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Prolactinoma and Gestation: A Reality

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Abstract

Prolactinoma, a prolactin producing adenoma, is the most common pituitary tumor in women of childbearing age. It often causes infertility and most of these tumors are smaller than 1 cm (microadenomas).

We report our experience with 11 pregnancies in 10 patients with microprolactinoma treated at the Endocrine Unit of a University Hospital in Rio de Janeiro, Brazil, through a period of 9 years. Age at diagnosis of prolactinoma and pregnancy confirmation, time elapsed between this diagnosis and pregnancy, prolactin levels at the diagnosis of prolactinoma and detection of pregnancy, pre-gestational use of dopamine agonists, and the occurrence of complications during pregnancy, birth and lactation were evaluated. With respect to the post-partum period, the levels of prolactin and the evolution of the tumor size are presented.

Ages at diagnosis of prolactinoma ranged from 13 to 34 years (mean=25.4 years), and by the time of the detection of pregnancy, 23 to 36 years (mean=31.2 years). The time elapsed between the diagnosis of prolactinoma and the detection of pregnancy ranged from 2 to 10 years (mean=5.8 years), and the pre-gestational prolactin values, from 17.1 to 63.3 ng/mL (mean=31.6 ng/mL). The average tumor size was 0.55 cm.

Regarding the pre-gestational treatment, 60% of the women used Cabergoline (CB) and 40% women used Bromocriptine (BC). Upon learning of the gestation, all of them stopped the medication, and thus they stayed throughout the entire pregnancy. There were no complications involving the conceptuses and only one patient did not breastfeed. All required a return to Dopaminergic Agonists (AD) use after gestation. The 10 patients responded to the reinsertion of AD with normalization of prolactin levels. We conclude that patients with prolactinoma can safely become pregnant with medical care.

Keywords: Pregnancy; Pituitary adenoma; Prolactinoma

Abbreviations:

CB: Cabergoline; BC: Bromocriptine; AD: Dopaminergic Agonists; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

Introduction

Pituitary tumors account for 10% to 15% of intracranial tumors, and their prevalence at autopsy is around 27%. Prolactinoma, a prolactin-producing pituitary tumor, is the most common-corresponding to 40% to 60% of all adenomas in this region of the brain. It is estimated to occur at 40 to 55 cases per 100,000 inhabitants [1,2].

About 90% of prolactinomas are small and intrasellar. They are more common in women of childbearing age, and the most common complaints are hypogonadism leading to infertility [1-3]. There is misinformation that women with prolactinoma should not get pregnant and breastfeed. The advent of AD such as BC and CB has led to success in the treatment of prolactinomas. This treatment has restored fertility and offered greater security to patients seeking to become pregnant [1-5].

We report our experience with 11 pregnancies in 10 patients with microprolactinoma treated at the Hyperprolactinemia Unit (total of 167 female patients) of the Endocrinology Service-Faculty of Medicine-University Hospital Clementino Fraga Filho of the Federal University of Rio de Janeiro (HUCFF-UFRJ) from April 2002 to July 2011.

Patients and Methods

Ten women who were able to conceive after being diagnosed with microprolactinomas were retrospectively evaluated. The diagnosis of microprolactinoma was based on the finding of prolactin levels equal to or greater than 60 ng/mL (normal range=5 to 20 ng/mL). It was also based on hypogonadotropic

hypogonadism associated with the presence of a pituitary tumor of less than 1 cm obtained via Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). The exclusion criteria were hyperprolactinemia potentially arising from other causes, at the time of conception, or previous surgery for treatment of pituitary adenomas.

The variables included age at the time of the diagnosis of prolactinoma and the confirmation of pregnancy; time between this diagnosis and the detection of pregnancy; prolactin levels at the time of diagnosis of prolactinoma and the confirmation of pregnancy. The pre-gestational use of DA was also analyzed. Complications involving gestation, fetal changes, stillbirth, and breastfeeding were assessed. Finally, the current levels of prolactin and tumor size were evaluated.

The statistical analysis was performed using Epi Info version 7.2.0.1 (Centers for Disease Control and Prevention, USA) and Prism 7 for Windows version 7.01 (GraphPad Software, Inc) programs. The project was approved by the Research Ethics Committee (CEP) - Faculty of Medicine and HUCFF - UFRJ, under number 191/06.

Results

Ten women (with 11 pregnancies) were studied. Their ages at diagnosis of prolactinoma varied from 13-34 years (mean=25.4 years). The ages of these patients when pregnancy was detected varied between 23 to 36 years (mean=31.2 years). Eleven pregnancies were considered, since one of our patients became pregnant twice. The time elapsed between the diagnosis of prolactinoma and the detection of gestation ranged from 2 to 10 years (mean=5.8 years), and the prolactin levels at the confirmation of gestation ranged from 17.1 to 63.3 ng/mL with an average value of 31.6 ng/mL. This data was calculated via the simple mean of the last three measures of prolactin for each patient except for two that had already arrived at the Endocrine Unit aware of their gestation and had not had prolactin levels measured in the previous six months (Table 1).

Table 2 shows the evolution of tumor size from the pre-gestational to the post gestational stage as well as the pre-gestational DA treatment and conduct during gestation. The adenomas were evaluated by CT or MRI depending on availability. The tumor size varied from normal resonance or the radiological information of "microprolactinoma" without specification. Tumor dimensions were on average 0.55 cm considering the largest tumor diameter. In the pre- gestational treatment of 10 women, 60% used CB and 40% CB. Upon learning of the gestation, all of them stopped the medication, and thus they stayed throughout the entire pregnancy.

Table 1: Age (diagnosis of prolactinoma and detection of pregnancy) and prolactin values (confirmation of pregnancy).

Patients	Ages at diagnosis of prolactinoma (years)	Age at detection of pregnancy (years)	Time between diagnosis and pregnancy (years)	Value of prolactin on confirmation of pregnancy (ng/mL)
1	25	30	5	44.7
1	25	34	9	17.6
2	22	32	10	17.1
3	24	28	4	27.2
4	13	23	10	63.3
5	26	30	4	31.7
6	26	34	8	21.2
7	31	36	5	38.2
8	34	36	2	23.6
9*	23	28	5	-
10*	30	32	2	-
Patient 1- two pregnancies				
*Patients without evaluation in the previous 6 months; returned to medical care when they got pregnant				

Among the 10 patients, one had preeclampsia, one had a fibroadenoma at 7 months gestation, and a third had intense headache and premature delivery with no direct relation to the prolactinoma. Only one patient did not breastfeed.

Table 2 shows that in 6 pregnancies there was no change in tumor size. Five subjects had a decrease in adenoma dimensions. All required a return to AD use after gestation. The 10 patients responded to the reinsertion of AD with normalization of prolactin levels (Table 2).

Table 2: Pregestational tumor size and treatment, conduct during pregnancy, Post gestational tumor size and prolactin.

Patients	Pre-gestational tumor size (cm)	Pre-gestational treatment	Conduct during pregnancy	Post gestational tumor size (cm)	Last prolactin level (ng/mL)
1	0.6	CB	Immediate CB Withdrawn	0.6	
1	Normal MRI	CB	Immediate CB Withdrawn	**NORMAL MRI**	13.6
2	0.7	CB	CB until 13th week	0.3	15.6
3	0.4	CB	CB until 5th week	0.4	8.2
4	0.7	CB	Immediate CB Withdrawn	**NORMAL TC**	2.7
5	0.4	CB	Immediate CB Withdrawn	**NORMAL TC**	19

6	Microprolactinoma	BC	Immediate BC Withdrawn	**NORMAL MRI**	23.3
7	0.4	CB	Immediate CB Withdrawn	0.4	12.4
8	0.4	BC	Immediate BC Withdrawn	**NORMAL TC**	18.5
9	0.8	BC	Immediate BC Withdrawn	0.6	20.2
10	Microprolactinoma	BC	Immediate BC Withdrawn	0.3	13.4

Discussion

Hyperprolactinemia interferes with the hypothalamic-pituitary-ovarian axis on several levels and is responsible for 30% to 40% of all cases of female infertility due to interruption of the secretion of hypothalamic releasing hormone (GnRH). This inhibits the release of Luteinizing (LH) and Follicle Stimulating Hormones (FSHs) with subsequent alteration of gonadal steroidogenesis [3,4]. This effect is related to the initial stages of suppression of the generation of kispeptin-a protein produced by arcuate and periventricular hypothalamic nuclei that stimulates GnRH release [5].

The prevalence of hyperprolactinemia among women with reproductive disorders is about 15% in those with anovulation and 43% when there is association of anovulation and galactorrhea [3,4]. Hyperprolactinemia usually is associated with both anovulation and infertility. Prolactinomas are diagnosed most often around 30 years and are a major cause of the latter [2,3].

The diagnosis of prolactinoma is based on complaints of hypogonadism associated with hyperprolactinemia and CT or MRI pituitary images showing an adenoma [1,2,6]. Most women have microprolactinomas (95%), but the preponderance in men is macroprolactinomas [6,7].

Treatment of hyperprolactinemia restores ovulation in 80% to 90% of cases [1-6,8]. Pituitary microsurgery and the possibility of the use of AD such as BC and CB (ergot derivatives that stimulate dopamine D2 receptors in both normal and tumor lactotrophs) resulted in a breakthrough in the treatment of prolactinomas and made clinical treatment the gold standard regardless of size and degree of tumor invasion [6,9].

AD normalizes prolactin levels in 75% to 85% of patients and restores ovulation in 80% to 90% of women with micro or macroprolactinoma. It reduces tumor growth in more than 25% in about 68% of the cases [1,2,4-6,8-10]. The most frequently used ADs in Brazil are BC and CB. BC has been commercially available for longer and is administered orally daily in doses of 1.25 mg/day to 7.00 mg/day. It has gastric side effects that lead to persistent intolerance (often confused with resistance) in about 10% of patients. BC has the largest number of publications showing that is it safe and effective in pregnant women [1-6,8-10].

CB has more prolonged action (longer half-life). It is administered orally in dosages of 0.125 mg/week to 1.000 mg/week-the latter being the most common dosage (one 0.5 mg tablet twice per week). It has fewer side effects and better therapeutic suitability [1-10]. And it has better results than BC in terms of treating prolactinomas. Consequently, it is the drug recommended as the first line for treatment of prolactinomas by the consensus published in February 2011 by the American and European Societies of Endocrinology [6]. During gestation, CB treatment was not related to higher incidences of fetal malformation, ectopic pregnancy, prematurity, or miscarriage [1-10].

Surgery is an alternative treatment to microprolactinomas – especially for cases of AD resistance and absence of adherence to medical treatment. It has good cure rates in experienced hands [1,6,11]. We chose to exclude any patient who had undergone pituitary surgery to maintain greater homogeneity in the sample.

Reduction of tumor size is rapid with clinical treatment. In some patients, it occurs in one to two weeks, but the largest decrease occurs in the first three months of treatment. However, in a minority (25%), tumor reduction is slower and may take from six months to a year [2,6,9]. The AD must be withdrawn as soon as the pregnancy is confirmed [1-6,8-10].

In our sample, the age of diagnosis of microprolactinoma ranged from 13 to 34 years; the diagnosis in very young women is based on complaints of menstrual irregularity, amenorrhea, and infertility. This leads to investigation of hyperprolactinemia and prolactin on girls and adolescents with primary amenorrhea.

The mean age in which our patients developed their pregnancies was 31 years-two years above the average age of the first pregnancy in Brazil according to data from the Ministry of Health, which reveals a higher incidence of first pregnancies between 15 and 29 years in our country [12].

In pregnant women without endocrine disease, serum prolactin levels increase progressively during pregnancy until about 200 ng/mL at term. There are similar secretory patterns seen in pregnant microprolactinoma patients but with greater amplitude peaks (5). In normal pregnancies, Quigley, et al. found mean prolactin levels of 30 ng/mL at the first trimester, 100 ng/mL at the second, and 200 ng/mL at the third [13]. There are individual variations (40 ng/mL-600 ng/mL)-especially at the end of the gestation.

Care should be taken in evaluating prolactin levels. They should never be considered in isolation. At our clinic, patients of childbearing age with hyperprolactinemia are first studied via prolactin and chorionic gonadotrophin to exclude gestation.

In our study, the mean values of prolactin at pregnancy were 35.4 ng/mL (range: 17.1 ng/mL to 63.3 ng/mL). However, two of our patients came to the Hyperprolactinemia Clinic after they

became pregnant and without prolactin doses in the previous six months. Molitch suggests that, in patients with hyperprolactinemia, fertility may be related to the cyclicity of prolactin response to AD, the ovulatory peak, and an increase in progesterone during the ovulatory and luteal phases [5].

Time under prolactinoma treatment is crucial for fertility and good pregnancy outcomes. However, we cannot adequately estimate this variable in the present study. The cost of the medication and side effects may lead to intermittent periods of AD use. Even if followed irregularly, it is possible that treatment duration may have influenced the evolution of pregnancies in our study because some patients had eight years of AD use.

Gestation leads to physiologically global lactotroph hyperplasia and a consequent increase in volume of the pituitary gland. This growth begins in the early weeks of gestation, and the gland increases by almost 1.2 cm in diameter throughout this period and in the immediate postpartum. The latter is accompanied by a concomitant increase in the size and population of lactotrophic cells and progressive elevation in prolactin levels. The increase of placental estrogen at gestation stimulates mitotic activity of lactotrophic cells and prolactin synthesis [4]. There is pituitary hyperplasia during pregnancy (up to 136% based on MRI). The gland can reach a volume of 11.8 mm soon after delivery. And the pituitary enlargement can be confused with a "pseudoadenoma". Therefore, one should avoid performing image studies of the pituitary gland during pregnancy or breastfeeding periods.

The first report of gestation in women with prolactinoma and AD use was published in 1979. There were concerns regarding a possible increase in tumor size and, on the other hand, the potential adverse effects of AD treatment both for the mother and the fetus [14].

Sixteen years later, Krupp and Monka reported 2,587 pregnancies in women with prolactinoma. There was no elevated risk of spontaneous abortion, multiple pregnancies, complications in pregnancy, differences in birth weight, or incidence of malformations. Most patients used AD for 22 days on average after conception; some used it throughout their gestation. There was no difference in the dosage of the drug or time of use during gestation in patients with normal conceptions and those with some type of malformation [14].

In microprolactinomas, AD should be discontinued as soon as pregnancies are confirmed. There is no need for MRI or visual field exam if there is no evidence of tumor growth [1-6,9,10,15]. Bronstein, et al. suggested that only patients who feature refractory headaches that respond to AD should remain in pharmacological treatment [9]. In two of our patients, AD treatment was initially maintained: one until the 5th and the other until the 13th week. This occurred because the medical team did not have prior knowledge of pregnancy status. Their evolution showed no complications for the mother or the fetus.

The risk of an important increase in tumor size during gestation is insignificant (<5% of cases). Data on pregnancy with microprolactinoma indicated that the possibility of neurological sequelae (headache, optic nerve compression or pituitary stalk compression) is approximately 1.6% to 5.5%. Imran, et al. [4] discontinued AD in most cases and recommended performing visual field examination at the time of confirmation of pregnancy with repeats only in the case of clinical symptoms. This is also the orientation of the consensus on hyperprolactinemia from other authors [2-6,9,10,15].

None of our patients needed MRI or returned to AD treatment during gestation. All had normal visual field in early pregnancy and without repetition.

Fetal exposure occurs at a critical time of organogenesis. It is essential to check that these drugs do not lead to adverse events during pregnancy or postnatal fetal development [16]. The safety of BC to the mother and the fetus has been documented in several studies in more than 6000 pregnancies. However, publications on CB security are rare and increase annually. They do not suggest a higher incidence of fetal malformations or prematurity [2,5,16].

The most commonly used AD is the potent action CB. It is long lasting, well tolerated, and has fewer side effects than BC [1,6]. Lebbe, et al. studied 100 pregnant women with CB and found spontaneous abortion in 10% and fetal malformations in 3%-4% [16]. These results agree with previous studies with CB such as those of Robert, et al. with 226 pregnancies, Ricci, et al. with 61, and Colao, et al. with 154 pregnancies [17-19]. All concluded that the frequency of abortions and malformations rates were similar to the general population [2,5,15,17].

The use of any AD in the first weeks of gestation has not been associated with increased spontaneous abortion, ectopic pregnancy, trophoblastic disease, congenital malformations, or multiple pregnancies. Some studies indicate that the use of CB during gestation might even be safer than BC [2,5]. We did not observe any fetal changes – even in those who used AD for a little longer.

Breastfeeding is not associated with the tumor growth. For obvious reasons, women who are breastfeeding should not receive AD. Although the sucking stimulus stimulates prolactin secretion, there is no evidence that it may cause tumor growth; hence there is no contraindication to breastfeeding. Our patients nursed as long as they judged it necessary [5,10,15,17]. Prolactin tends to fall rapidly after delivery but remains high during breastfeeding period. After about six months of breastfeeding interruption, the basal prolactin levels and pituitary size return to normal [1,4,5,9].

The reappearance of the menses is observed spontaneously in 75% of the patients, with persistence of hyperprolactinemia in only 62% of cases [17]. Several women ovulate after termination of pregnancy and no longer need AD treatment [17]. These patients should be evaluated every two months after childbirth or stopping breastfeeding. Interestingly, there is a decrease (50%-72% of cases) or even normalization (8%-29%) in the prolactin levels. In addition, Badawy, et al. [20] showed a reduction in tumor size in 27% of patients. The "curative" effect of gestation on prolactinomas does not have a clear explanation but has been attributed to the modification of tumor vascularization due to estrogenic stimulus resulting in necrosis and microinfarctions of the adenomatous tissue. This favorable phenomenon paradoxically suggests a good influence of

pregnancy on the prolactinoma [5,10,15]. We found that it was necessary to return to the AD immediately after stopping breastfeeding or sometime later but in doses smaller or equal to the pre-gestational period (Table 2). We conclude that patients with prolactinoma can safely become pregnant with medical care.

Conclusion

Patients with prolactinoma can safely become pregnant with medical supervision. The risk of an important increase in tumor size during gestation is insignificant. In our sample, there was no increase in tumor size during the gestation or breastfeeding periods. The use of AD in the first weeks of gestation has not been associated with complications for either patients or their offspring. It was necessary to reinstitute AD treatment after the interruption of breastfeeding.

References

1. Lamounier Filho A, Violante AHD (2009) Prolactinomas In: Rotinas diagnósticas e terapeuticas: Serviço de Endocrinologia do Hospital Universitário Clementino Fraga Filho In: Vaisman M, Conceição FL, Vieira Neto, L-Editora Altheneu, São Paulo, Brazil, pp. 15-26.
2. Maiter D (2016) Prolactinomas and pregnancy: From the wish of conception to lactation. Annales d`Endocrinologie 77: 128-134.
3. Schlechte JA (2003) Prolactinomas. N Engl J Med 349: 2035-2041.
4. Imran SA, Ur E, Clarke DB (2007) Managing prolactin-secreting adenomas during pregnancy. Can Fam Physician 53: 653-658.
5. Molich ME (2015) Management of the pregnant patient with a prolactinoma. European J Endocrinol 172: 205-213.
6. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, et al. (2011) Diagnosis and treatment of hyperprolactinemia: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 96: 273-288.
7. Braucks GR, Naliato ECO, Tabet ALO, Gadelha MR, Violante AHD (2003) Aspectos Clínicos e Terapeuticos de Prolactinomas em Homens - Arq Neuropsiquiatr 61: 1004-1010.
8. Kharlip J, Salvatori R, Yenokyan G, Wand GS (2009) Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. J Clin Endocrinol Metab 94: 2428-2436.
9. Bronstein MD, Paraiba DB, Jallad RS (2011) Management of pituitary tumors in pregnancy. Nature Reviews/Endocrinology 7: 301-310.
10. Randeva HS, Davis M, Prelevic GM (2000) Prolactinoma and pregnancy. BJOG 107: 1064-1068.
11. Na Y, Lijin J, Qi Z, Shuo Z, Xiaoxia L, et al. (2018) Long-term follow-up of female prolactinoma patients at child-bearing age after transsphenoidal surgery. Endocrine 22: 106-110.
12. Sociodemographic and health indicators in Brazil-Births in Brazil (2009) IBGE..
13. Quigley MM, Hammond CB, Handwerger S (1976) Prolactin after gonadotropin- induced pregnancy. Fertil Steril 27: 1165-1169.
14. Krupp P, Monka C (1987) Bromocriptine in Pregnancy: Safety Aspects -Klin Wochensch 65: 823-827.
15. Musolino NRC, Bronstein MD (2001) Prolactinomas and pregnancy. In: Bronstein md. pituitary tumors in pregnancy. Kluwer Academic Publishers, Boston, MA, USA, pp. 91-108.
16. Lebbe M, Hubinont C, Bernard P, Maitter D (2010) Outcome of 100 pregnancies initiated under treatment with cabergoline in hyperprolactinemic women. Clin Endocrinol 73: 236-242.
17. Robert E, Muatti L, Piscitelli G, Ferrari CI (1996) Pregnancy outcome after treatment with the ergot derivate, cabergoline. Reproductive Toxicology 10: 333-337.
18. Ricci E, Parazzini F, Motta T, Ferrari CI, Colao A (2002) Pregnancy outcome after cabergoline treatment in early weeks of gestation. Reproductive Toxicology 16: 791-793.
19. Colao A, Abs R, Barcena DG, Chanson P, Paulus W, et al. (2008) Pregnancy outcome following cabergoline treatment: extended results from a 12 year observational study. Clinical Endocrinol 68: 66-71.
20. Badawy SZ, Marziale J, Rosenbaum AE, Chang JK, Joy SE (1997) The long term effects of pregnancy and bromocriptine treatment on pregnancy-the value of radiologic studies. Early Pregnancy 3: 306-311.