Case Report

Management of prolactinoma with cabergoline treatment in a pregnant woman during her entire pregnancy

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ABSTRACT

Management of prolactinoma in pregnancy is a big challenge for the treating obstetrician as prolactin levels are normally raised in pregnancy and this creates a possibility of missing the diagnosis of prolactinoma. Women with micro adenomas and intrasellar macro adenomas do not require serial magnetic resonance imaging (MRI) or visual field testing as required in macro adenomas with extrasellar extension. A strict and vigil monitoring during each trimester for any clinical signs and symptoms related to tumor will suffice for the diagnosis of enlarging prolactinoma and for any active intervention required thereof. Dopamine agonists are the first choice of drugs to treat these tumors during pregnancy. Cabergoline is reported to be more effective and better tolerated as compared to traditional bromocriptine, with minimal risk of spontaneous abortion, congenital malformations or menstrual abnormalities. We are reporting a patient with macro prolactinoma who was treated successfully throughout her pregnancy with cabergoline. We achieved a very good control of prolactinoma without any significant alteration of dose and also without any adverse effects. We convey that cabergoline can be a first choice drug to treat macro prolactinomas in pregnancy also.

Key words: Bromocriptine, cabergoline, macroadenoma, microadenoma, pregnancy, prolactinoma

Introduction

Management of patient with prolactinoma during pregnancy is a big challenge to the obstetrician as prolactin levels elevation in pregnancy is a normal phenomenon and there are possibilities that one can misdiagnose this problem. Dopamine agonists are the drugs of choice for the treatment of prolactinomas.[1,2] Although the drug cabergoline has almost completely replaced bromocriptine in nonpregnant patients over the last decade, but still obstetricians are afraid to use it during pregnancy. We are reporting a case of prolactinoma who was successfully managed with cabergoline treatment throughout pregnancy.

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Case Report

A 27-year-old female, married for 1 years and 6 months presented in the gynecological outpatient department with chief complaints of irregular periods, blurring of vision, and infertility for the last one year. Clinical history and physical examination raised doubts towards possible presence of hyperprolactinemia. Her biochemical profile and radiologic investigations confirmed it as a case of pituitary macroadenoma, which measured 11.5 mm × 10.5 mm × 7.5 mm on MRI findings with serum prolactin 250 ng/ml [Figures 1 and 2]. The visual fields were absolutely normal as found out during the ophthalmological examination. She was prescribed cabergoline 0.5 mg orally twice a week for six months by the endocrinologist. After about one month of initiation of treatment, she presented with headache and blurring of vision. Her visual field charting was carried

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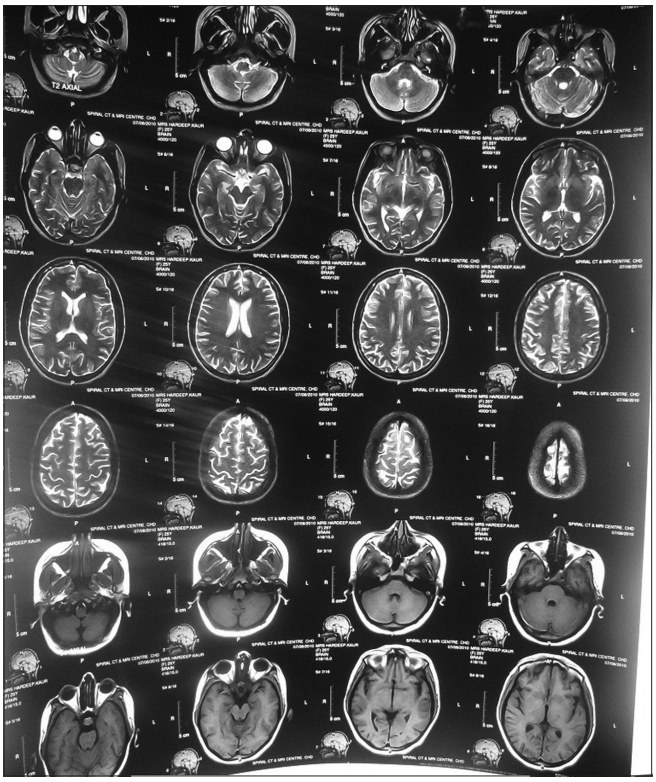

Figure 1: MRI image of the brain showing pituitary macroadenoma

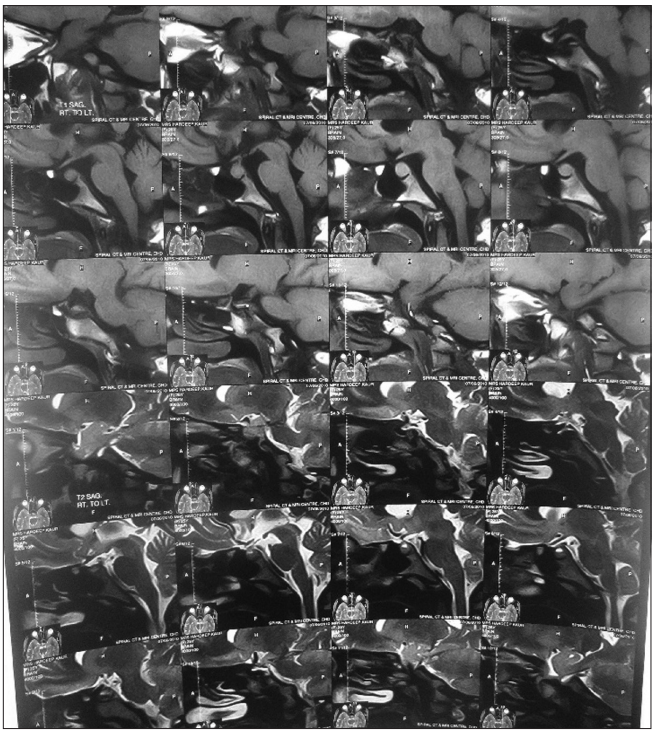

Figure 2: MRI of the brain showing prolactinoma

out, which was suggestive of bitemporal hemianopia. Her biochemical profile revealed increased prolactin levels (315.3 ng/ml). Endocrinologist's consultation was sought again and the dose of cabergoline was increased to 1.5 mg twice a week to which she responded fairly well. On her follow-up visit two weeks later, she gave the history of cessation of menstruation. During check-up, her urine pregnancy test was found out to be positive. The other relevant biochemical investigations were also carried out which included Hb electrophoresis, thyroid profile and serum cortisol and these were very much within the normal limits. She was supervised well during her entire antenatal period in our antenatal OPD clinic and a regular visual field charting was carried out at every visit. We had planned to stop the administration of cabergoline one week prior to the expected date of delivery (EDOD). MRI was again repeated at 30 weeks of gestation and there was no evidence of any significant alteration (12.7 mm × 13 mm × 10.7 mm). She was admitted in the emergency obstetrics ward at 36 weeks of pregnancy with onset of preterm labor. She delivered an alive and healthy male baby with a weight of 2.8 kg, and normal lactation was established soon after the birth. The post-partum period was uneventful without any complaint of headache or visual disturbance. After consultation with the endocrinologist, cabergoline was stopped after delivery and a repeat MRI was planned to be carried out six months later.

Discussion

Prolactin secreting adenomas are the most commonly encountered pituitary tumors in the women of child-bearing age.[1] Among the functioning pituitary tumors, prolactinomas represent 30% of all the pituitary tumors. In an autopsy series, incidence of pituitary adenomas was as high as 50%.[2] Since prolactinomas interferes with the functions of hypothalamic - pituitary - ovarian axis at various levels, it is believed to be responsible for about one-third of all cases of female infertility.[1]

Prolactinomas are the commonest pituitary tumors, which can complicate the pregnancy. Based on their size, prolactinomas are classified into macro adenoma (>1 cm) or micro adenoma (< 1 cm). Ninety percent of the pituitary tumors are intrasellar adenomas that rarely increase in size, while the rest are macro adenomas. Prolactin (PRL)-secreting lactotrophs that normally constitute up to 20% of the pituitary cells in men and in nulliparous women, increase to such an extent that by the end of pregnancy, they constitute up to as many as 50% of the total pituitary cells. Prolactin levels are lower than 25 ng/mL before conception and begin to rise at 5-8 weeks of gestation. At the end of the first trimester, serum prolactin levels are approximately 20-40 ng/mL. They increase further to 50-150 ng/mL and are 100-400 ng/mL at the end of the

second and third trimesters, respectively [Figure 3].[3]

Women with micro adenomas and intrasellar macro adenomas have a less than 3% chance of symptomatic tumor enlargement during pregnancy as compared to a more than 30% incidence in women with macro adenomas.[3] Molitch has summarized the recent findings on the effects of pregnancies on prolactinomas in which he has reported that the risk of clinically significant enlargement of macro adenoma in women with microprolactinomas is 1.3%, while the risk of enlargement in women with untreated macroprolactinomas is 23.2%. The most remarkable thing in our case was that the enlargement of the macroprolactinoma occurred during the first few weeks of pregnancy, which has not been reported in the literature till date. There is a less likely chance of symptomatic growth during pregnancy after its shrinkage with bromocriptine and that too even long after its discontinuation.[4,5]

If macro adenomas are treated with radiation therapy or surgery before conception, the risk of clinically significant tumor expansion falls from over 30% to less than 5%.[3] Therefore, contraception during treatment of patients with macroprolactinomas is always advised.

A computed tomography (CT) or MRI scan of the sella should be performed in all patients before conception to assess the tumor size along with the visual testing as the baseline. Women with micro adenomas and intrasellar macro adenomas do not require serial MRI examinations or visual field testing during pregnancy but should be monitored during each trimester for any clinical signs of tumor expansion such as headache, visual problems, nausea, vomiting, excessive thirst or urination, or extreme lethargy [Table 1]. Pregnant women with large tumors and those with extrasellar extension who have stopped dopamine agonists are at a risk for tumor growth, and therefore formal visual field testing should be done during each trimester.

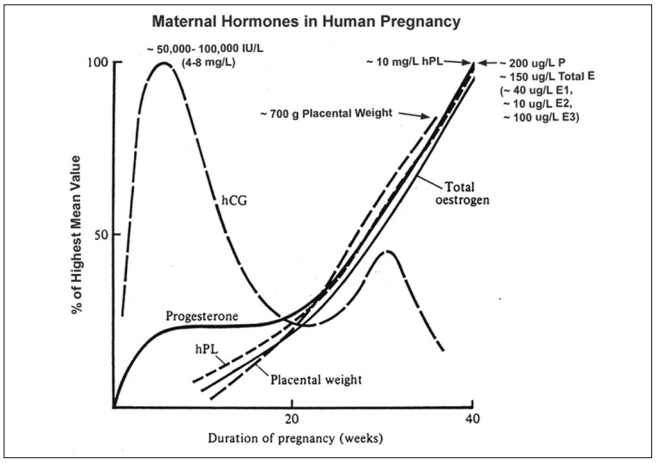

Figure 3: Various hormone levels during pregnancy

It is not necessary to measure serum prolactin throughout pregnancy because levels do not uniformly increase during gestation and do not correlate with tumor enlargement.[3] Bromocriptine normalizes prolactin levels and decreases tumor size in 80–90% of patients with micro adenomas and in 70% with large tumors.[6] The selective D2 receptor agonist cabergoline is more effective and better tolerated than bromocriptine and is also effective in treatment of tumors resistant to other dopamine agonists.[7,8]

Now, it has been reported by various research workers that there is no increase in the risk of spontaneous abortions, congenital malformations or neonatal abnormalities among the women who received cabergoline at the time of conception or during pregnancy.[9,10] In our case also the patient was treated with cabergoline before and throughout pregnancy without any congenital anomaly in the newborn. Presently, the baby has grown to 9 months old with all the normal milestones.

Although breast stimulation augments prolactin release, there is no evidence that breastfeeding has any adverse effect on tumor growth.[10] A CT or MRI scan should be performed postpartum to detect any asymptomatic tumor enlargement and if detected, repeated scans at 6 to 12 months' intervals are warranted. Dopamine agonists are indicated in such patients to shrink the size of tumor. Our patient could not get the MRI done at 6 months period due to monetary restraints but MRI was done at 8 month period, which revealed an increase in size of the tumor to 18.7 mm ×13.8 mm × 14.2 mm and her prolactin levels were estimated to be at 186.4 ng/ml. Surprisingly, she did not develop any visual symptoms in spite of the enlargement of the prolactinoma. Subsequently, she was put on 1.5 mg of cabergoline twice a week, although she did not have any symptoms related to the enlargement of tumor. This shows the importance of regular follow-up of patients in these type cases.

Table 1: The frequency of symptoms in descending disorder due to pituitary apoplexy

Symptoms or signs	Frequency (%)
Headache	90
Nausea and vomiting	56
Ocular palsy	55
Decreased visual acuity	55
Visual field defect	51
Photophobia	32
Fever	20
Reduced level of consciousness	18

Despite the tumor expansion and pituitary growth that occurs during gestation, observational studies have shown that pregnancy has a favorable effect on the natural history of preexisting prolactinomas. Women with prolactin-secreting micro adenomas who became pregnant during this interval had a higher rate of remission than women who did not become pregnant (35% vs. 14%). Prolactin levels are lower after delivery as compared to levels before conception and complete remission of hyperprolactinemia has been reported in 17–37% of women after pregnancy.[11-13] Changes in tumor vasculature resulting in pituitary necrosis, micro infarction, or hemorrhage have been suggested as potential mechanisms to explain how pregnancy might lead to normalization of prolactin.[14]

In conclusion, it seems possible to treat a patient with pituitary macro adenoma more effectively with cabergoline without any risk of congenital fetal anomaly provided she is monitored regularly for the clinical signs of tumor expansion. But for definite conclusions, we require more studies for the establishment of cabergoline as a better therapeutic alternative during the pregnancy. There is a strong need for strict and vigil supervision and regular monitoring for the early detection of clinical signs of tumor expansion as it may be life threatening in unsupervised patient if she comes late in labor. Cabergoline is a better alternative to bromocriptine in managing pituitary adenomas and can be a first choice of drug in pregnancy. It is also recommended that instead of stopping the treatment with cabergoline, a dose reduction would seem a better option as also evidenced by the increase in size of tumor and raised levels of prolactin.

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