# Pulmonary embolism associated with transfusion after severe post-partum haemorrhage: is less more?

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**Background** - Transfusion of red blood cells is associated with superficial vein thrombosis (SVT) and venous thromboembolism (deep vein thrombosis and/or pulmonary embolism, VTE). The present study investigated the prevalence of SVT and VTE in women transfused in the peri-partum period.

**Materials and methods** - We carried out an observational study in a tertiary level obstetrics department in the Apulia Region of Southern Italy to investigate VTE in women transfused during or after labour. The study included all women who delivered between January 1st and November 30th, 2018. A thrombotic event was defined as an admission with an ICD-9 code of SVT and VTE as a primary or secondary diagnosis. Maternal "near-miss" rate, as defined by the World Health Organization, was calculated and outcome of transfused women was recorded.

**Results** - From January 1st to November 30th, a total of 1,028 women delivered, 39% of them by caesarean section (CS). One-hundred and thirty-two women (12.8%) had been classified with one or more complication codes. Most complications occurred in women who underwent CS with an odds ratio (OR) of 7.0 (95% CI: 4.0-12.5; p=0.000). Twelve women (1.2%) were transfused in the peri-partum period, 7 of them had delivered by CS. The only thrombotic events recorded in the entire cohort of 1,028 patients were isolated pulmonary embolisms observed in 2 out of 12 transfused women. Overall, patients had received a mean of 7.5 units of packed red blood cells (1 patient also received 7 plasma units, while 1 patient also received 1 platelet unit). Consequently, the near-miss rate was 2.0/1,000 deliveries, which is not significantly different from that expected in Italy and in high-income countries.

**Conclusions** - Pulmonary embolism is a life-threatening complication, which can be associated with transfusion in the peri-partum period.

**Keywords:** *pulmonary embolism, venous thrombosis, transfusion, post-partum haemorrhage.*

## INTRODUCTION

*"...Each maternal death is a tear in the community fabric-a child without a mother, parents without a daughter, and partners without their other half [...]" (David Goodman, PhD, team lead, Maternal Health Team in the U.S. Centers for Disease Control and Prevention [CDC] Division of Reproductive Health).*

It has been estimated that 60% of pregnancy-related deaths in the United States are preventable[1]. Outcome morbidities that could improve with appropriate levels of maternal

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care include number of returns to the operating room, massive transfusions, severe maternal morbidity, and potential Intensive Care Unit (ICU) admissions. Known abnormal placentation (i.e., placenta accreta or percreta) or prior caesarean birth and current anterior placenta praevia represent a potential massive blood loss and need for advanced surgical services in order to reduce maternal mortality[2-5].

Patient Blood Management (PBM) in obstetrics is an approach aimed at a timely application of evidence-informed medical and surgical approaches designed to maintain haemoglobin concentration, optimise haemostasis, and minimise blood loss in order to improve patients' outcome. Recently, a multidisciplinary team of experts has indicated how anaemia prior to childbirth can be identified and corrected, thereby improving patient outcomes[6]. Several authors have set out recommendations to improve perinatal care of pregnant women, since it is known that, for example, pre-operative anaemia is associated with an increased incidence of post-operative adverse events, including death[7-9].

In Italy, the leading causes of direct deaths in pregnancy are haemorrhage and thromboembolism, followed by hypertensive diseases[10], and a great effort is currently being made by the Italian Ministry of Health to prevent avoidable maternal deaths[11]. Maternal "near-miss" is defined as a "woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days after termination of pregnancy"[12]. Many researchers believe that the term "near-miss" is a better indicator of maternity care than mortality in high-income countries[13] because of the relatively low mortality rate recorded there[1]. It has been suggested that severe post-partum haemorrhage (PPH) is associated with an approximately 5-fold higher risk of post-partum superficial vein thrombosis (SVT)[14]. A large population-based cohort study carried out in Sweden showed that red blood cell (RBC) transfusion, but not PPH alone, is an independent risk factor for post-partum venous thromboembolism (VTE). The risk is dose-dependent, progressively rising according to the increase in the number of transfused units[15].

Here we report data on the prevalence of vein thrombosis and/or pulmonary embolism (PE) in women transfused in the peri-partum period from an ongoing project aimed at reducing outcome morbidities in a tertiary Italian research hospital.

## MATERIALS AND METHODS

In the framework of a regional project devoted to the improvement of PBM in obstetrics, we started an audit in our tertiary obstetrics unit at the "Casa Sollievo della Sofferenza", Foggia, in the Apulia region of Southern Italy. In the area of Foggia, 43% of all women resident in the area are of childbearing age, similar to the percentage of all resident women in Apulia (42.5%).

The study included all women aged 15-49 years admitted consecutively to the obstetrics department in our research hospital from January 1st to November 30th, 2018. The hospitals' discharge databases were used to identify cases and the number of women who gave birth. ICD-9-CM procedure codes associated with blood transfusions were used to identify women who underwent allogeneic blood transfusions (99.00 to 99.09). Major and minor bleeding events were defined according to the International Society on Thrombosis and Haemostasis classification[16].

### Definition of SVT and VTE

Diagnoses were recorded according to the International Classification of Diseases, 9th revision (ICD-9): codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.5, 671.9, 673.2 and 673.3. At the time of acute thromboembolic event, one of the authors (EG) was asked to counsel and follow-up women with the diagnosis of VTE; the clinical and laboratory information presented here has, therefore, been extracted from the patients' medical records.

The study was approved by the local ethics committee (date: June 11th 2018; ICF: V1_27 Mag 2018; Protocol Number 91/CE).

### Statistical analysis

Categorical variables are presented as raw numbers and percentages, continuous variables as median and ranges. The significance of any difference in means was evaluated by non-parametric tests, whereas the significance of any difference in proportions was tested using the Fisher exact test or by $\chi^2$ test statistics as appropriate. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated.

## RESULTS

### Complications in the entire cohort

From January 1st to November 30th, 1,028 deliveries were recorded: 61% (n=627) were vaginal deliveries (VD) and

39% (n=401) caesarean section (CS). Deliveries according to the ICD-9-CM procedure codes are shown in **Table I**. Complications of the procedure occurred in 69 (17.2%) of the women undergoing CS and in 18 (2.9%) of those who had a VD (OR: 7.0, 95% CI: 4.0-12.5; p=0.000).

**Table I** - *Deliveries in the entire cohort according to ICD-9-CM procedure codes description*

| ICD-9-CM code | Description | N | % |
|---|---|---|---|
| **370** | Caesarean delivery with complications | 69 | 6.7 |
| **371** | Caesarean delivery without complications | 332 | 32.3 |
| **372** | Vaginal delivery with complications | 7 | 0.7 |
| **373** | Vaginal delivery without complications | 609 | 59.2 |
| **374** | Vaginal delivery with sterilisation and/or curettage | 11 | 1.1 |
| **375** | Vaginal delivery with surgery other than sterilisation and/or curettage | 0 | 0.0 |
| | Total | 1,028 | 100 |

Furthermore, 132 (12.8%) women had been classified as having one or more ICD-9-CM complications codes; 8 of them were diagnosed with haemorrhage (**Table II**). Among these, 3 were classified as major haemorrhage and required blood transfusion, whereas the remaining, all minor haemorrhages, were treated with haemostatic agents.

No DVT or SVT was observed. Two women suffered from PE in the post-partum period, and these were classified as "near-miss" events. Therefore, in our cohort we observed 2/1,028 (0.2%) severe maternal outcomes.

## Characteristics of the transfused women

Twelve women (1.2%) were transfused in the peri-partum period (i.e., pre-labour, intra-partum and post-partum); 7 of them delivered by CS. Median age of the entire sample was not significantly different from that of transfused women (31 years, [range 15-47] and 30 [range 17-35] respectively; p>0.05). Blood components used and the reason for transfusion are summarised in **Table III**.

As previously reported, 2 women had PE; they were also managed by one of the Authors (EG). Both had had an uneventful pregnancy and delivered by CS. **Table IV** shows their obstetric history and features of the index pregnancy. None of them had a history of obstetric complications (foetal loss, pre-eclampsia, diabetes) or chronic disease. None tested positive for thrombophilia.

**Table II** - *Women with one or more ICD-9-CM codes for complications (n=132)*

| ICD-9-CM code | Short description | Number of patients |
|---|---|---|
| ***415.1*** | ***Pulmonary embolism*** | ***2*** |
| **634.11** | Spontaneous abortion complicated by haemorrhage | 2 |
| **641.11** | Haemorrhage from placenta praevia | 1 |
| **666.12** | Other immediate post-partum haemorrhage | 2 |
| **666.24** | Delayed and secondary post-partum haemorrhage | 1 |
| **665.71** | Pelvic haematoma | 1 |
| **666.02** | Third-stage post-partum haemorrhage | 1 |
| ***641.21*** | ***Premature separation of placenta*** | ***10*** |
| ***656.31*** | ***Foetal distress affecting management of mother*** | ***14*** |
| ***658.11*** | ***Premature rupture of membranes*** | ***11*** |
| ***664.01*** | ***First-degree perineal laceration*** | ***16*** |
| ***642.01 642.11 642.31 642.41 642.51*** | ***Hypertensive disorders of pregnancy*** | ***14*** |
| ***667.02*** | ***Retained placenta without haemorrhage*** | ***1*** |
| ***667.12*** | ***Retained portions of placenta without haemorrhage*** | ***1*** |
| ***648.21*** | ***Maternal anaemia*** | ***7*** |
| **549.31 651.01 652.21 652.31 652.51 652.61 652.81 654.91 656.11 664.11 665.11 665.71 666.02 667.02 667.12 659.51 659.71 659.91 661.01** | Others | 48 |
| | Total | 132 |

Haemorrhagic complications at delivery are in white. Other complications during pregnancy or delivery are in Italic.

Both received 1 g of intravenous tranexamic acid within 3 hours from the onset of bleeding. **Table V** provides details of the laboratory data of the index pregnancies. A detailed description of the peri-partum management is provided below.

**Table III** - *Blood components used and reason for transfusion*

| Patient (age) | PRBC (n) | FFP (n) | PC (n) | Reason for transfusion | Timing |
|---|---|---|---|---|---|
| **Pt 1 (33 years)** | 9 | 7 | / | Haemoperitoneum after CS | Post-partum |
| **Pt 2 (36 years)** | 6 | 2 | 1 | Uterine atony after CS | Post-partum |
| **Pt 3 (32 years)** | 2 | / | | Anaemia after CS | Intra-partum |
| **Pt 4 (45 years)** | 2 | / | / | Uterine atony after CS | Post-partum |
| **Pt 5 (29 years)** | 1 | / | / | Uterine atony after CS (bigeminy pregnancy) | Post-partum |
| **Pt 6 (25 years)** | 2 | / | / | PPH after VD | Post-partum |
| **Pt 7 (26 years)** | 2 | / | / | Vaginal haematoma after VD (episiotomy) | Post-partum |
| **Pt 8 (31 years)** | 2 | / | / | Anaemia at admission (IUGR foetus), VD | Pre-labour |
| **Pt 9 (17 years)** | 2 | / | / | Uterine atony after CS (mechanical dystocia) | Post-partum |
| **Pt 10 (31 years)** | 3 | / | / | PPH after VD (retained placenta) | Post-partum |
| **Pt 11 (30 years)** | 2 | / | / | Anaemia at admission, CS | Post-partum |
| **Pt 12 (35 years)** | 3 | / | / | Anaemia at admission, VD | Pre-labour |

PRBC: packed red blood cells; FFP: fresh frozen plasma; PC: platelet concentrates; n: number of units; Pt: patient; CS: caesarean section; VD: vaginal delivery; PPH: post-partum haemorrhage; IUGR: intrauterine growth restriction.

**Table IV** - *Clinical characteristics of two women with post-partum pulmonary embolism*

| | Pt 1 | Pt 2 |
|---|---|---|
| **Age** | 33 | 36 |
| **Previous pregnancies, n** | 1 | 2 |
| **Previous CS** | 1 | 2 |
| **Previous pregnancy loss** | 0 | 0 |
| **Previous pre-eclampsia** | 0 | 0 |
| **Personal/family history VTE** | No | No |
| **Other pregnancy complications** | No | No |
| **Pre-pregnancy weight (kg)** | 55 | 57 |
| **Weight at delivery** | 66 | 67 |
| **Gestational week** | 38 | 38 |
| **Delivery mode** | CS | CS |
| **Neonate sex** | Male | Female |
| **Birth weight (g)** | 3,300 | 3,080 |

Pt: patient; CS: caesarean section; VTE: venous thromboembolism.

### Patient 1

A 33-year old woman at her second pregnancy, who had given birth in 2016 to a male weighing 3,520 g (40 weeks of gestational age) by CS because of foetal distress. In 2018, she had a CS at 38 weeks because of foetal transverse position (male, 3,300 g). She had only been anaemic at the end of the pregnancy. Two hours after delivery, her haemoglobin levels dropped. Ultrasound scan showed a haemoperitoneum and she was transfused before a laparotomy was performed that highlighted trauma of the left ovarian artery, requiring left annessiectomy. Seventy-two hours later, she showed severe dyspnoea and computed tomography (CT) angiography showed thrombosis at bifurcation of the right pulmonary artery with bilateral pleuric effusion in absence of deep vein thrombosis at lower limb or iliac vein thrombosis. The woman was transfused with 9 RBC units and 7 plasma units in 12 h because of haemoperitoneum due to trauma of the left ovarian artery. Her family history was negative for thromboembolic events and she did not have additional risk factors for VTE. She was first treated with nadroparin 3,800 U every 12 h; after 3 days she was switched to 5,700 U every 12 h and oral anticoagulant therapy with antivitamin K was started. To date, she is taking oral anticoagulants.

### Patient 2

A 36-year old woman with 2 previous uneventful pregnancies: in 2008, she had given birth to a female weighing 3,030 g (CS at 38 weeks because of podalic presentation) and in 2013 to a female weighing 2,960 g (CS at 38 weeks). After her third CS (November 5th, 2018), an uterine atony occurred with a dramatic drop in haemoglobin levels. For this reason, she underwent a hysterectomy and was transferred to the ICU. She was transfused with 6 RBC, 2 plasma units, and 1 platelet unit over 72 h. Twelve hours after hysterectomy she developed severe dyspnoea and CT angiography showed filling defects within the right segmental pulmonary arteries. A doppler ultrasound at lower limb excluded deep or superficial vein thrombosis. A CT scan of the

**Table V** - *Laboratory investigations in patients with pulmonary embolism-index pregnancy.*

| PATIENT 1 | | | | | |
|---|---|---|---|---|---|
| **Date** | **Before CS 19/6** | **After CS 19/6** | **PE 23/6** | **Discharge 11/7** | **N.V.** |
| **RBC (×10$^{12}$/L)** | 4.09 | 2.87 | 3.15 | 4.28 | 4.2-5.4 (10$^{6}$/μL) |
| **Hb (g/dL)** | 12.1 | 8.3 | 9.4 | 12.6 | 12-16 (g/dL) |
| **Plt (×10$^{9}$/L)** | 128 | 114 | 116 | 150 | 130-400 (10$^{3}$/μL) |
| **WBC (×10$^{9}$/L)** | 7.23 | 7.42 | 4.43 | 2.97 | 4.3-10.8 (10$^{3}$/μL) |
| **PT**<br>**INR** | 138%<br>0.9 | 71%<br>1.1 | / | 39*<br>1.67* | 70-130%<br>0.8-1.2 |
| **aPTT**<br>**ratio** | 27.9<br>1.07 | / | / | | 20-32 sec<br>0.8-1.2 |
| **PATIENT 2** | | | | | |
| **Date** | **Before CS 25/10** | **After CS 6/11** | **Pre-hysterectomy 6/11** | **Discharge 24/11** | **N.V.** |
| **RBC (×10$^{12}$/L)** | 3.48 | 3.36 | 2.38 | 3.56 | 4.2-5.4 (10$^{6}$/μL) |
| **Hb (g/dL)** | 11.8 | 10.0 | 7 | 10.9 | 12-16 (g/dL) |
| **Plt (×10$^{9}$/L)** | 176 | 73.000 | 55 | 373 | 130-400 (10$^{3}$/μL) |
| **WBC (×10$^{9}$/L)** | 8.77 | 19.7 | 20.5 | 7.19 | 4.3-10.8 (10$^{3}$/μL) |
| **PT**<br>**INR** | / | 98<br>1.0 | 122<br>1.1 | / | 70-130 %<br>0.8-1.2 |
| **aPTT**<br>**ratio** | / | 30.7<br>1.2 | 33.5<br>1.4 | / | 20-32 sec<br>0.8-1.2 |

*During anticoagulation. CS: caesarean section; PE: pulmonary embolism; N.V.: normal values; sec: seconds; RBC: red blood cells; Hb: haemoglobin; Plt: platelets; WBC: white blood cell count; PT: prothrombin time; aPTT: activated partial thromboplastin time.

abdomen excluded the presence of other vein thromboses. The patient was initially treated with enoxaparin 4,000 U every 12 h; after 3 days oral anticoagulant therapy with antivitamin K was started. To date, she is taking oral anticoagulants.

## DISCUSSION

Haemorrhage and thromboembolism are leading causes of direct deaths in pregnancy[16]. PE in the peripartum period has a rate of 0.23 per 1,000 deliveries[17]. Similarly to other authors, we found that onset of PE occurs mainly during the immediate post-partum period[17,18].

We recorded an incidence of severe maternal outcomes of 2.0/1,000 deliveries; this figure is not significantly different from that previously reported in Italy and in high-income countries[19]. Furthermore, in agreement with other Italian data, the most frequent cause was obstetric haemorrhage[19]. Both our patients had had previous CS and delivered by CS in the index pregnancy. Women undergoing a CS have a higher risk of becoming a near-miss compared with those who delivered vaginally[20-22]. Abnormal placentation and PPH are significantly more frequent in women with previous CS[23]. In Italy, as in other countries, the number of CS has risen significantly, due not only to advanced maternal age, but also to a rise in the numbers of defensive CS or for medico-legal concerns.

In our study 12 women out of 1,028 (1.2%) were transfused: those with severe PPH (n=2), who had received a significantly higher amount of RBC in a very narrow interval of time, showed signs and symptoms of PE in the hours following transfusion. Chauleur *et al*. found that RBC transfusion was associated with post-partum SVT (adjusted relative risk: 4.7 [1.5-15]); however, they did not find any VTE among 362 transfused women[14].

Our findings show that the two women diagnosed with PE had received a mean of 7.5 units of packed RBC, with 7 plasma units and 1 platelets unit in addition, respectively. A recent large study showed that transfusion of more than 3 units after PPH confers a 5-fold higher independent risk of VTE, with no significant increased risk in those treated with plasma in addition to RBC. This study also showed

that PPH is not in itself a risk factor for thromboembolic events[15].

It is worth noting that we observed isolated PE without any evidence of vein thrombosis in the legs or iliac veins, although we cannot exclude a cardiac thrombus origin or embolisation of the whole deep-vein thrombus; however, according to available data[24], this is not common.

Furthermore, isolated PE was documented in hormone-related VTE. Indeed, we have recently reported that isolated PE is significantly more frequent than deep vein thrombosis, either alone or combined with PE, in women undergoing hormone therapies in preparation for assisted reproductive techniques[25]. The possible explanation for the phenomenon is an acute inflammatory status in the lung probably mediated by fibrinogen and/or cytokines and, in turn, RBC are trapped in the microcirculation in the smaller pulmonary arteries. This could be the first stage of a rapidly progressing thrombosis in the pulmonary circulation[25,26].

Many factors can contribute to the increased thromboembolic risk in transfused patients: 1) the transfused RBC replacing lost whole blood may increase blood viscosity[15]; 2) the transfusion of stored erythrocytes itself affects coagulation[27], and the formation of microparticles due to RBC storage might propagate coagulation by exposing negative charged phospholipids and by initiating thrombin generation[28]; 3) tissue trauma (e.g., CS) is a powerful trigger for autonomic dysfunction and may lead to adrenergia and inflammation that together promote coagulation. Hypoxia may also stimulate the endothelium[24]; 4) transfusion of RBC units stored >20 days increases VTE risk[29]. Indeed, stored RBC units have low nitric oxide levels, and this causes vasoconstriction and higher lactate levels that result in a decreased pH and the release of proinflammatory cytokines. All these factors are known to modulate coagulation, enhancing hypercoagulability[29-31]. When transfusion is necessary, a possible strategy to reduce VTE risk in these patients is to prefer "young" instead of "old" RBC, as this assures longer inter-transfusion periods; however, this is still a subject of debate[32].

## CONCLUSIONS

In conclusion, these data should help define transfusion policies and obstetric practices. Furthermore, a multidisciplinary team should subsequently guarantee the application of shared protocols.

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## AUTHORSHIP CONTRIBUTIONS

EG and AO conceived the study and wrote the draft. DC, MM, FP, and LdL collected and analysed data; MC and GLT critically reviewed the draft. All Authors approved the final version of the manuscript.

*The Authors declare no conflicts of interest.*

## REFERENCES

1. Pattinson R, Say L, Souza JP, et al. WHO working group on maternal mortality and morbidity classifications. WHO maternal death and near-miss classifications. Bull World Health Org 2009; **87**: 734.
2. Brace V, Penney G, Hall M. Quantifying severe maternal morbidity: a Scottish population study. Br J Obstet Gynaecol 2004; **111**: 481-4.
3. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. Br Med J 2001; **322**: 1089-93.
4. Wen SW, Huang L, Liston R, et al. Severe maternal morbidity in Canada, 1991-2001. Can Med Assoc J 2005; **173**: 759-64.
5. Geller SE, Cox SM, Callaghan WM, Berg CJ. Morbidity and mortality in pregnancy: laying the groundwork for safe motherhood. Womens Health Issues 2006; **16**: 176-88.
6. Muñoz M, Peña-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018; **28**: 22-39.
7. Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007; **297**: 2481-8.
8. Ranucci M, Di Dedda U, Castelvecchio S, et al. Surgical and Clinical Outcome Research (SCORE) Group. Impact of preoperative anemia on outcome in adult cardiac surgery: a propensity-matched analysis. Ann Thorac Surg 2012; **94**: 1134-41.
9. Gupta PK, Sundaram A, Mactaggart JN, et al. Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. Ann Surg 2013; **258**: 1096-102.
10. Donati S, Senatore S, Ronconi A; Regional Maternal Mortality working group. Maternal mortality in Italy: a record-linkage study. Br J Obstet Gynaecol 2011; **118**: 872-9.
11. Donati S, Maraschini A, Lega I, et al. Regional Maternal Mortality Working Group. Maternal mortality in Italy: results and perspectives of record-linkage analysis. Acta Obstet Gynecol Scand 2018; **97**: 1317-24.
12. Say L, Souza JP, Pattinson RC; WHO working group on Maternal Mortality and Morbidity classifications. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol 2009; **23**: 287-96.

13. Pattinson RC, Say L, Makin JD, Bastos MH. Critical incident audit and feedback to improve perinatal and maternal mortality and morbidity. Cochrane Database Syst Rev 2005: CD002961.
14. Chauleur C, Cochery-Nouvellon E, Mercier E, et al. Analysis of the venous thromboembolic risk associated with severe postpartum haemorrhage in the NOHA First cohort. Thromb Haemost 2008; **100**: 773-9.
15. Thurn L, Wikman A, Lindqvist PG. Postpartum blood transfusion and haemorrhage as independent risk factors for venous thromboembolism. Thromb Res 2018; **165**: 54-60.
16. Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010; **8**: 202-4.
17. Lee MY, Kim MY, Han JY, et al. Pregnancy-associated pulmonary embolism during the peripartum period: an 8-year experience at a single center. Obstet Gynecol Sci 2014; **57**: 260-5.
18. Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. Thromb Haemost 1992; **67**: 519-20.
19. Donati S, Maraschini A, Lega I, et al. Regional Maternal Mortality Working Group. Maternal mortality in Italy: results and perspectives of record-linkage analysis. Br J Obstet Gynaecol 2004; **111**: 561-3.
20. Donati S, Senatore S, Ronconi A; Regional Maternal Mortality Working Group. Obstetric near-miss cases among women admitted to intensive care units in Italy. Acta Obstet Gynecol Scand 2012; **91**: 452-7.
21. Pallasmaa N, Ekblad U, Aitokallio-Tallberg A, et al. Cesarean delivery in Finland: maternal complications and obstetric risk factors. Acta Obstet Gynecol Scand 2010; **89**: 896-902.
22. van Dillen J, Zwart JJ, Schutte J, et al. Severe acute maternal morbidity and mode of delivery in the Netherlands. Acta Obstet Gynecol Scand 2010; **89**: 1460-5.
23. Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am J Obstet Gynecol 2012; **207**: 14-29.
24. van Langevelde K, Srámek A, Vincken PW, et al. Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique. Haematologica 2013; **98**: 309-15.
25. Grandone E, Di Micco PP, Villani M, et al; RIETE Investigators. Venous thromboembolism in women undergoing assisted reproductive technologies: data from the RIETE Registry. Thromb Haemost 2018; **118**: 1962-8.
26. van Langevelde K, Flinterman LE, van Hylckama Vlieg A et al. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. Blood 2012; **120:** 933-46.
27. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in-hospital mortality in patients with traumatic injuries. Crit Care 2009; **13**: R151.
28. Gao Y, Lv L, Liu S, et al. Elevated levels of thrombin-generating microparticles in stored red blood cells. Vox Sang 2013; **105**: 11-7.
29. Lelubre C, Vincent J. Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: a systematic review. Crit Care 2013; **17**: R66.
30. Esmon CT. The impact of the inflammatory response on coagulation. Thromb Res 2004; **114**: 321-7.
31. Byrnes JR, Wolberg AS. Red blood cells in thrombosis. Blood 2017; **130**: 1795-9.
32. García-Roa M, Del Carmen Vicente-Ayuso M, Bobes AM, et al. Red blood cell storage time and transfusion: current practice, concerns and future perspectives. Blood Transfus 2017; **15**: 222-31.