Clinical Endocrinology (2010) **73**, 147–148 doi: 10.1111/j.1365-2265.2010.03823.x

COMMENTARY

Prolactinomas and pregnancy

Mark E. Molitch

Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

(Received 27 April 2010; accepted 8 May 2010)

In this issue of *Clinical Endocrinology*, Lebbe *et al.*[1] report on their valuable experience in 100 pregnancies in hyperprolactinemic women being treated with cabergoline. There now are over 600 pregnancies in which such use of cabergoline has been reported, so it seems appropriate to put these data into the larger context and review the safety and efficacy of cabergoline compared to bromocriptine in women with prolactinomas who wish to become pregnant. Two major issues arise when ovulation and fertility are restored: (i) the effects of the dopamine agonist on early foetal development and pregnancy outcomes and (ii) the effect of the hormonal milieu of pregnancy on prolactinoma size.

Usually the dopamine agonist is stopped once a woman has missed her menstrual period and pregnancy is diagnosed, to limit foetal exposure. When used in this fashion in over 6000 pregnancies, bromocriptine has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, or multiple pregnancies and only 1·8% of births were affected by congenital malformations.[2,3] This compares quite favourably with the 3·0% rate expected in the normal population.[4,5]

With these 100 cases from Lebbe *et al.*, we now have similar data on exposure for cabergoline in 663 cases and such use has also not shown an increased frequency of spontaneous abortion, premature delivery, or multiple births.[1,6–15] Outcome data available for 545 pregnancies showed that only 2·2% had congenital malformations.[1,6–15] However, in addition, there were 11 pregnancies in which there were elective terminations for malformations,[1,6,14,15] so that if these are added in to the above numbers for pregnancy outcomes for cabergoline, then there were 23 malformations out of 556 pregnancies, or 4·1%. However, data on terminations because of malformations are not available for the general population or for women taking bromocriptine, so for congenital malformations the proper comparison then is 1·8% for bromocriptine, 2·2% for cabergoline, and 3·0% for the general population. In addition to these data, Lebbe *et al.*[1] also reported important follow-up studies of 177 infants born to mothers who used cabergoline during pregnancy, finding normal neonatal physical and mental development, similar to what was found previously for bromocriptine.[16] Because of a high incidence of adverse outcomes with quinagolide,[17] this drug cannot be recommended for hyperprolactinemic women who wish to become pregnant.

The second concern for women with prolactinomas during pregnancy is tumour growth. Oestrogens have known marked stimulatory effect on PRL synthesis and secretion, and the high oestrogen levels of pregnancy can stimulate lactotroph cell hyperplasia.[18] Prolactinoma enlargement during pregnancy results from both the stimulatory effect of these high oestrogen levels and the discontinuation of the dopamine agonist that had been responsible for tumour shrinkage.[18]

Data on symptomatic tumour enlargement in pregnant women with prolactinomas show that this risk is 2·2% (13/584) for women with microadenomas, 27·9% (56/201) for women with macroadenomas, and 4·3% (7/161) for women with macroadenomas who had been treated with either surgery or irradiation prior to pregnancy.[12,15,18] A very interesting aspect of this report by Lebbe *et al.*[1] was information on MRI scans taken routinely as part of their practice between 24 and 32 weeks of gestation in 34 women in whom the cabergoline had been stopped shortly after the pregnancy was diagnosed. Compared to prepregnancy scans, of the 12 with macroadenomas, five had no change in tumour size, none had a decrease in tumour size, three had an increase of <5 mm, and four had an increase of >5 mm in size; of the 22 with microadenomas, nine had no change in tumour size, three had a decrease in tumour size, eight had an increase of <5 mm in size, and two had an increase of >5 mm in size.[1] Thus, the frequency with which an increase in size occurs as shown in this study is far greater than that which comes to clinical attention that may need intervention. However, this is not usual practice and, although the information gained here is very interesting, it should not be interpreted as indicating a change in practice standards.

Should symptomatic tumour enlargement occur when either drug is stopped, reinstitution of the dopamine agonist is probably less harmful to the mother and child than surgery.[19] However, such medical therapy must be very closely monitored, and transsphenoidal surgery or delivery (if the pregnancy is far enough advanced) should be performed if there is no response to the dopamine agonist and vision is progressively worsening.

In summary, bromocriptine has the largest safety database and has a proven safety record for pregnancy. Although the database for the use of cabergoline in pregnancy is much smaller, the growing body of evidence suggests that it is safe as well.

Correspondence: Mark E. Molitch, Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave., Suite 530, Chicago, IL 60611, USA. Tel.: +1 312 503 4130; Fax: +1 312 926 8693; E-mail: molitch@northwestern.edu

Fortunately, the risk of tumour enlargement is small when the drugs are discontinued once pregnancy has been diagnosed. However, cautious, clinical monitoring for tumour growth during pregnancy is needed, especially in the woman with a pre-existing macroadenoma. Reinstitution of the dopamine agonist is indicated if symptomatic enlargement occurs and transsphenoidal tumour decompression is rarely necessary.

References

1 Lebbe, M., Hubinont, C., Bernard, P. *et al.* (2010) Outcome of 100 pregnancies initiated under treatment with cabergoline in hyperprolactinaemic women. *Clinical Endocrinology*, **73**, 230–236.

2 Krupp, P. & Monka, C. (1987) Bromocriptine in pregnancy: safety aspects. *Klinische Wochenschrift*, **65**, 823–827.

3 Krupp, P., Monka, C. & Richter, K. (1988) The safety aspects of infertility treatments. *Program of the Second World Congress of Gynecology and Obstetrics*, Rio de Janeiro, October, 1988.

4 Canfield, M.A., Honein, M.A., Yuskiv, N. *et al.* (2006) National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999–2001. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, **76**, 747–756.

5 Martin, J.A., Kung, H.-C., Mathews, T.J. *et al.* (2008) Annual summary of vital statistics: 2006. *Pediatrics*, **121**, 788–801.

6 Webster, J., Piscitelli, G., Polli, A. *et al.* (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *New England Journal of Medicine*, **331**, 904–909.

7 Ferrari, C., Paracchi, A., Mattei, A.M. *et al.* (1992) Cabergoline in the long-term therapy of hyperprolactinemic disorders. *Acta Endocrinologica*, **126**, 489–494.

8 Robert, E., Musatti, L., Piscitelli, G. *et al.* (1996) Pregnancy outcome after treatment with the ergot derivative, cabergoline. *Reproductive Toxicology*, **10**, 333–337.

9 Ciccarelli, E., Grottoli, S., Razzzore, P. *et al.* (1997) Long-term treatment with cabergoline, a new long-lasting ergoline derivative, in idiopathic or tumorous hyperprolactinaemia and outcome of drug-induced pregnancy. *Journal of Endocrinological Investigation*, **20**, 547–551.

10 Cannavò, S., Curtò, L., Squadrito, S. *et al.* (1999) Cabegoline: a first-choice treatment in patients with previously untreatd prolactin-secreting pituitary adenoma. *Journal of Endocrinological Investigation*, **22**, 354–359.

11 Verhelst, J., Abs, R., Maiter, D. *et al.* (1999) Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *Journal of Clinical Endocrinology and Metabolism*, **84**, 2518–2522.

12 Ricci, E., Parazzini, F., Motta, T. *et al.* (2002) Pregnancy outcome after cabergoline treatment in early weeks of gestation. *Reproductive Toxicology*, **16**, 791–793.

13 Bronstein, M.D. (2005) Prolactinomas and pregnancy. *Pituitary*, **8**, 31–38.

14 Colao, A., Abs, R., Bárcena, D.G. *et al.* (2008) Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. *Clinical Endocrinology*, **68**, 66–71.

15 Ono, M., Miki, N., Amano, K. *et al.* (2010) Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas. *Journal of Clinical Endocrinology and Metabolism*, **95**, 2672–2679.

16 Raymond, J.P., Goldstein, E., Konopka, P. *et al.* (1985) Follow-up of children born of bromocriptine-treated mothers. *Hormone Research*, **22**, 239–246.

17 Webster, J. (1996) A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety*, **14**, 228–238.

18 Molitch, M.E. (2006) Pituitary disorders during pregnancy. *Endocrinology and Metabolism Clinics of North America*, **35**, 99–116.

19 Cohen-Kerem, R., Railton, C., Orfen, D. *et al.* (2005) Pregnancy outcome following non-obstetric surgical intervention. *American Journal of Surgery*, **190**, 467–473.