CEOG Clinical and Experimental Obstetrics & Gynecology

Analysis of bromocriptine treatment in pregnant pituitary prolactinoma patients

W. Lian[1], N. Liu[2], R.Z. Wang[1], B. Xing[1], Y. Yao[1]

[1] Department of Neurosurgery, Peking Union Medical College Hospital, Beijing Chinese Academy of Medical Science & Peking Union Medical College, Beijing

[2] Department of Neurosurgery, The Second Affiliated Hospital, Shandong University of Traditional Chinese Medicine, Jinan (China)

Summary

Objective: To investigate the therapeutic effects and duration of bromocriptine treatment during pregnancy in patients with pituitary prolactinoma. *Materials and Methods:* A retrospective analysis of the clinical data of 230 female pituitary prolactinoma patients at the Beijing Union Medical College Hospital neurosurgery clinic from January 2001 to May 2014 was conducted. When confirmed pregnant, patients in the control group immediately stopped taking bromocriptine, but patients in the treatment group continued to take the same dose of bromocriptine. *Results:* The embryos stop rate in the control group was 16.7%, significantly higher than the rate in the natural population ($p < 0.05$), while the rate in the treatment group (0.9%) not statistically different from that of the natural population ($p > 0.05$). There was no significant difference in the embryonic malformation rate between the two study groups compared to the normal pregnancy group ($p > 0.05$). *Conclusion:* Pregnant pituitary prolactinoma patients should not stop bromocriptine treatment, but should instead continue with the same dose for four months. For patients with macroadenoma, bromocriptine should be taken during the entire pregnancy. Blood prolactin, progesterone, human chorionic gonadotropin (hCG), and visual dysfunction should be monitored every two weeks during treatment. Patients should be treated with progesterone and hCG if the blood levels become too low. If regular monitoring shows that prolactin has increased too fast and/or visual dysfunction worsened, the dose of bromocriptine should be increased. The authors have found that bromocriptine treatment during pregnancy significantly reduces the embryo stop rate without increasing the embryo deformity rate; therefore, bromocriptine treatment is safe and necessary during pregnancy of pituitary prolactinoma patients.

Key words: Pituitary adenoma; Prolactin; Pregnancy; Bromocriptine.

Introduction

Prolactinomas are the most common type of functional pituitary adenoma, accounting for 50% to 60% of the total cases [1]. These tumors, which often manifest as microadenomas, occur more in women than in men, and especially in women of reproductive age [2]. Although it is a benign tumor, hyperprolactinemia may occur, which can lead to rare menstruation or amenorrhea, galactorrhea, infertility, spontaneous abortion, premature ovarian failure, and other clinical symptoms [1, 3]. These symptoms can negatively impact the physical and mental health of patients and their families. Currently, female prolactinomas are treated with medication such as bromocriptine, a semisynthetic alkaloid bromide that consistently stimulates the dopamine receptor [4]. It is widely used in the clinic to treat female pituitary prolactinomas; however, for patients of childbearing age, the use of bromocriptine during pregnancy is still under debate. To further investigate the clinical efficacy of bromocriptine during pregnancy, the authors studied 230 cases of women of childbearing age with prolactinoma. By conducting a retrospective analysis of two different groups with or without the bromocriptine treatment, the authors show that bromocriptine treatment during pregnancy is safe, and, in fact, decreases the chance for spontaneous embryo abortion.

Materials and Methods

The study was approved by the ethics committee of Peking Union Medical College Hospital, Chinese Academy of Medical Science& Peking Union Medical College and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Diagnostic criteria included 1) patients that were diagnosed with amenorrhea, galactorrhea, or infertility; 2) serum prolactin levels were greater than 100 ng/ml; 3) brain MRI examination confirmed sellar tumors (size 3mm ~ 3cm).

Clinical data were collected from July 2001 to May 2014 at the Beijing Union Medical College Hospital neurosurgery clinic. There were 230 female prolactinoma patients, aged 22 to 41 years. None of the participants had previously given birth, and all had taken bromocriptine regularly for three months to six years before pregnancy. Bromocriptine treatment before pregnancy was effective as shown by normal serum prolactin levels and, in some patients, significantly reduced tumor size.

The control group consisted of 120 patients from January 2001 to December 2007. They discontinued bromocriptine treatment upon the initial discovery of pregnancy until after birth. The treatment group included 110 patients from January 2008 to May

Revised manuscript accepted for publication August 3, 2015

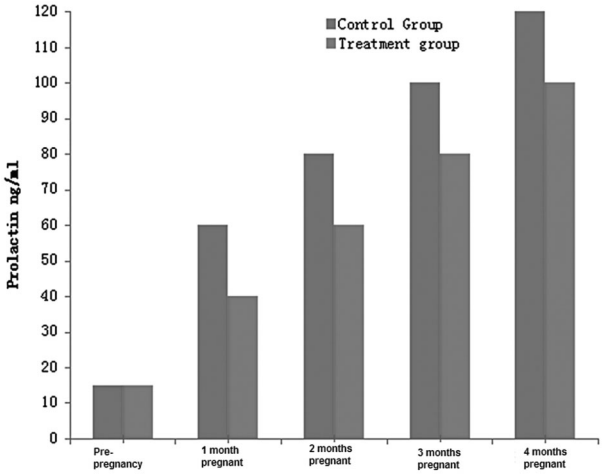

Figure 1. — Comparison of pre- and post-pregnancy serum prolactin levels.

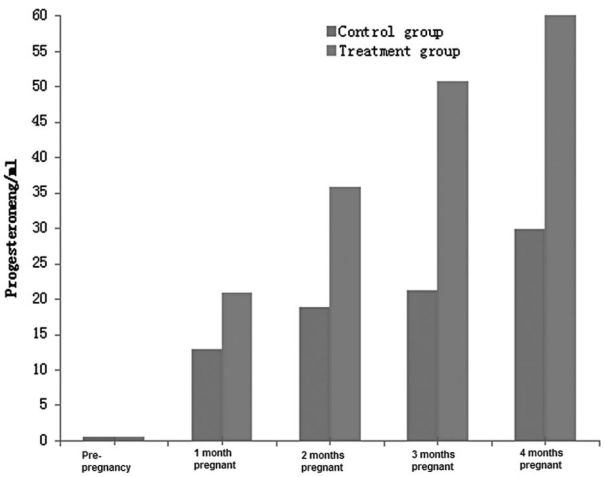

Figure 2. — Comparison of pre- and post-pregnancy progesterone levels.

2014. This group continued with the pre-pregnancy dose of bromocriptine for either four months or the entire pregnancy. Embryo stop rate and fetus malformation rate were calculated throughout the pregnancy.

Serum prolactin and progesterone levels pre- and post-pregnancy were measured by chemiluminescence. Embryonic growth and development were monitored regularly using B-ultrasound to collect embryo data and fetus malformation data.

Statistical analysis was performed using *t*-test and χ^2 test with $p < 0.05$ considered statistically significant.

Table 1. — *Embryo stop rate and fetus malformation rate of both groups and the normal population (%, n)*

Groups	Embryo stop rate	Fetus malformation rate
Treatment group	0.91 (1/110)	0 (0/110)
Control group	16.7 (20/120)	0.83 (1/120)

Treatment group compared with the control group showed a significance of $p < 0.05$ using the Statistical Test.

Results

The prolactin and progesterone levels of the control and treatment groups pre- and post-pregnancy are shown in Figures 1 and 2, respectively. As shown in Table 1, the embryo stop rate of the control group was significantly higher than those of the treatment group and the normal population. The difference was statistically significant. The embryo stop rate of the treatment group was not statistically different from the normal population. The fetus malformation rate of neither group was statistical different from the normal population.

Discussion

Analysis of the clinical data presented here suggest that cessation of bromocriptine treatment immediately after pregnancy in patients with pituitary prolactinoma can lead to a rapid increase of prolactin and a slow rise of progesterone. Low human chorionic gonadotropin (hCG) was also observed in some patients. The first trimester is a critical period of embryo formation, and low progesterone is not conducive to embryo development. In the control group, the prolactin increase inhibited the rapid rise of progesterone, and, as a result, the embryo stop rate was high. In the treatment group, bromocriptine prevented the sharp increase of prolactin, allowing progesterone to rise to a level that meets the needs of early embryonic development. Consequently, the treatment group showed a reduced embryo stop rate compared to the control group. The authors did not observe any significant difference of the fetus malformation rates between the treatment group and the normal population.

Pituitary prolactinoma and hyperprolactinemia

Prolactin is a protein hormone secreted by pituitary anterior eosinophils, pregnancy decidua, and immune cells. It plays an important role in the regulation of ovarian function and maintenance of pregnancy. Abnormally elevated levels of prolactin in the blood (known as hyperprolactinemia) can lead to ovulation and menstrual disorders, amenorrhea, galactorrhea, luteal dysfunction, and other anti-reproductive symptoms. Previous reports observed a 0.4% incidence rate of abnormal prolactin blood levels in the general population [5]. Pituitary prolactinoma is the most common cause of hyperprolactinemia with amenorrhea and lactation as the main symptom [6]. Furthermore, 30% to 50% of amenorrhea patients with prolactin increase were diagnosed with pituitary adenoma by CT scan or

MRI [7].

Prolactin is the only anterior pituitary hormone that is not negatively regulated by the hypothalamus [8]. The main inhibitor of prolactin may be dopamine, which inhibits prolactin production by acting on dopamine D2 prolactin cell surface receptors. Either in vivo or in vitro this neurotransmitter can quickly suppress the secretion of prolactin. Conversely, interference with dopamine can lead to the increase of prolactin secretion.

Pituitary prolactinoma treatment

Dopamine agonist-based drugs have become the preferred treatment for prolactinomas. The most commonly used medication is bromocriptine [9]; however, cabergoline [10], quinagolide [11], and pergolide [12] are used clinically in some countries. In China, only bromocriptine is approved to treat prolactinoma. Bromocriptine is a semisynthetic ergot alkaloid dopamine agonist that can effectively reduce the synthesis and secretion of prolactin, reduce tumor size, reduce the differentiation rate of cultured prolactinoma cells, and slow the growth of cancer cells. A large number of domestic and foreign clinical reports have confirmed the efficacy of bromocriptine in the treatment of prolactinomas. Bromocriptine can restore normal serum prolactin levels in 80% to 90% of patients, and it induces tumor shrinkage in 60% to 75% of macroadenoma patients. In addition, recovery of gonadal function was observed in 80% to 90% of microadenoma and 60% to 75% of macroadenoma patients.

After nearly 30 years of clinical application, bromocriptine has demonstrated efficacy and safety in the treatment of prolactinomas and is the treatment of choice for patients with prolactinomas who have fertility requirements. Bromocriptine treatment begins with a small dose that is gradually increased. This allows monitoring of the patient for any adverse side effects and an effective dosage. The effective daily dose range is 1.25 ~ ten mg, which is taken two to three times a day during meals and before bedtime. For the majority of patients, a 5.0 ~ 7.5 mg daily dose is sufficient; though macroadenoma patients may require more than ten mg. The dose can also vary depending on changes in serum prolactin levels. Upon reaching the treatment goal, physicians gradually reduce the dose to the maintenance dose within three to six months. If prolactin levels and tumor volume remain stable for six months or more while on a daily regimen of 2.5 mg bromocriptine, the dose can be reduced to a minimum maintenance dose. For most patients the minimum maintenance dose fluctuates between 1.25 ~ 2.5 mg/day. During the dose reduction and maintenance treatment period, patients should be regularly observed with monitoring of prolactin levels and radiographic changes.

Pituitary prolactinomas and pregnancy

Pituitary prolactinoma is caused by pituitary cell hyperplasia. Due to its slow growth, the tumor is considered biologically benign. The question of whether prolactinoma patients should continue to use drugs during pregnancy remains controversial. In recent years, most scholars have advocated for continuing medication during pregnancy to prevent the pituitary volume from increasing. Ionescu *et al.* [13] and others argue that bromocriptine does not have the potential for teratogenicity during pregnancy, and, in order to prevent tumor growth, patients should take the drug throughout pregnancy. Continuation of the medication also prevents pituitary apoplexy from occurring [14].

Due to the physical needs during pregnancy, the pituitary gland normally enlarges by 50% to 100%. Microadenomas also grow during pregnancy. Some issues arise regarding monitoring of tumor growth of these patients. First, physiological prolactin secretion during this period can lead to a prolactin blood concentration of 50 ~ 200 ng/ml. As a result, the prolactin level cannot be used to evaluate pituitary tumors. Second, pregnant patients are advised to avoid CT or MRI, which eliminates another monitoring tool. Therefore, the bromocriptine dose should be adjusted based on symptoms. Patient vision should be checked monthly; if tumor growth leads to vision impairment, headaches, or other related symptoms, the amount of medication should be increased throughout pregnancy until childbirth. Clinical reports showed that taking bromocriptine pre- or postpregnancy would not increase miscarriage, ectopic pregnancy, choriocarcinoma, or the incidence of congenital malformations [15]. Cheng *et al.* [16] suggest that pituitary microadenoma patients, in particular those who received medication or underwent surgery before pregnancy, should add bromocriptine to quickly control symptoms when signs of tumor growth occur during pregnancy [17]. To prevent the occurrence of tumor growth or pituitary apoplexy in pituitary macroadenoma patients, taking bromocriptine during pregnancy should not be interrupted.

The causes of embryo stop

Embryo stop is a special case of spontaneous abortion with an incidence rate of 13.4%. In these cases, the dead embryo or fetus is not discharged naturally from the uterus, and B-ultrasound shows an irregular gestational sac or fetal bud, no fetal heartbeat, or shrinking sac. There are many reasons why embryonic stop may occur. Endocrine factors have a significant impact, since embryo implantation and continued growth depends on the coordination of the endocrine system. In early pregnancy, the hormones estrogen, progesterone, and hCG are dominant. If there is a lack of maternal hormones embryo stops and miscarriage can occur. One of the most common causes is inadequate levels of progesterone, known clinically as luteal dysfunction. This state can lead to endometrial growth retardation and short luteal phase, thus affecting the cultivation and devel-

opment of fertilized eggs and resulting in early abortion. Embryo growth during the first trimester is unstable and the uterus is highly sensitive. High concentrations of progesterone inhibit uterine smooth muscle contraction, reduce the sensitivity of the uterus, sedate the enlarged uterus, ensure embryonic development, and support the early pregnancy. If progesterone level is lower than that of normal pregnant women, embryo stop and early abortion will often occur. Based on the present study, patients with pituitary prolactinoma who discontinue bromocriptine treatment immediately after becoming pregnant may have a rapid rise of prolactin, which, in turn, can cause luteal dysfunction and a slow increase of progesterone. After four months of pregnancy, embryonic development becomes stable and the hormones in pregnant women can maintain normal embryonic development. Consequently, the treatment can be stopped.

The effect of bromocriptine on fetuses

Reports have shown that bromocriptine was not teratogenic nor did it affect fetal development. Krupp *et al.* reported in detail a wide range of animal experiments and toxicological studies indicating that bromocriptine did not cause genetic mutations, embryo poisoning, or teratogenicity [26]. Ionescu *et al.* reported similar results on bromocriptine and teratogenicity during pregnancy [13]. A study performed in China showed that in 50 cases with a history of bromocriptine treatment during pregnancy, neonatal, and infant health was normal in five years of follow-up [27]. Studies that followed children of patients who took bromocriptine for one to ten years did not observe any abnormalities and the neonatal IQ and developmental quotient were normal [28]. A multi-center study of 2,437 women who used bromocriptine during pregnancy was carried out to evaluate its safety during pregnancy and to observe the development of infants to nine-year-olds. It was concluded that bromocriptine had neither teratogenic effects on fetuses nor adverse effects on children's development [28]. However, there are also reports that bromocriptine may pass through the placenta to reduce the cord blood prolactin levels and result in low birth weights [27]. Long-term effects on the fetus are not fully understood. Sheng *et al.* [18] speculated that, except for macroadenomas, pregnancy after bromocriptine treatment is similar to the natural process of pregnancy since the abortion rate, fetal malformation rate, and the rate of having twins did not increase significantly. Thus, the risk to mother and child is not significant [19].

Using the evidence cited above, many physicians suggest that both microadenoma and macroadenoma prolactinoma patients with fertility requirements choose a dopamine agonist as the first choice of treatment. For patients who are not sensitive to dopamine agonists, surgery is another option. So far bromocriptine has not been confirmed to have teratogenic effects on the fetus. It has not been confirmed whether bromocriptine affects the gonadal function and fertility of the offspring. However, most pregnant women are concerned about any medication during pregnancy. The literature shows that the use of bromocriptine during pregnancy does not lead to any significant difference in terms of the rate of preterm births or birth defects compared to the healthy population [20]. Liao *et al.* [21] did a follow-up study of 66 cases of neonates whose mothers took bromocriptine during pregnancy. No case of deformity was found. A follow-up study of 64 cases of children age six months to nine years old whose mothers took bromocriptine did not find any extraordinary health issues [22]. Radavelli-Bagatini *et al.* reported that bromocriptine did not have any significant effects on fetuses and newborns and had no effects on children's growth, development, and IQ [23].

Reports from other countries show a 1.11% incidence rate of embryo malformations in the normal population [25]. The domestic rate of China was reported to be about 1.37%. The present data show that the incidence in the control group was 0.83%, which is not significantly different from that of the normal population (Table 1). No case of fetal malformation was found in the treatment group, indicating bromocriptine during pregnancy did not have teratogenic effects on the fetuses in this study (Table 1).

Long-term follow-up

The 230 patients were followed up regularly from one month to up to six years post-birth. This study has shown that continuing bromocriptine on prolactinoma patients until four months pregnancy did not increase fetal spontaneous abortion, ectopic pregnancy, trophoblastic leaf disease, multiple pregnancies, or fetal congenital diseases. Long-term follow-up study of children did not show adverse long-term consequences. The results confirmed that the treatment did not cause ectopic pregnancy or trophoblastic disease. Neonatal and infant follow-up results showed both IQ and developmental quotient were within the normal ranges.

In conclusion, for pituitary microadenoma patients, bromocriptine can be continued during pregnancy until four months pregnancy. For macroadenomas, the treatment can continue throughout the pregnancy. It can not only reduce the abortion rate, but also control tumor growth during pregnancy. In addition, this treatment did not increase the neonatal malformation rate. For macroadenoma patients, blood prolactin, progesterone, hCG, and vision should be monitored. If progesterone and hCG are low, they should be administered to the patient. If prolactin rises too high and visual acuity decreases significantly, the tumor might have grown. The present authors suggest increasing the bromocriptine dose instead of performing surgery. Yao *et al.* [24] pointed out that any form of surgery during pregnancy increased the rate of miscarriage. In fact, abortion rate increased by about 1.5 times if surgery was performed three months before pregnancy, while surgery during late

pregnancy increased the risk by six-fold. From the available data, surgery has a greater impact on the fetus than drugs. The authors at the Department of Endocrinology at the Beijing Union Medical College Hospital, performed China's first systematic investigation of the growth process of "bromocriptine children". It was found that these children demonstrated no significant difference in their growth, intellectual, or psychological development compared to normal birth children. In this study, the authors conducted a six-year follow-up observation after the bromocriptine treatment during pregnancy and no adverse reactions were found. However, longer term follow-up is required to determine any late arising effects in the "bromocriptine children".

References

[1] Romijn J.A.: "Hyperprolactinemia and prolactinoma". *Handb. Clin. Neurol.*, 2014, *124*, 185.

[2] Pekic S., Stojanovic M., Popovic V.: "Contemporary issues in the evaluation and management of pituitary adenomas". *Minerva Endocrinol.*, 2015 Apr 22. [Epub ahead of print]

[3] Kawaguchi T., Ogawa Y., Tominaga T.: "Diagnostic pitfalls of hyperprolactinemia: the importance of sequential pituitary imaging". *BMC Res. Notes*, 2014, *7*, 555.

[4] Malik S., Hussain S.Z., Basit R., Idress N., Habib A., Zamant M., Islam N.: "Demographic characteristics, presentations and treatment outcome of patients with prolactinoma". *J. Ayub. Med. Coll. Abbottabad.*, 2014, *26*, 269.

[5] Harvey S., Martínez-Moreno C.G., Luna M., Arámburo C.: "Autocrine/paracrine roles of extrapituitary growth hormone and prolactin in health and disease: an overview". *Gen. Comp. Endocrinol.*, 2014, *14*, 423.

[6] Vilar L., Fleseriu M., Bronstein M.D.: "Challenges and pitfalls in the diagnosis of hyperprolactinemia". *Arq. Bras. Endocrinol. Metabol.*, 2014, *58*, 9.

[7] Tanei T., Nagatani T., Nakahara N., Watanabe T., Nishihata T., Nielsen M.L., *et al.*: "Use of high-field intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery for functioning pituitary microadenomas and small adenomas located in the intrasellar region". *Neurol. Med. Chir.*, 2013, *53*, 501.

[8] Majumdar A., Mangal N.S.: "Hyperprolactinemia". *J. Hum. Reprod. Sci.*, 2013, *6*, 168.

[9] Cho K.R., Jo K.I., Shin H.J.: "Bromocriptine therapy for the treatment of invasive prolactinoma: the single institute experience". *Brain Tumor Res. Treat.*, 2013, *1*, 71.

[10] Auriemma R.S., Pivonello R., Ferreri L., Priscitelli P., Colao A.: "Cabergoline use for pituitary tumors and valvular disorders". Endocrinol. *Metab. Clin. North Am.*, 2015, *44*, 89.

[11] Broekhof R., Gosselink M.J., Pijl H., Giltay E.J.: "The effect of aripiprazole and quinagolide, a dopamine agonist, in a patient with symptomatic pituitary prolactinoma and chronic psychosis". *Gen. Hosp. Psychiatry*, 2012, *34*, 209.e1-3.

[12] Mon S.Y., Alkabbani A., Hamrahian A., Thorton J.N., Kennedy L., Weil R., *et al.*: "Risk of thromboembolic events in patients with prolactinomas compared with patients with nonfunctional pituitary adenomas". *Pituitary*, 2013, *16*, 523.

[13] Ionescu O.,Vulpoi C., Cristea C.: "Hyperprolactincmia and pregnancy". *Rev. Med. Chirsocl. Med. Nat. Lasi*, 2002, *106*, 60.

[14] Janssen N.M., Dreyer K., van der Weiden R.M.: "Management of pituitary tumour apoplexy with bromocriptine in pregnancy". *JRSM Short Rep.*, 2012, *3*, 43.

[15] Saraiva J., Gomes L., Paiva S., Ruas L., Carvalheiro M.: "Giant macroprolactinoma and pregnancy". *Arq. Bras. Endocrinol. Metabol.*, 2013, *57*, 558.

[16] Cheng W.W., Zhang Z.J.: "Treatment of pituitary adenoma during pregnancy". *Zhonghua Fu Chan Ke Za Zhi*, 1996, *31*, 537. (Article in Chinese).

[17] Molitch M.E.: "Prolactinoma in pregnancy". *Best Pract. Res. Clin. Endocrinol. Metab.*, 2011, *25*, 885.

[18] Sheng Y.: "Drug treatment for hyperprolactinemia". *Journal of Practical Gynecology and Obstetrics,* 2007, *23*, 71.

[19] Witek P., Zieliński G.: "Management of prolactinomas during pregnancy". *Minerva Endocrinol.*, 2013, *38*, 351.

[20] Arduc A., Gokay F., Isik S., Ozuguz U., Akbaba G., Tutuncu Y., *et al.*: "Retrospective comparison of cabergoline and bromocriptine effects in hyperprolactinemia: a single center experience". *J. Endocrinol. Invest.*, 2015, *38*, 447.

[21] Liao Q.L., Lai W.J., Huang C.Y.: "Treatment of hyperprolactinemia with bromocriptine during pregnancy and pregnancy outcome". *China Clinical Practical Medicine*, 2007, *1*, 36.

[22] Saejong R., Dangrat C., Techatrisak K., Angsuwatthana S., Rattanachaiyanont M., Tanmahasamut P.: "Hyperprolactinemia: a 12-year retrospective study at gynecologic endocrinology unit, Siriraj Hospital". *J. Med. Assoc. Thai.*, 2013, *96*, 1247.

[23] Radavelli-Bagatini S., Lhullier F.L., Mallmann E.S., Spritzer P.M.: "Macroprolactinemia in women with hyperprolactinemia: a 10-year follow-up". *Neuro. Endocrinol. Lett.*, 2013, *34*, 207.

[24] Yao Y., Liu F.Y., Wang R.Z.: "Research status of prolactinomas". *Neurological Diseases and Mental Health,* 2008, *8*, 480.

[25] Himmetoglu O., Tiras M.B., Gursoy R., Karabacak O., Sahin I., Onan A.: "The incidence of congenital malformations in a Turkish population". *Int. J. Gynaecol. Obstet.*, 1996, *55*, 117.

[26] Krupp P., Ruch R., Turkalj I.: "Drugs in pregnancy: assessment of Parlodel.Prog". *Clin. Biol. Res.*,1985, *163C*, 211.

[27] Wang Q., Yang J., Dong X.C.: "Clinical observation of bromocriptine in the treatment of 25 cases of pregnancy combined with hyperpro-lactinemia". *China Pra. Med.*, 2014, *29*

[28] Krupp P., Monka C.: "Bromocriptine in pregnancy: Safety aspects". *Klinische Wochenschrift.*,1987, *65*, 823.

Corresponding Author:
W. LIAN, M.D.
Department of Neurosurgery
Peking Union Medical College Hospital
Chinese Academy of Medical Science &
Peking Union Medical College
No.1, Shuaifuyuan, Dongcheng District
Beijing 100730 (China)
e-mail: weilian996@163.com