in female patients. This study suggests that the observed increased mortality risk for exposure to red blood cell units from parous female donors does not depend on offspring sex. The increased risk of mortality seen in younger adult male patients is consistent with previous observations, but the underlying biological mechanism could not be identified in this study.

Introduction

Red blood cell transfusions are given to improve tissue oxygenation in patients suffering from anemia and hemorrhage. There is substantial variation in clinical practice leading to possible over-transfusion,[1] and furthermore transfusions are associated with harm, such as blood-borne infections and transfusion-associated circulatory overload.[2]

In 2011, an association was reported between transfusions of red blood cells from female donors and increased mortality in male patients under 50 years of age.[3] Later, this finding was replicated in an independent cohort.[4] This association was shown to be limited to female donors with a history of pregnancy, and it was estimated that this association could be responsible for one potentially preventable death per day in the Netherlands.[4,5] Although recent investigations from other countries have not found an effect of donor pregnancy on mortality after transfusion,[6,7] differences between blood product production methods and used materials, differences between donor and patient populations, as well as differences in applied methodology could explain the discrepancies in results between studies. Evidently, transfusion practices should not be changed based on these contradictory findings, yet better understanding of the biological mechanisms that gave rise to these results might enable targeted changes to blood transfusion practice.

The observation that younger adult male patients exposed to ever-pregnant donors were at increased mortality risk compared to other patient subgroups suggests that these patients are somehow 'sensitive' to a component of the red blood cell product. This sensitivity could be due to the involvement of male-targeted minor histocompatibility antigens (HY-antigens) as well as the transfusion indication.[8] Pregnant women have been shown to immunize against male antigens (e.g., HY-antigens) during pregnancy or delivery. At the same time, young men often receive blood for the indication of trauma, which is known to cause a transient immune suppression.[9] Thus, younger male patients could be more sensitive to the effects of unintentionally transferred immune cells in red blood cell transfusions because of the indication for the transfusion. Furthermore, they could be more sensitive to immune cells primed against HY-antigens. Accordingly, we hypothesize blood products from female donors who have male offspring are harmful to young male patients. We hypothesize that the effect of exposure could become apparent early, but also later in life, as can be seen by the diverging Kaplan-Meier curves in a previous publication.[4]

In order to investigate this hypothesis, we aimed to first replicate the previously found association of increased mortality in male patients receiving red blood cells from female donors with a history of pregnancy. Second, we aimed to quantify the association between mortality and red blood cell transfusions from female donors who gave birth to a son or who gave birth to a daughter. Third, we aimed to investigate these associations in different age subgroups of male patients, as effect measure modification by patient age has been observed previously.[3,4]

Three comparisons were performed (outlined in Figure 1): i) male donors (reference) compared to ever-pregnant female donors (exposure group 1) and never-pregnant female donors (exposure group 2); ii) male donors (reference) compared to ever-pregnant female donors with male offspring (exposure group 1) and female donors without male offspring (consisting of female never-pregnant donors and female ever-pregnant donors without male offspring, exposure group 2); iii) male donors (reference) compared to ever-pregnant female donors with female offspring (exposure group 1), and female donors without female offspring (consisting of female never-pregnant donors and female ever-pregnant donors without female offspring, exposure group 2).

Methods

The 'Mortality After Transfusion of Ever-pregnant donor Red blood cells' (MATER) study is an observational cohort study, including data between the January 1, 2005 and January 1, 2019 from two earlier cohort studies,[3,4] supplemented with data from recent years (2015-2018) and additional exposure information pertaining to donor pregnancy history. Patient data were collected to the 'Risk Factors for Alloimmunization after red blood Cell Transfusions' (R-FACT) study database (CCMO-NL29563.058.09; *clinicaltrials.gov: NCT01616329*).[3,10] During the study period, all blood products underwent a leukodepletion step as part of production, and an estimated 4% of units was irradiated prior to transfusion. The need for informed consent was waived by the Medical Ethics Review Board. This large cohort of patients with transfusion data was supplemented with data from the national registration of Dutch inhabitants (Basisregistratie Personen, 'BRP') on registered offspring of donors. Mortality data were obtained from the hospital administration at the hospital's end of data collection or the administrative end of study.[3,4]

Although the MATER study is an observational study, we expected that the potential for confounding in this study was small. As the information about donor sex and pregnancy is not available to treating physicians, in practice red blood cell units are allocated independently of donor characteristics (notably, sex and parity of the donor). However, the logistics of the distribution of blood products depend on a number of factors that we consider to be potential confounders (*Online Supplementary Figure S1*). In brief, confounders were included because they are predictive of both the distribution of blood products in the population, and the outcome. All information on potential confounders was obtained from the hospital administration and the R-FACT study at baseline.[3,10]

In order to be able to compare the effect of the different exposure categories, patients were censored at the time they received a transfusion from a different category than their previously received transfusions. This resulted in patients receiving more transfusions (and thus more likely to have a worse prognosis) being more likely to be censored, a phenomenon known as informative censoring.[11] Furthermore, the possibility exists that treatment-confounder feedback by hemoglobin present in the blood product further exacerbates the already existing bias in any analysis not adjusted for informative censoring.[6]

In order to correct for both confounding at baseline, and the informative censoring during follow-up and treatment-confounder feedback, inverse probability weighting (IPW) was applied.[12-14] Underlying disease severity of the patient and transfusion indication were not available, however, the number of transfusions was included in the IPW model and acted as a proxy for these variables. Weights were trimmed at a fixed level of 10, to reduce instability of the IPW estimator. Weighted marginal structural Cox proportional hazards models were fitted using the R packages ipw and survey.[14]

Analyses were stratified by patient sex and age (0-17, 18-50, 51- 71 and ≥71 years), as prespecified in the statistical analysis plan and in line with previous studies.[4,7] Sensitivity

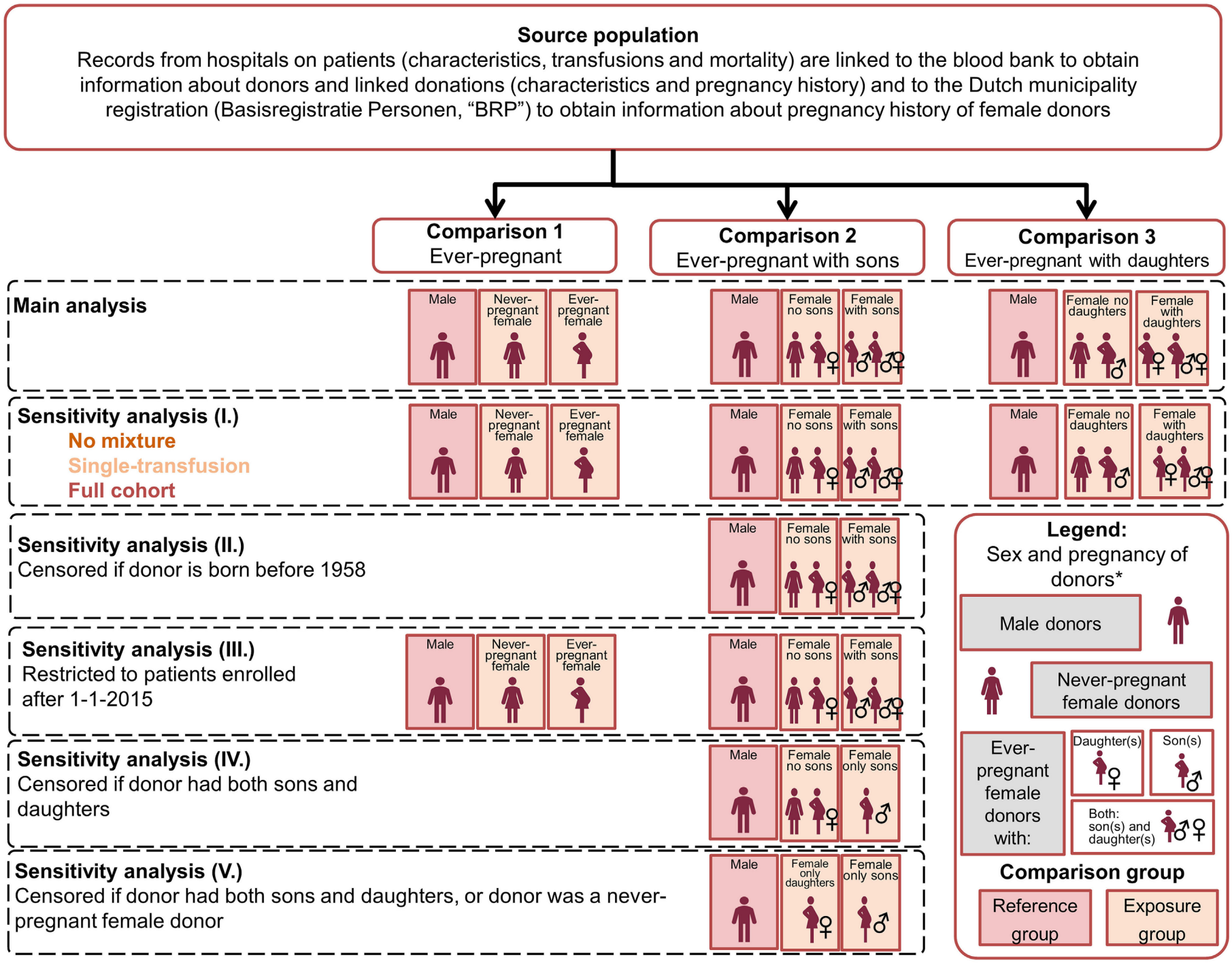

Figure 1. Schematic representation of exposure groups in main analysis and sensitivity analyses. The source population for the study and the different comparisons are visually represented. Comparisons were chosen with respect to donor pregnancy and sex of the offspring, and were adapted in the sensitivity analyses as shown, to correspond to the comparator of interest. *Donors classified according to sex of the donor from blood bank records and the sex of the offspring registered in the Basisregistratie Personen (BRP). Female ever-pregnant: female donors with a history of pregnancy; female never-pregnant: female donors without a history of pregnancy.

analyses (for overview, see *Online Supplementary Figure S2*) were performed to: evaluate alternative statistical analyses with methods similar to earlier research (I); test assumptions about data quality (II); form an independent study cohort not previously described (III); assess the effect of excluding donors with both sons and daughters (IV); assess the effect of excluding donors with both sons and daughters and in addition excluding never-pregnant female donors (V).

Analyses were performed in Stata, version 16;[15] data preparation and sensitivity analysis I), and R (version 3.6.3) and R Studio (version 2022.02.0+443) software (sensitivity analyses II-V). An extended methods section can be found in the *Online Supplementary Appendix*.

Results

Population

Table 1 contains donor and patient characteristics of the complete study population and the population included in the main analysis. The complete dataset contained data on 546,102 transfusions, and the donations linked to these transfusions originated from 134,046 male donors and 135,992 female donors. In total, 98,676 patients were included, and 51% (N=50,138) of the patients were female. During a median follow-up of 278 days (counted from the date of the first transfusion to the date of death, censoring or end of follow-up) 33,487 patients died (34%).

From the complete study population, only 56,825 patients

Table 1. Patient and transfusion characteristics.

Characteristics	Complete dataset		Main analysis*	
	Male patients	Female patients	Male patients	Female patients
Patients, N	48,538	50,138	28,115	28,710
Deaths, N (%)	18,191 (37)	15,296 (31)	4,280 (15)	4,008 (14)
Follow-up in days, median (IQR)†	1,081 (230-2,415)	1,372 (373-2,662)	151 (6-1597)	434 (11-2007)
Person-time, sum in years	191,573	223,156	69,558	85,898
Age in years of patients, median (IQR)	65 (50-75)	65 (42-77)	64 (39-75)	65 (36-77)
0 to 17, N (%)	6,681 (14)	5,395 (11)	5,931 (21)	4,819 (17)
18 to 50, N (%)	5,626 (12)	10,295 (21)	2,644 (9)	4,865 (17)
51 to 70, N (%)	18,412 (38)	14,636 (29)	9,687 (34)	7,787 (27)
≥71, N (%)	17,819 (37)	19,812 (40)	9,853 (35)	11,239 (39)
Transfusions of red blood cell units per patient, median (IQR)	3 (2-6)	2 (2-5)	2 (1-2)	2 (1-2)
Units of red blood cells transfused, N‡	301,250	244,852	49,992	51,052
Female donor, never-pregnant, N (%)	49,607 (16)	40,448 (17)	4,467 (9)	4,648 (9)
Female donor, ever-pregnant, male offspring, N (%)	58,782 (20)	47,378 (19)	6,602 (13)	6,721 (13)
Female donor, ever-pregnant, no male offspring, N (%)	18,415 (6)	15,089 (6)	6,644 (13)	6,749 (13)
Male donor, N (%)	172,316 (57)	140,126 (57)	36,662 (73)	37,447 (73)

*Consists of all the follow-up time during which patients either received all their red blood cell transfusions exclusively from 1 exposure category: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), or male donors. †Median follow-up time is defined as the median of longest time any patient is in 1 of the comparisons. Exposure categories are: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), male donors. ‡Includes units from female donors with offspring of unknown sex. IQR: interquartile range.

could be included in the cohort for the main analysis because they received only one exposure category on their first transfusion day, of whom 51% (N=28,710) were female. From this selected population, 8,288 deaths could be included in the main analysis (15%). The median age of the complete population was 65 (interquartile range (IQR), 46-76) and the median age in the main analysis was 64 years (IQR 37-76). Compared to the complete study population, patients included in the main analysis were followed-up for a shorter duration (median 278 days [IQR, 7-1,815] *vs*. 1,226 days [IQR, 297-2,547]). Patients in the main analysis also received fewer transfusions (median 2 [IQR, 1-2] transfusions *versus* three [IQR, 2-6] transfusions) and were more likely to receive transfusions from male donors (73%) compared to the complete population (57%). Linkage of donor records resulted in complete exposure information (99.7% for comparison 1, 99.3% for comparison 2 and 3). Of note, male patients on average had a substantially shorter length of follow-up than female patients, which was more pronounced in the ever-pregnant and never-pregnant exposure arm (*Online Supplementary Table S1*).

Donor and patient characteristics for the populations included in the sensitivity analyses can be found in *Online Supplementary Table S2*. In *Online Supplementary Table S3*, the study population restricted to patients aged 18 years and older is described. Absolute standardized mean differences (SMD) were calculated to assess balance after weighting for baseline factors for comparison 1 (*Online Supplementary Figures S3-5*). Balance was sufficient after weighting for all baseline characteristics (SMD <0.1), for the population comparing ever-pregnant donor exposure to male donors.

No increased risk of mortality after exposure to ever-pregnant donor units

Results for the three comparisons in the main analysis are reported in Figure 2. Exposure to female donors who have previously been pregnant compared to male donors was not associated with mortality (hazard ratio [HR]=0.96, 95% confidence interval [CI]: 0.88-1.04) in male patients (Figure 2). Exposure to ever-pregnant donors with sons and ever-pregnant donors with daughters was not associated with mortality in this analysis (comparison 2: HR= 0.91, 95% CI: 0.83-1.01); comparison 3: HR=0.94, 95% CI: 0.85-1.03). Blood products from never-pregnant female donors were protective (HR=0.88, 95% CI: 0.78-0.98) in male patients, compared to exposure to male donors. No other significant associations were observed.

For female patients, exposure to blood products from ever-pregnant donors was associated with decreased mortality compared to exposure to male donor units (HR=0.91, 95% CI: 0.83-0.99). Exposure to units from female donors with sons was not associated with mortality (HR= 0.93, 95% CI: 0.84-1.03) and exposure to units from ever-pregnant donors

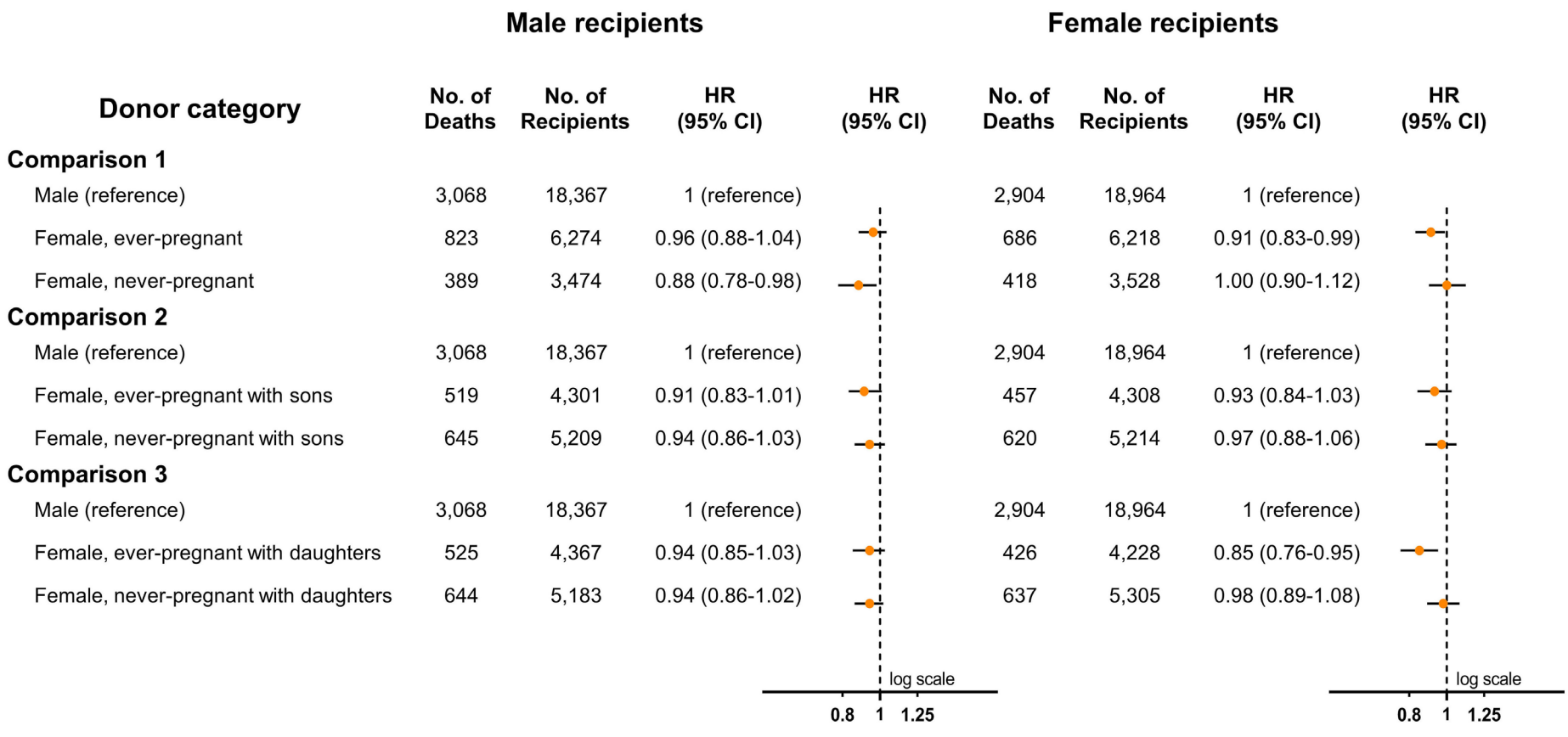

Figure 2. Mortality hazard ratio of male and female transfusion recipients of male, ever-pregnant (with sons or daughters) and never-pregnant female donor red blood cell products. Exposure to ever-pregnant donor red blood cell products compared to male donor exposure is not associated with mortality in the complete population of male patients, nor in the complete population of female transfusion recipients. Offspring sex is not predictive of patient mortality, with hazard ratios (HR) similar in size and direction for both male and female offspring sex. Female ever-pregnant: female donors with a history of pregnancy; female never-pregnant: female donors without a history of pregnancy.

with daughters was associated with decreased mortality, compared to male donor unit exposure (HR=0.85, 95% CI: 0.76-0.95). No significant associations were observed for exposure to blood products from never-pregnant donors, female donors without sons and female donors without daughters.

For reasons of conciseness, the remainder of the Results section will focus on male patients only.

For the main analysis, restricted to patients aged 18 years and older, HR were 0.99 (95% CI: 0.92-1.09) for male patients exposed to ever-pregnant donors, HR=0.98 (95% CI: 0.88-1.08) for exposure to ever-pregnant donors with sons and HR=0.99 (95% CI: 0.89-1.10) for exposure to ever-pregnant donors with daughters (*Online Supplementary Table S4*), all compared to exposure to male donors as reference. Exposure to never-pregnant female donors was significantly associated with decreased mortality (HR=0.87, 95% CI: 0.78-0.98). No other significant associations were observed.

Association between exposure to ever-pregnant donors and mortality in younger adult male patients

Results for the analysis stratified by age for male patients are reported in Table 2. In male patients aged between 18 and 50 years, receiving units from ever-pregnant donors was associated with mortality (HR=1.81, 95% CI: 1.31-2.51). Receiving units from ever-pregnant female donors with sons was similarly associated with mortality in this subgroup, with a HR of 1.86 (95% CI: 1.27-2.71), and exposure to units from ever-pregnant female donors with daughters was also associated with mortality (HR 1.58, 95% CI: 1.05-2.37)). There was a significant interaction of exposure with age in the exposure groups of ever-pregnant donors, ever-pregnant donors with sons and ever-pregnant donors with daughters (*P* value of 0.0001 [comparison 1]; *P*=0.001 [comparison 2]; *P*=0.020 [comparison 3]).

Results for female patients can be found in *Online Supplementary Table S5*. No significant associations were observed. The fully independent cohort of patients included after September 1, 2015 showed a similar magnitude and direction of the association between exposure to ever-pregnant donors and mortality for male (*Online Supplementary Table S6*) and female patients (*Online Supplementary Table S7*).

Sensitivity analyses

Sensitivity analyses were performed to verify the previously described assumptions about the data and the used methods, and the results were in agreement with the main result showing robustness of the methods to changes in these assumptions. Results for the sensitivity analyses can be found in the *Online Supplemental Appendix* (I, *Online Supplementary Table S8-10*, and II-V, *Online Supplementary Table S11*).

Table 2. Mortality hazard ratio of male transfusion recipients exposed to red blood cell transfusions from female (never-pregnant with male offspring or ever-pregnant with male offspring) *versus* male donors stratified by patient age.

	0-17 years			18-50 years			51-70 years			≥71 years			*P* for interaction*
Donor category	**Deaths N**	**Recipients N**	**HR (95% CI)**	**Deaths N**	**Recipients N**	**HR (95% CI)**	**Deaths N**	**Recipients N**	**HR (95% CI)**	**Deaths N**	**Recipients N**	**HR (95% CI)**	
Comparison 1													
Male (reference)	187	3,702	1 (ref.)	160	1,803	1 (ref.)	1,058	6,408	1 (ref.)	1,663	6,454	1 (ref.)	
Female, ever-pregnant	79	1,578	0.99 (0.74-1.32)	61	518	1.81 (1.31-2.51)	269	2,047	0.91 (0.79-1.05)	414	2,131	0.95 (0.85-1.08)	0.0001
Female, never-pregnant	21	651	0.63 (0.38-1.03)	13	323	0.56 0.30-1.02)	129	1,232	0.93 (0.72-1.20)	226	1,268	0.93 (0.80-1.08)	0.3140
Comparison 2													
Male (reference)	187	3,702	1 (ref.)	160	1,803	1 (ref.)	1,058	6,408	1 (ref.)	1,663	6,454	1 (ref.)	
Female, ever-pregnant with sons	51	1,166	0.90 (0.65-1.26)	40	343	1.86 (1.27-2.71)	168	1,353	0.91 (0.77-1.09)	260	1,439	0.92 (0.79-1.06)	0.0007
Female, never-pregnant with sons	41	1,036	0.77 (0.53-1.11)	34	459	1.19 (0.78-1.81)	215	1,815	1.01 (0.83-1.25)	355	1,899	0.96 (0.84-1.09)	0.3861
Comparison 3													
Male (reference)	187	3,702	1 (ref.)	160	1,803	1 (ref.)	1,058	6,408	1 (ref.)	1,663	6,454	1 (ref.)	
Female, ever-pregnant with daughters	60	1,176	0.98 (0.71-1.35)	34	354	1.58 (1.05-2.37)	172	1,396	0.92 (0.78-1.10)	259	1,441	0.93 (0.81-1.08)	0.0197
Female, never-pregnant with daughters	37	1,029	0.73 (0.49-1.06)	30	468	0.97 (0.64-1.47)	227	1,778	1.04 (0.86-1.24)	350	1,908	0.90 (0.79-1.02)	0.3144

*For the trend in interaction across the 4 presented categories of patient age. HR: hazard ratio; CI: confidence interval. Female ever-pregnant: female donors with a history of pregnancy; female never-pregnant: female donors without a history of pregnancy, ref.: reference.

Discussion

In this study of donor characteristics and transfusion recipient mortality, the observed mortality of male patients after exposure to ever-pregnant donor units was not explained by donor offspring sex. In the subgroup of male patients aged between 18 and 50 years, exposure to red blood cell products from ever-pregnant donors, regardless of the donor's offspring sex, was significantly associated with worse outcomes after transfusion (HR=1.86, 95% CI: 1.27-2.71). The association in the complete population of female patients was actually in the direction of moderate protection; an unexpected finding which we cannot explain (HR=0.91, 95% CI: 0.83-0.99). A small, statistically significant association was observed between exposure to never-pregnant donors and mortality in male patients, a finding which is also not expected from our hypothesis (HR=0.88, 95% CI: 0.78-0.98). Independent replication of any observed associations - other than those prespecified as the intended target of the study in the prespecified statistical analysis plan - is a prerequisite for them to not be considered the consequence of random variability.

Evidence on the topic of donor sex, pregnancy and patient outcomes has been conflicting. The finding presented here, that ever-pregnant donor exposure was associated with mortality in younger males, is consistent with a previous publication from our research group, and constitutes an independent replication of those earlier findings.[3,4] A recent publication[16] on a large pragmatic randomized controlled trial investigating donor sex found an increased risk of mortality after female donor exposure in patients aged 20-29 years, although the population was small and not stratified by patient sex. Other large observational studies, performed in the United States, Sweden and Denmark, have not shown any association with donor sex, donor pregnancy history and mortality.[6,7,17]

Analyses using traditional methods (sensitivity analysis I) were used to evaluate the magnitude and direction of bias due to informative censoring.[18] Indeed, in the single-transfusion cohort investigating exposure to ever-pregnant donors, potential bias in the direction of harm from 'rare' exposure was visible in these most selective, most censored analyses (HR=1.14, 95% CI: 1.02-1.28). This, as opposed to the main analysis, with a HR of 0.96 (95% CI: 0.88-1.04). We postulate previous work could have suffered more from this bias, due to missing data in the pregnancy history of the donor necessitating more frequent censoring of patient follow-up. Treatment-confounder feedback, with more transfusions given to patients receiving blood from female donors through lower hemoglobin concentration in products donated by female donors as compared to male donors, is a potential cause of bias here.[6] If chosen as exposure, any variable which affects the hemoglobin dose of the product may lead to bias if not accounted for correctly, because the hemoglobin dose of the product affects (in part) the time to next transfusion, and the number of transfusions is associated with underlying disease severity. As women have a lower normal level of hemoglobin compared to men, treatment-confounder feedback should be accounted for in the analyses. It is recommended that future investigations of blood product characteristics that relate to hemoglobin-raising capacity, e.g., product storage and any traits related to red blood cell storage and stress hemolysis,[19] incorporate measures to counteract this methodological artefact.

One of the strengths of this study is the large cohort of real-world data that was used and analyzed using appropriate methods. By pooling together into combined exposure groups the subgroups of ever-pregnant donors with both sons and daughters, and never-pregnant donors (depending on the comparison made), the main analysis had a large sample size. Expected challenges with regards to data quality and appropriateness of used methods were thoroughly investigated using sensitivity analyses, and these results were consistent with the main analysis. Thereby, these challenges were adequately addressed.

Limitations of the study include the granularity of the data, as the data were organized per day. This necessitated the exclusion of patients receiving transfusions from multiple categories on their first transfusion day, which could have led to bias and limited generalizability to patient populations requiring multiple transfusions early in the treatment course. Second, findings presented here are applicable to the study population of transfusion recipients between 2005 and 2019 in six hospitals in the Netherlands who received a median of two transfusions, and may not be generalizable to other settings, especially those with higher disease burden. Third, the use of inverse-probability weighted methods was only possible with larger intervals following the initial 4-week follow-up that was analyzed by transfusion day owing to sparse multivariable data, and this interval-censoring is a potential source of bias. Fourth, multiple comparisons were made but no adjustments for multiple testing were applied. However, all comparisons were prespecified and no *post hoc* analysis were included. Fifth, pregnancies resulting in miscarriages and stillbirths are not reported to the BRP and could, therefore, not be included in this study. Sixth, we did not have access to indication of the transfusion and underlying disease severity and were unable to assess balance for these factors after weighting. These limitations are mitigated by using multiple control conditions (e.g., never-pregnant donors and never-pregnant donors with daughters) and the inclusion of separate analyses for the fully independent cohort.

The aforementioned methodological limitations apply to the full population, and would not explain the repeated observation of increased mortality in younger adult male patients. The association between mortality and exposure to ever-pregnant donors in male patients aged between 18 and 50 years was also present in the pop-

ulation included after September 2015, which was not previously described in other publications, and thereby constitutes an independent replication of this previously observed finding (*Online Supplementary Table S10* for male patients; *Online Supplementary Table S11* for female patients). Methodological explanations were sought, and we hypothesized these male patients received multiple transfusions on their first day due to their transfusion indication, excluding them from the analysis and potentially introducing bias. However, after examining the frequency of exclusion due to mixture of exposures on the first day, this was not different between male and female patients for the different exposure categories (*Online Supplementary Table S12*). Additional investigations of weights distribution, patient characteristics and censoring can be found in the *Online Supplementary Appendix* (*Online Supplementary Tables S13-15*).

If some male patients are indeed sensitive to blood products from ever-pregnant female donors, there should be a biological rationale. Male patients could be sensitive to external stimuli due to their transfusion indication, as they more often receive large volumes of blood products in a short time frame, in a trauma setting. Micro-chimerism has been detected following transfusions for trauma indications, with reports of long-term engraftment of donor cells, but evidence is conflicting.[20] An explanation of the observed mortality in these patients, not related to sex of the offspring, is immunization of the female donor against inherited paternal human leukocyte antigens (IPA) of the fetus. However, the exact mechanisms underlying the observed increase in mortality following transfusions from ever-pregnant female donors in young men are incompletely understood and may be multifactorial.

To conclude, in this large observational cohort study, exposure to donors with male offspring is not associated with mortality. In young adult male patients, blood products from ever-pregnant female donors are consistently associated with mortality, which continues to be a concern. However, more research, specifically on transfusion indications and causes of death, is needed to understand the clinical relevance of this repeated observation. Transfusion policy changes which could be considered in the future (e.g., irradiation, matching for patient subgroups) must be based on a solid understanding of the underlying biological mechanism.

Disclosures

JJZ is in the scientific advisory council of Novartis, Amgen and Sanofi, and received a speaker's fee. All other authors have no conflicts of interest to disclose.

Contributions

SJV, CCD, RAM, RHHG and JGvdB designed the study. SJV, DE, KMKdV, DvdK, MJW, NCVP, FH, JJZ and JGvdB collected the data. SJV, CCD, RHHG and JGvdB analyzed and interpreted the data and wrote the manuscript. All authors revised and approved the final manuscript.

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Data-sharing statement

Individual participant data will not be shared. Requests for access to the data can be made to the corresponding author. All procedures relating to data management and analyses were stored and are available on request.

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