Acromegaly and pregnancy

Acromégalie et grossesse

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Résumé

Chez les patientes ayant un adénome somatotrope responsable d’une acromégalie, la survenue d’une grossesse impose d’envisager : (1) les conséquences de la grossesse sur l’adénome hypophysaire et les sécrétions de growth hormone (GH) et d’IGF-1, (2) les conséquences de l’hypersécrétion somatotrope (GH/IGF-1) pour la mère et le fœtus, (3) les conséquences du traitement chirurgical ou médical (agonistes dopaminergiques, analogues de la somatostatine, antagoniste du récepteur de la GH) chez la mère et le développement du fœtus.

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Abstract

In women with acromegaly due to growth hormone (GH)-secreting pituitary adenomas, the occurrence of pregnancy warrants consideration of: (1) the consequences of pregnancy on the pituitary adenoma including the tumor syndrome and GH/IGF-1 secretion, (2) the consequence of GH/IGF-1 hypersecretion on the pregnant woman and the fetus, (3) the consequences of pituitary surgery and medical treatment (dopamine agonists, somatostatin analogs, GH receptor antagonist) on the pregnant woman and the developing fetus.

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1. Introduction

Acromegaly is a rare condition generally related to pituitary adenoma leading to autonomous hypersecretion of growth hormone (GH) and insulin growth factor type-1 (IGF-1), with the consequent effects on multiple organs. Pituitary surgery, medical treatment including somatostatin analogs, dopamine agonists and GH-receptor antagonist, and exceptionally pituitary radiation form the basis for the treatment of GH-secreting adenoma.

Recently, the diagnosis of acromegaly has become more and more frequent in young women of reproductive age desiring pregnancy sometimes after pituitary surgery or during medical treatment.

In 2000, less than 100 pregnancies in women with acromegaly had been reported [1–3] whereas the number of patients with acromegaly consulting for desired pregnancy has increased steadily [4,5].

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In these acromegalic patients desiring pregnancy, the following aspects should be examined:

- the impact of the pituitary adenoma and GH and IGF-1 hypersecretion on the hypothalamo-pituitary-ovary axis;
- the impact of GH and IGF-1 hypersecretion on the mother and fetus;
- the impact of hormonal secretion observed during pregnancy on the volume of the pituitary adenoma, with the risk of a tumor syndrome, and on pituitary GH secretion and hepatic production of IGF-1;
- the impact of medical treatment including somatostatin analogs, dopamine agonists and GH-receptor antagonist on the fetus and neonate.

2. Impact of GH-secreting adenoma on the pituitary-ovary axis

GH-secreting pituitary adenoma can perturb the menstrual cycle and lead to infertility [6,7] by the following mechanisms:
Table 1
Percentage of pregnant acromegalic women with gravid hypertension or gestational diabetes as a function of control of GH/IGF-1 hypersecretion before pregnancy.

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Pregnant women (%)</th>
<th>Pregnant acromegalic women (%)</th>
<th>Controlled acromegaly (%)</th>
<th>Uncontrolled acromegaly (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravid hypertension</td>
<td>5–15</td>
<td>13.6</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>&lt;6</td>
<td>6.8</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

- hyperlactinemia related to adenomas secreting GH and prolactin or to stalk/hypothalamic dysfunction in patients with suprasellar extension of a pituitary macroadenoma;
- functional gonadotrophin insufficiency due to hyperprolactinemia or secondary to compression or destruction of the gonadotropic cells by a macroadenoma responsible for more or less complete anterior pituitary failure;
- ovarian dysfunction and dystrophy secondary to GH and IGF-1 hypersecretion.

Therapeutic intervention (pituitary surgery and radiation therapy) can lead to complications with early or late development of gonadotroph failure, requiring replacement therapy with the risk of multiple pregnancies. Conversely, medical treatment, with somatostatin analogs alone or in combination with dopamine agonists or GH-receptor antagonist, can reduce the size of the adenoma, control GH hypersecretion and restore normal ovarian function while maintaining normal pituitary function.

3. Impact of GH/IGF-1 hypersecretion on the fetus

Hypersecretion of GH does not increase the risk of fetal malformation or preterm birth. Increased birth weight has been reported [3], but was not confirmed in a recent French study, even in patients when GH/IGF-1 hypersecretion was not controlled before pregnancy [5].

4. Impact of GH/IGF-1 hypersecretion on the mother

Hypertension is observed in 17 to 35% of non-pregnant women with GH hypersecretion; carbohydrate intolerance or diabetes mellitus occurs in 30 to 35%. During pregnancy, these cardiovascular and metabolic complications are not constantly reported in previous case reports or small series of pregnant patients with acromegaly. However, the recent French study observed a moderate increase in the risk of gravid hypertension and gestational diabetes in pregnant women with acromegaly, especially when GH/IGF-1 hypersecretion was uncontrolled before pregnancy (Table 1) [5]. There is not perspective study examining the frequency of gravid hypertension or gestational diabetes in a large population of pregnant acromegalic patients. In any case, acromegalic women must be carefully monitored during pregnancy in order to detect gravid hypertension or gestational diabetes early and institute adequate treatment.

5. Impact of pregnancy on the GH-secreting pituitary adenoma

The size of the pituitary gland increases during normal pregnancy secondary to physiological hyperplasia of prolactin-secreting cells [8]. During pregnancy, women with a GH-secreting adenoma may develop tumoral syndrome with headache and signs of chiasm compression related to:

- physiological hyperplasia of prolactin-secreting cells;
- increased adenoma size due to increased hormone levels of the pregnancy, notably estrogen;
- discontinuation of medical treatment when inducing a significant reduction of the adenoma before pregnancy.

Acute forms of tumoral syndrome with decreased level of consciousness, meningeal signs and oculomotor disorders, correspond to pituitary apoplexy or hemorrhagic necrosis of the adenoma.

In the literature on microadenomas or postoperative residues measuring less than 12 mm or developing within the sphenoid sinus, tumoral complications are not reported. Patients with a macroadenoma have a 10% risk of developing a tumoral syndrome, exceptionally with visual field involvement [9–11]. Among cases of pregnancy reported in the French study [5], four patients with a macroadenoma developed visual field defects: in three patients the GH-secreting macroadenoma was diagnosed during pregnancy, the fourth had been treated with bromocriptin. Patients were treated with corticosteroids alone (two patients) or in combination with bromocriptin (one patient) or pituitary surgery at the end of the first trimester of pregnancy (one patient). Headache without visual field defect was reported during seven pregnancies (12%). Finally, MRI scan performed in 27 patients within 6 months of delivery showed that the size of the adenoma increased in three cases, decrease in two and remained stable in 22 (2 microadenomas and 20 macroadenomas) patients.

In clinical practice, regular trimester follow-up (headache, signs of chiasm compression) is advisable (Fig. 1). A pituitary tumor syndrome is rare in patients with a microadenoma or after surgical reduction of a GH-secreting macroadenoma, and in general breastfeeding can be proposed after an uncomplicated pregnancy. For patients with a macroadenoma diagnosed during pregnancy or after a short medical treatment (less than one year), follow-up visits should be proposed monthly. MRI should be performed if clinical signs of a tumor syndrome (headache, altered visual field) develop. Medical treatment can be proposed with dopamine agonists (bromocriptin, cabergolin), then in the event of therapeutic failure, pituitary surgery should be proposed. Breastfeeding is contraindicated in this situation.
6. Impact of pregnancy on GH/IGF-1 hypersecretion

In pregnant women without GH-secreting adenoma, placental secretion of GH occurs during the first weeks of gestation leading to an increase in plasma levels of IGF-1 from the second trimester, which in turn by negative feedback, decreases pituitary secretion of GH (Fig. 2) [12]. In women with a GH-secreting adenoma, secretion of placental GH also induces an increase in plasma IGF-1 level during pregnancy but not a decrease in the autonomous secretion of GH by the pituitary adenoma [13].

However:

- acromegalic patients often report an improvement in their clinical signs of acromegaly, especially during the first trimester of pregnancy;
- a decrease in IGF-1 level is observed, especially during the first trimester, while the GH level remains unchanged. Thus, in the French study, in 12 acromegalic patients, a significant decrease in mean IGF-1 level was observed during the first trimester of pregnancy in comparison with prepregnancy levels, without any significant change in GH levels (Fig. 3). This tissue resistance to GH, especially on liver, would be related to physiological increased estrogen levels during pregnancy [14]. Indeed during the second half of pregnancy, this antagonist effect of estrogens may be overridden by the increasing stimulus from placental GH secretion resulting in a variable increase in IGF-1 level during the second half of the pregnancy in these patients;
- variable decrease in pituitary GH concentrations has been reported in the second half of pregnancy, suggesting that adenoma secretion of GH is particularly sensitive to feedback control due to increased IGF-1 (in response to placental GH) [15].

Therefore, the diagnosis of GH/IGF-1 hypersecretion is difficult to establish during pregnancy because of the hepatic resistance to GH and the subsequent decrease in IGF-1 during the first months of pregnancy, and placental GH secretion leads to a physiological increase in IGF-1 level during the second half of pregnancy. Conversely, liver resistance to GH in response to increased estrogen levels would explain the improved clinical signs during the first trimester of pregnancy reported by the patients.

7. Foeto-maternal effects of treatments

As observed after any surgical procedure performed under general anesthesia, pituitary adenomectomy increases the risk of spontaneous abortion if performed during the first trimester of pregnancy, or of preterm birth if performed during the second half of pregnancy.

Dopamine agonists cross the foeto-placental barrier. There is a large body of pharmacovigilance data on bromocriptin and cabergolin, and less on quinagolid and pergolid, collected in patients treated for prolactinoma. No significant increase in the frequency of fetal malformations or postnatal developmental disorders has been reported for bromocriptin or cabergolin taken during pregnancy [16,17]. However, treatment with dopamine
agonists should be discontinued at the diagnosis of pregnancy in most acromegalic women. When a tumoral syndrome develops during pregnancy in an acromegalic patient, treatment should be instituted with bromocriptin or cabergolin and continued until delivery.

Somatostatin analogs are the main medical treatment indicated for acromegaly. Control of GH and IGF-1 secretion can be achieved in 50 to 70% of patients with a decrease in tumor size in 40 to 60%, especially when somatostatin analogs are first-intention treatment in patients with GH-secreting macroadenoma [18–20].

Somatostatin analogs cross the placenta: in animals, no teratogenic effect has been observed with high-dose somatostatin analogs. In the human placenta, most somatostatin receptors are subtype sstr-4 which have a weak affinity for somatostatin, and octreotide does not inhibit placental GH secretion [21]. In addition, subcutaneous injections of octreotide during the last weeks of pregnancy do not provoke changes in hormone levels (TSH, T41, T31, IGF-1) in the newborn, suggesting that somatostatin receptors are not immediately functional in the neonatal period [22]. To our knowledge, less than 40 women have been treated with octreotide or lanreotide administered by multiple daily subcutaneous injections or monthly injections of long-acting forms [23–26]. In general, treatment with somatostatin analogs was discontinued at the diagnosis of pregnancy (30/36) so that the embryo was exposed to octreotide or lanreotide only during the first weeks of pregnancy, especially in the women given long-acting release forms in monthly injections. Rarely, somatostatin analogs have been continued during all or part of the pregnancy, especially in women with resistant headache caused by their GH adenoma.

Most women treated with somatostatin analogs during pregnancy, have had an uncomplicated pregnancy and gave birth to infants with birth weight and size within the normal range, without malformations and with a normal postnatal development.

However:

- in a woman treated with slow-release somatostatin analog, regular obstetrical ultrasound follow-up revealed an intrauterine growth retardation that can be reversed by reducing the somatostatin analog dose [27];
- in a small series of acromegalic women, decreased birth weight of infants born to patients given somatostatin analogs was observed in comparison to neonates born to acromegalic women not treated with somatostatin analogs [3];
- in the study [5] of the French Pituitary Group, comparison of birth weights of infants born to 14 patients treated with somatostatin analogs alone or in combination with dopamine agonists during pregnancy demonstrated a significant risk of neonatal hypotrophy (Table 2) without visceral malformations compared with infants born to acromegalic women not treated with somatostatin analogs;
- finally, a recent case report of an acromegalic woman with severe and resistant headache showed that daily subcutaneous injections of somatostatin analog (1200–2400 µg/d) through-

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Somatostatin analog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>n</td>
<td>14</td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
</tr>
<tr>
<td>Hypotrophic</td>
<td>4 (28%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
</tbody>
</table>

* p < 0.01.

out pregnancy induced an acute decrease in uterine artery blood flow after each injection, but without any effect on the fetal outcome [26].

Therefore:

- contraception can be recommended in patients of childbearing age treated with somatostatin analogs for their acromegaly;
- treatment with somatostatin analogs, and in particular long-releasing forms, should if possible be discontinued before pregnancy, and in all cases at diagnosis of gestation.

On the other hand, withdrawal of somatostatin analogs has no consequences for the acromegalic mother or developing fetus and treatment can be resumed after hormonal and neuroradiographic assessment 3 to 6 months after delivery.

GH-receptor antagonist is a new modality proposed for the treatment of acromegaly. In animal studies, injections of GH-receptor antagonist have not caused any teratogenic effects. Exceptional case reports of uncomplicated pregnancies in acromegalic patients treated with GH-receptor antagonist have been reported [28,29]. In clinical practice, despite these pharmacovigilance data and absence of any reported maternal or fetal complications, GH-receptor antagonist should be discontinued at diagnosis of pregnancy in acromegalic patients.

Indeed, current data in the literature in a small number of acromegalic women have shown that medical treatments used to control GH and IGF-1 hypersecretion do not provoke maternal or fetal complications. Nevertheless, because of the lack of sufficient evidence from a large number of pregnancies, these treatments should be discontinued at the diagnosis of pregnancy, especially since their interruption does not cause any maternal or fetal consequences in the majority of acromegalic women.

Disclosure of interest

Philippe Caron is consultant, and he has written scientific articles and given conferences for Ipsen, Novartis and Pfizer laboratories.

References