ESE Clinical Practice Guideline on functioning and nonfunctioning pituitary adenomas in pregnancy

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Abstract

Pregnancies are rare in women with pituitary adenomas, which may relate to hormone excess from secretory subtypes such as prolactinomas or corticotroph adenomas. Decreased fertility may also result from pituitary hormone deficiencies due to compression of the gland by large tumours and/or surgical or radiation treatment of the lesion. Counselling premenopausal women with pituitary adenomas about their chance of conceiving spontaneously or with assisted reproductive technology, and the optimal pre-conception treatment, should start at the time of initial diagnosis. The normal physiological changes during pregnancy need to be considered when interpreting endocrine tests in women with pituitary adenomas. Dose adjustments in hormone substitution therapies may be needed across the trimesters. When medical therapy is used for pituitary hormone excess, consideration should be given to the known efficacy and safety data specific to pregnant women for each therapeutic option. In healthy women, pituitary gland size increases during pregnancy. Since some pituitary adenomas also enlarge during pregnancy, there is a risk of visual impairment, especially in women with macroadenomas or tumours near the optic chiasm. Pituitary apoplexy represents a rare acute complication of adenomas requiring surveillance, with surgical intervention needed in some cases. This guideline describes the choice and timing of diagnostic tests and treatments from the preconception stage until after delivery, taking into account adenoma size, location and endocrine activity. In most cases, pregnant women with pituitary adenomas should be managed by a multidisciplinary team in a centre specialised in the treatment of such tumours.

1. Overview of recommendations

General recommendations: Preconception stage

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.

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

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

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

General recommendations: pregnancy

R.2.1. We recommend that pregnant women with a known pituitary adenoma, in particular those with a large pituitary adenoma (>1cm), 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.

R.2.2. We recommend that pregnant women with diagnosed hypopituitarism should have regular clinical and hormonal follow-up by an endocrinologist and an advanced nurse practitioner where relevant.

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.

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

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.

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 (⊕⊕OO).

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

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 fetal surveillance.

R.3.2. In general, breastfeeding is feasible and not contra-indicated.

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.

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.

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.

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

R.4.5. We recommend awaiting re-assessment of pituitary imaging and function until after delivery and breast-feeding.

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 (⊕⊕⊕O).

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 (⊕⊕⊕O).

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

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 (⊕OOO).

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 (⊕⊕OO).

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 (⊕OOO).

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

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

Acromegaly

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

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.

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 (⊕OOO).

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

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

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.

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

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

R.6.10. We recommend re-assessing disease activity after pregnancy.

Cushing's disease

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

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.

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 should be carefully considered (⊕OOO).

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.

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

R.7.6. We recommend to re-assess disease activity after pregnancy.

R.7.7. We recommend that breastfeeding be considered.

2. Introduction: 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 postpartum with a height of up to 12 mm followed by a gradual decline to normal size within 6 months after delivery (1-3). This growth is related to lactotroph hyperplasia starting in the first month of pregnancy and due to the increased concentrations of oestradiol (E_2) (4).

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 (5-7). 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 (7, 8). 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 (5, 6).

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 (5, 8). Serum insulin-like growth factor-I (IGF-I) levels increase significantly above the age-specific reference range for non-pregnant women (5, 9).

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 (10, 11). hCG is a potent TSH receptor ligand and therefore a reciprocal circulating

pattern of TSH and hCG is present in the first trimester (10, 12). Due to increased concentrations of thyroxine binding globulin (TBG), circulating levels of total thyroxine (T4) and triiodothyronine (T3) are elevated (10, 11) in pregnancy, and interpretation of thyroid function tests therefore requires appropriate reference ranges (11, 13). 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 24h-urinary free cortisol excretion. The placenta produces large amounts of corticotropin releasing hormone (CRH) and its related urocortin peptides (14, 15), the circulating concentrations of which rise exponentially in the third trimester of pregnancy (16, 17). 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 (8, 18).

Increased placental vasopressinase activity is counterbalanced by increased pituitary vasopressin release in normal pregnancy but may manifest as transient diabetes insipidus or unmask incipient diabetes insipidus (19).

3. Methods

3.1. Guideline working group

These guidelines were developed on behalf of The European Society of Endocrinology (ESE), the chairs of the working group Anton Luger and Olaf Dekkers being appointed by the ESE Clinical Committee. Olaf Dekkers served as methodological expert, Beverly MK Biller as representative of the Endocrine Society, USA, Rasa Verkauskiene as European Society for Paediatric Endocrinology (ESPE) representative, Sofia Llahana as ESE Nurses Representative, Nienke Biermasz as European Neuroendocrine Association (ENEA) representative, Susan Webb as European Reference Network on Rare Endocrine Conditions (ENDO-ERN) representative, Fahrettin Kelestimur as Pituitary Society representative and Gesthimani Mintziori as European Young Endocrinologists and Scientists (EYES) representative. The other members were suggested by the chairs and approved by the Clinical Committee of ESE. The multidisciplinary team consisted of the following experts: endocrinologists Anton

Luger (Austria), Olaf Dekkers (the Netherlands), Jens Otto Jorgensen (Denmark), Philippe Chanson (France), Dominique Maiter (Belgium), Fahrettin Kelestimur (Turkey), Beverly MK Biller (USA), Susan Webb (Spain), Nienke Biermasz (the Netherlands), and Gesthimani Mintziori (Greece), an endocrine nurse Sofia Llahana (UK), an obstetrician and gynaecologist Felice Petraglia (Italy), a neurosurgeon Michael Buchfelder (Germany), and a paediatric endocrinologist Rasa Verkauskiene (Lithuania). Leonie Broersen joined the guideline working group for methodology support. The working group had two in-person meetings (February 2019 and November 2019) and communicated by phone and email. Consensus was reached upon discussion; minority positions were taken into account in the rationale behind recommendations. Prior to the process, all participants completed conflict of interest forms.

3.2. Target group

This guideline was developed for health care providers who may see pregnant patients with pituitary adenomas. In general, these women (with the exception of those with small nonfunctioning adenomas and microprolactinomas) should preferably be managed by a multidisciplinary team in expert pituitary centers, including Pituitary Tumor Centers of Excellence (PTCOE) (20) / Endo-ERN Reference Centers and their affiliated regional healthcare providers. General practitioners and patients might also find the guideline useful. The guideline can serve as a source document for the preparation of patient information leaflets and educational materials.

3.3. Aims

The purpose of this guideline is to provide clinicians with practical guidance for the management of patients with a pituitary adenoma during pregnancy or considering pregnancy. In clinical practice, both the recommendations and the clinical judgment of the treating physician should be taken into account. Recommendations are not meant to replace clinical acumen. Certain recommendations may not be feasible in individual countries and must be interpreted in the context of available resources.

3.4. Summary of methods used for guideline development

The methods used for establishing such guidelines have been described in detail previously (21). In short, the guideline used GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) as a methodological basis. The first step was to define clinical questions (see Section 3.5); the second step was a systematic literature search (see Section 3.6). After including all relevant articles for each clinical question, we rated the quality of the evidence, and estimated an average effect for specific outcomes where possible. The quality of the evidence behind the recommendations was classified as very low ($\oplus OOO$), low ($\oplus\oplus OO$), moderate ($\oplus\oplus\oplus O$), or strong ($\oplus\oplus\oplus\oplus$). Not all recommendations were formally graded (see below).

For the recommendations, we considered the quality of the evidence, the balance of desirable and undesirable outcomes, and individual values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc.) (22, 23). The recommendations are worded as “recommend” (strong recommendation) or “suggest” (weak recommendation). The meaning of a strong recommendation is that all reasonably informed persons (clinicians, politicians, and patients) would want the management in accordance with the recommendation. For a weak recommendation, most persons would still act in accordance with the guideline, but a substantial number would not (23).

Formal evidence syntheses were performed and graded only for recommendations addressing our initial clinical questions (see Section 3.5). Other recommendations were based on good practice, experience of the panelists and were not formally graded (24). All recommendations are accompanied by an explanation.

3.5. Clinical questions, eligibility criteria and endpoint definition

At the start of this guideline process, the committee members formulated 21 clinical questions regarding diagnosis, treatment, and outcome related to pregnant women with a pituitary adenoma. Out of these 21 clinical questions, the five most relevant questions were prioritized and formed the basis of a systematic literature search and review **(Table 1)**.

Discrepancies in results and estimations of our findings compared with previously published reviews (25, 26) are mainly due to strict application of inclusion criteria, e.g. not including review articles, which also minimizes risk of bias by including the same population multiple times.

3.6. Description of search and selection of literature **(Table 1 and Figure 1)**

We searched four electronic medical databases (PubMed, Embase, Web of Science, and COCHRANE). The literature search for questions I-III was performed in July 2019, and the literature search for questions IV-V was performed in September 2019. Additionally, all searches were repeated in PubMed in November 2019, references of included articles were checked to identify potentially relevant additional articles.

For question I (safety profile of medical treatment of prolactinomas in pregnancy), we identified 1235 papers, 46 were included, 3 were added after searching through the references, and 2 were added in November 2019, for a total of 51 studies. For sub-questions Ia (safety profile of medical treatment of hyperprolactinaemia in pregnancy) and Ib (safety profile of medical treatment from studies combining data of prolactinoma and hyperprolactinaemia in pregnancy), 26 additional studies were included. For question II (safety profile of medical treatment of acromegaly in pregnancy), we identified 381 papers, 47 were included. For question III (safety profile of medical treatment of Cushing's disease (CD) in pregnancy), we identified 248 papers, 10 met the inclusion criteria. For question IV (incidence of tumour growth in pregnancy), we included 4 studies on acromegaly, 18 studies on prolactinomas and one on non-functioning pituitary adenomas; no studies on CD could be included. For question V (safety of pituitary surgery), we included 28 papers. A flow diagram of study inclusion is presented in Figure 1. For the outcome "small for gestational age", birth weight and term of pregnancy were compared using population-based reference values from the United States (27).

3.7. Review process and endorsement of other societies

A draft of the guideline was reviewed by 4 experts in the field (see 'Acknowledgments' section) and was distributed to all ESE members for comments. In addition, the following

societies and networks were asked to review the guidelines: the European Association of Neurosurgical Societies, the Endocrine Society, USA, the European Reference Network on Rare Endocrine Conditions (Endo-ERN), and the European Neuroendocrine Association (ENEA). Furthermore, patient groups were approached to review the guidelines. All comments and suggestions were then discussed and implemented as thought appropriate by the panel.

4. Summary and interpretation of the evidence from systematic literature reviews

4.1. Clinical question I: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with prolactinoma?

We included 51 studies on medical treatment of prolactinomas during pregnancy (28-78), and another 26 studies on medical treatment of hyperprolactinaemia (including patients with prolactinomas in mixed populations) (79-104), see Appendix 1 Table 1 for description of the GRADE evidence and Appendix 1 Table 2 for details of included studies. In total, 837 pregnancies in patients with prolactinoma were included, resulting in 762 live infants. For hyperprolactinaemia from mixed aetiology, the numbers were 2144 pregnancies, resulting in 1873 live infants. Patients used mainly bromocriptine or cabergoline, but also (dihydro)ergocryptine, lergotrile, metergoline, and quinagolide during pregnancy. In the majority of patients with prolactinoma (553 pregnancies) medical treatment was stopped after confirmation of pregnancy (73.2%, 95% confidence interval [CI] 69.9-76.4%). Medical treatment was later restarted during pregnancy in 29 out of these 553 patients (5.2%, 95%CI 3.5-7.4%). A summary of safety and teratogenicity outcomes is shown in Appendix 1 Table 3. Of note, not all reported maternal events happened during the use of medication for prolactinoma or hyperprolactinaemia. No formal control groups were included, hampering firm conclusions.

There was one reported neonatal death after use of cabergoline for prolactinoma during pregnancy (no further data on duration or timing of treatment was provided). There were four cases of neonatal death after medical treatment for hyperprolactinaemia during

pregnancy, all of whom after treatment with bromocriptine (no further data provided). In women with prolactinomas there were 17 infants with malformations: 6 after use of bromocriptine, and 11 after use of cabergoline. Additionally, there were 30 malformations after medical treatment of hyperprolactinaemia during pregnancy: 5 after use of bromocriptine, and 25 after use of cabergoline. The data did not indicate a higher prevalence of congenital malformations after use of medication for prolactinoma (2.2%, 95%CI 1.3-3.5) or hyperprolactinaemia (2.5%, 95%CI 1.8-3.3) during pregnancy than in the general population (2.4% in Europe) (105).

In addition, safety and teratogenicity outcomes did not clearly differ between bromocriptine and cabergoline (see Appendix 1 Table 3). The most commonly reported (maternal) signal was the percentage of patients with symptomatic tumour growth (5.4%, 95% CI 3.9-7.1). Based on our review of tumour growth during pregnancy (see section 4.4), this was most likely observed predominantly in women with macroadenomas. Often, prolactinoma medication was restarted in these patients to treat symptoms of tumour progression.

4.2. Clinical question II: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with acromegaly?

We included 47 studies on medical treatment for acromegaly during pregnancy (55, 106-151), see Appendix 2 Table 1 for the GRADE evidence and Appendix 2 Table 2 for study details. In total, 146 patients were included, who had 159 pregnancies, resulting in 159 live infants. Patients used bromocriptine, cabergoline, unspecified dopamine agonists, octreotide, lanreotide, pasireotide, unspecified somatostatin analogues, or pegvisomant during pregnancy. A summary of safety and teratogenicity outcomes after medical treatment for acromegaly during pregnancy is shown in Appendix 2 Table 3. Importantly, not all reported maternal events occurred during the use of medication for acromegaly, as patients may have used the drugs for a shorter period. We performed subgroup analyses of patients using medication until pregnancy confirmation only, and of patients using medication during a larger part of pregnancy, i.e. also after pregnancy was confirmed.

In 79 pregnancies (71%), medical treatment for acromegaly was stopped after confirmation of pregnancy. There was one ectopic pregnancy during use of pegvisomant (146). There was one neonatal death from a pair of twins born after 28 weeks of pregnancy after use of

lanreotide (111). There were two malformations reported: a ureteral stenosis after octreotide LAR (2.6% out of 38 octreotide users, 95%CI 0.1-13.8%), and a single kidney after bromocriptine use. There was no indication from the data that congenital malformations are more prevalent after use of medication for acromegaly during pregnancy (1.3%, 95%CI 0.2-4.5) than in the general population (2.4% in Europe) (105). There was no clear difference in safety or teratogenicity between patients who used medication until confirmation of pregnancy only and patients who used medication during a longer period of pregnancy.

4.3. Clinical question III: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with Cushing's disease?

We included ten studies, reporting on 10 women, with medical treatment for Cushing's disease during pregnancy (152-161), some of which also involved patients with cortisol secreting adrenal adenomas. The GRADE evidence table is shown in Appendix 3 Table 1, and details of the studies are shown in Appendix 3 Table 2. Patients used metyrapone, ketoconazole, mitotane, and cabergoline during pregnancy. Adverse effects were reported in six out of ten mothers (60%, 95%CI 26-88%): gestational diabetes mellitus, pre-eclampsia, hypothyroidism, no milk for breastfeeding. Seven out of twelve infants (two pairs of twins) experienced adverse events (1 neonatal death; low birth weight, small for gestational age, pre-term, intensive care treatment), which is 58% (95%CI 28-85%). There were no congenital malformations reported. Numbers are too small to draw firm conclusions on preferred treatment and teratogenicity, based on published data.

4.4. Clinical question IV: What is the incidence of tumour growth during pregnancy in patients with a non-functioning or functioning (Cushing's disease, acromegaly, or prolactinoma) adenoma?

We included one study on tumour growth during pregnancy in non-functioning pituitary adenomas (162), 18 studies in patients with prolactinoma (44, 46, 51, 52, 55, 57, 64, 71, 72, 76, 78, 80, 162-167), and four studies in patients with acromegaly (55, 110, 119, 124); see Appendix 4 Table 1 for the GRADE evidence, and Appendix 4 Table 2 for details of included studies. Not all studies differentiated between micro- and macroadenomas. For non-

functioning pituitary adenoma, the only study reported on 16 pregnancies in 16 patients; for prolactinoma, studies reported on 753 pregnancies in 652 patients, with separate data on 146 microadenomas and 162 macroadenomas. For acromegaly, there were 128 pregnancies in 97 patients, with separate data on 17 microadenomas and 106 macroadenomas. There were no reported Cushing's disease cases.

Average tumour size before and after pregnancy was compared in 4 studies that showed unchanged (46), increased (80, 162), or reduced adenoma size (76). For non-functioning pituitary adenomas, symptomatic tumour growth (headache or visual defects) occurred in 6 patients (37.5%, 95%CI 15.2-64.6%) and radiologically confirmed tumour growth as defined by the individual studies was seen in 4 patients (25.0%, 95%CI 7.3-52.4%). In prolactinoma, symptomatic tumour growth during pregnancy was seen in 52 patients (9.0%, 95%CI 6.8-11.6%) and radiological tumour growth in 40 (10.6%, 95%CI 7.7-14.2%). For microprolactinomas, there were 7 patients with symptomatic tumour growth (15.2%, 95% CI 6.3-28.9%) and 15 with radiological tumour growth (14.4%, 95%CI 8.3-22.7%). For macroprolactinomas, there were 36 patients with symptomatic tumour growth (30.5%, 95%CI 22.4-39.7%) and nineteen with radiological tumour growth (13.9%, 95%CI 8.6-20.8%). In acromegaly, symptomatic tumour growth during pregnancy was seen in 9 patients (7.0%, 95%CI 3.3-12.9%) while radiological tumour growth occurred in 6 (5.4%, 95%CI 2.0-11.4%). For GH-producing microadenomas, 3 patients exhibited symptomatic tumour growth (30.0%, 95%CI 6.7-65.2%), and 2 only radiological tumour growth (25.0%, 95%CI 3.2-65.1%); however, the low number of patients precludes a firm conclusion regarding the true risk as can be seen from the wide confidence intervals. For GH-producing macroadenomas, there were 4 patients with symptomatic tumour growth (4.1%, 95%CI 1.1-10.2%), and 3 with radiological tumour growth (3.7%, 95%CI 0.8-10.3%).

4.5. Clinical question V: Is pituitary surgery safe for pituitary adenomas during pregnancy?

We included 28 studies on transsphenoidal surgery of pituitary adenomas during pregnancy (28, 49, 124, 135, 153, 157, 168-189), see Appendix 5 Table 1 for the GRADE evidence, and Appendix 5 Table 2 for study details. Pituitary surgery was performed in 33 cases during pregnancy. The vast majority of patients had hormone secreting macroadenomas (Appendix 5 Table 2). Surgery was performed during the first (n=2), second (n=24) and third (n=7)

trimester. The indications for surgery mainly included active Cushing disease, visual deterioration related to tumour growth or apoplexy. Surgery provided symptom relief in 25 cases out of 28 in whom effectiveness was reported (89.3%, 95%CI 71.8-97.7%). In total, nine women experienced surgery-related adverse events (diabetes insipidus, SIADH, cerebrospinal fluid leakage). This high percentage of adverse events might be related to the special indication for pituitary surgery in pregnancy being restricted to emergency situations. In total, nine infants showed adverse outcomes in the course of pregnancy (28.1%; 95%CI 13.7-46.7%). There was one miscarriage soon after surgery during the second trimester. Furthermore, there was one intrauterine death, and two cases of neonatal death not directly after surgery. Most adverse outcomes for infants occurred in mothers with Cushing's disease (eight out of nine infants with adverse events).

5. Recommendations and Rationale for the recommendations

5.1. General recommendations: Preconception stage

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 addition, side effects of medical therapy for the mother and foetus should be taken into account and discussed with women of reproductive age. In women with hypopituitarism, replacement therapy should be optimized, and assisted reproductive technologies (ART) should be discussed when appropriate. Women should be given relevant information about their chances of fertility and pregnancy depending on their diagnosis (see respective recommendations for each adenoma). Timing of pregnancy should be discussed and women should be encouraged to plan pregnancy after control of the underlying disease has been achieved. If unplanned pregnancy occurs, immediate

consultation should take place with a team that should include an endocrinologist, an obstetrician with expertise in managing high risk pregnancies for maternal indications and, in case of large pituitary adenomas, a dedicated pituitary neurosurgeon.

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

Rationale

The consulting endocrinologist should inform women seeking pregnancy that this is feasible in the majority of cases, that the outcome is generally good and that breast feeding is often possible (see respective recommendations for the different adenoma types and therapies). At the same time, it should be stressed that pregnancy constitutes a medical situation where expert knowledge and often collaboration between specialists from different fields is required. 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 (see **Table 2**), with special attention to possible associated metabolic or cardiovascular diseases.

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

Rationale

Due to possible compressive effects of macroadenomas, which may enlarge during pregnancy and possible adverse effects of therapies necessary to control size or function of pituitary adenomas, we advise discussing such patients in a multidisciplinary team including an endocrinologist, an obstetrician, a pituitary neurosurgeon and in some cases a neuroradiologist, a neuro-ophthalmologist and a reproductive endocrinologist. 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 non-functioning 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 (191) as surgery provides pituitary recovery in about 30% of cases (192, 193), in particular normalization of ACTH, cortisol and PRL (194). The surgical risk of a postoperative gonadotrophin deficiency and also a panhypopituitarism (14% (195)), which could impact on pregnancy course should be considered, and should be taken into account for the surgical decision.

R.1.4. We recommend that in women with a diagnosis of pituitary adenoma and hypopituitarism, hormone replacement therapy should be initiated or optimized 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 (196, 197). Women with childhood onset of hypopituitarism have much lower fertility rates (196-199).

The pre-conception consultation should include diagnosis of any pituitary deficiencies (see R.1.2.), initiation and optimisation of the replacement therapy aiming for mid-normal reference range values. The importance of adherence to treatment should be emphasised in relation to pregnancy outcomes and fetal health. Women with hypopituitarism and optimal replacement therapy often require ART (196, 200, 201), but in the absence of gonadotrophin deficiency they may conceive spontaneously (201, 202). 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 (199, 203-205). Even though pituitary hormone deficiency beyond gonadotropins has been correlated with reduced pregnancy rate and outcome, patients with hypopituitarism can be reassured that in vitro fertilisation (IVF) treatment is often successful (206).

Pituitary apoplexy occurring after the application of triptorelin, a GnRH analogue used for OS, has been described (207, 208), possibly due to previously undetected gonadotropinomas. It should be highlighted that although fertility outcomes and pregnancy rates for women with hypopituitarism are generally good, studies have shown that women

require multiple OS and/or ART cycles to achieve a live birth and the “take home baby rate” per cycle remains reduced (197, 201, 209).

5.2. General recommendations: pregnancy

R.2.1. We recommend that pregnant women with known pituitary adenoma, in particular those with a large pituitary adenoma (>1cm), 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

Pituitary adenomas may cause hypopituitarism, visual impairment or nerve palsies during pregnancy and therefore need special surveillance by an expert endocrinologist. Individualized management is needed throughout pregnancy, the frequency of consultations is determined by the clinical situation, and in uneventful cases, consultations can be limited. In patients with acromegaly and Cushing’s disease, special attention to glucose homeostasis and blood pressure is needed. Patients with a microprolactinoma or a nonfunctioning microadenoma will only need consultation with an endocrinologist during pregnancy if new symptoms such as headache or visual symptoms occur.

R.2.2. We recommend that pregnant women with diagnosed hypopituitarism should have regular clinical and hormonal follow-up by an endocrinologist and an advanced nurse practitioner where relevant.

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 (196, 200, 210, 211).

Patients on levothyroxine replacement therapy might require an increase in dose of up to 50% (11, 12). Free T4 levels should be used for monitoring, rather than TSH, which is not

reliable in patients with pituitary disorders (11, 212). Adequate dose should be checked during the first and second trimesters using gestational phase- and assay-specific reference values (13). Whereas an interval of 4-6 weeks has been suggested for fT4 measurement throughout pregnancy (200), not all members of this Clinical Guideline Committee monitor their patients that frequently.

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 22-24 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 (213). Dexamethasone should be avoided because it is insufficiently inactivated by placental 11β-HSD2 and may therefore cause harm to the foetus (196, 200, 210, 211, 214).

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 (19, 215).

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 (196, 200). Furthermore, large amounts of GH are secreted by the placenta during pregnancy. One large observational study revealed no relationship between GH replacement therapy regimens and pregnancy outcomes (216).

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. Patient and 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 (200, 210, 214, 217). 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 fetal circulation (218-221), its use is therefore to be avoided in most cases, especially in the first trimester. Relevant information can usually be obtained by unenhanced T1 and T2 weighted sequences. 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. Women with pituitary adenomas larger than 1 cm not previously treated with surgery or radiotherapy are at increased risk of visual field impairment during pregnancy (222). Together with the results of endocrine function and MRI, the neuro-ophthalmologic evaluation will guide the need for further action. The

frequency of neuro-ophthalmologic evaluations will be determined by signs and symptoms as well as by results of prior examinations.

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 (⊕⊕OO).

Rationale

In situations with chiasmal compression and severe loss of vision (impairment of visual acuity or OCT or severe visual field impairment) surgical decompression should be considered even if there is no detectable radiological enlargement of the tumour (191, 223, 224). Surgery provided symptom relief in 89.3% (95%CI 71.8-97.7%), see 4.5 for details. In case of other cranial nerve palsies or headache occurrence, particularly related to apoplexy, surgical resection should be individually discussed.

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

Rationale

Surgical indications for pituitary tumours are rare during pregnancy and surgery should generally be avoided. In cases of symptomatic tumour enlargement during pregnancy, medical treatment with dopamine agonists or somatostatin analogues may be attempted before undertaking transsphenoidal surgery. Severe visual disturbance related to pituitary apoplexy or tumour growth, and uncontrolled Cushing's disease are the main surgical indications during pregnancy.

There are no guidelines on transsphenoidal surgery in pregnancy. Evidence comes from small series (see 4.5) (223). The majority of cases published had surgery in the second trimester. The first trimester should be avoided if possible (225, 226). In the third trimester, preterm 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 centers, including Pituitary Tumor Centers of Excellence/Endo-ERN Reference Centers. The abovementioned

statements are supported by the neurosurgical literature on meningioma management during pregnancy (223, 227).

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

Rationale

Radiotherapeutical interventions are inappropriate during pregnancy due to their delay in the onset of effects and potential harm to the foetus.

5.3. 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 fetal 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 (228). A recent study showed that women with non-functioning adenomas were more likely to have Caesarean delivery compared to controls (relative risk 2.06, 95%CI 1.26-3.36). There was no solid evidence that pituitary tumours were associated with adverse pregnancy outcomes such as pregnancy-induced hypertension, pre-eclampsia, pre-term labour or still birth (162). Women should be informed early on in their pregnancy about the possibility of Caesarean delivery.

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 (110). 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 (157).

In women with ACTH deficiency, hydrocortisone stress dosing is recommended during labour, similar to that used in major surgical stress. Hydrocortisone 100 mg intravenously

should be initiated at the onset of active labour for vaginal delivery or pre-operatively for a Caesarian section. While it has been suggested that this should be followed immediately by a continuous intravenous infusion of hydrocortisone 200 mg/24 hours throughout labour for both vaginal delivery or Caesarian section (200, 210, 229), most members of this Clinical Guideline Committee are using lower doses. After delivery, the pregnancy hydrocortisone dose should be gradually tapered down to the pre-pregnancy dose (200, 210, 214, 217).

R.3.2. In general, breastfeeding is feasible and not contra-indicated.

Rationale

Individual concerns such as the need to control tumour size and activity as well as type of drug therapy employed need to be considered, please see specific chapters and list of drugs used for the treatment of pituitary adenomas (Appendix 6).

5.4. Nonfunctioning adenomas (NFAs)

In women with NFAs diagnosed prior to pregnancy, the general recommendations for the preconception stage, pregnancy, delivery and breastfeeding apply (see chapters 5.1-5.3).

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.

Rationale

As the pituitary gland expands during pregnancy, surgery should be considered on the basis of NFA size and proximity to the optic pathways (see R.1.3.). 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 (191), since surgery provides recovery of hypopituitarism in about 30% (192). The risk of postoperative pituitary deficiency, which is estimated around 14% (195) should be integrated in the surgical decision particularly in case of normal preoperative pituitary function.

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 (55, 162, 222). A study monitored 65 women with treatment naïve pituitary adenomas during 111 pregnancies; none of the patients with a microadenoma developed visual impairment after up to four full-term pregnancies (222). Additionally, new onset pituitary hormone deficiencies are unlikely.

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 (222). 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 (⊕OOO).

Rationale

The main indication for pituitary surgery during pregnancy is to protect visual function (191, 223, 224). A trial with cabergoline might be considered. Apoplexy is another rare but acute condition in a patient with NFA that may require surgical intervention. If possible, the first trimester should be avoided and in the third trimester preterm delivery should be considered (see R.2.7.).

R.4.5. We recommend awaiting re-assessment of pituitary imaging and function until after delivery and breastfeeding.

Rationale

A de novo radiological diagnosis of a pituitary mass lesion during pregnancy is usually based on symptomatic visual field defects and/or pituitary apoplexy. Before making a NFA diagnosis, other diagnoses should be excluded, e.g. CD, acromegaly, prolactinomas, hypophysitis. Re-assessment of pituitary imaging and function should be done between 3 and 6 months after delivery, preferably after breastfeeding but definitely before planning a following pregnancy, unless the clinical picture suggests otherwise.

5.5. Prolactinomas

A prolactinoma is expected to be present in 1/500 women of reproductive age (230) and is frequently associated with infertility (25, 231). Very high prolactin levels will usually cause amenorrhoea, while milder degrees of hyperprolactinaemia may cause oligomenorrhoea or luteal phase insufficiency (232). Furthermore, in the presence of regular cycles, abnormal prolactin concentrations might alter hormonal conditions for adequate embryo implantation (230).

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

Rationale

In agreement with guidelines from both the Pituitary Society and the Endocrine Society, we consider a desire for pregnancy as an indication for strict prolactin normalization in young women with a prolactinoma, even in those with mild hyperprolactinaemia and apparently regular normal cycles (232, 233). 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 (25, 234) and to counsel patients whether prompt conception is safe.

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 (⊕⊕⊕O).

Rationale

Dopamine agonists (DA) are the standard treatment for women in reproductive age with a micro- or a macroprolactinoma, restoring ovulation in 80-90% (234, 235). Few studies have directly compared the currently available DA in their efficacy to allow gestation (236). We suggest using cabergoline because it is better tolerated and has a higher efficacy than bromocriptine in both normalizing prolactin levels (63, 232, 237, 238) and inducing pituitary tumour shrinkage (232, 235, 239). Transsphenoidal adenomectomy is an option in selected cases (25, 230) such as intolerance or resistance to DA or personal preference. It is considered less efficient than medical therapy, leading in expert hands to a sustained normalization of prolactin levels in 70–80% of microadenomas, but only in 30–40% of macroadenomas (240, 241). However, in macroprolactinomas (25, 232, 233) it might reduce the risk of tumour enlargement during a subsequent pregnancy (25) and optimize the chances of prolactin normalization with subsequent DA treatment (242). The risk of postoperative pituitary deficiency remains very limited (240, 243).

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

Rationale

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 (232, 235).

We performed a systematic review of reports published until 2019 on pregnancies initiated under cabergoline treatment (n=1272), of which some patients used cabergoline during a larger part of pregnancy (see section 4.1 and Table 3). The 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 (80, 244, 245). 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 (25, 80, 230), one study with a follow-up of 61 children of up to 16 years reported 2 children who developed epilepsy (one after distress at birth because of abruptio placentae) and 2 with a pervasive developmental disorder (83). 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 (246). Thus, quinagolide appears to be less safe during pregnancy, although the available data are limited.

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 (⊕OOO).

Rationale

DA cross the placental barrier and, although the use of bromocriptine and cabergoline has not been associated with increased teratogenicity (see 4.1), it is recommended to discontinue treatment as soon as pregnancy is confirmed (25, 232, 233).

For women with a macroprolactinoma close to the optic chiasm, it should be confirmed that tumour volume has shrunk substantially prior to conception (25). After shrinkage, it is generally safe to discontinue DA. 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 (see R.5.8.). 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. However,

one study showed that a large proportion of cystic tumours can also be reduced by DA (247).

Limited safety data are available regarding the use of bromocriptine throughout gestation in mothers with hyperprolactinaemia (n=36 pregnancies and n=36 live infants) with no abnormalities noted in the infants except for one balanced translocation of chromosomes 8 and 12 (50), and one case of testicular ectopy, which corrected spontaneously after 7 months (57). The record is even smaller for cabergoline used throughout gestation (n=34 pregnancies and n=26 live infants), with no recorded malformations in live infants. There was one fetal death at week 34 in a mother suffering from severe pre-eclampsia (34). A report on 25 pregnancies from India with cabergoline therapy throughout pregnancy showed one fetal death, 3 missed abortions, 3 pregnancy terminations due to major congenital malformations, 2 premature deliveries and 18 live infants (64).

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

Rationale

Pregnancy is associated with a physiological elevation of prolactin concentrations (248, 249) and serum prolactin levels may increase about 10-fold throughout pregnancy, reaching levels of 150-300 µg/L at term (250-252). A similar prolactin secretory pattern is usually seen in pregnant women with a prolactinoma, often with a greater amplitude (25). However, in some prolactinoma patients, serum prolactin levels may not increase further during pregnancy and prolactin is therefore not a reliable marker of eventual tumour progression (25, 253). Therefore, we do not recommend prolactin measurements during gestation in prolactinoma patients. Furthermore, serum prolactin concentrations do not reliably predict the likelihood of normal breastfeeding (254).

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.

Rationale

Data are few regarding development of pituitary deficiencies during pregnancy in women with prolactinomas. In a study including 83 patients with prolactinoma, two patients developed TSH deficiency and one developed ACTH deficiency during pregnancy. All three had a macroadenoma and tumour growth was observed in two of them (55). Thus, in women with a microprolactinoma routine endocrine care is not mandatory and endocrinologists should be consulted only in case of symptoms or signs suggesting tumour growth or new onset hypopituitarism.

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 (⊕⊕OO).

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% (95% CI 22.4-39.7%), see section 4.4. A much smaller risk – between 1 and 4% – was observed in cases where the tumour had been operated, irradiated or sufficiently reduced by prolonged DA therapy before pregnancy (25, 36, 51, 76, 165). Data on 85 viable pregnancies in 46 patients with a macroprolactinoma demonstrated tumour growth-related symptoms 12 times in 9 patients (19.6%) including 3 cases of apoplexy (255).

Therefore, we recommend careful individualised follow-up with clinical evaluation, including visual field testing, visual acuity, OCT and in case of visual deterioration MRI assessment without gadolinium in pregnant women with a macroadenoma which could not be sufficiently reduced by prior treatment.

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 (⊕OOO).

Rationale

In case of symptomatic prolactinoma growth during pregnancy, restarting DA is effective in most cases and is therefore first choice (55, 76, 78, 80, 162). Cabergoline is slightly

preferable in terms of side effects and efficacy, the doses in pregnant women are similar to those in non-pregnant women and the lowest possible dose should be used.

Transsphenoidal surgery is indicated if medical treatment fails to rapidly induce sufficient tumour shrinkage and symptom relief. Rapid decompressive surgery is also indicated in many cases of progressively symptomatic pituitary apoplexy (181, 223), which may cause severe visual defects. In case of sudden and severe headache, ophthalmoplegia or limited visual field impairment, surgery should be discussed case-by-case (255). It may occur both in patients treated with DA (64) and in untreated pregnant women with a prolactinoma (247). However, haemorrhagic necrosis of a macroprolactinoma during pregnancy may also be minor or asymptomatic, thus not requiring surgery and having a favourable outcome without treatment (230).

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

Rationale

Lactation is considered safe and feasible. It is also considered safe to withhold DA treatment as long as breastfeeding is desired (81, 230). In individual cases of macroadenoma requiring DA throughout pregnancy, the advice to breastfeed and stop DA should be individualized (256). 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 the pregnancy and lactation. In various studies, these percentages range from 17-68%, on average 40% for a median time of 22 months (46). There is a higher number of remission in microprolactinomas (46%) than macroprolactinomas (26%). Biochemical remission may coincide with tumour disappearance, but small remnant tissue may also persist (46, 230). We therefore

recommend re-evaluating the status of the prolactinoma 1 to 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.

5.6. Acromegaly

Acromegaly may be associated with infertility, through several mechanisms (257), including hypopituitarism and hyperprolactinaemia related to a mixed GH-PRL-secreting adenoma or to pituitary stalk compression. Moreover, excess GH/IGF-I secretion may have a 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 (258) may worsen in pregnancy and thereby harm the foetus (110, 116, 124, 147). Therefore, control of acromegaly and its complications is recommended in women with acromegaly who wish to conceive. Glucose tolerance and blood pressure should be monitored during pregnancy. Tumour mass effect may also be a concern during pregnancy and needs to be carefully evaluated before pregnancy to determine appropriate treatment (see **Table 2**).

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

Rationale

Surgery is first line treatment in newly diagnosed women with acromegaly seeking pregnancy (259). If complete removal of the tumour is not feasible, debulking surgery is frequently indicated, especially if the tumour abuts the optic chiasm and impairs visual

function (even if the risk of growth during pregnancy is very low) (260). Decision making and intervention should take place in expert pituitary centers, including Pituitary Tumor Centers of Excellence/Endo-ERN Reference Centers .

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 (110, 116, 119, 124) and some patients may experience symptom relief during the first half of pregnancy (260). This, along with the very low risk of symptomatic tumour growth (7.0%, 95% CI 3.3-12.9%, see section 4.4), allows postponement or withdrawal medical or surgical treatment until after delivery unless the mass lesion demands treatment (260). On the other hand, in case of infertility, even if cycles are regular and PRL levels are normal, treatment of acromegaly may be useful to restore fertility (257).

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 (⊕OOO).

Rationale

If complete surgical removal of the adenoma is unfeasible (261), primary medical therapy may be considered even though no drug is approved by either EMA or FDA for the treatment of acromegaly during pregnancy. The potential risks of using these drugs must be weighed against their benefit for fertility and disease control. For more information see links to summaries of product characteristics (SPCs) and FDA and EMA categorization (Appendix 6).

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 (see section 4.2) (260). In 71% of the patients, first generation somatostatin analogue treatment was stopped before the end of the first trimester; a smaller number of patients continued treatment throughout pregnancy. Pregnancy was usually uneventful, and most women delivered healthy babies of appropriate height and weight at term, apart from one case of a large newborn (260). Lastly, 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. Despite their different category classification by FDA (see links in appendix 6), there is no evidence for preferring octreotide to lanreotide. There are insufficient data about pasireotide use in pregnancy to make any recommendation about this 2nd 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 (261). With the reassuring safety data reported in this guideline, continuation of depot first generation somatostatin analogues up to confirmation of pregnancy may however be acceptable and preferred by patients.

The experience with pegvisomant is limited. Data on 35 pregnancies (27 involving maternal and eight paternal pegvisomant exposures) in which pegvisomant treatment of the mother was interrupted as soon as the pregnancy was diagnosed, do not suggest adverse consequences of pegvisomant on pregnancy outcome (146). Data are however too limited to recommend this treatment during pregnancy, unless no other therapy controls severe symptoms of acromegaly.

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

Rationale

There is no indication based on available literature that treatment with cabergoline, octreotide or lanreotide during pregnancy results in more congenital malformations (1.3%) than in the general population (2.4% in Europe) (105), see section 4.2. However, as clinical

data on the safety of octreotide, lanreotide or pegvisomant are limited, women of childbearing age who receive these drugs should discontinue the treatment when pregnancy is confirmed as a safety precaution. Since the high oestrogen levels during pregnancy induce GH resistance, acromegaly symptoms tend to improve, and stopping drugs is generally regarded as safe. Only severe headache, serious endocrine symptoms or tumour volume issues may require reinstitution of drugs. In the infrequent cases when this is needed, we suggest to start dose titration with short acting sc octreotide aiming at the lowest possible effective dose.

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) (262), which cross-reacts with pituitary GH in most immunoassays (263). During the first trimester of normal pregnancy, maternal IGF-I levels decrease by about 30% (264) 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 (265); in some cases this peak is not observed (110, 116, 119, 124). Taken together, measurements of serum GH and IGF-I levels do not provide useful clinical information and are therefore not recommended (261).

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.

Rationale

During normal pregnancy, the pituitary size may increase by up to 45% during the first trimester, which may predispose to compressive symptoms (222). It is unclear if pregnancy may trigger growth of a pre-existing GH-secreting pituitary adenoma, but discontinuation of somatostatin analogue treatment may allow regrowth of the tumour (113, 126). Overall, symptomatic tumour growth during pregnancy in acromegaly is seen in 7.0% of patients (95% CI 3.3-12.9%), see section 4.4. Development of visual field defects during pregnancy is rare (124, 222, 260), whereas headache is more frequent (110, 116, 124). Surveillance with

neuroophthalmological evaluation and - in case of visual impairment - MRI without contrast is indicated.

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

Rationale

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 (223). Medical treatment with DA has also been used but is probably less effective (110, 117, 118, 122, 124, 143, 150, 266). The duration of the treatment depends on the severity of symptoms and some patients have been treated throughout with dopamine agonists or first generation somatostatin analogues (260). Treatment of hyperglycaemia and hypertension should follow general guidelines for pregnant women (110, 116, 147).

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

Rationale

Breastfeeding is generally possible and not contraindicated (106, 110-113, 116, 139). As a safety principle, somatostatin analogues and pegvisomant should be avoided in nursing mothers.

R.6.10. We recommend re-assessing disease activity after pregnancy.

Rationale

Shortly after delivery, a rebound of disease activity is frequently observed (110, 116, 124, 126, 139, 267); therefore early resumption of treatment may be indicated. A postpartum MRI should be performed in most patients with a previously documented adenoma, timing depending on disease severity, and known remnant. Gadolinium should not be used if the mother is breastfeeding.

5.7. Cushing's disease

Although this Guideline is focused on pituitary tumours and pregnancy, it is important to note that published data often include adrenal as well as pituitary cases of Cushing's syndrome (CS), and that hypercortisolism from any source may have a significant negative impact on the mother and foetus. 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) (26). This is in contrast to non-pregnant women, where CD is responsible for 70% of the cases.

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

Rationale

Pregnancy should be avoided in the presence of Cushing's syndrome of any aetiology, given the increased incidence of both maternal and foetal complications (18, 26, 268). Women with active CS show a high incidence of preterm deliveries, probably due to more frequent complications during pregnancy such as gestational diabetes mellitus, hypertension or preeclampsia; additionally, a higher rate of Caesarean section in comparison to cured CS is reported (51.7 vs. 21.9 %) (26). Foetal risks are also higher, and include deaths, preterm births, neonatal infections, hypoglycaemia, and respiratory distress. Foetal loss is higher in non-treated mothers (30.6% of cases), but also increased in women treated during pregnancy, either medically (20.8%) or surgically (12.5%). Other major foetal morbidities are preterm delivery (66.3% in untreated patients, 76.2% if treated medically, 56.1% if treated surgically during pregnancy) and low birth weight (68.3%, 68.8% and 73.3%, respectively) (18).

When foetal loss and global foetal morbidity are compared between active and cured CS, both are much higher in active disease (23.6 vs. 8.5% and 33.3 vs. 4.9%, respectively). In cured CS, both maternal and foetal risks tend to normalize. Prior obstetric complications are much more frequent than in the general population; since diagnostic delay in CS is very

common in non-pregnant women, this suggests there is a negative effect of undiagnosed hypercortisolism long before the diagnosis of CS.

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. However, biochemical confirmation is needed and this can be challenging. The HPA axis is activated during normal pregnancy producing increased levels of CRH (much of it originating from the placenta), ACTH and serum total and free cortisol (211). There is also increased hepatic production of cortisol binding globulin related to high levels of oestrogen, which further increases measured serum cortisol (211). Urine free cortisol (UFC) excretion increases up to 3-fold during pregnancy and overlaps with CS levels (269). Therefore, UFC values above this threshold are needed to be confident of the diagnosis. Suppression of cortisol by dexamethasone is blunted in pregnancy, so the 1mg overnight dexamethasone suppression test is not advised due to the risk of false positive results (269); up to 60% of normal pregnant women may fail to suppress below 50 nmol/L (1.8 μg/dL) (211). 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. Late night salivary cortisol levels also increase during pregnancy, but it has been reported that it may prove to be a valuable tool to diagnose CS in pregnancy with sensitivities of >80% and specificities of >93% using an ELISA-Cortisol EIA kit [salimetrics] and the following cut-offs: 0.255 μg/dL (7.0 nmol/L) for the 1st trimester, 0.260 μg/dL (7.2 nmol/L) for the 2nd trimester, and 0.285 μg /dL (7.9 nmol/L) for the 3rd trimester (270). If confirmed with other assays, this may become the diagnostic test of choice when CS is suspected in a pregnant woman.

When the diagnosis of CS has been established, biochemical testing to determine the location is also challenging; insufficient data are available for high dose dexamethasone and CRH testing to make a recommendation (271). 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. MRI with gadolinium could be performed during pregnancy given that no obvious adverse events have been reported, but the balance between the benefit and the potential risk should be carefully discussed. Bilateral inferior petrosal sinus sampling is not advised during pregnancy due to the radiation involved and the increased potential for venous thrombosis (272). 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 (⊕OOO).

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%) (26). Only ten cases of Cushing's disease with medical treatment during pregnancy were found in the literature (see section 4.3). Drugs most often reported were cabergoline, ketoconazole and metyrapone. However, none is approved for use in pregnancy. Adverse event rates were high for both mother (60%, 95%CI 26-88%) and infant (58%, 95%CI 28-85%) although no congenital malformations were reported. There are insufficient data about pasireotide and osilodrostat use in pregnancy; due to their side effects they should be avoided.

The limited number of cases described precludes any definite conclusion as to the best management for CS during pregnancy; it depends on the cause, the stage of pregnancy and the severity of hypercortisolism. However, 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 (18, 26, 272).

If treatment is considered necessary, surgery in the second trimester has been recommended as a first choice treatment but evidence is limited (see 4.5). No specific congenital malformations appear to be more frequent in babies delivered from CS patients (26).

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

The multidisciplinary team should include obstetricians, pituitary specialists, neonatologists, and specialised endocrine surgeons. Mild cases of CS, especially those discovered late in pregnancy, may be treated conservatively by controlling co-morbidities. In women who become pregnant while on anti-cortisolic treatment (exception cabergoline), there should be 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) (273). In a systematic review of pregnancies in women diagnosed with CS, 61 underwent surgery at a gestational age of 21 (range 17–26) weeks. Among these, 11 were transsphenoidal pituitary surgeries, 44 unilateral adrenalectomies and 6 bilateral adrenalectomies. Seventy-seven percent attained remission, 12% were still active and in 10% information was not available. Foetal loss (6.7% vs. 28.6%), preterm birth (56.1% vs. 80%), and low birth weight (70.6% vs. 100%) were lower if remission was attained after surgery compared to those not in remission (26).

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 3 cases of CD with good maternal-foetal outcome, but breast feeding would not be possible. No reports of pasireotide or osilodrostat use during pregnancy in CS are available. Mifepristone, a glucocorticoid receptor blocker available in some countries, is contraindicated as it is also a progesterone blocker used to terminate a pregnancy.

The possibility of premature delivery should be anticipated in CD, and consideration given to induced early delivery if indicated. When control is not possible, with life-threatening risks for the mother and the foetus, pregnancy termination for medical reasons should be discussed.

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 (274-277). A recent cohort study of 208 patients with CS (89.4% of pituitary origin) showed an overall thrombotic rate of 18% (276). Anti-thrombotic prophylaxis has been shown to reduce morbidity and mortality in Cushing's syndrome (275, 277). Separate from this, the risk of thrombosis is also increased in pregnancy. Therefore, risk might be even higher in pregnant women with CS. However, there are currently no data addressing the question of whether thromboprophylaxis would be beneficial and safe in pregnant women with CS. Given the clearly increased thrombosis risk, the panel concluded it is reasonable to consider prophylactic treatment with low molecular weight heparin.

R.7.6. We recommend to re-assess disease activity after pregnancy.

Rationale

A reassessment of cortisol excess should be conducted after delivery in women with Cushing's disease. 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 (272, 278). Restoration of normal dexamethasone suppressibility of cortisol, however, may take over a month after delivery (211) and CBG elevations may be seen up to 3 months post-partum (278). Therefore, re-assessment 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

Rationale

Breastfeeding is not contraindicated if the mother's general condition allows it, and she is not taking steroid synthesis inhibiting drugs, pasireotide or cabergoline.

Table 4 should be inserted here: Legend: Core recommendations

6. Suggestions for future research

Many questions still remain about the optimal management of pituitary tumours in pregnant women. We suggest that future research include the following questions:

- Is transsphenoidal surgery for pituitary adenomas safe during pregnancy?
- If surgery is needed for pregnant women with pituitary tumours, is there an optimal timing or can it be done during any trimester?
- Are pasireotide and pegvisomant safe and effective in pregnant women with acromegaly?
- Can the utility of trimester-based cutoffs for late-night salivary cortisol in pregnancy be confirmed?
- Are there any novel methods that would establish the diagnosis of Cushing's disease in pregnancy, given the activation of the hypothalamic-pituitary-adrenal axis in normal pregnancy?
- Does therapy with low molecular weight heparin (LMWH) reduce the risk of thromboembolic events in pregnant women with Cushing's disease?
- Is LMWH safe for pregnant women and the foetus when used in Cushing's disease?
- What are the benefits and risks of medical treatment in pregnant women with Cushing's disease, particularly the new drugs including pasireotide and osilodrostat?

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Declaration of Interest

BMK Biller: receipt of consultation fees from Ascendis, Aeterna Zentaris, Chiasma, Diurnal, Merck Serono, Novo Nordisk, Ono, Pfizer, Recordati, Strongbridge, Tiburio and grants or research support to Massachusetts General Hospital from Crinetics, Ionis, Novo Nordisk, Novartis; P Chanson: receipt of honoraria and/or consultation fees from Ipsen, Novartis, Pfizer and grants or research support from Ipsen, Novartis, Pfizer; JOL Jorgensen: receipt of honoraria and/or consultation fees from Ascendis, Ipsen, Novartis, Novo Nordisk, Pfizer and grants or research support from Novartis, Pfizer; A Luger: receipt of honoraria and/or consultation fees from Ipsen, Merck Serono, Novartis, Pfizer, Sandoz and grants or research support from Ipsen. Novartis, Pfizer; S Llahana: receipt of honoraria from Ipsen, Pfizer; R Verkauskiene: receipt of honoraria and/or consultation fees from Novartis, Pfizer, Sandoz, SWebb: receipt of honoraria and/or consultation fees from Corcept, Crinetics, HRA, Ipsen, Pfizer, Recordati and grants or research support from HRA. The other authors declare no conflict of interest.

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Figure 1: Flow diagram of study inclusion.

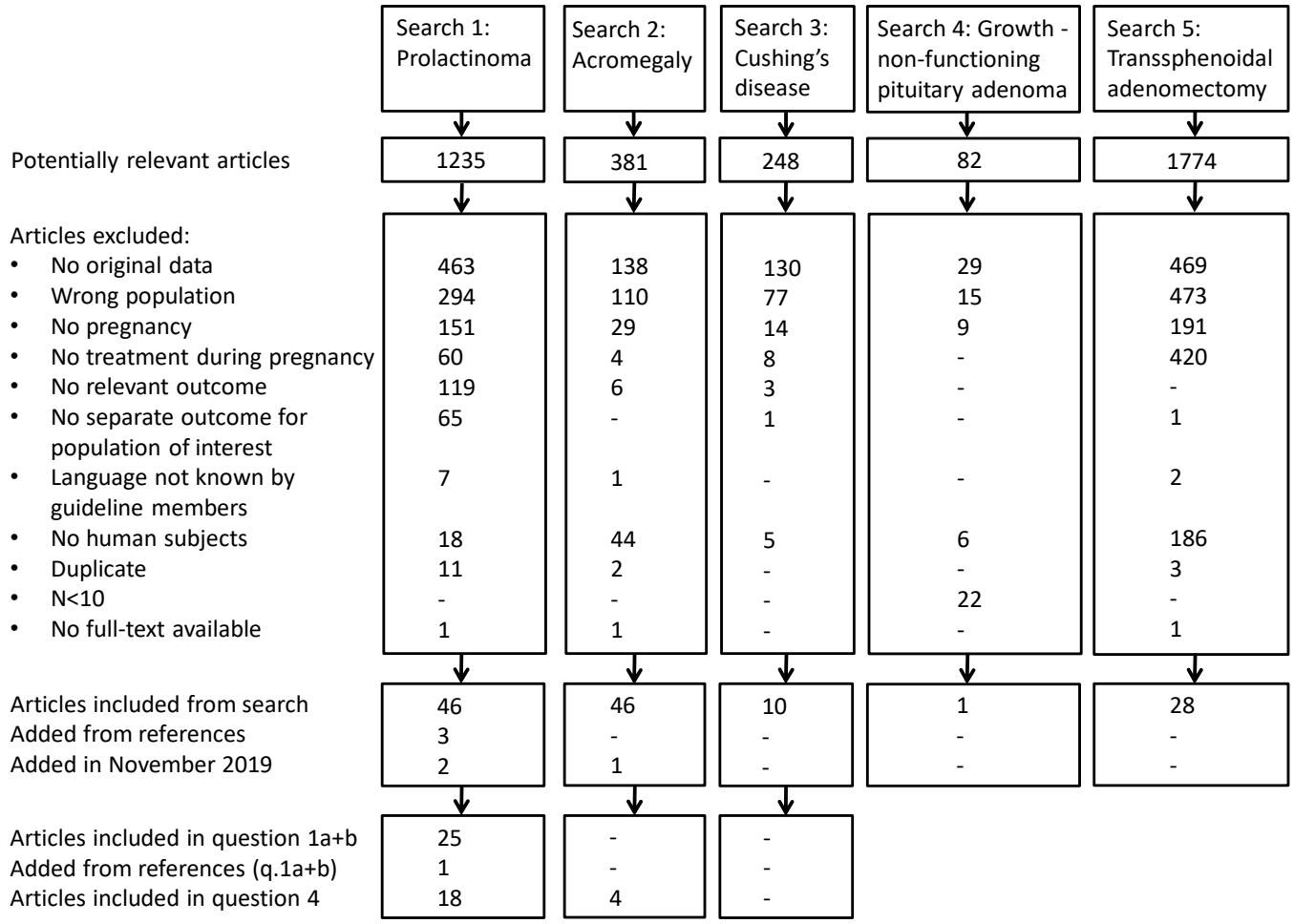

Table 1: Overview of the key clinical questions and outcome parameters.

Clinical question	Search criteria and key outcome parameters	Number of papers included
Question I: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with prolactinoma? Sub-question Ia: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with hyperprolactinaemia? Sub-question Ib: What is the safety profile and teratogenicity of bromocriptine and cabergoline during pregnancy in patients with prolactinoma and hyperprolactinaemia? Sub-question Ic: Is there a difference between patients who used medication only until confirmation of pregnancy and patients	Population: Patients with prolactinoma or hyperprolactinaemia and pregnancy Medication during pregnancy: bromocriptine, cabergoline, (dihydro)ergocryptine, lergotrile, metergoline, and/or quinagolide Outcomes of the mother (prolactinoma): diagnosis of prolactinoma during pregnancy, stop and restart of medical treatment after pregnancy confirmation, spontaneous abortion or miscarriage, clinical progress/tumour symptoms, headache, gestational diabetes, gestational hypertension, pre-eclampsia Outcomes of the mother (hyperprolactinaemia): spontaneous abortion or miscarriage, termination of pregnancy due to malformation Outcomes of the infant: malformations, low birth weight, pre-term, small for gestational age, macrosomia, neonatal death	Prolactinoma: 51 Hyperprolactinaemia: 77 (including the 51 papers on prolactinoma)

who used medication during a larger part of pregnancy?		
Question II: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with acromegaly? Sub-question IIa: Is there a difference between patients who used medication only until confirmation of pregnancy and patients who used medication during a larger part of pregnancy?	Population: Patients with acromegaly and pregnancy Medication during pregnancy: bromocriptine, cabergoline, dopamine agonist (unspecified), octreotide, lanreotide, pasireotide, somatostatin analogue (unspecified), and/or pegvisomant Outcomes of the mother: diagnosis of acromegaly during pregnancy, stop of medical treatment after pregnancy confirmation, spontaneous abortion or miscarriage, clinical progress/tumour symptoms, headache, gestational diabetes, gestational hypertension, pre-eclampsia Outcomes of the infant: malformations, low birth weight, pre-term, small for gestational age, macrosomia, neonatal death	47
Question III: What is the safety profile and teratogenicity of medical treatment during pregnancy in patients with Cushing's disease?	Population: Patients with Cushing's disease and pregnancy Medication during pregnancy: metyrapone, ketoconazole, mitotane, and/or cabergoline Outcomes of the mother: gestational diabetes, gestational hypertension, pre-eclampsia, hypothyroidism, no milk for breastfeeding Outcomes of the infant: malformations, low birth weight, pre-term, small for gestational age, neonatal death	10
Question IV: What is the incidence of tumour growth during pregnancy in patients with a non-functioning or functioning	Population: Patients with a non-functioning or functioning (prolactinoma, acromegaly, or Cushing's disease) adenoma and pregnancy (minimum 10 patients per study) Outcomes: tumour size before, during, and after surgery, symptomatic and/or	Acromegaly: 4 Prolactinoma: 18

(Cushing's disease, acromegaly, or prolactinoma) adenoma?	radiological tumour growth during pregnancy in total, and in microadenomas and macroadenomas separately	Non-functioning pituitary adenoma: 1
Question V: Is pituitary surgery safe for pituitary adenomas during pregnancy? Sub-question Vb: What is the effectiveness of pituitary surgery for pituitary adenomas during pregnancy?	Population: Patients with a pituitary adenoma and pregnancy Treatment: transsphenoidal adenomectomy Outcomes of the mother: diabetes insipidus, SIADH, cerebrospinal fluid leakage, gestational diabetes, gestational hypertension, pre-eclampsia Outcomes of the infant: low birth weight, pre-term, small for gestational age, neonatal death, miscarriage after surgery	28

Table 2: Work-up when pregnancy is considered.

Medical history with special attention to pituitary condition and its associated comorbidities
Physical examination including body mass index 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).

Table 3: Safety and teratogenicity outcomes after treatment of hyperprolactinaemia during pregnancy using cabergoline.

Study	Number of pregnancies; live infants	Spontaneous miscarriage	Low birth weight	Small for gestational age	Pre-term delivery	Malformation	Termination of pregnancy for malformation	Neonatal death
Cohort studies								
Auriemma 2013	143; 126	13	2	0	0	0	0	0
Colao 2008	329; 258	30	17	0	45	17	6	0
Domingue 2014	36; 39	0	0	0	4	0	0	0
Karaca 2018	45; 39	6	3	2	2	2	Not reported	0
Lebbe 2010	100; 88	10	9	5	8	3	3	0
Ono 2010	85; 83	2	9	Not reported	1	0	0	0
O'Sullivan 2019	41; 36	4	0	2	6	1	0	0
Rastogi 2016	48; 39	6	3	3	0	0	3	0
Ricci 2002	61; 49	6	6	Not reported	4	2	1	0
Sant' Anna 2019	233; 194	27	9	3	6	7	0	1
Stalldecker 2010	103; 90	7	1	1	8	3	0	0

Webster 1993	26; 22	0	0	0	0	0	1	0
Total cohort studies	1250; 1063	111 (8.9%)	59 (5.6%)	16 (1.7%)	84 (7.9%)	35 (3.3%)	14 (1.2%)	1 (0.1%)
Case reports / case series								
Almistehi 2018	1; 1	0	1	1	0	0	0	0
Bajwa 2011	1; 1	0	0	0	1	0	0	0
Banerjee 2009	4; 3	1	0	0	0	0	0	0
Cannavò 1999	6; 5	1	0	0	0	0	0	0
Couture 2012	1; 1	0	0	0	0	0	0	0
Galvão 2017	4; 4	0	0	0	Not reported	0	0	0
Jones 1994	2; 1	1	1	1	0	0	0	0
Jones 1997	1; 1	0	0	0	0	0	0	0
Mitsiakos 2019	1; 1	0	1	1	1	1	0	0
Shahzad 2012	1; 1	0	0	0	0	0	0	0
Total case studies	22; 19	3 (13.6%)	3 (15.8%)	3 (15.8%)	2 (13.3%)	1 (5.3%)	0 (0%)	0 (0%)

Total; % (95% CI)	1272; 1082	114; 9.0% (7.4-10.7%)	62; 5.7% (4.4-7.3%)	19; 1.8% (1.1-2.7%)	86; 8.0% (6.4-9.8%)	36; 3.3% (2.3-4.6%)	14; 1.1% (0.6-1.8%)	1; 0.1% (0.0-0.5%)

Table 4: Core Recommendations

	NFA (non-functioning adenomas)	Prolactinoma	Acromegaly	Cushing's disease
Pre-conception	In women with an NFA near the optic chiasm who are seeking pregnancy, surgery may be considered to reduce the risk of chiasmal compression and to enhance fertility	Aim for normalisation of even mild hyperprolactinaemia with cabergoline at the lowest possible dose to optimise chances to conceive	Consider surgery in active acromegaly before pregnancy	Advise against pregnancy during active Cushing's disease
Pregnancy	Nonfunctioning microadenomas bear a low risk for growth during pregnancy, there is no need for routine monitoring	No indication for prolactin testing Medical treatment should be stopped in most cases upon confirmation of pregnancy Close surveillance is needed in women with a macroprolactinoma	No indication for GH and/or IGF-1 testing Medical treatment should be stopped in most cases upon confirmation of pregnancy	Diagnosis of Cushing's disease and assessment of disease activity is challenging due to placental CRH production and activation of the hypothalamic-pituitary-adrenal axis, circadian rhythm however is preserved
Post-pregnancy	We recommend awaiting re-assessment of pituitary imaging and function until 3-6 months after delivery	A significant percentage of prolactinomas are biochemically in remission after pregnancy and lactation	Rebound of disease activity shortly after delivery is frequent	Re-assessment of disease activity should be performed 2-3 months post partum