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Letter to *Blood*

TO THE EDITOR:

Romiplostim drug presence in pregnancy and lactation

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Immune thrombocytopenia (ITP) treatments during pregnancy include IV immunoglobulin (IVIg) and corticosteroids because of the reassuring safety data. There are limited safety data with respect to pregnancy and lactation for the thrombopoietin receptor agonists (TPO-RAs) romiplostim or eltrombopag. The largest retrospective study reports 15 pregnant individuals with ITP who used a TPO-RA during pregnancy with no attributable neonatal complications.[1] Breastfeeding data were not systematically reported, but there was a case of thrombocytosis in a breastfed infant whose mother took eltrombopag in the postpartum period.[1] Other preclinical studies and case reports have reported TPO-RA use during pregnancy[2-8]; 1 study recounts romiplostim use in a breastfeeding individual with no neonatal complications; however, no laboratory values were reported.[9]

We present a prospective case study of a 34-year-old postpartum individual who received romiplostim during her first pregnancy as a treatment for refractory ITP in the setting of systemic lupus erythematosus and a history of recurrent thrombosis. Given the lack of safety data for romiplostim during the embryogenesis period, IVIg was administered in the first trimester but was switched back to romiplostim at 12 weeks of gestation after she sustained a transient ischemic attack following an IVIg infusion despite low-molecular-weight heparin and aspirin. Her platelet count stabilized during pregnancy with romiplostim 120 μg injection weekly (weight 62 kg; ~2 μg/kg).

Romiplostim is an Fc-peptide fusion protein analog of TPO that increases platelet production by binding to the TPO-R and is administered as a weekly subcutaneous injection (half-life, 3.5 days).[10,11] Because romiplostim contains a repeat of unique peptide sequences attached to a human Ig heavy constant γ 1 Fc domain, this creates a unique situation in which the drug can be detected using mass spectrometry.[12] To determine whether romiplostim is transferred into the placenta or breast milk, we measured romiplostim levels using proteomics in maternal and cord blood at the time of cesarean delivery, and in breast milk, maternal, and the infant's blood during the postpartum period (Figure 1). Measurements were compared using a blood sample when the participant was in the first trimester and not receiving romiplostim, blood from 2 nonbreastfeeding nonpregnant women (ie, nonpregnant controls), and breast milk from 2 postpartum controls. Informed consent was obtained, and the study was approved by the University of Calgary conjoint health research ethics board (REB21-0401).

Semiquantitative romiplostim drug levels were measured via mass spectrometry after samples were separated using sodium dodecyl sulfate–polyacrylamide gel electrophoresis (Figure 2A; supplemental Figures 1 and 2; supplemental Methods, available on the *Blood* website). The total spectral counts from the samples were derived from the identification of the mass spectrometry (MS)/MS spectra (Figure 2B-C). Sample time points included blood from the first trimester when not receiving romiplostim, maternal blood at delivery when receiving romiplostim, and cord blood at delivery as well as maternal blood, breast milk, and infant blood at 8 weeks postpartum and breast milk at 3 and 10 weeks postpartum (Figure 1; supplemental Table 1; supplemental Figures 1 and 2). Data were analyzed using MaxQuant.

As a qualitative measure of drug presence, we identified 2 unique domain peptides (QWLAAR and AGGGGGGG-GIEGPTLRQWLAARA). Confirming the presence of romiplostim, unique peptides were present in the participant's blood when receiving romiplostim as well as in the cord blood, breast milk, and her infant's blood (supplemental Figure 2). These same peptides were absent in the participant's blood when she was not receiving romiplostim and in breast milk and blood from controls. Romiplostim was detected in the cord blood at delivery (Figure 2C-D). We identified a relative difference in the total spectral counts between the mother's blood and cord blood (1.7-fold; P = .22), both of which were higher than those in 2 healthy nonpregnant control blood samples (P = .005 and P = .004, respectively; Figure 2C-D) and the sample taken during pregnancy when not receiving romiplostim. Postpartum, after at least 3 weeks of breastfeeding, milk samples were tested and had a higher romiplostim level 1 day after the dose (week 3) than 7 days after the dose (week 10) (P = .006; Figure 2E).

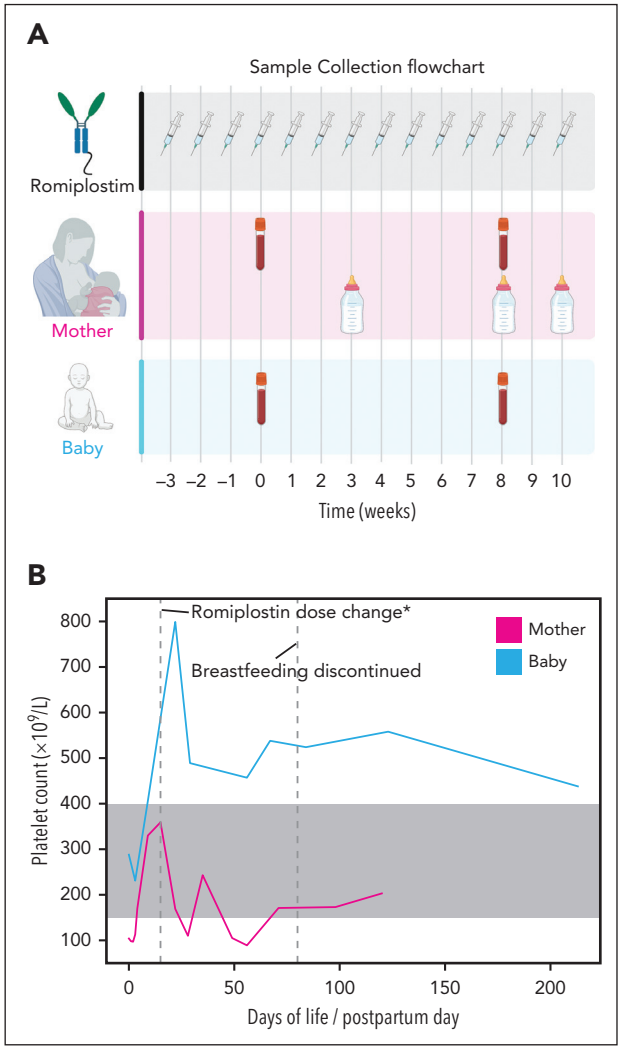

Figure 1. Sample collection flowchart and platelet count measurements. (A) Sample collection flowchart. (B) Platelet count measurements in the participant and her newborn infant based on the number of postpartum days.

On postpartum day 56 (0.75 days after the dose), the participant's blood had ~13.5 times more drug detected than the infant's blood taken at the same time (P = .0001; Figure 2F). On the day of delivery (36 weeks 4 days of gestation), the neonate's initial platelet count was normal (288 × 10^9/L). Breastfeeding was initiated after birth. On day 9 of life, thrombocytosis (406 × 10^9/L) was first observed in the neonate. The peak platelet count was 799 × 10^9/L on day 22 (Figure 1). The participant mother discontinued breastfeeding at ~11 weeks postpartum given the thrombocytosis and the presence of rare immature cells suggestive of blasts on the infant's peripheral blood smear, even though the flow cytometry was normal. Two weeks after discontinuing breastfeeding, no immature cells were identified, and the platelet count improved but was still elevated (457 × 10^9/L; Figure 1). Mild thrombocytosis (463 × 10^9/L) was observed at up to 11 months of age. The hemoglobin was 119 g/L at 3 weeks (local reference range based on age, 125-205 g/L), 99 g/L at 4 weeks (125-205 g/L), and 102 g/L at 2 months of age (100-180 g/L). The ferritin was normal (257 µg/L) at age 3 months, after the infant was administered empiric oral iron; however, no ferritin levels were measured before iron supplementation. Anemia was corrected at 11 months of age (141 g/L, 106-145 g/L). Liver enzyme (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and bilirubin) levels were normal on days 1, 3, and 22 of life. Serum creatinine was not measured on day 1, mildly elevated on day 3 (57 µmol/L, [10-40 µmol/L]), and normalized on day 22 (25 µmol/L). The infant had no complications for up to 22 months after delivery.

Although romiplostim is a large protein molecule (29 544 Da),[10,13,14] we found evidence of transplacental transfer. Reassuringly, the neonate's platelet count was normal at the time of delivery. In a mouse model of romiplostim exposure during pregnancy, only higher drug doses given during pregnancy increased fetal platelet counts;[15] our participant was on a low romiplostim dose, and the amount of romiplostim detected in the cord blood was less than that in maternal blood. Neonatal thrombopoiesis is different from that in adults, with a possible diminished response to romiplostim.[16] Other reasons for a normal neonatal platelet count on days 1 and 3 could have been maternal blood contamination at the time of cord blood collection or a protective effect of romiplostim from maternal platelet antibodies. In a case of refractory neonatal autoimmune thrombocytopenia because of maternal ITP, romiplostim normalized the neonate's platelet count.[17]

Romiplostim binds to the FcRn receptor and is thought to cross into the breast milk,[11] but because of its large size and polypeptide nature, it is assumed to have low oral bioavailability. Although romiplostim was detected in the infant's blood, it was at lower levels than that in the mother participant. The persistent mild thrombocytosis after breastfeeding cessation is contrary to only a TPO-RA effect and other factors, such as normal postnatal thrombocytosis and possible anemia may have contributed.[18,19] Immature white blood cells have not been reported with romiplostim use, but there is evidence that TPO-RAs promote multilineage hematopoiesis in other settings.[20-23] Infection or inflammation is unlikely but cannot be excluded.

The study limitations include having only a single participant and her infant, and infant testing only occurred at a single time point. This is still valuable data because the infant was delivered close to term, had mature gut absorption, and had been receiving breast milk for almost 2 months. Although we were able to report relative differences across samples, we were unable to calculate the relative infant dose because this formula requires drug concentrations, daily milk intake, and weights. Mass spectrometry-based proteomics is sensitive to the presence of drugs, but it is expensive and not easily scalable beyond a case study.

Our study revealed that romiplostim crosses the blood-placental barrier, is excreted into the breast milk, and detected in the infant in small but measurable amounts. These results will help inform physicians and patients when faced with a rare clinical scenario of romiplostim use during pregnancy and breastfeeding.

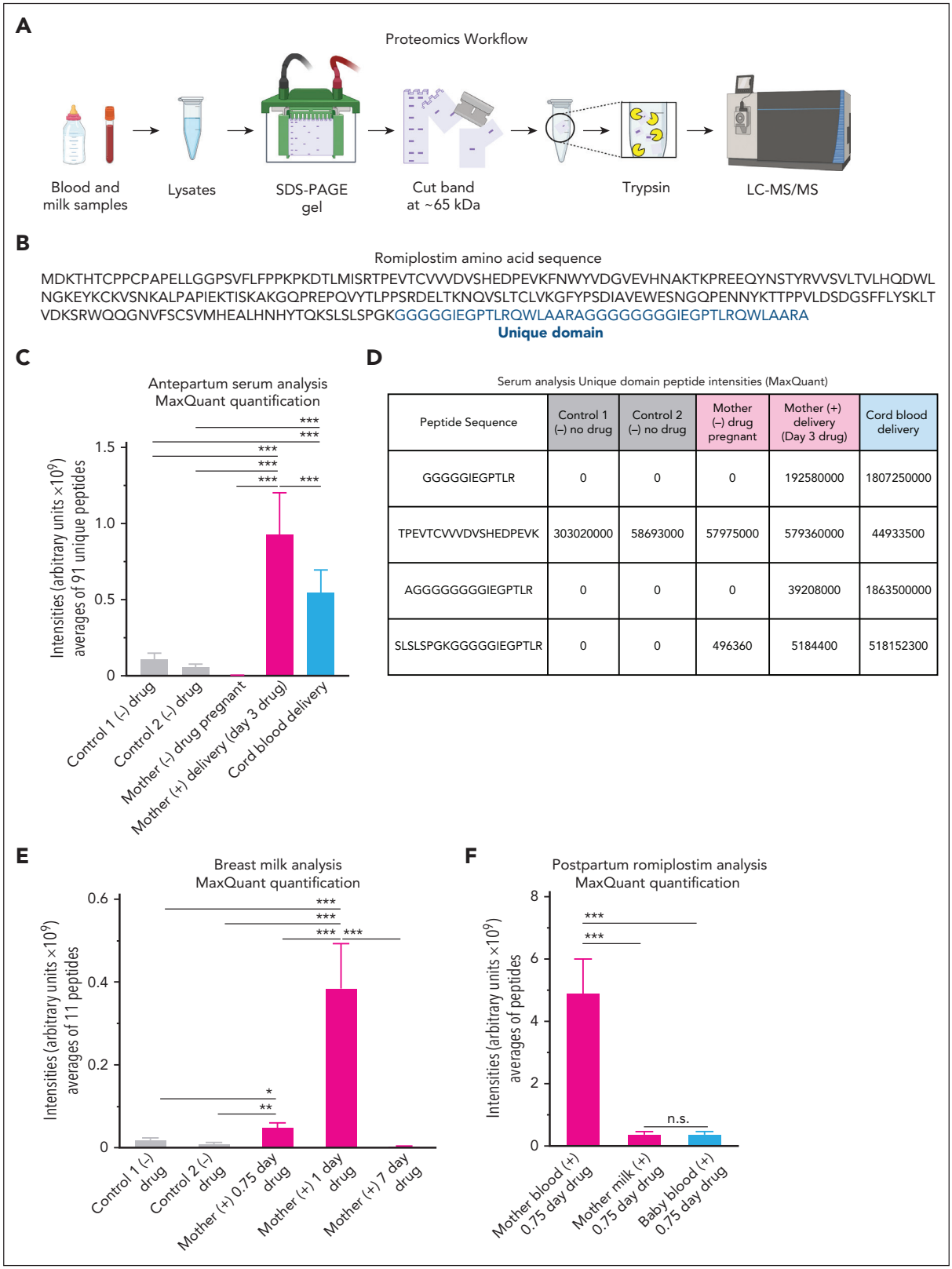

Figure 2. Romplostim serum and breast milk analysis. (A) Schematic of the proteomics workflow. (B) Romiplostim amino acid sequence, which highlights the unique domain (blue). (C) Serum measurements using unique peptide intensities, as identified using Maxquant analysis, of the pregnant participants' blood and cord blood at the time of delivery (day 3 after romiplostim dose) compared with a blood sample of the pregnant participant when not receiving romiplostim and 2 nonpregnant women (ie, nonpregnant controls). (D) Serum measurements using unique peptide intensities (MaxQuant) of the pregnant participants' blood and cord blood at the time of delivery (day 3 after romiplostim dose) compared with a blood sample of the same pregnant participant when not receiving romiplostim and 2 nonpregnant controls. (E) Breast milk analysis using unique peptide intensities, as identified using MaxQuant analysis, in the control milk from 2 postpartum individuals and the participant (mother) on days 0.75, 1, and 7 (trough level) after taking romiplostim. (F) Postpartum romiplostim analysis on the same day as the participant's blood and breast milk and infant's blood (day 0.75 after romiplostim dose). Significance is denoted using a Student *t* test: **P* < .05; ***P* < .01; and ****P* < .005.

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Authorship

Contribution: A.A.L developed the study protocol, collected samples, completed the clinical outcome review, and cowrote the first and subsequent drafts of the manuscript; S.R. developed the study protocol, interpreted laboratory results, and cowrote the first and subsequent manuscript drafts; D.Y. and S.A.C. performed the mass spectrometry experiments and data analysis; L.B. performed the mass spectrometry experiments; D.L., S.C., P.G. and A.E.C. contributed to clinical outcome review and the manuscript drafts; A.D. performed the mass spectrometry experiments, completed data analysis, interpreted the study results, and contributed to the first and subsequent drafts of the manuscript; and L.S. developed the research question and the study protocol, collected samples, and contributed to clinical outcome review, interpretation of laboratory results, and the first and subsequent manuscript drafts.

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Footnotes

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Data are available on request from the corresponding author, Leslie Skeith (laskeith@ucalgary.ca).

The online version of this article contains a data supplement.

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