Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 62; Numer/Number 2/2011
ISSN 0423–104X

A case of Cushing's syndrome in pregnancy

Rzadki przypadek zespołu Cushinga u kobiety w ciąży

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Abstract

Cushing's syndrome (also known as hypercortisolemia) is rare in pregnant women due to the menstrual disturbances and infertility in women with hypercortisolism. A diagnosis of pathological hypercortisolism in pregnant women is often difficult as some symptoms of the disease may be associated with a complicated pregnancy. Hypercortisolemia leads to serious complications for mother and foetus, and is associated with premature labour and high foetal mortality. Hormonal and radiological diagnostics in pregnancy are limited. The results of hormonal measurements and dynamic tests are difficult to interpret due to the physiological changes in the hypothalamo-pituitary-adrenal axis connected with pregnancy. The optimal time and method of treatment should be chosen cautiously case by case because of the possibility of maternal and foetal complications.

In this paper, we present a case of Cushing's syndrome secondary to adrenal adenoma in which the diagnosis was made in the 22nd week of pregnancy. Due to the advanced gestational status and mild symptoms of hypercortisolism, only symptomatic treatment was introduced. The patient was under continuous obstetric and endocrinological care. At 35 weeks of gestation, the pregnancy was terminated by emergency caesarean section because of premature detachment of the placenta. A male infant weighing 2,450 g was delivered; neither adrenal insufficiency in the child nor hypercortisolemia complications in the mother were observed.

(Pol J Endocrinol 2011; 62 (2): 181–185)

Key words: *Cushing's syndrome, pregnancy, adrenal adenoma, hypercortisolism*

Streszczenie

Zespół Cushinga rzadko występuje u ciężarnych ze względu na towarzyszące zaburzenia miesiączkowania i niepłodność kobiet z hiperkortyzolemią. Rozpoznanie zespołu Cushinga w czasie ciąży jest często trudne, ponieważ niektóre objawy hiperkortyzolemii mogą występować również w powikłanej ciąży. Właściwa diagnoza ma istotne znaczenie ze względu na możliwość wystąpienia poważnych powikłań u matki i płodu. Diagnostyka hormonalna hiperkortyzolemii w ciąży jest trudna do interpretacji, z powodu fizjologicznych zmian w osi podwzgórze–przysadka–nadnercza związanych z ciążą. Wykonanie badań obrazowych również jest ograniczone, a dodatkowe utrudnienia w ich interpretacji mogą wynikać z fizjologicznego powiększenia przysadki w ciąży. Decyzja co do czasu i sposobu leczenia hiperkortyzolemii w ciąży zależy między innymi od nasilenia objawów klinicznych i możliwych powikłań dla matki i płodu, powinna również uwzględniać ewentualne powikłania terapii. Opisujemy przypadek zespołu Cushinga w przebiegu gruczolaka kory nadnerczy, zdiagnozowany w 22. tygodniu ciąży. Ze względu na zaawansowaną ciążę i łagodne objawy hiperkortyzolemii chora była leczona objawowo i pozostawała w stałej opiece endokrynologicznej i ginekologicznej. W 35. tygodniu ciąża była rozwiązana przez cięcie cesarskie z powodu przedwczesnego odklejenia łożyska. U noworodka płci męskiej o wadze 2450 g nie obserwowano niewydolności kory nadnerczy ani innych powikłań hiperkortyzolemii u matki. **(Endokrynol Pol 2011; 62 (2): 181–185)**

Słowa kluczowe: *zespół Cushinga, ciąża, gruczolak nadnercza, hiperkortyzolemia*

Introduction

Pregnancy in women with hypercortisolism is very rare because of the menstrual disturbances and infertility associated with glucocorticoid excess [1–3]. The commonest cause of hypercortisolism in pregnancy is ACTH-independent Cushing's syndrome (in contrast to non-pregnant women, in whom pituitary adenomas predominate) [2]. The diagnosis of pathological hypercortisolism in pregnancy is very difficult as some symptoms of the disease, such as hypertension, glucose

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intolerance, striae on the abdomen, and edema, may occur in complicated pregnancies. Additionally, hormonal analyses and visual imaging in pregnancy are limited. The results of hormonal measurements and dynamic tests are not easy to interpret due to the physiological changes in the hypothalamo-pituitary-adrenal axis during pregnancy [1, 3]. The decision to treat Cushing's syndrome during pregnancy and the choice of treatment method are difficult and must be approached case by case depending on the etiology and severity of the disease and the time of gestation [1]. We describe a case of Cushing's syndrome secondary to an adrenal adenoma which was treated by adrenalectomy after delivery. High blood pressure and hypokalemia were corrected pharmacologically during pregnancy.

Case report

A 23 year-old in the 22nd week of her second pregnancy complained of weakness, dyspnea, and edema having lasted for six weeks. At first, she was hospitalised with suspected myocarditis, which was later excluded. Her medical history showed a 10-kilogram weight gain at the age of 18, along with truncal obesity, moon face and purple striae on her lower limbs and buttocks. Two years later, during her first pregnancy, she gained 30 kilograms; purple striae also appeared on the abdomen, breasts, thighs, and shoulders. She was normotensive. A glucose tolerance test was not performed. These symptoms did not retreat after labour. She did not observe any menstrual disorders before or after her first pregnancy.

Her second pregnancy was complicated first by hypertension, hypokalemia, and purple striae, and later also by weakness, dyspnea, and edema. For these reasons, she was directed to the Department of Endocrinology with a preliminary diagnosis of Cushing's syndrome.

Physical examination revealed typical Cushingoid signs, including truncal obesity, moon face, and purple striae on the breasts, abdomen, shoulders, and lower limbs, edema, and proximal muscle weakness (Fig. 1A, B). Her blood pressure ranged from 140/90 to 150/100 mm Hg. The basic biochemical examination was normal except for hypokalemia (3.45–3.78 mmol/Lh). Glucose tolerance following an oral glucose load was correct. Proteinuria was not observed. Twenty-four hour urinary free cortisol excretion was extremely high (1.624 μg/24 h, normal range: 13.8–75.3 μg/24 h). A diurnal cortisol rhythm was absent. The cortisol levels in the morning were 498.1 ng/mL at 5 am and 587.1 ng/mL at 8 am (normal range: 94–260 ng/mL) and at night were 505.3 ng/mL at 8 pm and 511.5 ng/mL at midnight (normal range: 18–127 ng/mL). The plasma ACTH level was less than 5.0 pg/mL (normal range: 0.0–46 pg/mL). Serum cortisol after 1 mg overnight dexamethasone suppression was 530.7 ng/mL. Abdominal ultrasonography did not reveal any pathology of the adrenal glands. In view of the suppressed plasma ACTH level, magnetic resonance imaging (MRI) was performed. The examination revealed a tumour measuring 2.2 × 3.0 cm in the left adrenal gland.

Due to considerable uterine contraction readiness at the end of the second trimester of pregnancy, and the mild symptoms of hypercortisolism, only symptomatic treatment was introduced. During hospitalisation, verapamil (240 mg per day), methyldopa (1,500 mg per day), and potassium chloride (2,346 mg K^+ per day) were administered.

Because of premature detachment of the placenta in the 35th gestational week, the pregnancy was terminated by emergency caesarean section. A 2,450-gram male infant with Apgar scores of 6 at 1 min and 7 at 5 min was delivered. The infant's diurnal serum cortisol level immediately after labour was low (20.9 ng/mL at 6 am, 39.5 ng/mL at 3 pm, 22.9 ng/mL at 6pm, and 13.5 ng/mL at midnight). Three weeks later, it was still low (11 ng/mL at 6 am, 11 ng/mL at midday, 41 ng/mL at 6 pm, and 11 ng/mL at midnight), but it rose significantly during the synacthen stimulation test. The serum cortisol concentration after administration of 100 μg ACTH (synacthen) was 139 ng/mL after 30 min, 171 ng/mL after 60 min, 205 ng/mL after 90 min, and 213 ng/mL after 120 min, with an initial level of 11 ng/mL. Plasma electrolytes were within the normal range. No exogenous steroid therapy was given.

Three weeks after labour, the patient underwent left adrenalectomy. A 1.6-cm tumour was found in the left adrenal gland. This was histologically shown to be a benign adrenal adenoma. Blood pressure normalised after surgery and serum cortisol level was below the normal range (7.5 ng/mL).

Three months after adrenalectomy, the patient continued to receive glucocorticoid replacement therapy (20 mg of hydrocortisone in the morning and 10 mg in the afternoon). Twenty-four hour urinary free cortisol excretion during glucocorticosteroid replacement was normal (51.94 μg/24 h). Diurnal cortisol rhythm was still low: 6.86 ng/mL at 5.30 am, 7.26 ng/mL at 8 am, 21.54 ng/mL at 8 pm, and 4.62 ng/mL at midnight. The plasma ACTH level was still below 5.0 pg/mL. Two months later, the serum cortisol concentration at 8am was 78.2 ng/mL. Thirty minutes after the synacthen injection it rose to 114.9 ng/mL and after one hour it had fallen to 64.6 ng/mL.

Almost two years after the surgery, the woman was again hospitalised at the Department of Endocrinology, Diabetology and Isotope Treatment. All signs typical for hypercortisolism, such as truncal obesity, moon face, and purple striae on the breasts, abdomen, and lower limbs, which had been observed before the

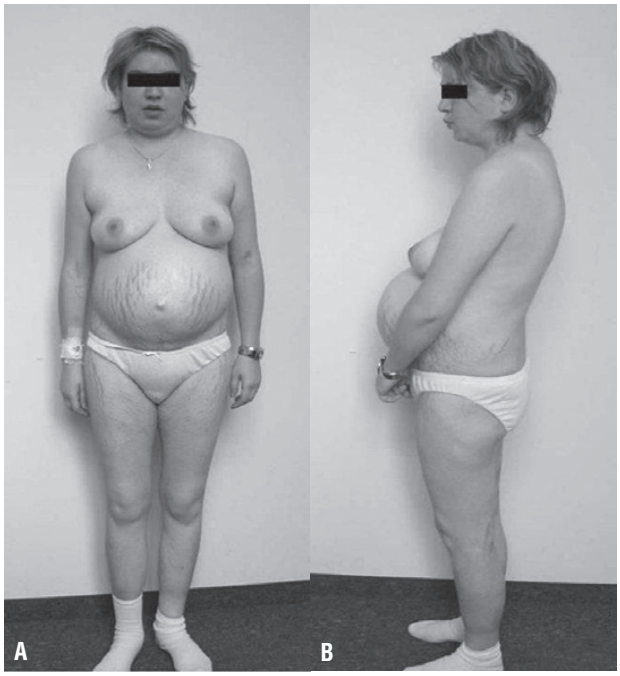

Figure 1 A, B. *23 year-old pregnant woman with Cushing's syndrome before adrenalectomy*

Rycina 1 A, B. *23-letnia ciężarna kobieta z zespołem Cushinga przed adrenalektomią*

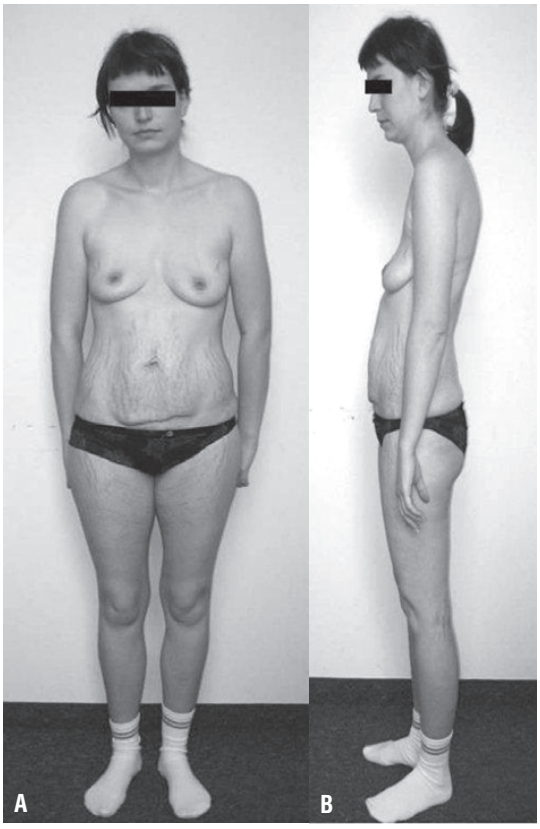

Figure 2 A, B. *23 year-old woman with Cushing's syndrome two years after adrenalectomy*

Rycina 2 A, B. *23-letnia kobieta z zespołem Cushinga 2 lata po adrenalektomii*

adrenalectomy, had disappeared (Fig. 2A, B). Physical examination revealed only colourless striae in place of the purple ones. The patient had lost 10 kilograms. The substitution with glucocorticosteroids (20 mg of hydrocortisone in the morning and 10 mg in the afternoon) was still applied. The hormonal measurements and dynamic tests revealed hypofunction of the remaining right adrenal gland. Twenty-four hour urinary free cortisol excretion without glucocorticosteroid substitution was low (2.81 ng/24 h). Diurnal cortisol rhythm was also still low (59.4 ng/mL at 5.30 am, 116.8 ng/mL at 8 am, 41.3 ng/mL at 8 pm, and 8.9 ng/mL at midnight). The plasma ACTH level was normal (30.9 pg/mL). The response of the right adrenal gland after synacthen injection was weak: the initial serum cortisol level was 116.8 ng/mL. It rose only to 133.8 ng/mL after 30 minutes, and had fallen to 64.6 ng/mL after one hour.

Discussion

The diagnosis of hypercortisolism in pregnant women is often difficult due to the resemblance of Cushing's syndrome, particularly mild forms of it, to some symptoms of complicated pregnancy [1, 3]. Hypertension, glucose intolerance, or diabetes mellitus may occur in pregnancy and are also part of the clinical presentation of Cushing's syndrome [1, 3]. Weight gain connected with hypercortisolism is mainly truncal, and limbs are thin due to myopathy. In contrast, adipose tissue in pregnancy is more uniform. Only occasionally do easy bruising, hirsutism, acne, and edema suggest Cushing's syndrome. Hence, pregnancy makes the diagnosis more difficult and may delay it, especially in mild cases [1, 3].

Hormonal diagnostics of hypercortisolism in pregnancy may be complicated because of physiological alterations in the hypothalamic-pituitary-adrenal axis and placental production of CRH and ACTH [2–5]. Only a small fraction of circulating cortisol is free and biologically active, while most of it is bound, primarily with corticosteroid-binding globulin (CBG). Total and free cortisol, as well as CBG serum levels increase in pregnancy, while the circadian rhythm of cortisol secretion is normal [1, 3, 5, 6].

The cortisol circadian rhythm in our patient was abnormal, without the typical diurnal variation. The plasma cortisol level increased considerably in the morning and at noon (two-fold) and stayed at a constant level in the evening and during the night. The 24-hour urinary excretion of free cortisol was extremely high. The morning ACTH plasma concentration was

undetectable, although ACTH levels normally increase during pregnancy [1, 3]. Biochemical examinations revealed hypokalemia despite long-term oral administration of potassium chloride.

During physiological pregnancy, the urinary free cortisol excretion is usually normal, but it may also increase two- or three-fold. Salivary cortisol reflects the free fraction of cortisol in serum and may be useful in the diagnosis of hypercortisolism during pregnancy. This parameter increased more than two-fold in the third trimester in comparison with non-pregnant women [7]. The 1-mg overnight dexamethasone suppression test is not accurate in patients during pregnancy because placental ACTH is not suppressed by glucocorticoids, while dexamethasone may increase placental CRH and placental ACTH activity [6]. Suppressibility may also be impaired due to increased cortisol binding by CBG [1, 3]. In non-pregnant patients, the cortisol level decreases by 50% or, according to some authors, by 87%, after suppression [3, 8]. A similar reduction occurs in the first trimester of pregnancy. In contrast, during the second and third trimesters, physiological suppression does not reach 50%. Hence an interpretation of the dexamethasone suppression test in gestation is difficult and depends on gestational age [3, 8]. Our patient did not undergo the high-dose (8 mg) dexamethasone suppression test, as the results of hormonal and radiological investigations were unequivocal. This allowed the mother and foetus to avoid excessive diagnostic investigation. We did not observe suppression after the 1 mg overnight dexamethasone test.

Adrenal ultrasonography (USG) or MRI can be safely performed for adrenal tumour detection. MRI can also be useful in locating pituitary tumours, but it is not always easy to interpret due to the physiological enlargement of the pituitary gland during gestation. It may mask the tumour, which is undetectable in almost half of patients with Cushing's disease [1, 3, 9]. Abdominal USG did not detect the left adrenal tumour in our patient, which was located by MRI.

Cushing's syndrome in pregnancy is dangerous to the mother and foetus; therefore, correction of hypercortisolism should be performed as soon as possible. The commonest maternal complication is gestational hypertension, which occurs, according to different studies, in 60-80% of cases (compared to 10–15% of pregnant women without hypercortisolism). Abnormal carbohydrate metabolism, including diabetes mellitus, appears in 15–25% of pregnant women with Cushing's syndrome (compared to 5–6% of pregnant women without hypercortisolism). Preeclampsia and eclampsia, pulmonary embolism, pulmonary edema, or congestive heart failure are rarely observed [1, 3, 11]. Delivery by caesarean section in the presence of hypercortisolism leads to wound infection or rupture in 40% of cases [3, 12]. Maternal mortality is hard to estimate and, according to some authors, reaches 4% to 4.5% of cases. More than 60% of pregnant women with Cushing's syndrome deliver prematurely [3].

Foetal mortality is high (spontaneous abortion and stillbirths) and the early neonatal death rate due to extreme prematurity and postnatal infections ranges from 1.5 to 20%. Intrauterine growth retardation occurs in 15% of pregnant women with hypercortisolism, mainly in association with gestational hypertension and diabetes. The early spontaneous abortion rate may be underestimated because of delays in diagnosing Cushing's syndrome [1, 3, 12]. Excessive glucocorticosteroid levels crossing the placenta may suppress the foetal hypothalamic-pituitary-adrenal axis; nevertheless, neonatal adrenal insufficiency is rare. Kreines et al. described three cases of clinical adrenal gland insufficiency and atrophy in newborns of hypercortisolic mothers [1, 3, 12]. In these cases, substitution of glucocorticosteroids is necessary. Adrenal function in our patient's child was within norms, which was confirmed in the test with ACTH.

The decision to treat Cushing's syndrome during pregnancy and the choice of treatment method are difficult. Both the abandoning of therapy and therapy itself may pose serious risks. It is believed however, that hypercortisolism in pregnancy should be cured immediately after establishing the diagnosis. The choice of treatment must be individualised, depending on the etiology and gravity of the disease and the gestational status. Patients with mild Cushing's syndrome diagnosed in advanced pregnancy may be placed under observation only. The risk of complications due to hypertension and diabetes must be minimised by hypotensive medication and dietary regimen and, if necessary, by insulin therapy. Surgery may be performed after delivery [1, 3].

The commonest cause of Cushing's syndrome in pregnancy, adrenal gland adenoma, may be treated by unilateral adrenalectomy during gestation. Classical or laparoscopic methods have been performed in practice. The end of the first trimester and the first half of the second trimester are considered the best time for surgery because uterine contraction readiness is the smallest. In the third trimester, conservative treatment and early delivery are preferred [3], although Aishima et al. successfully treated a patient with Cushing's syndrome at this gestational stage by retroperitoneal laparoscopic adrenalectomy [14]. Transsphenoidal surgery is preferred for ACTH-dependent pituitary adenoma, both in pregnant and non-pregnant patients.

Pharmacological treatment may be considered in patients with serious symptoms of hypercortisolism, when surgical therapy is contraindicated or during preparation for surgery. Although no adverse foetal or

neonatal side effects have been reported, the experience with drugs is limited. Metyrapone, cyproheptadine, ketoconazole, and aminoglutethimide are used to treat Cushing's syndrome in pregnancy [1, 14–18]. Metyrapone is chosen most often, with effective suppression of hypercortisolism. No adverse effects on the foetus have been described [16–18]. Kasperlik-Załuska et al. described the case of a woman with recurrent Cushing's syndrome during three pregnancies. During the last gestation, the only successful pregnancy, metyrapone was administered [18]. The recommended dose of metyrapone is 2.5–3.0 g per day [16, 18]. Treatment of Cushing's syndrome in pregnancy with ketoconazole and aminoglutethimide was rarely performed due to possible embryotoxic and teratogenic effects [14, 15, 19, 20]. The diagnosis of Cushing's syndrome in the woman described above was made in the 22nd week of gestation. Due to the considerable uterine contraction readiness at this stage of pregnancy, and the mild hypercortisolism symptoms, only symptomatic treatment was introduced. The patient was not treated with adrenal steroid synthesis inhibitors.

Conclusions

The case presented above leads to the conclusion that hormonal diagnostics towards Cushing's syndrome should be introduced in pregnant woman suffering from hypertension, hyperglycemia, myopathy and hypokalemia, or evidence of androgen excess. Early diagnosis of hypercortisolism in pregnancy depends on increased alertness and allows the avoidance of the serious complications of hypercortisolism for the mother and foetus.

The treatment has to be individualised and depends on the stage of the pregnancy and the gravity of the clinical symptoms. Data on the safety of pharmacotherapy during pregnancy is still insufficient. The complications of untreated hypercortisolism, on the other hand, may be serious.

The risk of sudden pregnancy complications which would require an immediate pregnancy termination is high. Therefore, hypercortisolemic pregnant women should be kept under close obstetric care.

The neonate of a hypercortisolemic mother requires the diagnosis of the hypothalamo-pituitary-adrenal axis and the possible introduction of replacement glucocorticoid treatment.

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