Hyperprolactinemia and Infertility

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KEYWORDS

• Prolactin • Infertility • Bromocriptine • Cabergoline
• Pituitary tumor

HYPERPROLACTINEMIA

Prolactin-secreting pituitary tumors are a common cause of gonadal dysfunction and infertility. This overview of the management of hyperprolactinemia in the infertile woman reviews the effect of pregnancy on tumor size, the choice of a dopamine agonist, and the potential effects of dopamine agonist therapy on fetal development. The article concludes with recommendations for treatment when fertility is not an issue and issues related to long-term follow-up of prolactinomas.

Clinical Presentation

When pregnancy, medications, thyroid, renal, and hepatic disease are excluded, the most likely cause of hyperprolactinemia is a prolactin-secreting pituitary tumor. Ninety percent of prolactinomas in women are microadenomas (<10 mm) (**Fig. 1**A) and present with menstrual dysfunction and infertility.[1] In general prolactin levels correlate with tumor size and hypopituitarism and neurologic deficits are uncommon in small tumors. Macroadenomas (>10 mm) (see **Fig. 1**B) are less common, are associated with higher prolactin levels, and usually present with neurologic dysfunction in addition to hypogonadism. Women with prolactinomas also present with low bone mass as a result of the inhibitory effect of prolactin on estrogen.[2,3]

Hyperprolactinemia is present in 15% to 20% of women undergoing evaluation for infertility.[4] In some studies the severity of hyperprolactinemia roughly correlates with the degree of menstrual dysfunction. In an infertility clinic in Brazil, Bahamondes and colleagues[5] reported hyperprolactinemia in 55% of women with amenorrhea, in 37% with oligomenorrhea, and in 9% with normal menses. Galactorrhea occurs in 50% to 80% of women with hyperprolactinemia and may occur with or without menstrual dysfunction.[1,4]

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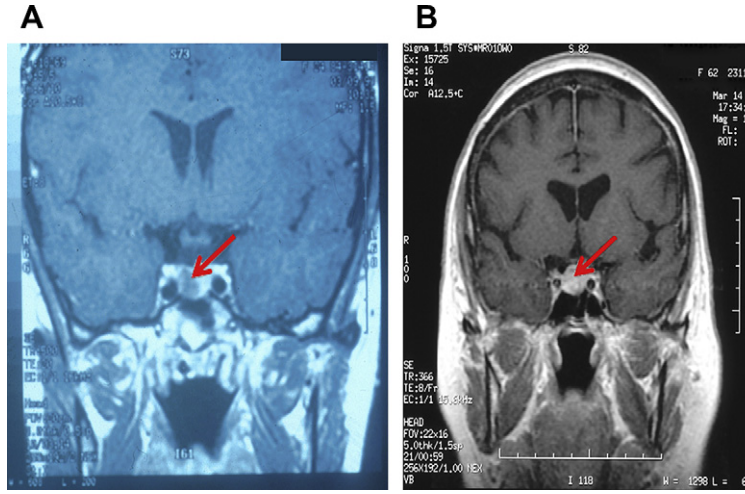

Fig. 1. (*A*) Pituitary microadenoma. (*B*) Pituitary macroadenoma.

Pathophysiology

The regulation of prolactin secretion is mediated through the inhibitory effects of hypothalamic dopamine. In animals and humans hypersecretion of prolactin leads to inhibition of gonadotropin-releasing hormone (GnRH) secretion. In hypogonadal rats hypothalamic GnRH secretion increases the number of pituitary GnRH receptors. In contrast, hypogonadal rats with hyperprolactinemia have fewer pituitary GnRH receptors, a diminished GnRH receptor response to GnRH, and a decline in luteinizing hormone (LH) pulse frequency and pulse amplitude, all of which reverse after correction of hyperprolactinemia.[6,7] Hyperprolactinemic women have diminished LH pulse frequency that normalizes after correction of hyperprolactinemia.[8,9] Except in women who have large tumors, treatment with physiologic doses of GnRH leads to normal or supranormal LH secretion in most patients with hyperprolactinemia.[9–11]

Although the primary abnormality in hyperprolactinemia is a decrease in hypothalamic GnRH secretion, prolactin also has a direct inhibitory effect on the ovaries, leading to decreased estrogen synthesis. Prolactin receptors are present in animal and human ovaries[12,13] and synthesis of estrogen and progesterone decreases when human ovarian cells are exposed to supraphysiologic concentrations of prolactin.[14,15]

Luteal phase insufficiency accounts for 3% to 10% of cases of infertility, and hyperprolactinemia has been reported in up to two-thirds of patients with luteal phase defects.[16,17] A luteal phase defect leads to poorly developed endometrium and failure of embryo implantation and is often the cause of infertility in hyperprolactinemic women who have normal menstrual cycles.[5,16] A small percentage of women with hirsutism have hyperprolactinemia but it is not clear how (or whether) the prolactin increase may contribute to increased hair growth. The underlying problem in many of these women is likely the polycystic ovarian syndrome.[18]

Principles of Treatment

The goals of therapy are to normalize prolactin, reduce tumor size, and restore gonadal function and fertility, and the treatment of choice is a dopamine agonist. Before the elucidation of the role of dopamine in the regulation of prolactin secretion,