

[ CASE REPORT ]

## Successful Management of Acute Congestive Heart Failure by Emergent Caesarean Section Followed by Adrenalectomy in a Pregnant Woman with Cushing's Syndrome-induced Cardiomyopathy

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### Abstract:

Congestive heart failure (CHF) is rare during pregnancy. We herein report a 35-year-old woman who developed CHF with severe left ventricular dysfunction at 35 weeks' gestation. She underwent emergency Caesarean section followed by intensive-care treatment for CHF. The diagnosis of Cushing's syndrome (CS) caused by adrenal adenoma was confirmed by endocrinological examinations and histology after adrenalectomy. She was discharged on heart failure medications and glucocorticoid replacement therapy. Both the symptoms and cardiac function had recovered after 12 months of follow-up. This case highlights the importance of considering CS-induced cardiomyopathy as a cause of CHF in pregnant women.

**Key words:** Cushing's syndrome, adrenal adenoma, pregnancy, congestive heart failure, dilated cardiomyopathy, emergency cesarean section

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### Introduction

Cushing's syndrome (CS) is a rare endocrine disorder caused by chronic overproduction of cortisol. The incidence of CS has been reported to be 2.0-2.7/million/year (1). CS is associated with increased mortality and morbidity, including cardiovascular disorders (2). Several cases of dilated cardiomyopathy (DCM) with or without congestive heart failure (CHF) have been reported (3). However, the management of pregnancy in patients with CS is accompanied by several issues. Pregnancy in CS patients is extremely rare because of menstrual irregularity and infertility due to hypercortisolism (4). The diagnosis of CS during pregnancy may be difficult, as its symptoms and laboratory findings are similar to those of pregnancy. Importantly, CS in pregnancy is associ-

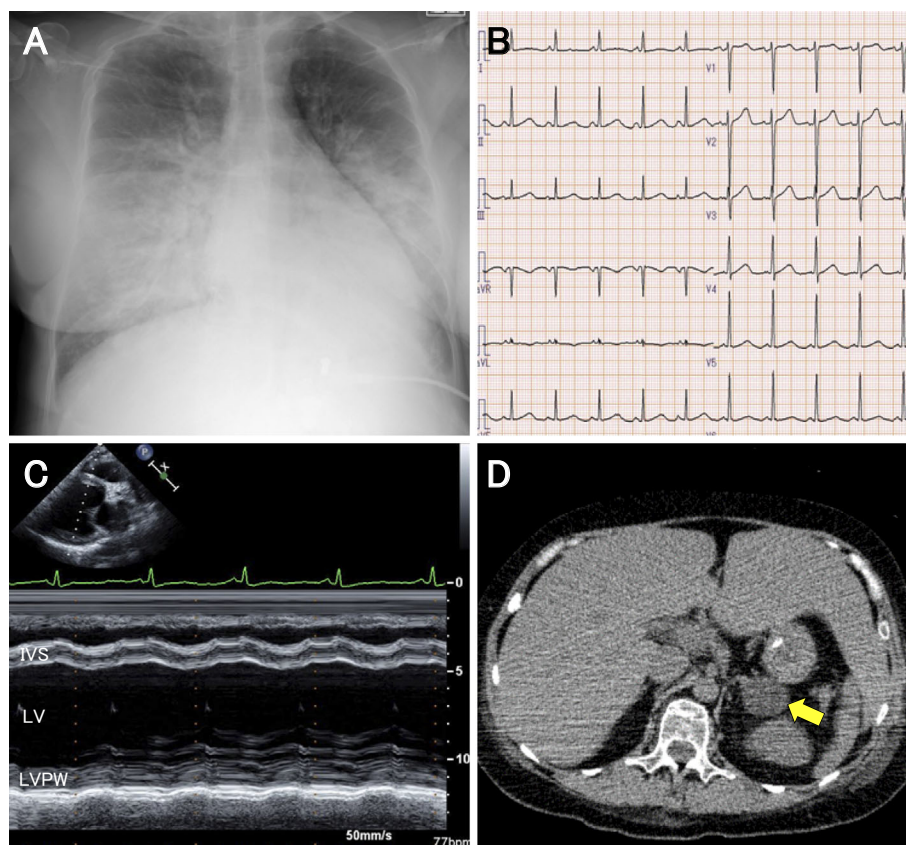
ated with significant maternal and fetal morbidity (5). In addition, CS sometimes leads to DCM during pregnancy. CHF during pregnancy is a rare but serious condition (6). It usually occurs late in pregnancy or early postpartum and poses management challenges.

We herein report a 35-year-old woman who developed CHF with severe left ventricular (LV) dysfunction at 35+3 weeks' gestation. After emergency Caesarean section, she was managed in the intensive-care unit (ICU) for CHF. The diagnosis of adrenal CS was made based on the endocrine and radiographic findings as well as a pathological examination after adrenalectomy. Both the cardiac function and histopathological findings had improved according to an endomyocardial biopsy (EMB) after 12 months of follow-up. Thus, adrenal CS-induced cardiomyopathy was determined to be the main cause of her CHF.

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**Figure 1.** Examinations performed on admission (A-C) and the 3rd hospital day (D). A: Chest X-ray showing a butterfly shadow in the lung fields, enlargement of the cardiac silhouette, and left pleural effusion, suggesting congestive heart failure. B: A 12-lead ECG showing sinus tachycardia at a rate of 107 with a low T-wave in the V5-V6 leads. C: Echocardiography showing markedly a dilated LV with a severely impaired systolic function. D: A 30-mm left adrenal mass (yellow arrow) detected on abdominal computed tomography. LV: left ventricle, LVPW: left ventricular posterior wall, IVS: interventricular septum

## Case Report

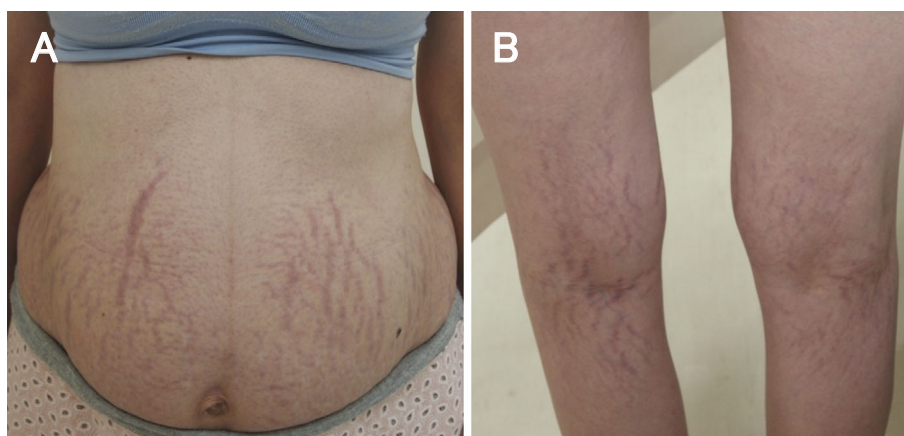
A 35-year-old woman, with no remarkable medical history was referred to our hospital for hypertension (147/69 mmHg) and obesity with a weight gain of 18 kg (baseline 45 kg) at 16 weeks into her second pregnancy. Her first pregnancy had been five years earlier and uneventful.

She was followed-up without medication because the results of hematological [white blood cells (WBCs) 11,700/ $\mu$ L (neutrophils 8,920/ $\mu$ L, eosinophils 40/ $\mu$ L, basophils 40/ $\mu$ L, lymphocytes 2,130/ $\mu$ L), hemoglobin 13.0 g/dL, and platelet count  $2.5 \times 10^5$ / $\mu$ L], renal (creatinine 0.32 mg/dL), thyroid (TSH 1.04  $\mu$ IU/mL, free T3 2.4 ng/mL, free T4 1.0 ng/dL), and urine function tests (no protein and no glucose by dipstick) had been nearly normal, and her blood pressure at home ranged from 120/70 to 130/80 mmHg. Her blood pressure was stable for months.

However, at 35+3 weeks' gestation, she was transferred to the emergency department because of paroxysmal nocturnal dyspnea. On arrival, her blood pressure was 173/142 mmHg, heart rate 107/min, respiratory rate 35/min, and oxygen satu-

ration 80% with O<sub>2</sub> administration at 10 L/min by reservoir mask. An arterial blood gas analysis showed type II respiratory failure and hyperlactatemia [pH 7.39, partial pressure of arterial oxygen (PaO<sub>2</sub>) 53.1 torr, partial pressure of carbon dioxide in arterial blood (PaCO<sub>2</sub>) 59.1 torr, HCO<sub>3</sub><sup>-</sup> 16.9 mmol/L, lactate 9.8 mmol/L]. A laboratory examination revealed a WBC count of 19,700/ $\mu$ L (neutrophils 13,710/ $\mu$ L, eosinophils 40/ $\mu$ L, basophils 60/ $\mu$ L, lymphocytes 5,350/ $\mu$ L), hemoglobin 15.1 g/dL, and platelet count  $1.9 \times 10^5$ / $\mu$ L. Her serum level of aspartate aminotransferase (AST) was 44 U/L, alanine aminotransferase (ALT) 32 U/L, lactate dehydrogenase (LDH) 331 U/L, blood urea nitrogen (BUN) 7 mg/dL, creatinine 0.46 mg/dL, Na 139 mEq/L, K 4.6 mEq/L, brain natriuretic peptide 720 pg/mL, C-reactive protein (CRP) 0.2 mg/dL, and HbA1c 6.1%, and proteinuria was present (1+ on dipstick).

Chest X-ray showed a butterfly shadow in the lung fields, enlargement of the cardiac silhouette, and left pleural effusion (Fig. 1A), suggesting pulmonary congestion. A 12-lead electrocardiogram showed sinus tachycardia at a rate of 107 with a low T-wave in the V5-V6 leads (Fig. 1B). Echocardiography showed a markedly dilated left ventricle (LV)



**Figure 2.** Skin findings. A skin examination revealed red skin streaks on her abdomen (A) and the back of the knees (B).

**Table 1.** Endocrinological Findings after Cesarean Section.

ACTH, pg/mL	05:00 a.m.	<1.0
	11:00 p.m.	<1.0
Cortisol, µg/dL	05:00 a.m.	27.6
	11:00 p.m.	29.9
UFC, µg/day		832*
Cortisol after 8 mg-DST, µg/dL		25.5

ACTH: adrenocorticotropic hormone, UFC: urinary free cortisol, 8 mg-DST: overnight 8 mg dexamethasone suppression test

\*In-house normal range, <355 µg/day

with a severely impaired systolic function (LV end-diastolic diameter, 60 mm; LV ejection fraction, 29%) (Fig. 1C), functional mitral valve regurgitation, and no pericardial effusion. She was diagnosed with CHF based on the clinical findings. Her condition improved partially with non-invasive positive pressure ventilation combined with an intravenous calcium channel blocker (nicardipine). Further intensive-care support was considered to be required.

Considering her serious condition and the risk of developing fetal acidosis due to placental hypoperfusion and hypoxia, a decision to perform emergent Caesarean section was made by a multidisciplinary team, including cardiologists, obstetricians, emergency doctors, anesthesiologists, and neonatologists. The procedure was performed under general anesthesia. A male infant weighing 2,395 g, with Apgar scores of 3 and 6 at 1 and 5 minutes, respectively, was delivered. The pH and partial pressure oxygen (pO<sub>2</sub>) of the umbilical artery were 6.88 and 11.1 mmHg, respectively. The infant was initially treated in the neonatal ICU, and then his subsequent clinical course was good.

After the operation, she was managed in the ICU with mechanical ventilation and pharmacological agents, such as inotropes, vasodilators, and diuretics. The signs and symptoms of CHF gradually improved. On the 3rd hospital day, she underwent unenhanced abdominal computed tomography

(CT) as screening for secondary hypertension, which revealed a left adrenal tumor (30 mm) with a mean CT number of 7 Hounsfield unit (Fig. 1D). Chemical shift magnetic resonance imaging revealed a lower signal intensity in the tumor on the opposed-phase image than the in-phase image, similar to adrenal cortical adenoma. A physical examination also showed red skin streaks on her abdomen (Fig. 2A) and the back of the knees (Fig. 2B), although their onset timing during gestation was unclear. We subsequently performed several endocrinological evaluations (Table 1). Basal morning and midnight cortisol levels were 29.9 and 27.9 µg/dL, respectively, with undetectable adrenocorticotropic hormone (ACTH) concentration. The 24-hour urine free cortisol level was more than twice the upper limit of the normal range, and the serum cortisol level was not suppressed after an overnight 8 mg dexamethasone suppression test (Table 1). Based on these findings, she was clinically diagnosed with CS due to a left adrenal tumor. Other causes of secondary hypertension were ruled out.

On the 17th hospital day, cardiac catheterization was performed to evaluate her cardiac function. The LV end-diastolic and pulmonary wedge pressures were elevated, and the cardiac index was reduced (Table 2). Coronary angiography showed normal coronary arteries. An endomyocardial biopsy (EMB) showed non-specific myocardial hypertrophy and fibrosis without specific evidence of secondary cardiomyopathies or myocarditis (Fig. 3A and B). Transmission electron microscopy (TEM) showed ultrastructural myocardial abnormalities, including myofibril and mitochondrial degeneration (Fig. 3C). Cardiac magnetic resonance imaging showed a globally dilated heart (LV end-diastolic volume, 225 mL) and global hypokinesis of the LV (LV ejection fraction, 28%) (Table 2). An increased native T1 time and extracellular volume (ECV) fraction were also noted. Considering her clinical course, adrenal CS-induced cardiomyopathy was indicated as a cause of CHF. Thus, she was treated with metyrapone to reduce the endogenous cortisol production.

On the 32nd hospital day, she underwent laparoscopic left



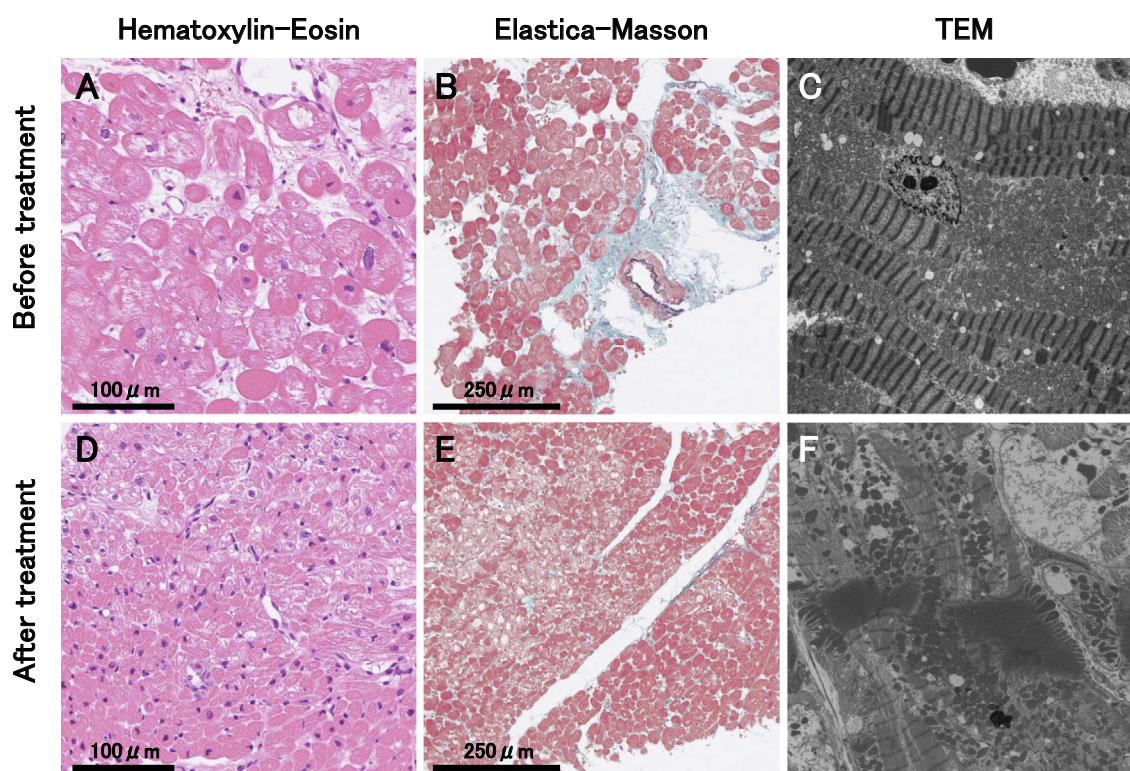
**Table 2. Hemodynamic Data before and 1 Year after the Adrenalectomy.**

	Before	At 1-year follow-up
Catheterization data		
PAP, mmHg	50/22 (36)	22/4 (12)
mRAP, mmHg	10	3
mPAWP, mmHg	32	7
AoP, mmHg	95/75 (84)	145/89 (125)
CI, L/min/m <sup>2</sup>	2.3	2.9
SvO <sub>2</sub> , %	58.2	68.1
SVR, dyne/sec/cm <sup>-5</sup>	1,626	2,548
CMR data		
LVEDVI, mL/m <sup>2</sup>	140.8	96.1
LVESVI, mL/m <sup>2</sup>	100.2	46.1
LVEF, %	29	52
T1 mapping, ms	1,349	1,295
ECV, %	49.3	32.0

AoP: aortic pressure, CI: cardiac index, CMR: cardiac magnetic resonance, CO: cardiac output, ECV: extracellular volume, LVEDVI: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, LVESVI: left ventricular end-systolic volume index, mPAWP: mean pulmonary artery wedge pressure, mRAP: mean right atrial pressure, PAP: pulmonary artery pressure, SvO<sub>2</sub>: mixed venous blood oxygen saturation, SVR: systemic vascular resistance

adrenalectomy. The resected adrenal tumor was histopathologically confirmed as adrenal cortical adenoma (Weiss criteria, score 0) (7). She was discharged on a beta-blocker (bisoprolol 0.625 mg, once daily) and angiotensin-converting enzyme inhibitor (perindopril 2 mg, once daily) combined with glucocorticoid replacement therapy (hydrocortisone 10 mg in the morning and 5 mg at noon).

Eight months later, the hypothalamus-pituitary-adrenal axis had normalized, and glucocorticoid was discontinued. At the follow-up examination 12 months after adrenalectomy, she had no complaints of dyspnea or exercise intolerance. The marked recovery of both her hemodynamics and cardiac function was confirmed (Table 2). As indicated by the reduction in the native T1 and ECV fraction (Table 2), a second EMB on light microscopy showed no progression of myocardial degeneration but mild improvement of interstitial fibrosis (Fig. 3D and E). No progressive deterioration of the cardiac ultrastructure was noted on post-treatment TEM (Fig. 3F). The infant followed an uneventful course without developing any complications related to chronic fetal hypercortisolism.



**Figure 3.** Histological findings before (A-C) and 12 months after the adrenalectomy (D-F). A and D: EMB samples stained with Hematoxylin and Eosin staining. Pre-treatment histology showed myocardial degeneration, including hypertrophy of cardiomyocytes with various sizes of nuclei and cytoplasmic vacuolization (A). Similar findings, but without deterioration, were still present in the post-treatment histology (D). B and E: EMB samples stained with Elastica-Masson staining. Mild histological improvement in myocardial fibrosis was observed in E compared with B. C and F: TEM images of EMB samples. Myofibril and mitochondrial degeneration was seen pre- (C) and post-treatment (F) but without obvious deterioration post-treatment. EMB: endomyocardial biopsy, H&E: Hematoxylin and Eosin staining, TEM: transmission electron microscopy

## Discussion

CS is a rare endocrine disorder caused by long-term exposure to cortisol overproduction (8). As cortisol production by the adrenal glands is regulated by pituitary ACTH, CS can be divided into two categories: ACTH-dependent and ACTH-independent CS. ACTH-dependent CS accounts for about 80-85% of all CS cases, of which 80% are due to pituitary adenomas (also known as Cushing's disease), with adrenal adenoma responsible for 10% of CS cases and the most common cause of ACTH-independent CS (8). Importantly, in pregnant women, the prevalence of adrenal adenoma (40-50%) is higher than that of pituitary adenoma (30%) (9).

CS is associated with various comorbidities, including hypertension, diabetes, dyslipidemia, obesity, infection, osteoporosis, and depression (8). Metabolic abnormalities in CS can increase the risk of cardiovascular complications, such as myocardial infarction, stroke, and venous thromboembolism, which lead to premature death (10). Importantly, CS during pregnancy is also associated with significant maternofetal morbidity and mortality. The most common cause of maternal complication is hypertension, followed by diabetes and preeclampsia (11). Fetal complications include premature birth, intrauterine growth retardation, and spontaneous abortion (5). Furthermore, a previous systematic review showed that the activity of CS differentially impacts the maternal and fetal/newborn outcomes (5). Patients with active CS experienced more complications in pregnancy and had a worse fetal prognosis than those with a history of CS who had been treated or cured at the time of pregnancy. In addition, newly diagnosed CS during pregnancy adversely affected the overall fetal morbidity and mortality (5). These lines of evidence indicate that the early diagnosis and treatment are essential for ensuring a good outcome in the management of CS in pregnancy.

However, diagnosing CS during pregnancy can be difficult for several reasons. First, CS is rarely associated with pregnancy because of menstrual irregularity and infertility due to hypercortisolism (4). Second, the clinical and laboratory signs of CS can be similar to those of pregnancy (e.g. metabolic state and hormonal imbalance) (12). Third, there is a general reluctance to perform invasive diagnostic tests during pregnancy due to safety concerns for the fetus. Although our patient had suffered an 18-kg weight gain at 16 weeks of gestation, she underwent no further examination (e.g. echocardiography and abdominal ultrasound) because of normal results on routine laboratory studies for secondary hypertension and subsequent blood pressure measurement. Thus, our case indicates that the diagnosis of CS is challenging and requires a high degree of suspicion in the early pregnancy period.

CHF during pregnancy is a rare but serious condition. CHF usually occurs late in pregnancy or early postpartum and poses substantial management challenges. The incidence

of peripartum CHF was estimated to be 0.024% in a large national population-based database in Taiwan (6). Although the precise etiology was unclear in cases without structural heart disease, peripartum cardiomyopathy (PPCM) may be involved in most cases. Interestingly, pre-pregnancy or gestational hypertension was significantly associated with developing peripartum CHF (6). In our case, the most likely diagnosis at the time of admission was PPCM-induced CHF because she had no history of heart disease and developed CHF with severe LV dysfunction in near-term pregnancy (13). However, we were unable to perform diagnostic examinations to make a correct diagnosis in an emergency situation.

Four cases of patients with CS who developed CHF during pregnancy have been reported (14-17). All patients presented with hypertension and were diagnosed with adrenal CS during or after pregnancy. In the majority of cases, the delivery was preceded by adrenalectomy, since adrenalectomy is the first choice of treatment for adrenal CS-even during pregnancy-to improve the maternofetal outcomes by normalizing the cortisol level (8).

Regarding the management of CHF during pregnancy, due to the abundance of obstetric issues, careful consideration is required, including the optimal timing, mode of delivery, and anesthetic technique (18). Caesarean delivery may be preferred in patients with symptoms or signs of CHF because of intolerance of the prolonged stresses of labor. In our case, a multidisciplinary team approach was adopted to manage her complicated medical condition. The factors contributing to deciding between CHF treatment and early delivery included the anticipated risks and benefits of continuing pregnancy to the mother and the fetus (19). The decision was ultimately made to perform emergency Caesarean delivery under general anesthesia.

An association between CS and DCM has been reported in several cases (3, 14, 17). Although the underlying mechanism remains unclear, some studies have suggested that a direct effect of cortisol on the myocardium through glucocorticoid receptors is involved in the cardiac remodeling of CS, independent of hypertension (20, 21). It is important to recognize that cardiac dysfunction can be reversed after treatment for CS (22). However, a few studies have reported that the changes in histopathological findings on EMB were associated with cardiac functional recovery. Frustaci et al. reported that CS-induced cardiomyopathy was characterized by cardiomyocyte hypertrophy, myofibrillarolysis, and myocardial fibrosis, all of which were resolved after adrenalectomy (23). In our case, despite the marked improvement of the cardiac function, the follow-up EMB showed only mild regression of myocardial interstitial fibrosis. This may be explained by the possibility that the recovery of the cardiac function precedes the histological recovery in the myocardium. Alternatively, an increased hemodynamic load in pregnancy may have exacerbated the patient's HF in association with underlying CS-induced cardiomyopathy, and the functional recovery reflects hemodynamic resolution after deliv-

ery. This patient is being closely followed in the cardiovascular and endocrinology outpatient departments with a good clinical course thus far.

### Conclusions

Our case highlights the importance of timely decision-making for pregnant women in an emergency situation by a multidisciplinary approach as well as considering CS-induced cardiomyopathy as a cause of CHF during pregnancy.

**The authors state that they have no Conflict of Interest (COI).**

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