

REPRODUCTIVE ENDOCRINOLOGY

High-dose cabergoline improves pregnancy rates in women with prolactinomas

An individualized treatment regimen with high-dose cabergoline may help women with tumor-related hyperprolactinemic infertility to achieve pregnancy, say researchers from Japan. “Our findings should be very encouraging for both patients and physicians because it became apparent that every infertile patient with prolactinoma could conceive safely with cabergoline, independent of tumor size or drug resistance or intolerance,” declare Masami Ono and Nobuhiro Miki, two of the investigators involved in this prospective study.

Prolactinoma is the underlying cause of infertility in a high proportion of women of reproductive age; however, two important issues must be considered before fertility treatment can be initiated in such cases. First, tumors can be resistant to first-line treatment with bromocriptine, which forces many women to abandon the idea of having children. Second, macroprolactinomas can enlarge during pregnancy, resulting in visual problems and severe headaches. This complication is conventionally prevented by pregestational surgical debulking of the tumor or radiation therapy before receiving medical therapy.

In 2008, Ono and colleagues found that individualized high-dose treatment with cabergoline brought about biochemical normalization of hyperprolactinemia and hypogonadism in nearly all of the 150 patients (both men and women) with prolactinoma that they examined. However, the issue of female fertility was not addressed in that study. Ono *et al.* have now followed up on their previous observations and determined the efficacy and safety of cabergoline for the induction of pregnancy in a group of infertile women with drug-resistant or previously untreated prolactinomas. In addition, they evaluated pregestational cabergoline therapy as an alternative to surgery or radiation therapy in women with macroprolactinomas.

The researchers enrolled 85 infertile women aged 24–40 years, 56 of whom

had microprolactinomas; the remaining 29 women had macroprolactinomas. The study participants were bromocriptine-resistant ($n = 31$), bromocriptine-intolerant ($n = 32$) or previously untreated ($n = 22$).

Patients with prolactinomas do not exhibit a uniform response to dopamine agonist therapy. As a consequence, Ono *et al.* decided to administer cabergoline on the basis of individual serum prolactin levels, with rapid dose escalation. The dose of cabergoline was increased at 2-week to 4-week intervals; the maximum incremental rate was 3 mg per week per 3 months and the maximum daily dose was 3 mg. “The quick (step-wise) dose escalation was carried out to shorten or minimize the period of exposure to rising estrogen levels before achieving normalization of hyperprolactinemia,” Ono and Miki explain. “Decreased estrogen in hyperprolactinemic amenorrhea is often restored before, rather than after, complete amelioration of hyperprolactinemia, and estrogen can antagonize the inhibitory action of dopamine on prolactin secretion.”

Treatment with high-dose cabergoline restored ovulation and normalized serum prolactin levels in all of the women. Furthermore, all prolactinomas shrunk in response to therapy. A total of 95 pregnancies were recorded for 80 of the study participants, 15 of whom conceived twice. The dose of cabergoline at first pregnancy was 0.25–9.00 mg per week in the cohort as a whole, and 2.00–9.00 mg per week in the women who were bromocriptine-resistant. No pregnancy-related complications were reported and none of the mothers experienced visual impairment or headaches. No minor or major malformations or developmental delays were detected in the 83 live births.

The study by Ono and colleagues has made two important contributions to the medical therapy of women with prolactinoma. First, it provides novel data on the efficacy of cabergoline for induction of pregnancy in women with tumoral



hyperprolactinemia. “To our surprise, we achieved a very high rate of successful pregnancy (94%) despite the fact that the patients consisted only of those with prolactinoma, which is generally more resistant to dopamine agonists than non-tumoral hyperprolactinemia, and included many difficult-to-treat patients, such as bromocriptine-resistant and bromocriptine-intolerant individuals, women with a long-term history of amenorrhea and women at least 35 years of age at the pregnancy,” state Ono and Miki. Second, the study demonstrates that pregestational pharmacologic tumor debulking is effective.

The results of this study are encouraging and suggest that cabergoline could prove a useful tool for pregnancy induction in women with tumor-related hyperprolactinemia. Nevertheless, the ultimate goal of medical therapy remains complete extinction of the prolactinoma.

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