

MANAGEMENT OF PITUITARY TUMORS IN PREGNANCY

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Abstract

Pituitary tumors account for about 10–15 % of all intracranial neoplasms. Adenomas are the most common type of pituitary tumors. There are various options for treating pituitary tumors, such as surgery, medication therapy or radiotherapy. The treatment of choice depends on the size and functionality of the tumor. The first line of treatment for patients with pituitary prolactinomas are dopamine agonists, while the treatment of choice for non-functioning macroadenomas, acromegaly and Cushing's disease is surgery. The hypothalamic-pituitary-gonadal axis is frequently compromised in patients with pituitary tumors, resulting in amenorrhea and impaired fertility in women. Advancements in treatment have made conception and pregnancy possible for women with pituitary adenomas.

KEYWORDS: acromegaly, Cushing disease, non-functioning pituitary tumors, pituitary tumors, pregnancy, prolactinoma

INTRODUCTION

Pituitary tumors, constitute 10 to 15 % of all intracranial neoplasms. They are categorized according to pathohistological findings into pituitary adenomas, pituitary carcinomas, spindle cell oncocytoma, pituicytomas, granular cell tumors and craniopharyngeomas. The most common pituitary tumors are pituitary adenomas: benign epithelial tumors of the pituitary gland. They are divided into hormone-secreting (also known as functioning) and non-secreting (also known as non-functioning) tumors.

Pituitary tumors frequently compromise the hypothalamic-pituitary gonadal axis (gonadotrophic axis) due to mass effect or hyperprolactinemia.

About 40% of pituitary adenomas are prolactinomas; 15% are growth hormone (GH)-producing tumors, 10% are glycoprotein (thyroid-stimulating hormone (TSH), luteinizing hormone (LH) or follicle stimulating hormone (FSH)) producing, and <1% secrete thyroid-stimulating hormone (TSH). Prolactinomas and corticotrophic adenomas are more common in women and can potentially impair a woman's fertility by interfering with gonadotropic hormone secretion.

In patients with non-functioning macroadenomas, fertility is usually impaired by the destruction of gonadotroph cells or hyperprolactinemia caused by pituitary stalk destruction. Sometimes, pregnancy increases the size of nonfunctioning

pituitary adenomas.¹ If conception is planned, the tumor should be treated first to prevent its potential growth.²

Consequently, the induction and management of pregnant women with endocrine diseases poses a challenge for endocrinologists, gynecologists and pediatricians alike. Hormone therapy for ovulation induction and surgical therapy for pituitary adenomas have made pregnancy possible for many women with this condition. Nevertheless, this approach has its consequences on both mother and fetus health. The aim of this article is to summarize basic pathophysiology, clinical presentation and treatment advancements based on the latest reviews and research.

PROLACTINOMAS

Prolactinomas, which constitute about 40 % of all pituitary adenomas, are the main cause of hyperprolactinemia, excessive concentrations of the hormone prolactin in the blood. Symptoms of hyperprolactinemia are galactorrhea, amenorrhea, anovulation and, consequently, infertility. According to size, prolactinomas smaller than 10 mm in diameter are classified as microprolactinomas, while larger tumors (≥ 10 mm) are classified as macroprolactinomas.

Non-functioning pituitary tumors can compress the pituitary stalk and block the flow of dopamine (prolactin inhibiting factor) from the brain to the prolactin-secreting cells caus-

ing hyperprolactinemia. This is commonly known as “stalk effect”.^{2,3,4,5} Because of this dopamine inhibitory effect on PRL secretion, dopamine agonists such as bromocriptine, pergolide and cabergoline are used in the treatment of prolactinomas.⁵

TREATMENT

Medical treatment with dopamine agonists (DA) is the first-line approach to treating prolactinomas. Bromocriptine (BEC), as a dopamine agonist, decreases not only the synthesis and secretion of PRL, but also the rate of tumor cell division and mass growth.⁶ In patients with microprolactinomas, proper dosage of BEC leads to normalization of PRL levels within days to a few weeks of starting. On the other hand, normalization in patients with macroadenomas is often incomplete. Decrease in PRL levels is an important indicator of tumor mass reduction, implying that patients who do not show a drop in PRL levels do not have any tumor shrinkage.⁷

After PRL normalization, the drug dose is slowly tapered to the lowest dose possible. Follow-up consists of periodical evaluation of symptoms, PRL level measurement, and imaging studies.

Cabergoline is long-acting DA approved in Croatia for patients who do fail to respond to BEC therapy or fail to achieve adequate regulation of prolactin secretion on BEC. It’s also indicated in patients with unregulated acromegaly (which is discussed later in the text), in combination with somatostatin agonists.

TREATMENT DURING PREGNANCY

Medical treatment with DA normalizes prolactin levels in 86% cases, restoring fertility in most patients.⁹ Bromocriptine is the therapy of choice for inducing pregnancy in these patients because of its long safety record. General advice is to discontinue therapy with BEC during pregnancy after the

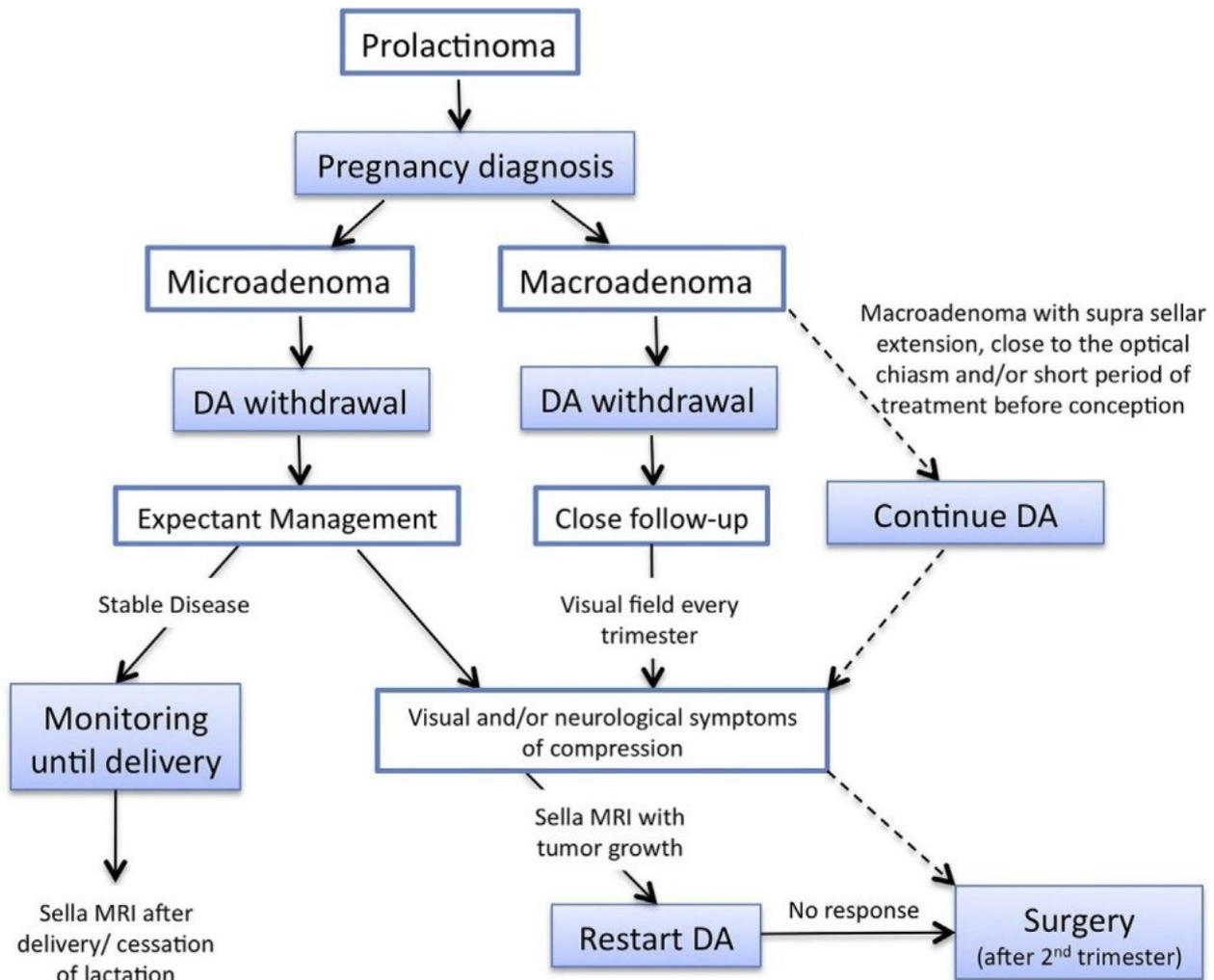


Figure 1. Prolactinoma management during pregnancy. DA, dopamine agonist.
 Source: Araujo PB, Neto LV, Gadelha MR. Pituitary Tumor Management in Pregnancy. *Endocrinol Metab Clin North Am.* 2015;44(1):181-197. doi:10.1016/j.ecl.2014.10.015. Copyright © 2015 Elsevier Inc.

first skipped period as a precaution against unwanted fetal exposure to the agent, in spite of the fact that teratogenic effects have not been reported with BEC therapy.¹² Studies with Cabergoline show similar results.¹³ Due to physiologic doubling in the volume of the pituitary gland, which normally occurs during pregnancy, once a woman with prolactinoma conceive, the most important issue (especially with macroadenomas) is the possibility of tumor enlargement.^{14,15} The aim of prolactinoma management during pregnancy is to keep the adenoma as far away as possible from the optic chiasm. In cases with suspicion of tumor enlargement, visual field testing and magnetic resonance imaging (MRI) should be performed at any point in the pregnancy. This recommendation should be followed for any type of pituitary adenoma that exhibits enlargement during pregnancy.² There are two approaches to medical treatment of prolactinomas, different for microadenomas and macroadenomas, as they show different rates of enlargement during pregnancy (Figure 1) Microprolactinomas do not show significant enlargement (1-5%), indicating low complication risk, so the drug should be safe to discontinue when pregnancy is confirmed.¹⁶ Careful monitoring is nevertheless needed. On the other hand, a significant number of women with macroadenomas show tumor enlargement (15-35%) during gestation, and therefore, the decision on drug treatment should be individual. Individuals resistant to drugs are candidates for transsphenoidal surgery.^{2,14}

ACROMEGALY

Acromegaly is a rare disorder characterized by hypersecretion of growth hormone (GH) and elevated circulating levels of insulin-like growth factor-I (IGF-I), which is secreted by the liver as a response to GH stimulation. Acromegaly is predominantly caused by a GH-secreting pituitary adenoma (somatotropinoma). Fifteen percent (15%) of pituitary adenomas produce GH.^{4,14}

IGF-I has been the most reliable biochemical indicator of acromegaly. IGF-I is useful not only in diagnosis, but also in monitoring the efficacy of therapy. Another simple diagnostic approach is to measure serum GH after a 3-hour oral glucose tolerance test.¹⁷

To explain the pathophysiology of acromegaly in pregnant and non-pregnant individuals, it is necessary to examine the two main variants of GH: GH normal (GH-N), expressed predominantly in somatotrophs (cells in anterior pituitary), and GH variant (GH-V), expressed selectively in the placenta. GH-V is a hormone which stimulates the production of maternal IGF, which, through negative feedback action, inhibits maternal pituitary secretion of GH-N. Therefore, during normal pregnancy, GH-V is persistently elevated, replacing GH-N as the predominant form of GH in the second trimester.¹⁸ On the other hand, in pregnant women with acromegaly, both GH-N and GH-V levels are persistently elevated, due to

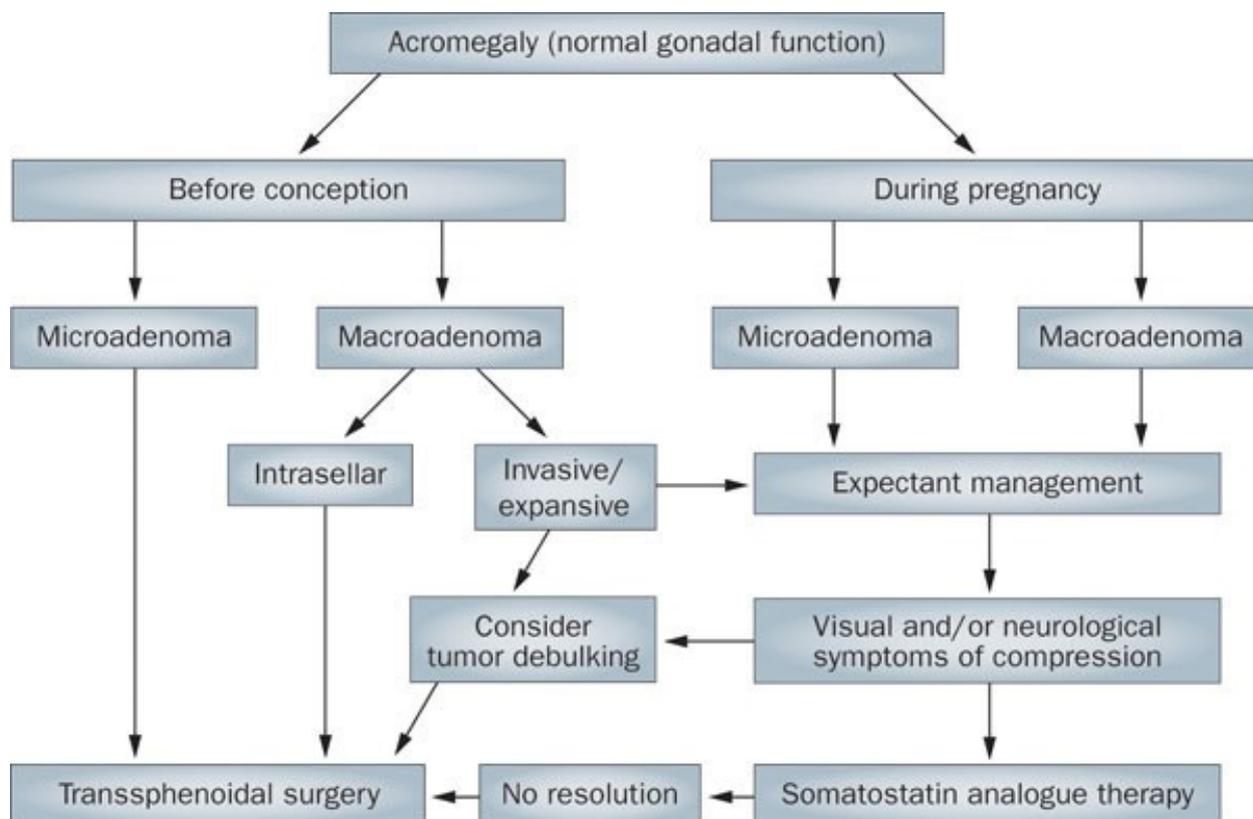


Figure 2. Therapeutic management of pregnant women with acromegaly. Source: Bronstein MD, Paraiba DB, Jallad RS. Management of pituitary tumors in pregnancy. Nat Rev Endocrinol. 2011;7(5):301-310. doi:10.1038/nrendo.2011.38. Copyright © 2011 Nature Publishing Group

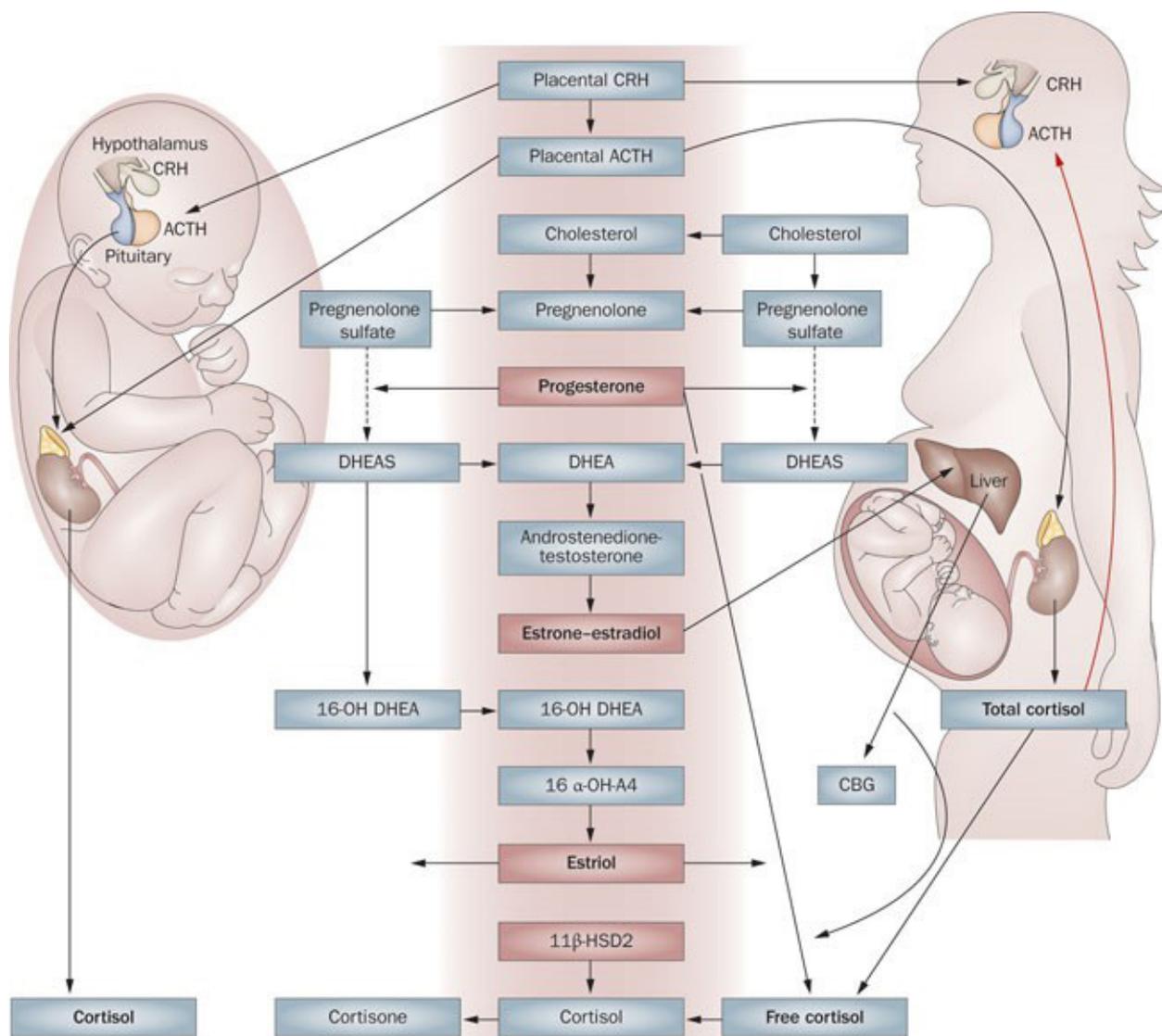


Figure 3. Hypothalamic–pituitary–adrenal (HPA) axis during pregnancy. 16 α -OH-A4, 16 α -hydroxyandrostenedione; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.

Source: Bronstein MD, Paraiba DB, Jallad RS. Management of pituitary tumors in pregnancy. *Nat Rev Endocrinol.* 2011;7(5):301-310. doi:10.1038/nrendo.2011.38.

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autonomous secretion of GH-N. IGF levels are as elevated in normal pregnancy as they are in pregnancy with acromegaly. This can complicate the diagnosis of acromegaly during pregnancy, as current standard immunoassays cannot distinguish between GH-N and GH-V. Even though hypogonadism, hyperprolactinemia, insulin resistance and polycystic ovary syndrome are possible reasons for fertility impairment in women with acromegaly, some case reports have shown acromegaly to actually increase a woman's fertility, regardless of medical treatment.^{2,5}

Most patients with acromegaly do not have an increase in tumor size during pregnancy.¹⁰ Metabolic complications are also uncommon, and neonatal outcome is largely unaffected.¹⁴ However, pregnancy can exacerbate the disease symptoms, such as headaches, visual disturbances, vascular and metabolic complications, heart disease, diabetes mellitus, and hypertension.²

TREATMENT

There are two different approaches in the treatment of acromegaly – surgical and medical. The decision which to use depends on whether acromegaly was diagnosed before conception, or during pregnancy (Figure 2). Transsphenoidal surgery is the treatment of choice before conception.² There are only two documented cases of transsphenoidal surgery in patients who were already pregnant. In both cases, the diagnosis of acromegaly was made at the last trimester due to visual complaints.⁵

Two major groups of drugs are used in the medical treatment of acromegaly: somatostatin analogs (SA) and dopamine agonists (DA). SA cross the placental barrier, which raises questions about their potential influence on intrauterine and postnatal growth. Current research has yet to confirm the validity of these concerns. A retrospective multicenter study

of 59 pregnancies in 46 women, done by Caron et al. showed that neonates born to women with acromegaly treated with SA are usually of normal size.¹⁹ Mafei et al showed only reversible and mild changes in the maternal-fetal hemodynamic in women exposed to SA.²⁰ Despite the lack of well-controlled studies, the general recommendation is that women planning to get pregnant should discontinue SA therapy 2 to 3 months before conception, depending on their clinical status¹⁰ DA, on the other hand, have been reported to reduce the tumor size and to normalize GH and IGF-1 levels, without increasing the risk of fetal malformations. Further research into the subject matter is necessary to definitely confirm the safety of both drug groups for use in pregnancy.²

CUSHING SYNDROME

Cushing's syndrome (CS) is a disorder caused by prolonged, abnormal exposure to excess glucocorticoids. The most common causes are excessive cortisol-like medication, such as prednisone; pituitary corticotropinomas; or a neoplasm that produces or results in the production of excessive cortisol by the adrenal glands, such as an adrenal adenoma, adrenal carcinoma or an ectopic neuroendocrine corticotropin-secreting tumor. The term "Cushing's disease" refers to Cushing's syndrome caused specifically by a tumor or hyperplasia of the pituitary producing excess ACTH, which stimulates the production and release of excess cortisol. This syndrome was named after famed American neurosurgeon Harvey Cushing, who first described the disease in 1932.²¹

Since Cushing disease is a rare condition there are only few case reports in literature describing pregnant women with it.²²

In non-pregnant women, Cushing's disease is the most frequent endogenous cause of Cushing's syndrome. On the other hand, adrenal adenomas are the most common cause of Cushing's syndrome in pregnant women. In Cushing's disease, high cortisol levels associated with androgens (excess androgen secretion can occur in any form of Cushing's syndrome) can block pituitary gonadotropin secretion, leading to fertility impairment. Cushing's disease in pregnant women presents a considerable diagnostic and therapeutic challenge for the clinician, as it increases the risk of maternal and fetal morbidity.²¹

Pregnancy dramatically affects the hypothalamic-pituitary-adrenal (HPA) axis (Figure 3). In a normal pregnancy, estrogen levels are elevated, leading to an increase in the hepatic production of corticosteroid-binding globulin (CBG), the principal carrier for cortisol in the circulation. These events are the main trigger for an increase in maternal total plasma cortisol and plasma free cortisol. The high concentration of another pregnancy-related hormone, progesterone, has a protective effect - because of its anti-glucocorticoid activity, pregnant women do not develop hypercortisolism despite the hypercortisolaemia. Additionally, the high activity of the enzyme corticosteroid 11beta-dehydrogenase isozyme 2 (11beta-HSD2) in the fetus produces inert forms of glucocorticoids, such as cortisone, protecting the fetus from exposure to maternal cortisol and allowing only 10-20% of cortisol to pass the placental barrier.²

TREATMENT

The aim of both surgical and medical treatment in patients with CS during pregnancy is a reduction in maternal symptoms and neonatal complications.¹² The treatment of choice in patients with Cushing's disease is surgery before conception. The first-line approach for pregnant women with Cushing's syndrome is pituitary or adrenal surgery, ideally between 12th and 29th weeks of gestation.

For those in whom surgery is unsuccessful or contraindicated, the treatment of choice is pharmacotherapy. A general guideline for management is to use drugs that affect adrenal glands. The most commonly used drugs are ketoconazole and metyrapone. Ketoconazole is the safest and most widely used drug for non-pregnant women with CS. This drug inhibits P450 enzymes which have the main role in cortisol synthesis and conversion of 11-deoxycortisol into cortisol. However, in pregnant women with CS, it has been documented to cause uterine growth retardation.²³

Metyrapone is another drug widely used in patients with hypercortisolism during pregnancy. It blocks cortisol synthesis by reversibly inhibiting steroid 11β-hydroxylase. This stimulates ACTH secretion, which in turn increases plasma 11-deoxycortisol levels. This drug has no known association with congenital abnormalities in the fetus, but it has been known to exacerbate hypertension and pre-eclampsia in women.²⁴

The ideal approach would be treatment with drugs that affect the hypothalamus-pituitary axis, but these drugs have to undergo further investigation.²

CLINICALLY NON-FUNCTIONING PITUITARY ADENOMAS

Non-functioning adenomas are not common during pregnancy since the fertility of these patients is usually impaired. Pituitary hyperplasia is defined as a non-neoplastic increase in one or more functionally distinct types of pituitary cells. Lactotroph hyperplasia is induced by elimination of D2 receptor activity due to dopamine's lack of inhibitory effect. This phenomenon, which occurs during all pregnancies, can cause tumor enlargement, pushing the tumor towards the optic chiasm. In these cases the treatment of choice are dopamine agonists, as they relieve the mass effect symptoms. Surgery is reserved for unresponsive cases or cases with tumor apoplexy.^{1,4}

TSH- SECRETING PITUITARY ADENOMAS

To date, there are only three documented cases of pregnant women with TSH-secreting pituitary adenoma, which is not enough for any relevant conclusions to be made.²⁵

CONCLUSION

Ovulation induction, conception, and pregnancy control in all female patients with pituitary tumors, regardless if they are diagnosed before or during pregnancy, present a significant challenge for clinicians. This is especially true since the management of pituitary tumors itself can potentially put the health of both the mother and the fetus at risk.

Therapy with DA in women with prolactinoma usually leads to fertility restoration. Once the woman with prolactinoma is pregnant, further management depends on size of the tumor. While microprolactinomas show low rate of growth during gestation, meaning DA therapy can be discontinued, macroprolactinomas show significant enlargement, implying the necessity for individualized therapy to prevent complications. Surgery is an option in drug-resistant cases.

Treatment of choice in patients with acromegaly depends on whether the tumor is diagnosed before or after conception. In the first scenario, treatment of choice is transphenoidal surgery. In the second scenario, if the tumor is diagnosed during gestation, or the patient is planning to conceive, the general recommendation is that women should discontinue medical therapy with a long-acting SA, as they cross the placental barrier. DA, on the other hand, have been reported to reduce the tumor size and to normalize GH and IGF-1 levels, without increasing the risk of fetal malformations.

Therapy of choice for Cushing disease is surgery before conception. The aim of the procedure is to reduce maternal symptoms and neonatal complications. If CS is diagnosed during gestation, pituitary or adrenal surgery are recommended. In cases where surgery is unsuccessful or contraindicated, medical treatment is an option. The two drugs most commonly used for treating CS are ketoconazole and metyrapone. While ketoconazole is widely used for non-pregnant patients, in pregnant women it can cause uterine growth retardation so it is not recommended. On the other hand, metyrapone is widely used for treating hypercortisolism during pregnancy. In patients with non-functioning pituitary adenomas, where pregnancy is rare, first line therapy is surgery.

Pituitary tumors represent a significant clinical problem for both doctors and patients. They can cause various disturbances, including infertility, loss of libido and psychological disruption, impacting women's lives and health in many aspects. As this article demonstrates, significant effort has been put towards improving the early diagnosis and treatment, allowing these women safe fertility restoration, ovulation induction and pregnancy.

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LIJEČENJE TUMORA HIPOFIZE U TRUDNOĆI

Sažetak

Tumori hipofize čine 10-15% svih intrakranijskih novotvorina. Najčešći tip tumora hipofize su adenomi. Terapijske opcije koje dolaze u obzir kod navedenih tumora su : medikamentozno liječenje, operativni zahvat ili radioterapija. Koji će se oblik liječenja primijeniti ovisi o veličini te o funkcionalnosti odnosno nefunkcionalnosti tumora. Kod bolesnika s prolaktinomima hipofize prva linija liječenja su dopaminski agonisti dok je kod nefunkcionalnih makroadenoma, bolesnika s akromegalijom i Cushingovom bolesti primarni oblik liječenja kirurški zahvat. Kod bolesnika s tumorima hipofize dolazi do deficijencije osi hipotalamus-hipofiza- spolne žlijezde što se kod žena očituje kliničkom slikom amenoreje te smanjenom plodnošću. Razvoj novih metoda liječenja učinio je začecje i trudnoću mogućima ženama s adenomima hipofize.

KLJUČNE RIJEČI: akromegalija, Cushingova bolest, nefunkcionalni tumori hipofize, prolaktinom, trudnoća, tumori hipofize

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