

Transfusion-related acute lung injury : etiological research and its methodological challenges

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Chapter 5

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, multi-center 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

83 clinical TRALI cases were included; 67 cases received only red cells, 13 only plasma rich products and 3 both. Among red cell recipients the relative risk of TRALI after a transfusion from a female donor was 1.2 (95% confidence interval: 0.69 to 2.1) and among plasma rich product recipients the RR was 19 (1.9 to 191). The p-value for the difference between red cells 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 red cells from female donors are not.

Introduction

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 six hours after the end of a transfusion, in the absence of 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 leukocyte antibodies,^{7,10-12} as summarized in several recent reviews.^{13,14}

Leukocyte antibodies are induced by previous exposure to allo-antigens. Such alloexposures occur either through pregnancies or through blood transfusions and organ or stem cell transplantation. As a consequence leukocyte antibodies are much more prevalent in female than in male donors.¹⁵⁻¹⁸ Since the UK 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.

Design 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 the current 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 serological 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 six hours before the onset of symptoms. Only those patients receiving all transfusions from donors of a single sex were eligible for inclusion in the present 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 six 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 six 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 acute respiratory distress syndrome (ARDS).^{5,6} Finally, specifications of blood products were recorded and all products containing 250 mL or more of plasma (all plasma and platelet products) were classified as plasma rich, while all other products (red cells, always leukoreduced 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 analyses

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 three units of red cells from a donor population in which 40% of red cells are donated by female donors has a probability of receiving all three 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 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 odds ratio was treated as negligible. The odds ratios are interpreted as relative risks (RR) throughout.

To estimate the population attributable risk (PAR) we calculated the average 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 an average fraction p of female donors, the PAR equals:

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

Where the RR is estimated by the OR from the matched analysis. The odds ratio and its variance (both from the matched analysis) were then used to calculate the population attributable risk and the corresponding 95% CI, according to standard formulas.²⁶

Data were analyzed according to whether the transfused products were red cells or "plasma rich" (i.e. either plasma or platelets). Effect modification by product type was quantified by calculation of a ratio of relative risks (RRR) 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 was conform 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/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 email 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 six hours after a transfusion. Of these patients 67 (81%) had received only red cells, 13 (16%) had received only plasma rich products (7 plasma, 6 platelets) and 3 (3.6%) had received both red cells and plasma rich products. On average the TRALI patients had received 1.8 transfusions (range 1-8) in the six hours preceding the onset of symptoms.

Of 67 cases caused by a transfusion of red cells 23 had another risk factor for acute lung injury, and in 17 no chest X-rays were available (3 patients had both). Therefore, of the cases caused by a transfusion of red cells 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 2 had another risk factor for acute lung injury, while in 1 (8%) a chest X-rays was not available, and the remaining 10 (77%) were classified as TRALI patients according to all criteria of the Canadian consensus definition.

Tab	le 1: Distribution	1 of patients accordin	ng to product type	, donor sex, and geog	graphical location	
	Re	od cells	[d	asma	Pla	itelets
	TRALI	Reference group	TRALI	Reference group	TRALI	Reference group
Source of patients	patients (유/♂ donors)	(percentage \downarrow donors)	patients $(2/3^{\circ} \text{ don ors})$	(percentage \downarrow donors)	patients $(\mathbb{Q}/\hat{\mathcal{S}}$ donors)	(percentage \downarrow donors)
Denver, CO, USA	5/3	45%	N.A.	N.A.	N.A.	N.A.
Netherlands	5/16	41%	-/2	10%	-/1	41%
Poland	$1/19^{*}$	22%	-/1*	22%	-/2	2%
Rochester, MN, USA	6/5*	43%	3/1*	47%	2/-	47%
Spain	4/3	50%	N.A.	N.A.	1/-	50%
Finland	2/-	51%	1/-	51%	N.A.	N.A.
United Kingdom	1/-*	50%	2/-*	50%	N.A.	N.A.
Values are numbers of patier occurred over time the repres	its and percentage of sented fractions are we	donations from female don sighted averages, weighted	tors in the correspondir for the number of TRA	ig reference group. Where our the content of the section of the se	changes in fractions do	nated by female donors
N.A.: Not applicable (i.e. no * Patients receiving both plas	Unisex TRALI cases and and red cells were	associated with this product counted in both categories	t type in this country or s (only in this table). Th	region, n=0) is occurred three times, onc	ce in Poland, once in Ro	ochester and once in the
UK.						

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 red cells and plasma the fraction of products donated by female donors ranged from 0.22 in Poland to 0.51 in Finland, while for platelets it ranged from 0.02 in Poland to 0.50 in Spain (Table 1).

Female donors and TRALI risk

Among 67 red cell recipients the relative risk (RR) of clinical TRALI after a transfusion from a female donor was 1.2 (95% CI 0.69 to 2.1) in the matched analysis; among 13 recipients of plasma rich products (plasma or platelets) the RR was 19 (1.9 to 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/ARDS (i.e. Canadian consensus definition), the RR for 30 red cell recipients remained similar at 0.86 (95% CI 0.37 to 2.02) while the RR for 10 recipients of plasma rich products increased to 66 (1.3 to 3465) (Table 2).

The ratio of the relative risks of red cell and plasma rich product recipients was 16 (1.5 to 170), the p-value for the difference in relative risks between these groups was 0.023. After limiting to the Canadian consensus definition the ratio became 77 (1.3 to 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 (population attributable risk, PAR) was 7.0% (-17% to 26%) among red cell recipients, and 86% (17 to 98%) among recipients of plasma rich products (Table 3).

Table 2: Relative risk for developing TRALI after atransfusion from a female donor				
Product type	All c	ases	Canad	ian consensus*
Red cells	1.2	(0.69 to 2.1)	0.86	(0.37to 2.0)
Plasma rich	19	(1.9 to 191)	66	(1.3 to 3465)
Values are relative * Only those ca Canadian consens	e risk and ses defi us confei	l (between parenthese ned completely acco rence. 5,6	s) 95% conf rding to th	idence intervals. ne definition of the

Table 3: Percentage of TRALI cases preventable by the					
exclusion of female donors					
Product type	All c	All cases		Canadian consensus*	
Red cells	7.0	(-17 to 26)	-5.9	(-45 to 23)	
Plasma rich	86	(17 to 98)	96	(-126 to 100)	

Values are percentages of population attributable risk (PAR) and (between parentheses) 95% confidence intervals. 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

Discussion

The risk of TRALI was increased among recipients of plasma rich products from female donors, but not among recipients of red cells 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 leukocyte antibodies ²⁴ 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 can not 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 can not have biased our results with respect to donor sex as a risk factor for TRALI. The separate effect estimates for red cells 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. Firstly, since we analyzed red cells and plasma rich products separately, the fraction of TRALI cases caused by each product type in the background population is irrelevant. Secondly, 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 red cells.

The most surprising finding was this lack of association of female donors and the risk of developing a TRALI in red cell 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 was conform 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 red cell 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 red cell recipients. Only for recipients of plasma rich products did restriction to consensus definition cases cause an increase in relative risk - 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 red cell 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 red cells would be misclassified TACO. This is especially unlikely since a strong association with donor sex was observed in recipients of plasma rich products, indicating 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 for methodology and selection criteria. We found 6 such studies: 4 with a contemporary control group and 2 with a before/after comparison (Table 4).

None of these 6 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/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 4 publications with a contemporary control group 1 only included six cases and 1 included only three cases. The remaining 2 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 receipients, 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 methodology which we advocate here and elsewhere,²⁵ is aimed at overcoming these potential shortcomings. Furthermore, our study makes a clear distinction in the analyses between plasma rich products and red cells and shows a striking difference between the associations of female donors with TRALI caused by these products.

Table 4: Six publications investigating the relation				
between female donors and TRALI				
Publication	Quantitative interpretation	Description		
	limited by			
Gajic 2007 ³⁶	Difference in number of	Amount of female plasma		
	transfusions	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	Risk of TRALI compared		
	transfusions	between male-only and		
		mixed plasma recipients		

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 can not be estimated directly from our data. The literature gives estimates of the contribution of red cells to the occurrence of TRALI varying from one third to more than 90%.²⁸⁻³² Based on the literature and our own previously published experience²⁹ we assume that on average approximately half of all TRALI cases are caused by transfusion of red cells alone. Therefore, exclusion of female donors from donation of plasma rich products might prevent roughly half of all TRALI cases.

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

References

- SHOT. Serious Hazards of Transfusion (SHOT): SHOT Annual Report 2008 2009 [cited 2010 Jan 19] Available from http://www.shotuk.org/home.htm.
- TRIP. "Transfusie Reacties in Patiënten" (TRIP): TRIP rapport 2008 2010 [cited 2010 Jan 19] Available from http://www.tripnet.nl/.
- 3. Engelfriet CP. Haemovigilance. Vox Sang. 2006 Apr;90(3):207-41.
- 4. Eder AF, Herron R, Strupp A, Dy B, Notari EP, Chambers LA, Dodd RY, Benjamin RJ. Transfusionrelated acute lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion. 2007 Apr;47(4):599-607.
- 5. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus.Med.Rev. 2005 Jan;19(1):2-31.
- Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004 Dec;44(12):1774-89.
- Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985 Nov;25(6):573-7.
- Moore SB. Transfusion-related acute lung injury (TRALI): clinical presentation, treatment, and prognosis. Crit Care Med. 2006 May;34(5 Suppl):S114-S117.
- Wallis JP. Transfusion-related acute lung injury (TRALI): presentation, epidemiology and treatment. Intensive Care Med. 2007 Jun;33 Suppl 1:S12-S16.
- Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang. 2005 Jul;89(1):1-10.
- 11. Dry SM, Bechard KM, Milford EL, Churchill WH, Benjamin RJ. The pathology of transfusion-related acute lung injury. Am.J.Clin.Pathol. 1999 Aug;112(2):216-21.
- 12. Kopko PM. Review: transfusion-related acute lung injury: pathophysiology, laboratory investigation, and donor management. Immunohematol. 2004;20(2):103-11.
- 13. Sachs UJ. Pathophysiology of TRALI: current concepts. Intensive Care Med. 2007 Jun;33 Suppl 1: S3-S11.
- 14. Cherry T, Steciuk M, Reddy VV, Marques MB. Transfusion-related acute lung injury: past, present, and future. Am.J.Clin.Pathol. 2008 Feb;129(2):287-97.
- Boulton-Jones R, Norris A, O'Sullivan A, Comrie A, Forgan M, Rawlinson PS, Clark P. The impact of screening a platelet donor panel for human leucocyte antigen antibodies to reduce the risk of transfusionrelated acute lung injury. Transfus.Med. 2003 Jun;13(3):169-70.
- 16. Densmore TL, Goodnough LT, Ali S, Dynis M, Chaplin H. Prevalence of HLA sensitization in female apheresis donors. Transfusion 1999 Jan;39(1):103-6.
- 17. Payne R. The development and persistence of leukoagglutinins in parous women. Blood. 1962 Apr;19:411-24.
- Triulzi DJ, Kleinman S, Kakaiya RM, Busch MP, Norris PJ, Steele WR, Glynn SA, Hillyer CD, Carey P, Gottschall JL, et al. The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. Transfusion. 2009 May 18.
- Wright SE, Snowden CP, Athey SC, Leaver AA, Clarkson JM, Chapman CE, Roberts DR, Wallis JP. Acute lung injury after ruptured abdominal aortic aneurysm repair: The effect of excluding donations from females from the production of fresh frozen plasma*. Crit Care Med. 2008 May;19.
- 20. Jutzi ML. Swiss haemovigilance data and implementation of measures for the prevention of transfusion associated acute lung injury (TRALI). Transfusion Medicine and Hemotherapy 2008 Apr;35(2):Apr.

- 21. Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, Navarrete C, Lucas G, Soni N, Morgan C, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion. 2008 Oct 28.
- 22. Win N, Chapman CE, Bowles KM, Green A, Bradley S, Edmondson D, Wallis JP. How much residual plasma may cause TRALI? Transfus.Med. 2008 Oct;18(5):276-80.
- 23. Miettinen OS. Design of Sampling of the Base. In Theoretical Epidemiology, Principles of Occurence Research in Medicine. 1 ed. New York: Wiley Medical; 1985. p. 69-83.
- Middelburg RA, van Stein D, Briet E, van der Bom JG. The role of donor antibodies in the pathogenesis of transfusion-related acute lung injury: a systematic review. Transfusion. 2008 Jun 18;48(10):2167-76.
- 25. Middelburg RA, LeCessie S, Briët E, Vanderbroucke JP, van der Bom JG. A solution to the problem of studying blood donor related risk factors when patient have received multiple transfusions. Transfusion 2010;50(9):1959-66.
- Rothman KJ, Greenland S. Attributable fraction estimation. In Modern Epidemiology. 2 ed. 1998. p. 295-7.
- 27. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ. 2003 Jan 25;326(7382):219.
- Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. Transfus.Med.Rev. 2004 Jul;18(3):184-8.
- van Stein D, Beckers EA, Sintnicolaas K, Porcelijn L, Danovic F, Wollersheim JA, Brand A, van Rhenen DJ. Transfusion-related acute lung injury reports in the Netherlands: an observational study. Transfusion. 2009 Aug 18.
- Zupanska B, Uhrynowska M, Michur H, Maslanka K, Zajko M. Transfusion-related acute lung injury and leucocyte-reacting antibodies. Vox Sang. 2007 Jul;93(1):70-7.
- 31. Gajic O, Moore SB. Transfusion-related acute lung injury. Mayo Clin.Proc. 2005 Jun;80(6):766-70.
- Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L, Clarke G, Ambruso DR. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood 2003 Jan 15;101(2):454-62.
- 33. Bux J, Sachs UJ. The pathogenesis of transfusion-related acute lung injury (TRALI). Br.J.Haematol. 2007 Mar;136(6):788-99.
- 34. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest 2004 Jul;126(1):249-58.
- 35. Silliman CC, McLaughlin NJ. Transfusion-related acute lung injury. Blood Rev. 2006 May;20(3):139-59.
- Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, O'byrne MM, Evenson LK, Malinchoc M, Degoey SR, et al. Transfusion Related Acute Lung Injury in the Critically Ill: Prospective Nested Case-Control Study. Am.J.Respir.Crit Care Med. 2007 Jul 12;.
- 37. Sanchez R, Bacchetti P, Toy P. Transfusion-related acute lung injury: a case-control pilot study of risk factors. Am.J.Clin.Pathol. 2007 Jul;128(1):128-34.
- Imoto S, Araki N, Shimada E, Saigo K, Nishimura K, Nose Y, Bouike Y, Hashimoto M, Mito H, Okazaki H. Comparison of acute non-haemolytic transfusion reactions in female and male patients receiving female or male blood components. Transfus.Med. 2007 Dec;17(6):455-65.
- Nakazawa H, Ohnishi H, Okazaki H, Hashimoto S, Hotta H, Watanabe T, Ohkawa R, Yatomi Y, Nakajima K, Iwao Y, et al. Impact of fresh-frozen plasma from male-only donors versus mixed-sex donors on postoperative respiratory function in surgical patients: a prospective case-controlled study. Transfusion. 2009 Jul 16.

Appendix: Systematic review of the literature

To compare our results with what was known in the literature, we performed a systematic review. On December 24 2009 we searched the PubMed database for all publication on TRALI and donor sex using the search strategy: ("transfusion related acute lung injury"[All Fields] OR TRALI[All Fields]) AND (("female"[MeSH Terms] OR "female"[All Fields]) OR ("sex"[All Fields] OR "sex"[MeSH Terms]) OR ("male"[MeSH Terms] OR "male"[All Fields]) OR ("gender"[All Fields]) AND ("donor"[All Fields] OR "donors"[All fields]).

We retrieved 125 publications, 100 contained original data, of which 86 had TRALI as their primary focus. Of these 86, only 22 actually investigated donor sex as a risk factor, while most only mentioned donor sex in relation to antibody testing in a case report or case series. Only 4 of the 22 remaining publications included a contemporary control group and two made a before/after comparison (Table 4). This left only six publications that actually made the comparison we were interested in. The evidence available, from the selected publications, for a relation between female donors and TRALI risk was summarized (Table 4).