Results of a Single-Center Observational 10-Year Survey Study on Recurrence of Hyperprolactinemia after Pregnancy and Lactation

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Context: The current survey study investigated the recurrence rate of hyperprolactinemia after cabergoline (CAB)-induced pregnancy and after lactation as well as safety of CAB exposure during early gestation.

Patients and Methods: From 1997–2008, 143 pregnancies were recorded in 91 patients with hyperprolactinemia (age 30.4 $\pm$ 4.7 yr, 76 microadenomas, 10 macroadenomas, and five nontumoral hyperprolactinemia). CAB therapy was discontinued within wk 6 of gestation in all. Pregnancies were monitored until delivery or termination, during and after lactation, twice yearly up to 60 months. The incidence of abortions, premature delivery, and fetal malformations was also analyzed.

Results: Pregnancies resulted in 13 (9.1%) spontaneous abortions and 126 (88.1%) live births. No neonatal malformations and/or abnormalities were recorded. In 29 of 91 patients (three with macroadenomas), treatment with CAB had to be restarted within 6 months after lactation because of hyperprolactinemia recurrence, whereas in 68% of cases, no additional therapy was required up to 60 months. No tumor mass enlargement was observed. All patients but three were breastfeeding, 35 (38.5%) for less than 2 months and 56 (61.5%) for 2–6 months. Three months after cessation of lactation and 60 months after pregnancy, no difference in prolactin levels was found between patients nursing for less than 2 months and 2–6 months.

Conclusions: Fetal exposure to CAB at conception does not induce any increased risk of miscarriage or malformations. Pregnancy is associated with normalization of prolactin levels in 68% of patients. Breastfeeding does not increase the recurrence rate of hyperprolactinemia. **(*J Clin Endocrinol Metab* 98: 372–379, 2013)**

Prolactinomas are the most common pituitary secreting tumors (1), accounting for approximately 40% of pituitary adenomas. Their incidence is 4-fold higher in women than in men and greater in the reproductive age (1–5). These tumors are frequently a cause of female hypogonadism and infertility. Hyperprolactinemia is commonly associated with anovulation, and correction of prolactin (PRL) excess with dopamine agonists (DAs) restores ovulation in 90% of cases (2–8). Pregnancy induces important changes in the pituitary gland, and in turn, pituitary hormones play a key role in inducing and maintaining pregnancy. In fact, the rise of β-human chorionic gonadotropin and consequently of estrogens and progesterone leads to hyperplasia of pituitary lactotroph cells associated with increased serum PRL levels and enlarged pituitary size (9).

After the introduction of bromocriptine (BRC) as first-line treatment in prolactinomas since the 1970s, more

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Abbreviations: BRC, Bromocriptine; CAB, cabergoline; DA, dopamine agonist; LBF, long breastfeeding; MRI, magnetic resonance imaging; NTHP, nontumoral hyperprolactinemia; PRL, prolactin; SBF, short breastfeeding.

than 6000 pregnancies in women harboring a PRL-secreting pituitary adenoma have been described (2–4, 9, 10). When taken for up to the first 4 wk after conception, BRC has not been associated with increased rates of spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations (3, 4, 9, 10). Experience with use of cabergoline (CAB) in pregnancy is still accumulating, and approximately 800 pregnancies have been described to date (2). Data on maternal and fetal exposure to CAB during the first weeks of pregnancy have been reported in just over 350 cases, and such use has not shown an increased percentage of spontaneous abortion, premature delivery, multiple pregnancy, or congenital abnormalities (11–16). According to The Endocrine Society Clinical Practice Guidelines for management and treatment of prolactinomas (17), therapy with CAB and other DA is recommended to be discontinued shortly after confirmation of pregnancy, because all DA have been shown to cross the placenta in humans and animals. This recommendation excludes women with invasive macroprolactinomas at risk to have tumor expansion during pregnancy.

In contrast, whether and when CAB should be restarted after pregnancy is still a matter of debate. In patients with macroprolactinomas, in the occurrence of symptomatic tumor growth, the DA reinstitution is generally successful in inducing tumor shrinkage so that transsphenoidal surgical debulking during pregnancy is seldom necessary (2). Moreover, after delivery, PRL levels might be lower than before pregnancy so that only a proportion of patients need to restart medical therapy (18–23), but the prevalence of control of hyperprolactinemia and of tumor volume after delivery has never been investigated in detail. So far, pregnancy has been reported to be a factor that triggers a return of PRL to normal (15), and complete normalization of PRL after pregnancy has been reported in 17–29% of hyperprolactinemic women treated with DA (20, 21).

Additionally, whether and how long women with hyperprolactinemia might breastfeed after delivery is still unknown (2).

The current 10-yr survey study aimed at investigating the recurrence rate of hyperprolactinemia after pregnancy, safety of exposure to CAB during early pregnancy, and safety and prolongation of breastfeeding on PRL levels and tumor mass.

Patients and Methods

Inclusion and exclusion criteria

This observational survey study included patients over 18 yr old with a previously established diagnosis of hyperprolactinemia treated with CAB only. Main inclusion criteria were 1) pregnancy occurring while on treatment with CAB and 2) written informed consent with respect to confidentiality statement of data collection according to the Italian privacy policy. Exclusion criteria included 1) pregnancy occurring before or while on treatment with DA different from CAB, 2) biochemically documented hypopituitarism or any other illness that could have an impact on pregnancy, 3) suspicion of drug or alcohol abuse, and 4) denial of consent with respect to confidentiality statement of data collection according to the Italian privacy policy.

Patients

One hundred eight consecutive hyperprolactinemic women had at least one pregnancy between January 1, 1998, and Decembe 31, 2007. Pituitary magnetic resonance imaging (MRI) revealed a microadenoma in 82 patients, a macroadenoma in 21 patients, and nontumoral hyperprolactinemia (NTHP) in five patients. Conception was suggested to be avoided in microadenomas until at least three regular menstrual cycles were confirmed and in macroadenomas until tumor shrinkage by at least 25% of basal volume was documented along with the resumption of regular cycles. Seventeen patients were excluded from the analysis because of gestation while on therapy with BRC in six patients (all with microadenomas), large invasive macroadenomas requiring CAB continuation throughout pregnancy in three patients, and hypopituitarism in replacement therapy in eight patients with macroadenoma (eight with hypocortisolism and seven with hypothyroidism). Therefore, data collected in 91 women (76 with microadenoma, 10 with macroadenoma, and five with NTHP), aged 30.4 ± 4.7 yr, were included in the study. All patients were receiving CAB at the time of conception. As previously reported (24, 25), 13 women had been previously treated with BRC at the dose of 26.25 ± 16.26 mg/wk (median dose of 17.5 mg/wk) and one with quinagolide at the dose of 0.525 mg/wk before starting CAB therapy. The profile of patients at study entry is shown in Table 1.

Treatment protocol

At the time of conception, all patients were receiving medical treatment with CAB, and three patients with macroadenoma had previously also undergone unsuccessful neurosurgery. Mean CAB dose at the time of discontinuation was 0.69 ± 0.35 mg/wk (median dose, 0.5 mg/wk) and 0.67 ± 0.24 mg/wk in patients

TABLE 1. Profile of patients at study entry

	Profile
Patients (n)	91
Patients' age (yr)	30.4 ± 4.7
Baseline PRL (μg/liter)	143.3 ± 174.6
PRL at conception (μg/liter)	16.7 ± 39.9
Microadenoma [n (%)]	76 (83.5)
Macroadenoma [n (%)]	10 (11)
NTHP [n (%)]	5 (5.5)
CAB dose (mg/wk) (median)	0.69 ± 0.35 (0.5)
Previous BRC treatment [n (%)]	13 (14)
BRC dose (mg/wk) (median)	26.25 ± 16.26 (17.5)
Previous QGL treatment [n (%)]	1 (1)
QGL dose (mg/wk)	0.525
Previous surgery [n (%)]	3 (3.2)

QGL, Quinagolide.

with macroprolactinoma. In the whole patient population, treatment duration before pregnancy was 46.5 ± 39.4 months (range 3–209 months). Before pregnancy, CAB induced a significant decrease in PRL levels (143.3 ± 174.6 *vs.* 16.7 ± 39.9 μg/liter, $P = 0.0001$), with PRL normalization in all patients but one harboring a microadenoma. At 1–6 months before attempts to become pregnant, patient were asked to have a MRI exam to evaluate tumor size. Diameters were measured in the three orthogonal plans, and tumor volume was calculated in line with the Di Chiro and Nelson formula (26): volume = height × width × depth × π/6. Compared with baseline evaluation, tumor mass showed complete disappearance in 51%, shrinkage over 25% in 13%, empty sella in 2%, and no change in 31% of patients (Fig. 1). In patients with macroprolactinoma, CAB treatment induced a significant decrease in tumor volume (588 ± 287 *vs.* 221 ± 285 ml, $P = 0.005$) by 58% compared with baseline evaluation, with complete disappearance of tumor mass in one case and shrinkage over 25% in seven patients.

This survey study has been conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study protocol

The present study is an observational survey study. Patients were recommended to discontinue treatment with CAB as soon as pregnancy was confirmed by serum β-human chorionic gonadotropin measurement. In all patients, CAB was withdrawn within wk 6 of gestation. Serum PRL levels were assessed 1–6 months before pregnancy, 3 months after cessation of lactation, and thereafter every 3–6 months for a mean follow-up of 60 months after delivery, whereas hormonal evaluation was not performed during pregnancy and breastfeeding, as previously suggested (2, 17). Patients were followed up every 3 months during pregnancy with a clinical investigation. In patients with macroadenomas who had not undergone previous pituitary surgery (seven patients), our clinical approach was to perform a visual field testing every 3 months; a new pituitary MRI was scheduled if a patient developed headache or visual disturbances during gestation suggesting tumor expansion. Recurrence of hyperprolactinemia was defined as a serum PRL of greater than 25 μg/liter on two samples more than 1 wk apart at least 3 months after stopping breastfeeding. Pregnancies were monitored until delivery or termination according to routine clinical practice. At the end of pregnancy, information was recorded regarding the date of delivery and gestational age, with births occurring after 37 wk of gestation being considered term deliveries and those occurring before a full 37 wk being considered preterm, in line with the World Health Organization criteria. Primary endpoints included the evaluation of remission and recurrence rate of hyperprolactinemia after pregnancy. Patients who permanently discontinued CAB were defined as group A, whereas those requiring treatment restarting were defined as group B. According to breastfeeding duration, patients were classified as follows: less than 2 months, short breastfeeding (SBF); 2–6 months, long breastfeeding (LBF). The incidence of abortions, premature delivery, and fetal malformations or abnormalities was also examined.

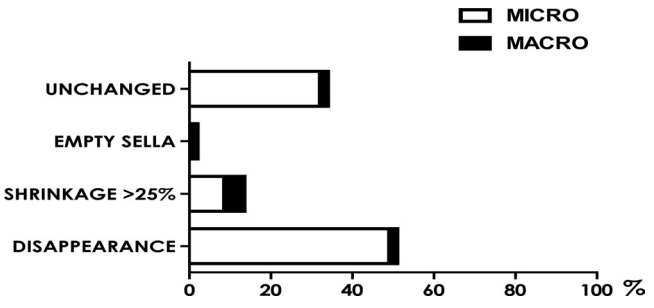

FIG. 1. The outcome of medical therapy with CAB on tumor volume before pregnancy. Compared with baseline evaluation, MRI showed complete disappearance in 51%, shrinkage over 25% in 13%, empty sella in 2%, and no change in 31% of patients.

Hormonal assays

During the study period, many different PRL assays have been used. All PRL levels reported in the study have been analyzed according to international standards. Hyperprolactinemia was defined as a serum PRL level of greater than 25 μg/liter on two different samples more than 1 wk apart.

Statistical analysis

Data were analyzed using SPSS Software for Windows, version 19.0 (SPSS, Inc., Cary, NC). Data are reported as mean ± SD. The comparison between the numerical data before and after pregnancy was made by nonparametric Wilcoxon test. Nonparametric Mann-Whitney *U* test was made to compare patients permanently discontinuing CAB and those requiring treatment restarting. The comparison between prevalence was performed by χ^2 test corrected by Fisher's exact test when necessary. The correlation study was done by calculating the Pearson's correlation coefficients. Linear regression analysis was done to evaluate the association of remission from hyperprolactinemia with nadir PRL during CAB treatment, pregestational PRL, postlactation PRL, CAB dose and duration, and tumor size. Significance was set at 5%.

Results

Pregnancy outcome

As shown in Table 2, during our observation period, 143 pregnancies occurred, including 141 spontaneous and two medically assisted (one intracytoplasmic sperm injection and one *in vitro* fertilization) gestations. Pregnancies resulted in 126 live births (88.1%) and 17 abortions (11.9%), including three voluntary (2.1%), one therapeutic (0.7%), and 13 spontaneous (9.1%) abortions. All live-birth deliveries were at term, and all infants but two (98.6%) had normal birth weights of 2500–4000 g. The sole therapeutic abortion was due to umbilical strangulation. No stillbirths, premature deliveries, multiple or ectopic pregnancies, trophoblastic disease, or congenital abnormalities were recorded in our patient cohort. In abortions, CAB dose at the time of conception was similar to that in live births (0.75 ± 0.47 *vs.* 0.66 ± 0.5 mg/wk, $P = 0.3$). Fetal exposure to CAB was less than 6 wk in both abortions and live births.

TABLE 2. Pregnancy outcome

	n (%)
Total pregnancies	143
Spontaneous pregnancy	141 (98.6)
ICSI	1 (0.7)
IVF	1 (0.7)
Live births	126 (88.1)
Abortions	17 (11.8)
Voluntary	3 (2.1)
Therapeutic	1 (0.7)
Spontaneous	13 (9.1)
Term deliveries	126 (100)
Preterm deliveries	0 (0)
Normal birth weight	124 (98.4)
Low birth weight	2 (1.6)
Stillbirths	0 (0)
Premature deliveries	0 (0)
Multiple pregnancies	0 (0)
Ectopic pregnancies	0 (0)
Trophoblastic disease	0 (0)
Congenital malformations	0 (0)

ICSF, Intracytoplasmic sperm injection; IVF, *in vitro* fertilization.

Remission and recurrence rates

After CAB withdrawal, no patient experienced headache, visual loss, or impairment of hyperprolactinemia-related symptoms during pregnancy, and none needed to be restarted on CAB during pregnancy. Pituitary MRI was repeated 3–6 months after delivery and did not show tumor volume increase in any patient after CAB discontinuation. As a whole, at the first evaluation 3 months after cessation of lactation, PRL was only slightly but not significantly increased compared with pregestational levels (25.9 ± 26.2 *vs.* 16.7 ± 39.9 μg/liter, $P = 0.08$, Fig. 2) and were faintly but significantly correlated to CAB dose administered before pregnancy (r = 0.27, $P = 0.0049$, Fig. 3). As shown in Table 3, in 62 of 91 patients (68%, group A), medical therapy was not further required and patients were classified as in complete clinical and biochemical remission. Group A included patients with successful full-term pregnancies (50 with microadenomas, seven with macroadenomas, five with NTHP, Table 3). In 29 patients (32%, group B), treatment with CAB had to be restarted after pregnancy because of recurrence of hyperprolactinemia. Group B included 22 patients after successful full-term pregnancies (20 microadenomas and two macroadenomas) and seven patients after abortion (six microadenomas and one macroadenoma). In 27 of 29 women of group B (93.1%), pituitary MRI before pregnancy showed no change in tumor size. As a whole, CAB was restarted in 34% of microadenomas, 30% of macroadenomas, 38.4% of women receiving BRC as first-line treatment before CAB, and 41.2% of patients after abortion. In Group B, CAB was restarted at a similar dose compared with that given before gestation (0.62 ± 0.5 *vs.* 0.69 ± 0.35 mg/wk, $P = 0.82$). Duration of CAB treatment before pregnancy was similar in group B and group A (37 ± 45 *vs.* 44 ± 36 months, $P = 0.43$). At the linear regression analysis, nadir PRL during CAB treatment, pregestational PRL, postlactation PRL, CAB dose and duration, and tumor size were found to be not significantly associated with remission from hyperprolactinemia.

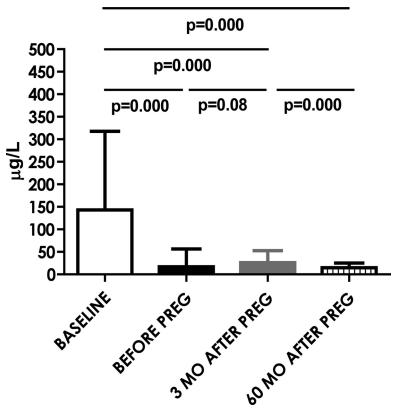

FIG. 2. The outcome of medical therapy with CAB on PRL levels. Before pregnancy (PREG), CAB induced a significant decrease in PRL levels (143.3 ± 172.9 *vs.* 16.4 ± 39.5 μg/liter, $P = 0.0001$), with prolactin normalization in all patients but one harboring a microadenoma. Three months (MO) after pregnancy, PRL levels were slightly but not significantly increased compared with pregestational evaluation (25.7 ± 26 *vs.* 16.4 ± 39.5 μg/liter, $P = 0.08$), whereas after 60 months, PRL levels were further reduced compared with the 12-month follow-up (14.7 ± 10.2 *vs.* 25.7 ± 26 μg/liter, $P = 0.0001$).

Impact of breastfeeding on PRL levels and remission rate

All patients but three had 1–6 months breastfeeding: 35 (38.5%) nursed for less than 2 months (SBF) and 56 (61.5%) for 2–6 months (LBF). Pregestational PRL did not significantly differ between SBF and LBF patients (14.6 ± 12.1 μg/liter, $P = 0.172$). Compared with the last evaluation after lactation, PRL levels were slightly reduced (13.2 ± 11.2 *vs.* 9.3 ± 6.5 μg/liter, $P = 0.08$) in SBF women and significantly reduced (17.1 ± 9.5 *vs.* 11.3 ± 4.7 μg/liter, $P = 0.0001$) in LBF patients after 60 months. As shown in Fig. 3, PRL levels at 3 months (13.2 ± 11.2 *vs.* 17.1 ± 9.5 μg/liter, $P = 0.07$) and 60 months (9.3 ± 6.5 *vs.* 11.3 ± 4.7 μg/liter, $P = 0.09$) after cessation of lactation, and remission of hyperprolactinemia (64 *vs.* 61%, $P = 0.9$) 60 months after the end of breastfeeding did not differ between patients with SBF and those with LBF.

Discussion

The present study first demonstrates that pregnancy induces complete remission from hyperprolactinemia in two thirds of women after discontinuation of medical therapy with CAB and that breastfeeding does not increase the risk

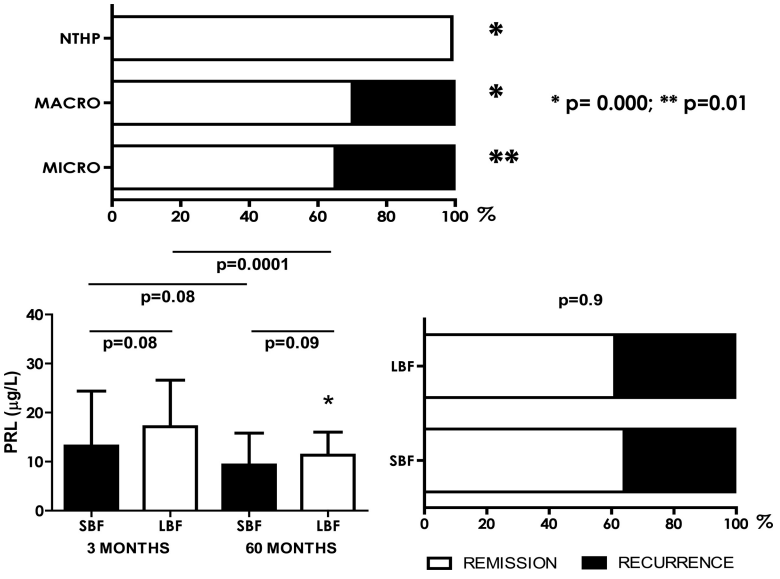

FIG. 3. *Top*, Remission and recurrence rates of hyperprolactinemia after pregnancy. As a whole, CAB was permanently discontinued in 50 patients (66%) with microadenomas, seven (70%) with macroadenomas, and five (100%) with NTHP. *Bottom*, The impact of breastfeeding on PRL levels (*left*) after 3 and 60 months follow-up and on remission and recurrence rates (*right*) after 60 months follow-up. LBF, 3–6 months breastfeeding; SBF, less than 3 months breastfeeding.

of recurrence. Even taken during the first weeks after conception, CAB is safe and not associated with maternal and/or fetal disease.

Data on PRL normalization and on remission from hyperprolactinemia after gestation are scarce. In some patients, postpartum PRL levels and tumor size are reportedly reduced as compared with values before pregnancy (21). Therefore, women with significant PRL decrease may be ovulatory and not need resumption of DA treatment (2). However, only six papers (18–22, 27) have carefully investigated the effects of pregnancy on PRL levels. Particularly, in two independent studies (18, 19), pregnancy has been found to induce a rapid and significant fall in PRL levels shortly after delivery. In the other four studies (20–22, 27), the impact of pregnancy on hyperprolactinemia has been analyzed in 340 women (Table 4), and a total remission rate of 26.2% has been reported. Noteworthy, Crosignani *et al.* (21) observed that pregnancy was apparently even more effective than dopaminergic treatment in normalizing PRL levels, with 29% of women being normoprolactinemic after pregnancy compared with 13% of DA-treated patients. In the present study, we found that after CAB discontinuation, 66% of patients with microprolactinomas, 70% with macroprolactinomas, and 100% with NTHP were in complete remission 12 and 60 months after delivery. These findings are in line with Colao *et al.* (28), reporting that 2–5 yr after CAB withdrawal, remission rates were 76% in NTHP, 70% in microprolactinomas, and 64% in macroprolactinomas. Recurrence rate at 5-yr follow-up was higher among patients with macroprolactinomas and those with microprolactinomas who had small remnant tumors visible on MRI at the time of treatment withdrawal compared with those patients whose MRI scans showed complete tumor disappearance at the time of withdrawal (28). Data of 7-yr follow-up confirmed a long-term remission in microprolactinomas and NTHP, whereas most macroprolactinomas recurred (23). In both studies by Colao *et al.* (23, 28), patients having pregnancies were not considered for the analysis to exclude any possible impact of pregnancy and lactation on disease remission. The data of the current study are also consistent with those published by Musolino and Bronstein (13), who reported a significant postpartum decrease in PRL levels in 60% of microadenomas and 72% of macroadenomas. Whether the improvement of hyperprolactinemia is due to the autoinfarction of the tumor is yet to be clarified. Underlying mechanisms are still unknown, and a possible role of estrogen and/or dopamine status has been hypothesized (2–4, 8, 13). Interestingly, in our patient cohort, CAB treatment had to be restarted in women with no MRI evidence of tumor shrinkage before pregnancy

TABLE 3. Remission (group A) and recurrence (group B) rates of hyperprolactinemia after pregnancy

	Group A	Group B	*P*
Patients [n (%)]	62 (68)	29 (32)	
PRL levels at diagnosis of hyperprolactinemia (µg/liter)	116.5 ± 63.3	161.7 ± 107.5	0.014
PRL nadir during therapy with CAB (µg/liter)	6.6 ± 6.8	10.9 ± 21.4	0.15
PRL levels during therapy with CAB before conception (µg/liter)	11.5 ± 11.3	13.2 ± 18.4	0.6
PRL levels 3 months after pregnancy (µg/liter)	17.5 ± 13.3	36.5 ± 31.6	0.0001
PRL levels 60 months after pregnancy (µg/liter)	10.9 ± 13.2	25 ± 20.5	0.0001
Microadenoma [n (%)]	50 (66)	26 (34)	0.01
Macroadenoma [n (%)]	7 (70)	3 (30)	0.0001
NTHP [n (%)]	5 (100)	0	0.0001
CAB dose (mg/wk)	0	0.62 ± 0.5	
CAB duration before pregnancy (months)	44 ± 36	37 ± 45	0.59

TABLE 4. Remission rate from hyperprolactinemia after pregnancy: review of literature

First author, year	Ref.	No. of patients	Remission rate (%)
Rjosk, 1982	18	65	
Bricaire, 1988	19	15	
Crosignani, 1989	20	54	17
Crosignani, 1992	21	176	29
Jeffcoate, 1996	22	70	35
Huda, 2010	27	40	10
Total		420	26.2[a]
Auriemma, current study		91	68

[a] Remission rate has been calculated on 340 patients with available data.

despite DA therapy as well as in 40% of patients who experienced abortions independently of DA outcome on tumor size. Tumor enlargement after CAB discontinuation did not occur during pregnancy and lactation. Nevertheless, only in patients with macroadenoma, our clinical approach was to cautiously perform a visual field testing every 3 months, even though strict indications have not been suggested by international guidelines (17). Symptomatic tumor enlargement has been reported to rarely occur during gestation and to be highly dependent upon adenoma size, stimulatory effects of placental estrogens, and previous surgery and/or radiotherapy (3). By reviewing more than 700 pregnancies in women with prolactinomas described in literature (29–40), Molitch (2) found that the increase in tumor size has been observed in 2.7% of microadenomas, 4.8% of macroadenomas with previous transsphenoidal surgery and/or radiotherapy, and 23% of macroadenomas that had no previous surgery or irradiation. Moreover, Ikegami *et al.* (41) found that patients who had undergone previous surgery had lower postpartum PRL levels compared with those not cured by surgery and subsequently treated with DA. In our patient population, only three women had been treated by surgery before starting CAB, and all were in complete remission after pregnancy without any further treatment with DA.

No definitive data are currently available on safety of breastfeeding in hyperprolactinemic women. Ikegami *et al.* (41) reported that in prolactinoma, low PRL levels after delivery contributed to decreased milk production and poorer breastfeeding. In his study, no patient showed a rapid increase in PRL levels or complained of symptoms evocative of tumor enlargement, suggesting that breastfeeding is not associated with an increased risk of tumor expansion. In our cohort, all patients but three had 1–6 months breastfeeding. No patient experienced tumor expansion symptoms or sudden rise in PRL levels during lactation, and at both 12 and 60 months follow-up, PRL levels were within the normal range. Moreover, we found that exposure to CAB during early pregnancy is safe. In fact, 88.1% of pregnancies resulted in successful full-term live births, whereas the rate of spontaneous abortions in this population was 9.1%. The data of the present study are in line with the results previously reported by Robert *et al.* (10.2%) (15), Ricci *et al.* (9.8%) (14), and Colao *et al.* (9.1%) (42) in another patient population and confirm that CAB treatment does not increase the abortion rate given that the incidence of spontaneous abortion in our series is lower than the 12–15% reported in the U.S. general population (43), the 11% in Europe (44), and the 11–14% in Italy (Report on hospitalizations for spontaneous abortions between 1990 and 2009, www.istat.it). We also found no increase in the risk of low birth weight (<2500 g) among infants of women receiving treatment with CAB before their pregnancy. In our cohort, the prevalence of low birth weight (1.4%) was in fact lower than the 6.8% reported by Robert *et al.* (15), the 12.2% reported by Ricci *et al.* (14), the 6.6% reported by Colao *et al.* (42), and the 6.1% reported by the last survey in Italy in 2009 (www.epicentro.iss.it/temi/materno/indice-materno.asp). Neonatal abnormalities, including minor and major defects, were not recorded in our series. Worldwide and Italian estimation of congenital malformations are, respectively, 6% (www.marchofdimes.com/downloads/2011Annual_ReportOnline.pdf) and 5.8% (www.epicentro.iss.it/temi/materno/indice-materno.asp). Outcome data with respect to congenital abnormalities have also been previously reported in several series (2, 14, 15, 38–40, 42), ranging from 3% recorded by Lebbe *et al.* (39) to 8.2% reported by Colao *et al.* (42). Major malformations, including trisomy 21, rhombencephalo-synapsis, hydrocephaly, spina bifida, are even rarer, ranging from 1% reported by Stalldecker *et al.* (40) to 5.2% reported by Colao *et al.* (42). Follow-up studies of infants up to 12 yr after exposure to CAB during gestation showed no physical or developmental abnormalities in the series by Ono *et al.* (38), a slight retardation in verbal fluency in two and incontinence in one among the 88 children followed by Lebbe *et al.* (39), and neurological features, including seizures and autism spectrum disorders, in four children followed by Stalldecker *et al.* (40). Besides the 91 patients included in the present study, we also followed up three women requiring DA continuation throughout pregnancy because of large invasive macroadenomas (unpublished data). In these patients, no case of miscarriage, abortion, low birth weight, or congenital malformation was recorded after delivery. This observation further confirms safety of CAB in pregnant women even when administered during gestation.

In conclusion, in our cohort, pregnancy normalized PRL levels in two thirds of patients treated with CAB be-

fore gestation, and breastfeeding did not increase the risk of tumor enlargement and recurrence of hyperprolactinemia. Based on the findings of the current study, there is no evidence to discourage pregnancy and lactation in women with tumoral and nontumoral hyperprolactinemia who want to conceive. Discontinuation of medical therapy with CAB does not increase the risk of disease recurrence after gestation, and pregnancy itself seems to induce the improvement of hyperprolactinemia. When administered in the first weeks of gestation, CAB is safe and not associated with an increase in the risk of abortions, miscarriages, or congenital malformations. Additional studies are still needed to confirm and extend these data.

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