


# Continuous Use of Etanercept During Pregnancy Does Not Affect TNF-Alpha Levels in Umbilical Cord Blood

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**Abstract:** TNF-alpha-targeted therapies during pregnancy is a topic of interest in rheumatology. Etanercept (ETN) is expected to have lower transplacental transfer, however, clinical evidence is lacking on the usefulness and safeness of continuing etanercept throughout pregnancy. We here described the first reported case of relapsing polychondritis where continuous use of ETN throughout pregnancy was required. The patient was a pregnant Japanese woman who presented with bilateral ear cartilage redness, swelling, saddle nose and severe subglottic oedema. Due to severe systemic and life-threatening disease, we decided to continue using ETN throughout pregnancy and resulted in successful vaginal delivery. The treatment with ETN was successful and TNF-alpha levels in umbilical cord blood were not affected. The infant did not have any signs of chondritis although levels of anti-type 2 collagen antibodies in maternal and umbilical cord blood were similar, suggesting that anti-type 2 collagen antibodies crossed the placenta. This case is an important clinical experience that strengthens the safety to continue ETN during the entire pregnancy if necessary.

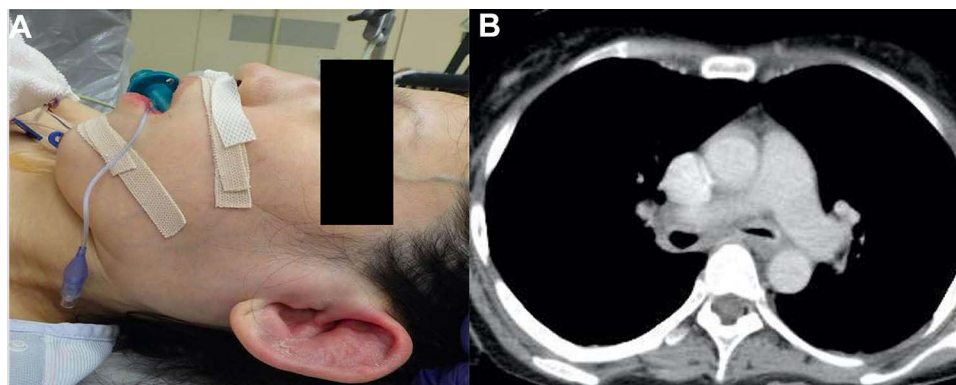
**Keywords:** etanercept, relapsing polychondritis, pregnancy, TNF-alpha, anti-type 2 collagen antibody

## Introduction

Treating autoimmune diseases during pregnancy with TNF-alpha inhibitors (TNFi) is a big topic of interest in rheumatology.<sup>1</sup> There have been some important studies recently discussing when to stop TNFi therapy before childbirth.<sup>2</sup> ETN is a dimeric fusion protein consisting of the ligand-binding domain of TNF-alpha receptor p75 with the Fc region of human IgG1. ETN is expected to have lower transplacental transfer<sup>3</sup> and is approved to use during the gestation period.<sup>4</sup> However, there are no published studies about the kinetics of TNF-alpha or autoantibody levels in maternal and cord blood when ETN was used continuously during pregnancy. In this report, we describe the first case of a pregnant woman with relapsing polychondritis where continuous ETN use was required due to severe systemic disease.

## Case Presentation

The patient was a 39-year-old Japanese woman who presented at 27 weeks of gestation. She had been aware of nasal pain and wheezing for 3 months. She noticed swelling of her left ear at 3 weeks before hospitalization. On the day of admission, she was emergently transported to our hospital. She presented with bilateral ear cartilage redness, swelling, and a saddle nose (Figure 1A). Arterial oxygen saturation decreased to below 90%. Flexible fiberoptic laryngoscopy revealed severe subglottic oedema. Chest CT showed stenosis of the main bronchi (Figure 1B). Biopsy of auricular cartilage revealed inflammatory cells infiltrating the cartilage. Based on these clinical and histological findings, she was diagnosed with relapsing polychondritis.<sup>5</sup> Foetal growth was consistent with expected growth for gestational age. After intubation, pulse methylprednisolone therapy (1 g/day for 3 days) was performed, followed by oral prednisolone therapy at 60 mg/day and subcutaneous injection of ETN (25 mg twice weekly). She was weaned off the ventilator on hospital day 17. During the prednisolone taper, azathioprine (50 mg/day) was started on hospital



**Figure 1** Clinical findings on the day of admission. **(A)** The patient presented with ear cartilage redness, swelling, and a saddle nose. **(B)** Chest CT on the day of admission.

day 33. Ear cartilage redness and the saddle nose remained but did not worsen. During gestational week 36, a female infant was delivered vaginally. The infant was of appropriate size and development for gestational age (Apgar score, 9) and did not have any signs of chondritis. ETN was last given 2 days before delivery. Before ETN treatment, the maternal blood serum TNF-alpha concentration was 26.7 ng/mL. At delivery, it was 8.35 ng/mL. Umbilical cord blood TNF-alpha concentration was 60.2 ng/mL (Table 1). Levels of anti-type 2 collagen antibodies in maternal and umbilical cord blood were 25.3 EU/mL and 27.8 EU/mL, respectively (Table 1).

**Table 1** Kinetics of TNF-Alpha and Anti-Type 2 Collagen Antibody Levels in Maternal Serum, Umbilical Cord Blood Serum, and Serum from a Healthy Control

	Maternal Blood Serum		Cord Blood Serum	Serum from a Healthy Control
	Gestational Week 27 at Admission	Gestational Week 36 at Delivery		
TNF-alpha*(ng/mL)	26.7	8.35	60.2	7.93
Anti-type 2 Collagen Ab**(EU/mL)	108.7	25.3	27.8	N/A

**Notes:** \*TNF-alpha levels were measured using the Luminex<sup>®</sup> Human Cytokine/Chemokine Magnetic Bead Panel. \*\*Anti-type 2 collagen antibody levels were measured using ELISA.

## Discussion

Relapsing polychondritis is a systemic autoimmune disease that causes repeated inflammation of cartilage. Although swelling of the ear cartilage and saddle nose are the main symptoms, laryngotracheal bronchial disease occurs in approximately 26% of primary cases and 48% of all patients during the disease.<sup>6</sup> In general, oral steroids and immunosuppressants such as methotrexate or azathioprine are used for treatment. However, in severe cases with airway complications, administration of biologics has been recently recommended.<sup>7</sup> Pregnant women sometimes suffer from relapsing polychondritis. In a retrospective observational study of 25 pregnant women with relapsing polychondritis, pregnancy did not modify the course of the disease and no symptoms with chondritis were observed in neonates.<sup>8</sup> However, this study did not include critically severe patients and no patients had airway complications. Therefore, there is little evidence available on how to care for pregnant women with life-threatening relapsing polychondritis. This is the first reported case of severe relapsing polychondritis treated with TNFi during pregnancy and resulted in successful vaginal delivery. Consistent with the previous study,<sup>8</sup> chondritis was not observed in neonates.

Other unique aspects of this case are the duration of ETN usage and the kinetics of TNF-alpha and autoantibody levels. At delivery, the maternal blood serum TNF-alpha concentration was comparable to levels in healthy subjects,

while umbilical cord blood TNF-alpha concentration was elevated. These data suggest that ETN was effective and TNF-alpha levels in maternal blood decreased accordingly but did not affect TNF-alpha levels in umbilical cord blood even though the drug was used throughout the pregnancy. Regarding the kinetics of anti-type 2 collagen antibodies, which are positive in approximately 33% of patients with relapsing polychondritis and correlate with disease activity,<sup>9</sup> antibody titres were initially high but decreased after treatment. At delivery, levels of anti-type 2 collagen antibodies in maternal and umbilical cord blood were similar, suggesting that anti-type 2 collagen antibodies crossed the placenta.

EULAR published points to consider (PtC) that recommended discontinuation of ETN at gestational weeks 30–32<sup>10</sup> and it can be used if indicated throughout pregnancy. However, more evidence is needed on the usefulness and safeness of continuing etanercept throughout pregnancy. In this case, the mother's life was threatened; therefore, we decided to continue using ETN with the patient's consent after a full explanation of the risks and benefits. This report helps to reinforce the theory that ETN is safe to give during pregnancy. Also, this is the first report about the kinetics of TNF-alpha and autoantibody levels in a pregnant woman who continuously received a TNFi during pregnancy. This case is an important clinical experience that strengthens the safety to continue ETN during the entire pregnancy if necessary.

## Consent Statements

Patient samples were obtained after informed consent was provided by the subjects, in accordance with the Declaration of Helsinki and with approval from the ethical review board of the Graduate School of Medicine, Osaka University, Japan (no. 18370-3 and no. 11122-5). Consent of patient was obtained according to CARE guideline, using Patient Consent Form (provided by the Taylor & Francis group). Consent to publish the report is also obtained.

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## Disclosure

The authors have declared no conflicts of interest in this work.

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