Approach to the management of rare clinical presentations of macroadenomas in reproductive-aged women

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Abstract

Objective: To describe 2 cases of macroadenomas with atypical presentation in women desiring pregnancy that illustrate important considerations in the management approach for macroadenomas in reproductive-aged women.

Patient(s): Case 1 was a 26-year-old woman referred to our institution for possible tumor resection after pituitary apoplexy during her first pregnancy. Instead, she underwent treatment with cabergoline for a year with goals of normalization of prolactin and decrease in tumor size to <1 cm before trying to conceive. Case 2 was an 18-year-old woman with a macroadenoma intolerant to dopamine agonists. She underwent stereotactic radiosurgery, with marked reduction in tumor size and normalization of prolactin levels. She conceived and delivered a healthy infant 3 years after radiosurgery.

Conclusion: Management of macroadenomas in women desiring pregnancy requires careful consideration of alternatives to surgery which could impair pituitary function and fertility and awareness of treatment goals that can minimize the risks for pituitary apoplexy and vision loss during pregnancy. It is important to increase awareness of these options prior to initiation of treatment and conception.

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1. Introduction

Hyperprolactinemia due to prolactinoma is an important and treatable cause of infertility in women [1]. Most prolactinomas are microadenomas (lesions <1 cm) and may be associated with galactorrhea, amenorrhea, and infertility. In contrast, macroadenomas (lesions ≥1 cm) have the potential of causing progressive mass effects, including visual field defects, headaches, or development of hypopituitarism. When considering treatment of macroadenomas in reproductive-age women, clinicians must not only consider restoration of fertility, they must also be aware of potential complications during pregnancy, including vision loss, pituitary apoplexy, and effects of therapy on the fetus. These considerations highlight the need to be vigilant about the duration of medical therapy and treatment goals prior to trying to conceive and communicate the importance of these decisions to the patient and care providers to minimize the risk for complications during pregnancy. For women intolerant or resistant to medications, alternatives to surgical resection of macroadenomas must be carefully considered because of the risk for impaired pituitary function after surgery.

We report 2 challenging cases of macroadenomas in reproductive-aged women to illustrate the decision-making process. We also include a review of the relevant literature describing management approaches.

2. Cases

2.1. Case 1

A 26-year-old G0 woman with a history of a macroadenoma was referred for possible surgical resection of the tumor. She reported eight years of oligomenorrhea, with six to nine menstrual cycles per year. At age 23, she was found to have a prolactin level of 14,869 pmol/l (normal: 130–1174 pmol/l) during a work-up for infertility. Pituitary magnetic resonance imaging (MRI) revealed a 1.9 cm × 1.3 cm pituitary mass consistent with an adenoma. Thyroid function tests, serum cortisol and IGF-1 levels were normal. The patient was initiated on oral contraceptives and bromocriptine (2.5 mg, twice daily) which decreased her prolactin...
prolactin to 1304 pmol/l. Repeat imaging was obtained which demonstrated no change in tumor size at 6 months. Because symptoms of nausea and dizziness limited her compliance with bromocriptine, she was switched to cabergoline (0.25 mg, twice weekly). After three months of cabergoline, prolactin decreased further to 174 pmol/l and the tumor decreased slightly in size to 1.9 cm × 0.8 cm. The patient missed one refill of oral contraceptives and became pregnant 1 month later. Dopamine agonist (DA) therapy was discontinued when the pregnancy was confirmed.

During the third trimester, at 28 weeks gestation, the patient presented with an acute onset of severe headache. MRI showed apoplexy into the tumor, which increased in size to 1.4 × 2.0 × 1.2 cm, with evidence of right cavernous sinus invasion (Fig. 1A–C). Visual field testing was normal. She started glucocorticoid replacement therapy because of low random cortisol levels (96.6 nmol/l) and concern for secondary adrenal insufficiency. Cabergoline was reinitiated at 0.25 mg twice weekly. The remainder of her pregnancy was uneventful; she delivered a full-term, 3.1-kg healthy baby via vaginal delivery with vacuum assistance.

Postpartum, DA therapy was changed back to bromocriptine and oral contraceptives were restarted. One week after delivery, the tumor had slightly increased to 1.4 × 2.4 × 1.4 cm. After 6 months of bromocriptine, her prolactin level was 1304 pmol/l and repeat imaging showed a decrease in size (1.1 × 1.4 × 1.0 cm) with persistent right cavernous sinus invasion. Repeat imaging another 6 months later showed no change in size. She was able to taper off hydrocortisone within a year of delivery.

With no significant change in size of the tumor on DA therapy, she was referred to our institution for consideration of surgery to reduce the risk of pituitary apoplexy in a subsequent desired pregnancy. With the cavernous sinus invasion decreasing the chance for surgical cure and considering the risks of pituitary injury and impaired fertility, we recommended that she switch to cabergoline therapy for a year with the goal of stabilizing the adenoma and reducing its size to <1 cm before trying to conceive again. With cabergoline, her prolactin decreased further to 478 pmol/l. After additional 10 months of cabergoline therapy, MRI showed the tumor had decreased to <1 cm, and her prolactin remained at 522 pmol/l. She discontinued oral contraceptives and became pregnant 4 months later. Her pregnancy has been uneventful through the third trimester of pregnancy. Prolactin levels were not closely monitored during her second pregnancy as they are not reliable throughout gestation. The levels can significantly increase with pregnancy per se.

2.2. Case 2

An 18-year-old G0 woman presented with a 4-year history of galactorrhea and an 8-month history of secondary amenorrhea. Her prolactin level was 7174 pmol/l (reference, 130–1174 pmol/l). Thyroid function tests, serum cortisol and IGF-1 levels were normal. A brain MRI showed a normal-appearing sella with an asymmetric, hypoenhancing 1.1 cm soft-tissue mass in the left cavernous sinus, consistent with a pituitary adenoma (Fig. 1D–E). Medical therapy was attempted with both bromocriptine and subsequently cabergoline but the patient developed nausea and severe fatigue with both medications. She also reported side effects to oral contraceptive pills. Given her symptoms, intolerance to dopamine agonists, and tumor location in the cavernous sinus, gamma knife radiosurgery was recommended. She underwent stereotactic radiosurgery with 50 Gy as the maximal dose and 25 Gy administered to the margins of the tumor without complications. A repeat MRI 1 year after radiosurgery showed significant involution of the mass in the left cavernous sinus. Her prolactin levels over the 2-year period after radiosurgery progressively decreased from 7174 to 1304 pmol/l. Pituitary function remained intact. The galactorrhea resolved, menstrual periods resumed, and she was able to spontaneously conceive 3 years after radiosurgery; she delivered a full-term, 3.5-kg healthy baby via vaginal delivery. Six years after radiosurgery, her prolactin levels continued to be normal (435 pmol/l), with normal pituitary function, and the child has normal development.

3. Discussion

These cases illustrate the decision-making process involved when considering therapeutic options for macroprolactinomas before, during,
and after pregnancy. Questions that patients and providers should discuss include:

3.1. What are the Treatment Goals for Macroadenomas Before Conception?

For a reproductive-age woman with a macroadenoma who desires fertility, preconception treatment must consider risk reduction for tumor complications during pregnancy, along with the goal of restoring and maintaining fertility and ovarian function. Dopamine agonists are the first recommended treatment for most prolactin-producing macroadenomas [2]. Bromocriptine has the larger safety database (6239 pregnancies vs 789 for cabergoline) [3]; thus, bromocriptine is typically recommended as the initial treatment. However, no increase in fetal anomalies has been reported with cabergoline exposure in the first trimester. The optimal duration of DA therapy before conception that minimizes pregnancy risk is not known. In one prospectively followed cohort, treatment until tumor size is <1 cm (for macroadenomas) and until women had at least 3 normal menstrual periods was not associated with complications during pregnancy [4]. Dopamine agonists generally are discontinued when pregnancy is confirmed [2]. Transsphenoidal resection of the tumor may be considered for macroadenomas that are resistant to dopamine agonists or are in proximity to or encroaching the optic chiasm because these tumors may enlarge during pregnancy and compromise vision. The risks of surgery must also be considered with regard to impairment of pituitary function and fertility. Fig. 2 illustrates the decision-making process during the management of prolactinomas in women taking into consideration desires for pregnancy, tumor size and response to medical therapy.

3.2. What are the Risks During Pregnancy?

When considering treatment of prolactinomas during pregnancy as in case 1, several concerns must be addressed: the potential effects of various therapies on the fetus and the risks of tumor growth and tumor-related complications in the mother.

The pituitary gland normally increases in size during pregnancy [5]. Lactotroph hyperplasia caused by elevated estrogen levels is thought to be the cause for the pituitary enlargement [6]. Growth of prolactinomas (2–8 mm) has also been reported during pregnancy [7], and the risk of tumor growth appears to be higher in macroadenomas (22.9%) compared with microadenomas (2.7%) [3].

3.3. What is the Risk of Apoplexy and Hemorrhage in Pregnancy? Does a History of Pituitary Apoplexy in Prior Pregnancy Change Management Considerations During a Subsequent Pregnancy?

Pituitary apoplexy is a rare complication of prolactinomas (prevalence, 0.08%) [8]. Hemorrhage within a prolactinoma during pregnancy is exceedingly rare, with 5 cases reported in macroadenomas and 2 in microadenomas [9,10]. Given the paucity of cases of pituitary apoplexy during pregnancy, most data are from case series of nonpregnant patients. Patients with prolactinoma and apoplexy usually develop apoplexy within 1 week to 12 months after initiation of dopamine agonists [10]. No data are available about the risk of recurrent apoplexy and likely reflects the very low risk of a recurrent event. Without data to guide who would benefit from continuing dopamine agonists during pregnancy, practice varies. Dopamine agonists might be continued or restarted during pregnancy for macroadenomas with suprasellar extension, especially if the patient has mass effect symptoms [2].

3.4. What are the Potential Harmful Effects to the Fetus When Dopamine Agonists are Reinitiated or Continued During Pregnancy?

Data are limited on the safety of dopamine agonists after the first trimester. A total of 13 patients from case reports and small case series received treatment with bromocriptine or cabergoline later in pregnancy with no reported adverse outcomes to the fetus [3,7,11]. In Case 1, DA therapy was reinitiated during the third trimester of pregnancy after the patient developed pituitary apoplexy and MRI demonstrated enlargement of the tumor. During her second pregnancy, because the tumor had reduced in size on cabergoline, DA therapy was discontinued once pregnancy was confirmed without the development of complications. Even for the same patient, treatment considerations may change in subsequent pregnancies depending on response to medical therapy.

3.5. When is Radiosurgery Considered in the Treatment of Prolactinomas?

Case 2 exemplifies use of an unconventional therapy for prolactinomas. Stereotactic radiosurgery is not standard therapy for prolactinomas, but it can be considered in the following scenarios:

Fig. 2. Treatment approaches for reproductive-aged women with prolactinomas. DA indicates dopamine agonist; TSS, transsphenoidal surgery.
1) patient is intolerant or unresponsive to medical therapy for which transsphenoidal surgery is unlikely to provide significant benefit (e.g., tumors with extensive cavernous sinus extension); and 2) tumor is unresponsive to medical therapy and transsphenoidal surgery. For the reproductive-age woman desiring to maintain fertility, tumor location is important when assessing the risk of pituitary dysfunction after transsphenoidal surgery or stereotactic radiosurgery. For patient 2, the location of the tumor primarily in the left cavernous sinus made transsphenoidal surgery less likely to result in a cure but decreased her risk of pituitary injury from stereotactic radiosurgery. However, for patient 1, radiosurgery was not considered. She had tolerated DA therapy, and the location of the tumor within the sella increased the risk of pituitary injury from radiosurgery potentially causing hypogonadotropic hypogonadism and impairing fertility. Moreover, the effect of tumor shrinkage from radiosurgery may take years.

3.6. What are the Expected Benefits and Risks of Radiosurgery?

Rates of biochemical remission after radiosurgery (defined as normalization of prolactin levels without dopamine agonists) range from 18% to 46% [12,13]. In patients who did not achieve biochemical remission, an additional 46% had clinical improvement, with or without dopamine agonists (14% vs 32%, respectively) [12]. The most common and clinically important adverse effect is pituitary dysfunction, which occurs in 15% to 42% of cases [12,14], and would be of particular importance in terms of fertility and additional risks during pregnancy for the reproductive-age woman. To our knowledge, no rates of pregnancy after radiosurgery for prolactinomas have been published. Here, we report the first case of a successful pregnancy without pituitary dysfunction or complications 3 years after radiosurgery for prolactinoma.

4. Conclusion

In this report, we present cases that illustrate individualized approaches to the treatment of macroprolactinomas in reproductive-aged women. Management of macroprolactinomas in women desiring pregnancy requires careful consideration of alternatives to surgery which could impair pituitary function and fertility and awareness of treatment goals that can minimize the risks for pituitary apoplexy and vision loss during pregnancy. It is important to increase awareness of these options prior to initiation of treatment and conception.

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