Increased Risk of Mortality with Female to Male Blood Product Transfusions

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Abstract

Background: Blood product transfusions are one of the most common procedures in the US. These transfusions are considered safe but there is still a risk of complications and mortality. The most common cause of transfusion related mortality being transfusion related acute lung injury (TRALI). TRALI is an acute lung condition that results in dyspnea, cough, and hypoxemia. It is hypothesized that TRALI is an antibody mediated phenomenon that is associated with female donors, as female and multiparous women have more HLA/HNA antibodies in their blood. This review is to investigate if there is increased mortality with the use of female blood products in male recipients.

Methods: An exhaustive literature search using MEDLINE, Web of Science, and CINAHL via EBSCO-host was conducted. The following search terms were used: female, male, transfusion, mortality, donor, and pregnancy. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: The literature search yielded 5 qualifying studies, all were retrospective cohort studies. The studies indicated that the use of female blood products did increase mortality among male recipients. Four of the 5 studies did show an increase in mortality among male recipients of female blood product donation. One study found increased mortality among male recipients specifically receiving multiparous female blood products. Another study reported increased mortality among male recipients receiving more than 2 units of female plasma. One study found no increased risk to male recipients receiving female blood products.

Conclusion: Four of the 5 studies reviewed did show consistent results that men are negatively affected by use of female blood products. One study showed no increased risk. Further research is needed to determine the exact cause of increased male mortality and TRALI pathophysiology. In addition, investigations are needed to determine the best use of female blood products. These studies are just a start in truly understanding how sex mismatched blood transfusions affect patients' bodies in the short and long term.

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Degree Name
Master of Science in Physician Assistant Studies

Keywords
Transfusion, mortality, female donor, male, TRALI, blood, pregnancy

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Increased Risk of Mortality with Female to Male Blood Product Transfusions

Haley Robinson
and
Kiersten Sperry

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
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Faculty Advisor: Dr. Pedemonte
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Haley Robinson is a native of Minnesota. She attended the University of Minnesota Duluth where she majored in Biology with a minor in Healthcare Management. Haley worked as a phlebotomist while completing her degree before continuing on to the Physician Assistant program at Pacific University of Oregon.

Kiersten Sperry is a native of Utah. She attended the University of Utah where she majored in Health Promotion and Education. Before beginning the Physician Assistant Program at Pacific University, she has worked in a variety of healthcare areas including HIV prevention, drug rehabilitation, Women’s health and anatomical donation services.
Abstract

**Background:** Blood product transfusions are one of the most common procedures in the US. These transfusions are considered safe but there is still a risk of complications and mortality. The most common cause of transfusion related mortality being transfusion related acute lung injury (TRALI). TRALI is an acute lung condition that results in dyspnea, cough, and hypoxemia. It is hypothesized that TRALI is an antibody mediated phenomenon that is associated with female donors, as female and multiparous women have more HLA/HNA antibodies in their blood. This review is to investigate if there is increased mortality with the use of female blood products in male recipients.

**Methods:** An exhaustive literature search using MEDLINE, Web of Science, and CINAHL via EBSCO-host was conducted. The following search terms were used: female, male, transfusion, mortality, donor, and pregnancy. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

**Results:** The literature search yielded 5 qualifying studies, all were retrospective cohort studies. The studies indicated that the use of female blood products did increase mortality among male recipients. Four of the 5 studies did show an increase in mortality among male recipients of female blood product donation. One study found increased mortality among male recipients specifically receiving multiparous female blood products. Another study reported increased mortality among male recipients receiving more than 2 units of female plasma. One study found no increased risk to male recipients receiving female blood products.

**Conclusion:** Four of the 5 studies reviewed did show consistent results that men are negatively affected by use of female blood
products. One study showed no increased risk. Further research is needed to determine the exact cause of increased male mortality and TRALI pathophysiology. In addition, investigations are needed to determine the best use of female blood products. These studies are just a start in truly understanding how sex mismatched blood transfusions affect patients’ bodies in the short and long term.

**Keywords:** Transfusion, mortality, female donor, male, TRALI, blood, pregnancy
Acknowledgements

To our parents: Who always believed in us and pushed us toward our goals. Thank you for your endless support!
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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

RBC    Red Blood Cells
FFP    Fresh Frozen Plasma
TRALI  Transfusion Related Associated Lung Injury
FDA    Food and Drug Administration
HLA    Human Leukocyte Antigen
HNA    Human Neutrophil Antibody
HR     Hazard Ratio
RR     Relative Risk
Increased Risk of Mortality with Female to Male Blood Product Transfusions

BACKGROUND

It is estimated that around 5 million Americans receive a blood transfusion annually and this consists of over 100 million red blood cell (RBC) units.\textsuperscript{1,2} These transfusions commonly consist of RBCs and fresh frozen plasma (FFP). Blood product transfusions are considered a generally safe procedure, however, the leading cause of transfusion mortality is transfusion-related acute lung injury (TRALI).\textsuperscript{3} It is estimated by the Food and Drug Administration (FDA) that 38\% of transfusion related deaths were attributed to TRALI.\textsuperscript{4} TRALI is defined as an acute lung injury that can be distinguished by pulmonary edema resulting in decreased oxygen exchange and bilateral infiltrates on chest X-ray shortly after a blood transfusion.\textsuperscript{5} The exact cause of TRALI is undetermined\textsuperscript{3}; however, the proposed pathophysiology is that anti-leukocyte antibodies, such as human leukocyte antigen (HLA) and human neutrophil antibodies (HNA), activate pulmonary
neutrophils in the transfusion recipient. This activation results in endothelial damage and pulmonary edema producing symptoms of dyspnea, cough, and hypoxemia.

In those who develop TRALI, 70% of patients will require mechanical ventilation and ICU admission, with up to a 47% mortality rate. TRALI has been connected to all blood products including RBCs, FFP, and platelets. The highest incidence of cases and fatalities are associated with plasma rich products such as FFP. In up to 85% of TRALI cases, antibodies can be identified in blood products administered, specifically HNA and HLA Class 1 and 2 antibodies. TRALI has been implicated to be associated with transfusions from female blood product donors, specifically multiparous females to male recipients. Pregnancy is a major immunizing event, and multiparous females create more antibodies during each pregnancy and the amount of HLA antibodies subsequently increase with parity. In Clippel et al, 31% of multiparous women had HLA antibodies in their blood compared to
only 4.2% of nulliparous women screened. It is estimated that 17% of plasma units from female donors contain HLA antibodies.\textsuperscript{7} This raises the question if blood products should be further screened for HLA/HNA antibodies specifically in multiparous women, or if blood products from females should still be even be used for transfusion. The UK implemented a policy in 2003 to eliminate female plasma products regardless of history of pregnancy\textsuperscript{11} in attempt to reduce the incidence of TRALI and therefore mortality. This systematic review is aimed at examining the link of increased mortality of blood product transfusions from female donors to male recipients.

**METHODS**

An exhaustive literature search using MEDLINE, Web of Science, and CINAHL via EBSCO-host was conducted. The following search terms were used: female, male, transfusion, mortality, donor, and pregnancy. The references from relevant articles were also searched. Included were studies that used female donor RBCs or FFP, male recipients of such products, and whose primary outcome was
mortality. Other inclusion criteria required studies to be published in English in the last 20 years and human only studies. Studies were excluded if they were published over 20 years ago or evaluated other outcomes not relevant to the clinical question. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).12

RESULTS

The initial result of the search yielded 235 articles for review. After eliminating duplicates and screening results for relevant articles, there were a total of 5 articles that met eligibility criteria. All of the articles were retrospective cohort studies 9,2,13,14,7 (See Table 1.)

Caram et al

This retrospective cohort study9 consisted of 31,118 first time transfusion recipients from 6 major Dutch hospitals between May 30, 2005 and September 1, 2015. All participants were in a no-donor-mixture cohort where each participant received RBC transfusions from exclusively male donors, or exclusively all female donors with a history of pregnancy, or exclusively all female donors without a history of
pregnancy. Exclusion criteria included any patient included in a prior study measuring mortality after a female blood product transfusion to create an independent cohort.\(^9\)

Donor information such as age, sex, and history of pregnancy were obtained via Sanquin, the national Dutch blood supply. All RBC transfusion products in the Netherlands are leukocyte reduced by filtration and ABO-RhD identically matched to recipient. The only outcome assessed was mortality at any time during follow up, which ended September 1st, 2015. This information was obtained through a nationally linked computer system which was considered complete due to the legal requirement for reporting all deaths to this system.

Survival statistical analysis was performed via the Stata version 14.1 and p values less than 0.05 were considered statistically significant.\(^9\)

Overall, 106 041 units of RBCs (76% from male donors, 12% ever pregnant female, 12% never pregnant female) were transfused to 42 132 patients. The average recipient was 66 years old and received an average of 2 units RBCs. The hazard ratio (HR) of
males who were exposed to RBCs from ever-pregnant female donors was 1.13 (CI, 1.01-1.26, p value 0.03) and represented a statistically significant risk of mortality. The highest risk of mortality was seen in transfusion of RBCs from ever-pregnant females to male recipients 50 years of age and younger. The risk of mortality from ever-pregnant female RBC transfusion was only increased with male recipients and did not result in an increased HR for female recipients. Transfusions from never-pregnant female donors did not confer a greater mortality risk in male or female recipients.\(^9\)

Limitations to this study included information about history of pregnancy was missing for 44% of female donors and therefore only selected cases with complete data available were analyzed. The effect of increased mortality was only significant in patients less than 50 years old which could make the findings tentative. Overall, this study demonstrated a significant increase in mortality of male recipients of multiparous donors.\(^9\)

**Middelburg et al**
This cohort study evaluated mortality after blood product transfusions in relation to donor sex from April 2004 - May 2009 at the Leiden University Medical Center. All blood product and patient information was obtained from the Sanquin Blood Bank. Restrictions were applied to the study to allow the effect of donor sex to be analyzed. These restrictions included patients who received a single transfusion from a single donor, or patients who received multiple transfusions from only male or only female donors to allow unisex analysis. Mortality information was obtained from the nationally linked computer system to register deaths in the Netherlands. This is legally required and therefore the data is deemed complete and was monitored until April 2010.

The cohort consisted of 11,211 patients who received a total of 96,009 transfusions. The study separated patients into two cohort groups from the full cohort to be able to perform an accurate analysis. Single donor recipient-cohort were individuals who only received one transfusion and consisted of 1377 patients. Unisex recipient-cohort
consisted of 3806 patients, this cohort analyzed recipients given multiple transfusions from either the same sex or opposite sex but not mix sex transfusions. This is described further below.\textsuperscript{14}

The single donor recipient cohort was analyzed using Kaplan-Meir curves, log-rank tests and direct comparison of mortality over the five year span. The blood transfusions given to each patient is considered to be random since the sex of the donor blood was not known at time of transfusion. During the five year follow up 233 patients died during that period with a median duration of 881 days.\textsuperscript{14}

The unisex recipient cohort analyzed both blood transfusions given to same sex recipients and opposite sex recipients from the same or opposite sex donor. To correctly analyze this information the researchers used a propensity score calculated by a Cox regression model. This was calculated because there was a risk of confounding variables based on the total number of blood donations given to the medical facility by sex. The propensity score was calculated using all blood transfusion data within the five year span to estimate blood
product type and donor sex ratios. This information was then used to calculate sex matched and sex mismatched prognostic values (i.e. number of transfusions, recipient age, recipient sex). Of the 3806 patients 847 died during the follow up period with an median duration of 773 days.  

The hazard ratio (HR) for the unisex recipient cohort receiving female blood product donation as opposed to male blood product donation was 1.1 (95% CI, 0.91-1.2). A HR of 1.2 (95% CI, 0.98-1.5) in male recipients and 0.92 (95% CI, 0.73-1.2) in female recipients was also calculated. Surprisingly, this data shows that there may be a positive female donor/recipient relationship. The researchers further analyzed their sex mismatched data to identify any other possible relationships between donor sex and recipient sex.  

HR for sex mismatched and sex matched transfusions in the unisex cohort was 1.2 (95% CI, 0.98-1.4). Mortality among male recipients from female donations was increased in the single donation cohort. This was not seen among female recipients given male blood
products. The mortality also increased greatly when analyzed over time with a 5.8 death per 100 male recipients (95% CI, -0.70 to 12) over a 90 day period whom received female blood products.\textsuperscript{14}

This study demonstrated an increase in mortality among males recipients who receive female donors blood products. This increase in mortality was also demonstrated to increase over time. However overall blood transfusions from female donors does not appear to significantly increase mortality to both sexes when compared to blood transfusions from male donors as a whole.\textsuperscript{14}

This study has the strength that allocation of blood products was completely random and not influenced by donor sex and had no confounding variables. The study also is able to demonstrate the real impact that different types of blood products from different sexes would pose to same and different sex recipients. Many other studies focus on plasma rich products but this study in particular used all blood products types. Weaknesses of this study is lack of power these results could still be explained by chance although that is unlikely. Also
researchers were unable to completely study the exact cause of death for each patient. More studies are needed to determine if the increased mortality is due to chance or other biological causes.\textsuperscript{14}

**Chasse et al**

This longitudinal cohort study\textsuperscript{2} investigated the effect of donor sex on RBC transfusion recipient survival from October 25, 2006 to December 31, 2013. Information of the blood donors was obtained from Canadian Blood Services and 4 participating academic hospitals in Canada. To be included in the study, recipients of any age had to have received at least one RBC transfusion during the above dates and have valid health insurance. Mortality data was gathered from the Ontario Registered Persons Database. Data was analyzed based on a Cox proportional hazards regression model to account for cumulative RBC transfusions over time and average follow up was 2.3 years. All RBC units were leukoreduced before transfusion.\textsuperscript{2}

The cohort consisted of 30 503 recipients, 80 755 blood donors, and 187 960 units of RBCs transfused. The average age of patients was 69, 52.1\% were female, and received an average of 3
units RBCs. A Charlson Comorbidity Index of at least 5 was present in 20.7% of patients. Death occurred in 43% of recipients. Donors of opposite sex was associated with an increased mortality. There was an 8% increase risk of death in male recipients for each additional RBC unit transfused from a female donor compared to a male donor (HR 1.08; CI, 1.06-1.09, P <0.001). The decreased survival associated with female donors was observed across all Charlson Comorbidity Index subgroups. In absolute terms, the 1-year mortality rate of 36.4% in recipients of 6 female RBC units, would result in an absolute risk reduction in mortality of 9.3% (CI, 8.3%-10.4%) when compared to male donor transfusions. This is reported as a number needed to treat of 11.²

Blood donor data was masked from the prescribing physicians and the female donor exposure being randomly distributed to recipients allowed this study to have characteristics of a randomized clinical trial such as allocation concealment and double-blinding. RBC transfusions from female donors was statistically significantly
associated with an increased mortality of recipients. This study suggests that clinical trials are warranted as this appears to affect transfusion recipient outcome.²

Tynell et al

This retrospective cohort study⁷ evaluated short term mortality after plasma transfusions from female donors. The information from this study was gathered from The Scandinavian Donations and Transfusions (SCANDAT) database from 30 Swedish hospitals. Eligibility criteria included required known birthdate, blood type, recipient to be at least 18 years old, and had their first allogeneic plasma transfusion between January 1, 1990 and December 31, 2002. Patients were excluded from the study if they had an organ or hematopoietic stem cell transplant on or before the date of their first plasma transfusion.⁷

The cohort of 92,565 patients were followed for 14 days after their first plasma transfusion to identify any deaths from any cause. The median age of the cohort was 70 years old with 55% of
patients being male. A Poisson regression model was used to estimate the relative risk (RR) of death in patients who received a plasma transfusion from a female donor. At least one unit of female plasma was given to 68% of patients. These same patients also required a larger number of plasma and RBC units. A total of 7800 (8.43%) recipients died during follow up, 8.85% in patients exposed to female plasma, and 7.53% in the unexposed patients.  

RRs were calculated by using patients who were exposed to female donor plasma and patients who were not exposed. The patients were of similar age, sex, and received the same volume of plasma at the same hospital within the same calendar year. For patients receiving one to two units of female plasma there was no evidence of increased risk with RRs of 1.01 and 1.00 respectively. Patients who received 3 to 4 units had RR of 1.16 (CI, 1.06-1.27, p value 0.002) showing a significant increase in mortality compared to patients who received male only plasma. The highest incidence of mortality was seen in patients who received 5 or more units of female plasma and whose
death after diagnosis was attributed to respiratory or circulatory morbidity or adverse reaction, with a RR of death of 1.72 (CI, 1.29-2.29, p value 0.0002). When comparing this subset of patients by the recipients sex, the RR of death of male recipients was 1.80 (CI, 1.25-2.60, p value 0.002) compared to the RR of 1.30 (CI, 1.10-1.52, p value 0.002) of their female counterparts.\(^7\)

By applying the observed RR of comparison of exposure to female plasma in patients whose discharge diagnosis death was attributed to respiratory or circulatory morbidity, or adverse reactions it is estimated that there would be 8.8 fewer deaths for every 10 000 patients transfused if male only plasma was used. This study demonstrated a possible volume effect as the risk of mortality was seen in patients who received 3 or more units of plasma. Strengths of this study included a large sample size over twelve years which helped ensure generalizability and provides risk estimates with high precision. \(^7\)
Limitations include possible confounding factors such as critically ill patients receiving more units of plasma are more likely to receive plasma from a female donor. Due to this being a retrospective study, the possibility that there was a non random distribution of male and female units among patients with different prognoses cannot be ruled out. There was also insufficient data to investigate the donor parity status. Overall, this study concludes that plasma transfusions from female donors confers a short-term survival disadvantage on male recipients.7

**Desmarets et al**

A retrospective cohort study13 was performed by the French Blood Services and two university hospitals to examine the relationship of donor sex of transfused RBCs on 1 year survival in patients who underwent cardiac surgery. The national blood service in France has a register of all transfused blood units and transfusion recipients. Data was gathered from this database to obtain information such as donor sex, while recipient data was gathered from the university hospitals.
Eligibility criteria included adult patients who were transfused for the first time between January 2007 and December 2011. Patients must have also undergone cardiac surgery during this time, the most common surgery in the cohort was valvular replacement.\textsuperscript{13}

The cohort included 2715 patients with the median age being 72, of which 63.1\% were male patients. The median number of units transfused was 2 per patient: 17.8\% of patients received only products from the same sex, 17.9\% received products from donors of the opposite sex, while 64.3\% of patients received a partial sex match. Males had a higher rate of receiving sex-matched blood products than females. The rate of sex-mismatch increased when patients required 5 or more units of RBCs.\textsuperscript{13}

This study found that patients had no increased risk of mortality by receiving RBCs from opposite sex donors. Males who received female only blood products had a HR of 0.98 (CI, 0.59-1.63) while males who received a mix of female and male RBCs had an increased HR of 2.14 (1.52-3.03). This effect was more pronounced in
female RBC recipients who were transfused with male only RBCs with a HR of 2.03 but was not found significant (CI, 0.87-4.43; p value 0.17).

The limitations of this study include a possible selection bias as the linkage between the transfusion register and the hospital discharge abstracts were only able to link about 80% of the initial population. They also used diagnosis related groups (DRGs) to measure patients comorbidities, clinical setting, and underlying illness. DRGs are used to examine the use of hospital resources and were not designed to perform this type of study and do not provide a precise description of the patient’s condition, however mortality was still able to be measured. Overall, this study concluded that RBC transfusions from opposite sex donors is safe and there was no significant effect in male recipients.13

**DISCUSSION**

Four of these studies9,2,14,7 have demonstrated that there is a link between female blood donors and increased mortality among
male recipients. Each researched a different sub group, ie. multiparous, plasma, and RBC products but overall there was an associated increase in mortality when males receive female blood products. There is an obvious link that antibodies play a role in these reactions but the studies were not able to definitively state the overall cause because the pathophysiology behind these reactions is so complex.

Caram et al\textsuperscript{9} found increased risk with use of ever pregnant females blood products to male recipients with a hazard ratio (HR) of 1.13 (CI, 1.01-1.26, p value 0.03). This data gives merit to the hypothesis that pregnancy can create harmful antibodies in female blood products. Could then a practice of not using ever-pregnant female blood in transfusion medicine be feasible? The UK believes in this risk and recently created a policy advising to stop the use of female blood products in transfusions.\textsuperscript{11} Middleburg et al\textsuperscript{14} also found that mortality could even be increased over a 90 day period when males received female blood products with 5.8 death per 100 male
recipients (95% CI, -0.70 to 12). Should there then be more follow up after transfusions among recipients regardless of type of transfusion? Chasse et al\textsuperscript{2} did contribute a 8% increase risk of death in male recipients for each additional RBC unit transfused from a female donor compared to a male donor (HR 1.08; CI, 1.06-1.09, \(P<0.001\)).

The highest incidence of mortality was seen in patients who received 5 or more units of female plasma and whose death after diagnosis was attributed to respiratory or circulatory morbidity or adverse reaction, with a RR of death of 1.72 (CI, 1.29-2.29, \(p\) value 0.0002). When comparing this subset of patients by the recipients sex, the RR of death of male recipients was 1.80 (CI, 1.25-2.60, \(p\) value 0.002) compared to the RR of 1.30 (CI, 1.10-1.52, \(p\) value 0.002) of their female counterparts.\textsuperscript{7} Understanding the cause of death would ultimately help determine the exact cause of increased mortality. Tynell et al\textsuperscript{7} did not find it feasible to monitor if TRALI was the cause of death because there is no unique diagnosis for TRALI or death code, however, 1477 patients died with respiratory or cardiac complications
which suggests possible TRALI. More detailed health records are needed among individuals who suffer from an adverse event after transfusion to better understand this phenomenon.

Because these reactions are so complex it would be hard at this time to make recommendations to change the current practice of blood transfusions. From these studies it is apparent that plasma rich products pose a greater risk of mortality than plasma poor. However, plasma poor products such as RBCs are more common transfusion components than plasma rich products. Female donors make up a large portion of the donor pool and the feasibility and implications to completely exclude females needs to be investigated.

Possible avenues to protect patients from these reactions were suggested by Clippel et al including creating new screening methods to reduce the likelihood of adverse reactions by screening for specific antibodies for example HLA/HNA antibodies. Kent et al also suggested instead of using female blood products for transfusion, using these blood products for productions of other products not used
acutely. The point was also made that there would be 8.8 fewer deaths for every 10,000 patients transfused if male only plasma was used as compared to exposure to female plasma in patients who death was contributed to respiratory or circulatory morbidity.\textsuperscript{7}

Desmartes et al\textsuperscript{13} did not find increased risk associated with female blood donors although this study did have significant selection and author bias which makes the quality of this evidence very low. Due to these biases within the study we do not know how reliable this data is when examining the risks of using female blood products.

**CONCLUSION**

Based on recent studies, there appears to be an increased risk of mortality among men who are transfused with female blood products. This increased risk is more associated with plasma rich products like FFP, however it is still seen in RBC type transfusion. The investigators hypothesized that this phenomenon is due to HLA/HNA antibodies in female donors, particularly multiparous, reacting in male
recipients. This antibody reaction is likely contributing to mortality via TRALI, however the exact pathophysiology is still unknown.

More research is needed to investigate exactly what is causing these blood reactions including studies involving HLA/HNA and other associated antibodies. Females donations contribute to a large majority of transfusion products, however, implications of removing female blood products from the donor pool need to be considered. More studies, specifically RCTs, are needed to determine the risk associated with using female blood products and a way in which we can reduce mortality risk to male recipients.
REFERENCES


## TABLES

### Table 1: Quality Assessment of Reviewed Articles

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* a The Desmatets et al study had 2 authors who worked for the French Blood Services who supported the study