

Cabergoline use for cushing's disease during pregnancy: Mini review

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Abstract

Cushing disease (CD) rarely occurs during pregnancy and is associated with significant maternal and fetal comorbidity. The usual first-line treatment is surgery, and when surgery, is not feasible, medical therapy is usually considered. However, treatment of CD during pregnancy has consisted of conservative management without specific treatment. Cabergoline, is the drug of choice for treating hyperprolactinemia, is also found to be effective in reducing hypercortisolism in CD and used off-label for treating CD during pregnancy. Data concerning the safety of cabergoline use in pregnancy did not show any potential adverse effect of the drug on pregnancy outcome.

Introduction

Pregnancy rarely occurs in a patient with Cushing's syndrome (CS), due to the effect of hypercortisolism on the reproductive axis [1-3]. To date, approximately 263 cases of Cushing's syndrome have been reported in the literature [4].

The etiology of CS diagnosed during pregnancy is different from the general population as adrenal adenoma account for the most frequent cause of reported cases and only about 40% caused by ACTH-secreting pituitary adenoma [5]. However, the occurrence of pregnancy often is associated with significant maternal and fetal morbidity. Maternal complications include hypertension, preeclampsia, impaired glucose tolerance, diabetes and premature labor [5]. The fetus may experience increased risk for prematurity, intrauterine growth retardation, miscarriage, and stillbirths [5].

The treatment aims are to reduce maternal and fetal risks and poor outcomes of CS in pregnancy. Although well-controlled hypercortisolism has not been shown to decrease the incidence of premature births or rates of intrauterine growth restriction, it does appear to reduce stillbirth [6,7]. Treatment of CS in pregnancy has consisted of conservative management, medical therapy as well as surgery. Drug therapy is now the preferred second-line option for patients with CS after surgery. Various drugs are now available, including dopamine agonists (DAs), metyrapone, and ketoconazole. This review focuses on medical therapy with cabergoline.

Rationale for the use of cabergoline in cushing disease

The dopamine action is mediated by five specific receptors subtypes (D1-D5) [8]. The different dopamine receptor (DR) subtypes have different distributions and different roles in the various organs [8].

The D2 receptor is the predominant DR subtype in pituitary gland [9,10]. The expression of dopamine binding sites on corticotroph pituitary adenomas was demonstrated by Pivonello, *et al.* [11]. DA was hypothesized to induce a suppression of ACTH secretion and inhibition of cell growth in corticotroph pituitary adenoma, acting through DRs

expressed in ACTH-secreting pituitary tumors [11]. Bromocriptine was the first DA to be used in a treatment of corticotroph pituitary tumors with variable result [12,13].

Cabergoline was reported reduces cortisol secretion in 60%, but the normalization of cortisol secretion in only 40% of patients [11]. Being more effective and tolerated than bromocriptine, it is potentially useful for the treatment of CD [11].

Responsiveness to treatment with cabergoline

Ideally, CD should be appropriately treated surgically before pregnancy, because of the potential untoward effects on maternal and fetal health.

The optimal approach to women with active CD who become pregnant is controversial.

In patients with CD during pregnancy, 39.9% received treatment during gestation. Of these, 11.3% women only received medical treatment. DA have been successfully used for CD during pregnancy in minority of patients with no major adverse effects noted [4].

Furthermore, cabergoline doses for CD in pregnancies varied from 1-7 mg/wk (with a median dose of 3.5 mg/wk) as compared to lower doses of cabergoline (0.125-4.0 mg/wk) used to treat hyperprolactinemia in pregnant patients [14,15].

Although cabergoline is an FDA pregnancy category B drug, there are no clinical trials has as yet tested the safety of high-dose cabergoline for Cushing disease in pregnancy [16].

Woo, *et al.* reported a case of CD managed with high-dose cabergoline throughout pregnancy up to 10 mg per week with favorable maternal and fetal outcome [16].

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Other reports in a patient with pregnancy-induced CS, use of a combination of ketoconazole with cabergoline dose ranged only from 0.12–0.25 mg, with no adverse effect, were noted on pregnancy outcome [17].

Furthermore, a recent case report described a woman with CD who underwent a non-curative pituitary surgery and who conceived spontaneously four months after initiating cabergoline and was maintained at the dose of 2 mg/week, throughout gestation with complete clinical and biochemical remission and no maternal or fetal complications were evident [18].

Overall, normalization of UFC excretion could be obtained in two patients who submitted to cabergoline alone and in one undergoing the combination of cabergoline with ketoconazole.

Safety aspects of using Cabergoline during pregnancy

Experience with the use of cabergoline during pregnancy is limited as compared to bromocriptine. Most data on the safety of the use of cabergoline during pregnancies in women treated with cabergoline from women with prolactinomas [19,20].

Pregnancies with exposure of the fetus during the first few weeks of pregnancy have been reported in over 900 prolactinoma cases has not demonstrated an increased risk of spontaneous abortion, premature delivery, or multiple births [19].

Outcome data with regards to malformations were available for 822 cases with a finding of only 2.4% major malformations [21-23].

Use of cabergoline throughout gestation in 15 women with prolactinoma, with no abnormalities, noted [24].

A follow-up study up to 12 years of 223 children whose mothers took cabergoline in the first few weeks of gestation showed no abnormalities in their physical or mental development [25,26].

Cabergoline was in CD during pregnancy with higher dose well tolerated, and none of the published cases had a side effect or interrupt the treatment. Moreover, none of the patients experienced any significant cardiac symptom or sign [16-18].

Conclusion

The data collected from these cases suggest that Cabergoline therapy during gestation may be both safe and effective in the management of active CD during gestation. This limited data provides some preliminary evidence that cabergoline therapy if needed for active CD even with higher doses, may be continued during pregnancy without unwanted concerns regarding fetal growth and development. However, further studies are needed to determine the role of cabergoline use and safety in pregnant women with CD.

Declaration of interest

The author declares that they have no conflict of interest.

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