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Adrenal Disorders in Pregnancy. A Comprehensive Review and Prospects for Future Research

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Abstract:

Introduction and purpose: Adrenal disorders cover a spectrum of conditions, including adrenal insufficiency, Cushing's syndrome and others. Each disorder has its own implications for pregnancy and requires an individualised approach. This review aims to provide a comprehensive overview of adrenal disorders during pregnancy, such as endogenous Cushing's syndrome, adrenal insufficiency, primary aldosteronism, and pheochromocytoma.

Brief description of the state of knowledge: During pregnancy, a number of adaptive processes take place in a woman's body including changes in the endocrine system. Given all these changes, adrenal diseases pose both diagnostic and therapeutic challenges. The symptoms of adrenal diseases often overlap with those observed during physiological pregnancy. Adrenal disorders during pregnancy if unrecognised or treated inadequately, can lead to negative consequences for the mother and foetus, indicating the importance of awareness of these conditions among physicians.

Conclusions: Treating and diagnosing adrenal diseases during pregnancy is a major challenge for doctors. It is crucial to diagnose adrenal diseases in pregnant women as early as possible, and to meticulously plan pregnancies for women diagnosed before conception to prevent the negative consequences of untreated adrenal disorders. Optimal control of treatment before conception should be sought. Access to specialised centres with multidisciplinary teams experienced in treating these conditions is crucial for optimal maternal and foetal care.

Keywords: Pregnancy; Cushing's syndrome; Adrenal insufficiency; Primary aldosteronism; Pheochromocytoma.

Introduction and purpose

Pregnancy is a unique physiological state characterised by multidirectional adaptive changes that are designed to adapt a woman's body to a pregnancy. Among these changes, there are

also changes in the endocrine system, which are crucial to the proper development of pregnancy. Taking all of these changes into account, adrenal diseases present both diagnostic and therapeutic challenges. Signs and symptoms of the adrenal diseases often overlap those presented in the physiological pregnancy. Adrenal disorders during pregnancy are relatively rare conditions. However, undiagnosed or treated inadequately may lead to negative maternal and foetal outcomes which indicates the importance of awareness of those conditions among physicians. Adrenal disorders cover a spectrum of conditions, including adrenal insufficiency, hypercortisolism (Cushing's syndrome) and others. Each disorder has its own implications for pregnancy and requires a customised approach taking into consideration the impact on maternal health, foetal development and perinatal outcomes. For better understanding of those conditions it is necessary to familiarise with the physiological changes that occur in the endocrine system during pregnancy. This review aims to provide a comprehensive overview of adrenal disorders during pregnancy such as endogenous Cushing's syndrome, adrenal insufficiency, primary aldosteronism, pheochromocytoma. This review also aims to increase understanding, promote a multidisciplinary approach, and improve the clinical management and outcomes of pregnant women affected by adrenal disorders.

Physiology of the endocrine changes during pregnancy.

A pregnant woman's body adapts to pregnancy through a series of adaptive changes including changes in the endocrine system. Among the various pathways being modified, dynamic changes occur in the hypothalamic-pituitary-adrenal (HPA) axis and mineralocorticoid production during pregnancy. Awareness of these complex hormonal adaptations is key to elucidating their impact on maternal health, foetal development and overall pregnancy outcomes as well as understanding pregnancy-related endocrine disorders.

Key alterations within the HPA axis include increased Corticotropin-Releasing Hormone (CRH) production leading to hypercortisolemia that is observed during physiological pregnancy [1]. The secretion of cortisol from the adrenal glands is regulated by central negative feedback mechanisms which helps maintain homeostasis. During pregnancy, the concentration of CRH in the blood increases significantly, especially in the second and third trimesters. Placental CRH stimulates the maternal pituitary to produce adrenocorticotropic hormone (ACTH) consequently stimulates the adrenal glands, leading to increased cortisol production. This cascade is further amplified as rising cortisol levels can stimulate additional

placental CRH production, creating a positive feedback loop. Maternal cortisol levels surge dramatically throughout gestation, reaching approximately threefold higher levels compared to non-pregnant states by the third trimester. This increase in cortisol is attributed partly to the stimulation of corticosteroid-binding globulin by oestrogen, leading to elevated free cortisol levels [2]. The passage of cortisol through the placenta is partially inhibited by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 which converts cortisol to inactive cortisone. This enzyme activity protects the foetus from excessive exposure to maternal cortisol [1]. However, glucocorticoid overexposure, even with this inhibition, can still have adverse sequelae for the developing foetus, highlighting the delicate balance of hormonal regulation during pregnancy and its potential impact on foetal development [3]. Those processes are presented in Figure 1.

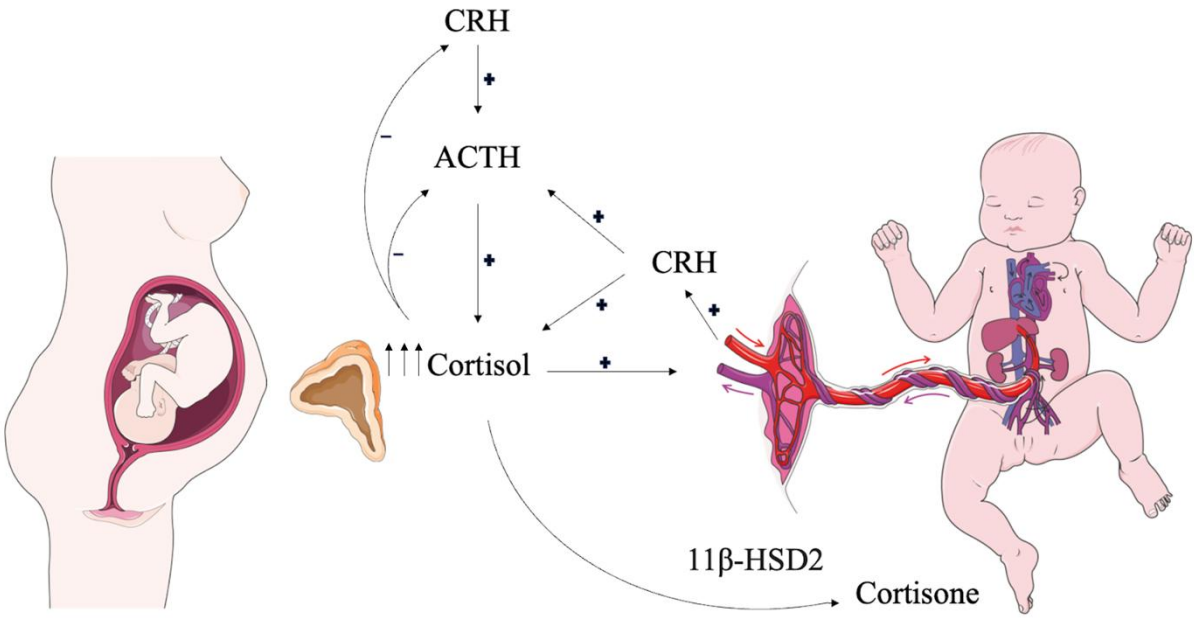

Figure 1. Alterations within the hypothalamic-pituitary-adrenal axis during pregnancy.
CRH - corticotropin-releasing hormone
ACTH - adrenocorticotropic hormone
11β-HSD2 - 11 β-hydroxysteroid dehydrogenase type 2
The figure was created using medical images from https://smart.servier.com/

During pregnancy, the renin-angiotensin-aldosterone system (RAAS) undergoes significant changes to adapt to the physiological changes associated with pregnancy. The RAAS plays a role in regulating blood pressure, electrolyte balance and fluid volume in the body to ensure

adequate perfusion. Estrogens, produced mainly by the developing placenta, stimulate hepatic synthesis of angiotensinogen, and there is also a sharp increase in plasma renin concentration and activity. The above changes lead to elevated levels of angiotensin II, stimulating aldosterone production in the glomerular zone of the adrenal glands [4, 5]. Despite a tenfold increase in aldosterone levels, pregnant women usually do not show symptoms of hyperaldosteronism due to the antagonistic effect of progesterone on mineralocorticoid receptors and potential vascular resistance to angiotensin II. However, the mechanisms that allow most women to remain normotensive among these hormonal fluctuations remain elusive [6, 7]. Those processes are presented in Figure 2.

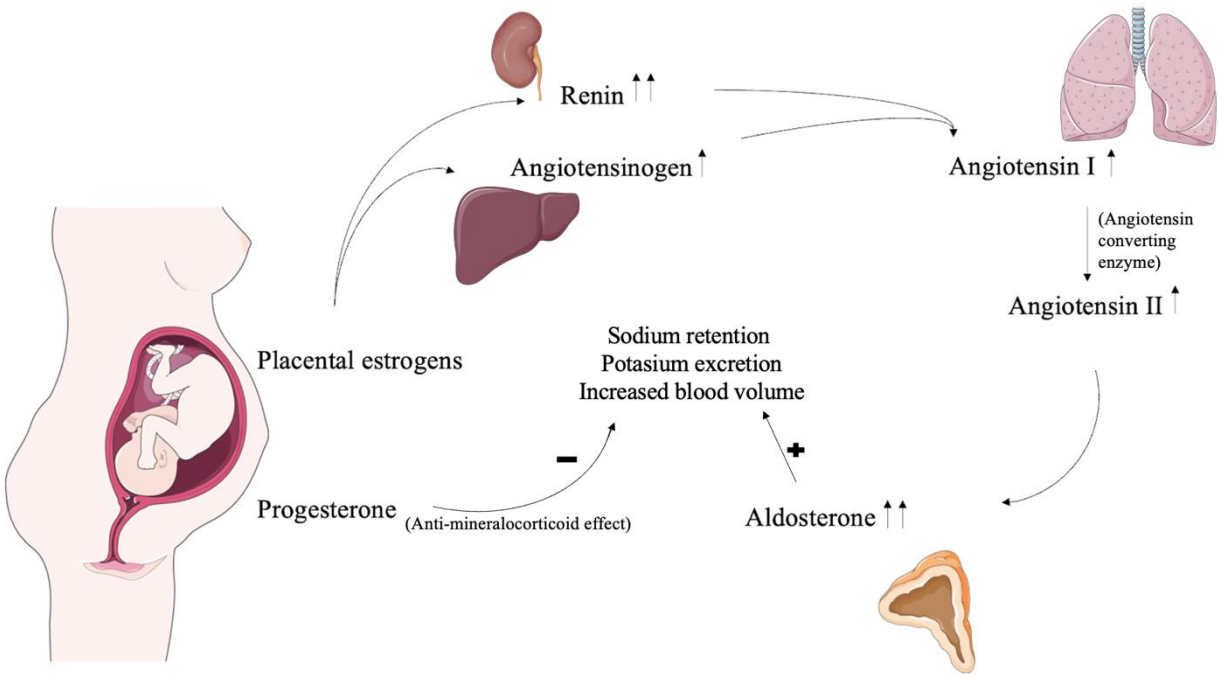

Figure 2. Renin-Angiotensin-Aldosterone System (RAAS) Activity during pregnancy.
The figure was created using medical images from https://smart.servier.com/

Endogenous Cushing's syndrome during pregnancy

Endogenous Cushing's syndrome during pregnancy is very uncommon. The presence of hypercortisolemia disrupts fertility by impacting the functioning of the hypothalamic-pituitary-ovarian (HPO) axis, leading to substantial challenges in conception. Consequently, pregnancy occurrences among women affected by Cushing's syndrome are infrequent.

The diagnostic process is challenging due to physiological changes that occur in the HPA axis during healthy pregnancy that are leading to hypercortisolemia. There are significant

similarities between the symptoms and signs commonly observed in a normal, healthy pregnancy and those present in a pregnancy affected by Cushing's syndrome. Placenta releases CRH, which results in secretion of the ACTH by the pituitary gland and cortisol by adrenals. Increases in urinary and serum free cortisol levels during pregnancy were observed, alongside a progressive elevation in night-time salivary cortisol, although diurnal variation becomes less pronounced. Notwithstanding the rise in maternal cortisol concentration, foetal cortisol levels remain lower than maternals as a consequence of placental metabolism of circulating cortisol. However pathological alterations in cortisol levels have an impact on the foetus. [8, 3]

Women with active Cushing's syndrome during pregnancy showed a higher frequency of adverse foetal outcomes such as foetal loss, preterm birth, and low birth weight. They were also more prone to pregnancy complications such as gestational diabetes mellitus, gestational hypertension, increased risk of preeclampsia, and higher rates of Caesarean section [9].

The aetiology of endogenous Cushing's syndrome in pregnant women include adrenal adenoma, Cushing's disease, adrenal carcinoma, ectopic sources, pregnancy-induced, and bilateral hyperplasia. Adrenal origin is the most common, contrasting with the non-pregnant population where Cushing's disease dominates [9].

During the diagnostic process it is crucial to apply appropriate diagnostic tests taking into consideration their potential risks to mother and foetus. Urinary free cortisol (UFC) concentration is increased during physiological pregnancy, although levels greater than 3 folds may indicate Cushing's syndrome. Overnight dexamethasone suppression test or low-dose dexamethasone suppression test are not reliable as there is a high positive false rate. Late night salivary cortisol (LNSC) measurement might be helpful in diagnosing CS as loss of diurnal variability was observed in pregnant women with Cushing's Syndrome. In pregnancy, concentration of ACTH above reference value might suggest ACTH - dependent CS, although non-suppressed ACTH levels cannot reliably exclude adrenal Cushing's syndrome. CRH administration, desmopressin stimulation, and high-dose dexamethasone suppression test are not recommended due to limited evidence and potential risks during pregnancy. The use of imaging studies in the diagnostic process is limited due to the potential risks outweighing the benefits. In pregnant patients, the imaging examination should be non-contrast MRI (magnetic resonance imaging). Among patients with no discernible adenoma on MRI without contrast,

the use of gasoline contrast should be carefully considered. CT (computed tomography) should be waived during the diagnostic process during pregnancy [10].

Data on the treatment of Cushing's syndrome in pregnancy are limited due to the rarity of this condition among pregnant women. Patients should be under the care of referral centres. Individual approach, caution and careful monitoring in treatment are recommended. The table below
(Tabele 1.) presents therapeutic options described in the literature based on the published case reports. Symptomatic treatment of complications of hypercortisolemia such as hypertension and hyperglycemia should also be carefully managed [11, 12].

Tabele 1. Suggestion of the treatment strategy [10, 11, 12].

<table>
<tr><th>Severity of hypercortisolism</th><th>Stage of pregnancy</th><th>Type of intervention</th><th>Management</th></tr>
<tr><td rowspan="2">Mild hypercortisolism</td><td>First or third trimester</td><td>Pharmacological treatment</td><td rowspan="4">Metyrapone (Quick onset of action. Side effects such as hypertension, hypokalemia and edema.)
Ketoconazole (Promising results. Teratogenic in animal studies – not observed in humans. Potential feminization of male foetus if administered in the first trimester.)
Cabergoline (Safe during pregnancy. The effects remain unclear. Limited data.)
Cyproheptadine (Not recommended. Lack of efficiency.)
Mitotane (Not recommended. Teratogenic)
Aminoglutethimide (Not recommended. Cases of pseudohermaphroditism of foetus)</td></tr>
<tr><td>Second trimester</td><td>Pharmacological treatment</td></tr>
<tr><td rowspan="3">Moderate or severe hypercortisolism</td><td>First or third trimester</td><td>Pharmacological treatment</td></tr>
<tr><td rowspan="2">Second trimester</td><td>Pharmacological treatment if surgery refused by patient</td></tr>
<tr><td>Surgical treatment</td><td>Transsphenoidal surgery if pituitary adenoma.
Unilateral adrenalectomy if adrenal adenoma. *
Bilateral adrenalectomy in severe, rapidly progressing cases should be considered. *</td></tr>
</table>

			*Unilateral and bilateral adrenalectomy were performed on pregnant women showing favourable outcomes improving perinatal morbidity and mortality rates.

Adrenal insufficiency

Adrenal insufficiency (AI) is characterised by insufficient or absent production of cortisol by the adrenal cortex. Depending on the aetiology, AI has been classified as primary, secondary and tertiary. Primary AI results from conditions directly affecting adrenal glands and lead to a deficiency in glucocorticoid, mineralocorticoid, and adrenal androgens, resulting in various physiological disturbances. Primary AI aetiology include Addison's disease, congenital adrenal hyperplasia, adrenoleukodystrophy, infectious diseases, intake of certain medications, bilateral adrenalectomy and others. Secondary AI results from pathological functioning of HPA, resulting in insufficient ACTH production which results in cortisol and adrenal androgen deficiency, the aetiology include pituitary adenoma or craniopharyngioma, surgery and radiation therapy, Sheehan's syndrome or pituitary apoplexy. Tertiary AI results from HPA axis suppression most commonly caused by exogenous glucocorticoid use.

Symptoms may be subtle at first, leading to delayed diagnosis, but untreated AI can lead to life-threatening adrenal crisis. Glucocorticoid replacement is necessary for all forms of AI, although mineralocorticoid replacement is not required in patients with ACTH deficiency [13]. Patients with AI may experience adverse metabolic profiles, reduced quality of life and increased mortality. In patients of reproductive age, AI can affect fertility, reproduction and pregnancy outcomes, and diagnosis during pregnancy presents unique challenges [14, 15].

Appropriate medical care and patient-specific treatment have improved maternal and foetal outcomes in most women with adrenal insufficiency. Although there is a higher rate of deliveries by caesarean section, especially in cases of hypopituitarism and Addison's disease. Adrenal crisis can occur during pregnancy, factors that can trigger them include infections, hyperemesis, or noncompliance with therapy [16]. Miscarriage rates vary depending on the cause, congenital adrenal hyperplasia (CAH) has a higher incidence of miscarriage compared to other etiologies. Intrauterine growth restriction and preterm delivery are possible

complications, possibly related to impaired placental function and dysregulation of the hypothalamic-pituitary-adrenal axis [17].

The diagnosis of AI during pregnancy is rare. Most often, the AI is diagnosed before pregnancy. The diagnosis is challenging due to overlapping symptoms with pregnancy-related complaints such as fatigue and nausea, as well as hyperpigmentation, particularly seen in primary adrenal insufficiency. Hyponatremia exceeding expected levels in pregnancy can also signal AI, especially in patients with a history of autoimmunity. Paired early morning cortisol and ACTH are recommended as a screening test to diagnose adrenal insufficiency [18]. Interpretation of diagnostic biochemistry is complicated by physiologic hypercortisolism in pregnancy, requiring trimester-specific cutoff values for cortisol levels. While the Synacthen short test remains the preferred diagnostic method for AI, its use is limited due to safety concerns in pregnancy. Alternative methods, such as salivary cortisol measurement, show promise, but require validated reference ranges for pregnancy for clinical use [19].

The challenge for specialists is to properly manage the pregnancy in such a patient. Pregnancy in women with adrenal insufficiency should be meticulously planned and monitored. The appropriate dosage of glucocorticosteroids should be determined before conception. Counselling on ai treatment during pregnancy should include informing the patient of the need to adjust the dosage and route of administration of the daily glucocorticoid in case of fever, infection, surgery, persistent vomiting, and active labour in order to prevent adrenal crisis. Patients It is advisable to monitor the patient for or clinical symptoms and signs of glucocorticoid over- and under-replacement e.g for overreplacement: gestational diabetes, hypertension and under-replacement: hyperemesis, electrolyte imbalance, postural hypotension [20].

Limited data on glucocorticosteroid dosing during pregnancy in patients with AI results in lack of clear recommendations. However, treatment aims to achieve physiological glucocorticoid replacement and it is suggested to adjust the doses by increasing hydrocortisone by 20–40% from 24 weeks gestation [21].

Women diagnosed with primary adrenal insufficiency (PAI) during pregnancy should begin mineralocorticoid replacement therapy, with doses based on individual needs. Increasing hydrocortisone doses during pregnancy provides some mineralocorticoid activity. Taking into consideration increasing progesterone levels (progesterone shows anti-mineralocorticoid

effect), an increase of the dose of fludrocortisone might be required, guided by clinical evidence. Monitoring is based on clinical parameters such as orthostatic hypotension, changes in serum electrolytes and signs of volume reduction, as plasma renin activity cannot be used [20].

Primary aldosteronism in pregnancy

Primary aldosteronism (PA) is a condition characterised by overproduction of aldosterone from the adrenal glands, leading to increased sodium reabsorption, potassium excretion, and arterial hypertension. Primary hyperaldosteronism is an extremely rare condition among pregnant women. Only about 80 cases of PA during pregnancy have been described in the literature. However, this may be due to the significant underdiagnosis of patients since PA is considered a major cause of secondary hypertension. The conviction that PA always co-occurs with hypokalemia is now being abandoned and is deemed that in most cases patients will not present hypokalemia [22]. Aetiology of primary hyperaldosteronism include unilateral aldosterone-producing adrenal adenoma, bilateral adrenal hyperplasia of the zona glomerulosa and familial hyperaldosteronism. During pregnancy significant physiological changes occur in the RAAS which leads to increased plasma renin concentration and aldosterone production. Significantly higher concentration of aldosterone during pregnancy leads to sodium retention followed by increased volume of fluids contributing to physiological adaptations observed in a healthy pregnancy [23]. Regardless of all those changes during physiological gestation women do not present symptoms of hyperaldosteronism such as hypertension and hypokalemia, probably because of production of vasodilatory prostaglandins and progesterone, which counteracts aldosterone activity [24].

Pregnancy-related complications among women with PA include pre-eclampsia (PE), with a prevalence three times higher than observed in the general population, preterm birth, higher ratio of caesarean section due to uncontrolled hypertension or severe intrauterine growth restriction. However, since mild forms of PA during pregnancy might be underdiagnosed, it is more likely that the complications presented are mostly due to severe forms of PA. Additionally, hypokalemia associated with PA poses a potential maternal risk, including cardiac arrhythmias and paralysis. Familial hyperaldosteronism type 1 appears to have maternal and foetal outcomes similar to the general population [5].

PA should be suspected in pregnant women with moderate to severe hypertension, especially if it appeared before 20 weeks of pregnancy, concurrent hypokalemia supports the preliminary assessment. Screening test for PA is the determination of the aldosterone-renin ratio (ARR). ARR significantly higher, High plasmatic aldosterone concentration (PAC) together with lower plasma renin activity (PRA) or direct renin concentrations (DRC) support a strong suspicion of PA [25]. Limitations and difficulties in diagnosis are due to the lack of dedicated reference ranges for pregnant women, and the physiological adaptive changes that occur during pregnancy. Confirmatory tests such as saline infusion or captopril challenge should not be performed during pregnancy and it is recommended to postpone them after pregnancy. If the control of hypertension with pharmacological treatment is adequate the diagnostic imaging might be postponed after gestation. Acceptable imaging tests during pregnancy are ultrasound and MRI of the adrenal glands [26].

Therapeutic measures should be directed toward controlling blood pressure values and maintaining potassium concentrations within reference values. To control blood pressure, medications that are standardly used during pregnancy for this very purpose are used: α-methyldopa, beta blockers (such as labetalol), and calcium antagonists (like nifedipine). The use of eplerenone (mineralocorticoid receptor antagonist) used to treat PA is considered a safer alternative to spironolactone which use during pregnancy is contraindicated [27].Adrenalectomy may be considered in pregnant women with severe hypertension not controlled by pharmacotherapy and persistent hypokalemia, particularly if unilateral adrenal lesions are present [28, 29].

Pheochromocytoma

Pheochromocytoma is a rare tumour of the adrenal medulla that produces catecholamines and can lead to hypertensive crises . It is a rare condition among pregnant women. It is characterised by high maternal and foetal mortality if not recognised quickly. Although, advancements in medical care have led to a marked decrease in adverse outcomes over the years.

Common manifestations of pheochromocytoma include hypertension, palpitations, tachycardia, headaches, sweating, pallor and anxiety. Tumore might remain asymptomatic in approximately 25% of cases [30]. The diagnostic process might be challenging due to similarities with more prevalent conditions like gestational hypertension and pre-eclampsia.

Indicators favouring a pheochromocytoma diagnosis include hypertension onset before 20 weeks' gestation, episodic hypertension, and orthostatic hypotension, typically absent in gestational hypertension. Conversely, pheochromocytoma-related hypertension rarely presents with ankle edema or elevated plasma uric acid levels, commonly observed in gestational hypertension or pre-eclampsia. Symptom exacerbation commonly occurs during the third trimester due to compression of the gravid uterus, yet it was also noted during the first trimester when the diagnosis of pheochromocytoma was established prior to conception [31].

During healthy pregnancy concentration of the catecholamines remains within normal ranges as for non- pregnant individuals, although normal ranges for pregnant subjects have not been clearly established [32]. In a patient with a clinical suspicion of pheochromocytoma, biochemical tests such as fasting supine plasma normetanephrine and 24 h urinary fractionated metanephrines and catecholamines should be performed. It is necessary to take into account the medications taken by the patient, since some of them may interfere with the result of the test. Imaging test in pregnant women is MRI without contrast [33].

Pharmacological approaches to treating pheochromocytoma include α-adrenergic blockade. Phenoxybenzamine is commonly used, although its placental passage can lead to hypotension or respiratory depression in the newborn. Alternatives, such as doxazosin or prazosin, offer potential benefits due to their shorter half-lives and more selective targeting of the α1 receptor. Preceding adrenalectomy, α-blockade treatment significantly reduces maternal and foetal mortality. In cases of tachycardia and hypertension during pregnancy due to pheochromocytoma, the use of beta-blockers and calcium channel blockers may be necessary to prevent adverse outcomes such as intrauterine growth restriction or foetal death [31]. Drugs such as metoclopramide, steroids and sympathomimetics should be avoided during pregnancy because of their potential to cause sudden, catastrophic catecholaminergic release and hypertensive breakthroughs. An early diagnosis, before 24 weeks of pregnancy, allows for adrenalectomy to prevent the growing uterus from compressing the tumour [33]. Conversely, if the diagnosis occurs in the third trimester of pregnancy, resection is usually postponed after the end of pregnancy [32]. Studies show no significant difference in mortality rates between pre-partum resection and medical management followed by post-partum resection. When deciding on surgical treatment, each patient should be approached individually [34].

Conclusions

Managing and diagnosing adrenal diseases during pregnancy poses a major challenge for physicians especially considering the physiological adaptive changes in the endocrine system that occur in women during pregnancy. It should be noted how important it is to diagnose adrenal diseases in pregnant women as early as possible, and to plan ahead for pregnancy in women whose diagnosis is made before conception to prevent the negative outcomes of untreated adrenal disorders. It should be taken into consideration that pregnancy during inadequately managed adrenal conditions is not recommended, emphasising the importance of obtaining optimal treatment results before conception. Education of the patients is also important to minimise potential adverse outcomes for both the foetus and the mother. Access to expert centres with multidisciplinary teams experienced in managing these conditions is paramount for optimal maternal and foetal care.

Author's Contribution

Conceptualization: K. Filipek; Methodology: N. Zalewska; Software: J. Kawka; Check: K. Filipek; Formal Analysis: ; Investigation: K. Filipek, A. Baranowska, N. Zalewska, F. Czyżewski, W. Mrugała, S. Mrugała, B. Skierkowski, M. Muciek, K. Baranowska; Resources: A. Baranowska, K. Filipek, N. Zalewska, F. Czyżewski, W. Mrugała, S. Mrugała, B. Skierkowski, M. Muciek, K. Baranowska; Writing – Rough Preparation: K. Filipek A. Baranowska, K. Baranowska, N. Zalewska; Writing – Review and Editing: K. Filipek; Visualization: K. Filipek, J. Kawka, F. Czyżewski, M. Muciek, ; Supervision: B. Skierkowski, W. Mrugała, S. Mrugała, M. Muciek; Project Administrator: K. Filipek

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