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Outcomes of Patients with Macroprolactinoma Desiring Pregnancy: Follow-Up to 23 Years from a Single Center

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ABSTRACT

Macroprolactinomas are rarely seen in women, and pregnancy is a risk factor for tumor growth. More studies are needed to determine appropriate management for macroprolactinoma and pregnancy. The aim of our study is to evaluate effects of treatment with dopamine agonists on macroadenoma before and during pregnancy, safety of dopamine agonists on fetus, post-pregnancy prognosis and long-term results. This is a single center retrospective study. Thirty-four pregnancies occurred in 21 patients under medical therapy. Prolactin levels, treatment results, tumor diameter changes, maternal-fetal outcomes, and disease activity were evaluated. The median tumor size at the time of diagnosis was 15 mm (10–28). Residual adenoma diameter was smaller in those receiving medical therapy longer than one year till the conception (p = 0.047). Treatment was discontinued in 28 pregnancies after pregnancy confirmation, and 6 patients were exposed to bromocriptine throughout pregnancy. There was no symptomatic tumor growth during gestation. Among 27 live births, none of the fetuses developed neonatal malformation except for a case of Down syndrome. While early remission rate after pregnancy was 9.5 %, this rate reached 33.3 % at last follow-up visit. Lowered PRL levels at postpartum period (p = 0.040), smaller tumor size at last follow-up visit (p = 0.030), and total disappearance of tumor (p = 0.026) were the contributor factors for remission. Use of dopamine agonist over one year may reduce the risk of symptomatic tumor growth during pregnancy in patients without invasive or large macroprolactinoma before pregnancy. Exposure to dopamine agonists seems generally safe for the fetus.

Introduction

Prolactinomas are the most frequent secretory pituitary adenomas, and they usually occur as microadenomas in the reproductive age of young women, while macroadenomas are unusual to be detected [1]. Medical treatment with dopamine agonists [Bromocriptine (BRC) and Cabergoline (CAB)] can restore fertility, normalize prolactin (PRL) levels, and induce tumor shrinkage in 80–90 % of the patients [2]. When treatment of macroprolactinomas in reproductive-age women is considered, we do not only take into account the restoration of fertility, but we must also be aware of potential complications during pregnancy, and effects of therapy on the fetus. It may be necessary to continue dopamine agonists (DA) throughout pregnancy as the risk of tumor growth may increase in these patients [2–5]. For this reason, especially in selected patients, whose tumors are invasive or adjacent to the optic chiasm, it would be appropriate to continue DA therapy throughout pregnancy if they had no previous surgery or radiotherapy [2, 6]. Concerning the choice of DA induction during pregnancy, BRC makes the first choice due to the availability of more data on its use and shorter half-life compared to CAB [4, 7, 8].

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In recent years, exposure to DAs during the period of conception and in the first weeks of pregnancy has been reported to pose no significant risk for neither the mother nor the child [2, 3, 6, 9–11]. Still, more data are needed to ensure the reliability of CAB, which is a controversial issue, especially in terms of its use in pregnancy induction [2, 12]. On the other hand, it is difficult to give clear information about the prognosis of macroprolactinomas due to the lack of available treatment guidelines of these rare tumors [2]. In most previous studies, these rare tumors have been evaluated all together with hyperprolactinemia and microprolactinomas [1, 3, 6, 13–16]. Therefore, the aim of this study is to evaluate the effects of treatment with DAs on tumors before and during pregnancy, the safety of DAs on the fetus, and the prognosis after pregnancy while performing long-term follow-up (up to 23 years) of pregnant women diagnosed with macroprolactinoma.

Subjects and Methods

In this retrospective study, we reviewed women with macroprolactinomas treated with DAs at a single center (pituitary outpatient clinic of Istanbul University Hospital) between 1996–2019. Diagnosis of macroprolactinoma was based on elevated PRL levels (> 250 ng/ml) and the presence of a pituitary adenoma (≥ 10 mm) on magnetic resonance imaging (MRI) [4]. There were two cases with PRL level < 250 ng/ml with cystic adenoma and shrinkage induced by the DA treatment. The inclusion criteria were being diagnosed with macroprolactinoma, having at least one pregnancy under DA treatment and, admitting follow-up regularly during pregnancy and after delivery. Early pregnancy outcomes of three patients within cohort were previously presented in the multicenter study performed by Karaca et al. [17]. We included long-term follow-up results of these three patients in this study. Based on medical records, data (age, PRL level and maximal tumor diameter on MRI) at diagnosis of prolactinoma and preconception period; treatment modalities (DA type, dose, duration, and the cumulative dose of DA until pregnancy); tumor mass effect (headache and/or vision disturbance); pregnancy and fetal outcomes (gestational age, pregnancy complications, and the presence of malformations or other abnormalities in the newborn); data (PRL level, maximal tumor diameter, in remission or not) of early postpartum/after lactation and last follow-up were evaluated.

Serum PRL levels were analyzed by using electrochemiluminescence immunoassay (normal range; 4.7–23.3 ng/ml). MRI findings of the patients were evaluated by the same neuroradiologist. After the confirmation of pregnancy, clinical evaluation performed every 1–2 months. When necessary, patients were checked for visual field at intervals of 2–3 months. The cumulative dose of DAs was calculated from the initial dose of DA until pregnancy was detected. When pregnancy was detected, period during which the fetus was exposed to the DA (BRC or CAB) was calculated. As accordance with the studies in the literature, DA treatment was continued throughout the pregnancy in patients with large macroadenoma or invasive tumors, whose tumor reductions till conception were less than 50 %, and who used DA treatment less than one year prior to pregnancy [16, 18, 19]. The medical conditions of the newborns were obtained from the evaluation records of neonatologists. Subsequent child neuropsychological development information was obtained from the mothers' reports [16]. The first MRI control of patients without visual impairment was performed 3 months after cessation of breast-feeding or within the first year of delivery. Follow-up duration was calculated from the date of delivery or cessation of lactation up to the last visit (up to 23 year). Most recent disease activity was evaluated from the last records. Regardless of MRI findings, remission was defined as PRL normalization without medical treatment [13]. Evaluation of factors contributing remission were analyzed based on first pregnancy results.

This study was performed in accordance with the Helsinki recommendations. A written informed consent was taken from patients, and the study was approved by the Ethics Committee of Istanbul University hospital.

Statistical analyses

Statistical analyses were performed using SPSS version 22.0. Normal distribution was evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistical methods [mean, standard deviation (SD), median, minimum, maximum, frequency and percentage] were reported for each data. In two independent group comparisons, the Mann–Whitney U-test was used for non-normally distributed quantitative variables. Non-normally distributed qualitative variables were compared using the Fisher's exact test. A p-value of < 0.05 was accepted as statistically significant.

Results

The data of the patients (n = 21) at diagnosis and preconception were summarized in ▶ **Table 1**. Residual tumor diameter was lower in patients treated with DA more than one year before pregnancy compared to patients treated with less than one year [6.79 ± 3.75 (2–15) mm vs. 9.86 ± 3.24 (4–13) mm, respectively, p = 0.047].

Evaluation of maternal outcomes revealed that 27 (79.4 %) of 34 spontaneous pregnancies resulted in live births, five pregnancies (14.7 %) (CAB, n = 3; BRC, n = 2) ended with miscarriage and two patients (5.8 %) had voluntary curettage. When the pregnancy was confirmed, median cumulative doses of DAs at the first trimester were 168 (70–420) mg for BRC and 4 (3–9) mg for CAB. Among 27 live births, DA was withdrawn in 21 (78 %) pregnancies after confirmation of conception. In six patients (22 %) DA was continued throughout the pregnancy since their tumor reduction till conception were 0–33 % and DA treatment duration were less than one year before pregnancy. In four out of six patients, CAB was replaced by BRC, and in two out of six patients BRC was maintained until delivery. The median cumulative dose of BRC throughout gestation was 542 (468–1155) mg. None of the patients, in whom the DA treatment was withdrawn experienced headache and/or visual disturbance during gestation. Only one patient developed gestational diabetes. Sixteen patients (76.1 %) had one child, four patients (19 %) two and one patient (4.7 %) had three children during follow-up.

We did not observe any adverse pregnancy events such as stillbirth, preterm birth, multiple or ectopic pregnancy. There was no statistical difference between pregnancies terminated with miscarriage or live births in terms of DA dose at time of conception (1.8 ± 1.1 vs. 1.7 ± 1.2 mg/week, respectively in CAB group, p > 0.05; and 6.8 ± 0.8 vs. 4.5 ± 3 mg/day, respectively in BRC group, p > 0.05).

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▶ **Table 1** Data of patients at diagnosis and preconception.

Patient	Data
Patients, n	21
Age, years	28 (18–35)
Baseline	
PRL level, ng/ml	319 (103–1080)
Maximum adenoma size, mm	15 (10–28)
Initial DA treatment	
BRC, n (%)	12 (57.1%)
CAB, n (%)	9 (42.9%)
DA treatment duration in preconception, months	24 (2–79)
Age at first pregnancy, years	31 (20–39)
Preconception	
PRL level (ng/ml)	19 (1.5–57)
Cumulative dose of CAB, mg	44.2 (8–298)
Cumulative dose of BRC, mg	1387.5 (105–4575)
Maximum residual tumor size, mm	
<1 year of DA treatment	11 (4–13)
≥1 year of DA treatment	7 (2–15)
Tumor shrinkage	
≥50%, n	8 (38.1%)
<50%, n	13 (61.9%)

Data are presented as median (min–max) or number (percent). PRL: Prolactin; DA: Dopamine agonist; BRC: Bromocriptine; CAB: Cabergoline.

Evaluation of remission in early postpartum period is summarized in ▶ **Table 2**. Residual tumor diameter at post-partum period was smaller in remission group in comparison to non-remission group [0 mm vs. 6.89 ± 4 mm (0–14), respectively, p = 0.029].

The median follow-up time after first pregnancy was seven years (2–23). The mean PRL concentration of cohort was 45.4 ± 55 (3.7–187) ng/ml. The mean residual tumor diameter within cohort was 4.7 ± 4 (0–12) mm. Late remission was achieved in seven patients (33.3%) (▶ **Table 3**). The factors that contribute to the remission in the last follow-up visit were lowered PRL levels at postpartum period (p = 0.040), smaller tumor size at last follow-up visit (p = 0.030) and total disappearance of the tumor (p = 0.026). There was no relationship between remission rates and consecutive pregnancies. According to the information obtained from the birth records, none of the fetuses developed neonatal malformation, except for a previously published case of Down syndrome, who was exposed to 2.5 mg/day BRC for 6 weeks [17]. The mothers declared that none of the children had any health problems during their development, and that 27 children had normal neuropsychological development. The girl diagnosed with Down syndrome was also receiving special education.

Discussion

In the present retrospective study, 34 spontaneous pregnancies occurred after the initiation of DA treatment (BRC in 20 and CAB in 14). Although BRC is generally seen as the first-line treatment in pregnant patients with prolactinomas, it is known that CAB can be given as an alternative when it is not well tolerated [4]. BRC is the first DA approved for use in our country, and therefore it has been prescribed more frequently than CAB in patients with prolactinoma.

Risk of tumoral growth during gestation is an important concern in macroprolactinomas. Symptomatic tumor enlargement for macroadenomas that had not had prior surgery or irradiation was reported as 21.0% and for macroadenomas with prior surgery/irradiation as 4.7% [2]. In our study, none of our patients underwent pre-pregnancy surgery or radiotherapy, and no tumor growth symptoms such as headache and/or visual impairment occurred during pregnancy.

Adenoma size at diagnosis seem to be a significant factor for tumor progression, with the exception of macroadenomas that are not large or giant at pregnancy. Therefore, continuing DA treatment during pregnancy could be an easy way to protect patients from potential tumor growth for invasive tumors as suggested by the guideline [20]. Almalki et al. [8], reported that in a survey of DA agonist use during pregnancy in Canada, DAs were discontinued in only 65% of pregnant patients with macroadenoma and only 18% of patients with "large, > 2.9 cm" macroadenoma. Similar to the above study, DA treatment was discontinued in 82% of pregnant women with macroadenoma in our study. The maximum tumor diameter was 2.8 cm in our patients at the time of diagnosis, which was smaller than previously described as large macroadenoma (2.9 cm) [2]. On the other hand, Holmgren et al. [19] had reported that treatment with BRC for more than 12 months before conception seemed to reduce the risk of tumor enlargement. In our study, median tumor shrinkage was higher in patients using DA treatment more than one year. The study of Barraud et al. [21] reported that 9.6% of symptomatic tumor growth in pregnant macroprolactinomas was due to the insufficient initial DA response and growth was observed less in those with > 50% reduction in tumor size before pregnancy. In this study, macroprolactinoma diameters at diagnosis (10–43 mm) were larger than those of our patients (10–28 mm). On the other hand, we continued DA treatment throughout the pregnancy in patients whose tumor size had shrunk by less than 50%, close to optic chiasm, had a short treatment duration. In present study, the shrinkage of tumor less than 50% with DA treatment did not lead to symptomatic tumor growth during pregnancy in contrary to findings reported by Barraud et al. [21]. Our results were similar to those publications reporting the use of DA before pregnancy for at least 12 months as protective against tumor growth in macroadenomas, and reporting that large tumor size and shorter length of DA treatment before pregnancy will be indicators of symptomatic tumor growth during pregnancy [16, 19]. In our study, all patients breastfed their children, and lactation had no effect on tumor diameter and remission, which were compatible with the literature [7, 20–22].

Concerning DA exposure, BRC has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, or multiple pregnancies [1, 23, 24]. In current study, miscarriage rates were similar between patients using CAB and

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▶ **Table 2** Characteristics of patients with or without remission after lactation at early postpartum period.

	Remission (n = 2; 9.5 %)	No remission (n = 19; 90.5 %)	p
Age at diagnosis, years	23 (18–28)	28 (19–35)	0.329†
Treatment duration preconception, months	18 (12–24)	24 (2–79)	0.694†
Preconception			1.000‡
BRC, n	1 (50 %)	11(57.9 %)	
CAB, n	1 (50 %)	8 (42.1 %)	
PRL, ng/ml			
Baseline	485 (310–660)	319 (103–1080)	0.531†
Preconception	11	28 (1.5–57)	0.447†
Postpartum	19.5 (18–21)	95 (27–151)	0.023†
Tumor size, mm			
Basal	15 (12–18)	15 (10–28)	0.809†
Preconception	4.5 (2–7)	9 (2–15)	0.230†
Post-partum	0	7 (0–14)	0.029†
No tumor visible, n	2 (100 %)	1 (5.2 %)	0.014‡
Lactation duration, months	9 (6–12)	6 (2–24)	0.606†

Data are presented as median (min–max) or number (percent). Bold values are statistically significant ($p < 0.05$). p-Values were calculated using the Mann–Whitney U-test, or the Fisher's exact test. † Mann Whitney U-Test, ‡ Fisher's exact test. n: Number; PRL: Prolactin; BRC: Bromocriptine; CAB: Cabergoline.

▶ **Table 3** Data of patients at last follow-up visit (up to 23 years).

	Remission (n = 7; 33.3 %)	No remission (n = 14; 66.7 %)	p
PRL, ng/ml			
Baseline	465 (103–677)	311.5 (119–1080)	0.636†
Preconception	11 (1.5–57)	28 (3–49)	0.482†
Postpartum	27.3 (18–150)	99 (41–151)	0.040†
At last control	18 (10.9–24)	22 (3.7–187)	0.144†
Follow-up period after postpartum, years	11 (1–23)	6.5 (2–15)	0.189†
Tumor size, mm			
Basal	15 (10–28)	14.5 (10–20)	0.746†
Preconception	7 (2–11)	9.5 (2–15)	0.102†
Postpartum	2 (0–14)	7 (1–12)	0.147†
Last control	1 (0–9)	6.5 (1–12)	0.030†
No tumor visible, n	3 (42.9 %)	0	0.026‡
Tumor shrinkage in percent (%)			
Baseline/last follow-up visit	91.7 (40–100)	55 (10–94)	0.041†
Preconception/last follow-up visit	85.7 (14–100)	27.8 (8–80)	0.034†

Data are presented as median (min–max) or number (percent). Bold values are statistically significant ($p < 0.05$). p-Values were calculated using the Mann–Whitney U-test, or the Fisher's exact test. † Mann–Whitney U-Test, ‡ Fisher's exact test. n: Number; PRL: Prolactin.

BRC, and their rate (14.7 %) did not exceed the spontaneous miscarriage rates reported in our country [25]. In a recent study by Barraud et al. [21], miscarriages rate was reported as 14.3 % in their macroprolactinoma cohort. The retrospective nature of our study limited the evaluating of other factors influencing the risk of miscarriages such as usage of drugs, folic acid, nicotine, etc.

Since organogenesis occurs in the first 8 weeks of gestation, the effects of DA on the fetal development are another important con-

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cern. Due to the larger published data available on BRC and the shorter half-life it possess compared to CAB, BRC remains the first choice of DA treatment in women who are desiring pregnancy. In the literature, no adverse outcomes such as premature birth and fetal malformations reported from the studies performed on more than 6000 and 1000 women exposed to BRC and CAB, respectively, during their first weeks of pregnancies [2]. Recently, Araujo et al. [3], reported that fetal exposure to BRC or CAB from the first month and beyond the first trimester in their patient cohort with 24 micro and 5 macroadenomas is not associated with an increased risk of adverse neonatal or pregnancy disclosures, except for only one patient (3.1 %), who had a congenital malformation (club foot). On the other hand, in a multicenter study conducted from our country with functional and nonfunctional pituitary adenomas, Karaca et al. [17] reported corpus callosum agenesis and Down syndrome in two offsprings exposed to BRC during pregnancy, and microcephaly, cleft lip and neural tube defects in 3 offsprings exposed to CAB. The mother of the child with Down syndrome in this cohort was following up in our outpatient clinic, and BRC has discontinued when pregnancy confirmed. In this patient, advanced mother age (38 years old) was a risk factor for Down syndrome. In the present study, no developmental abnormality was found in any of the newborns exposed to DA except one with Down syndrome, which might be coincidental. In the literature, there are two more reported neonates with Down syndrome, who had histories of maternal CAB use in the first trimester, but not reintroduced, and amongst maternal age was advanced in one with no detailed information in the other case, reported to show no clear evidence about the relationship between DA and Down syndrome [16, 26]. On the other side, BRC has been used throughout the gestation in over 100 women, and no adverse effects other than a case of undescended testicle and another with a talipes deformity has been reported [27–29]. In the present study, 6 patients had medical treatment with BRC throughout the pregnancy, and no malformations were detected in the fetuses. Sant'Anna et al. [16] reported cases of epilepsy, attention deficit hyperactivity disorder, language delay, head support delay in children aged up to 19 years. In the present study, 26 children had normal neuropsychological development aged up to 23 years.

Recently, postpartum remission rates have been reported to be between 9–36 % in macroprolactinomas [13, 14, 16, 30]. In our study, early postpartum remission was 9.5 %, which was compatible with the above studies and it was increased to 33.3 % in the long-term follow-up. In the literature, most of the studies evaluated micro and macroadenomas together. In these studies, advanced maternal age (35–45 years), smaller initial adenoma size, lower PRL levels at diagnosis and postpartum period were reported as the predictors of remission at last follow-up visit [3, 6, 13, 14, 16]. Domingue et al. [13] reported that normalization of pituitary MRI after pregnancy were independently associated with remission in a retrospective two-center study, which included only 19 macroadenomas. Compared to the above studies, in our study lower PRL levels at postpartum period and both the disappearance of the tumor and smaller tumor size were the factors contributing to remission at the last follow-up visit.

The present study may possess some limitations due to its retrospective nature. On the other hand, the advantage of our study is to present data on women with macroadenomas are from single-center and have the longest follow-up period compared to the literature. Longer follow-up periods are important in screening possible adverse effects of DAs exposure and observing prognosis of these tumors.

In conclusion, despite current concerns, there is no maternal or fetal adverse consequences of exposure to DA in macroprolactinomas during the first trimester or throughout the pregnancy. Symptomatic progression of macroprolactinomas during pregnancy is uncommon, when the tumor was not large in size and invasive before pregnancy. Therefore, continuation of DA should be discussed in order to reduce the risk of tumoral growth in selected pregnant cases. Spontaneous remission can be achieved after pregnancy. In order to determine the appropriate management guidelines for macroprolactinomas with planned pregnancy, further studies with multi-center and large patient cohorts are needed.

Conflict of Interest

The authors declare that they have no conflict of interest.

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