

HYPERPROLACTINEMIA AND PREGNANCY

Clinical Series

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SUMMARY

We report 15 cases of pregnancy in 11 patients with hyperprolactinemia. These patients initially went to our Gynecologic Endocrinology Center for various menstrual troubles. They were all treated with bromocryptine, except one whose hyperprolactinemia was diagnosed when she had already started a gonadotropin therapy, since HPRL assays performed elsewhere had given normal results.

In 6 patients we diagnosed prolactin-secreting pituitary adenoma. Only two patients underwent adenomectomy.

All patients gave up bromocryptine as soon as their pregnancy was detected.

Two patients had two subsequent pregnancies, another one had three. All pregnancies were single. The only twin pregnancy followed a gonadotropin therapy.

One of the 15 pregnancies ended with abortion at the 12th week; another one (twin) with spontaneous delivery at the 37th week; 13 with term-delivery. They all had physiologic courses, except for one case of threatened abortion and one case of diabetes insipidus at the 9th month.

None of the 15 newborns (7 SGA and 8 AGA) showed malformations.

No sign or symptom of tumour growth was detected in the patients affected by pituitary adenoma.

INTRODUCTION

Several cases of female infertility are ascribable to increased pituitary prolactin production. In about one third of the cases hyperprolactinemia is supported by pituitary adenomas⁽¹⁾ and the frequency of adenomas is currently believed to be much higher.

Spontaneous pregnancy is extremely rare in hyperprolactinemic women^(2, 3, 4). On the other hand very many cases have been reported where fertility was restored by a causal treatment of this dysendocrinia, whether medical, surgical or radiation^(5, 6, 7, 8, 9). The medical therapy mainly consist of the administration of bromocryptine (Parlodel, Sandoz), a dopaminergic drug that inhibits pituitary prolactin secretion⁽¹⁰⁾. This treatment was shown to be unquestionably effective both in cases of functional hyperprolactinemia and in patients with adenomas^(11, 12). In the latter, surgical therapy (transphenoidal adenomectomy)⁽¹³⁾ or radiotherapy (external pituitary irradiation or Y⁹⁰ implantation)⁽¹⁴⁾ may be necessary.

However, the opinions differ widely about the best therapy in case of adenoma. Some Authors advocate surgical treatment in all cases^(13, 15), on the grounds that the smaller the lesion the better the outcome, while others suggest medical therapy and keep surgery for macroadenomas or tumours extending outside the sella⁽¹⁶⁾. This attitude is warranted by the low tendency (if any) of these tumours to grow, and experience proved that medical therapy can normalize prolactin levels even in case of adenoma⁽¹⁸⁾. Pregnancy already makes the hypophysis grow physiologically in size and weight. The remarkable estrogen increase adds up to stimulate prolactin secretion. Therefore, in adenoma bearers wishing to have children most Authors^(8, 11, 19) advocate precautionary surgical or radial interventions beside bromocryptine in order to prevent complications, like visual disturbances, severe headaches, paresis of the

Table 1. — *Clinical data of hyperprolactinemic patients.*

No.	Age	Para	Symptomatology	Diagnosis
1) F. M.	24	0000	Secondary amenorrhea	Functional hyperprolactinemia
2) L. G.	31	1103	Secondary amenorrhea and galactorrhea	Functional hyperprolactinemia
3) N. A.	28	1001	Secondary amenorrhea and galactorrhea	Functional hyperprolactinemia
4) M. L.	29	0000	Secondary amenorrhea	Functional hyperprolactinemia
5) C. G.	29	0000	Oligomenorrhea	Functional hyperprolactinemia
6) S. D.	28	0000	Secondary amenorrhea	Prolactin secreting pituitary microadenoma
7) E. L.	22	0000	Secondary amenorrhea and galactorrhea	Prolactin secreting pituitary microadenoma
8) P. M.	26	0000	Secondary amenorrhea	Prolactin secreting pituitary microadenoma
9) M. M. G.	24	0000	Secondary amenorrhea and galactorrhea	Prolactin secreting pituitary microadenoma
10) M. A.	33	0000	Secondary amenorrhea and galactorrhea	Prolactin secreting pituitary macroadenoma
11) B. C.	20	0000	Primary amenorrhea and galactorrhea	Prolactin secreting pituitary macroadenoma

oculomotor and/or abducent nerves, serious nausea and persistent vomiting, caused by the rapid growth of the adenoma or by an intratumoral haemorrhagia. Such complications have been reported in about one third of the patients^(6, 19).

But, for the time being, it is still impossible to explain or even predict the different behaviour of adenomas in pregnancy⁽²⁰⁾.

However, since the above listed troubles, if they happen, produce no permanent sequelae⁽⁶⁾ and the adenoma often remains totally asymptomatic⁽⁹⁾ throughout the gestational period, the non-interventionist attitude can be justified.

On the other hand, everybody agrees to stop the bromocryptine treatment as soon as pregnancy is detected, although it seems that this drug does not increase the risk of miscarriage, multiple pregnancy and neonatal malformations^(5, 9).

MATERIAL AND METHODS

We report 15 pregnancies in 11 hyperprolactinemic patients between the age of 20 and 33 (mean: 26.7).

Pituitary adenomas were detected in 6 of them. These patients went to the day-care gynecologic Endocrinology Center of our Clinic for various menstrual pathologies: oligomenorrhea (1 case); secondary amenorrhea (4 cases); amenorrhea and galactorrhea (6 cases). 9 of the patients were nulliparae, one was I-para and one II-para (tab. 1).

Hyperprolactinemia was detected during the routine diagnostic iter carried out at our Center⁽²¹⁾.

The meagreness of our patients is due to the fact that their original motivation for coming was not pregnancy but the resumption of normal menses. Furthermore, all the reported pregnancies started after the beginning of a specific therapy; their course was monitored and the delivery took place in our Clinic.

Plasma prolactin assays were performed in our laboratory by radioimmunologic method, using Biodata kits. In each case we performed standard skull Rx and hypocyloid stratigraphy of the sella turcica in order to find any pituitary adenoma.

Pituitary computed axial tomography was performed on two patients (M.A. and B.C.) with remarkable deformation of the sella turcica, to diagnose whether the adenoma had suprasellar extension.

Once the diagnosis was established each patient was prescribed a bromocryptine therapy (Parlodel, Sandoz), of 1 to 3 tablets per die per os, the dose depending on initial prolactinemic

Table 2. — *Characteristics and results of the therapy in hyperprolactinemic patients.*

No.	Therapy	HPRL ng/ml before after	Menses after therapy	Therapy duration before conception	No. pregn. after therapy	Gestational age at ther. susp.
1) F.M.	Parlodel 1 c/die	82.5 11.0	yes	8 months	3	7 week
	Parlodel 1 c/die	70.5 10.5	yes	1 month		6 week
	None	— —	yes	—		
2) L.G.	Parlodel 1 c/die	50.0 10.0	yes	10 months	1	6 week
3) N.A.	Parlodel 1 c/die	75.0 5.5	no	1 month	1	12 week
4) M.L.	Parlodel 2 c/die	140.0 50.0	yes	7 months	1	12 week
5) C.G.	Parlodel 2 c/die	73.8 38.0	yes	Conception occurred after therapy suspension	1	—
6) S.D.	Pergonal + Profasi	400.0 —	no	—	2	—
	Parlodel 3 c/die	390.0 32.0	yes	10 months		10 week
7) E.L.	Parlodel 2 c/die	140.0 21.0	yes	12 months	2	12 week
	Parlodel 2 c/die	77.4 9.5	yes	12 months		10 week
8) P.M.	Parlodel 2 c/die	210.0 10.2	no	1 month	1	6 week
9) M.M.G.	Parlodel 2 c/die	72.0 10.8	yes	3 months	1	6 week
10) M.A.	Adenectomy + Parlodel 1 c/die	400.0 10.0	no	10 months	1	16 week
11) B.C.	Adenectomy	> 300 10.0	yes	Conception occurred 18 months after intervention	1	—

levels and on those during the period of treatment. Only one patient (S.D.) was treated with gonadotropins because the prolactin assays, originally performed by an outer laboratory, had shown normal levels. However, before inducing ovulation, we took control blood samples. After a few days, the assays results were available, showing clear hyperprolactinemia. The gonadotropin treatment had meanwhile been suspended owing to serious ovarian hyperstimulation with ascites, which made laparotomy necessary for suspect twisting of the funiculus in one of the macropolycystic ovaries. In the immediate post-operative course the patient was found to be pregnant. After delivery (a twin birth), a bromocryptine therapy was started which was followed by another conception 7 months later.

In one case (M.A.) the medical therapy was supported by a surgical intervention of transphenoidal adenectomy because very high prolactinemia and radiologic examinations showed a pituitary macroadenoma. The patient really cared about her pregnancy and the fear of further complications suggested this approach. However, since the prolactinemic levels were still not normal after surgery, the medical therapy was continued (1 c/die).

Another patient (B.C.) underwent transphenoidal adenectomy because of her intolerance to the repeatedly attempted medical therapy (she com-

plained of nausea, vomiting and lipothymia). In this case too HPRL values (> 300 ng/ml) and X-rays examinations of the sella showed the presence of a macroadenoma. In both cases histologic examination of the operatory fragment revealed a pituitary chromophobe adenoma.

E.L. was another particular case. After the diagnosis of pituitary adenoma we started medical therapy, since the patient showed no wish to become pregnant. Pregnancy (the possibility of which she had been informed of, like all other patients) was diagnosed at one of the periodical controls.

After delivery, the bromocryptine therapy was resumed and the surgical intervention planned. But, once again, the lady changed our plans by coming back pregnant to our Center.

C.G., oligomenorrhoic, had long been wishing to become pregnant. During the bromocryptine therapy her menses became regular. She decided to interrupt the therapy and became pregnant after about two months. This fact, together with her previous infertility and remarkable hyperprolactinemia, lead us to include her in our series.

In all patients the therapy was suspended as soon as pregnancy was detected.

The course of pregnancy was periodically monitored by obstetrical examinations, routine hematological tests, fetal echographies, urinary HCG

Table 3.

No.	Pregnancy course	Outcome	Type of delivery	Newborn	Newborn's malformation	Breast feeding
1) F. M.	1) Threatened abortion at 8th week 2) Threatened abortion at 4th month, then uterine hypercontractility 3) Physiologic	Abortion at 12th week Delivery at 38th week Term delivery Term delivery	Curettage Spontaneous » Spontaneous	— ♂ 2700 g ♂ 2600 g ♂ 2400 g	— None None None	— 40 days Agalactia No (Parlodel)
2) L. G.	»	»	»	♀ 3540 g	AGA	None
3) N. A.	»	»	Assisted	♀ 2520 g	SGA	None
4) M. L.	»	»	»	♀ 3330 g	AGA	None
5) C. G.	»	»	»	♀ 2280 g ♀ 1900 g ♂ 3850 g	SGA SGA AGA	None None None
6) S. D.	1) Physiologic 2) »	Twin delivery at 37th week Term delivery	Spontaneous »	♂ 2890 g	SGA	None
7) E. L.	1) » 2) »	» »	Assisted »	♀ 3450 g	AGA	No (Parlodel) No (Parlodel)
8) P. M.	»	»	»	♀ 3160 g	AGA	None
9) M. M. G.	»	»	»	♀ 3250 g	AGA	None
10) M. A.	»	»	»	♂ 3900 g	AGA	None
11) B. C.	Physiologic until 8th month Diabetes insipidus 9th month	»	»	♂ 3550 g	AGA	None

SGA = small for gestational age; AGA = adequate for gestational age.

assays in the first trimester, plasma HPL and oestriol in the second and third trimester, following the protocol established at our Clinic the best we could (22). In the 6 patients with pituitary adenoma the visual field determination was checked every 3 months.

No drug was taken by or prescribed to patients during pregnancy.

RESULTS

The bromocryptine treatment normalized or significantly reduced prolactin levels in all patients. In 8 cases menses resumed while 3 patients directly passed from amenorrhea to pregnancy (tab. 2).

With the exception of C.G. – who became pregnant 2 months after drug withdrawal – and B.C. – who, after the intervention, resumed spontaneous though irregular menses with normal prolactinemia – the treatment went on for an average of 7 months before conception occurred. 3 patients got pregnant after only one month of treatment; one after 3 months; 3 after 7 months and the remaining 4 patients took the drug for 10-12 months before they became pregnant.

It is fair to say, however, that the period of treatment was determined by the patients' subjective wish (and attempts) to become pregnant rather than by the objective effectiveness of the drug. In other words, it was up to the patients, who had been informed of the possibility of becoming pregnant, to decide whether and when to conceive.

The time of the diagnosis determined the gestational age at which bromocryptine was suspended: 16th week in one case, 10-12th in 5 cases, 6-7th in 5 cases (mean: 9.4 weeks). Our work was significantly limited by our patients also in this aspect, as they showed up for control very irregularly. Pregnancy had an uneventful course in 9 patients.

Examinations and tests showed no risk for either the mother's or the fetus' well-being. Notably, none of the 6 adenoma bearers showed symptoms ascribable to

tumour growth nor did the repeated visual fields examinations ever show any change. Only B.C. suffered from diabetes insipidus at the 9th month (potus 11 litres/die) with no further complication. This diabetes disappeared shortly after the delivery without any treatment.

In F.M. the first pregnancy ended up in spontaneous miscarriage at the 12th week with curettage. The first menses, about 2 months after the abortion, were spontaneous since for a few months the patient refused the prescribed therapy.

However, since no other menses appeared and prolactin levels stayed approximately at 70 ng/ml, the patient – wishing a new pregnancy – resumed a Parlodel therapy (2 cpr/die). She got pregnant after about one month. At the fourth month there was a threatened abortion for which rest and tocolithic therapy were prescribed. Then, uterine hypercontractility appeared, and was treated with ritodrine chlorhydrate. At the 38th week, the patient gave spontaneous birth to a healthy boy weighing 2,700 g. After the delivery, spontaneous and regular menses reappeared. No therapy was therefore prescribed. After 2.5 years a third pregnancy began and had a physiologic course until the birth of a boy weighing 2,600 g.

The remaining 11 patients delivered at term, 3 spontaneously and 8 with assisted delivery (tab. 3).

All pregnancies were single. The only twin pregnancy (S.D.) occurred after gonadotropin treatment and ended with spontaneous delivery at the 37th week.

The newborns were all alive and lively, free from malformations. 8 of them were of normal weight (AGA) and 7, including the two twins, were small for gestational age (SGA); 7 were males, 8 females.

In our opinion, the low weight of F.M.'s child was due to placental insufficiency caused by uterine hypercontractility. The weight of the twins, born from a I-para with previous involuntary infertility, is not surprising.

Among the other patients who gave birth to low-weight children, E.L. and M.L. were I-para with long previous infertility; L.G. was II-para but her second pregnancy had ended with the premature delivery of twin boys weighing 1,400 and 1,500 g and was followed by 8 years of infertility.

We therefore suggest that the low weight of these 7 newborns is due to anamnestic dysendocrine factors in these individual patients. This opinion is supported by the normal weight of both E.L.'s and S.D.'s second children.

From our data, we do not suspect bromocryptine to have a negative effect on fetal growth, since we do not see any link between weight at birth and dose, treatment duration and gestational age at which the drug administration was stopped. This is confirmed by F.M.'s second child, born at term after a physiologic pregnancy neither preceded by nor started with bromocryptine, who weighed 2,600 g.

The data concerning breast feeding are of no particular significance.

In 5 cases lactation was inhibited by bromocryptine. 2 of the other patients breast-fed normally for several months; 3 experienced hypogalactia lasting up to 40 days. One puerpera is currently breast-feeding and the amount of milk is normal. No patient complained of complications in puerperium.

CONCLUSIONS

Bromocryptine can be successfully used to restore fertility in cases of hyperprolactinemia even supported by pituitary adenoma.

There is no correlation between treatment duration before conception or administration in the first weeks of pregnancy and children's weight at birth. No malformation was detected in the newborns.

The incidence of miscarriage (1/15) and multiple delivery (the only twin preg-

nancy occurred after gonadotropin therapy) was very low.

The patients with prolactin-secreting adenomas had physiologic pregnancies without symptoms or signs of hypophyseal growth.

Only one patient suffered from diabetes insipidus at the 9th month with no consequences for either the mother or the fetus. In our opinion, on the basis of these data, no special obstetric management is required, and the medical therapy is to be preferred in any case, in view of pregnancy too. Surgical intervention must be taken into consideration only in case of macroadenoma (diameter > 1 cm) or adenoma overflowing the sella.

Should signs of hypophyseal growth appear, the bromocryptine therapy could be resumed in pregnancy with no risk for the fetus. In particularly serious cases, neurosurgical intervention can always be envisaged (⁶).

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