DIAGNOSIS AND TREATMENT OF PATIENTS WHO HAVE BECOME STERILE DUE TO PROLACTIN-SECRETING PITUITARY ADENOMA

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SUMMARY

The present study reports the endocrinological and radiological features of 10 hyperprolactinaemic patients with macro (4 patients) and microadenoma (6 patients) of the pituitary.

A more affected hormonal situation seems to be present in patients where more pronounced radiographic changes are found.

In the light of this evidence it appears that polytomography of the sella is mandatory wherever a microadenoma of the pituitary has to be ruled out. CB-154 treatment appears to be mostly effective in the tratment of hyperprolactinaemic patients, resulting within few months in resumption of menses and ovulation.

The risk of pregnancy and the possible therapeutic approaches to the problem are discussed.

INTRODUCTION

About 25-30 % of all pituitary tumours are prolactin-secreting, and only one third of the prolactin-secreting tumours give rise to galactorrhoea.

In any patient with a non-functioning chromophobe adenoma of the pituitary, expansion of the tumour along the midline also leads to hyperprolactinaemia, because of the destruction of the inhibitory areas placed under the control of the secretion of prolactin (PRL).

In other cases, however, the tumour itself is capable of producing PRL.

A concentration of PRL of between 30 and 200 ng/ml is not pathognomonic of a prolactin-secreting tumour, since if any tumour is involved with the hypothalamus, this may lead to diminution of PIF and thus to hyperprolactinaemia, while concentrations of PRL of more than 500 ng/ml are almost certainly associated with a PRL-secreting pituitary tumour.

Among patients affected by hyperprolactinaemia, true micro-adenomas, not involving any enlargement of the sella turcica, are fairly common; on the other hand a sella turcica that is definitely enlarged is a relatively uncommon finding among these patients.

Pituitary adenomas of considerable size may lead to alterations in the visual field or in the fundus oculi, but in this case they are observed in patients with a long history of hypogonadism, sterility and menstrual changes.

The menstrual changes may or may not be associated with galactorrhoea. Three distinct syndromes of amenorrhoea and galactorrhoea have been described:

1) the Chiari-Frommel syndrome;
2) the Argonz-del Castillo syndrome;
3) the Forbes Albright syndrome.

The medical literature is full of examples that demonstrate the artificiality of the eponymous classification, since in the same patient galactorrhoea may or may not appear post-partum, and yet a pi-

tuitary tumour may become evident months or years later ([1, 2]).

In order to establish the cause of the hyperprolactinaemia, with or without amenorrhoea and galactorrhoea, some laboratory controls can be done. It is certainly important to identify a pituitary tumour or an organic lesion that may be the aetiological factor in the hyperprolactinaemia, in order to distinguish such situations from conditions that may only lead to an increase in the prolactinaemia.

If there is any suspicion of a hypothalamic-pituitary lesion, tests of pituitary function are indicated. Such tests measure the PRL, HGH, TSH, LH, FSH, both basically and under specific stimulus ([3-7]). Tests that can be used for PRL include suppression tests with L-DOPA (0.5 g orally), CB-154 (2.5 mg orally), or with a load of H_2O (20 cc per kg weight) ([8-10]). These tests may furnish interesting information, but they have not been found to be as useful as had been hoped initially, in the differential diagnosis between the organic and functional causes of hyperprolactinaemia, even though, for example, patients with PRL of more than 200 ng/ml and with absence of response to TRH are probably carriers of a tumour.

For these reasons, it seems clear that the diagnosis of PRL-secreting pituitary adenoma is in the last analysis a radiological diagnosis based on:

— standard X-ray of the skull;
— xerographic test;
— stratigraphic test;
— hypocycloid polytomography;
— computerized axial tomography.

Hardy has classified pituitary adenomas from the radiological point of view into two groups, with corresponding radiological changes in the sella.

1) The enclosed adenoma: is a tumour which remains enclosed within the anatomical confines of the sella. Two degrees are distinguished:

1st degree: the sella turcica is of normal dimensions (length 17 mm, height 14 mm, area 208 mm, laterally), but careful tomographic study may demonstrate that the sella is asymmetrical, especially in relation to the antero-inferior wall, where the PRL-secreting cells are found in the greatest concentration. In such cases the tumour is < 10 mm in diameter and is called a *microadenoma.*

2nd degree: the sella turcica is enlarged but its floor is intact.

2) The invasive adenoma: in such cases the tumour has eroded the base of the sella.

3rd degree: the erosion is localized to one area of the sella;

4th degree: the whole floor of the sella is diffusely eroded or destroyed, giving the appearance of a « ghost » sella.

If the PRL values are increased, that is, even if no increase in the size of the hypophysis can be demonstrated radiologically ([11]), it is possible and even probable that a certain number of such patients will in the end appear to have pituitary adenomas. There are in fact many findings in the literature that support the slow growth of these tumours over a period of many years.

Once patients with a PRL-secreting pituitary tumour have been treated with drugs that inhibit PRL, they become very fertile, except obviously when a gonadotrophin deficit coexists.

On the other hand there is a risk that such tumours, becoming enlarged during the third trimester of pregnancy, may produce considerable visual disorders due to compression of the optic chiasm. It is not possible to define the nature of this risk, but it can be avoided by means of therapy designed to remove part of the hypophysis radiologically or surgically, before starting treatment with ergocryptine, which will restore fertility.

Changes in the hypophysis have been found during pregnancy ([12, 13]).

The mean weight of this gland in nulliparae is about 0.6 g, and during the first pregnancy this weight increases to about 1 g.

After pregnancy there is a partial return to the initial weight, that is, the weight becomes stable at about 0.75 g, or slightly more than this if there have been several pregnancies. This variation justifies increasing the vertical diameter of the hypophysis from 6.8 to 8.4 mm.

It seems clear that such an increase in volume cannot lead to any compression of the optic chiasm if this is normally situated (the chiasm is normally from 4 to 10 mm above the diaphragma selli).

Many authors have claimed that a great number of women present with changes in the visual field during the latter part of pregnancy, and that these regress following delivery, which seems to indicate that such changes cannot be related to any compression and must therefore be functional, contrary to what is found in the case of tumours ([14-17]).

Prolactin-secreting pituitary adenomas can be dealt with as follows:

1) No treatment.

2) Medical treatment: drugs that inhibit proclatin-CB-154 (2-bromo-α-ergocryptine, Parlodel Sandoz) ([18-21]).

This drug, with a stimulant action on the pituitary dopaminergic receptors, has been shown to be very useful in actively suppressing the liberation and synthesis of prolactin on the part of the prolactin-secreting cells. It has a direct action at pituitary level, and an action on the hypothalamus has also been suggested. Treatment with this drug in handled individually in relation to the response of the prolactinaemia: in general a start is made with the lowest doses (2.5 mg per day), in fractionated doses, and these are then gradually increased until a maintenance dose is reached: this oscillates between 5 - 7.5 mg administered in two or three fractions per day (the duration of action of the drug being 8 - 12 hours). But in extreme cases the dosage may certainly be increased until it reaches 20 mg/day or more.

On this drug, most patients resume menstruation within the first three months of treatment (usually in 6-7 weeks).

Patients suffering from pituitary tumours may require a longer period of time as compared with those with the functional forms; treatment is obviously destined to failure if accompanied by altered gonadotrophin synthesis. Generally the drug is well tolerated; among the side-effects may be mentioned: nausea, hypotension, vertigo, lassitude, visual disorders. It should be noted that once the treatment has been withdrawn the symptoms tend to reappear, even with the functional forms.

3) Radiotherapy with:

a) protons,

b) fixing with Yttrium,

c) cobalt therapy.

If the tumour is radiologically evident, Child ([14]) implants Yttrium-90 in low dosage (20 rads) if the suprasellar extension is not too obvious, associated if necessary with CB-154, clomifene or HMG in order to induce ovulation.

If the tumour is radiologically uncertain, medical therapy is employed and the pituitary is checked during pregnancy, Yttrium-90 being implanted if necessary. With reference to the results obtained, this author treated 7 pregnant patients with Yttrium-90 and found no pituitary complications nor visual changes.

Gomez *et al.* ([22]) reported 16 cases of pituitary adenoma treated and followed up in a long-term trial (6 years), of whom 8, part of whose pituitaries were selectively removed surgically via the trans-sphenoid route, rapidly recovered normal prolactin levels and with subsequent disappearance of the disorders. The other 8 were given

radiotherapy with cobalt (4500 rads in 20 sessions); in this case there was slower improvement of the syndrome.

Besser ([18]) suggested prophylactic treatment for a pituitary tumour from the start of pregnancy, by means of external irradiation of the fossa by linear acceleration (4500 rads of a linear accelerator of 15 MeV), at least three months before pregnancy begins.

In his experience this treatment seems to prevent extension of the adenoma and the development of visual disorders, and in this way serious problems during pregnancy could be avoided.

4) Surgical treatment: as regards the surgical approach to a pituitary adenoma, either the trans-sphenoidal or the intracranial route might be considered, bearing in mind that each route has its special indications.

Nowadays there is a tendency to prefer the trans-sphenoidal route ([23-24]) (except in cases in which there is irregular multinodal, supra-sellar extension of the tumour or expansion of the tumour into the frontal or temporal lobes, as shown by neuro-radiological techniques).

In relation to the degree of development of the adenoma, surgical treatment may comprise:

a) total, non-selective removal of the tumour, including healthy tissue;

b) partial, selective removal (without removal of any healthy tissue);

c) partial, non selective removal;

d) total, selective removal.

In making our own personal contribution to the problem, we should like now to refer to our experience of the diagnosis and treatment of hyperprolactinaemic patients, with radiological evidence of pituitary changes, with the principal aim of discussing what may be the therapeutic management when any problem of sterility exists.

MATERIAL AND METHODS

10 hyperprolactinaemic patients with radiological evidence of pituitary changes by standard X-ray or hypocicloid polytomography of the sella entered the study.

The clinical findings provided by these patients are summarized in Table 1.

The samples were obtained each morning at the same time in order to avoid circadian variations. When the trial required several samples at brief intervals, a Butterfly no. 19 needle was inserted into a vein of the arm, and left in situ with an infusion of physiological solution. This infusion was stopped at time desired and after having removed 2 cc of blood to avoid any dilution of the sample, about 3 cc of blood was collected in heparinized plastic tubes.

The heparinized blood samples were centrifuged at 4° C and the plasma thus obtained was conserved at — 20° C until required for analysis.

In order to determine the hormonal pulsatility, the samples were taken every 15 min. For the suppression test with CB-154, 2.5 mg of drug was administered orally and the blood samples were obtained every 15 min for a period of 150-180 min.

For the Gn-RH and TRH test: 100 γ of Gn-RH (Ayerst) and 200 γ of synthetic TRH were injected intravenously through the Butterfly no. 19 needle and the samples were obtained at the following times: — 30', — 10,0', 10', 20', 30', 45', 60', 90', 120', 180'.

For the GH test: 0,2 14 of insulin/kg b.w. were injected i.v. and samples obtained at — 10', 0,30', 45', 60', 90', 120'.

The glycaemia of the blood samples confirmed the hypoglycaemic effect of dose of insulin that was injected.

Treatment with CB-154 (2-bromo-ergocryptine-Parlodel Sandoz) was undertaken with increasing doses until a dose of 7.5 mg was reached, subdivided into 2-3 daily doses of 2.5 mg each. Single doses are indicated in the figure. The hormones FSH, LH, PRL and GH were measured by radio-immunological analysis (method of second antibody) during the course of the same analysis, using commercially available kits (Biodata).

Plasma progesterone was determined by means of Sorin kits.

RESULTS

The pulsatile patterns of gonadotrophins and prolactin of the patients have been described in detail elsewhere ([33]).

It seems clear from our data that wherever evident radiological changes are

Table 1.

Patient	Age	Pregnancy	Amenorrhoea (for years)	Galactorrhoea (intensity)	Roentgenologic grading (see text)	Changes in F.O. and V.F.	PRL (*) ng/ml	FSH (*) mUI/ml	LH (*) mUI/ml	Response to Gn-RH (**)	Response to TRH (**)	Response of GH to insulin (**)
1 C.A.	26	—	A_3	+	1	—	96	7	3	>	=	=
2 G.L.	28	—	A_3	++	1	—	110	7.9	3	=	<	=
3 B.A.M.	35	—	A_4	++	1	—	240	4.2	13.5	=	not performed	=
4 F.A.	27	—	A_3	+	1	—	205	3	3	<	<	=
5 M.F.	28	—	A_4	+	1	—	43	11.3	24	>	=	=
6 M.A.M.	28	—	A_1	++	1	—	280	5.3	3	<	<	=
7 V.M.E.	25	—	A_6	++	2	—	280	3	3	<	<	=
8 C.M.P.	35	+	A_9	++	3	—	320	12.8	6.6	<	<	=
9 P.M.R.	27	—	A_4	—	3	+	342	3	3	<	<	=
10 F.C.	27	—	A_9	—	3	—	410	3	3	<	<	=

* Max values found in a 3 hours period with a 15' sampling.
** > response enhanced.
= normal response.
< response reduced or absent.

encountered, higher values of PRL and lowered values of gonadotrophin both as regards basal tone and pulsatility, are found. The results of the dynamic tests are summarized in table 1.

It is evident, again that wherever a clear radiographic change exists in the sella turcica, the hormonal situation appears to have been mostly affected.

The CB-154 test in our hands did not provide decisive results probably due to the short observation time.

On the other hand long term treatment with CB-154 was very effective as expected in reducing prolactinaemia and galactorrhoea, and in restoring menstruation and ovulation, within 4 months, with the exception of patient 10 (F. C.), were CB-154 administration 7.5 mg/day up to 8 months failed to restore menstruation.

This effect seems clearly to be connected with the re-establishment of gonadotrophic activity (basal tone, pulsatility, response to Gn-RH (figg. 1, 2, 3, 4).

It is important to note that, although ovulation could be recovered even in the presence of PRL values that were still not perfectly normal, insufficiency of the corpus luteum was occasionally found in this situation (short luteal phase) on the base of the B.B.T. (fig. 3).

DISCUSSION AND CONCLUSIONS

In this study we examined the hormonal situation of hyperprolactinaemic patients with changes in the sella turcica due to pituitary adenoma ruled out by standard x-ray or hypocycloid polytomography of the sella ([25]).

The inverse ratio between PRL and gonadotrophins is confirmed by our trial ([26, 27]) in the sense that very high values of PRL are often accompanied on the one hand by absence of gonadotrophic pulsatility, and on the other by absence of response to Gn-RH.

Inhibition of PRL by CB-154, by removing the presumably functional block at the hypothalamic- pituitary level, clearly enables the gonadotrophins to return to their normal values, in patients where is not present any deficit of gonadotrophins due to compression of the adenoma upon the gonadotrophin-secreting cells.

Therefore, where the oligomenorrhoea and anovularity of our patients were related to the hyperprolactinaemia, treatment with CB-154 effectively restored fertility.

The problem of the pituitary adenoma still remains, however; its possible growth during pregnancy can produce visual disorders due to compression of the optic chiasm.

Wolf ([28]) reported a case in which there was marked aggravation of a pituitary adenoma beginning at the third month of pregnancy (probably in relation to the intake of oestrogen and progestagens) such as to require hypophysectomy in the 5th month of pregnancy (in a situation in which, due to the anatomical variations of the hypophysis, selective removal of the tumour is more difficult).

Gemzell ([29]) reported an instance of 4 women with pituitary adenoma and pregnancy induced by HPG. During pregnancy these women suffered from headache, bilateral disorders of the visual field or altered visual acuity. In one woman the disorders were so serious as to require an operation in the 2nd trimester.

The other three, as soon as the disorders were more slight and the possibility of an irreversible lesion of the optic tract was not present, were able to terminate their pregnancies without an operation.

Child ([14]) also described nine patients who had pituitary adenomas during pregnancy.

Seven patients were treated by the implantation of Yttrium-90 and their pregnancies proceeded to term without any problems.

The other two, who were not treated,

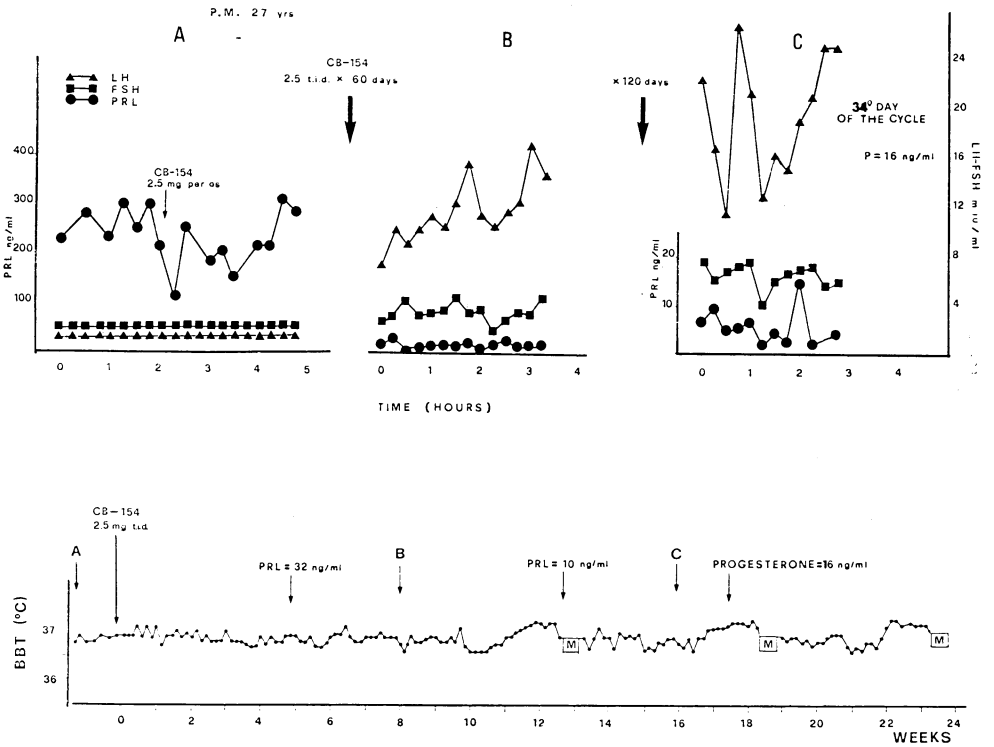

Fig. 1. — Effect of PRL levels on pulsatile patterns of LH and FSH.

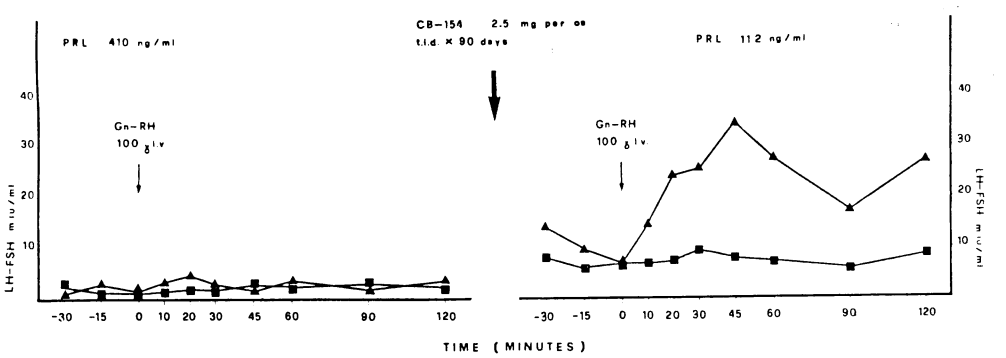

Fig. 2. — Effect of Hyperprolactinemia on LH-FSH response to Gn-RH.

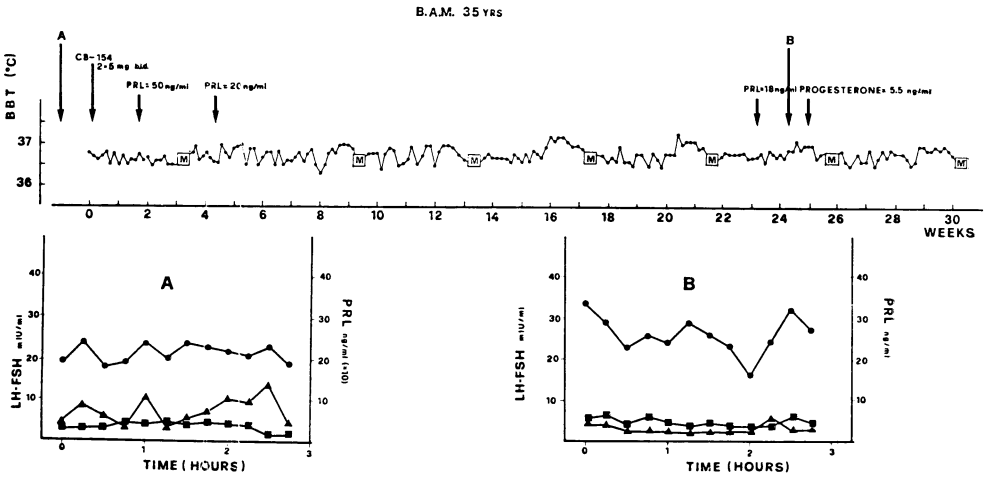

Fig. 3. — Effect of PRL levels on pulsatile patterns of LH and FSH.

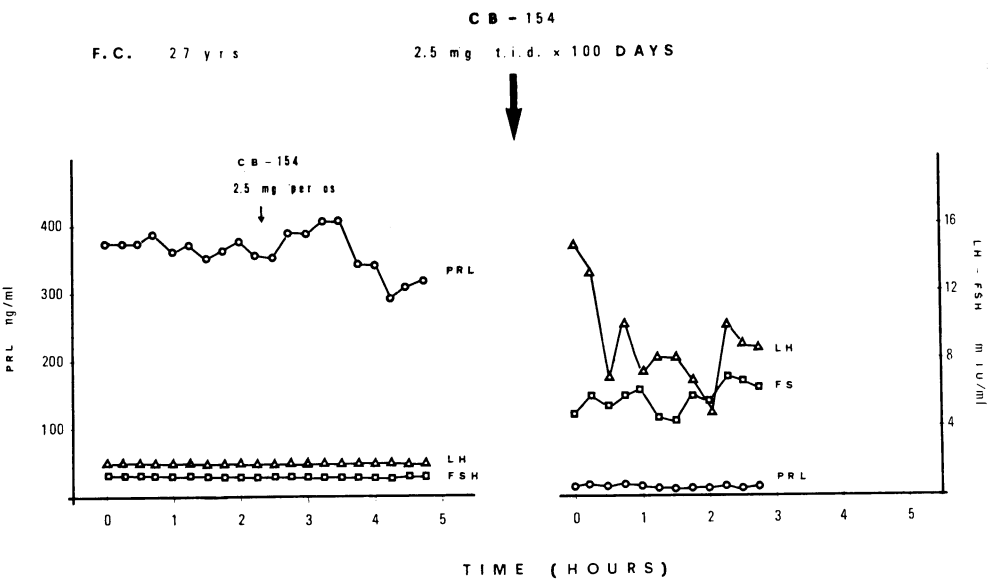

Fig. 4. — Effect of PRL levels on pulsatile patterns of LH and FSH.

had complications consequent upon the growth of the tumour during pregnancy: one had a bitemporal deficit in the 2nd trimester, treated by an emergency implant of Yttrium-90; the other had diabetes insipidus, during the third trimester; this resolved spontaneously after delivery.

This author also cited other cases reported in the literature in which the rapid growth of the neoplasm required emergency treatment.

Falconer ([15]) reported two cases of pituitary tumour and para-sellar tumour respectively, which presented with visual disorders during pregnancy; and he solved this problem by advising as selective treatment, wherever vision was definitely compromised, at any stage of pregnancy, surgery followed by adequate therapy so as to ensure the prolongation of pregnancy.

Swyer et al ([16]), in discussing the problem of visual disorders, present in some pregnancies after the induction of ovulation, even when no condition of evident adenoma was present, stated that a pituitary or para-pituitary neoplasm could be assumed.

Recadot ([30]) examined 157 cases of pituitary adenoma and found a clear correlation between the haemorrhagic character of the adenoma and previous exposure to oestrogenic and progestagenic hormones.

The idea thus arises from the literature that the PRL-secreting hormones must be treated with radiotherapy or surgically before ovulation can be induced or pregnancy started.

All the forms of treatment examined may have their adverse aspects: the syndrome may recur and there may be side-effects allied to the therapy. An alternative route is suggested by Nillius et al. ([31]), who have recently reported their experiences with bromo-cryptine alone.

The treatment was withdrawn as soon as pregnancy was diagnosed. Three of these patients conceived without any problems, and another three are now pregnant. Severe headache that occurred in one patient was cured with analgesics, and in another the visual field was affected, but markedly improved post partum.

From these results the authors conclude that some patients with PRL-secreting adenomas may start a pregnancy after therapy with CB-154 alone, provided that they are given strict supervision during pregnancy, and should be prepared for operation whenever complications arise.

This viewpoint is supported by the fact that, out of 342 pregnancies documented by Sandoz (32), in whom ergocryptine was made use of for longer or shorter periods of time, no teratogenic effects on the foetus were discovered, nor any special problems.

In the event of pregnancy, therefore, it is possible to cope with the possible disorders due to adenoma (headache, disorders of the visual field, visual disor-

Table 2.

1) General, gynaecological ond ophthalmic assessment.

2) Basal and dynamic endocrinological assessment before and after treatment with CB-154 (the absence of response to increasing doses of CB-154 over long periods of time suggests the involvement of synthesis of gonadotrophins).

3) Radiological assessment: standard X-ray and polytomography of sella turcica:

   a) *sella turcica normal:* induction of ovulation, and pregnancy with monthly ophthalmic assessment. Where complications should occur treatment with CB-154 should be stated.

      If insufficient, the following procedures have to be considered:

      — Neuro-surgical assessment;
      — Radiotherapy;
      — Induction of delivery.

   b) *sella turcica changed:* neuro-surgical assessment; treatment with CB-154; radiotherapy.

ders) by treatment with CB-154, a drug that has shown itself capable of reducing the problems allied to the expansion of the PRL-secreting adenoma, viz., the signs of compression and demineralization of the sella turcica.

One consideration arises from the examination of these findings: the occurrence of pregnancy, when a pituitary adenoma has been suspected, sets serious problems of diagnosis and treatment.

The factors to be assessed are: the willingness of a couple to initiate pregnancy, the possibilities of treatment, the possible risks.

In conclusion, and on the basis of our personal experience and data from the literature, we consider that the following management should be considered (Table 2).

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