

Unintended First-Trimester Exposure to Two Distinct Thrombopoietin Receptor Agonists in Consecutive Pregnancies Without Maternal or Fetal Harm

Ardışık Gebeliklerde Farklı Trombopoetin Reseptör Agonistlerine İstem Dışı İlk Trimester Maruziyeti: Maternal ve Fetal Olumsuzluk Saptanmayan Bir Olgu

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To the Editor,

Managing immune thrombocytopenia (ITP) during pregnancy remains challenging, particularly in women refractory to corticosteroids and intravenous immunoglobulin (IVIg). Thrombopoietin receptor agonists (TPO-RAs) may be considered as rescue therapy, but their use in pregnancy is off-label and current guidelines advise caution, especially during the first trimester [1]. Available evidence is limited; observational studies report high maternal platelet response rates and generally acceptable neonatal outcomes, while exposure during organogenesis remains rare [2,3,4]. In a registry of 186 romiplostim-exposed pregnancies, no specific teratogenic pattern was identified [4]. Pharmacokinetic data indicate that romiplostim can be detected in breast milk and in infant serum at low levels, whereas direct human data on placental transfer remain limited [5]. Case reports describe eltrombopag use in refractory cases or late pregnancy, including isolated first-trimester exposure without adverse outcomes [6,7,8]. Additional experience with recombinant human thrombopoietin and hetrombopag has also reported reassuring maternal and neonatal results, although mostly outside early gestation [9,10]. Overall, first-trimester exposure to TPO-RAs remains uncommon and data obtained during organogenesis are particularly limited.

We describe a young female patient with chronic steroid-refractory ITP who experienced two consecutive pregnancies with unintended first-trimester exposure to two different TPO-RAs.

The first pregnancy was diagnosed at 8 weeks of gestation while the patient was receiving romiplostim (3 µg/kg weekly; last dose 5 days before confirmation). Given documented steroid refractoriness, corticosteroids were not pursued. After

counseling, the patient elected to continue the pregnancy. Romiplostim was discontinued immediately and IVIg was initiated at intervals of 2-3 weeks. Platelet counts showed a dynamic course throughout the pregnancy; management aimed to avoid platelet counts of $<50 \times 10^9/L$ during the first and second trimesters and $<80 \times 10^9/L$ during the third trimester. Key platelet values at pregnancy recognition, pre-delivery, and postpartum week 6 and neonatal platelet counts are summarized in Table 1. The pregnancy progressed without maternal hemorrhagic complications and a healthy term infant without structural anomalies was delivered. The neonate had transient thrombocytopenia at birth ($51 \times 10^9/L$) without bleeding, which resolved spontaneously. Fetal surveillance included routine obstetric follow-up and a detailed fetal anatomy ultrasound, which revealed no abnormalities. IVIg was continued during breastfeeding without adverse events.

Following cessation of breastfeeding, eltrombopag was initiated for ongoing ITP. Despite contraception counseling, a second unplanned pregnancy was diagnosed at 7 weeks of gestation while the patient was taking eltrombopag at 75 mg daily. The drug was discontinued immediately and IVIg was restarted at intervals of 2-3 weeks. Platelet targets similar to those of the first pregnancy were maintained, with a delivery goal of $\geq 100 \times 10^9/L$. The second pregnancy and delivery were uncomplicated and the neonate had normal platelet counts. TPO-RAs were deliberately avoided during lactation because of limited human safety data and pharmacokinetic evidence of romiplostim transfer into breast milk and infant serum.

This case documents sequential unintended first-trimester exposure to romiplostim and eltrombopag during organogenesis with favorable maternal and fetal outcomes. In contrast, most published experience with TPO-RAs is limited to third-trimester

Table 1. Maternal and neonatal platelet course outcomes across both pregnancies.

Timepoint	Pregnancy #1 (romiplostim exposure), platelets (x10 ⁹ /L)	Pregnancy #2 (eltrombopag exposure), platelets (x10 ⁹ /L)	Notes
Pre-pregnancy baseline	85	122	Chronic ITP history
Pregnancy recognized (GA week)	68 (week 8)	115 (week 7)	TPO-RA stopped immediately
Post-discontinuation + IVIG initiation	15	27	IVIG administered every 2-3 weeks; platelet targets $\geq 50 \times 10^9/L$ in the 1 st and 2 nd trimesters and $\geq 80 \times 10^9/L$ in the 3 rd trimester
Pre-delivery (last count)	177	128	Delivery target of $\geq 100 \times 10^9/L$
Neonatal platelet count at birth	51	142	Transient neonatal thrombocytopenia in pregnancy #1 without bleeding
Postpartum (6 weeks)	179	120	No bleeding/thrombosis

ITP: Immune thrombocytopenia; GA: gestational age; IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin receptor agonist.

rescue use. Information on early gestational exposure, including reports involving eltrombopag, romiplostim, recombinant human thrombopoietin, or hetrombopag, remains rare [2,3,4,9,10]. Given evidence of developmental toxicity in animal models, current guidance advises avoiding elective TPO-RA use during pregnancy, particularly in the first trimester; therefore, our observations should be interpreted strictly as descriptive and not as evidence of safety.

Although uncommon, prolonged or earlier exposure has been reported with heterogeneous outcomes. Patil et al. [11] described romiplostim use throughout pregnancy with platelet control but significant neonatal complications, highlighting unresolved safety concerns. In contrast, Mendicino et al. [12] reported eltrombopag use throughout pregnancy, including the first trimester, without maternal or neonatal complications. In their comprehensive review, Rottenstreich and Bussel [3] emphasized that first-trimester exposure remains infrequent and that available data are insufficient to draw firm conclusions during organogenesis. Our case illustrates a practical, guideline-concordant approach in which inadvertent early TPO-RA exposure was managed by prompt drug discontinuation, multidisciplinary monitoring, and IVIG-based therapy tailored to gestational platelet targets [1].

In conclusion, unintended first-trimester exposure to TPO-RAs does not necessarily mandate pregnancy termination when agents are discontinued promptly and alternative therapy is instituted. Nevertheless, elective use of TPO-RAs during pregnancy, and especially during organogenesis, should be avoided, and women of reproductive age require careful counseling. Further prospective data are needed to define safety across all trimesters.

Keywords: Eltrombopag, First-trimester pregnancy, Immune thrombocytopenia, Romiplostim, Thrombopoietin receptor agonists

Anahtar Sözcükler: Eltrombopag, Birinci trimester gebelik, İmmün trombositopeni, Romiplostim, Trombopoetin reseptör agonistleri

Ethics

Informed Consent: Written informed consent for publication was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: F.D.K.; Concept: F.D.K.; Design: F.D.K.; Data Collection or Processing: A.K., F.D.K.; Analysis or Interpretation: A.K., F.D.K.; Literature Search: A.K., F.D.K.; Writing: F.D.K.

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