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Klotz Communications: Pituitary and pregnancy

Prolactinoma and pregnancy: From the wish of conception to lactation

Prolactinome et grossesse : du désir de conception à l'allaitement

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Abstract

Prolactinoma is a common cause of infertility in young women and treatment with dopamine agonists (DA) allows restoration of fertility in over 90% of the cases. Both bromocriptine and cabergoline have shown a good safety profile when administered during early pregnancy. In particular, data on exposure of the fetus or embryo to cabergoline during the first weeks of pregnancy have now been reported in more than 900 cases, and do indicate that cabergoline is safe in this context. There is no increase in the frequency of spontaneous miscarriage, premature delivery, multiple births or neonatal malformations, and follow-up studies of the children for up to 12 years after fetal exposure to cabergoline did not show any physical or developmental abnormalities. These women should therefore continue DA treatment until pregnancy has been initiated. Treatment discontinuation is recommended at that time in women with microprolactinoma or non-compressive macroprolactinoma. For microprolactinomas, the risk of symptomatic tumour enlargement during pregnancy is very low (2–3%). It is higher for macroprolactinomas (20–30%) and careful follow-up is advised, including MRI without contrast injection if symptoms or visual disturbances develop. If a symptomatic tumour enlargement does occur, reinitiation of the dopamine agonist (BRC or CAB) is indicated rather than surgery. Breast-feeding has no harmful effect on tumour growth and DA treatment, if still needed, may be postponed as long as breast-feeding is desired. Finally, about 40% of women with a microprolactinoma or an intermediate size macroprolactinoma may be in prolonged remission after one or more pregnancies.

Keywords: Prolactinoma; Hyperprolactinaemia; Cabergoline; Bromocriptine; Pregnancy; Gestation

Résumé

Le prolactinome est une cause fréquente de stérilité et le traitement par les agonistes dopaminergiques (AD) permet la restauration d'une fertilité normale dans plus de 90 % des cas. Tant la bromocriptine que la cabergoline ont démontré un bon profil de sécurité lorsqu'ils sont administrés au début de la grossesse. En particulier, des données sur l'exposition du fœtus à la cabergoline pendant les premières semaines de grossesse ont été maintenant rapportées dans plus de 900 cas et elles indiquent que ce médicament n'a pas d'effet délétère dans ce contexte. Ainsi, il n'y a pas d'augmentation de la fréquence des fausses couches spontanées, des accouchements prématurés, des naissances multiples ou des malformations néonatales. Le suivi des enfants jusqu'à l'âge de 12 ans n'a pas non plus montré d'anomalies du développement moteur ou intellectuel. Le traitement par AD peut donc être poursuivi jusqu'à ce que la grossesse ait démarré. L'arrêt du traitement est recommandé à ce moment chez les femmes porteuses d'un microprolactinome ou d'un macroprolactinome non compressif. En cas de microprolactinome, le risque de croissance symptomatique de la tumeur pendant la grossesse est très faible (2–3 %). Il est plus élevé en cas de macroprolactinome (20–30 %) et un suivi attentif est alors conseillé, notamment la réalisation d'une IRM sans injection de contraste si des symptômes ou des troubles visuels apparaissent. Si une croissance symptomatique de la tumeur se produit, la reprise du traitement par AD (BRC ou CAB) est indiquée et une chirurgie est rarement nécessaire. L'allaitement n'a pas d'effet nocif sur la croissance de la tumeur et le traitement par AD, s'il est encore nécessaire, peut être reporté aussi longtemps que l'allaitement est souhaité. Enfin, environ 40 % des femmes ayant un microprolactinome ou un macroprolactinome de taille intermédiaire sont en rémission prolongée de leur hyperprolactinémie après une ou plusieurs grossesses.

Mots clés : Prolactinome ; Hyperprolactinémie ; Cabergoline ; Bromocriptine ; Grossesse ; Gestation

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1. Introduction

Prolactinomas are common pituitary tumors with an estimated prevalence of 40 to 55 cases per 100,000 [1–3]. This disorder has a large female predominance (female-to-male ratio of 8:1) and a median age at diagnosis of 30 years [4,5]. Thus, a prolactinoma is expected to be present in every 1200 women, and more specifically in every 500 women of childbearing age. Whatever its size, the presence of a prolactinoma is usually responsible for anovulation and infertility in such young women wishing to become pregnant. High prolactin concentrations reduce ovulation rate, impair progesterone secretion and might alter hormonal conditions for adequate embryo implantation if fertilization would have nonetheless occurred. Medical treatment with dopamine agonists will very often correct these symptoms, reduce tumour size and allow pregnancy in more than 90% of the cases [6–11]. However, the wish and eventual occurrence of a pregnancy in a woman with a prolactinoma raise several issues concerning both the mother and the fetus. In this paper, we will discuss these issues at the light of an exemplative case.

2. Clinical case (1)

Aude is a 24-year-old, otherwise healthy nurse seeking medical advice for a secondary amenorrhea following the recent withdrawal of her contraceptive pill with a wish of pregnancy. She also complains of moderate bilateral galactorrhoea. She is not taking any medication. Hormonal evaluation reveals a marked hyperprolactinaemia (PRL 655 μg/L; normal values: 5–25) with hypogonadotropic hypogonadism. Other hormonal concentrations are normal. A pituitary MRI shows a 18 × 17 × 16 mm, largely cystic macroadenoma without obvious cavernous sinus invasion or compression of the optic nerves (Fig. 1). Ophthalmologic examination is normal. Before starting discussing any treatment option, Aude strengthens the fact that she wants to become pregnant as soon as possible...

3. Discussion (1)

The two first questions raised by this case are to know whether the fertility potential is compromised in this young lady and what would be the best therapeutic option.

Several studies have now shown that dopamine agonists are highly effective in restoring fertility in women with a micro- or a macroprolactinoma and thus represent the first choice treatment in this condition [6,9–12]. Although it is well known that cabergoline is better tolerated and more efficacious than bromocriptine [13], few studies have directly compared both drugs in their efficacy to allow gestation, showing only a slight advantage in favour of cabergoline [7]. In a series of 85 infertile women with prolactinoma (31 BRC-resistant, 32 BRC-intolerant and 22 drug-naïve patients), up-titrated doses of cabergoline restored ovulatory cycles in 85 (100%) and allowed pregnancy in 80 (94%) [10]. Even in a population of 29 young women with a prolactinoma diagnosed during childhood or adolescence, all who wished to conceive could become pregnant after medical (± surgical) treatment of their prolactinoma. They had 25 pregnancies, only one medically-assisted, without any obstetrical or fetal complication [14].

Transsphenoidal selective adenomectomy may be another option in young patients with a prolactinoma and an immediate desire of conception [15]. In expert hands, surgery will lead to a sustained reduction in PRL levels in 70–80% of microadenomas, but in only 30–40% of macroadenomas [5]. Moreover, surgery may entail some morbidity, in particular postoperative pituitary hormone deficits. As in every patient with a prolactinoma, pituitary surgery should therefore be proposed to those young women who cannot tolerate dopamine agonists, who are not responsive to maximally tolerated doses of DAs or those who elect to undergo surgery for personal reasons, such as poor compliance to drug therapy [5,6]. Patients with a large macroprolactinoma may sometimes require high doses of cabergoline and may also be good candidates for surgery, even though tumour resection is incomplete. Surgical debulking not only improves subsequent hormonal control under medical treatment [16], but also reduces the risk of tumor enlargement during pregnancy [9,11].

The patients who do not respond to either treatment modality may need additional hormonal maneuvers to facilitate ovulation, such as clomiphene citrate, gonadotropin stimulation [17] or in vitro fertilization (IVF). Noticeably, the mean age of prolactinoma women at first conception is older than in the general population (31.8 years vs. 30.0 years, respectively) and the need for medically-assisted reproduction is more frequent [12]. It is not known whether medical correction of hyperprolactinaemia may improve the success rate of IVF in these women.

4. Clinical case (2)

After informed discussion with the patient and her husband, medical therapy was started with cabergoline at a dose of 2 × 0.5 mg/week. The medication was well tolerated and efficient, as regular menses resumed after one month, galactorrhoea resolved and PRL concentrations were normalized after 2 months (3.0 μg/L). After 4 months of treatment, PRL concentration were undetectable (< 0.5 μg/L) and a new pituitary MRI showed a 30%-reduction in prolactinoma size (11 × 14 × 12 mm). Three months later, a first pregnancy was diagnosed while the patient was still on cabergoline.

5. Discussion (2)

Two new issues arise now:

- What are the effects of the dopamine agonist (cabergoline in the current situation) on early fetal development?
- And what is the risk for symptomatic tumour growth during pregnancy?