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Female donors and transfusion-related acute lung injury: A case-referent study from the International TRALI Unisex Research Group

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Abstract

BACKGROUND—Although quantitative evidence is lacking, it is generally believed that the majority of cases of transfusion-related acute lung injury (TRALI) are caused by female blood donors. We aimed to examine the relation between female donors and the occurrence of TRALI.

STUDY DESIGN AND METHODS—We performed an international, multicenter case-referent study. TRALI patients who were diagnosed clinically, independent of serology or donor sex, and had received transfusions either only from male donors or only from female donors (unisex cases) were selected. The observed sex distribution among the donors of these TRALI patients was compared to the expected sex distribution, based on the relevant donor populations.

RESULTS—Eighty-three clinical TRALI cases were included; 67 cases received only red blood cells (RBCs), 13 only plasma-rich products, and three both. Among RBC recipients the relative risk (RR) of TRALI after a transfusion from a female donor was 1.2 (95% confidence interval [CI], 0.69–2.1) and among plasma-rich product recipients the RR was 19 (95% CI, 1.9–191). The *p* value for the difference between RBCs and plasma was 0.023.

CONCLUSION—Our data support the notion that plasma from female donors is associated with an increased risk of TRALI, while RBCs from female donors are not.

Transfusion-related acute lung injury (TRALI) is currently recognized as the most important of the severe side effects of transfusions.^{1–4} TRALI is characterized by the development of acute respiratory distress within 6 hours after the end of a transfusion, in the absence of

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

circulatory overload.^{5,6} It is clinically indistinguishable from acute respiratory distress syndrome (ARDS), but it is rarer and has a better prognosis. The estimated incidence is 1:5000 transfusions and the mortality is estimated to be between 5 and 10%.⁷⁻⁹ Treatment is mostly supportive and in the majority of cases (80%) recovery is rapid and complete.⁷⁻⁹ Different etiologies for TRALI have been suggested, but most research has been focused on the role of donor white blood cell (WBC) antibodies,^{7,10-12} as summarized in several recent reviews.^{13,14}

WBC antibodies are induced by previous exposure to alloantigens. Such alloexposures occur either through pregnancies or through blood transfusions and organ or stem cell transplantation. As a consequence WBC antibodies are much more prevalent in female than in male donors.¹⁵⁻¹⁸ Since the United Kingdom first started to exclude plasma from female donors for transfusion in 2004, several other countries have also implemented or are considering to implement this policy to prevent TRALI.^{1,19,20} Although some encouraging data on the effects of such measures have been published,^{19,21} the evidence does not allow quantitative estimation of the effect of excluding plasma from female donors. Furthermore, the question arises whether for blood products that contain only small volumes of plasma, female donors also confer an increased risk of TRALI.²²

To obtain a quantitative estimate of the contribution of blood products from female donors to the occurrence of TRALI is complicated because most TRALI patients have received transfusions from female as well as from male donors. However, some TRALI patients have received transfusions only from female or only from male donors, which we called unisex cases. The ratio of female to male donors among these unisex TRALI cases can be compared directly to the expected value calculated from the fraction of female donors in the respective total donor populations. We set out to quantify the association of female donors with the occurrence of TRALI by studying TRALI patients who had received transfusions either from female donors only or from male donors only.

MATERIALS AND METHODS

Design and study population

We performed a case-referent study consisting of TRALI patients who had been diagnosed clinically, without knowledge of serology or donor sex. Case-referent study is essentially synonymous to case-control study, but it is considered a more appropriate name in some situations.²³ In this study the TRALI case patients were compared to a reference value from the complete donor population, rather than to control patients without TRALI, thus rendering the name case-referent study more appropriate.

Since TRALI is a rare complication and TRALI patients who have received transfusions only from female or only from male donors are inevitably even rarer, no single research group or country is likely to be able to collect enough of these cases to perform a meaningful study. To overcome this problem we performed an international collaborative project.

We included only TRALI patients defined on clinical criteria alone, because TRALI that is defined by serologic criteria (i.e., on the basis of presence of antibodies in donor blood) has the problem of circularity in reasoning since the diagnosis demands the presence of antibodies that are more frequent among female donors.²⁴ We contacted groups who had previously published TRALI cases defined on clinical criteria alone, independent of serology or donor sex, and asked them to join the International TRALI Unisex Research Group.

Measurements

TRALI cases—We asked each contributing group to identify all TRALI patients from their records. From all patients previously recorded as TRALI patients, we further asked the collaborating groups to verify the sex of the donors of all products transfused within 6 hours before the onset of symptoms. Only those patients receiving all transfusions from donors of a single sex were eligible for inclusion in this study. For these patients the presence of the other inclusion criteria for this study was checked retrospectively. The selection criteria were that the patient had presented with acute dyspnea (as a clinical sign of hypoxemia), within 6 hours after transfusion, without evidence of circulatory overload. For these patients, which we call “clinical TRALI” patients, we recorded the number of transfusions, the types of transfused products, and the sex of the involved donors. Furthermore, we collected data on all criteria of the definition of TRALI according to the Canadian consensus conference; these criteria were acute dyspnea, within 6 hours after transfusion, without evidence of circulatory overload, in the presence of new or worsening bilateral lung infiltrates in chest X-rays, and the absence of other risk factors for acute lung injury (ALI) or ARDS.^{5,6} Finally, specifications of blood products were recorded and all products containing 250 mL or more of plasma (all plasma and platelet [PLT] products) were classified as plasma rich, while all other products (red blood cells [RBCs], always leuko-reduced and always containing less than 50 mL of plasma) were classified as plasma poor.

Reference population—Each collaborating group also reported fractions of donations made by female donors as registered in their donation databases. For each TRALI patient we documented a unique fraction: the fraction of female donors of the specific blood product, in the country or region of the reporting group, at the date of occurrence of the TRALI.

Statistical analysis

Our analysis follows the line of reasoning of one of the methods that we have proposed earlier,²⁵ which we briefly and informally recapitulate here. For each TRALI patient we first calculated that patient’s individual probability of receiving all transfusions from a female donor. This probability was equal to the individually matched fraction of donations made by female donors in the relevant donor population, raised to the power of the number of these products received by that patient. For example, a TRALI patient receiving 3 units of RBCs from a donor population in which 40% of RBCs are donated by female donors has a probability of receiving all 3 units from female donors of $(0.40)^3 = 0.064$. For patients who received different product types, the probabilities were first calculated for the different product types separately and then those probabilities were multiplied. The probability of receiving all transfusions from male donors was calculated in the same way (in the example $(0.60)^3 = 0.216$). Adding these two probabilities gives the probability of receiving all transfusions from donors of the same sex (in the example $0.064 + 0.216 = 0.28$), which is the probability of being a unisex case. We then calculated an expected fraction of unisex cases caused by a female donor, by dividing each probability of receiving all transfusions from female donors by the probability of being a unisex case (in the example $0.064/0.28 = 0.229$).

The odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated with a matched analysis. The observed value for each individual case (i.e., 1 or 0, for all female or all male donors) was matched to the fraction of cases expected to be caused by female donors, as calculated for that individual case. In this matched analysis, the size of the reference group, which was based on national registration data, was relatively so much larger than the number of cases (one per stratum) that the contribution of the reference group to the variance of the OR was treated as negligible. The ORs are interpreted as relative risks (RRs) throughout.

To estimate the population-attributable risk (PAR), we calculated the mean of the fractions of female donations from the different donor populations, by weighting for the number of TRALI patients contributed by each population. It can be shown^{25,26} that, for a mean fraction p of female donors, the PAR equals

$$\text{PAR} = \frac{pRR - p}{pRR + (1 - p)},$$

where the RR is estimated by the OR from the matched analysis. The OR and its variance (both from the matched analysis) were then used to calculate the PAR and the corresponding 95% CI, according to standard formulas.²⁶

Data were analyzed according to whether the transfused products were RBCs or “plasma rich” (i.e., either plasma or PLTs). Effect modification by product type was quantified by calculation of a ratio of RRs and corresponding 95% CI, according to standard formulas.²⁷

All analyses were repeated among the subgroup of patients of whom we had sufficient information to assess whether the diagnosis conformed to the Canadian consensus criteria:^{5,6} patients who had bilateral infiltrates proven in chest X-rays and who had no other risk factors for ALI and/or ARDS (i.e., excluding “possible TRALI”). In this way we could compare the results in all clinical TRALI patients with those patients that had TRALI according to the Canadian consensus definition.

RESULTS

Population characteristics

Based on a previous literature study,²⁴ we identified 43 different research groups from 52 publications, describing clinically defined TRALI patients. All groups for whom e-mail addresses could be retrieved were contacted. Apart from the Netherlands, six more groups had the relevant data available and were interested in collaborating on this study. Collected data pertained to cases occurring between June 1991 and October 2007.

A total of 83 clinical TRALI patients were included, all presenting with acute dyspnea, without evidence of circulatory overload, within 6 hours after a transfusion. Of these patients 67 (81%) had received only RBCs, 13 (16%) had received only plasma-rich products (seven plasma, six PLTs), and three (3.6%) had received both RBCs and plasma-rich products. On average the TRALI patients had received 1.8 transfusions (range, 1–8) in the 6 hours preceding the onset of symptoms.

Of 67 cases caused by a transfusion of RBCs, 23 had another risk factor for ALI, and in 17 no chest X-rays were available (three patients had both). Therefore, of the cases caused by a transfusion of RBCs a total of 30 (45%) were classified as TRALI patients according to all criteria of the Canadian consensus definition. Of 13 cases caused by transfusion of a plasma-rich product two had another risk factor for ALI, while in one (8%) a chest X-ray was not available, and the remaining 10 (77%) were classified as TRALI patients according to all criteria of the Canadian consensus definition.

The distribution of patients, according to product type and geographical location, with numbers of cases associated with male and female donors and corresponding percentage of female donors in the reference group are given in Table 1. For both RBCs and plasma the fraction of products donated by female donors ranged from 0.22 in Poland to 0.51 in Finland, while for PLTs it ranged from 0.02 in Poland to 0.50 in Spain (Table 1).

Female donors and TRALI risk

Among 67 RBC recipients the RR of clinical TRALI after a transfusion from a female donor was 1.2 (95% CI, 0.69–2.1) in the matched analysis; among 13 recipients of plasma-rich products (plasma or PLTs) the RR was 19 (95% CI, 1.9–191; Table 2). After restricting the analyses to cases who had proven bilateral infiltrates in chest X-rays and no other risk factors for ALI and/or ARDS (i.e., Canadian consensus definition), the RR for 30 RBC recipients remained similar at 0.86 (95% CI, 0.37–2.02), while the RR for 10 recipients of plasma-rich products increased to 66 (95% CI, 1.3–3465; Table 2).

The ratio of the RRs of RBC and plasma-rich product recipients was 16 (95% CI, 1.5–170); the p value for the difference in RRs between these groups was 0.023. After limiting to the Canadian consensus definition the ratio became 77 (95% CI, 1.3–4410) and the p value for a difference between the groups became 0.046.

The percentage of cases preventable by the exclusion of female donors (PAR) was 7.0% (95% CI, –17% to 26%) among RBC recipients and 86% (95% CI, 17%–98%) among recipients of plasma-rich products (Table 3).

DISCUSSION

The risk of TRALI was increased among recipients of plasma-rich products from female donors, but not among recipients of RBCs from female donors. A strong association of female donors with the risk of TRALI was expected because, according to the literature, most TRALI cases are caused by donor WBC antibodies²⁴ and the prevalence of these antibodies in female donors is several times higher than in male donors.^{15–18}

A unique feature of this study was the restriction to unisex TRALI cases: patients who had received transfusions either only from male or only from female donors. Most patients who develop TRALI have received transfusions from several donors of either sex, and the one donor causing the TRALI cannot be directly identified; therefore, the sex of the causal donor remains unknown. In our study, since only patients with donors of a single sex were included, the sex of the causal donor was known even if the causal donor was not identified. Our approach solves the problem of attenuation caused by transfusions from multiple donors.²⁵

Due to the international collaborative effort of this study, TRALI patients were selected from several different centers or countries with different sized background populations. It is therefore not possible to compare the selected patients with the unselected part of the total population of TRALI patients, since there is no single identifiable background population. However, since all TRALI patients were originally diagnosed independently of donor sex and serology, this cannot have biased our results with respect to donor sex as a risk factor for TRALI. The separate effect estimates for RBCs and plasma-rich products are therefore valid in any population, but remain specific for those products. To apply them to a different population all that is needed is to know the relative contribution of the different product types in that population.

The main limitation of this study, pertaining only to the results for plasma-rich products, is the limited number of cases caused by these products. The selection of unisex cases causes an indirect selection of cases with few transfusions, who in turn will have rarely received only transfusions of plasma-rich products. Although the distribution of product types among the patients in our study may well be different from the background population, no bias will be introduced by the selection. First, since we analyzed RBCs and plasma-rich products separately, the fraction of TRALI cases caused by each product type in the background

population is irrelevant. Second, the lesser number of transfusions received by TRALI patients in our study, in comparison to other published series, should not cause bias either. The mechanism by which TRALI is caused is considered to be an immunologic reaction to a single transfusion²⁵—which is independent of the number and type of the other transfusions received by the patient. In spite of the small number of cases caused by plasma-rich products, a strong association of plasma-rich products from female donors with an increased risk of TRALI was observed, while no such association was observed for RBCs.

The most surprising finding was this lack of association of female donors and the risk of developing a TRALI in RBC recipients. To appreciate this finding we considered an alternative explanation: if not all included cases were really TRALI patients, the effect of donor sex would be diluted, obscuring a true association. One source of such misdiagnosis could be the patients of whom we did not have all information to be certain that the diagnosis conformed to the Canadian consensus conference. However, the exclusion of these patients did not support the notion that the effect was diluted by their inclusion among the clinical TRALI patients. In this analysis increasingly stringent selection criteria reduce the number of potentially misclassified patients. Misclassified patients would contribute donors to the analyses who did not actually cause a TRALI case. These donors would therefore follow the sex distribution of the reference group, thus causing the TRALI group to become more similar to the reference group. Excluding those patients would therefore increase the difference between the TRALI group and the reference group. However, no such increase was observed in RBC recipients who, if anything, showed an inverse association with female donors after exclusion of clinical TRALI patients who did not fulfill all criteria of the consensus definition. Therefore, misclassification of TRALI patients does not seem a likely explanation for the lack of association between donor sex and the risk of TRALI in RBC recipients. Only for recipients of plasma-rich products did restriction to consensus definition cases cause an increase in RR—which indicates that the association might even be stronger.

Another possible source of misclassification could be transfusion-associated circulatory overload (TACO). In accordance with the Canadian consensus definition the exclusion of TACO was based on the criterion of “no evidence of circulatory overload,” which does not specify the type of evidence of which the presence should be excluded. The absence of circulatory overload is therefore mainly based on clinical judgment, which makes this criterion the most subjective in the definition. However, to explain our findings in RBC recipients almost complete misclassification of these patients would be necessary. Even with the subjective nature of this clinical judgment, it seems unlikely that nearly all observed TRALI patients related to RBCs would be misclassified TACO. This is especially unlikely since a strong association with donor sex was observed in recipients of plasma-rich products, indicating that those patients were not misclassified. Furthermore, unisex cases have on average received only few transfusions, which also reduces the risk of TACO.

To compare our findings with what was known from the literature, we performed a systematic review of the literature to summarize the direct evidence of the relation between female donors and TRALI (see Appendix S1, available as supporting information in the online version of this paper) for methodology and selection criteria. We found six such studies: four with a contemporary control group and two with a before-after comparison (Table 4).

None of these six publications investigated the difference between plasma-rich and plasma-poor products. Publications that make before-after comparisons (i.e., before and after introduction of a male-only plasma measure) run the risk of clinical suspicion or reporting bias. Only a small portion of TRALI patients are reported, either through lack of clinical suspicion and/or recognition or through poor reporting. The fraction of TRALI patients that

is reported is inconsistent and highly variable over time and is likely to change strongly after well publicized and dramatic measures for the prevention of TRALI (i.e., the exclusion of female donors). Therefore, a difference in the number of reported TRALI patients before and after implementation of this preventive measure does not necessarily correspond to a real difference in the number of TRALI patients.

Of the four publications with a contemporary control group, one only included six cases and one included only three cases. The remaining two did not correct for a difference in the number of transfusions (Table 4). TRALI patients have on average received more transfusions than other patients, which are used as control patients in these studies. Both the chance of receiving male-only plasma and the amount of female plasma received depend on the total number of transfusions. A higher number of transfusions is strongly related to a higher risk of TRALI. Without correction this precludes quantitative conclusions from an observed difference in either the prevalence of TRALI between male-only and mixed plasma recipients or a difference in the amount of female plasma received between TRALI patients and control patients.^{24,25}

Considering the limitations of previous studies, their quantitative conclusions are uncertain. The method which we advocate here and elsewhere²⁵ is aimed at overcoming these potential shortcomings. Furthermore, our study makes a clear distinction in the analyses between plasma-rich products and RBCs and shows a striking difference between the associations of female donors with TRALI caused by these products.

Several countries have implemented policies excluding female donors from the donation of plasma, to prevent TRALI.^{1,19,20} Our findings suggest that the vast majority of the TRALI cases caused by plasma-rich products are indeed preventable by the exclusion of female donors. However, to estimate the overall effect on the occurrence of TRALI, we also need to estimate the relative contribution of plasma-rich products to the occurrence of TRALI, which cannot be estimated directly from our data. The literature gives estimates of the contribution of RBCs to the occurrence of TRALI varying from one-third to more than 90%.^{28–32} Based on the literature and our own previously published experience²¹ we assume that on average approximately half of all TRALI cases are caused by transfusion of RBCs alone. Therefore, exclusion of female donors from donation of plasma-rich products might prevent roughly half of all TRALI cases.

In TRALI caused by RBC transfusions our data indicate the role of female donors to be negligible. This suggests that current RBC preparation procedures, by reducing the amount of plasma in the product, already suffice to effectively reduce the risk posed by donor WBC antibodies in these products. Therefore, removing the small amount of remaining WBC antibodies from RBCs is likely to have only limited effect. This is in agreement with current thinking about the pathogenesis, which suggests that RBCs may cause TRALI by different mechanisms.^{30,33–35}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

ALI	acute lung injury
ARDS	acute respiratory distress syndrome
PAR	population-attributable risk

RR(s)	relative risk(s)
TACO	transfusion-associated circulatory overload

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TABLE 1
Distribution of patients according to product type, donor sex, and geographic location^{*}

Geographical location	RBCs		Plasma		PLTs	
	TRALI patients (number of female/male donors)	Reference group (percentage female donors)	TRALI patients (number of female/male donors)	Reference group (percentage female donors)	TRALI patients (number of female/male donors)	Reference group (percentage female donors)
Denver, CO	5/3	45	NA	NA	NA	NA
The Netherlands	5/16	41	—/2	10	—/1	41
Poland	1/19 [†]	22	—/1 [†]	22	—/2	2
Rochester, MN	6/5 [†]	43	3/1 [†]	47	2/—	47
Spain	4/3	50	NA	NA	1/—	50
Finland	2/—	51	1/—	51	NA	NA
United Kingdom	1/— [†]	50	2/— [†]	50	NA	NA

^{*} Values are numbers of patients and percentage of donations from female donors in the corresponding reference group. Where changes in fractions donated by female donors occurred over time the represented fractions are weighted means, weighted for the number of TRALI patients in each period. NA = not applicable (i.e., no unisex TRALI cases associated with this product type in this country or region, n = 0).

[†] Patients receiving both plasma and RBCs were counted in both categories (only in this table). This occurred three times, once in Poland, once in Rochester, and once in the United Kingdom.

TABLE 2RR for developing TRALI after a transfusion from a female donor^{*}

Product type	All cases	Canadian consensus [†]
RBCs	1.2 (0.69–2.1)	0.86 (0.37–2.0)
Plasma rich	19 (1.9–191)	66 (1.3–3465)

^{*} Values are reported as RR (95% CI).[†] Only those cases defined completely according to the definition of the Canadian consensus conference.^{5,6}

TABLE 3Percentage of TRALI cases preventable by the exclusion of female donors ^{*}

Product type	All cases	Canadian consensus [†]
RBCs	7.0 (–17 to 26)	–5.9 (–45 to 23)
Plasma rich	86 (17–98)	96 (–126 to 100)

^{*} Values are reported as percentages of PAR (95% CI). Negative PAR values can only be interpreted as indicative of some protective effect, but not of any size of that effect.

[†] Only those cases defined completely according to the definition of the Canadian consensus conference.^{5,6}

TABLE 4

Six publications investigating the relation between female donors and TRALI

Publication	Quantitative interpretation limited by:	Description
Gajic 2007 ³⁶	Difference in number of transfusions	Amount of female plasma compared between TRALI patients and controls
Sanchez 2007 ³⁷	Statistical power	Only six cases (pilot study)
Imoto 2007 ³⁸	Statistical power	Only three cases
Wright 2008 ¹⁹	Before-after comparison	Number of reported cases before vs. after male-only plasma measure
Chapman 2009 ²¹	Before-after comparison	Number of reported cases before vs. after male-only plasma measure
Nakazawa 2009 ³⁹	Difference in number of transfusions	Risk of TRALI compared between male-only and mixed plasma recipients