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Cushing's syndrome in pregnancy: a review of reported cases

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Abstract

Cushing's syndrome (CS) causes hypogonadotropic hypogonadism and anovulatory infertility due to hypercortisolism, and it is very rare in pregnancy. CS in pregnancy is associated with important maternal-foetal morbidity and mortality, such as preeclampsia and premature delivery.

A systematic search was conducted in the MEDLINE library to retrieve articles reporting cases of CS in pregnant women, during the period between 2010 and 2020.

Thirty-five reported cases are presented focusing on the ability of diagnosis, treatment therapies, and foetal outcomes.

Diagnosis of CS during pregnancy can be challenging and is often delayed, adrenal adenoma being the predominant cause. Both medical treatment and surgery aiming at restoring the cortisol balance reduce maternal and foetal complications. **(Endokrynol Pol 2021; 72 (1): 64–72)**

Key words: *Cushing's syndrome; pregnancy; hypercortisolism; adrenocortical adenoma; pituitary adenoma; review*

Introduction

Cushing's syndrome (CS) results from prolonged exposure to high levels of glucocorticoids. Being a rare syndrome, CS has an incidence in the general population of about 40–70 per million every year, affecting mainly adults, and especially women usually aged 30 to 50 years [1]. The most common cause is the administration of excessive doses of glucocorticoids resulting in iatrogenic or exogenous syndrome. On the other hand, endogenous Cushing syndrome has a low incidence up to 0.7–2.4 per million population per year and can be further classified as adrenocorticotropic hormone (ACTH)-dependent (80–85% of cases) or ACTH-independent (15–20%) [2]. The vast majority of ACTH-dependent Cushing syndrome is caused by a pituitary adenoma that produces high levels of ACTH, thus leading to extreme cortisol production by the adrenal glands (Cushing disease). Other causes include ectopic ACTH or corticotropin-releasing hormone (CRH) release, which are related to multiple endocrine neoplasia type 1, small-cell carcinoma of the lung or pulmonary carcinoid tumour, pancreatic neuroendocrine tumours (NETs), thymic NETs, gastrinomas, medullary thyroid cancer, and pheochromocytoma. ACTH-independent causes of endogenous Cushing syndrome include adrenal tumours (adenoma or carcinoma) and macro- or micronodular adrenal hyperplasia [3].

Cushing syndrome in pregnancy is exceptionally rare because hypercortisolism can lead to hypogonadotropic hypogonadism, impaired ovulation, and consequently infertility. The predominant aetiology of CS in pregnant women is adrenal adenoma (in 40–60% of the cases). A diagnosis of Cushing syndrome in pregnancy is difficult and is often delayed due to an overlap between symptomatology and the physiological effects of pregnancy such as hypertension, hyperglycaemia, weight gain, striae, and mood changes [4] (Fig. 1).

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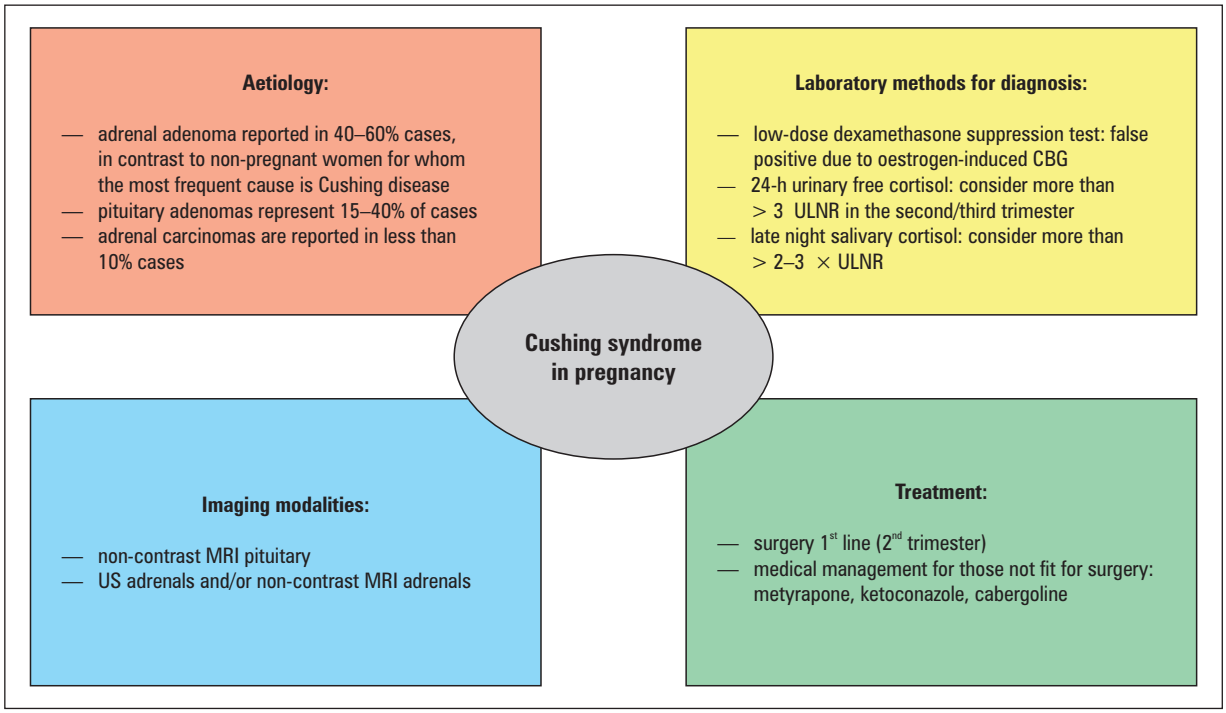

Figure 1. *General characteristics of Cushing syndrome in pregnancy [4, 11]. ULNR — upper limit of normal range; MRI — magnetic resonance imaging; US — ultrasound scan; CBG — corticosteroid-binding globulin*

Pregnant women normally have increased levels of CRH, ACTH, and cortisol secreted mainly by the placenta and the hypothalamic-pituitary-adrenal axis (HPA) activation during the first trimester. More specifically, according to recent clinical data serum cortisol is expected to rise up to 1.6-fold by the 11th week of gestation while urinary free cortisol can increase up to three times the normal range. Moreover, the placental secretion of ACTH and CRH can lead to non-decreased ACTH levels in 50% of women with adrenal CS and attenuated response to dynamic tests such as CRH test, desmopressin test, and high-dose dexamethasone suppression test. One additional restriction is found in the used imaging modalities because only ultrasound and MRI are preferred and the use of gadolinium is contraindicated in most cases [5]. Taking all the above mentioned into account, it is easily assumed that accurate diagnosis of Cushing syndrome during pregnancy can be very challenging, thus complicating the appropriate and early treatment of these patents, which is vital for preventing the morbidity associated for both the mother and the foetus.

Herein, we review published cases in the literature about pregnant women with CS, aiming to investigate the different causes and treatment options of CS in pregnancy.

MEDLINE library systemic research

A systematic search was conducted in the MEDLINE (via PubMed) library in order to retrieve articles focusing on Cushing's syndrome in pregnant women during the period between 2010 and 2020. The search strategy was based on the use of keywords such as Cushing's syndrome, pregnancy, and hypercortisolism. The PRISMA approach was used for the selection of the publications included in the review. A total of 102 records were identified. Following removal of the duplicates, the publications that could not be electronically retrieved, and the reviews, 32 records remained. The full-text articles assessed for eligibility amounted to 32, and none of them was excluded. The inclusion process is presented in Figure 2.

Table 1 summarises all case reports used in the review.

A review of reported cases

Herein, we reviewed the literature during the period between 2010 and 2020 and described a range of 35 pregnant women diagnosed with CS. Despite the published case reports and reviews, knowledge in this field is rather limited because CS in pregnant women is extremely rare.

Concerning the aetiology of Cushing's disease in pregnant women, it is reported that adrenal adenoma is the main cause, contrary to adenoma of the pituitary gland [5]. The cases presented in this review are in agreement with existing literature because approximately 80% of the patients presented an adrenal

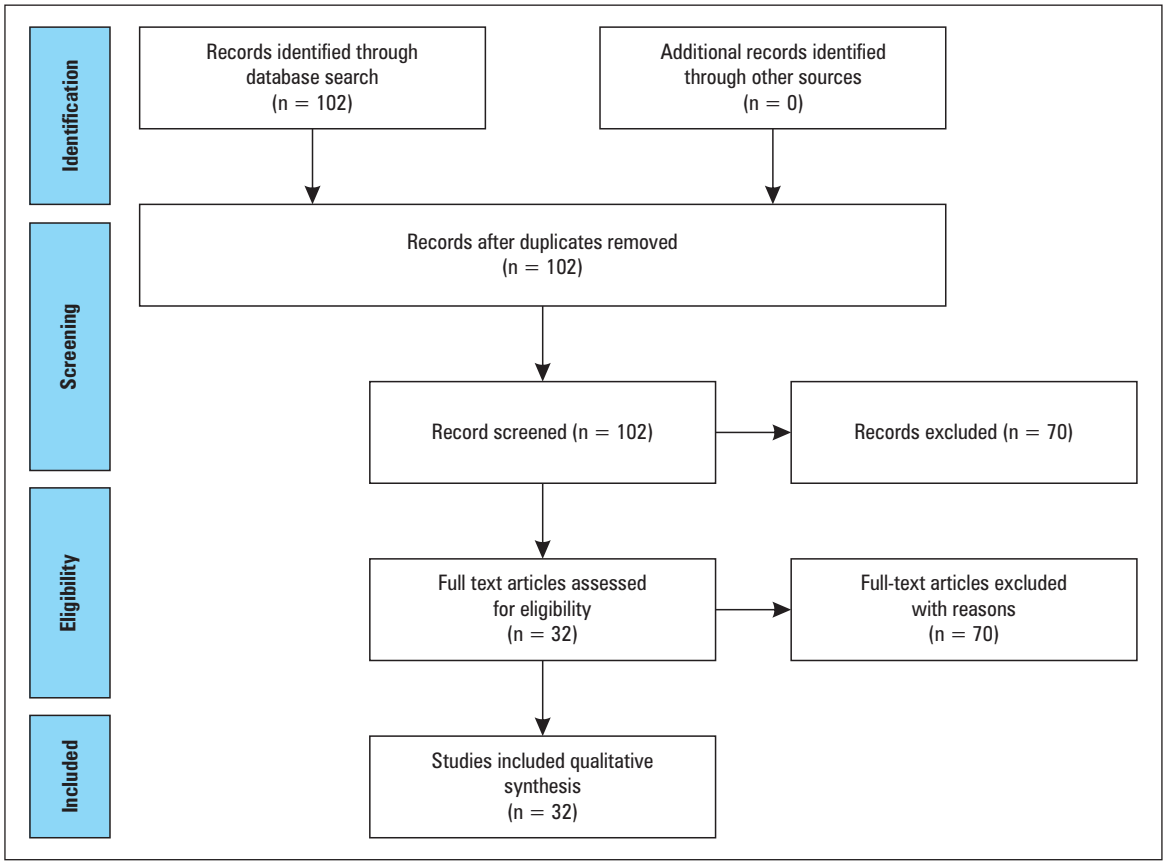

Figure 2. *Prisma flow diagram for the current review*

adenoma. This may be attributed to the fact that patients with an adrenal adenoma are most likely to be purely cortisol producing, thus their ovulatory function remains unaffected. Alternatively, pregnancy-induced hCG levels might have triggered a pre-existing subclinical CS in these patients due to the aberrant expression of LH receptors in adrenocortical cells of an adrenal adenoma, whereas pre-pregnancy LH levels might be insufficient for the development of CS [6].

A high rate of maternal complications may arise from uncontrolled CS during pregnancy. Even in treated cases, some patients develop complications such as preeclampsia or premature delivery. The most commonly described maternal complications include the following: hypertension (68%), diabetes (25%), preeclampsia (14%), osteoporosis and fractures (5%), heart failure (3%), and maternal death (2%). The most common foetal complication is prematurity (43%), followed by intrauterine growth restriction (21%), stillbirth (6%), spontaneous abortion or intrauterine death (5%), and hypoadrenalism (2%) [7]. However, higher foetal survival rates were observed in women treated during pregnancy [8].

Given that Cushing's disease is linked to high morbidity, early diagnosis and effective treatment are important. Concerning the diagnosis of this syndrome, it can be difficult and demanding during pregnancy because the typical features of the syndrome and the pregnancy can overlap. According to existing literature, analysis and measurement of the urinary cortisol level and circadian rhythm of plasma cortisol constitutes an effective strategy to detect Cushing's syndrome during pregnancy. Late-night salivary cortisol is reported in various cases to be the best approach to detect patients with endogenous hypercortisolism [5]. A more difficult approach for the diagnosis of CS is the overnight dexamethasone suppression test, which evaluates clinical hypercortisolism in patients presenting adrenal incidentalomas. An alternative diagnosis involves pheochromocytoma and primary aldosteronism. In the majority of the cases presented in this review adenoma was detected via magnetic resonance imaging. Therefore, magnetic resonance imaging can be considered as a useful tool for identifying this syndrome caused by adrenal incidental tumours during pregnancy [9]. However, it is essential that new clinical studies, using additional techniques and predictors targeting the recognition of Cushing syndrome, are conducted.

Concerning the treatment of Cushing syndrome, the most commonly recommended strategy is surgery

Table 1. *Case reports of pregnant women with Cushing's syndrome included in the review*

Author	Maternal characteristics	Cushing syndrome			Clinical features during pregnancy	Foetal outcomes
		Diagnosis	Imaging modality	Treatment		
Boronat et al. [15] (2010)	A 26-year-old with primary infertility and hypertension.	ACTH-dependent CS (CD diagnosed before pregnancy in treatment with ketoconazole waiting for transsphenoidal surgery)	MRI: 10 mm pituitary adenoma	Ketoconazole (200 mg bid) until 13th week Transsphenoidal surgery at 16th week Metyrapone 250–500 mg bid after 20th week Alphametildopa (250 mg *tid*)	Abdominal obesity Gestational diabetes Hypertension	Induction of labour at 34 weeks A 2480-g male baby
Choi et al. [16] (2011)	A 31-year-old at 30 weeks of gestation with hypertension	ACTH-independent CS	US: 26 mm right adrenal mass	Hydralazine and labetalol Laparoscopic adrenalectomy (postpartum)	Severe preeclampsia Disseminated intravascular coagulopathy Pulmonary oedema	Urgent C-section at 31 weeks A 1670-g female baby Moderately SRDS
Holgado-Galicia et al. [17] (2011)	A 22-year-old at 26 weeks with severe hypertension	ACTH-independent CS	US: Left adrenal mass	Hydralazine, methyldopa and nifedipine Adrenalectomy (postpartum)	Gestational diabetes Severe hypertension Preeclampsia	Urgent C-section for preterm labour and foetal distress at 28 weeks Baby expired after 4 days
Holgado-Galicia et al. [17] (2011)	A 33-year-old at 20 weeks with bipedal oedema	ACTH-independent CS	MRI: 30 mm right adrenal mass	Adrenalectomy (postpartum)	Gestational diabetes Osteoporosis Cushingoid phenotype	Urgent C-section for preterm labour and foetal distress at 31 weeks The baby remained in an incubator for 1 month
Schiemer et al. [18] (2011)	A 28-year-old with obesity and type 2 diabetes	ACTH-independent CS (diagnosed before pregnancy)	MRI: 31 mm left adrenal mass	Metyrapone after the 1st trimester Adrenalectomy at 20th week	Type 2 diabetes	Urgent C-section at 28 weeks due to reduced foetal movement A 940-g male baby with tracheomalacia
Toutounchi et al. [19] (2011)	A 21-year-old at 24 weeks with hypertension and overweight	ACTH-independent CS	MRI: 57 mm left adrenal mass	Doxazosin Laparoscopic adrenalectomy at 24th week	Severe hypertension	SVD at 38 weeks A healthy baby
Achong et al. [20] (2012)	A 25-year-old at 12 weeks with hypertension	ACTH-independent Cushing Pregnancy induced' ACTH-independent CS due to aberrant LH/hCG receptor (LHCGR) expression	MRI normal adrenal glands	Metyrapone at 18th week	Severe hypertension Preeclampsia Liver function abnormalities Headaches	Urgent C-section at 32 weeks A 2150-g male baby Admission to the neonatal intensive care unit for prematurity, respiratory distress, and jaundice

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Table 1. *Case reports of pregnant women with Cushing's syndrome included in the review*

Author	Maternal characteristics	Cushing syndrome			Clinical features during pregnancy	Foetal outcomes
		Diagnosis	Imaging modality	Treatment		
Borna et al. [21] (2012)	A 33-year-old at 30 weeks with hypertension, gestational diabetes	ACTH-independent CS	MRI: 43 mm right adrenal mass	Methyldopa (metyrapone was unavailable) and insulin Adrenalectomy (postpartum)	Severe hypertension Gestational diabetes Severe preeclampsia	Urgent C-section at 31.5 weeks A 1500-g male baby Moderate respiratory distress syndrome
Gopal et al. [22] (2012)	22-year-old at 7th month with gestational diabetes and hypertension	ACTH-dependent CS	MRI: pituitary microadenoma	Conservative management with strict glycaemic control, antihypertensives, potassium supplementation Transsphenoidal surgery (postpartum)	Gestational diabetes Hypertension Cushingoid phenotype	SVD at 34 weeks Healthy female baby
Kotteas et al. [23] (2012)	28-year-old at 22 weeks with severe hypertension	ACTH-independent CS	US: 55 mm left adrenal mass	Adrenalectomy (open laparotomy) during at 24th week	Preeclampsia Hypertension Cushingoid phenotype	C-section at the 36 weeks A 1800-g male baby
Sammour et al. [24] (2012)	A 32-year-old at 28 weeks with cushingoid phenotype	ACTH-independent CS	US: 40 mm right adrenal mass	Laparoscopic right adrenalectomy excision at 32nd week	Gestational diabetes	SVD at 39 weeks A 2480-g healthy female baby
Chang et al. [25] (2013)	A 38-year-old at 27 weeks with hypertension	ACTH-independent CS	MRI: 25 mm right adrenal mass	Adrenalectomy at 29th week	Oligohydramnios Hypertension Hypokalaemia Cushingoid phenotype	SVD at 38 weeks A 2450-g healthy female baby
Xu et al. [26] (2013)	A 27-year-old at 18 weeks with cushingoid phenotype	ACTH-independent CS "Pregnancy induced" ACTH-independent CS	US: hyperplasia of bilateral adrenals	Insulin and potassium	Hypertension Gestational diabetes Hypokalaemia	Patient decided to terminate pregnancy
Aslzare et al. [27] (2014)	A 31-year-old at 4 months with recently diagnosed CS	ACTH-independent CS	MRI: adrenal hyperplasia	Bilateral laparoscopic adrenalectomy at 4 months of gestation	Hypertension	C-section at 7 months because of fetoplacental abnormality Preterm infant with intrauterine growth retardation
Diri et al. [28] (2014)	A 26-year-old at 12 weeks with Hypertension	ACTH-independent CS	MRI: 35 mm right adrenal mass	Methyldopa Metyrapone at 13th week Laparoscopic adrenalectomy at 14th week	Hypertension Headaches Cushingoid phenotype	SVD at 41 weeks A 3000-g baby

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Table 1. *Case reports of pregnant women with Cushing's syndrome included in the review*

Author	Maternal characteristics	Cushing syndrome			Clinical features during pregnancy	Foetal outcomes
		Diagnosis	Imaging modality	Treatment		
Katulski et al. [29] (2014)	A 38-year-old at 19 weeks with the suspicion of Conn syndrome	ACTH-independent CS	US and MRI: a 30 mm right adrenal mass	Potassium tablets Methyldopa 250 mg *qds* Adrenalectomy (postpartum)	Hypertension Headaches Hypokalaemia Diabetes gestational	C-section at 35 weeks A 2660-g female baby
Spaniol et al. [30] (2014)	A 24-year-old at 18 weeks with hypertension and a cardiac myxoma	ACTH-independent CS PPNAD Carney complex	MRI: normal adrenal glands	Metyrapone 250 mg *bid* Bilateral adrenalectomy (four months postpartum)	Preeclampsia Severe hypertension Cushingoid phenotype	Urgent C-section at 26 weeks A 650-g female baby
Wang et al. [31] (2015)	A 24-year-old at 32 weeks with cushingoid phenotype	ACTH-independent CS	MRI: 25 mm left adrenal mass	Potassium supplements Laparoscopic adrenalectomy (postpartum)	Hypokalaemia	SVD at 36 weeks A 3460-g male baby
Nassi et al. [32] (2015)	A 26-year-old 19 weeks with severe hypertension	ACTH-independent CS	US and MRI: 34 mm right adrenal mass	Methyldopa and nifedipine Potassium supplements Laparoscopic adrenalectomy at 21st week	Hypertension Severe hypokalaemia	C-section at 36 weeks A 2550-g healthy male baby
Costenaro et al. [33] (2015)	A 39-year-old with a prior diagnosis of CD at age of 25 years	ACTH-dependent CS (recurrent CD)		Ketoconazole until 7th week and resumed at 16th week (100 mg *qds*) Methyldopa 250 mg *bid*	Gestational diabetes Hypertension	SVD at 36 weeks A 2770-g healthy female baby
Martínez García et al. [34] (2015)	21-year-old at 27 weeks with cushingoid phenotype	ACTH independent CS	MRI: 45 mm left adrenal mass	Metyrapone Laparoscopic adrenalectomy at 29th week	Hypertension Hypokalaemia Gestational diabetes	SVD at 33 weeks A 2270-g healthy male baby
Abbassy et al. [35] (2015)	A 38-year-old pregnant woman with recurrent CD after 8 years of remission	ACTH-dependent CS (recurrent of CD)	MRI: 4 mm pituitary adenoma	2nd transsphenoidal surgery at 18th week	Hypertension	SVD at 39 weeks A 3600-g healthy baby
Trinh et al. [36] (2016)	A 32-year-old at 15 weeks gestation with peripheral oedema and weight gain	ACTH -independent CS	MRI: 40 mm left adrenal mass	Laparoscopic adrenalectomy at 18th week	Hypokalaemia Gestational diabetes	Termination of pregnancy at 20 weeks due to sized cleft lip and palate of the foetus

Table 1. *Case reports of pregnant women with Cushing's syndrome included in the review*

Author	Maternal characteristics	Cushing syndrome			Clinical features during pregnancy	Foetal outcomes
		Diagnosis	Imaging modality	Treatment		
Nakhleh et al. [37] (2016)	A 29-year-old with recurrent CD	ACTH-dependent CS (recurrent CD)	MRI: pituitary adenoma remnant	Cabergoline started before pregnancy at 3.5 mg/week and titrated down from to 2 mg/week at 7th week	Cushingoid phenotype	Elective C-section.at 40 weeks A 3370-g healthy female baby
Dogansen et al. [38] (2017)	A 27-year-old with recurrent pregnancy loss and diabetes mellitus	ACTH-dependent CS	MRI: 7 mm pituitary adenoma	Transsphenoidal surgery at first trimester	Gestational diabetes Cushingoid phenotype	SVD at 38 weeks A 2700-g healthy female baby
Andreescu et al. [6] (2017)	A 31-year-old at 32 weeks with oedema and cushingoid phenotype	ACTH-independent CS	Postpartum CT: 38 mm left adrenal mass	Enalapril and labetalol Potassium suppletion Laparoscopic adrenalectomy (postpartum)	Hypertension Preeclampsia Hypokalaemia	Induced vaginal delivery at 35 weeks A 2340-g healthy female baby
Andreescu et al. [6] (2017)	A 28-year-old 33 weeks with hypertension gestational diabetes.	ACTH-independent CS	MRI: 33 mm left adrenal mass	Laparoscopic adrenalectomy (postpartum)	Hypertension Gestational diabetes Liver test abnormalities	SVD at 38 weeks A 2740-g healthy baby boy
Andreescu et al. [6] (2017)	25-year-old at 28 weeks with gestational diabetes and cushingoid phenotype	ACTH-independent CS	Postpartum CT: 34 mm left adrenal mass	Laparoscopic adrenalectomy (postpartum)	Gestational diabetes Depression	SVD at 38 weeks A 3775-g healthy baby boy
Zieleniewski et al. [39] (2017)	31-years old woman with 3-years history of hypertension and osteoporosis with cushingoid phenotype	ACTH-independent CS	US: enlargement of the left adrenal gland	Metyrapone (0.5 g *tid*) and ketoconazole (0.4 g bid) Methyldopa (500 mg *tid*) and amlodipine (10 mg/daily) Adrenalectomy (postpartum)	Hypertension	C-section at full term. A 3100-g healthy baby boy
Pourali et al. [40] (2017)	A 29-year-old at 27 weeks with oedema, weakness, and hypertension	ACTH-independent CS	US: 30 mm right adrenal mass	Antihypertensive therapy Laparoscopic adrenalectomy (postpartum)	Hypertension Preeclampsia Cushingoid phenotype	Pregnancy was terminated at the 28th week of gestational age with misoprostol due to preeclampsia A 880-g baby male
Sek et al. [14] (2017)	A 36-year-old woman with prior CD	ACTH-dependent CS (recurrent CD)		Cabergoline 0.25 mg twice weekly throughout the pregnancy	Uneventful pregnancy,	SVD at 40 weeks A 3195-g healthy male baby
Jolly *et al*. [11] (2019)	A 30-year-old at 13 weeks with prior history of CD	ACTH-dependent CS (recurrent CD)	MRI: 4.5 mm pituitary adenoma	Transsphenoidal surgery at 23rd week	Gestational diabetes	Urgent C-section at 38 weeks Baby died 36 hours later due to complications of congenital diaphragmatic hernia

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Table 1. *Case reports of pregnant women with Cushing's syndrome included in the review*

Author	Maternal characteristics	Cushing syndrome			Clinical features during pregnancy	Foetal outcomes
		Diagnosis	Imaging modality	Treatment		
Zhang et al. [41] (2019)	A 35-year-old at 16 weeks of gestation with hypertension and cushingoid phenotype	ACTH-independent CS	MRI: 32 mm right adrenal mass	Methyldopa up to 1 g *bid* Laparoscopic adrenalectomy at the 26th week	Severe hypertension Gestational diabetes	C-section at 40 weeks A 3500-g healthy baby
Eto et al. [42] (2020)	A 34-year-old at 21 weeks with hypertension and cushingoid phenotype	ACTH-independent CS diagnosed postpartum	Postpartum CT: 28 mm right adrenal mass	Nifedipine 40 mg/day Laparoscopic adrenalectomy (postpartum)	Severe hypertension HELLP syndrome	Urgent C-section at 28 weeks because of HELLP syndrome and foetal growth arrest A 793-g female baby
Sakota et al. [43] (2020)	A 35-year-old at 16 weeks with hypertension and obesity	ACTH-independent CS (diagnosed postpartum)	Postpartum CT: 30 mm left adrenal mass	Nicardipine Laparoscopic adrenalectomy (postpartum)	Hypertension Myocardial hypertrophy and fibrosis CHF	Urgent C-section at 35 weeks due to heart failure A 2395-g male baby

ACTH — adrenocorticotropin; CS — Cushing syndrome; CD — Cushing disease; LH — luteinizing hormone; hCG — human chorionic gonadotropin; MRI — magnetic resonance imaging; CT — computerised tomography; US — ultrasound scan; *bid* — twice a day; *tid* — three times a day; *qds* — four times a day; SRSD — severe respiratory distress syndrome; HELLP — Hemolytic anemia, Elevated Liver enzymes, Low Platelet counts; CHF — congestive heart failure; C-section — caesarean section; SVD — spontaneous vaginal delivery; PPNAD — primary pigmented nodular adrenocortical disease

treatment [5]. In almost 80% of the cases in this review, surgery was the treatment option. Whatever the type of the surgery (pituitary or adrenal), the period between the end of the first trimester and the beginning of early second trimester is considered as the most appropriate, being associated with fewer maternal and foetal complications [10]. Some case reports showed the possibility of surgery during the third trimester, with a higher risk of prematurity. For instance, laparoscopic adrenalectomy for CS in pregnancy was found to be a safe and efficacious procedure up to 32 weeks of gestation, leading to a reduction in perinatal mortality and maternal morbidity rates, but with little effect on the occurrence of preterm birth and intrauterine growth restriction [11]. There are very limited data on the efficacy and the risks induced by bilateral adrenalectomy for hypercortisolism during pregnancy: if this option is chosen, the ideal time frame is the same as for unilateral adrenalectomy. Physicians should keep in mind that patients treated surgically for hypercortisolism are likely to have adrenal insufficiency for the rest of the pregnancy.

Apart from that, medical management is often used, aiming to control the cortisol excess for those who are not eligible for surgery or have had failure of surgery. Antisteroidogenic agents, such as metyrapone have been found to be effective at controlling hypercortisolism, but they may worsen hypertension because of deoxycorticosterone accumulation, thus increasing the frequency of preeclampsia. Metyrapone also passes through the placental barrier and may thus affect foetal adrenal steroid synthesis [12]. Ketoconazole has been used less as a therapeutic option and has not caused any complications to the foetus and the mother during pregnancy in the cases reported. However, one should take the potential teratogenicity and increased rate of abortion observed in animal studies into consideration [4]. Additionally, cabergoline was used in various cases of Cushing disease as an alternative option. Indeed, in two reported cases, a pregnancy was obtained while on high-dose cabergoline and maintained throughout pregnancy with complete remission [13, 14]. There are no reports of use of pasireotide during pregnancy and mitotane contraindicated due to a risk of teratogenicity.

Conclusions

In conclusion, Cushing's syndrome is extremely rare during pregnancy, with limited cases to be reported in literature. Diagnosis of CS in pregnancy is considered as a demanding task, and early recognition is important for maternal and foetal outcome. There is no consensus on the management of CS during pregnancy, and the individualised risk-benefit ratio should be considered.

Disclosure

The author reports no conflicts of interest in this work.

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