Blood Transfusions in Obstetrics: Past, Present and Future

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Abstract: The history of transfusion medicine took a turn after the discovery of blood types and blood storage possibilities at the beginning of the 20th century. Although complications as a result of blood product transfusions have since dramatically decreased, minor to fatal complications still exist and give reason to limit administration in situations where possible risks outweigh the benefits. New guidelines have been published in order to reduce the number of unnecessary blood product transfusions. Unfortunately past papers show that the new guidelines are not yet fully implemented. In Switzerland no recent study has been published in regards to the administration of blood products. Therefore the goal of our retrospective study is to calculate the trend and evaluate the practice of transfusion medicine at the University Hospital of Zurich in the department of Obstetrics. Women who gave birth and received at least one red blood cell, platelet or fresh frozen plasma (FFP) transfusion where selected from the department's database. Complete information was found for 241 cases from January 1996 to February 2007. Information was collected from the department's computer programs, completed and compared with archive data. Data was collected in regards to: demographics, type of delivery, blood loss, number and type of transfusions received, hematological lab values, patient complications, complications during and after labor, and type of anemia treatment. Although we expected to see a decreasing trend in red blood cell transfusions, our results show an increasing percentage of patients receiving blood transfusions after the year 2004. Furthermore, our data shows a number of FFP, platelet and red blood cell (RBC) transfusions being administered inappropriately with discrepancies in data administration. Educational outreach and quality assurance checks are options, which could help improve the acknowledgment, understanding and administration of the practice of blood product transfusion in our clinic.

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Blood Transfusions in Obstetrics: Past, Present and Future

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1. Summary

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Although we expected to see a decreasing trend in red blood cell transfusions, our results show an increasing percentage of patients receiving blood transfusions after the year 2004. Furthermore, our data shows a number of FFP, platelet and red blood cell (RBC) transfusions being administered inappropriately with discrepancies in data administration. Educational outreach and quality assurance checks are options, which could help improve the acknowledgment, understanding and administration of the practice of blood product transfusion in our clinic.

1.a Zusammenfassung

Zu Beginn des 20. Jahrhunderts, mit der Entdeckung der Bluttypen und der Möglichkeit, Blut zu konservieren, hat sich die Transfusionsmedizin grundlegend verändert. Es ist seither gelungen, Komplikationen nach Bluttransfusionen dramatisch zu reduzieren. Trotzdem existieren noch immer zahlreiche, mit unter tödliche Risiken, die die Anwendung auf Situationen limitieren, in welchen die Vorteile mögliche Risiken überwiegen. So sind denn auch Richtlinien publiziert worden, um die Anzahl unnötiger Blutttransfusionen zu verringern. Leider zeigen bisher veröffentlichte Studien, dass diese Richtlinien bisweilen nur teilweise zur Anwendung kommen. In der Schweiz ist seit Jahren keine Studie mehr im Zusammenhang mit der Anwendung von Bluttransfusionen veröffentlicht worden. Die nun vorliegende, in der Abteilung für Geburtshilfe des Universitätsspitals Zürich durchgeführte, retrospektive Studie soll den Trend in der dort praktizierten Transfusionsmedizin bestimmen und die Anwendung von Bluttransfusionen auswerten.
In die Studie aufgenommen wurden die Daten derjenigen Patientinnen, welchen mindestens ein Erythrozytenkonzentrat, eine Thrombozyten- oder FFP- (fresh frozen plasma) Transfusion in der obgenannten Abteilung verabreicht wurde. In 241 dieser Fälle konnte auf vollständige Datenfiles der Patientinnen zurückgegriffen werden. Sämtliche Fälle stammen aus der Zeit von Januar 1996 bis Februar 2007. Die Informationen - dem Computerprogramm der Abteilung für Geburtshilfe entnommen - wurden anschliessend mit auf Papier vorhandenen Archivdaten verglichen und gegebenenfalls ergänzt. Folgende Daten fanden Einzug in die Studie: demographische Daten, Geburtsart, Blutverlust, Anzahl und Art der verabreichten Transfusionen, hämatologische Laborwerte, Komplikationen der Patientinnen, Komplikationen während oder nach der Geburt, Art der Anämietherapie.
Obwohl in der Anwendung von Bluttransfusionen von einem rückläufigen Trend ausgegangen werden musste, zeigen unsere Resultate eine Zunahme seit dem Jahr 2004. Zusätzlich geben die Daten Auskunft über die Anzahl nicht adäquat applizierter Erythrozytenkonzentrate, Thrombozyten- und FFP-Transfusionen sowie über vorhandene Diskrepanzen in der Datenerfassung.

Eine gezielte Personal-Schulung und regelmässige Qualitäts-Kontrollen könnten dazu beitragen, das nötige Verständnis und die entsprechende Sensibilisierung in der praktischen Anwendung und Administrierung von Bluttransfusionen an unserer Klinik zu erlangen.

2. Introduction

Although administration of blood products has become safer than in the past, it remains a medical procedure that entails considerable risk. Therefore appropriate use of blood products today concern both physicians and the public[1]. As a consequence, several national health care organizations have introduced new guidelines addressing the proper administration of blood products[2-4]. The historical "10/30" rule (hemoglobin 10 g/dl /hematocrit 30%) once used as a trigger for red blood cell (RBC) transfusion is outdated, and new points of consideration have been advocated. However, reports show that the practice of these new guidelines has not yet been fully implemented, and practices vary greatly amongst physicians and institutions. Reports show up to 50% of patients being transfused inappropriately according to new transfusion guidelines[5-10]. In Switzerland no recent review has been published, looking at the appropriateness of blood product transfusion. Therefore, the goal of our retrospective study is to evaluate the practice of transfusion medicine at the University Hospital of Zurich in the department of Obstetrics.

History of blood transfusions

The first successful human-to-human blood transfusion recorded was performed by James Blundell in the early 1800's, a British obstetrician who was alarmed by the unacceptably high numbers of deaths due to postpartum hemorrhage[11]. Animal-to-human transfusions had been attempted as early as 1667 by Richard Lower in London and Jean Baptiste Denis in France[11]. However, the goal of these lamb-to-human transfusions was the treatment of mental problems through the infusion of animal humors contained in blood[11]. This procedure was banned the same year it began. James Blundell preformed ten transfusions between 1825 and 1830, five of which proved beneficial to his patients. He thus made the connection between the potential benefits of transfusions in the prevention of death from hemorrhage[11]. Considering that his success was limited to 50%, he strove to find alternatives such as saving the patient's own shed blood, hence the beginning of autotransfusion[11].

Jennings published a bibliography and review of 243 transfusions performed up to 1873, also showing a complete recovery rate of 47%[12]. In the year 1901 Landsteiner's description of the ABO red cell antigen system dramatically reduced the risk of death from transfusion reactions[13]. Preventing coagulation for blood storage purposes was not possible until after 1915, when Dr. Richard Lewisohn in New York, found the optimum concentration of sodium citrate to mix with donor blood[14]. One year later, F.P. Rous and J.R. Turner developed a citrate-glucose solution, which allowed blood to be stored for weeks after collection and still remain viable for transfusion[13]. This made the establishment of the first blood depot possible in 1917, where type O blood was collected and stored, including citrate-glucose solution, in advance of the arrival of casualties during World War I[14]. World War I and II increased demand and urged further research for better storage and supply of blood products.

Based on this vast wartime experience the general opinion was that blood products were safe for widespread human use. However, infectious disease transmission was already a concern in the 1930's when modern day transfusions began. The most frequently transmitted disease was Syphilis[15]. Hepatitis soon followed in the 1940's becoming the most common infectious risk of transfusion until screening tests became available in the 1970's for Hepatitis B and early 1990s' for Hepatitis C[15]. In 1980 the discovery of human immunodeficiency virus (HIV) quickly and dramatically raised awareness about the threat of infectious risk. Since intensified blood donor evaluation, deferral of high-risk donors, and successive implementation of more sensitive screening tests, infectious risks of transfusions have been minimized particularly with respect to HIV and HCV transmission[11,15].

Transfusion Complications

Although the maternal mortality rate has decreased dramatically since James Blundell's time, according to the World Health Organization severe bleeding is still the most common cause of maternal death (25%), followed by infections

and eclampsia[16]. This puts women in labor at higher risk for needing blood transfusions, and thus at higher risk for possible complications as a result of receiving blood products. Complications can be divided into two groups: clinically symptomatic noninfectious complications and transfusion transmitted infectious complications. Although patients may still perceive that HIV transmission is the most likely adverse outcome of transfusions, severe noninfectious complications now account for most of the significant morbidity and mortality from blood transfusions in developed countries[17]. Noninfectious complications include: febrile nonhemolytic transfusion reaction, circulatory overload, transfusion related acute lung injury, acute hemolytic transfusion reaction, graft-versus-host disease and allergic reactions.

Febrile nonhemolytic transfusion reactions (FNHTR) are very common, clinically benign complications caused by pyrectic cytokines either transmitted via blood transfusion or produced by the recipient as a reaction to the donated blood[18]. They are characterized by a rise $\geq$1°C in temperature, which may be accompanied by chills, rigors, or anxiety unrelated to other medical conditions[19]. They occur at an incidence of approximately 0.5% to 6% during or after RBC transfusion. With the use of platelet transfusions the incidence has been reported to be as high as 38%[20].

Circulatory overload is one of the most common transfusion complications. One study found an incidence of 1 of 3'168 patients transfused with RBC's[21]. Circulatory overload is the result of increased venous pressure due to an increase in blood volume from transfused products with subsequent congestive heart failure and pulmonary edema[22].

Transfusion related acute lung injury (TRALI) was listed as the third leading cause of transfusion-related mortality in 1985[23], and the leading cause in 2004[24]. Diagnosis of TRALI is established if a patient has no preexisting acute lung injury (ALI) prior to transfusion, and during or within 6 hours after completion of the transfusion there is: acute onset of

respiratory distress, hypoxemia, no evidence of left atrial hypertension (ie. circulatory overload), and no temporal relationship to an alternative risk factor for ALI[25].

Acute hemolytic transfusion reactions (AHTR's) due to incompatible blood transfusions are currently the second leading cause of transfusion-related mortality, with the majority due to ABO-incompatible RBC transfusions[25] causing intravascular hemolysis[22]. AHTR is most frequently the result of human error. A survey of transfusion errors in New York State over a 10 year period found the erroneous administration to be one in every 19'000 RBC units administered, with blood being administered to the wrong recipient representing 38% of the errors[26]. Overall the incidence of fatal complications due to erroneous administration is approximately one in every 1'500'000 units of blood administered[27].

Transfusion-associated Graft-versus-host disease (TA-GVHD) is a life-threatening T lymphocyte mediated immune response with a 90-100% mortality rate, death occurring one to three weeks after transfusion[28]. This complication is almost universally fatal because it targets not only the host's or recipient's endothelial lining, but the bone marrow as well[22]. As a result TA-GVHD causes bone marrow aplasia and pancytopenia marking the terminal stage of this disease[22]. Currently irradiation is the only way to prevent TA-GVHD, which inactivates T lymphocytes in cellular blood products[22].

Many screening tests have been developed since the beginning of modern day transfusions in order to prevent the transmission of diseases via blood donations. Consequently the risk of acquiring a transmitted disease is low as seen in the table below:

Bacterial Contamination	1:10'000 – 100'000[18]
Hepatitis B Infection	1:100'000 – 1'000'000[18], 1:205'000[15]
Hepatitis C Infection	Less than 1:10'000'000[18], 1:1'935'000[15]

HIV-Infection	1:2'135'000[15], 1:2'100'000[25]

The following screening tests are available: hepatitis B surface antigen, antibodies to HIV-1 and HIV-2, hepatitis C virus, and syphilis[29]. In the USA Human T Cell Lymphotrophic Virus (HTLV) and West Nile Virus screens are also routinely performed[15].

The risk of bacterial contamination is often underrated. In allogenic blood components an estimated 1 in 3'000 platelets and 1 in 30'000 red blood cells are contaminated. Serious septic reactions, including death in nearly a third of confirmed cases, were reported in approximately 1 in 100'000 platelet transfusions and 1 in 5 million red blood cell transfusions[15]. The risk of septic reactions potentially progressing to septic shock is far greater with platelets than with red blood cells and other blood components, due to the warmer storage temperature platelets require. This provides far better growth potential for bacteria than refrigerated red blood cell storage[15].

Literature Review

Considering the possible complications, which can result from blood product transfusion, this form of therapy should only be applied when appropriate. The question remains, when is the use of blood products appropriate and when not? As mentioned earlier, although several National Health Organizations have published new guidelines regarding the use of blood products, there is no universally recognized algorithm. Nevertheless when comparing new guidelines, many recommendations are equal or similar. For example, a common agreement regarding the transfusion of RBC's is that a patient's hemoglobin level, although important, should not be the sole deciding factor when deciding whether to transfuse[3-5,30]. Factors which should also be included in deciding whether the use of RBC is appropriate are: signs and symptoms of hypoxia, the rate of ongoing blood loss, evidence of end-organ compromise and the risk of coronary artery disease[4]. Furthermore, guidelines offer numerical suggestions to aid in the decision of, and the

retrospective analysis of, appropriately transfusing blood products. For example a Canadian Expert Working Group stated that when patients are clinically stable and not at risk for coronary artery disease, transfusing RBC's is more likely to be beneficial when Hb is less than 6 g/dl, but not when greater than 8 g/dl, as long as normal blood volume is maintained and patient assessment is ongoing[4]. The American Society of Anesthesiologists published similar results stating that RBC transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dl and is almost always indicated when it is less than 6 g/dl[2].

New guidelines have also been published regarding the transfusion of fresh frozen plasma (FFP) and platelets. Similar to new RBC transfusion guidelines, the patient's clinical situation should play a important role in the decision making process and numerical triggers are offered to help verify whether administration is appropriate or not. FFP is indicated for massive blood transfusions, urgent reversal of Warfarin therapy, correction of known coagulation factor deficiencies for which specific concentrates are unavailable, and correction of microvascular bleeding when prothrombin and partial thromboplastin are over 1.5 times the normal value[2]. It is contraindicated for augmentation of plasma volume or albumin concentration[2]. Platelets are usually required if surgical and obstetric patients with microvascular bleeding show a platelet count less than 50 $x10^9/l$ and are rarely required when greater than 100 $x10^9/l$[2]. They are also required in case of inherited or acquired platelet function disorders.

3. Patients and Methods

Before beginning our retrospective study, a letter of approval was required from the ethics subcommittee for Gynecology and Obstetrics in Zurich. The study was approved as StV34/2006 in February 2007. We then selected patients from the database of the department of Obstetrics in the University Hospital of Zurich. The women selected had given birth and had received at least one of the following blood product transfusions: RBC, fresh frozen plasma and/or platelets. Patient cases were applicable when patient admittance occurred after January 1996, due to incomplete patient data prior to this date. Using patient identification numbers and case numbers, these selected patients were used as the basis for our retrospective study.

Each patient was given a new case number (1-247) and listed in the statistical software Excel® (Microsoft® Excel® 2004 for Mac Version 11.3.7). Using two computer programs, Perinat® and KISIM, data was collected for each of these 247 cases and documented in the Excel® table. The software Perinat® (Version 4.0) was developed in the department of Obstetrics and Gynecology at the University Hospital of Zurich. The program is a clinical information system where patient information is listed upon admittance and completed during the patient's stay in the hospital. The program KISIM (Version 8.11) developed by Cistec AG Zürich, stands for „Klinisches Information System Innere Medizin", and is the software used at the University Hospital to view patient data, lab data and other results collected for hospital use.

In our study we collected patient information for the following criteria: demographic data (patient's age, week of pregnancy reached, parity, gravidity and number of fetus's carried during pregnancy), type of delivery, blood loss during the operation, number and type of transfusions received, hemoglobin levels (before birth, after birth, before leaving hospital), duration of stay in hospital, patient complications, complications during and after labor, and type of anemia treatment (iron intravenous with or without

recombinant human erythropoetin). For the criteria, which are not numerical, such as patient complications and complications during and after labor, a legend was first created assigning a number to every type of complication, so that this information could also be listed in the statistical computer program Excel®. Complications during and after labor were defined as complications directly related to the action of giving birth: lacerations, atonic uterus, placental complications, premature detachment of placenta, bleeding due to placenta retention after birth, blood clotting problems due to a large volume of blood loss or because of DIC (disseminated intravascular coagulation) during labor. Patient complications were defined as problems, which were not only specific to the action of giving birth: blood loss, hemoglobin under 7 g/dl, blood pressure problems, preeklamptic state, HELLP syndrome, and diseases diagnosed before pregnancy which could have effected the patient during the labor period.

All demographic data, the type of delivery, and the number of fetus's carried was taken from the computer program Perinat®. Estimated blood loss values were taken from the operation notes. Operation notes were viewable either in Perinat® or in KISIM, where copies of the operation documents were viewable for patients who arrived later than January 2004. The number of transfusions received were taken from Perinat® when available, and otherwise from the KISIM operation notes. In order to find hemoglobin and platelet values before birth, after birth and when leaving the hospital, these dates and times were first found in the program Perinat® and then matched with the appropriate lab values found in KISIM. The duration of stay in the hospital was calculated using admittance and discharge dates taken from Perinat®. Patient complications and complications at birth were taken from both Perinat® and KISIM operation notes. The type of anemia treatment was taken from Perinat®.

If any information was missing in Perinat® or KISIM, the needed numbers and facts were accessible in the department's paper archives. In order to find the paper archive for each

patient, one needed to find the patient's social insurance number by which each patient is filed.

As mentioned earlier, the product of this data collection was listed in an Excel® table. Six cases were excluded from our list, due to incomplete patient data, leaving us with 241 complete cases. Using Excel® we were able to calculate statistical values such as mean, median, and standard error, and draw several trend-lines.

4. Results:

Demographic characteristics

The average age of all the women included in our study was 31.5 years, with a low of 17 and a high of 51 years. The distribution shown in percent per age group of 5 years is listed in table 1. The mean week of pregnancy reached was 34.5 weeks. This shows that the majority of patients (69.7%) who required transfusions delivered preterm babies, 29.5% delivered term babies and only 0.4% delivered babies postterm. The mean parity of the women who required transfusions was 1.6 and the mean gravidity 2.1. Regarding the number of fetuses carried: 88% of the women carried one, 12% two and 0.4% carried three fetuses or more during pregnancy.

Type of delivery:

Of the patients receiving transfusions, a regular caesarean section was preformed for 68% of deliveries; another 13% required emergency caesarean section, making a total of 84% requiring a caesarean section. 15% of the women delivered their babies spontaneously and 5% required vaginal operative assistance. Of all the women who gave birth at our clinic, the percentage of women having a caesarean section increased annually from 0.3% in 1998 to 0.4% in the year 2006. Of these patients 3% received a RBC, platelet and/or FFP transfusion, 0.9% at least one RBC transfusion.

Estimated Blood Loss:

The average blood loss per patient needing any kind of transfusion was 1318 mL. The median for the same group of

patients was 700 mL. The average blood loss per patient who required at least one RBC transfusion was higher, 2356 mL. The median being 2000 mL.

Transfusions

From January 1996 to February 2007, 241 women who gave birth at the University Hospital of Zurich received a transfusion. In figure 2 the percentages of women receiving transfusions per year are shown. Complete data concerning the number of transfusions was only available after January 1999, therefore trend lines could only be drawn for the time between January 1999 to December 2006. When analyzing the data, two separate perspectives were used: one showing results for women who received any of the three types of transfusions (FFP, platelets, RBC), and the other showing only the women who received at least one RBC transfusion. This was done in order to analyze the selected group as a whole, but also to gain results for specifically those patients who received at least one RBC transfusion, excluding for example women who received only FFP transfusions.

After the year 1999 results show a decreasing trend for women requiring some type of transfusion until the year 2004, as seen in figure 3. The peak percentage reached 1.9% in the year 2000, after which it continuously declined to 0.5% in 2004. In the years following, the trend shows an increase reaching 1.4% in 2006.

The overall trend for women who gave birth and received at least one RBC transfusion was quite different, also seen in figure 3. From the year 1999 to 2002 the rates increased from 0.4% to 0.7%. After the peak in 2002 the values dropped to a minimum of 0.2% in 2004. Similar to the trend of women requiring some type of transfusion, the trend increased to a peak of 1.1% in 2006. In figure 4 the number of patients receiving RBC transfusions per year is shown alongside the total number of RBC transfusions administered per year.

The second trend line drawn for transfusions was one used to depict the mean number of RBC transfusions used per patient. These results are shown in figure 5, where one can see that the overall trend from the year 1999 to 2006 is a decrease in the number of RBC transfusions used per case, beginning at a mean of 9.0 transfusions per patient in 1996 and ending with 2.2 in 2007. However, the years 2001 and 2004 stand out on their own with peak values of 9.3 and 8.5 transfusions per patient.

When analyzing the distribution of the type of transfusion received by patients, again two perspectives were analyzed. Figure 6 shows the transfusion distribution for all 241 patients between the years 1996 and February 2007. Figure 7 depicts the transfusion distribution for those patients who received at least one RBC transfusion. In the first group of all 241 patients 32% of the transfusions administered were RBC, and in the second group 46% of the transfusions received were RBC.

Of all 241 patients 14% received platelet transfusions. The distribution of the patients' lowest platelet counts can be seen in figure 8. 88% of the patients received FFP transfusions. The distribution of the number of FFP transfusions used per patient can be seen in figure 9.

Hemoglobin (Hb) values

The average hemoglobin value for women receiving some type of transfusion was: 11.8 g/dl before birth, 8.3 g/dl after birth and 9.6 g/dl before leaving the hospital. These averages were lower for all three categories for women who received at least one RBC transfusion: 11.5 g/dl before birth, 6.6 g/dl after birth and 8.8 g/dl before leaving the hospital.

The increase in hemoglobin, per day spent in hospital after birth, is listed in tables 2, 3 and 4. This was highest for patients who received at least one RBC transfusion rising 0.4 g/dl per day. Patients who received no treatment or recombinant human erythropoietin (rhEPO) therapy with no RBC transfusion experienced a hemoglobin rise of 0.1 g/dl per day.

The average blood loss correlating to each therapy group is also listed in table 4.

Hemoglobin values after labor were further analyzed by sorting all 241 patient hemoglobin values into 3 groups: hemoglobin values 10.0 g/dl and higher, hemoglobin values between 7.0-9.9 g/dl, and hemoglobin values lower than 7.0 g/dl, as seen in figure 12. The same was done for those patients receiving at least one RBC transfusion. In the first group 34% had a hemoglobin value lower than 7.0 g/dl when transfused. For patients who received at least one RBC transfusion 71% had a hemoglobin value lower than 7.0 g/dl when transfused. This leaves 29% with a hemoglobin value higher than 7.0 g/dl after birth, receiving a transfusion including at least one RBC transfusion. In figure 13 these 29% are further sorted into 4 groups in order to show the hemoglobin distribution for those patients who received a RBC transfusion and had a hemoglobin level higher than 7.0 g/dl.

Duration of stay

The average duration of stay for women receiving some type of transfusion was 8.6 days and the average for women who received at least one RBC transfusion was slightly shorter at 8.4 days. For patients who received rhEPO therapy, the average stay was 8.7 days. When viewing the trend line seen in figure 14, the average stay of patients who received at least one RBC transfusion declined from 1996 to 2007, beginning at 13.2 days in 1996 and ending at 7.1 days in 2007.

Patient complications and complications during labor

Patient complications were divided into 8 categories: patients experiencing no complication, complications due to diseases diagnosed before pregnancy, preeclampsia, HELLP, hemoglobin values lower than 7.0 g/dl during labor or after labor, substantial blood loss, hypotension due to blood loss, and a category for other complications. The frequencies of these patient complications are shown in figure 15. The three most frequent patient complications listed in the operation notes were: substantial blood loss (39%), hemoglobin value under 7.0

g/dl (34%) and preeclampsia (33%). The patient complications, for patients who received at least one RBC, are shown on figure 16.

Complications during or after labor were divided into nine categories: no complication, complications due to placenta retention and consequential blood loss, premature detachment of the placenta, other placental complications (for example placenta previa, accreta), lacerations during labor, atonic uterus, disseminated intravascular coagulation (DIC) and hypocoagubility due to large volumes of blood loss. Their frequencies are shown in figure 17. The three most frequent complications during or after labor were: atonic uterus (16.7%), lacerations (12.8%) and other placenta complications (9.3%). Figure 19 shows the frequency of experiencing zero, one, two, three or 4 complications during or after labor; most women (43%) had no labor complications. For women who received at least one RBC transfusion, the ranking for the different complications was similar, however the frequency for each higher, as seen on figure 18.

Anemia Treatment

As seen in table 5, according to Perinat® data alone 147 patients (61%) received anemia treatment with recombinant human erythropoietin (Eprex®). However table 6 shows that 19.3% of the patients, who did not have Eprex® selected in Perinat®, did receive Eprex® as written in the archive data. Thus including archive data, 69.3% of all the women in our study received Eprex®. The documentation variety and distribution for both medications in Perinat® (properly selected in designated medication field, written in procedure notes, or not documented) are shown in figure 20.

Table 1: Demographics of all 241 patients receiving any type of transfusion: RBC, FFP and/or platelets

Average Age giving birth		**SD**
Mean	31.5	0.4
Median	32.0	
Age in years	**Number of Patients**	**Percent**
15-19	2	0.8%
20-24	29	12.0%
24-29	56	23.2%
30-34	85	35.3%
35-40	52	21.6%
40 and over	17	7.1%
Stay in hospital (days)		**SD**
Mean	8.6	0.2
Median	8.0	
Pregnancy Duration		**SD**
Average (weeks)	34.5	0.4
Percent preterm (<37+0 weeks)	69.7%	
Percent term	29.5%	
Percent postterm (≥ 43+0)	0.4%	
Gravidity		**SD**
Mean	2.1	0.1
Median	2.0	
Parity		**SD**
Mean	1.6	0.1
Median	1.0	

Table 2: Hemoglobin values, duration of stay and average hemoglobin increase per day for all 241 patients

	Hb (g/dl)	**SD**
Hb-average before birth	11.8 g/dl	0.1
Hb-average after birth	8.3 g/dl	0.2
Hb-average at end of stay	9.6 g/dl	0.1
Average duration of hospital stay	8.6 days	0.2
Rise in Hb pro day in hospital	0.2 g/dl	0.0

Table 3: Hemoglobin (Hb) values, duration of stay and average hemoglobin increase per day for all 97 patients receiving RBC transfusion(s) (with or without Eprex®) therapy

	Hb (g/dl)	**SD**
Hb-average before birth	11.5 g/dl	0.2
Hb-average after birth	6.6 g/dl	0.2
Hb-average at end of stay	8.8 g/dl	0.2
Average duration of hospital stay	8.4 days	0.4
Rise in Hb per day in hospital	0.3 g/dl	0.0

Table 4: Hemoglobin (Hb) increase per day according to treatment with either RBC transfusion(s) or Eprex® and average blood loss per group of patients

	Average Hb increase per day (g/dl)	**Average blood loss (mL)**
No Eprex® therapy, no RBC transfusion	0.1	531.9
Eprex® therapy, no RBC tranfusion	0.1	653.3
RBC transfusion, no Eprex®	0.4	1866.7
RBC transfusion and Eprex®	0.3	2501.7

Table 5: Number of patients where Eprex® and/or Venofer® therapy was listed in the Perinat® program

	Number of patients	**Percentage of patients**
Eprex® selected in designated therapy field or found in procedure notes	147	61.0%
Venofer® selected or found in procedure notes	80	33.2%
Eprex® and Venofer® selected or found together in procedure notes	56	23.2%
Patients with no Eprex® therapy indicated	94	39.0%

Table 6: Number of patients receiving Eprex® therapy including those listed in the Perinat® program and those by whom Eprex® therapy was found in archive data

	Number of patients	**Percentage of patients**
Patients checked in archive (patients with no Eprex® therapy indicated in the Perinat® program)	94	39.0%
Patients excluded because no archive files available	11 → leaving 83 available cases	
Number and percentage of 83 patients checked in archive who received Eprex® therapy	16	19.3%
Number and percentage of patients receiving Eprex® including archive data	167	69.3%

Figure 1: Distribution of labor types: spontaneous, vaginal operative assistance, caesarean section and emergency caesarean section of all 241 patients who received a transfusion: RBC, platelets and/or FFP

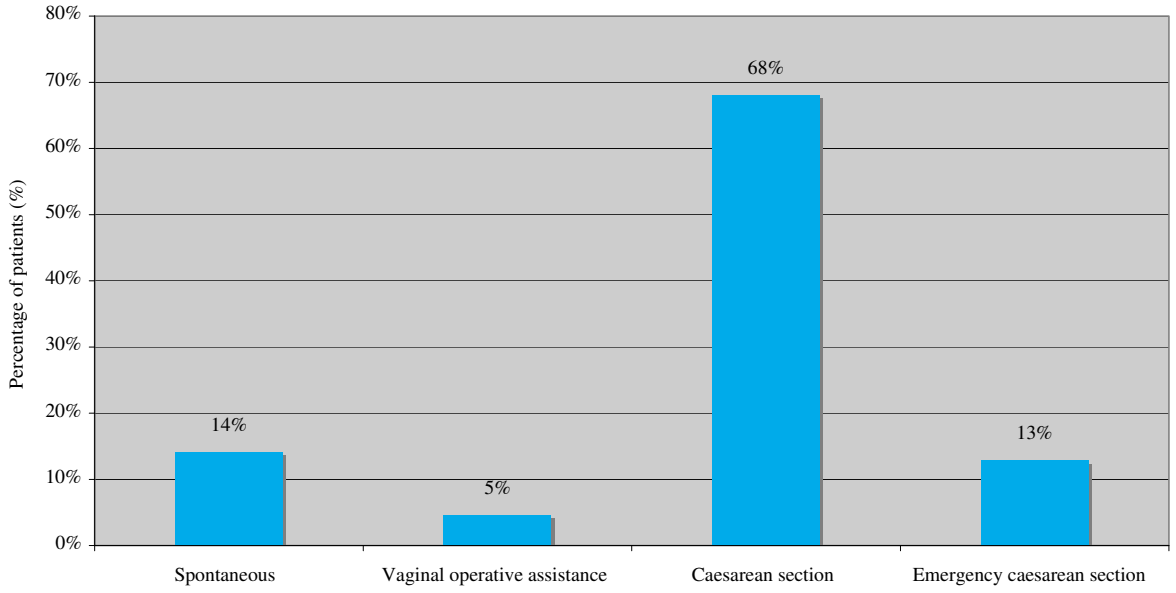


Figure 2: Percentage of patients admitted to the department of obstetrics who received a transfusion: RBC, platelet, and/or FFP

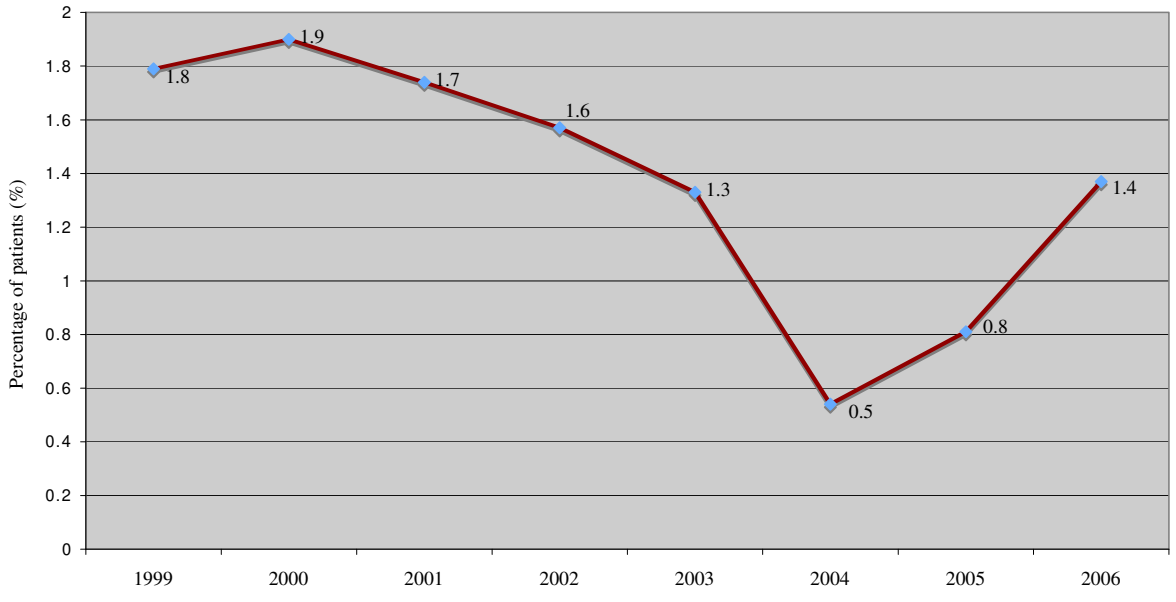


Figure 3: Percentage of patients per year who received at least one RBC transfusion in comparison to percentage of patients who received any type of transfusion (RBC, platelets, FFP)

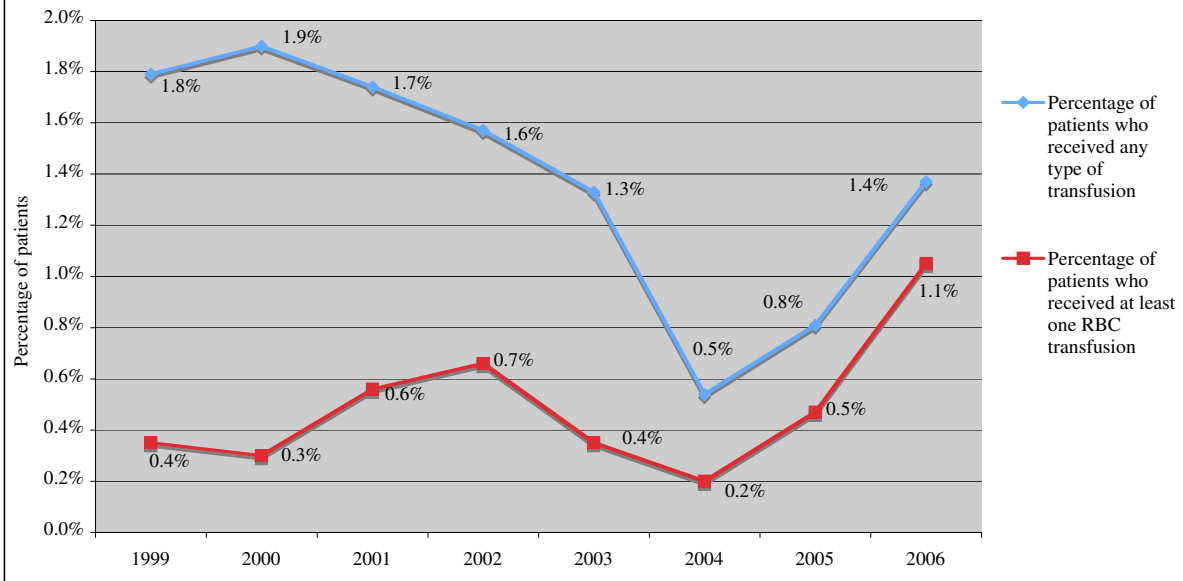


Figure 4: Number of patients receiving RBC transfusions per year and total number of RBC transfused per year

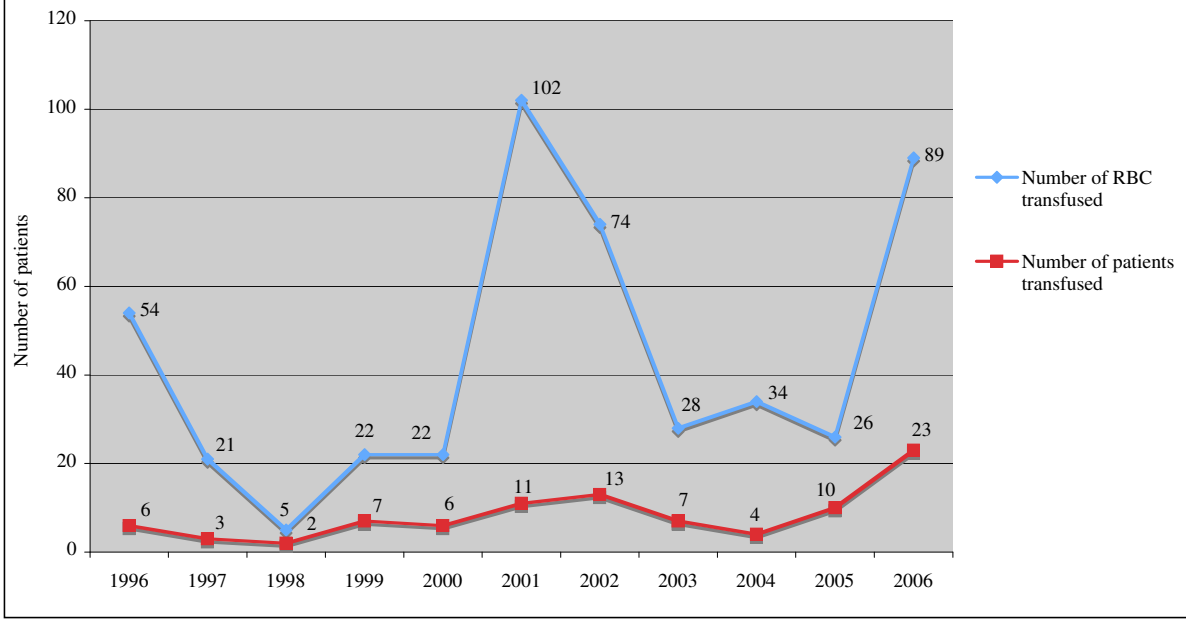


Figure 5: Mean and median number of RBC transfusions received per patient per year

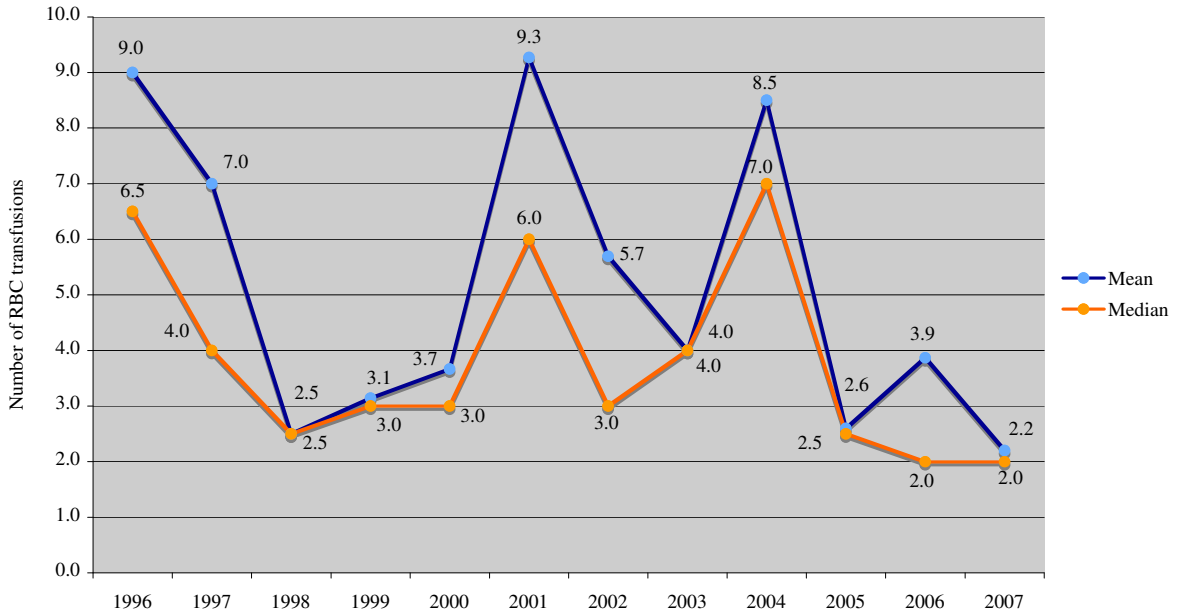


Figure 6: Transfusion distribution for all 241 patients who received FFP, platelet and/or RBC transfusions

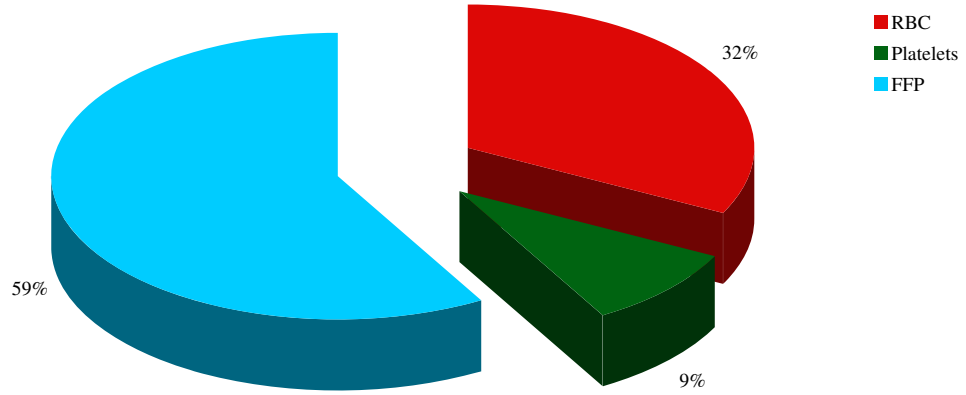


Figure 7: Transfusion distribution for patients receiving at least one RBC transfusion

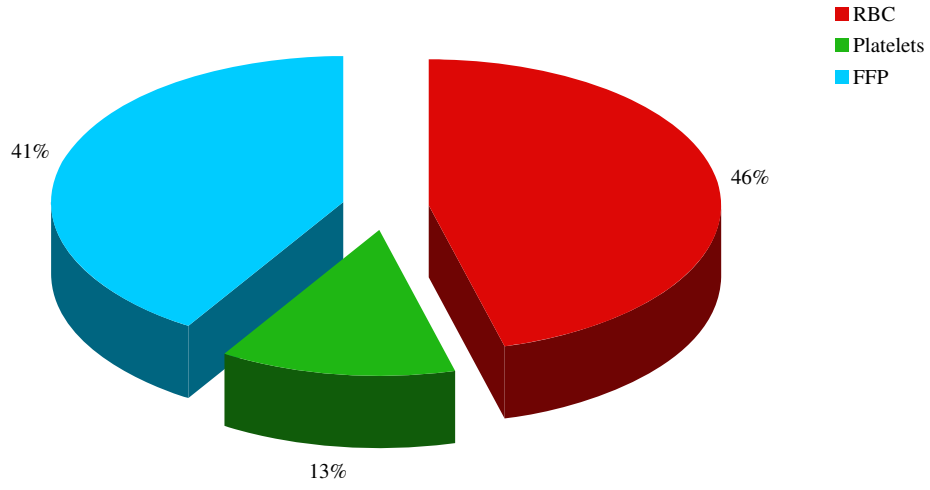


Figure 8: Lowest platelet count (pro µl) for patients who received at least one platelet transfusion

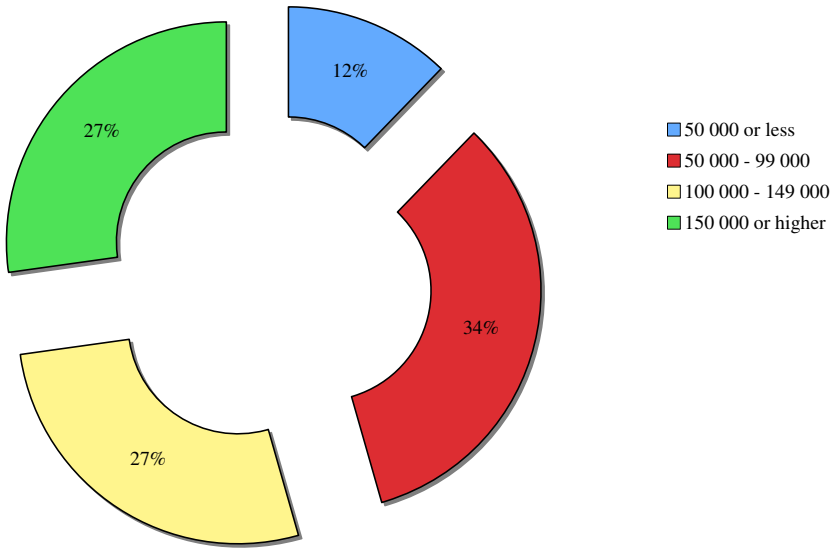


Figure 9: Number of FFP transfusions administered per patient

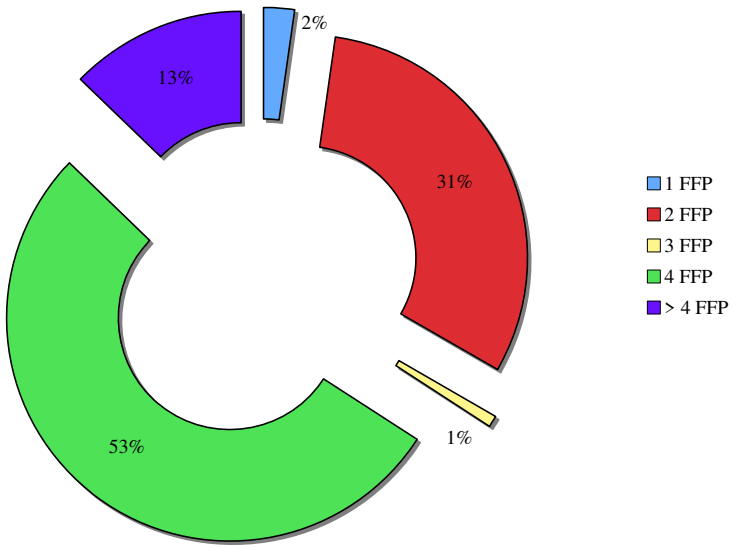


Figure 10: Mean hemoglobin (Hb) values of all 241 patients who received any type of transfusion: before labor (1), after labor (2) and before leaving the hospital (3)

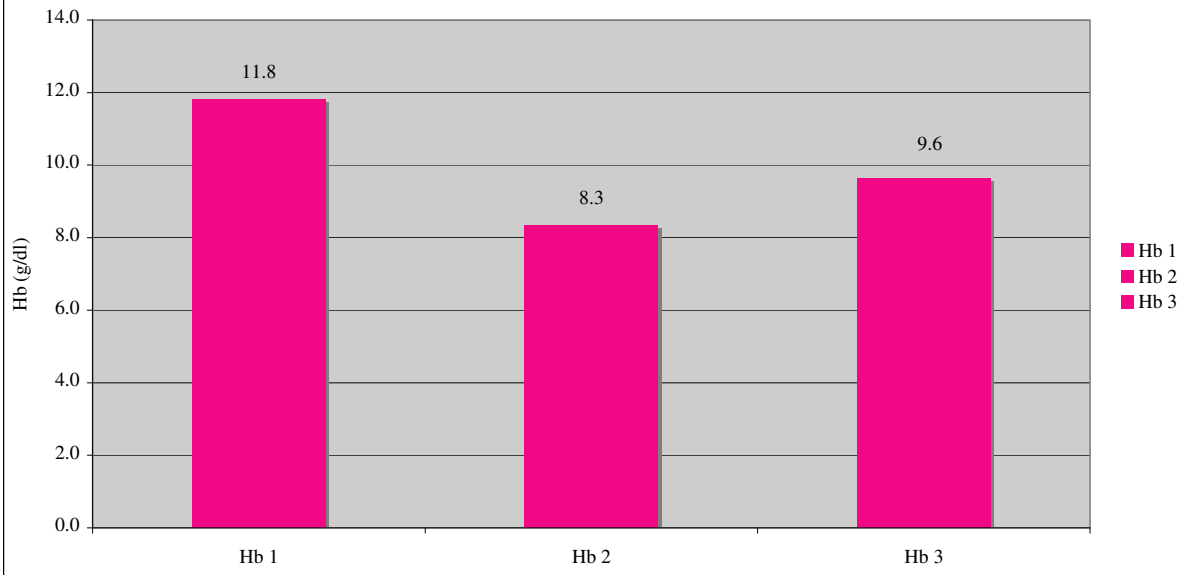


Figure 11: Mean hemoglobin (Hb) values of all 97 patients who received at least one RBC transfusion: before labor (1), after labor (2) and before leaving the hospital (3)

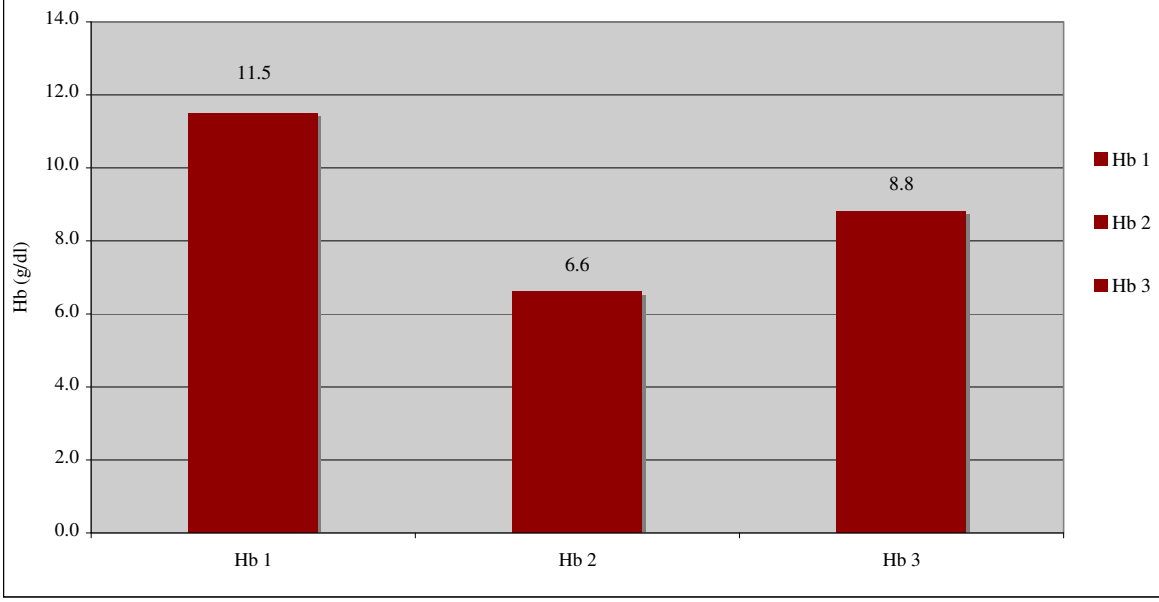


Figure 12: Hemoglobin (Hb) values after labor for all 241 patients receiving a transfusion: FFP, platelets and/or RBC transfusions

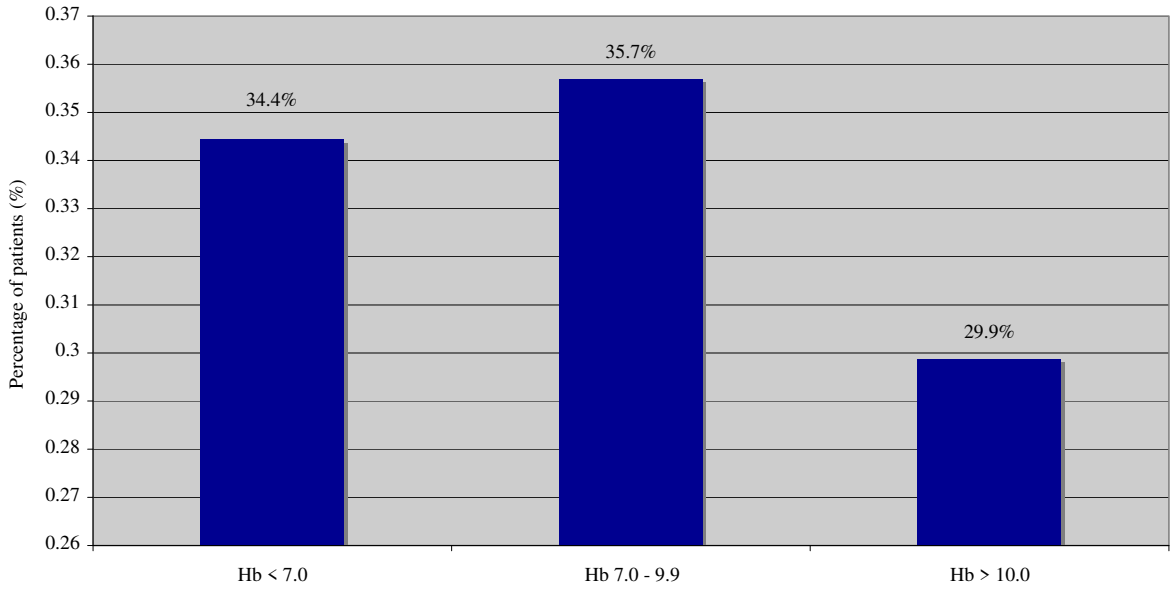


Figure 13: Distribution of lowest hemoglobin (Hb) values recorded for 97 patients who received at least one RBC transfusion

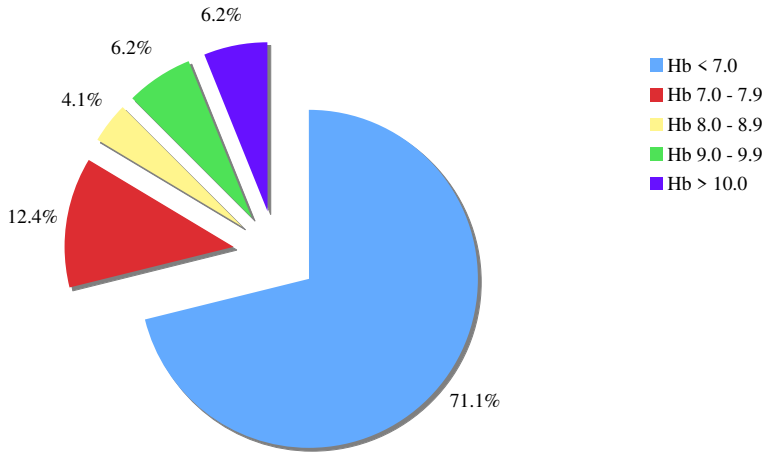


Figure 14: Average duration of stay per year for patients who received at least one RBC transfusion

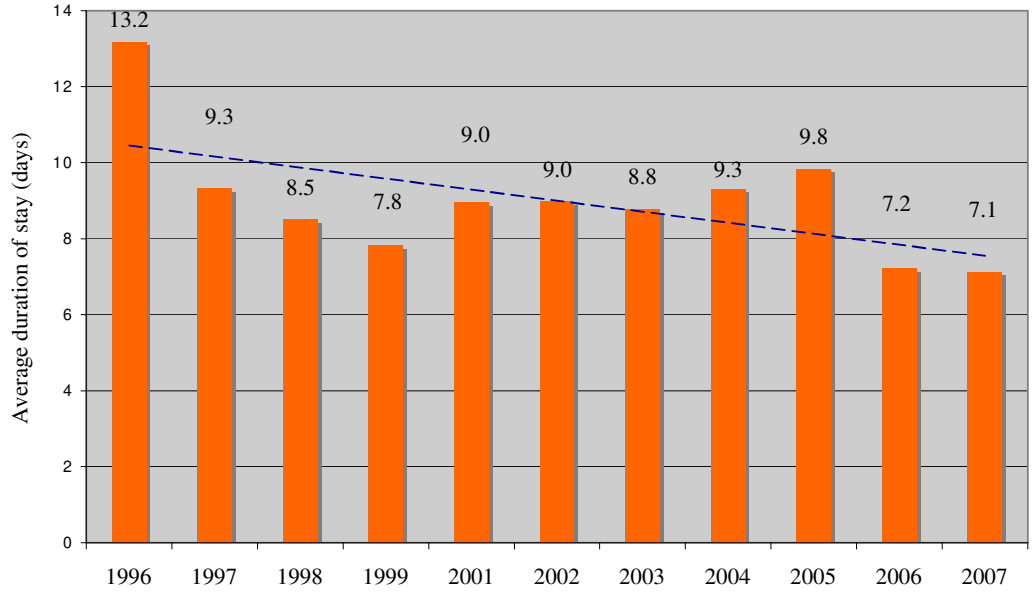


Figure 15: Specific patient complication distribution for all 241 patients receiving FFP, platelet and/or RBC transfusions

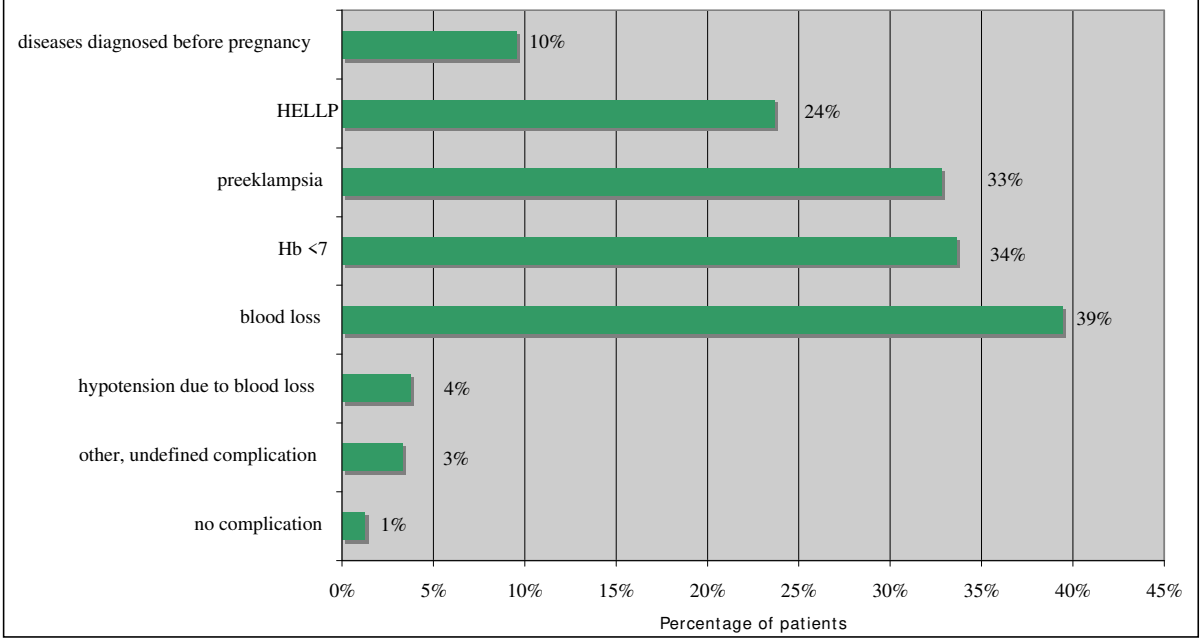


Figure 16: Specific patient complication distribution for women who received at least one RBC transfusion

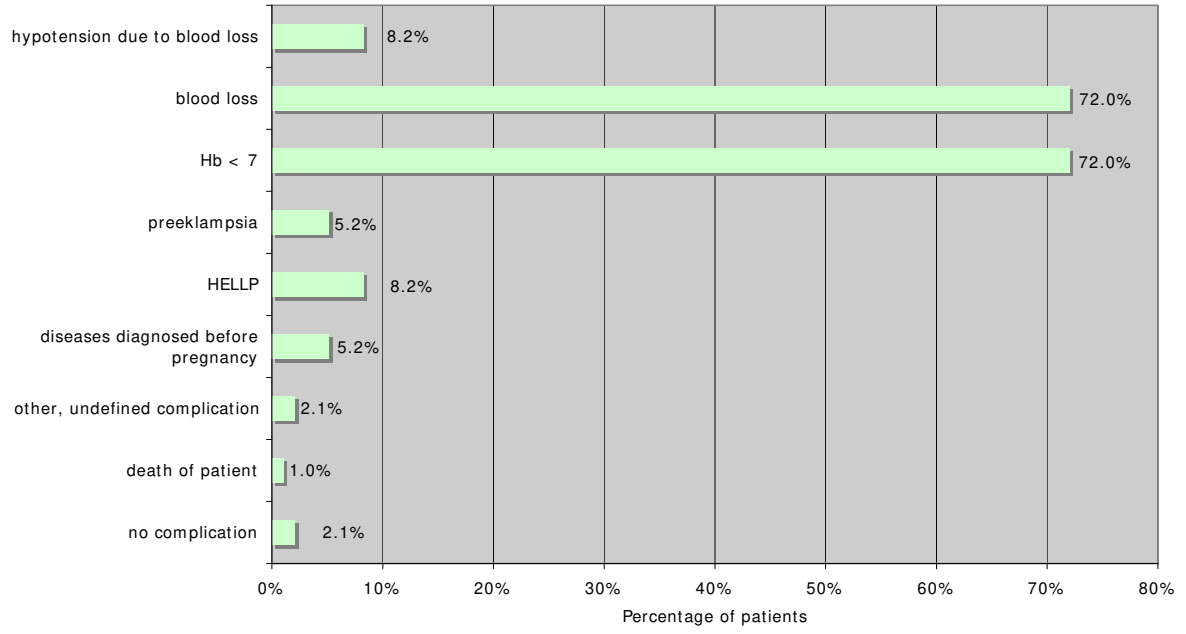


Figure 17: Distribution of specific labor complications for all 241 women who received any type of transfusion: FFP, platelet and/or RBC transfusions

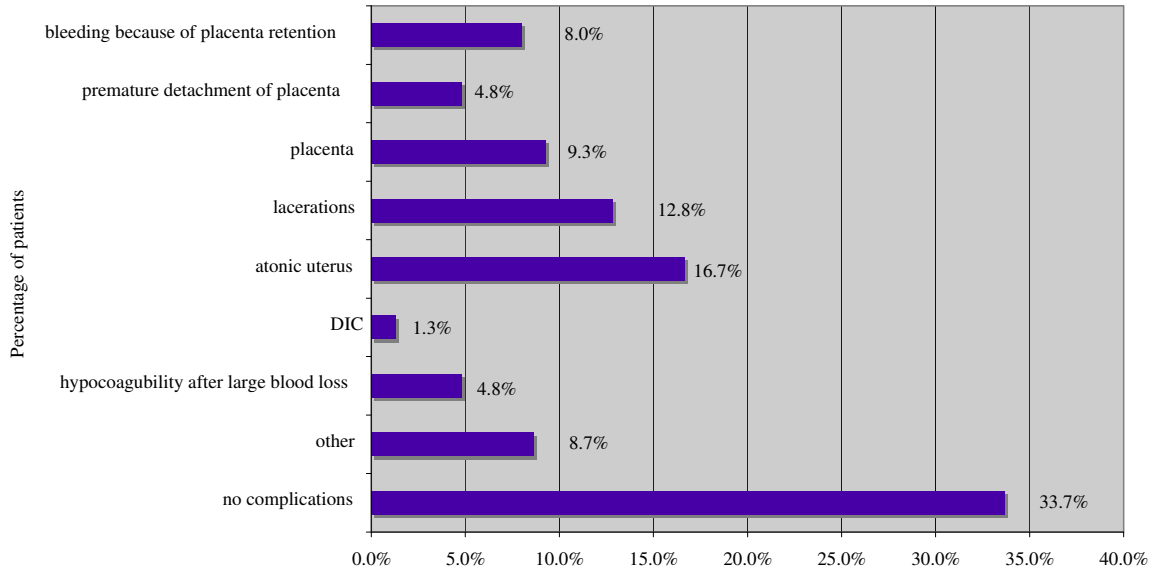


Figure 18: Distribution of labor complications for patients who received at least one RBC transfusion

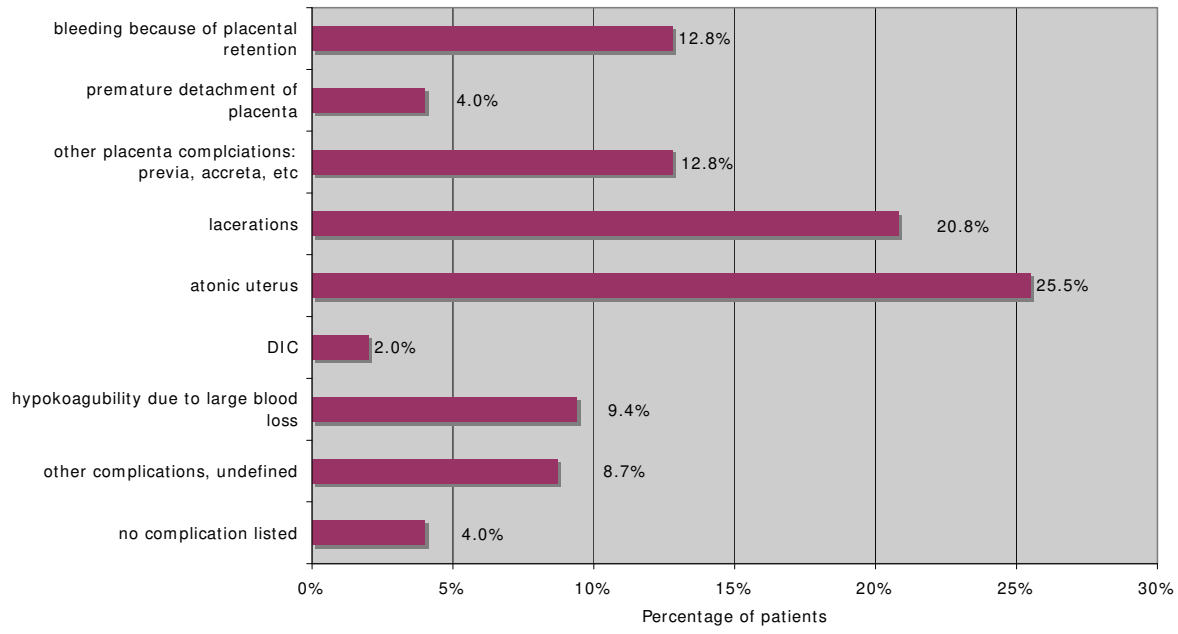


Fig. 19: Percentage of patients experiencing one, two, three or four complications during or after labor

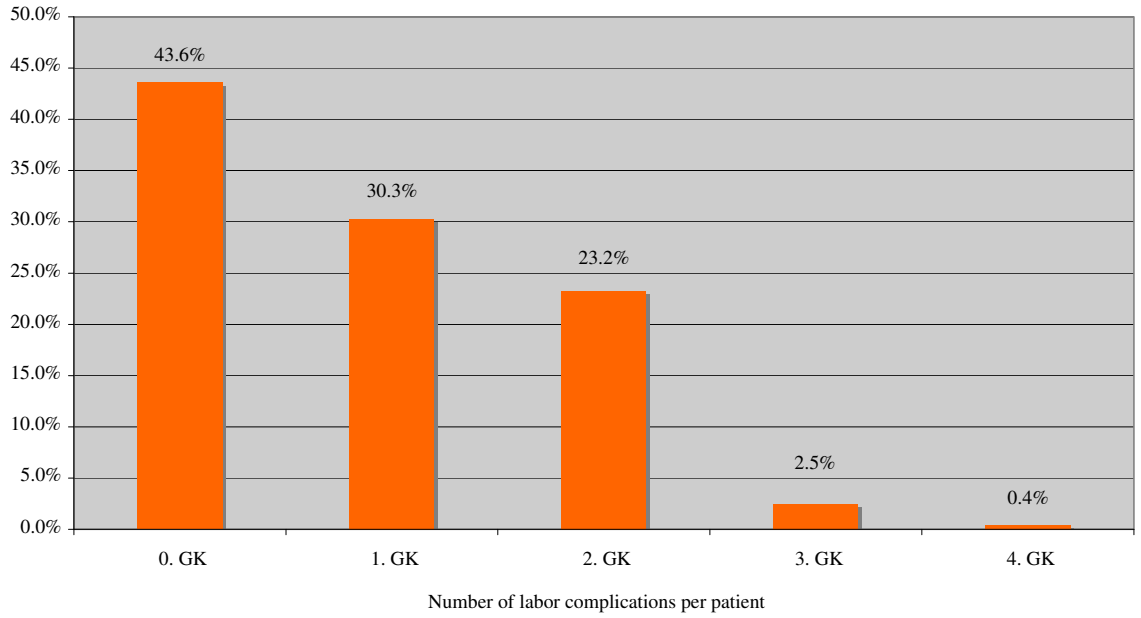
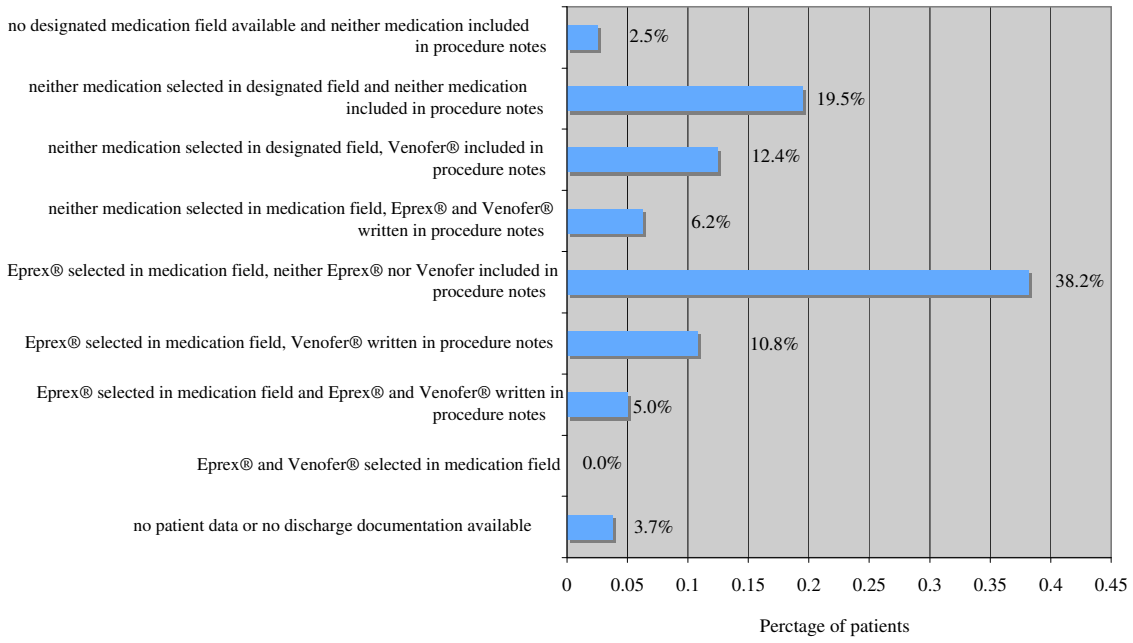


Figure 20: Distribution of erythropoietin (Eprex®) and intravenous iron therapy (Venofer®) documentation in the computer program Perinat®



5. Discussion

The transfusion of blood products can be beneficial and in some circumstances a lifesaving therapy. Unfortunately blood products also carry a risk of complications from mild to severe and fatal. Having acknowledged the serious possible consequences, new guidelines were published to update the knowledge and practice of transfusion medicine. Examples of such guidelines are those published in the British Journal of Haematology, guidelines from the American Society of Anesthesiologists and the Canadian Expert Working Group[2-4,30]. The aim of these guidelines was to reduce the number of unnecessary blood transfusions and the resulting consequences. Reports related to these guidelines show a decreasing trend in the amount of transfusions being administered[31-33]. Nonetheless they also reveal that a percentage of transfusions are still being administered inappropriately[5-10], and that new practice guidelines have not yet been fully implemented. In accordance to these results, our retrospective study shows a decrease in the transfusion trend up to 2004, however a recent increase in the two years following, with transfusions being administered inappropriately or without proper documentation.

Transfusion Trends

Over the past 20 years reports have shown a reduction in the rate of blood transfusions applied in obstetric practice. A Swiss study published in 1980 declared 18% of postpartum women receiving blood transfusions[31]. In the year 1990 Klapholz reported only 2% of women requiring blood transfusions during the peripartum period[32]. And in the year 2006 Basket and O'Connell stated that the rate of blood transfusions recorded in deliveries over a period of 22 years dropped 8-fold, from 1.82% to 0.25%[33].

In our clinic, the percentage of patients who received at least one RBC transfusion varied from 0.7% in the year 1999 to 1.1% in the year 2006. These values are similar to other European results. For example, the British Journal of Obstetrics and Gynecology reported RBC transfusion rates in obstetrics varying from 0.2% to 2.6%[34]. Silverman et al.

report 0.7% of all obstetrics-related admissions receiving an RBC transfusion[5].

In our clinic the transfusion trend portrays an overall decrease in transfusions received by patients up to the year 2004, as seen in figure 2. This is true for both patients receiving any type of transfusion and patients receiving at least one RBC transfusion. However, in contrast to the previous papers mentioned above, our results show an unexpected increase in the percentage of patients receiving transfusions for both groups after the year 2004.

This increase in the number of transfusions administered since 2004 is contrary to the average number of transfusions used per patient. Figure 5 shows a decrease from an average of 8.5 to 2.2 transfusions administered per patient from 2004 to 2007. Our value of 2.2 transfusions administered per patient in the year 2007 is comparable with previous results, for example Silverman et al. reporting a median of 2.0 transfusions per patient[5].

Of the women receiving a RBC transfusion in our clinic, 81% had a caesarean section (including emergency caesarean sections) listed as their type of labor. Several papers mention caesarean section as a risk factor for receiving a transfusion[32-35]. Of all the women who gave birth in our clinic, the percentage who had a caesarean section increased annually from 0.3% in 1998 to 0.4% in the year 2006. Of all patients requiring a caesarean section 3% received a transfusion, 0.9% at least one RBC transfusion. These numbers are comparable to Gombotz's report, showing 3% of caesarean section patients receiving a blood transfusion[36]. Other reports show percentages ranging from 1% to 7%[35,37,38].

Besides caesarean section, several papers mention placenta previa as a factor increasing the odds of requiring a transfusion[32-35]. Further obstetric complications reported to increase the risk of requiring a blood transfusion are: uterine atony, retained placenta and tissue trauma[32-35]. Our results show that atonic uterus was the most frequent labor

complication for both women receiving any of RBC, platelet and/or FFP transfusions (16.7%) and for the group of women receiving at least one RBC transfusion (25.5%). The next most frequent complications were lacerations, followed by placental retention and other placenta complications such as previa, or accreta. For each complication listed the percentages are higher for patients receiving at least one RBC transfusion, as seen on figures 17 and 18.

Hemoglobin (Hb) value

Although current transfusion guidelines imply that a numerical trigger should not be used as the sole determining factor to transfuse RBC, they offer Hb values to be used alongside the patient's clinical symptoms. As mentioned in the literature review section, most papers agree that a RBC transfusion is not recommended when the Hb value is higher than 10 g/dl[3], and almost always needed when under 6 g/dl[2,4].
Several papers have been published verifying that these new guidelines are also beneficial to patient outcome. The largest prospective trial done was performed as a team effort combining 11 Canadian institutions, sponsored by the Canadian government. Over 800 intensive care patients were randomly transfused at a liberal (10g per dl) or restrictive (7g per dl) transfusion trigger. The surprising results of this study are the following: the overall mortality was not significantly different between the two groups, and there was a trend towards a lower mortality in the restrictive group[39].

In order to assess the appropriateness of the transfusions administered in our clinic, we chose a less restrictive Hb parameter of 7 g/dl, also used by past studies to determine the appropriateness of RBC transfusions in hospitals[5]. Consequently patients who received a RBC transfusion and had Hb values higher than 7 g/dl were classified as inappropriately transfused. As seen in figure 8, this was the case for 29% of our patients. Six percent of patients had an Hb value over 10 g/dl, which even by the old criteria would have been described as inappropriate. These results affirm past reports such as Silvmerman et al. stating that up to 32%

of RBC units were classified as not appropriate[5]. The Canadian Medical Association reviewed 189 articles from 1966 to 1996 concerning the clinical practice involving RBC transfusions. They found rates of 4% to 66% of the transfusions to be unnecessary. The CMAJ published an article in 1997 to assess RBC transfusion practices and to determine the impact of implementing recently published guidelines from the American College of Physicians. According to guidelines 55.3% of transfusions were judged unnecessary[8]. A review of Australian studies shows reports of 30-50% inappropriately transfused RBC[30]. This data supports the assumption that transfusion practice varies greatly, that transfusions are being administered inappropriately according to new guidelines and that there is room for improvement.

Blood loss

As stated in several journals, another criteria used to judge the necessity of blood transfusions is blood loss[3,30]. The British Journal of Haematology states that RBC transfusion is required when blood loss estimates are greater than 2000ml and probably required when blood loss estimates are between 1500-2000ml[3]. Of all the women in our study, 68% had an estimated blood loss recorded that was less than 1500ml. Of the women who received at least one RBC transfusion, 31% had an estimated blood loss of less than 1500ml. Taking Hb values into consideration, of the women who received at least one RBC transfusion and also had an estimated blood loss recorded that was less than 1500ml, 15% had an Hb value of 7 g/dl or higher, thus transfused inappropriately by these two criteria (blood loss less than 1500 ml and Hb 7 g/dl or higher).

Platelet Transfusion

Platelet transfusion poses a far greater risk for infectious complications than RBC transfusions[15]. The American Society of Anesthesiologist Task Force on Blood Component Therapy suggested that surgical and obstetric patients with microvascular bleeding usually require a platelet transfusion if the platelet count is less than 50 $x10^9/l$ and rarely require therapy if it is greater than 100 $x10^9/l$[2]. Australian

guidelines post similar recommendations stating that it is appropriate to maintain platelet counts over 50 $x10^9$/l in patients undergoing surgery[30]. As seen in figure 6 only 12% of the women who received platelets had a value below 50 $x10^9$/l noted as their lowest platelet count, and 54% had a platelet count of over 100 $x10^9$/l. As mentioned earlier, inherited platelet disorders could lead to the use of platelet transfusions at higher platelet counts. However, only one of our 241 patients had ITP (idiopathic thrombocytopenic purpura) recorded as a preexisting disease influencing platelet function. This would suggest that a large number of the platelet transfusions were administered inappropriately. Inappropriate platelet transfusions were also found in past reports, for example in the review published by the Commonwealth of Australia, where up to 33% of platelets where found to be inappropriately administered, most commonly used for bleeding in the perioperative period[30].

Fresh frozen plasma (FFP) Transfusion

Reasons for FFP transfusions are: massive transfusion (more than one blood volume), microvascular bleeding with elevated INR, TTP (thrombotic thrombocytopenic purpura) or adult HUS (hemolytic uremic syndrome), serious bleeding or need of invasive surgery in a patient with multiple coagulation-factor deficiencies or acquired single coagulation-factor deficiency[4]. In other words, FFP should not be used for volume expansion[40] or as a prophylactic measure in the setting of a massive transfusion[4]. In past studies inappropriate FFP transfusions have been recorded at a rate as high as 83.3%[6,9,30]. In our study the majority (59%) of transfusions administered where FFP. Unfortunately we did not attempt to register PT and PTT in our data collection, therefore we could not retrospectively analyze if lab triggers where properly recorded and applied. However, only 26% of our patients experienced an estimated blood loss greater than 2000ml, and only 6.1% experienced DIC or hypocoagubility. Therefore it is quite likely that a number of FFP transfusions were administered inappropriately. An article by the Medical Journal of Australia published 31% of FFP having been transfused inappropriately[6]. Mozes found

FFP transfusions having the highest rate of inappropriate blood product transfusion, in comparison to other blood products, finding 83.3% inappropriate[9]. It was interesting to see that 66% of our patients received four or more Units of FFP, and 84% of patients receiving FFP had a caesarian delivery.

Recombinant human erythropoietin (rhEPO) therapy versus RBC transfusion

New guidelines agree that RBC transfusions should not be infused for the treatment of anemia in stable patients, when alterative therapies with fewer potential risks are available and appropriate[4,41]. Several studies show that recombinant human erythropoietin (rhEPO) combined with intravenous iron therapy offer an effective treatment for postpartum anemia[42,43] and can reduce the need for allogenic blood transfusions[44].

In our patient group we analyzed the effect of rhEPO therapy and RBC transfusions on the duration of hospital stay. The results are shown in table 2. The average duration of stay for all of our patients was 8.6 days. Unexpectedly, the duration of stay was longer for the group of patients receiving rhEPO therapy (and no RBC transfusion) with an average of 8.7 days. This could be due to the higher average blood loss of the patient group receiving rhEPO as shown in table 4. Another confounder could be the initial Hb upon admittance. The group receiving rhEPO had an average Hb value 0.13 g/dl lower than the overall average.

We also analyzed the difference in the average Hb increase per day depending on treatment. For those receiving no RBC transfusion and no rhEPO therapy the average recorded was 0.1 g/dl per day. To our surprise this was identical to the group who did receive rhEPO and no RBC transfusion. As mentioned earlier, this could be due to the rhEPO therapy group's higher average blood loss as seen in table 4. These findings were not consistent with past reports on the infuence of rhEPO. For example Breymann et al. reported rhEPO in combination with iron being more effective in treating postpartum anaemia than

iron therapy only[45]. After 7 days the results showed an increase of up to 2.0 g/dl for patients receiving rhEPO in combination with parenteral iron, whereas patients with iron showed a maximum increase of 1.4 g/dl[46]. A confounder, which could have had an affect on our therapy results was the discrecpency of proper therapy documentation, discussed below. As expected, those who received a RBC transfusion showed the quickest Hb recovery of 0.4 g/dl per day, reflecting the effectiveness of RBC transfusions in emergent situations

Discrepency issues

During our study, it became obvious that certain administrative factors had an influence on the results of our retrospective study. These also have an effect on the ongoing quality of patient administration. During our study it was necessary to use four sources of data in order to complete accurate numbers for the use of blood products. These four sources were: Perinat®, KISIM lab documents and operation notes, anesthesiologist's reports and other paper archive reports. Discrepancies were noted between the different sources analyzed. Although operation notes in Perinat® were almost always accurate in regards to when transfusions were used during operations, often the actual number of transfusions applied and the reasons behind the decision were missing. Anesthesia notes were accurate in regards to the number of transfusions administered, however they were only applicable for the transfusions applied during an operation. If a patient received transfusions in the intensive care unit or in the maternity ward, these transfusions were not included in discharge papers. The number of RBC transfusions was often listed in a slot reserved for number of FFP used or vice versa, which came to light after comparing paper archives with Perinat® information. In regards to patient therapy, although Perinat® offers a designated field for patient therapy including separate selection options for Eprex® (rhEPO) and Venofer® (intravenous iron therapy) this simple documentation form was only complete in a small number of cases. Often

Venofer® and Eprex® could be found in the procedure notes, but not selected in the designated field. The variation of documentation (proper selection of designated field or inclusion in procedure notes) is shown in figure 20. For example, although both Eprex® and Venofer® both have designated fields, not once were both medications selected, even though according to practice guidelines every patient who receives Eprex® should also receive Venofer®. In Perinat® 147 patients had Eprex® therapy listed, thus leaving 94 Patients with no Eprex® therapy, as shown in table 5. These 94 patients where reviewed in the archive showing 19.3% of the non-Eprex® patients listed in Perinat®, actually receiving Eprex®, as seen in table 6.

What can be done

Reports show that a brief, focused educational outreach visit by transfusion specialists can substantially improve the appropriateness of blood product use in surgery[8,47]. A study performed on an obstetrics and gynecology service showed a 75% decrease in the total number of packed cells, and a 60% decrease in the number of patients undergoing transfusions per month[1]. This came after a year-long process of provider education and quality assurance audits in 1990. A Canadian Review of clinical practice literature on allogenic RBC transfusions found grade A1-A2 evidence that educational outreach programs improve RBC utilization and appropriateness of transfusions and also grade A1-A2 evidence for the use of intra-operative algorithms increasing the appropriate use of blood products[8]. Our goal is to organize a presentation of our results and to educate health professionals by providing information sessions or information pamphlets. The establishment of a transfusion-use checklist, where the reason for transfusion administration can easily be documented, could improve quality assurance. If all doctors would be required to complete this checklist before or after the administration of every blood product, more accurate data would be available to ensure proper administration. These results could lead to

a second retrospective study assessing the future trend of transfusion medicine, the influence of obligatory documentation and the most common reasons for transfusion administration. A further goal could be the organization of a computer program information session for all doctors who work with the program Perinat®, demonstrating and explaining the importance of proper, complete therapy documentation. A long-term goal could be the establishment of an algorithm for the use of RBC transfusions, platelets and FFP transfusions specifically for the department of Obstetrics at the University Hospital of Zurich.

Conclusion

Although we expected to see a decreasing trend in blood product transfusion from the year 1996 to 2006, our results show an increasing percentage of patients receiving blood transfusions after the year 2004. Furthermore, our data shows a number of FFP, platelet and RBC transfusions being administered inappropriately with discrepancies in data administration. Educational outreach and quality assurance checks are options, which could help improve acknowledgment, understanding and administration of the practice of blood product transfusion in our department.

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