JAMA | Original Investigation

Association of Blood Transfusion From Female Donors With and Without a History of Pregnancy With Mortality Among Male and Female Transfusion Recipients

Camila Caram-Deelder, MSc; Aukje L. Kreuger, MD; Dorothea Evers, MD; Karen M. K. de Vooght, PhD; Daan van de Kerkhof, PhD, MD; Otto Visser, PhD, MD; Nathalie C. V. Péquériaux, PhD; Francisca Hudig, PhD, MD; Jaap Jan Zwaginga, PhD, MD; Johanna G. van der Bom, PhD, MD; Rutger A. Middelburg, PhD

IMPORTANCE Transfusion of red blood cells from female donors has been associated with increased mortality in male recipients.

OBJECTIVE To quantify the association between red blood cell transfusion from female donors with and without a history of pregnancy and mortality of red blood cell recipients.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of first-time transfusion recipients at 6 major Dutch hospitals enrolled from May 30, 2005, to September 1, 2015; the final follow-up date was September 1, 2015. The primary analysis was the no-donor-mixture cohort (ie, either all red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy, or all exclusively from female donors with a history of pregnancy). The association between mortality and exposure to transfusions from ever-pregnant or never-pregnant female donors was analyzed using life tables and time-varying Cox proportional hazards models.

EXPOSURES Red blood cell transfusions from ever-pregnant or never-pregnant female donors, compared with red blood cell transfusions from male donors.

MAIN OUTCOMES AND MEASURES All-cause mortality during follow-up.

RESULTS The cohort for the primary analyses consisted of 31 118 patients (median age, 65 [interquartile range, 42-77] years; 52% female) who received 59 320 red blood cell transfusions exclusively from 1 of 3 types of donors (88% male; 6% ever-pregnant female; and 6% never-pregnant female). The number of deaths in this cohort was 3969 (13% mortality). For male recipients of red blood cell transfusions, all-cause mortality rates after a red blood cell transfusion from an ever-pregnant female donor vs male donor were 101 vs 80 deaths per 1000 person-years (time-dependent "per transfusion" hazard ratio [HR] for death, 1.13 [95% CI, 1.01-1.26]). For receipt of transfusion from a never-pregnant female donor vs male donor, mortality rates were 78 vs 80 deaths per 1000 person-years (HR, 0.93 [95% CI, 0.81-1.06]). Among female recipients of red blood cell transfusions, mortality rates for an ever-pregnant female donor vs male donor were 74 vs 62 per 1000 person-years (HR, 0.99 [95% CI, 0.87 to 1.13]); for a never-pregnant female donor vs male donor, mortality rates were 74 vs 62 per 1000 person-years (HR, 1.01 [95% CI, 0.88-1.15]).

CONCLUSIONS AND RELEVANCE Among patients who received red blood cell transfusions, receipt of a transfusion from an ever-pregnant female donor, compared with a male donor, was associated with increased all-cause mortality among male recipients but not among female recipients. Transfusions from never-pregnant female donors were not associated with increased mortality among male or female recipients. Further research is needed to replicate these findings, determine their clinical significance, and identify the underlying mechanism.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Rutger A. Middelburg, PhD, Plesmanlaan 1a, 2333 BZ Leiden, the Netherlands (r.a.middelburg@lumc.nl).

Transfusion of red blood cells is among the most commonly performed procedures in hospitals.[1] It has been reported that mortality was increased after transfusion of red blood cells from female donors compared with male donors.[2-7] The most common cause of transfusion-related mortality is transfusion-related acute lung injury (TRALI), which has also been shown to be associated with transfusions from female donors.[8-10] Furthermore, TRALI is associated specifically with transfusions from female donors with a history of pregnancy.[11,12] This raises the question whether the increased mortality after red blood cell transfusions could also depend on a history of pregnancy of the donor. However, for TRALI it has been shown that only plasma-rich products confer a pregnancy-related antibody-mediated risk, whereas red blood cells do not.[10,11] The increased mortality in recipients of red blood cells from female donors may be related to either immunologic phenomena or other mechanisms.

Any proposed immunologic mechanism is likely to be dependent on a history of pregnancy of the donor. An absence of association with pregnancy status of the donor would suggest that other, nonimmunologic, mechanisms are more likely.

The aim of the current study was therefore to quantify the association between red blood cell transfusion from female blood donors, with and without a history of pregnancy, and patient mortality in female and male transfusion recipients.

Key Points

Question Is there an association between red blood cell transfusion from female donors with and without a history of pregnancy and recipient mortality?

Findings In this cohort study that included 31 118 patients who received red blood cell transfusions, receipt of a transfusion from an ever-pregnant female donor was associated with a statistically significant increase in all-cause mortality among male recipients of red blood cell transfusions (hazard ratio, 1.13) but not among female recipients (hazard ratio, 0.99).

Meaning Receipt of red blood cell transfusion from female donors with a history of pregnancy was associated with increased mortality among male recipients; further research is needed to replicate these findings, determine their significance, and define the underlying mechanism.

Methods

Study Design

As previously described, a retrospective cohort of first-ever transfusion recipients, transfused from May 30, 2005, to September 1, 2015, in 6 major Dutch hospitals, was established.[13,14] All patients included in a previous study of mortality after transfusion of red blood cells from female donors were excluded from the current analyses to create an independent cohort.[2]

Ethical approval for this study was obtained from the institutional review board of the Leiden University Medical Center and from local review boards of all participating centers. The review boards waived the need for informed consent, because only routinely collected data were processed after coding to remove identifying information.

Population

Primary analyses were performed in a "no-donor-mixture" cohort, to avoid dilution of effects from mixing patients who received red blood cell transfusions from both male and female donors. This cohort consisted of patients who received all their red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy (never-pregnant donors), or all exclusively from female donors with a history of pregnancy (ever-pregnant donors). Follow-up time was censored at the time these inclusion criteria were violated. This censoring could occur at time 0, in which case recipients contributed zero follow-up time and were not included in the denominator. Similarly, a "single-transfusion" cohort also was selected, consisting of patients who received only a single transfusion. Additionally, all analyses were repeated in the full cohort, to check whether any observed association potentially depended on the selection of the no-donor-mixture cohort. The race/ethnicity of recipients and donors was not recorded.

Recorded Data

Recipent Data

Information on transfusion recipients' dates of birth, dates of death, and sex, as well as transfusion dates, product types, and identification codes of transfused red blood cells, were provided by the hospitals from electronic records of the blood transfusion services. All transfusions, given for any indication, were included. Mortality data were verified by the hospitals until the date of data extraction. Mortality data were considered complete because of the use of a nationally linked computer system and the legal requirement for reporting all deaths to this system. The final follow-up date was September 1, 2015.

Donor and Blood Product Data

Information on donor dates of birth, sex, and pregnancy before donation (see the Supplement for details) were provided by Sanquin (the national Dutch blood supply) and linked to recipients' data using the product identification codes of transfused red blood cells. All blood products in the Netherlands are leukocyte-depleted by prestorage filtration, and nearly all products are transfused ABO-RhD identically.

Pregnancy of Female Blood Donors

At their first donation, female blood donors self-reported any previous pregnancy. At all subsequent donations, they reported whether they had been pregnant since the previous donation. However, since some female donors had their first-ever donation prior to the establishment of the current electronic recording system at the Sanquin blood bank, the answer to the question at first donation could be missing.

When the first donation was registered and the question answered as never-pregnant, the pregnancy status was considered never-pregnant until the first subsequent donation at which a pregnancy was reported. If the first donation was missing, the pregnancy status was considered unknown until the first subsequent donation at which a pregnancy was reported.

Missing Data

Information about donors' pregnancy history was not specifically recorded and was therefore missing for 44% of donations from female donors (eTable 2 in the Supplement). However, missingness depended solely on logistic factors (ie, changes in the electronic recording of donor information over the years). These data were therefore expected to be "missing completely at random" (as also shown in eTable 3 in the Supplement), allowing a valid "complete case" analysis.[15] We therefore selected only cases with complete data available.

Statistical Analyses

All statistical analyses were performed in Stata version 14.1.[16] The only outcome assessed was all-cause mortality at any time during follow-up, as specified per participating center (eTable 1 in the Supplement).

Survival analyses were performed with follow-up starting on the day of the first red blood cell transfusion. Follow-up ended at death or on the reference day, determined for each hospital separately (eTable 1 in the Supplement). The reference day was the last day for which the hospital had provided data. Follow-up time of recipients in the different cohorts was censored at the time the inclusion criteria for that cohort were first violated. To increase homogeneity, follow-up time of patients who received more than 15 transfusions was censored at the time of the 16th transfusion. All analyses were stratified by recipients' sex. Transfusions of other blood products were ignored, because receipt of these blood products was not correlated with sex and pregnancy history of the donor of red blood cells (eTable 3 in the Supplement).

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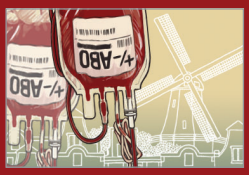


Animated Summary Video Mortality After Transfusion From Female Blood Donors With and Without a History of Pregnancy

All reported *P* values are 2-sided, and $P < .05$ was considered statistically significant. No adjustments for multiple comparisons were performed.

Kaplan-Meier Analyses

Kaplan-Meier curves were constructed for the single-transfusion cohort. The analyses were limited to 3 years of follow-up. At this time, differences in cumulative incidence between different groups and 95% CIs for these differences were calculated according to standard formulas (additional details reported in the Supplement).

Time-Varying Cox Proportional Hazards Models

Cox proportional hazards models, including both time-varying and fixed variables, were fit to correct for potential confounding. All confounding variables (ie, center [fixed], recipients' ABO-RhD blood group [fixed], age of the donor [time-varying], cumulative number of transfusions [time-varying], calendar year [time-varying], and an interaction term for center and number of transfusions [time-varying]) were included in the models as categorical variables, with as many categories as there were exposure levels (details on potential confounders are reported in the Supplement).

For the time-varying analyses, values of variables could change on each day with red blood cell transfusion. At each day with red blood cell transfusion, the cumulative number of red blood cell transfusions and of red blood cell transfusions from male, female never-pregnant, and female ever-pregnant donors, up to and including that day, were determined.

Exposures (ie, cumulative number of transfusions from never-pregnant or ever-pregnant female donors [time-varying]) were included in the models as continuous variables. Consequently, hazard ratios (HRs) should be interpreted on a multiplicative scale. However, since the model estimates the HR based on observed numbers of transfusions only, the HRs should not be extrapolated beyond the observed mean number of transfusions in each cohort (see eTable 3 in the Supplement for an illustration of this interpretation). The proportional hazards assumption was checked for all models and no gross violations of this assumption were detected, implying that the HR can be interpreted as a valid estimate of the average HR over the observed period.

Separate models were run for the 2 different exposures (ie, never-pregnant and ever-pregnant). For the no-donor-mixture cohort, this meant exclusion of patients who received any transfusions from the other exposure group, any transfusions with unknown pregnancy history, or a mixture of exposed (ie, ever-pregnant or never-pregnant, depending on the analyses) and unexposed (ie, male) red blood cell units. This way, the exposure group of interest was always compared directly with male donors, since all other units were excluded. For the full model, recipients of transfusions both from the exposure group of interest and from male donors were additionally included.

Effect Measure Modification

We previously reported effect measure modification by age of the transfusion recipients.[2] A primary objective of this study therefore was to repeat these analyses after stratification by age of the recipient for prespecified categories of age (0-17, 18-50, 51-70, and ≥71 years). Effect-measure modification was formally quantified by adding interaction terms for age (*P* value for interaction trend across 4 categories, from a Z distribution using standard errors estimated from the observed information matrix) and sex of the recipient to the final model.

Table 1. Characteristics of Female and Male Transfusion Recipients and Red Blood Cell Transfusions in the Different Cohorts

Characteristics	No-Donor-Mixture Cohort[a]		Single-Transfusion Cohort[b]		Full Cohort	
	Male (n=14 995)	Female (n=16 123)	Male (n=8463)	Female (n=8496)	Male (n=20 217)	Female (n=21 915)
Deaths, No. (%)	1982 (13)	1987 (12)	606 (7)	590 (7)	3597 (18)	3378 (15)
Follow-up, median (IQR), d	144 (6-1041)	351 (14-1275)	15 (1-717)	22 (1-781)	274 (18-1106)	479 (44-1316)
Person-time, sum in years	24 339	31 637	10 266	10 971	35 281	45 904
Age of patients, median (IQR), y	65 (45-75)	66 (39-78)	63 (3-75)	64 (21-78)	66 (50-75)	66 (43-78)
0 to 17	2813 (19)	2303 (14)	2534 (30)	2085 (25)	2986 (15)	2439 (11)
18 to 50	1427 (10)	2873 (18)	603 (7)	1073 (13)	2140 (11)	4246 (19)
51 to 70	5244 (35)	4253 (26)	2406 (28)	1966 (23)	7460 (37)	6112 (28)
≥71	5511 (37)	6694 (42)	2920 (35)	3372 (40)	7631 (38)	9118 (42)
Blood group, No. (%)						
O Rh+	5426 (36)	5812 (36)	2945 (35)	2854 (34)	7366 (36)	7874 (36)
O Rh−	932 (6)	1024 (6)	502 (6)	562 (7)	1279 (6)	1388 (6)
A Rh+	4977 (33)	5416 (34)	2670 (32)	2699 (32)	6805 (34)	7479 (34)
A Rh−	930 (6)	1051 (7)	476 (6)	548 (6)	1286 (6)	1433 (7)
B Rh+	1240 (8)	1361 (8)	700 (8)	751 (9)	1698 (8)	1952 (9)
B Rh−	185 (1)	220 (1)	99 (1)	110 (1)	250 (1)	318 (1)
AB Rh+	433 (3)	452 (3)	249 (3)	251 (3)	611 (3)	647 (3)
AB Rh−	75 (1)	86 (1)	50 (1)	45 (1)	114 (1)	115 (1)
Not defined	797 (5)	701 (4)	772 (9)	676 (8)	808 (4)	709 (3)
Transfusions of red blood cell units per patient, median (IQR)	2 (1-2)	2 (1-2)	1 (1-1)	1 (1-1)	2 (1-3)	2 (2-3)
Units of red blood cells transfused, No. (%)	28 663	30 657	8463	8496	52 637	54 004
From male donors	25 190 (88)	27 155 (89)	6189 (73)	6243 (73)	40 022 (76)	41 267 (76)
From female ever-pregnant donors	1818 (6)	1810 (6)	1190 (14)	1160 (14)	6528 (12)	6454 (12)
From female never-pregnant donors	1655 (6)	1692 (6)	1084 (13)	1093 (13)	6087 (12)	6283 (12)

Abbreviation: IQR, interquartile range.

[a] Consists of all the follow-up time during which patients either received all their red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy (never-pregnant donors), or all exclusively from female donors with a history of pregnancy (ever-pregnant donors).

[b] Consists of patients with only a single red blood cell transfusion during the period in which they were followed up. Follow-up time was censored at the time this inclusion criterion was violated.

Results

Population

A total of 42 132 patients received 106 641 units of red blood cells (76% from male donors, 12% from ever-pregnant donors, 12% from never-pregnant female donors). The median number of transfused units per recipient was 2 (interquartile range [IQR], 2-3). These recipients were followed up for a median of 380 days (IQR, 27-1217), had a median age of 66 years (IQR, 46-77), and 21 915 (52%) were female. The number of deaths was 6975 (17%). Among this full cohort, 31 118 patients received 59 320 units of red blood cells exclusively from 1 of the 3 types of donor (ie, the no-donor-mixture cohort: either all units exclusively from male donors, exclusively from female donors without a history of pregnancy [never-pregnant donors], or exclusively from female donors with a history of pregnancy [ever-pregnant donors]). These recipients were followed up for a median of 245 days (IQR, 9-1172) and had a median age of 65 years (IQR, 42-77); 16 123 (52%) were female. The number of deaths in the no-donor-mixture cohort was 3969 (13%). **Table 1** shows a comparison of recipient characteristics between the no-donor-mixture cohort, single-transfusion cohort, and full cohort, stratified by recipient sex.

Donors' Pregnancy History and Mortality After Red Blood Cell Transfusions

Primary Analyses: No-Donor-Mixture Cohort

The HR for death after 1 additional unit of red blood cells from a never-pregnant female donor, compared with a unit from a male donor, was 0.93 (95% CI, 0.81 to 1.06) for male recipients and 1.01 (95% CI, 0.88 to 1.15) for female recipients (**Table 2**).

The HR for death after 1 additional unit of red blood cells from an ever-pregnant female donor, compared with a unit

Table 2. Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) Donors vs Male Donors in the No-Donor-Mixture, Single-Transfusion, and Full Cohorts[a]

	Male Recipients			Female Recipients		
Donor Category	No. of Deaths Among Recipients/ No. of Recipients	HR (95% CI)[b]	*P* Value	No. of Deaths Among Recipients/ No. of Recipients	HR (95% CI)[b]	*P* Value
No-Donor-Mixture Cohort[c]						
Male	1722/12 212	1 [Reference]		1752/13 332	1 [Reference]	
Ever-pregnant female	1873/13 669	1.13 (1.01-1.26)	.03	1871/14 770	0.99 (0.87-1.13)	.92
Never-pregnant female	1831/13 538	0.93 (0.81-1.06)	.29	1868/14 685	1.01 (0.88-1.15)	.92
Single-Transfusion Cohort[d]						
Male	434/6189	1 [Reference]		433/6243	1 [Reference]	
Ever-pregnant female	532/7379	1.23 (0.98-1.54)	.08	517/7403	1.12 (0.88-1.42)	.37
Never-pregnant female	508/7273	0.96 (0.74-1.25)	.75	506/7336	1.00 (0.77-1.30)	.99
Full Cohort[e]						
Ever-pregnant analysis						
Male	2538/15 304	1 [Reference]		2448/16 617	1 [Reference]	
Ever-pregnant female	2689/16 338	1.08 (1.02-1.15)	.02	2567/17 654	0.99 (0.93-1.07)	.87
Never-pregnant analysis						
Male	2521/15 163	1 [Reference]		2447/16 608	1 [Reference]	
Never-pregnant female	2630/16 091	1.06 (0.99-1.14)	.08	2563/17 593	0.96 (0.89-1.03)	.23

Abbreviation: HR, hazard ratio.

[a] All models adjusted for calendar year, blood group (ABO-RhD), hospital, age of donor, cumulative number of transfusions, and an interaction term for hospital and cumulative number of transfusions.

[b] Hazard ratios per transfused unit compared with receiving a unit from a male blood donor.

[c] Consists of all the follow-up time during which patients received all their red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy (never-pregnant donors), or all exclusively from female donors with a history of pregnancy (ever-pregnant donors).

[d] Consists of participants who received only a single red blood cell transfusion during the period of follow-up. Follow-up time was censored at the time this inclusion criterion was violated.

[e] Recipients in the full cohort could receive mixed blood from never-pregnant and male donors (for the never-pregnant analysis) or from ever-pregnant and male donors (for the ever-pregnant analysis); therefore, the number of male recipients receiving blood from never-pregnant female donors differs from the number receiving blood from ever-pregnant female donors.

from a male donor, was 1.13 (95% CI, 1.01 to 1.26) for male recipients and 0.99 (95% CI, 0.87 to 1.13) for female recipients (Table 2).

The highest HRs for death after transfusion of red blood cells from ever-pregnant female donors were observed in male recipients 50 years and younger (**Table 3**).

Secondary Analyses 1: Single-Transfusion Cohort

The 3 years cumulative incidence of death among male recipients was 13.5% after a transfusion from a male donor, 13.1% after a transfusion from a never-pregnant female donor (difference, 0.4% [95% CI, −3.8% to 3.0%]), and 16.9% after a transfusion from an ever-pregnant female donor (difference, 3.5% [95% CI, −0.3% to 7.2%]) (**Figure**).

The cumulative incidence of death among female recipients was 12.6% after a transfusion from a male donor, 12.0% after a transfusion from a never-pregnant female donor (difference, 0.6% [95% CI, −3.7% to 2.6%]), and 15.9% after a transfusion from an ever-pregnant female donor (difference, 3.3% [95% CI, −0.5% to 7.1%]) (Figure).

Secondary Analyses 2: Full Cohort

The HR for death after 1 additional unit of red blood cells from an ever-pregnant female donor, compared with a male donor, was 1.08 (95% CI, 1.02 to 1.15) for all male recipients, 1.18 (95% CI, 0.82 to 1.69) for male recipients aged 0 through 17 years, and 1.43 (95% CI, 1.13 to 1.82) for male recipients aged 18 through 50 years (Table 3). For female recipients, the HR for death after 1 additional unit of red blood cells from an ever-pregnant female donor, compared with a male donor, was 0.99 (95% CI, 0.93 to 1.07).

Additional Results

Cumulative incidences of death, in the single-transfusion cohort, at different follow-up times, are reported in eFigure 3 and eTable 5 in the Supplement. eTable 3 reports the distribution of donor types according to recipient sex and plasma and platelets transfusions received. Data on numbers of recipients, transfusions, and deaths per subgroup—also for all female donors combined, regardless of pregnancy history—are reported in eTable 2 and eTables 6-8 in the Supplement. Results of analyses of red blood cells corrected for plasma and platelet transfusions are reported in eTables 9-10 in the Supplement. Results of analyses for female donors with unknown pregnancy history are shown in eTable 11 and eFigure 4 in the Supplement. A direct comparison between ever-pregnant and never-pregnant female donors is reported in eTable 12 in the Supplement. Analyses of platelet transfusions are reported in eTables 13-14 in the Supplement.

Effect Measure Modification

The tests for interaction for the association between transfusion of red blood cells from ever-pregnant donors vs male

Table 3. Mortality Hazard Ratio of Male Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female Ever-Pregnant Donors vs Male Donors in the No-Donor-Mixture, Single-Transfusion, and Full Cohorts, Stratified by Patient Age[a]

Donor Category	No. of Deaths Among Recipients/No. of Recipients, by Recipient Age				*P* Value for Interaction[b]
	0-17 y	18-50 y	51-70 y	≥71 y	
No-Donor-Mixture Cohort[c]					
Male (reference)	107/2251	84/1170	598/4292	933/4499	
Ever-pregnant female	124/2556	94/1296	645/4775	1010/5042	
HR (95% CI)[d]	1.63 (1.02-2.61)	1.50 (0.98-2.30)	1.10 (0.91-1.33)	1.06 (0.90-1.26)	.10
P value	.04	.06	.31	.47	
Single-Transfusion Cohort[e]					
Male (reference)	53/1993	16/411	129/1686	236/2099	
Ever-pregnant female	70/2287	23/504	152/2049	287/2539	
HR (95% CI)[d]	2.84 (1.58-5.12)	2.29 (0.89-5.93)	0.79 (0.50-1.25)	1.06 (0.78-1.46)	<.001
P value	.001	.09	.32	.71	
Full Cohort					
Male (reference)	124/2421	146/1565	922/5570	1346/5748	
Ever-pregnant female	141/2645	156/1649	969/5917	1423/6127	
HR (95% CI)[d]	1.18 (0.82-1.69)	1.43 (1.13-1.82)	1.01 (0.91-1.12)	1.02 (0.93-1.12)	<.001
P value	.37	.003	.85	.63	

Abbreviation: HR, hazard ratio.

[a] All models are adjusted for calendar year, blood group (ABO-RhD), hospital, age of donor, cumulative number of transfusions, and an interaction term for hospital and cumulative number of transfusions.

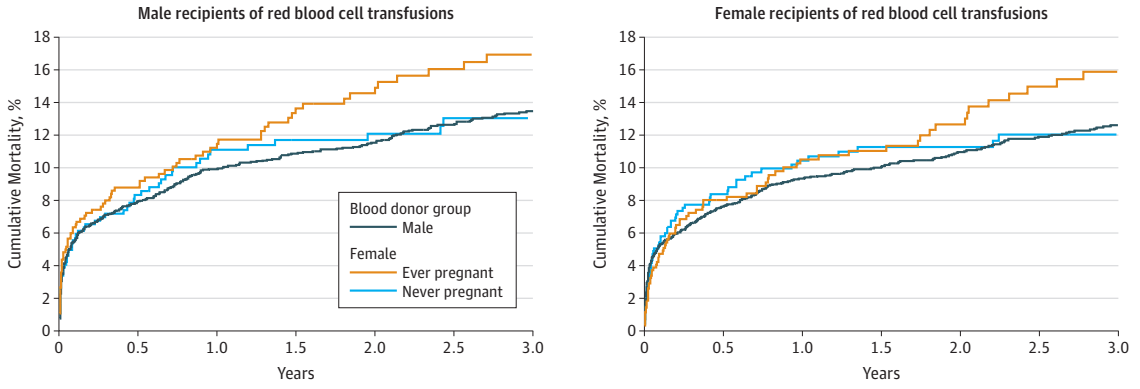
[b] For the trend in interaction across the 4 presented categories of patient age.

[c] Consists of all the follow-up time during which patients received all their red blood cell transfusions exclusively from male donors, or all exclusively from female donors without a history of pregnancy (never-pregnant donors), or all exclusively from female donors with a history of pregnancy (ever-pregnant donors).

[d] Hazard ratios per transfused unit compared with receiving a unit from a male blood donor.

[e] Consists of patients who received only a single red blood cell transfusion during the period of follow-up. Follow-up time was censored at the time this inclusion criterion was violated.

Figure. Cumulative Incidence of Death According to Sex of the Transfusion Recipient and Sex and Pregnancy History of the Donor in the Single-Transfusion Cohort



The single-transfusion cohort consists of all the follow-up time during which patients had received only a single transfusion. Follow-up time was censored at the time this inclusion criterion was violated. Median follow-up for male recipients of red blood cell transfusions exposed to male donors, 16 (interquartile range [IQR], 1-780) days; to female ever-pregnant donors, 12 (IQR, 1-567) days; and to female never-pregnant donors, 14 (IQR, 1-563) days. Median follow-up for female recipients of red blood cell transfusions exposed to male donors, 24 (IQR, 1-846) days; to female ever-pregnant donors, 21 (IQR, 1-584) days; to female never-pregnant donors, 17 (IQR, 1-640) days.

donors and mortality among male vs female recipients regardless of recipient age did not meet statistical significance (P = .30 for interaction for the no-donor-mixture cohort, P = .54 for the single-transfusion cohort. and P = .58 for the full cohort). The strength of the association between transfusion of red blood cells from ever-pregnant donors and

mortality of male recipients was different for recipients of different ages, as indicated by the *P* value for interaction trend (Table 3).

Similarly, the differences between male and female recipients in the strength of association of transfusions from ever-pregnant donors with mortality of recipients 50 years and younger were statistically significant (*P* = .03 for interaction for the no-donor-mixture cohort, *P* = .01 for the single-transfusion cohort, and *P* = .01 for the full cohort).

Discussion

The results from this large retrospective cohort study suggest that the association of transfusions of red blood cells from female donors with increased mortality among male recipients was related to the pregnancy history of female donors and the age of the patient. Male recipients who received a transfusion from an ever-pregnant female donor had a statistically significant increase in mortality compared with those who received a transfusion from a male donor or from a female donor without a history of pregnancy. There was no significant association between pregnancy status of female donors of red blood cells and mortality among female recipients of red blood cell transfusions.

The association of increased mortality among male patients who received transfusions from ever-pregnant donors suggests a possible mechanism based on immunologic changes occurring during pregnancy. Of all changes occurring during pregnancy, the immunologic ones are the most enduring. An alternative explanation could be a difference in iron status between ever-pregnant female and male donors. Iron deficiency in donors has recently been shown to be associated with worse recovery of red blood cells after transfusion in a murine model.[17] Some studies also report differences in red blood cell physiology between the sexes.[13-17] Results from studies on the association of donor sex and recipient mortality, including the current study, tend to be consistent in showing associations for male recipients but not for female recipients.[2-6] This specificity for male recipients seems difficult to explain based on differences in red blood cell physiology, supporting a possible role for a sex-specific immunologic mechanism. It is difficult to predict whether the small amount of plasma in red blood cell transfusions contains enough antibodies to confer an increased risk of mortality, but it cannot be ruled out. Furthermore, leukocyte-depleted red blood cell transfusions routinely contain fewer than 1 million leukocytes. However, to allow for naturally occurring variation, quality control standards allow up to 5 million leukocytes in a small percentage of products. These could include both antigen-specific lymphocytes or regulatory T cells.

Some differences exist between results reported from studies on the association between donor sex and recipient mortality.[2-6] These differences could, in the light of the current results, potentially be explained by a combination of differences in prevalence of a history of pregnancy among donors and differences in age distribution of recipients.

This study has several strengths. The large size of the cohort allowed selection of the no-donor-mixture cohort and enabled study of patients who received blood transfusions from only 1 type of donor (ie, male vs previously pregnant female vs never pregnant female). However, the selection of a no-donor-mixture cohort could limit generalizability. The recipients in the no-donor-mixture cohort receive fewer transfusions, since the probability of receiving mixed transfusions increases with the total number of transfusions. Similarly, the censoring of recipients who received 16 or more transfusions could limit generalizability to this group.

This study also has limitations. First, the difference in effect size and direction between male and female recipients was not significant among recipients of all ages, only among those 50 years and younger. This makes the findings very tentative, and they require validation in other studies. Second, this study was retrospective, and data were recorded for routine clinical practice and not specifically for this study. This could cause both inaccuracy of data and unavailability of data. Third, there were missing data, particularly regarding pregnancy status for the women donating red blood cells. Fourth, information on cause of death was not available. Fifth, there may have been residual confounding or confounding by an unidentified variable. Sixth, the analysis included a large number of comparisons, but there was no adjustment for multiple comparisons.

Conclusions

Among patients who received red blood cell transfusions, receipt of a transfusion from an ever-pregnant female donor, compared with a male donor, was associated with increased all-cause mortality among male recipients but not among female recipients. Transfusions from never-pregnant female donors were not associated with increased mortality among male or female recipients. Further research is needed to replicate these findings, determine their clinical significance, and identify the underlying mechanism.

ARTICLE INFORMATION

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Author Affiliations: Center for Clinical Transfusion Research, Sanquin Research, Leiden, the Netherlands (Caram-Deelder, Kreuger, Evers, Zwaginga, van der Bom, Middelburg); Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands (Caram-Deelder, Kreuger, van der Bom, Middelburg); Department of Immunohaematology and Blood Transfusion, Leiden University Medical Centre, Leiden, the Netherlands (Evers, Zwaginga); Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, Utrecht, the Netherlands (de Vooght); Department of Clinical Chemistry and Haematology, Catharina Hospital, Eindhoven, the Netherlands (van de Kerkhof); Department of Haematology, VU Medical Center, Amsterdam, the Netherlands (Visser); Department of Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands (Péquériaux); LabWest, Haga Teaching Hospital, The Hague, the Netherlands (Hudig).

Author Contributions: Ms Caram-Deelder and Dr Middelburg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Caram-Deelder, Zwaginga, van der Bom, Middelburg.

Acquisition, analysis, or interpretation of data: Caram-Deelder, Kreuger, Evers, de Vooght, van de Kerkhof, Visser, Péquériaux, Hudig, van der Bom, Middelburg.
Drafting of the manuscript: Caram-Deelder, Middelburg.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Caram-Deelder, Kreuger, van der Bom.
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Supervision: Visser, van der Bom, Middelburg.

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