

# Proteinuria as a novel risk factor for allogeneic blood transfusion irrespective of single or twin pregnancy

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## Summary

**Objective:** To clarify whether isolated proteinuria (IP) is an independent risk factor for blood transfusion (BT) for postpartum hemorrhage (PPH), and whether risk factors for BT identified in single pregnancy also apply to twin pregnancy. **Materials and Methods:** A retrospective cohort study of consecutive women who gave birth at Jichi Medical University Hospital, Japan, between 1 April 2006 and 31 December 2016 was performed. Single or diamniotic twin deliveries producing healthy infants of  $\geq 22$  weeks were included. We analyzed the correlations between BT and 13 candidate risk factors that may be potentially associated with PPH in single and twin pregnancies. **Results:** We included 11,423 pregnancies: 10,523 (92.2%) single and 900 (7.8%) twin pregnancies. In single pregnancies, multivariate analysis indicated that placenta previa (PP), abruptio placentae, IP, chronic or gestational hypertension, preeclampsia (PE), HELLP syndrome, and tocolytic treatment (OR: 10.4, 19.1, 3.7, 3.6, 4.0, 18.9, and 2.0, respectively) were independent factors for the increased risk of allogeneic BT. In twin pregnancies, multivariate analysis revealed that PP, abruptio placentae, IP, PE, and HELLP syndrome were independent factors for the increased risk of allogeneic BT (OR: 8.3, 103, 3.9, 4.3, and 39.6, respectively). **Conclusion:** IP was a novel risk factor for BT in both single and twin pregnancies. Although risk factors for BT were very similar between single and twin pregnancies, intravenous tocolysis was and was not a risk factor in single and twin pregnancies, respectively.

**Key words:** Cesarean section; Proteinuria; Tocolysis; Transfusion; Twin.

## Introduction

Massive postpartum hemorrhage (PPH) often requires blood transfusion (BT), and BT administration around the time of delivery is often used as a surrogate marker of massive PPH. The presence of risk factors for BT allows obstetricians to prepare for PPH; therefore, identifying the risk factors is clinically significant.

For massive PPH, and thus BT, a number of risk factors have been identified, including preeclampsia (PE) [1-6]. Several studies have reported that isolated proteinuria (IP), defined as proteinuria without hypertension, precedes PE, suggesting that IP and PE share a common pathophysiology [7-9]. We have long had the clinical impression that patients with IP more frequently suffer massive PPH, thereby requiring BT, than those without IP. Our first aim was to test our clinical impression, that is, whether IP is an independent risk factor for BT for PPH.

Twin delivery is considered a high-risk factor for BT. However, it is not known whether risk factors for BT identified in single pregnancy also apply in twin pregnancy; the second aim of the study was to examine this. We conducted a retrospective observational study of more than 10 years of data in a tertiary perinatal center in Japan.

## Materials and Methods

This was a retrospective cohort study of consecutive women who gave birth at Jichi Medical University Hospital between 1 April 2006 and 31 December 2016. Approval

from the Institutional Review Board (IRB) was obtained for this study (16-005: 25 May 2016). The IRB concluded that written informed consent from each patient was not necessary. The inclusion criteria were single or diamniotic twin deliveries producing live infants of  $\geq 22$  weeks. The exclusion criteria were monochorionic monoamniotic twins ( $n = 4$ ), triplets ( $n = 7$ ), and intrauterine fetal deaths ( $n = 105$  single fetuses, both fetuses in 92 twins, one fetus in 11 twins).

From electronic medical records, we extracted 13 candidate risk factors that may be potentially associated with allogeneic BT, namely maternal age, parity, previous CS, history of myomectomy, uterine myoma, low-lying placenta, placenta previa (PP), abruptio placentae, IP, hypertensive disorder (chronic hypertension + gestational hypertension + PE), hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, tocolytic treatment, and cesarean section (CS). We also retrieved data on the volume of blood loss at delivery and the volume of allogeneic BT, including red blood cell concentrate (RBC), fresh frozen plasma (FFP), or platelet concentrate (PC) within 24 hours of delivery.

We examined the following conditions and parameters: low-lying placenta (defined as the location of the edge of the placenta within 2 cm of the uterine internal ostium, as determined by vaginal ultrasound), PP (marginal, partial or total PP, as determined by vaginal ultrasound) [10, 11], anti-hypertensive treatment (administration of at least one of the following agents: oral/intravenous [IV] nifedipine, oral/IV

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Table 1. — *Clinical characteristics of participants.*

|                             | Singleton (n = 10,523) | Twin (n = 900)   | <i>p</i> -value* |
|-----------------------------|------------------------|------------------|------------------|
| Maternal age (years)        | 33 (29-36)             | 32 (29-36)       | 0.198            |
| Maternal age > 35           | 3,874 (36.8)           | 302 (33.6)       | 0.052            |
| BMI (kg/m/m)                | 26.6 (23.5-29.2)       | 26.5 (24.2-30.2) | 0.517            |
| Multiparity                 | 3,641 (34.6)           | 226 (25.1)       | < 0.001          |
| Previous CS                 | 2,101 (20.0)           | 56 (6.2)         | < 0.001          |
| History of myomectomy       | 318 (3.0)              | 20 (2.2)         | 0.217            |
| Uterine myoma               | 847 (8.0)              | 34 (3.8)         | < 0.001          |
| Low lying placenta          | 205 (1.9)              | 10 (1.1)         | 0.095            |
| Placenta previa             | 334 (3.2)              | 10 (1.1)         | < 0.001          |
| Abruptio placentae          | 84 (0.8)               | 4 (0.4)          | 0.32             |
| Isolated proteinuria        | 127 (1.2)              | 44 (4.9)         | < 0.001          |
| Hypertensive disorder†      | 497 (4.7)              | 84 (9.3)         | < 0.001          |
| HELLP syndrome              | 29 (0.3)               | 6 (0.7)          | 0.053            |
| Tocolytic treatment‡        | 806 (7.7)              | 543 (60.3)       | < 0.001          |
| CS                          | 4,835 (45.9)           | 858 (95.3)       | < 0.001          |
| GA at delivery (day)        | 270 (263-279)          | 257 (245-261)    | < 0.001          |
| Blood loss at delivery (mL) | 475 (276-780)          | 900 (630-1,250)  | < 0.001          |
| Allogeneic BT               | 132 (1.3)              | 31 (3.4)         | < 0.001          |
| RBC (units)                 | 6 (4-8)                | 4 (4-11)         | 0.688            |
| FFP (units)                 | 6 (4-10)               | 8 (4-12)         | 0.505            |
| PC (units)                  | 10 (10-20)             | 20 (20-20)       | 0.229            |

Data are expressed as median (interquartile range) or number (%).

\*Mann-Whitney U test or Fisher's exact test, as appropriate.

†includes chronic hypertension, gestational hypertension, or preeclampsia. ‡Tocolytic treatment defined as use of at least one of the following agents during pregnancy: IV ritodrine, IV isoxsuprine, or IV magnesium sulfate. BMI, body mass index; BT, blood transfusion; CS, cesarean section; HELLP, hemolysis, elevated liver enzymes, and low platelets; GA, gestational age; RBC, red blood cell concentrate; FFP, fresh frozen plasma; PC, platelet concentrate.

hydralazine, oral labetalol, or oral methyldopa during pregnancy), and chronic hypertension (> 140 or > 90 mmHg systolic or diastolic blood pressure, respectively) in the first trimester. We also examined the following conditions and parameters: gestational hypertension and PE (proteinuria and/or hypertension, as defined by guidelines [12]), proteinuria (a protein level of  $\geq 0.3$  g/day in urine collected for 24 h, a positive result [ $\geq 1+$ ] in the dipstick test, or a positive result [ $> 0.27$  g/gCr] in the protein-to-creatinine ratio [13, 14]), HELLP syndrome (elevated AST and LDH levels above the upper normal ranges [30 and 216 U/L, respectively] and a platelet count of  $\leq 150,000/\mu\text{L}$  [15]), and tocolytic treatment (administration of at least one of the following agents: IV ritodrine hydrochloride, IV isoxsuprine hydrochloride, or IV magnesium sulfate).

Blood was transfused when the hemoglobin level was < 6.0 g/dL, systolic blood pressure was < 90 mmHg due to hemorrhage, or estimated blood loss was > 2,000 mL. For BT, autologous blood was transfused when available, and if autologous BT was unavailable or insufficient, allogeneic blood was transfused. Autologous transfusion was prepared up to 1,000 mL for women with PP, a low-lying placenta, or rare blood type. We also retrieved data on the volume of allogeneic BT, including RBC, FFP, and PC transfused

from the start within 24 hours after CS in cases of CS and from the start of labor until 2 hours after delivery in cases of vaginal delivery. One unit of RBC, FFP, and PC was 140, 120, and 20 mL, respectively.

We analyzed associations between allogeneic BT and 13 risk factors for single and twin pregnancies. Continuous variables were expressed using medians (ranges), and categorical variables were expressed as percentages. Mann-Whitney *U*-test and Fisher's exact probability test were used to assess significant differences. Significant risk factors determined by univariate analysis were used for multivariate analysis. Multivariate logistic regression analysis was used to identify independent risk factors for allogeneic BT. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.0.2) [16]. In all analyses, *p*-values < 0.05 were considered significant.

## Results

During this 11-year period, there were 11,547 deliveries at our institute. Of these, 11,423 met our inclusion criteria, and there were 10,523 (92.2%) single and 900 (7.8%) twin

Table 2. — Risk factors for allogeneic blood transfusion in 10,523 singleton pregnancies.

| Characteristics                     | Allogeneic blood transfusion |                  |                   |                       |
|-------------------------------------|------------------------------|------------------|-------------------|-----------------------|
|                                     | (+) (n = 132)                | (-) (n = 10,391) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
| Maternal age > 35 (years)           | 57 (43.2)                    | 3,817 (36.7)     | 1.3 (0.9-1.9)     | -                     |
| Multiparity                         | 49 (37.1)                    | 3,592 (34.6)     | 1.1 (0.8-1.6)     | -                     |
| Previous CS                         | 30 (22.7)                    | 2,071 (19.9)     | 1.2 (0.8-1.8)     | -                     |
| History of myomectomy               | 4 (3.0)                      | 314 (3.0)        | 1.0 (0.4-2.7)     | -                     |
| Uterine myoma                       | 10 (7.6)                     | 837 (8.1)        | 0.9 (0.5-1.8)     | -                     |
| Low lying placenta                  | 1 (0.8)                      | 204 (2.0)        | 0.4 (0.1-2.7)     | -                     |
| Placenta previa                     | 38 (28.8)                    | 296 (2.8)        | 13.8 (9.3-20.4)   | 10.4 (5.8-18.7)       |
| Abruptio placentae                  | 13 (9.8)                     | 71 (0.7)         | 15.9 (8.6-29.5)   | 19.1 (9.7-37.7)       |
| Isolated proteinuria                | 4 (3.0)                      | 123 (1.2)        | 2.9 (1.1-8.0)     | 3.7 (1.3-10.8)        |
| Hypertensive disorder               |                              |                  |                   |                       |
| Chronic or gestational hypertension | 10 (7.6)                     | 309 (3.0)        | 2.9 (1.5-5.6)     | 3.6 (1.8-7.3)         |
| Preeclampsia                        | 8 (6.1)                      | 170 (1.6)        | 4.2 (2.0-8.7)     | 4.0 (1.8-9.0)         |
| HELLP syndrome                      | 6 (4.5)                      | 23 (0.2)         | 21.5 (8.6-53.6)   | 18.9 (7.0-50.9)       |
| Tocolytic treatment                 | 42 (31.8)                    | 764 (7.4)        | 5.9 (4.1-8.5)     | 2.0 (1.2-3.4)         |
| Cesarean section                    | 97 (73.5)                    | 4,738 (45.6)     | 3.3 (2.2-4.9)     | 1.3 (0.9-2.1)         |

\*Significant predictive factors determined by univariate analyses were used for multivariate analyses.

CS, cesarean section; HELLP, hemolysis, elevated liver enzymes, and low platelets.

pregnancies (267 [30%] monochorionic diamniotic and 633 [70%] dichorionic diamniotic twins).

Table 1 shows the demographic and clinical characteristics of patients. The rates of multipara, previous CS, uterine myoma, and PP in single pregnancies were significantly higher than those in twin pregnancies. The rates of IP, hypertensive disorder (chronic hypertension + gestational hypertension + PE), tocolytic treatment, CS, allogeneic BT, and blood loss at delivery in twin pregnancies were significantly higher than those in single pregnancies. Of 10,523 single pregnancies, 132 (1.3%) received allogeneic BT. Of 900 twin pregnancies, 31 (3.4%) received allogeneic BT. No patient received “FFP only” or “PC only”; thus, we refer to all 163 (132 + 31) patients as the “allogeneic BT” group.

Table 2 shows the relationships between allogeneic BT and risk factors in single pregnancies. In univariate analysis, several factors increased the risk of allogeneic BT, namely PP, abruptio placentae, IP, chronic or gestational hypertension, PE, HELLP syndrome, tocolytic treatment, and CS. These significant factors were used in multivariate analyses, and we found that PP, abruptio placentae, IP, chronic or gestational hypertension, PE, HELLP syndrome, and tocolytic treatment were independent risk factors for allogeneic BT (OR: 10.4, 19.1, 3.7, 3.6, 4.0, 18.9, and 2.0, respectively).

Table 3 shows the relationships between these risk factors and allogeneic BT in twin pregnancies. In univariate analyses, several factors increased the risk of allogeneic BT, namely low lying placenta, PP, abruptio placentae, IP, PE, HELLP syndrome, and tocolytic treatment. These significant factors were used in multivariate analyses, and we found that PP, abruptio placentae, IP, PE, and HELLP syn-

drome were independent risk factors for allogeneic BT (OR: 8.3, 103, 3.9, 4.3, and 39.6, respectively). We also compared monochorionic (n = 267) with dichorionic (n = 633) twins; however, there was no difference between the two groups (data not shown).

## Discussion

We made two novel observations. Firstly, IP was a risk factor for BT in both single and twin pregnancies. Secondly, risk factors for BT were almost identical between single and twin pregnancies.

To our best knowledge, this is the first report of IP as an independent risk factor for BT. We believe that this may be the case because some cases of IP share a common pathophysiology with that of PE. Pregnant women with PE tend to be of advanced age, and they were often treated with magnesium sulfate, with both phenomena increasing blood loss. However, even if these confounders are adjusted for, PE can increase the PPH risk by 2- to 5-fold [1-6]. In patients with PE, various hemostatic abnormalities exist. For example, platelet counts can decrease, even before the clinical manifestations of PE [17, 18]. In addition, the soluble fms-like tyrosine kinase-1 level has been reported increase, suggesting that it is closely associated with coagulability/hemostasis [19]. Although the precise mechanism is still unclear, the incidence of PPH in patients with PE is higher than that in healthy individuals. Recent diagnostic criteria for PE do not necessarily indicate the presence of proteinuria. However, a significant number of patients with IP later develop PE. Thus, if a patient with IP (without hypertension) is delivered in a certain gestational week, hypertension may become evident later (if pregnancy had continued) and not manifest at the time of delivery. Thus,

Table 3. — Risk factors for allogeneic blood transfusion in 900 twin pregnancies.

| Characteristics                     | Allogeneic blood transfusion |               |                   |                       |
|-------------------------------------|------------------------------|---------------|-------------------|-----------------------|
|                                     | (+) (n = 31)                 | (-) (n = 869) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
| Maternal age > 35 (years)           | 13 (41.9)                    | 289 (33.3)    | 1.5 (0.7-3.0)     | -                     |
| Multiparity                         | 8 (25.8)                     | 218 (25.1)    | 1.0 (0.5-2.4)     | -                     |
| Previous CS                         | 3 (9.7)                      | 53 (6.1)      | 1.7 (0.5-5.6)     | -                     |
| History of myomectomy               | 2 (6.5)                      | 18 (2.1)      | 3.3 (0.7-14.7)    | -                     |
| Uterine myoma                       | 2 (6.5)                      | 32 (3.7)      | 1.8 (0.4-7.9)     | -                     |
| Low lying placenta                  | 2 (6.5)                      | 8 (0.9)       | 7.4 (1.5-36.5)    | 2.2 (0.1-33.3)        |
| Placenta previa                     | 2 (6.5)                      | 8 (0.9)       | 7.4 (1.5-36.5)    | 8.3 (1.6-44)          |
| Abruptio placentae                  | 3 (9.7)                      | 1 (0.1)       | 93.0 (9.4-922)    | 103 (7.9-1,350)       |
| Isolated proteinuria                | 3 (9.7)                      | 41 (4.7)      | 3.3 (1.1-11.4)    | 3.9 (1.1-14.3)        |
| Hypertensive disorder               |                              |               |                   |                       |
| Chronic or gestational hypertension | 3 (9.7)                      | 44 (5.1)      | 2.4 (0.7-8.5)     | 1.5 (0.3-7.1)         |
| Preeclampsia                        | 4 (12.9)                     | 33 (3.8)      | 3.5 (1.1-10.6)    | 4.3 (1.4-13.5)        |
| HELLP syndrome                      | 3 (9.7)                      | 3 (0.3)       | 30.9 (6.0-160)    | 39.6 (6.5-241)        |
| Tocolytic treatment                 | 19 (61.3)                    | 524 (60.3)    | 1.0 (0.5-2.2)     | -                     |
| Cesarean section                    | 31 (100)                     | 827 (95.2)    | -                 | -                     |

\*Significant predictive factors determined by univariate analyses were used for multivariate analyses.

CS, cesarean section; HELLP, hemolysis, elevated liver enzymes, and low platelets.

we contend that some patients with IP have a hemorrhagic tendency similar to those with PE, making this condition an independent risk factor for BT. We did not measure the aforementioned biochemical indices in patients with IP, and thus, further studies are needed.

The second important finding was that most of the risk factors for BT were similar between single and twin pregnancies, with only one exception, intravenous tocolysis. Regarding the risk of PPH in single versus twin pregnancies, there are few studies on the topic. A previous study [20] has reported differences in risk factors for PPH between single and twin pregnancies. For the former population, the risk factors were preterm delivery, PP, and abruptio placentae, whereas for the latter population, they were > 40 years of age, > 41 weeks of gestation, hypertensive disorders, and PP. However, abruptio placentae may also cause massive PPH in twin pregnancies. A total of 4,601 cases were included in the aforementioned study, a much smaller number compared to the present study. Thus, we believe that our results adequately reflect the real-world circumstances.

Intravenous tocolysis was and was not a risk factor for single and twin pregnancies, respectively. In Japan, long-term tocolysis during hospitalization is a routine practice. Although a previous study demonstrated that long-term tocolysis did not improve neonatal outcomes [21], many Japanese obstetricians believe that long-term tocolysis prolongs pregnancy in patients with threatened preterm labor [22]. Furthermore, many Japanese obstetricians still utilize long-term tocolysis. Indeed, the preterm birth rate in Japan was 5.6% in 2016, the lowest in the world [23]. In cases of CS under tocolysis (e.g., premature rupture of membranes), the uterorelaxant effects of tocolytic agents may persist dur-

ing CS, thereby causing or worsening atonic bleeding. Twin pregnancy itself is a strong risk factor for atonic bleeding, and thus, the effects of tocolytic treatment may be small. Thus, tocolysis may not be an independent risk in twin pregnancy.

Here, we focused on the presence or absence of BT, not the volume of blood loss, because accurate measurement of blood loss at delivery is difficult. It is frequently underestimated in cases of vaginal delivery, whereas it is overestimated in cases of CS, with the latter being mainly due to the mixing of amniotic fluid and blood that is measured. Thus, we set BT (+) versus (-) as the endpoint, similar to that used in previous studies. We believe that BT +/- represents massive PPH +/-, thereby reflecting real-world circumstances.

In conclusion, IP was a novel risk factor for BT in both single and twin pregnancies. Risk factors for BT were similar between single and twin pregnancies. This study was performed in a single center. This resulted in a relatively small study number (weakness), whereas it also enabled us to study patients under different management practices (strength). Determining risk factors for PPH is clinically important. We previously showed risk factors for BT at PP as a probability index of BT [24], which currently helps us to determine for whom and the extent to which BT should be given. Therefore, risk-factor evaluation has contributed to our daily practice. However, further studies are needed to examine the extent to which the present findings contribute to daily practice.

#### Abbreviations

BT, blood transfusion; CS, cesarean section; FFP, fresh frozen plasma; IP, isolated proteinuria; IRB, Institutional Review Board; MD, monochorionic diamniotic; PC,

platelet concentrate; PE, preeclampsia; PP, placenta previa; PPH, postpartum hemorrhage; RBC, red blood cell concentrate.

### Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Jichi Medical University (approval number: 16-005).

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### Conflict of Interest

The authors declare no conflict of interest.

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