
بسم الله الرحمن الرحيم
علی خمسه

ESE CLINICAL PRACTICE GUIDELINE ON FUNCTIONING AND NONFUNCTIONING PITUITARY ADENOMAS IN PREGNANCY

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The pituitary gland and endocrine milieu in pregnancy :

Pregnancy changes the morphology and function of the pituitary gland.

The gland size increases and reaches its maximal volume in late pregnancy and the first days post-partum with a height of up to 12 mm followed by a gradual decline to normal size within 6 months after delivery.

This growth is related to lactotroph hyperplasia starting in the first month of pregnancy and due to the increased concentrations of oestradiol (E2) .

The placenta is a hormone-producing organ that interacts with the pituitary gland.

Starting in the first weeks of pregnancy, the placenta produces oestrogens and progesterone, which increase exponentially until delivery, whereas ovarian production subsides .

When interpreting hormone concentrations in pregnancy, increased production of binding proteins due to increased oestradiol concentrations has to be considered.

In parallel, due to the stimulatory effect of oestradiol, there is an increased prolactin (PRL) production with serum concentrations reaching approximately 6- and 10-fold the upper limit of the reference range of non-pregnant women in the second and third trimester, respectively

Human placental lactogen (hPL), which is structurally related to PRL and growth hormone (GH), is released into the maternal circulation from the first weeks of gestation until delivery.

From gestational week 5, the placenta produces increasing amounts of GH (hPGH), resulting in suppression of circulating pituitary GH to undetectable levels after gestational week 24 .

Serum insulin-like growth factor-I (IGF-I) levels increase significantly above the age-specific reference range for non-pregnant women.

Human chorionic gonadotrophin (hCG) is detectable in the maternal circulation after embryo implantation, peaks around week 10 and thereafter declines until week 20 to lower levels .

hCG is a potent TSH receptor ligand.

Due to increased concentrations of thyroxine-binding globulin (TBG), circulating levels of total thyroxine (T4) and triiodothyronine (T3) are elevated in pregnancy, and interpretation of thyroid function tests, therefore, requires appropriate reference ranges .

Free T4 levels decline during pregnancy to levels in the low reference range for non-pregnancy.

Pregnancy is associated with activation of the maternal hypothalamic–pituitary–adrenal (HPA) axis that leads to increased levels of circulating adrenocorticotropic hormone (ACTH) and cortisol (both free and total) as well as 24 h urinary-free cortisol excretion.

The placenta produces large amounts of corticotropin-releasing hormone (CRH) and its related urocortin peptides , the circulating concentrations of which rise exponentially in the third trimester of pregnancy .

The placenta has also 11β-hydroxysteroid dehydrogenase type 2 activity converting cortisol to cortisone. Although the concentration of plasma cortisol is elevated during pregnancy, the diurnal pattern is preserved .

Increased placental vasopressinase activity is counterbalanced by increased pituitary vasopressin release in normal pregnancy but may manifest as transient diabetes insipidus .

Recommendations and rationale for the recommendations:

R.1.1. We recommend that women of reproductive age with a diagnosis of a pituitary adenoma be counselled about their potential fertility and pregnancy outcomes as early as possible .

Rationale

Pituitary function might be impaired due to compression by or hormonal hypersecretion from the pituitary adenoma.

In women with hypopituitarism, replacement therapy should be optimised, and assisted reproductive technologies (ART) should be discussed when appropriate.

R.1.2. We recommend that women of reproductive age with a diagnosis of pituitary adenoma, functioning or nonfunctioning, who consider pregnancy, be managed by an endocrinologist.

Rationale

The woman's age is a major determinant of fertility and pre-conception counselling should also include an obstetrician with expertise in maternal-fetal medicine and reproductive medicine.

An endocrine work-up including all anterior pituitary functions should be performed , with special attention to possible associated metabolic or cardiovascular diseases.

Table 3 Work-up when pregnancy is considered.

Medical history with special attention to pituitary condition and its associated comorbidities
Physical examination including BMI calculation and blood pressure
Routine laboratory values including electrolytes, glucose, liver and kidney function tests, lipids, urine dipstick
Representative evaluation of pituitary hormone status (overproduction and deficiency), and reproductive status
Consider: Early morning cortisol, ACTH, fT4, TSH, E_2, LH, FSH, progesterone (on day 21 of menstrual cycle), SHBG, PRL, IGF-I, DHEA-S, testosterone, AMH (on day 3 of menstrual cycle)*
Representative tumour volume status, with dedicated pituitary MRI depending on initial size (macroadenoma) and time since last evaluation
Representative neuro-ophthalmological evaluation if clinically indicated (depending on size and location of the lesion, especially if it is in contact with the optic chiasm)

*Anti-Muellerian hormone (AMH) plasma concentrations are underestimated in hypogonadotropic hypogonadism (190).

R.1.3. We recommend that management of women of reproductive age with a large pituitary adenoma (>1 cm), Cushing's disease or acromegaly, who consider pregnancy, be discussed in a multidisciplinary team .

Rationale

Compression of the optic chiasm with visual field impairment is an indication for pre-pregnancy pituitary surgery, a tumour in close vicinity to the optic chiasm is a possible indication for surgery.

For women with a nonfunctioning pituitary macroadenoma and no visual field impairment, who are seeking pregnancy, the decision to operate prior to planned pregnancy may also take into account the presence of gonadotrophin deficiency as surgery provides pituitary recovery in about 30% of cases , in particular normalisation of ACTH, cortisol and PRL .

The surgical risk of a postoperative gonadotrophin deficiency and also a panhypopituitarism (14%), which could impact on pregnancy course should be considered.

R.1.4. We recommend that in women with a diagnosis of pituitary adenoma and hypopituitarism, hormone replacement therapy should be initiated or optimised prior to becoming pregnant .

***Rationale** :*

In women with hypopituitarism, reported fertility rates range from 47 to 76%, and reached over 80% in women with isolated hypogonadotropic hypogonadism after ART .

Women with hypopituitarism and optimal replacement therapy often require ART.

Initiation and optimisation of GH replacement for at least 3 months prior to conception has been shown to improve the success rate of ART and ovulation stimulation (OS) in women with concomitant gonadotrophin deficiency.

Pituitary apoplexy occurring after the application of triptorelin, a GnRH analogue used for OS, has been described , possibly due to previously undetected gonadotropinomas .

General recommendations: Pregnancy

R.2.1. We recommend that pregnant women with known pituitary adenoma, in particular those with a large pituitary adenoma (>1 cm), Cushing's disease or acromegaly, and those with pituitary deficiencies, should be followed by an endocrinologist and an advanced nurse practitioner where relevant.

The frequency depends on the underlying condition and individualised needs **.**

Rationale

Women with pituitary adenomas and hypopituitarism require regular follow-up at least every trimester to monitor for adequate substitution doses and/or to identify signs or symptoms of any newly developed pituitary insufficiencies or complications associated with functioning adenomas, mainly GH or ACTH-producing.

Patients on levothyroxine replacement therapy might require an increase in dose of up to 50% .

Whereas an interval of 4–6 weeks has been suggested for fT4 measurement throughout pregnancy .

In women with adrenal insufficiency, there is usually no need to alter the doses of glucocorticoid replacement therapy during the first half of pregnancy, but an increase by 20–40% may be needed from week 22 to 24 onwards, since free cortisol increases during this period in healthy women.

Hydrocortisone is the preferred choice for glucocorticoid replacement during pregnancy; prednisone is also an option as it does not cross the placenta.

Only 10–12% of the maternal prednisolone concentration reaches the foetus .

Dexamethasone should be avoided because it is insufficiently inactivated by placental 11β-HSD2 and may therefore cause harm to the foetus.

The desmopressin dose might need to be increased during the third trimester due to placental vasopressinase activity and the patient should be informed that in case of polyuria and increase of desmopressin, serum sodium concentration should be checked to avoid hyponatraemia.

Administration of desmopressin appears to be otherwise safe in pregnancy .

GH replacement is usually stopped after conception or by the end of the first trimester; the benefit–risk balance for GH in pregnancy cannot be assessed.

R.2.3. We recommend that women and their partners be provided with education for glucocorticoid stress dose adjustment and measures on how to prevent or manage adrenal crisis during pregnancy .

Rationale:

Symptoms such as persistent nausea, hyperemesis, and excessive fatigue are common in pregnancy.

These can also be triggers or symptoms of the onset of an adrenal crisis and vigilance is therefore mandated.

partner education regarding stress-coverage dosage of hydrocortisone (sick day rules), access to a hydrocortisone injection kit and glucocorticoid emergency card, and training on self-injecting are crucial to prevent and promptly manage an adrenal crisis.

In case of an adrenal crisis, fluid replacement (best with 0.9% saline IV) and immediate parenteral administration of hydrocortisone 100 mg (IV, IM, SC) are potentially life-saving for the mother .

Fetal monitoring by cardiotocography (CTG) and ultrasound is also necessary to ensure the well-being of the unborn child .

R.2.4. We recommend performing an MRI without contrast in pregnancy in case of symptoms of tumour progression or apoplexy.

Rationale

MRI is considered safe in pregnancy and should be used in symptomatic patients with impairment of visual fields or visual acuity, cranial nerve palsies or severe headache usually after neuro-ophthalmologic evaluation.

Gadolinium can cross the placenta and reach the foetal circulation , its use is therefore to be avoided in most cases, especially in the first trimester.

Routine MRI follow-up during pregnancy is not recommended .

R.2.5. We recommend that neuro-ophthalmologic examination in pregnancy be performed for adenomas impinging visual pathways or in case of suspected tumour progression or pituitary apoplexy .

Rationale

Due to the possible risk of tumour impingement of the visual pathways, a neuro-ophthalmologic evaluation including determination of visual acuity, visual fields and, if available, optical coherence tomography (OCT) analysing retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC) should be performed in symptomatic patients, which will aid the decision about whether a MRI is indicated.

R.2.6. We recommend considering surgery in pregnant women with deterioration of vision, ophthalmoplegia or severe headache attributable to tumour enlargement if medical tumour treatment is unfeasible or ineffective (⊕⊕◯◯).

R.2.7. If surgery is indicated, we suggest to perform trans sphenoidal surgery in the second trimester if the clinical course allows this (⊕⊕◯◯).

In cases of symptomatic tumour enlargement during pregnancy, medical treatment with dopamine agonists or somatostatin analogues may be attempted before undertaking transsphenoidal surgery .

Transsphenoidal surgery in first trimester should be avoided if possible .

In the third trimester, pre-term delivery before non-obstetrical surgery should be considered.

Emergency operations (e.g. severe loss of vision or ophthalmoplegia) must be considered and performed at any time during pregnancy preferably in expert pituitary centres .

R.2.8. We recommend not to perform radiotherapy during pregnancy .

General recommendations: Delivery and breastfeeding

R.3.1. We suggest that pregnant women with pituitary adenomas should receive standard obstetrical care but recommend close maternal and foetal surveillance.

Rationale *:*

A systematic review of 31 pregnancy outcomes in women with hypopituitarism found no neonatal complications or congenital anomalies in the newborns.

However, these women had higher rates of caesarean deliveries, transverse lie and small for gestational age neonates compared to controls .

Special monitoring of the newborns for the risk of hypoglycaemia is needed in case of maternal hyperglycaemia and/or hypertension, disorders that may occur in GH and ACTH secreting pituitary adenomas.

In rare pregnancies with Cushing's disease, the risk for prematurity and intrauterine growth restriction is elevated and there were individual reports of coarctation of the aorta, transient neonatal jaundice, hypoglycaemia and adrenal insufficiency requiring temporary treatment with hydrocortisone.

R.3.2. In general, breastfeeding is feasible and not contraindicated.

Nonfunctioning adenomas (NFAs)

R.4.1. In women with a NFA near the optic chiasm who are planning a pregnancy, surgery may be considered to reduce the risk of chiasmal compression and to enhance fertility.

Additionally, it has been suggested that for women with a macroadenoma and no visual field impairment, who plan pregnancy, surgery may be considered in order to optimize fertility.

R.4.2. We suggest that for women with intrasellar nonfunctioning microadenomas and an uneventful pregnancy, there is no need for routine endocrinological follow-up during pregnancy .

Rationale

The majority of previously treated NFAs do not enlarge during pregnancy .

R.4.3. We recommend that for macroadenomas and/or extrasellar NFAs, neuro-ophthalmologic and, if indicated, MRI examination should be performed only in case of symptoms of tumour progression or pituitary apoplexy during pregnancy.

Rationale:

In contrast to microadenomas, six of eight primiparous patients with macroadenomas (range 1.2–2.5 cm) in the above-mentioned study developed visual field impairment

In case of macroadenomas in contact or close to the chiasm, systematic visual examination should be considered.

Visual examination frequency and type of tests (with or without optical coherence tomography) depend on the local practices and should be adapted case-by-case.

R.4.4. We recommend that in case of a clinical need to reduce adenoma volume during pregnancy, surgery is the preferred option (⊕◯◯◯).

The main indication for pituitary surgery during pregnancy is to protect visual function .

A trial with cabergoline might be considered .

R.4.5. We recommend awaiting reassessment of pituitary imaging and function until after delivery and breastfeeding .

A de novo radiological diagnosis of a pituitary mass lesion may be created during pregnancy .

Reassessment of pituitary imaging and function should be done between 3 and 6 months after delivery, preferably after breastfeeding.

Prolactinomas:

R.5.1. We recommend treating women with a prolactinoma, who are actively seeking pregnancy, with a dopamine agonist and strive for normalisation of prolactin concentrations and restoration of regular ovulatory cycles (⊕⊕⊕◯).

Rationale

we consider a desire for pregnancy as an indication for strict prolactin normalisation in young women with a prolactinoma, even in those with mild hyperprolactinaemia and apparently regular normal cycles.

It is important to inform patients that restoration of ovulation and fertility may be immediate when they start dopaminergic treatment, even before normal menses return.

R.5.2. We recommend medical treatment as first-choice therapy for women with a prolactinoma and actively seeking pregnancy; transsphenoidal surgery can be considered in individual cases (⊕⊕⊕◯).

Dopamine agonists (DA) are the standard treatment for women in reproductive age with a micro- or a macro-prolactinoma, restoring ovulation in 80–90%.

Transsphenoidal adenomectomy is considered less efficient than medical therapy, leading in expert hands to a sustained normalisation of prolactin levels in 70–80% of microadenomas, but only in 30–40% of macroadenomas

The risk of postoperative pituitary deficiency remains very limited.

R.5.3. We recommend cabergoline as medical treatment at the lowest possible effective dose until pregnancy is confirmed (⊕⊕◯◯).

Treatment with dopamine agonists should not be withdrawn in women seeking pregnancy and, as discussed above, due to its higher efficacy and better tolerance,cabergoline is considered first choice in this population.

We performed a systematic review of reports published until 2019 on pregnancies initiated under cabergoline treatment (*n* = 1272), observed rates of spontaneous miscarriage (9.0%), pre-term delivery (8.0%) and neonatal malformations (3.3%) are similar to those reported for bromocriptine and do not clearly deviate from those reported in an age-matched population not on DA therapy .

While some follow-up studies of children for up to 12 years after foetal exposure to cabergoline do not suggest an increased risk of developmental and or/ metabolic abnormalities , one study with a follow-up of 61 children of up to 16 years reported two children who developed epilepsy (one after distress at birth because of abruptio placentae) and two with a pervasive developmental disorder .

However, the relationship of such disorders with previous cabergoline exposure cannot be proven.

Regarding the use of quinagolide, the manufacturer's data include 176 pregnancies, in which this drug was given for a median duration of 7 weeks; 24 spontaneous abortions, 1 stillbirth and 9 foetal malformations were reported .

Thus, quinagolide appears to be less safe during pregnancy.

R.5.4. We recommend stopping the dopamine agonist once pregnancy is established. However, dopamine agonists may be given for a longer gestational period in specific circumstances (⊕◯◯◯).

For women with a macroprolactinoma close to the optic chiasm, it should be confirmed that tumour volume has shrunk substantially prior to conception.

If adenoma size is not controlled, several options are available.

First, DA therapy seems to be safe and, in special circumstances, can be continued throughout the pregnancy, particularly if the adenoma is abutting the optic chiasm.

Second, DA can be started later in pregnancy in case of symptomatic tumour growth.

Cabergoline is slightly preferable due to its better tolerability, higher efficacy and longer duration of action.

Alternatively, partial or complete resection by transsphenoidal surgery prior to conception can be considered, in particular for cystic lesions that are often considered less responsive to medical therapy and good candidates for surgery.

R.5.5. We recommend not measuring prolactin during pregnancy .

R.5.6. We suggest that for women with a small intrasellar microprolactinoma, and normal pituitary function pre-pregnancy, there is no need for routine endocrinological follow-up during pregnancy.

R.5.7. We suggest careful and regular monitoring for tumour growth in pregnant women with a large macroprolactinoma or a prolactinoma close to the optic chiasm (⊕⊕◯◯).

Rationale

Overall, symptomatic tumour growth during pregnancy occurs in 9.0% (95% CI: 6.8–11.6%) of prolactinomas.

However, in women with a macroprolactinoma, the risk is reported to be considerably higher, 30.5%.

R.5.8. We recommend to consider restarting dopamine agonists in pregnancy in case of symptoms of progressive prolactinoma growth. Surgery should be used only in case of medical failure or symptomatic apoplexy (⊕◯◯◯).

R.5.9. For women with a prolactinoma, breastfeeding is usually feasible and not contraindicated, but we recommend to take into account individual circumstances like tumour size and symptoms .

Rationale

In individual cases of macroadenoma requiring DA throughout pregnancy, the advice to breastfeed and stop DA should be individualized.

Breastfeeding while taking a DA is not possible and should be avoided anyway.

R.5.10. We recommend reassessing prolactinoma status after every pregnancy before considering restarting therapy.

Rationale

There is a subset of prolactinomas that will involute during pregnancy and lactation.

There is a higher number of remission in microprolactinomas (46%) than macroprolactinomas(26%).

We, therefore, recommend re-evaluating the status of the prolactinoma 1–3 months after the lactation period, with clinical assessment, prolactin measurement, and MRI in cases of previous macroadenomas.

In case of remission, we recommend clinical and hormonal follow-up at 6 months and yearly thereafter, since recurrence may occur in up to 65% of cases.

Acromegaly

Acromegaly may be associated with infertility, through several mechanisms , including hypopituitarism and hyperprolactinaemia , direct effect on hypothalamic gonadotropin-releasing hormone (GnRH) secretion or induce polycystic ovary disease-like conditions .

R.6.1. In women with acromegaly considering pregnancy, we recommend assessment of disease activity, comorbidities and fertility status .

Rationale

Impaired glucose tolerance, diabetes mellitus and hypertension associated with active acromegaly may worsen in pregnancy and thereby harm the foetus .

Tumour mass effect may also be a concern during pregnancy and needs to be carefully evaluated before pregnancy to determine appropriate treatment

R.6.2. In women with newly diagnosed acromegaly seeking pregnancy, surgery is recommended as first-line therapy.

R.6.3. In women with mild acromegaly, no comorbid conditions and regular ovulatory cycles, pregnancy is considered safe and medical or surgical treatment can be postponed until after delivery.

Rationale

In patients with mildly elevated IGF-I levels, either newly diagnosed or after surgical treatment, maternal IGF-I levels usually decrease during pregnancy as the high oestrogen levels induce hepatic resistance to GH and some patients may experience symptom relief during the first half of pregnancy.

This, along with the very low risk of symptomatic tumour growth (7.0%, 95% CI: 3.3–12.9%), allows postponement or withdrawal of medical or surgical treatment until after delivery.

R.6.4. We suggest that for women with acromegaly seeking pregnancy and who have an indication for medical treatment, somatostatin analogues or cabergoline can be used until confirmation of pregnancy if surgery is not an option. Pegvisomant should be reserved for selected uncontrolled cases (⊕◯◯◯).

Rationale

In the available literature, there is no clear indication that treatment with cabergoline, octreotide or lanreotide during pregnancy increases adverse events for mother or child.

Specifically, treatment with cabergoline and first-generation somatostatin analogues does not result in increased prevalence of congenital malformations.

no excess teratogenic risk of octreotide and lanreotide was reported, but the number of exposed pregnancies was too low to allow firm conclusion about the safety of these drugs.

There are insufficient data about pasireotide use in pregnancy to make any recommendation about this second generation somatostatin receptor ligand.

The Endocrine Society guideline suggests withdrawal of depot somatostatin analogue 2 months prior to conception and to switch to short-acting octreotide .

R.6.5. We recommend to consider stopping drugs for acromegaly once pregnancy is established (⊕◯◯◯).

R.6.6. We recommend not to measure GH and IGF-I during pregnancy.

Rationale

During normal pregnancy, the placenta produces a GH variant (hPGH) , which cross-reacts with pituitary GH in most immunoassays.

During the first trimester of normal pregnancy, maternal IGF-I levels decrease by about 30% and thereafter may increase to reach a peak at 37 weeks of gestation that is two-fold elevated as compared to the pre-pregnancy level.

R.6.7. We suggest that for pregnant women with large adenomas, or adenomas close to the optic chiasm, regular neuro-ophthalmologic and, if necessary, pituitary MRI examination be performed .

It is unclear if pregnancy may trigger the growth of a pre-existing GH-secreting pituitary adenoma, but discontinuation of somatostatin analogue treatment may allow regrowth of the tumour .

R.6.8. We suggest to consider starting or restarting medical treatment for tumour control and severe clinical symptoms attributable to acromegaly (⊕◯◯◯).

Medical treatment with octreotide or lanreotide is suggested as first-line treatment in the event of symptomatic tumour enlargement with visual loss or neurological complications, even though surgery in the second trimester, in general, is considered safe.

R.6.9. In acromegaly, breastfeeding is feasible and not contraindicated, but we recommend to take individual circumstances like drug use and disease activity into account.

Rationale

As a safety principle, somatostatin analogues and pegvisomant should be avoided in nursing mothers

R.6.10. We recommend reassessing disease activity after pregnancy .

Shortly after delivery, a rebound of disease activity is frequently observed .

Cushing's disease:

Hypercortisolism leads to hypogonadism and infertility; thus, pregnancy in CD is very rare. When women with CS do become pregnant, it is most often of adrenal origin (60% of cases).

R.7.1. We recommend that women with active Cushing's syndrome be advised not to get pregnant .

Women with active CS show a high incidence of pre-term deliveries, probably due to more frequent complications during pregnancy such as gestational diabetes mellitus, hypertension or pre-eclampsia; additionally, a higher rate of Caesarean section in comparison to cured CS is reported (51.7% vs 21.9%)

Foetal risks are also higher, and include deaths, pre-term births, neonatal infections, hypoglycaemia, and respiratory distress.

R.7.2. Evaluation of hypercortisolism during pregnancy is difficult; we suggest to consider testing only for high clinical suspicion of new diagnosis of Cushing's disease

Rationale

Making a new diagnosis of CS during pregnancy can be challenging because some of the clinical features overlap those occurring in normal pregnancy, including hyperglycaemia, central weight gain, hypertension, fatigue, skin pigmentation, facial plethora and the development of striae.

Clinical features which are not typical of normal pregnancy include striae on sites other than the abdomen and striae that are wider and more purple than usual for pregnancy, easy bruising, skin thinning, spontaneous fractures and proximal myopathy.

The HPA axis is activated during normal pregnancy, producing increased levels of CRH (much of originating from the placenta), ACTH and serum total and free cortisol .

There is also increased hepatic production of cortisol binding globulin related to high levels of oestrogen, which further increases measured serum cortisol .

Urinefree cortisol (UFC) excretion increases up to three-fold during pregnancy and overlaps with CS levels.

suppression of cortisol by dexamethasone is blunted in pregnancy, so the 1 mg overnight dexamethasone suppression test is not advised due to the risk of false-positive results.

Because cortisol circadian rhythm is maintained in normal pregnancy (although at a higher level of cortisol), late night salivary cortisol or midnight serum cortisol levels have been suggested as possible diagnostic tests.

with sensitivities of >80% and specificities of >93% using an ELISA-Cortisol EIA kit (salimetrics) and the following cutoffs: 0.255 µg/dL (7.0 nmol/L) for the first trimester, 0.260 µg/dL (7.2 nmol/L) for the second trimester, and 0.285 µg /dL (7.9 nmol/L) for the third Trimester.

If a pituitary source is suspected based on high normal to elevated ACTH, pituitary MRI can be performed without gadolinium, although many corticotroph adenomas are small and may be missed.

When adrenal CS is suspected based on suppressed or low normal ACTH, ultrasound imaging of the adrenals may be performed but abdominal MRI without contrast seems best to characterise the adrenal mass.

R.7.3. We recommend that in women with Cushing's disease, medically treated and considering pregnancy, pros and cons of different therapeutic options to reduce cortisol concentrations should be carefully considered (⊕◯◯◯).

Rationale

Treatment during pregnancy has been reported in less than 100 cases of endogenous CS of any origin, either surgery (24%), medical treatment (11%) or both (4.7%).

Drugs most often reported were cabergoline,ketoconazole and metyrapone.

However, none is approved for use in pregnancy.

untreated CS is associated with more maternal and foetal morbidity.

While medical or surgical treatment decreased the risk of perinatal mortality and maternal morbidity, it did not protect from prematurity or intrauterine growth restriction .

If treatment is considered necessary, surgery in the second trimester has been recommended as a first-choice treatment, but the evidence is limited.

R.7.4. We recommend that pregnant women with active or medically treated Cushing's disease should be managed by a multidisciplinary team expert in high-risk pregnancies.

Rationale

Mild cases of CS, especially those discovered late in pregnancy, may be treated conservatively by controlling comorbidities.

In women who become pregnant while on anti-cortisolic treatment (exception cabergoline), there should be a discussion about the fact that little is known about possible teratogenic effects as well as maternal risk and pregnancy termination.

In women who develop severe CD while pregnant, the first option to consider is surgery (pituitary adenomectomy or laparoscopic adrenalectomy)

Medical therapy can be contemplated when surgery is contraindicated, or initially after diagnosis for symptomatic control.

Metyrapone has been most commonly used; as it may worsen hypertension and/or decrease potassium, blood pressure and potassium should be regularly monitored.

Ketoconazole is another option for treatment, although fewer outcome data are available.

Cabergoline has only been reported in three cases of CD with good maternal–foetal outcome, but breast feeding would not be possible.

Mifepristone, a glucocorticoid receptor blocker available in some countries, is contraindicated as it is also a progesterone blocker used to terminate a pregnancy.

R.7.5. We suggest to consider treating pregnant women with active Cushing's disease with prophylactic anticoagulation (low molecular weight heparin).

Rationale

CS increases the risk of thrombotic events up to 10-fold, which has been attributed to an increase in plasma clotting factors and impaired fibrinolysis .

Anti-thrombotic prophylaxis has been shown to reduce morbidity and mortality in Cushing's syndrome.

R.7.6. We recommend to reassess disease activity after pregnancy.

Rationale

In a woman without CS, the pregnancy-related HPA axis activation subsides within days after delivery and is typically back to non-pregnant levels within a few weeks .

Restoration of normal dexamethasone suppressibility of cortisol, however, may take over a month after delivery and CBG elevations may be seen up to 3 months post-partum .

Therefore, reassessment of disease state after delivery in a woman with CD is generally advised 2–3 months post-partum.

R.7.7. We recommend that breastfeeding be considered.


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