Cushing’s syndrome during pregnancy with different clinical courses: Two case reports

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Cushing’s syndrome (CS) during pregnancy is a rare metabolic condition associated with hypertension, hyperglycaemia, and foetal growth restriction (FGR). Here, we report two cases of CS during pregnancy with different clinical courses. Caesarean section was performed in Patient 1 at 26 weeks of gestation due to uncontrollable hypertension and severe FGR. She was diagnosed with CS after delivery. Patient 2 exhibited severe hypertension and was diagnosed with CS at 19 weeks of gestation. Surgical treatment significantly decreased her blood pressure, and she delivered a mature baby at 39 weeks of gestation. For Patient 1, microscopic findings of the placenta were compatible with preeclampsia, while the placenta of Patient 2 showed almost normal pathological findings, although the placenta was extremely small. These two cases indicate that, while maternal hypertension might affect placental growth, placental function could be recuperated by appropriate blood pressure control in the early stage of gestation.

Introduction

Cushing’s syndrome (CS) is a cluster of clinical signs and symptoms resulting from prolonged exposure to excessive glucocorticoids, and its incidence is estimated to be 0.2–5.0 per million.1) Exogenous CS is most commonly caused by iatrogenic corticosteroid administration, while endogenous CS results from excessive production of cortisol caused by conditions such as pituitary adenoma or adrenal hyperplasia. CS during pregnancy is a very rare metabolic condition that is associated with significant maternal and foetal morbidity. In particular, hypertension and preeclampsia are the most common complications of CS in pregnancy and can result in foetal growth restriction (FGR).2)

Here we report two cases of CS during pregnancy that had different clinical courses and discuss the importance of blood pressure management in the early stage of pregnancy based on their placental pathological features.

Case 1

A 31-year-old, gravida 2, para 1, woman with an uneventful pregnancy six years ago started to take methyldopa (750 mg/day) due to slight hypertension (137/98 mmHg) at 18 weeks of gestation. Her blood pressure gradually increased to 150/90 mmHg despite the use of antihypertensive agents, methyldopa 750 mg/day, and hydralazine 200 mg/day, and she was referred to our hospital and hospitalized at 24 + 6 weeks of gestation. On admission, her blood pressure was 147/97 mmHg, and proteinuria was not detected. Body mass index (BMI) in the pre-pregnant state was 20.3, and impaired glucose tolerance was not detected during the pregnancy. Magnesium sulphate treatment was initiated, hypertension was ameliorated, and antihypertensive agents were ceased. The baby’s estimated weight was 660 g (−1.8 SD) at 26 weeks of gestation, and the patient’s blood pressure began to increase again up to 170/100 mmHg at 27 weeks of gestation. Nifedipine (40 mg/day) and methyldopa (500 mg/day) were administered to address the hypertension. At 28 + 2 weeks of gestation, late
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deceleration was detected on a foetal heart rate monitor, and the end-diastolic flow velocity on the umbilical artery was absent on ultrasonography. Furthermore, the patient’s blood pressure was too high (190/140 mmHg) to control, and an emergency caesarean section was performed. A 768 g (−2.5 SD) male baby was delivered with an Apgar score of 6–8 and an umbilical artery pH of 7.258. The placental weight was 180 g, corresponding to the 10–25th percentile for gestational age, and a small infarction (1.0 cm) was detected (Figure 1A). Histopathologically, findings of maternal vascular malperfusion (MVM), decidual vasculopathy (⁎), syncytial knots (arrowheads), and intravillous fibrin deposits (arrows) were detected. Villous maturation was accelerated. Bar: 200 μM.

Figure 1. Pathological findings of the placenta in Patient 1.
(A): Macroscopic findings. Small infarction was detected (circle).
(B, C): Haematoxylin-eosin section (× 10). Decidual vasculopathy (⁎), syncytial knots (arrowheads), and intravillous fibrin deposits (arrows) were detected. Villous maturation was accelerated. Bar: 200 μM.

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After the delivery, the patient’s blood pressure did not exceed 140 mmHg, and she was taking 20 mg of nifedipine; however, one month later, her blood pressure was 172/112 mmHg without medication. She then visited a cardiologist and started to take amlodipine 5 mg/day and methyldopa 750 mg/day. Follow-up visits every 3 months were continued, and 19 months later, the physician noticed her moon face. Serum levels of cortisol were markedly elevated at 19 μg/dl (reference range, 5–15 μg/dl), and plasma adrenocorticotropic hormone (ACTH) level was less than 1.0 pg/ml (reference range, 7.2–63.3 pg/ml). Abdominal computed tomography (CT) revealed a left adrenal mass of 3 cm, and laparoscopic left adrenalectomy was performed 22 months after caesarean section. The final diagnosis was CS caused by adrenocortical adenoma. The postoperative course was uneventful, and her blood pressure normalized soon afterwards.

Case 2

A 36-year-old, gravida 2, para 1, woman with an uneventful pregnancy ten years ago visited an obstetrician and was diagnosed at 14 + 6 weeks of gestation. At that time, her blood pressure was 168/98 mmHg. One week later, she was referred to our hospital due to general fatigue. She
exhibited severe hypertension (192/120 mmHg), and treatment with nifedipine 20 mg/day and methyldopa 1,000 mg/day was started. Body mass index (BMI) in the pre-pregnant state was 21.5, and a 75 g oral glucose tolerance test on admission revealed gestational diabetes mellitus. Glucose levels were 73 mg/dl, 170 mg/dl, and 176 mg/dl at fasting, 1 hour later, and 2 hours later, respectively. Blood examination revealed high cortisol (39.8 μg/dl) and low ACTH (< 1.0 pg/ml). In addition, a left adrenal mass of 2.8 cm was detected by ultrasound examination and abdominal magnetic resonance imaging (MRI). At 19 + 5 weeks of gestation, she underwent laparoscopic left adrenalectomy, and her blood pressure decreased significantly to lower than 120/80 mmHg. The subsequent clinical course of pregnancy was favourable; however, emergency caesarean section was performed due to repeated severe variable deceleration after labour onset at 39 + 3 weeks of gestation. She delivered a male baby weighing 2,684 g (~1.0 SD) with an Apgar score of 8–9 and an umbilical artery pH of 7.198. The placental weight was 280 g, which was lower than the 3rd percentile for gestational age, and a small infarction (1.0 cm) was detected (Figure 2A). Histopathologically, there were no MVM findings, including decidual vasculopathy and accelerated villous maturation, and almost all of the placenta presented normal villi without ischaemic change (Figure 2B).

**Discussion**

CS during pregnancy is extremely uncommon, with fewer than 220 cases reported as of 2016, likely because hypercortisolism alters normal ovulation. According to a recent large-scale systematic review conducted by Caimari et al., the major aetiologies of CS during pregnancy were adrenal adenoma (44.1%) and Cushing’s disease, i.e., pituitary adenoma (28.2%). Despite various symptoms, the diagnosis of CS in pregnancy could be missed because the typical clinical signs, such as weight gain, fatigue, hyperglycaemia, and hypertension, often overlap with those observed in normal pregnancy accompanied by physiological hypercortisolism. Indeed, only 50% of CS cases were diagnosed during pregnancy, and 35.9% were diagnosed after pregnancy. Hypertension and hyperglycaemia are the most common complications of CS in pregnancy. Therefore, careful examination including cortisol and ACTH levels or imaging studies is necessary with CS in mind, particularly if pregnant women present with inexplicable hypertension or hyperglycaemia, especially in the early stage of pregnancy. In this regard, ultrasound examination is non-invasive and useful for detecting tumors in the adrenal gland, and thus should be performed early in examination and prior to abdominal MRI scans.

Once a diagnosis of CS is made during pregnancy, timely treatment is critical because CS can lead to severe complications, such as preeclampsia and FGR. Lindsay et al. reported that the rate of live births increased from 76% to 89% in women with CS who were treated at a mean gestational age of 20 weeks. Surgical therapy is considered more effective than drug therapy, including metyrapone and ketoconazole, and surgery should be
performed during the second trimester. Laparoscopic adrenalectomy in cases of adrenal tumours has been found to be safe and effective in terms of maternal morbidity rates. However, its effect on FGR appears to be limited.\textsuperscript{5}

Consistent with previously reports, Patient 1 experienced severe hypertensive disorder in pregnancy, placental dysfunction, FGR, and preterm birth due to delayed diagnosis and treatment. On the other hand, timely surgical treatment brought about favourable maternal and foetal outcomes for Patient 2. Intriguingly, the placental pathological findings of these two cases were quite different and highly suggestive. For Patient 1, the macroscopic and microscopic findings of the placenta were compatible with its clinical course. Specifically, the small-sized placenta was related to FGR, and decidual vasculopathy, increased syncytial knots, and matured villi were associated with the placental ischaemic changes of early onset preeclampsia.\textsuperscript{6} For Patient 2, the placenta was extremely small for the gestational age of 39 weeks, even though the state of CS and maternal blood pressure were well controlled and foetal growth was acceptable after surgical treatment. In fact, the pathological findings of Patient 2 reflected this favourable progress after surgery. That is, there were no microscopic abnormal findings that accounted for the small placenta. These pathological findings provided two important indications: (1) maternal severe hypertension around the formative period of the placenta might inhibit placental growth later in pregnancy; and (2) the function of villi could be recuperated by appropriate blood pressure control.

The precise mechanisms by which maternal hypertension affects placental growth have remained largely unknown. One plausible explanation is that maternal hypertension could induce abnormal turbulent blood flow and strong shear stress in the intervillous space, thereby injuring trophoblasts and altering the production of angiogenesis factors.\textsuperscript{7,8} Based on the observation of Patient 2, the function of the villi might be reversible after the normalization of blood pressure, although the size of the placenta could be regulated by severe hypertension at the early stage of pregnancy. However, to obtain a desirable pregnancy outcome, blood pressure control should be achieved by 20 weeks of gestation at the latest. This is supported by the aforementioned study, which revealed a high live birth rate among women with CS treated by the early second trimester.\textsuperscript{4} Moreover, we recently reported that tight control of blood pressure early in pregnancy, i.e., by no later than 16 weeks of gestation, was associated with good pregnancy outcomes in patients with chronic hypertension.\textsuperscript{9} The administration of sufficient antihypertensive therapy from the early stage of pregnancy has been supported worldwide,\textsuperscript{10} and there is hope that further research will provide additional scientific evidence.

In addition to the influence of hypertension on placental development, that of glucocorticoids should also be considered. Many observational studies have found that increased exposure of the foetus to glucocorticoids may lead to FGR.\textsuperscript{11} Furthermore, according to microarray analysis, maternal glucocorticoid administration induced significant changes in the gene expression profile of the placenta.\textsuperscript{11} Therefore, the small placentae of the current cases might be partially attributed to excessive maternal glucocorticoid levels, although the underlying molecular mechanisms have yet to be elucidated. However, it is very difficult to distinguish the specific effect of excessive glucocorticoids on the resulting hypertension.

In conclusion, to achieve a good pregnancy outcome in patients with CS, early diagnosis and timely management, including surgery and strict blood pressure control, are necessary.

Conflict of interest
None.

Informed consent
Written informed consent was obtained from the patients for publication of this case report.

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