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Pregnancy and Pituitary Diseases

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ABSTRACT

Pregnancy is a period in which the anatomy and physiology of the pituitary gland change significantly. Normal pituitary gland functions are necessary for fertility and the continuation of pregnancy. The presence of a pituitary disease requires management with a multidisciplinary approach to protect the health of the mother and fetus, and it is recommended that these patients become pregnant in a planned manner. Treatment should be considered before pregnancy for pituitary adenomas with a risk of growth. Non-contrast magnetic resonance imaging (MRI) may be performed safely during pregnancy, but the ideal approach is to postpone the MRI until after the birth if possible, and if it is not possible, to take it without contrast. If there are no signs of compression in pituitary adenomas, no treatment is necessary during pregnancy. However, due to increased fetal and maternal morbidity and mortality in Cushing's disease, treatment is necessary even if there is no compression. In the presence of compression findings, dopamine agonists can be used in all types of pituitary adenomas. Surgery may be performed in the second trimester for pituitary adenomas that cause compression unresponsive to medical treatment and for Cushing's disease. In pregnant women with pituitary insufficiency, replacement doses should be adjusted according to the gestational week. The diagnosis and treatment of pituitary diseases in this period is more complex and specific than in the non-pregnant period and require a multidisciplinary approach.

Keywords: Pregnancy, pituitary gland, pituitary hormones, pituitary disease

Introduction

Physiological Changes During Pregnancy

Pregnancy is a period in which endocrine system functions show significant changes. The anatomical and physiological changes occurring in the pituitary gland make the diagnosis and the treatment of pituitary diseases more complex than in the non-pregnant state. As a result of hyperplasia and hypertrophy in lactotroph cells, the size of the pituitary gland may increase up to 40% and 70%, reaching 2-3 times, in the second trimester and third trimester, respectively. The gland height measured in coronal sections of pituitary magnetic resonance imaging (MRI) is a good indicator of pituitary volume. The mean height of the pituitary gland is normally 5-10 mm and may grow up to 12 mm during pregnancy.[1,2] In the first postpartum days, the gland size reaches its maximum and usually returns to its normal size within 6 months after delivery (Figure 1).[3]

As of the eighth week, prolactin (PRL) levels begin to rise and may reach levels of 200-400 ng/mL toward delivery. The increase in PRL levels is necessary for lactation and usually regresses to normal limits around 6 weeks postpartum, even if the mother breastfeeds.[2,4,5] Follicle-stimulating hormone and luteinizing hormone levels begin to decrease as of 6-7 weeks due to high estrogen and progesterone levels and regress to undetectable levels during the second trimester and normalize toward the postpartum first year.[1,6]

The hypothalamopituitary–adrenal axis is activated by placental-derived corticotropin-releasing hormone. Urinary free cortisol, plasma 17-hydroxycorticosteroid, adrenocorticotropic hormone (ACTH), plasma total and free cortisol levels increase as the increased estrogen stimulates the synthesis of corticotropin-binding globulin in the liver. The placental 11B-hydroxysteroid dehydrogenase type 2 enzyme protects the fetus from this maternal hypercortisolemia by converting the active form of cortisol and corticosterone to the inactive forms.[6,7]

Placental growth hormone (GH-V) production begins at the fifth week and peaks up to the 36th-37th weeks. During pregnancy, insulin-like growth factor 1 (IGF-1) production from the liver is increased due to the effect of increased GH-V, and thus pituitary GH secretion is suppressed.[6,8,9]

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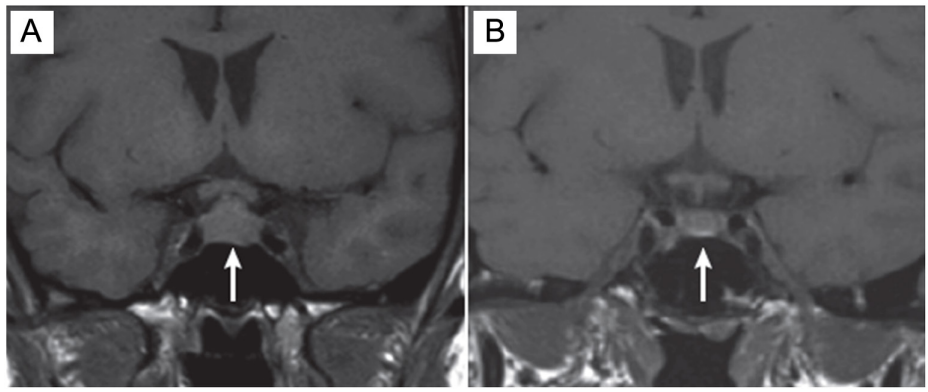

Figure 1. Enlargement of the pituitary gland during pregnancy. Coronal magnetic resonance imaging scans depict the pituitary gland (arrows) of a pregnant woman in the third trimester, and (A) 6 months after delivery (B) Adapted from reference.[3]

Human chorionic gonadotropin, which increases especially during the first trimester, is similar in chemical structure to thyroid-stimulating hormone (TSH) and suppresses TSH levels by binding to TSH receptors, albeit with low affinity. In the following trimester, TSH levels tend to increase and rise to the normal range.[1]

Total thyroid hormone levels increase by up to 50% with the increase in thyroxine binding globulin synthesis from the liver due to increased estrogen levels. Free thyroid hormone levels increase slightly during the first trimester, but then decrease and generally remain within the normal range. However, low serum thyroxine (T4) levels may be seen in the second half of pregnancy due to both physiological changes and analytical problems.[10]

The osmotic threshold, which is decisive in the secretion of arginine vasopressin (AVP), decreases by 10 mosm/kg during pregnancy. Blood volume increases and serum sodium levels decrease by 4-5 meq/L.[11] Arginine vasopressin degradation is increased due to placental vasopressinase production, which can lead to transient diabetes insipidus (DI) during pregnancy. In addition, the existing DI may worsen in the majority of cases.[6]

Pituitary Diseases During Pregnancy

Prolactinoma

Pregnancy can impact prolactinomas in various ways. This includes the potential risk of an existing prolactinoma enlarging due to increased estrogen levels, the additive effect of lactotroph hyperplasia on mass effects, and rebound growth when dopamine agonists (DAs) are discontinued in prolactinomas. The risk of symptomatic enlargement is low in microprolactinomas, medically treated macroprolactinomas, and prolactinomas that have previously undergone surgery or radiotherapy.[12-14]

In routine clinical practice, cabergoline is the preferred DA due to its higher binding affinity to the dopamine receptor type 2, longer half-life, and better tolerance in non-pregnant subjects. While bromocriptine has been traditionally preferred over cabergoline during pregnancy due to its longer history of use and safety data, there is a growing body of evidence supporting the safety and effectiveness of cabergoline during pregnancy.[4,14] Both bromocriptine (in approximately 6000 cases) and cabergoline (in around 1000 cases) have been shown to be safe during the early weeks of pregnancy, with an average of 6 weeks of pregnancy.[14,15]

Although studies have demonstrated that DAs do not increase the risk of conditions like miscarriage, ectopic pregnancy, and congenital malformation, it is still recommended to discontinue their use and reevaluate the situation when pregnancy is confirmed. This recommendation remains unless the patient has an invasive and very large macroadenoma. Despite the absence of data indicating that the use of DAs during pregnancy raises the adverse events in the fetus, it is important to note that studies in this area are limited.[4,12]

A study involving 230 pregnant women with prolactinoma showed that continuation of bromocriptine during pregnancy did not increase the risk of embryological malformations.[16]

In a study, 83 pregnancies in 60 patients with prolactinoma were analyzed, of which 78 had used DAs at the time of conception. After confirmation of pregnancy, medical treatment was used in 14 cases, 3 of which were due to adenoma growth and 11 due to a high risk of adenoma growth, and in 11 of them, bromocriptine was used, and in 3 of them, cabergoline was used. There was no difference in terms of pregnancy complications between patients who discontinued and those who did not discontinue treatment, as well as between patients receiving bromocriptine and cabergoline.[13]

Studies have also monitored children whose mothers used DA during pregnancy for an extended period. Among 64 children whose mothers used bromocriptine and were followed up for 6 months to 9 years, no anomalies were observed.[17] Similarly, among 83 children

MAIN POINTS

- The management of pituitary diseases in pregnant individuals requires special considerations and they are advised to plan their pregnancies carefully.
- Before planning a pregnancy, it is necessary to plan treatment for pituitary adenomas that may grow or have a negative impact.
- For pituitary adenomas, there is no need for specific treatment unless compressive signs or clinically severe Cushing's disease occurs.
- Dopamine agonists may be used to alleviate compression due to their direct effects on tumors and lactotroph hyperplasia exaggerating compression in various types of pituitary adenomas.
- Hypopituitarism needs special considerations, such as adjustment of hormone replacement, taking into account the physiological changes.

whose mothers used cabergoline and were followed for 3 months to 6.5 years, no anomalies were found.[18] There were a few instances of mild issues, such as verbal fluency retardation, difficulty in bladder control, seizures, and pervasive developmental disorders in children whose mothers used cabergoline during gestation.[19]

For women with prolactinoma planning pregnancy, it is advisable to perform an MRI to assess the pituitary adenoma's status before conception. The risk of adenoma growth during pregnancy is lower in patients who have been using DA for more than a year before becoming pregnant. However, routine MRI procedures are not recommended during pregnancy unless the patient experiences symptoms.[13,20]

Surgical intervention may be considered if there is a pregnancy plan in case of unresponsiveness and intolerance to medical treatment, adenoma growth despite treatment, and macroadenoma with a risk of growth. Although it is known that surgery may slightly increase the risk of iatrogenic pituitary hormone deficiency and infertility, preservation of pituitary functions was observed in more than 90% of patients.[21]

In planned pregnancies, discontinuation of DAs before pregnancy is recommended, unless there are specific reasons necessitating their use during pregnancy (Figure 2). If patients with microadenomas become pregnant while on treatment, DAs should be discontinued, and the patients should be closely monitored with monthly check-ups. If symptoms such as headaches and visual disturbances arise, a non-contrast MRI can be performed. DAs may be resumed if there are indications of compression on MRI or a significant increase in the adenoma's size.[4,9,20]

The treatment and monitoring of macroadenomas during pregnancy should be tailored to each patient's specific situation in unplanned pregnancies. In cases of macroprolactinomas with intrasellar localization and no compression of the optic chiasm, it may be considered to discontinue DAs during pregnancy. However, these patients should undergo close clinical follow-ups, with visual field assessments every trimester. For patients with larger macroadenomas, those with suprasellar extension, and those where the adenoma is in close proximity to the optic chiasm, it is advisable to continue DAs. The goal is to ensure the safety of both the mother and the fetus while effectively managing the macroadenoma.[4,9,20] In recent years, the use of cabergoline during pregnancy has increased significantly in our clinical practice. If a patient with a prolactinoma exhibits signs of adenoma compression and does not respond to medical treatments, surgical intervention may be considered. This could be done during the second trimester of pregnancy, or if the fetus has reached a sufficient level of development, planning for delivery may also be considered as part of the treatment strategy.

Monitoring PRL levels during pregnancy has limited benefits. This is because not every tumor growth is necessarily accompanied by an increase in PRL levels, and conversely, not every increase in PRL levels indicates adenoma growth. Furthermore, discontinuation of DAs will also result in increased PRL levels. If there is a sudden and significant

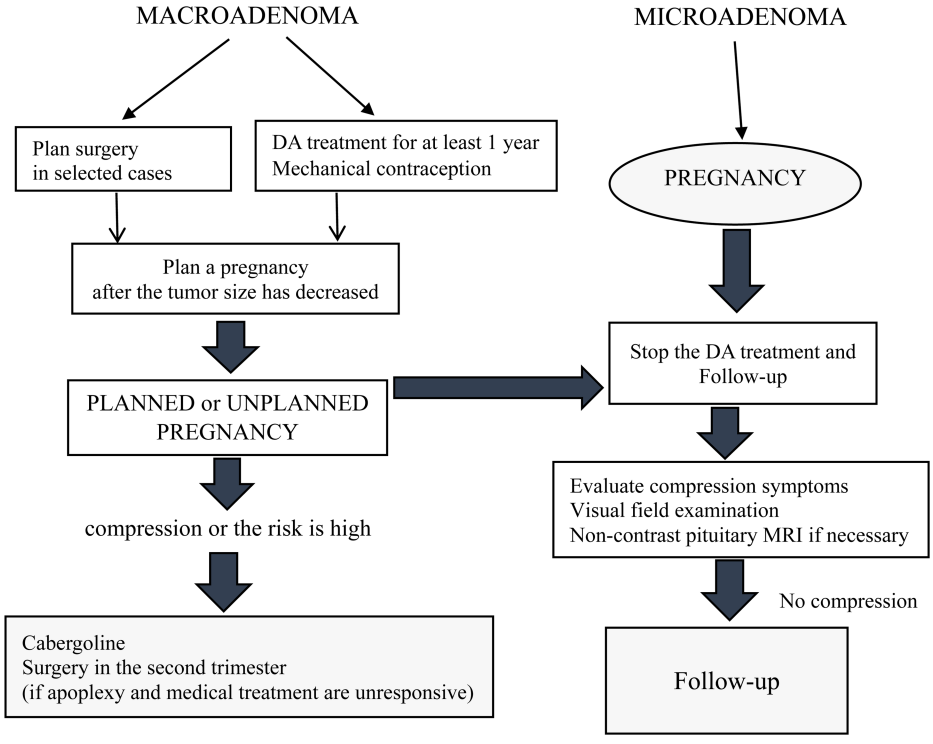

Figure 2. Approach to the patients with prolactinoma planning pregnancy and during pregnancy. Dopamine agonist (DA) treatment should be discontinued as soon as pregnancy is confirmed. During pregnancy, quarterly clinical follow-ups should be conducted to assess compression symptoms. If necessary, peripheral visual field testing and non-contrast pituitary MRI can be planned. For patients with macroadenomas planning pregnancy, it is necessary to reduce the adenoma with at least 1 year of DA treatment, and mechanical contraception should be used. In cases resistant to medical treatment, pituitary surgery can be considered. In unplanned pregnancies, cabergoline treatment can be initiated, and in cases with resistant/progressive neuroophthalmological symptoms, pituitary surgery in the second trimester may be considered. MRI, magnetic resonance imaging.

decrease in PRL levels along with symptoms of mass effect, it may be an indicator of apoplexy.[4]

While breastfeeding can increase PRL levels, there have been no adverse effects observed on tumor growth and recurrence. PRL levels should be assessed after discontinuation of breastfeeding or 2 months postpartum for non-breastfeeding individuals. However, patients with uncontrolled macroadenomas threatening the visual field can be managed with DA treatment, even if breastfeeding is not possible.[14,20]

The follow-up of prolactinoma during pregnancy and in patients planning pregnancy should be tailored to individual circumstances. Typically, the process is relatively uncomplicated for patients with microadenomas, but it is crucial to conduct pre-pregnancy evaluations and minimize risks for patients with macroadenomas.

Acromegaly

For women with acromegaly, several factors are crucial when planning pregnancy. These include ensuring that the disease is well-controlled before conception, considering previous and current treatments, and evaluating the pituitary hormone reserve. Ideally, pregnancy should be planned when the acromegaly is completely under control, and the patient is not on medication. Uncontrolled acromegaly, with excess GH and IGF-1, can lead to metabolic complications such as obesity, hyperglycemia, preeclampsia, preterm birth, intrauterine fetal growth retardation, and macrosomia. Cardiac involvement, such as hypertension and hypertrophic cardiomyopathy, can theoretically be observed in uncontrolled patients. These complications have rarely been rarely evaluated in the literature.[22,23] It is important to manage the disease effectively to reduce these risks during pregnancy.

No adverse effect of pregnancy on the course of acromegaly has been demonstrated. However, cases with different courses such as tumor growth, stable course, and improvement during pregnancy has been reported.[22] Fifty-nine pregnancies of 46 acromegalic women were evaluated, and enlargement of the existing adenoma was detected in 4 patients.[24]

The IGF-1 levels may decrease during the first trimester in acromegalic women. With the dominance of GH-V during the second trimester, IGF-1 levels tend to increase, and pituitary GH is suppressed. Cross-reaction between placental and pituitary GH in many GH assays can lead to incorrect measurements of GH, suggesting either high or low GH levels. However, this issue can be avoided by using assays that are ultrasensitive to pituitary GH.[22,25]

In pregnancy, given that the diagnosis of acromegaly does not require treatment as long as there are no mass effect, diagnostic tests can be postponed until delivery, taking into consideration the limitations of these tests. Routine follow-up of GH and IGF-1 levels during pregnancy is not recommended in acromegalic women either.[22,26]

In unplanned pregnancies in acromegalic women without signs of tumor compression, it is advisable to discontinue medical treatments including somatostatin analogs (SAs), pegvisomant, and DAs and monitor the patient clinically. If pregnancy is planned, it is recommended to stop SAs 2 months before conception and pegvisomant 1 month before pregnancy. If severe headaches and visual field impairments occur during pregnancy, a non-contrast MRI should be scheduled. In cases of significant adenoma growth, medical and surgical treatment options may be considered.[27]

The most significant concern associated with SA use during pregnancy is the potential for adverse effects on fetal growth, which have been reported in some cases. According to the U.S. Food and Drug Administration (FDA) classifications, lanreotide is categorized as class C, and octreotide is categorized as class B for pregnancy. Animal studies involving lanreotide have demonstrated adverse effects, including reduced fetal weight. It is crucial to weigh the potential risks and benefits of SA use during pregnancy on an individual basis and under the guidance of a health-care professional. Safety data concerning these medications during pregnancy is still limited, and further research is needed to gain a better understanding of their effects on fetal development.[22,26,28]

In a study, 21 pregnancies of 19 acromegalic patients were examined. Three patients received medical treatment after pregnancy confirmation. One patient received cabergoline and octreotide-LAR until the sixth week and then continued with bromocriptine until delivery. Another patient used bromocriptine throughout pregnancy, and the last patient received cabergoline and lanreotide-LAR until the eighth week, and cabergoline was resumed at the 32nd week due to headaches. One newborn had unilateral congenital cataract, craniosynostosis, and microcephaly; 4 had preterm birth; 2 had macrosomia, and 2 had low birth weight. Of the 21 pregnancies, 7 occurred without medical treatment for acromegaly, while 14 occurred under medical treatment, and there was no difference in terms of birth problems and miscarriage rates among these patients.[13]

There are limited case reports available regarding the use of pegvisomant, which is a GH receptor antagonist, during pregnancy. It has been noted that placental passage of pegvisomant is either minimal or absent. Despite being categorized as FDA class B, which suggests no known risk during pregnancy based on animal studies, pegvisomant is generally not recommended for use during pregnancy. This is due to the limited data and experience with its use in pregnant individuals, and it is typically reserved for very exceptional cases.[22,24,28] The recommendations for approach to acromegalic patients planning pregnancy and during pregnancy were shown in Figure 3.

Cushing's Disease

More than 80% of Cushing's syndrome (CS) patients are women, with the majority in their reproductive years. The occurrence of pregnancy is rare due to the significantly increased risk of infertility. In the available literature, approximately 200 cases of CS during pregnancy have been documented, with the majority of them originating from the adrenal glands.[6,29] Although CS can pose significant risks to both the mother and the fetus, the fetus may be partially protected from hypercortisolemia through the inactivation of active glucocorticoids by placental (11β-HSD type 2).[6,7]

After achieving full biochemical remission in women with CS, pregnancy planning can be considered.[30] The disease may worsen during pregnancy and the postpartum period. Additionally, there have been reported cases that developed during pregnancy and normalized after delivery.[6,8]

During pregnancy, certain physiological conditions such as hypertension, hyperglycemia, weight gain, striae, and mood changes can sometimes mask the symptoms of CS. However, symptoms such as severe acne and hirsutism, easy bruising, larger and more pronounced purple striae, muscle weakness, and hypokalemia should raise a higher level of suspicion for the presence of CS.[29,30]

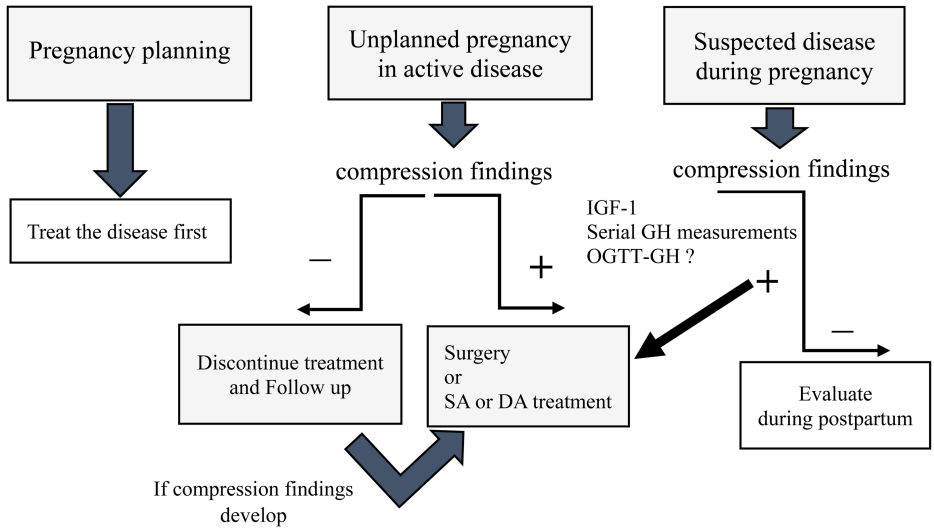

Figure 3. Approach to the acromegalic patients planning pregnancy and during pregnancy. In acromegalic patients planning pregnancy, the disease should ideally be in remission. In cases of active disease during an unplanned pregnancy without signs of compression, treatment should be discontinued. However, if there are signs of compression, pituitary surgery, somatostatin analog, or dopamine agonist treatment should be considered. If there are no signs of compression in cases of suspected acromegaly during pregnancy, the diagnosis should be postponed to the postpartum period. If signs of compression are present, diagnostic parameters are challenging.

Early diagnosis and treatment of CS during pregnancy is crucial due to its high-risk obstetric nature. It is important to note that there is no single biochemical parameter that can definitively and easily diagnose CS during pregnancy. Interpreting the dexamethasone suppression test during pregnancy is challenging due to high cortisol levels in pregnant individuals. Reduced cortisol suppression with dexamethasone can lead to false-positive results. While the 24-hour urinary free cortisol level remains relatively stable during the first trimester of a normal pregnancy, it can increase up to 2 times the baseline in the second and third trimesters. Elevated levels exceeding 3 times the upper limit of the normal range serve as the most reliable markers for diagnosing CS during pregnancy (Figure 4).[6,29,30]

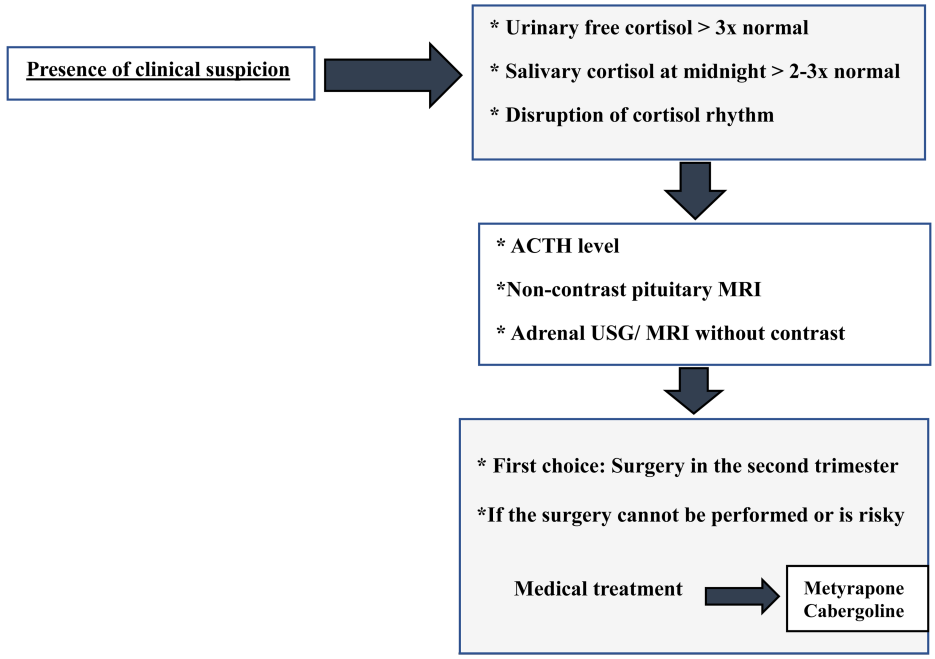

Figure 4. The approach to Cushing's syndrome during pregnancy. In the clinical suspicion of Cushing's syndrome during pregnancy, the following criteria are significant for diagnosis: Urinary free cortisol >3 times the normal level, midnight salivary cortisol >2-3 times the normal level, and disruption of cortisol rhythm. Adrenocorticotropic hormone levels, non-contrast pituitary magnetic resonance imaging (MRI), and adrenal ultrasound/non-contrast MRI can provide insights for the differential diagnosis. The initial choice for treatment is surgery in the second trimester. However, if it is risky or cannot be performed, metyrapone and/or cabergoline can be used.

Midnight salivary cortisol levels in pregnant women are similar to those of non-pregnant women. However, they decrease in the postpartum period compared to the last period of pregnancy.[29] An increase in midnight salivary cortisol levels of 2-3 times the upper reference levels can be used as a reliable marker for CS during pregnancy.[30] A serum midnight cortisol level above 5-7.5 µg/dL may also be significant for CS.[6,8]

If clinical suspicion is high, diagnostic tests should be promptly conducted to address fetal and maternal complications sooner. It is important to note that the absence of ACTH suppression does not exclude adrenal CS. For adrenal gland assessment, ultrasound and non-contrast MRI should be considered. MRI can be safely used for pituitary evaluation, especially in the second and third trimesters. However, the utility of non-contrast pituitary MRI is limited.[30,31]

The treatment of CS during pregnancy is crucial but challenging. Mild cases may be managed conservatively with close monitoring and addressing comorbidities. In cases of non-mild disease, surgical treatment can be considered in the second trimester if the ACTH-secreting pituitary adenoma is localized. Successful surgeries can result in high live birth rates, reaching up to 87%. Adequate management of adrenal insufficiency treatment is necessary for patients undergoing surgery, and dose escalation of hydrocortisone may be required in the third trimester.[29,30] In cases of severe CS, medical treatment should be considered if surgery is not feasible or poses a significant risk.[6]

A limited number of cases related to the medical treatment of CS during pregnancy has been reported in the literature. The primary treatment objective should be to maintain the urinary cortisol level close to the upper limit.[29,31]

Metyrapone is a drug that inhibits the 11 beta-hydroxylase enzyme with an increased risk of hypertension and preeclampsia and suppression of fetal adrenal steroid synthesis as it crosses the placenta.[29,30]

Ketoconazole is an anti-steroidogenic drug that has demonstrated its ability to control hypercortisolemia during pregnancy in a small number of cases. It crosses the placenta and is categorized as class C by the FDA during pregnancy. It carries the potential for teratogenic effects and an increased risk of miscarriage. Due to its antiandrogenic properties, it may lead to feminization of a male fetus. Close monitoring for maternal hepatotoxicity is necessary, and it may be considered with careful follow-up in patients who cannot undergo surgery and cannot tolerate metyrapone.[29,30]

Mitotane is teratogenic, and its use during pregnancy is contraindicated. There is insufficient information available regarding the use of pasireotide during pregnancy.[30]

Cabergoline may serve as an alternative medication and is generally considered a safe option during pregnancy. Dopamine 2 receptors have been identified in 80% of corticotrophic pituitary adenomas. There have been reported cases of pregnant individuals who initiated cabergoline at 3.5 mg/week and were successfully treated with a maintenance dose of 2 mg/week without major adverse effects.[30,32]

Bilateral adrenalectomy may be considered as the last resort for patients with a severe, uncontrolled, and aggressive course of CD during pregnancy.[9]

Other Pituitary Adenomas

Non-functional pituitary adenomas are relatively less common during pregnancy. This is primarily because most of them are microadenomas and remain asymptomatic during pregnancy. Furthermore, infertility issues may arise in patients with macroadenomas due to mass compression, surgical interventions, and radiation therapy-related hypogonadism. In cases of infertility, when pregnancy is desired, surgical intervention may be necessary to alleviate the hypogonadism resulting from mass compression.[33]

Non-functioning pituitary adenomas may rarely enlarge and cause compression during pregnancy, primarily due to lactotroph cell hyperplasia. Occasionally, pituitary apoplexy accompanied by visual impairment may serve as the initial sign of a pituitary adenoma during pregnancy.[2] Therefore, patients with pituitary adenomas should be closely monitored for the risk of apoplexy during pregnancy. If there are progressive symptoms and signs related to optic chiasm compression during follow-up, surgical intervention in the second trimester is often the most effective treatment method. In the third trimester, a more conservative approach is generally more appropriate.[1] DAs can effectively reduce physiological lactotroph hyperplasia and may alleviate optic chiasm compression. However, in cases of severe apoplexy characterized by progressive visual impairment unresponsive to DA, surgery is the most effective option.[7,13]

Thyroid-stimulating hormone-secreting adenomas (TSHoma) are very rare, and information on TSHoma during pregnancy is scarce, primarily relying on a few case reports.[1,34] Based on these cases, pregnancy is not contraindicated, but the risk of infertility has increased. If SAs are used, pregnancy should be discontinued upon detection, and it should not be resumed unless the tumor has progressed. Depending on the tumor progression and symptom status, SAs and/or DAs may be considered. Maintaining euthyroidism is crucial for both the mother and fetus, and anti-thyroid drugs may be preferred in this regard, as long as there are no signs of compression.[7,34,35]

Gonadotropin-secreting adenomas are very rare during the reproductive period and can lead to ovarian hyperstimulation syndrome, posing a risk of infertility. Since dopamine type 2 receptors are detected, pregnancy may be achieved with DAs treatment.[36]

Pituitary Apoplexy

Pituitary apoplexy is a sudden-onset medical emergency characterized by hemorrhage or infarction in pituitary tumors and, more rarely, in normal gland tissue. It can often present as the initial manifestation of an unknown pituitary adenoma in 80% of cases. During pregnancy, the enlarged pituitary gland increases the pressure in the sella turcica and exerts pressure on the surrounding structures. Vascular structures in the pituitary region become more vulnerable, and ischemic necrosis with or without hemorrhage can occur. Pituitary apoplexy is more common in cases of macroadenomas and non-functioning adenomas.[37]

The most common complaint among pregnant women is a sudden and severe headache, occurring in 81% of patients. Apoplexy can lead to symptoms such as visual loss, ophthalmoplegia, and hypopituitarism. To make a diagnosis, a non-contrast pituitary MRI should be arranged, and blood tests should be conducted to assess the anterior pituitary hormone panel.[37,38]

In some cases, pituitary apoplexy may be self-limiting. There are 2 primary approaches to managing pituitary apoplexy. The conservative

approach involves close monitoring, hormone replacement for deficiencies, and the use of DA treatment. The alternative approach is surgical decompression. Surgical intervention should be considered within a multidisciplinary framework when the condition progresses toward a deterioration in consciousness and the development of severe and progressive neuro-ophthalmological deficits.[37,38]

Hypopituitarism

Patients with hypopituitarism have a lower likelihood of ovulatory cycles and pregnancy compared to those with isolated hypogonadotropic hypogonadism. They also face a higher risk of miscarriage. However, with appropriate hormone replacement therapy, spontaneous pregnancy is possible. The reported pregnancy rate in these patients is 47%, with a delivery rate of 42%.[39] However, ovulation induction and/or assisted reproductive techniques may often be required. Some pregnancy complications, including miscarriage, anemia, gestational hypertension, premature birth, and postpartum hemorrhage, are more common.[9]

Central Adrenal Insufficiency

The diagnosis of adrenal insufficiency may be missed because nausea, weakness, and mild hyponatremia can be observed as physiological symptoms during pregnancy. Morning salivary cortisol levels have been shown to remain relatively stable and can be a valuable factor in the diagnosis during pregnancy. A morning basal cortisol level below 3 µg/dL is diagnostic. When basal hormone levels are not diagnostic, the ACTH stimulation test can be performed, but carefully interpreted keeping in mind that pregnancy is associated with higher cortisol levels. Peak cortisol levels above 30 µg/dL during the 250 µg ACTH stimulation test can rule out adrenal insufficiency, while peak cortisol levels above 18-20 µg/dL during the test using 1 µg ACTH may be considered sufficient. However, the insulin tolerance test and metyrapone test are contraindicated during pregnancy due to the potential risks to both the fetus and the mother.[6,9]

Hydrocortisone is typically the preferred treatment for adrenal insufficiency during pregnancy. Another option may be prednisolone, but dexamethasone should be avoided since it is not inactivated by the placenta. The dose of hydrocortisone should be individualized, typically ranging from 12-15 mg/m^2/day. Lower doses may suffice for central adrenal insufficiency compared to primary insufficiency. Dose requirements may increase during the second and third trimesters of pregnancy, and the appropriate dose should be adjusted based on clinical findings, with an increase if necessary. Patients and their families should be informed about the symptoms and signs of adrenal crisis. During delivery, similar to major surgical procedures, parenteral hydrocortisone should be administered and continued until the patient can resume oral medication.[9,39]

Central Hypothyroidism

Thyroid hormones are crucial for fetal development, and as a result, the mother's thyroid hormone requirement increases during pregnancy. In cases of secondary hypothyroidism, when pregnancy is detected, the current dose should be increased by 20%-50%, and the appropriate dose should be maintained with follow-up appointments every 4-6 weeks. Many laboratory kits provide trimester-specific ranges for TSH and free T4 levels. The treatment goal within these specified ranges is to adjust the dose to keep the free T4 level in the upper half of the normal range. If these ranges are not available, total T4 levels can also be monitored. Since total T4 levels increase by 50% during pregnancy, the treatment objective is to maintain the total T4 level between the upper limit of the reference range and 1.5 times that upper limit. After delivery, the dose should be returned to pre-pregnancy doses.[1,39]

Growth Hormone Deficiency

If pregnancy does not occur despite the use of other hormone replacement therapies and assisted reproductive techniques, positive effects have been demonstrated in several cases of hypopituitarism by adding GH treatment. The typical approach is to discontinue GH treatment once pregnancy is achieved. However, if treatment is to be continued, it should be limited to the first trimester. This limitation is due to the fact that after the 20th week of pregnancy, GH-V typically provides the necessary effects, rendering additional GH treatment unnecessary. Further prospective studies are necessary to assess the safety of GH treatment in pregnant women, considering both the well-being of the mother and the fetus.[36,39]

Diabetes Insipidus

The most prevalent cause of DI during pregnancy is gestational DI, which is also referred to as transient DI of pregnancy. This condition is characterized by an increased secretion of placental vasopressinase and the degradation of AVP by the seventh week of pregnancy. The secretion of vasopressinase reaches its peak during the second and third trimesters and is gradually eliminated from the maternal circulation within 4-6 weeks after childbirth. It is more frequently observed in multiple pregnancies, and its occurrence is directly correlated with the size of the placental mass.[40]

While gestational DI is primarily observed during the second and third trimesters of pregnancy, central DI can potentially manifest in earlier weeks. In patients without a prior DI diagnosis, making a differential diagnosis can be challenging. It is important to note that gestational DI typically resolves within 4-6 weeks after delivery. When central DI is suspected, especially in cases involving factors like a compressing mass, bleeding, or trauma, a non-contrast pituitary MRI may be recommended. The absence of the normal hyperintense signal in the posterior pituitary on T1-weighted MRI sequences can be indicative of central DI. However, it is worth considering that the hyperintense signal in the posterior pituitary can naturally disappear during the course of a normal pregnancy.[40,41]

The diagnosis of DI is primarily established through clinical assessment and laboratory tests. Water restriction testing is generally not recommended due to the potential risks of dehydration, hypernatremia, and uteroplacental insufficiency for both the fetus and the mother. Hypertonic saline infusion tests and desmopressin challenge tests can be utilized in the differential diagnosis of DI. A urinary osmolality increase of less than 50% following desmopressin administration helps differentiate nephrogenic DI from other conditions. Measurements of copeptin and apelin can be useful in the differential diagnosis of DI during gestation.[41,42]

Desmopressin, the synthetic form of vasopressin, is more resistant to degradation by vasopressinase and is used in the treatment of central and gestational DI. While the nasal form is commonly preferred, other treatment options include subcutaneous, intravenous, oral, and sublingual administration. The primary goal of treatment is to increase patient comfort by reducing nighttime urination frequency and maintaining daily urine output at around 2-3 L. In cases of known DI, an increase in pre-pregnancy doses may be necessary. Mild cases can be managed by replacing fluid loss.

Desmopressin is considered safe during pregnancy, and its uterotonic effect on the uterus is minimal. Standard treatment doses typically range from 1-2 µg subcutaneously or intravenously 1-2 times a day, 5-20 µg nasally 2-3 times a day, and 60-120 µg sublingually 2-3 times a day (as 10 µg per each nasal puff), although higher doses may be required. To prevent water overload, patients should only drink water when they are thirsty. It may also be advisable to skip a dose once a week to achieve fluid balance. Throughout the treatment, intermittent monitoring of serum sodium levels, serum and urine osmolality, fluid intake, and urine output is essential. Urine osmolarity should be maintained within the range of 400-800 mOsm/kg.[40-42]

Patients with central DI may generally revert to their pre-pregnancy treatment doses after childbirth. In the case of gestational DI, the need for treatment typically diminishes within 4-6 weeks following delivery. Desmopressin is excreted in very small amounts in breast milk, and it is considered safe during breastfeeding since the quantity passed to the infant is not significant.[40]

Sheehan's syndrome

Sheehan's syndrome is a condition characterized by varying degrees of dysfunction in the anterior, and rarely posterior, pituitary gland. It arises from ischemic necrosis of the pituitary gland, typically caused by severe postpartum uterine bleeding and hypovolemia. The incidence of Sheehan's syndrome has been gradually decreasing with the advancement of modern obstetric practices. The average age at diagnosis is relatively high, around 52.8 years. The pituitary gland, which enlarges during pregnancy and experiences increased blood demand, becomes more vulnerable to postpartum hypovolemia. However, not every patient with Sheehan's syndrome experiences postpartum hemorrhage, and the exact cause of this condition is not entirely understood. Some autoimmune and genetic factors have been proposed as potential causes. Given that the pituitary gland lacks the capacity to regenerate after damage, the consequences of this damage are typically permanent. Following the initial pituitary infarction, a slowly progressive pituitary dysfunction occurs.[3,43]

It exhibits a clinical spectrum ranging from isolated hypopituitarism to panhypopituitarism. The etiology of hypopituitarism has been evaluated in a multicenter etiology study in Turkey, and Sheehan's syndrome has been identified as the most common etiological factor among non-tumoral causes in women.[44] While it can present with a mild clinical course in some cases, a potentially life-threatening course may occur if early diagnosis is not achieved. The most common hormone deficiencies are in GH and PRL, while the thyroid and ACTH axes are less frequently affected. In rarer cases, DI may develop as a result of involvement of the posterior pituitary.[45] It can also manifest as acute hypopituitarism during the postpartum period.[46] It is crucial to differentiate Sheehan's syndrome from other conditions that can lead to hypopituitarism, especially considering lymphocytic hypophysitis in the postpartum period. Treatment primarily involves hormone replacement to address hormone deficiencies. Hormone replacement therapy does not correct pituitary dysfunction or prevent its progression, but it does reduce patient morbidity and mortality.[8] Successful pregnancies can occur in individuals with Sheehan's syndrome-associated hypopituitarism through hormonal replacement therapy and the utilization of assisted reproductive techniques, and although rare, the potential for pregnancy is possible.[47,48] Unlike other causes of hypopituitarism, panhypopituitarism is more common in Sheehan's syndrome, and GH deficiency tends to be more severe.[49] Growth hormone replacement therapy has been shown to enhance the quality of life for patients with Sheehan's syndrome.[3,8]

Conclusion

Pregnancy is a period during which the anatomy and physiology of the pituitary gland undergo significant changes. As a result, the management of pituitary diseases in pregnant individuals requires special considerations. Typically, patients with pituitary diseases are advised to plan their pregnancies carefully. Before planning pregnancy, it is essential to assess and consider treatment options for pituitary adenomas that may grow during pregnancy or negatively impact the pregnancy process. For pituitary adenomas, there is no need for specific treatment unless compressive signs or clinically severe CD occurs. Dopamine agonists may be used to alleviate compression due to their direct effects on tumors and lactotroph hyperplasia exaggerating compression in various types of pituitary adenomas. Surgical intervention is reserved for cases that do not respond to medical treatment and cause compression, or for cases of severe CD preferably during the second trimester of pregnancy. Hypopituitarism also needs special considerations, such as adjustment of hormone replacement, taking into account the physiological changes. The presence of a pituitary disease during pregnancy necessitates a multidisciplinary approach to ensure the well-being of both the mother and fetus.

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