

Clinical Course and Outcome of Pregnancies in Women with Hyperprolactinemia : Ramathibodi's Experience

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Abstract : *The clinical course and outcome of pregnancies in women with hyperprolactinemia were determined. There were 18 pregnancies in 15 patients who had been treated with bromocriptine and lisuride. Outcome of pregnancies were 12 full term, 2 induced abortion, 1 spontaneous abortion, 1 ectopic pregnancy, 1 dead fetus in utero and 1 preterm delivery. Tumor complications occurred in 3 pregnancies of two patients. One patient with microprolactinoma had severe headache which was rapidly relieved by bromocriptine. The other patient developed severe headache in her first pregnancy and visual field defect in the second pregnancy. She had macroprolactinoma with suprasella extention. The complications were effectively treated with bromocriptine. It is concluded that pregnancy is considerably safe in most hyperprolactinemic patient treated with bromocriptine or lisuride. As soon as pregnancy is diagnosed the medication should be discontinued. Tumor complication during pregnancy is infrequent in women with functional hyperprolactinemia and in women with microprolactinoma. Patient with macroprolactinoma and suprasella extention, however, have a high risk of complication during pregnancy. Thus, tumor size should be reduced either by surgery and/or medication before allowing the patient to become pregnant. The rare tumor complication occurring during pregnancy is usually treated effectively by the reinstitution of a prolactin inhibiting agent. (Thai J Obstet Gynaecol 1989;1:115-22.)*

Key words : clinical course, outcome of pregnancy, hyperprolactinemia

Hyperprolactinemia is a common cause of secondary amenorrhea and anovulatory infertility^(1, 2). The major cause of hyperprolactinemia is pituitary adenoma secreting prolactin (prolactinoma). Since the assay of serum prolactin and

several prolactin inhibiting agents have become available, the treatment of these patients has been effective in most cases. The ovulatory and pregnancy rates are high during the medical treatment⁽³⁾. Prolactinoma, however, causes

concern to both the patients and obstetricians as its enlargement during pregnancy may be rapid, thus, resulting in tumor complications such as headache and visual field defect. Previously it was advocated that such patients should be treated with either surgery or radiotherapy before attempting to conceive⁽⁴⁻⁶⁾. Experiences gained during the last decade have shown that neither surgery nor radiotherapy provides a definite cure for most infertile women with prolactinoma⁽⁷⁾. At present, most authorities are of the opinion that medical treatment is suitable for most infertile patients with hyperprolactinemia including those who have prolactinomas^(8, 9).

The purpose of this study was to determine the clinical course and outcome of pregnancies in hyperprolactinemic women treated with prolactin inhibiting agents at Ramathibodi Hospital.

Materials and Methods

Since 1983 bromocriptine has been used to treat infertile women with hyperprolactinemia attending the Gynaecologic Endocrinology clinic at Ramathibodi Hospital. From 1988 lisuride, another prolactin inhibiting agent, has also been used as an alternative. From 1983 to 1988 fifty-two patients, aged 20 to 36 years with hyperprolactinemia were treated with prolactin inhibiting agents, forty cases were treated with bromocriptine and the other twelve with lisuride. Eighteen from 40 and 5 from 12 patients in the bromocriptine and lisuride groups desired pregnancy. Bro-

mocriptine and lisuride treatment resulted in 16 pregnancies in 13 patients and 2 pregnancies in 2 patients respectively. The clinical course and outcome of these 18 pregnancies were determined.

Results

The clinical characteristics of these patients are shown in Table 1. All but two patients presented with amenorrhea and galactorrhea. Two patients had amenorrhea without galactorrhea. Pre-treatment serum prolactin levels varied from 80 to 700 ng/ml. Radiological studies revealed microprolactinoma in 7 patients and macroprolactinoma with suprasella extension in one patient. Normal radiological findings were found in 7 patients. Before pregnancy 13 patients were treated with bromocriptine and the other two were treated with lisuride. Two patients in the bromocriptine group had pituitary surgery previously. The medication was discontinued immediately after pregnancy was confirmed. The patients were informed of the risk of pituitary enlargement during pregnancy and the symptoms and signs of such a complication. Regular antenatal care was provided. Tumor complications such as headache and visual problems were noted during every antenatal visit. Those who had complaints were sent to the ophthalmologic clinic for visual field determination.

Summary of the outcome of pregnancies is shown in Table 2. Twelve full term and one preterm pregnancies resulted in viable newborns. No multiple

Table 1 Patients' clinical characteristics

No.	Age	Symptom	Pretreatment prolactin (ng/ml)	Radiological finding	Treatment before pregnancy	Outcome of pregnancy	Tumor complication
1	22	A-G	200	microadenoma	bromocriptine*	induced abortion	no
2.1	26	A-G	165	microadenoma	bromocriptine*	normal full term	no
2.2	31	A-G	56	microadenoma	bromocriptine*	normal full term	no
3	20	A-G	96	normal	bromocriptine	normal full term	severe headache +
4	29	A-G	144	microadenoma	bromocriptine	normal full term	no
5.1	32	A-G	120	microadenoma	bromocriptine	normal full term	no
5.2	34	A-G	80	microadenoma	bromocriptine	normal full term	no
6.1	26	A-G	700	macroadenoma with suprasella extention	bromocriptine	spontaneous abortion	no
6.2	27	A-G	150	microadenoma	bromocriptine	dead fetus in utero at 28 weeks	severe headache +
7	34	A-G	400	microadenoma	bromocriptine	preterm delivery at 35 week	severe headache and bitemporal hemianopia
8	35	A-G	120	normal	bromocriptine	normal full term	no
9	30	A-G	350	normal	bromocriptine	induced abortion	no
10	28	A	57	normal	bromocriptine	normal full term	no
11	30	A	90	normal	bromocriptine	normal full term	no
12	24	A-G	443	normal	bromocriptine	normal full term	no
13	31	A-G	76	normal	bromocriptine	ectopic pregnancy	no
14	26	A-G	152	microadenoma	lisuride	normal full term	no
15	36	A-G	109	microadenoma	lisuride	normal full term	no

* previous pituitary surgery
+ reinstitution of bromocriptine

A = Amenorrhea
A-G = Amenorrhea with galactorrhea

Table 2 Summary of the outcome of pregnancies

Outcome	No.	per cent
Total pregnancies	18	100
Normal full term	12	66.7
Induced abortion	2	11.1
Spontaneous abortion	1	5.5
Ectopic pregnancy	1	5.5
Dead fetus in utero	1	5.5
Preterm delivery	1	5.5

pregnancy occurred. Tumor complications during pregnancies were recorded during three pregnancies in two patients (Table 1). One patient with microadenoma had severe headache. The symptom rapidly disappeared after bromocriptine therapy. The other patient with macroprolactinoma and suprasella extension had two pregnancies. During her first pregnancy, she developed severe headache which was relieved by bromocriptine. Unfortunately, the fetus died in utero at 28 weeks of gestation from unknown cause. One year later she became pregnant again. Severe headache and visual field defect (bitemporal hemianopia) occurred from 24 weeks of gestation. She was treated with bromocriptine 7.5 mg/day. Headache was relieved and visual field defect did not deteriorate. She delivered a healthy newborn spontaneously at 35 weeks of gestation. The visual impairment had completely disappeared at postpartal check up 6 weeks after delivery. Most patients could breast-feed their infants normally.

Discussion

The clinical course and outcome

of most pregnancies in hyperprolactinemic women treated with prolactin inhibiting agents at our clinic is satisfactory. Our results confirm other previous study⁽⁹⁾. One of the concerns while treating hyperprolactinemic infertile women with prolactin inhibiting agents is the outcome of pregnancy. Since the medication is generally continued until pregnancy is diagnosed, every patient thus receives the drug during early gestation. Information gathered during the last fifteen years has assured the both bromocriptine and lisuride treatment are safe. Abortion, multiple pregnancy and fetal malformation were similar to the general population^(10, 11). Postnatal development was also normal^(12, 13). However, for general precaution the medical treatment should be discontinued as soon as pregnancy is diagnosed. Only when tumor complications occur, should prolactin lowering agent such as bromocriptine be reinstated.

In this study, tumor complications occurred during 3 pregnancies. The course of pregnancies in patients with macroprolactinoma and functional hyperprolactinemia is considerably safe. Severe headache occurred only in one patient with macroprolactinoma and was rapidly relieved by bromocriptine. Patients with macroprolactinoma and suprasella extension, however, developed tumor complications in both pregnancies. High risk of tumor complications is high in patients who have a large tumor extending outside the sella turcica.

In 1979, Gemzell and Wang⁽⁵⁾ reviewed the outcome of pregnancies in

women with pituitary adenoma. They found tumor complications occurring during pregnancy in 5 per cent of patients with microprolactinoma and 25 per cent with macroprolactinoma. Since this figure of tumor complication was rather high, they advocated that these patients should have been treated with surgery and/or radiotherapy before attempting to conceive. It was interesting to note that most of these patients had no biochemical evidence of hyperprolactinemia. They were treated with ovulation inducing agents other than bromocriptine. The compilation of data from 1980 to 1984 has shown contradictory results⁽⁹⁾. Of 488 term pregnancies in 430 hyperprolactinemic patients (285 had prolactinoma), only 11 (2.2 per cent) had tumor complications during pregnancy. Ten (2 per cent) had a visual complication and one had diabetes insipidus. At present, most authors are of the opinion that hyperprolactinemic infertile women with microprolactinoma and macroprolactinoma without suprasella extention can effectively be treated with dopamine agonists without prior surgery⁽⁷⁾. Cases of macroprolactinoma with extrasella extention tumor should be treated either by surgery or medication or both. Tumor size should be reduced and confined only in the sella turcica before allowing the patient to become pregnant.

From review of the literature, most of the patients who had tumor complications could effectively be treated with bromocriptine⁽¹⁴⁻¹⁹⁾. Surgery was performed in a few cases⁽⁹⁾. If pregnancy is near term, induction of labor is

advocated⁽²⁰⁾. Tumor complications rapidly disappeared after delivery. Due to the low incidence of tumor complications and the availability of effective treatment should such complications occur, we thus accepted the policy of medical treatment of women with hyperprolactinemia including those with prolactinomas without prior surgery. Pituitary surgery requires an experienced surgeon. In unskilled hands, incomplete resection of tumor or damage to adjacent pituitary cells is frequent. Post-operative persistence of elevated prolactin levels or panhypopituitarism may follow. Thus, further treatment will be more complicated. Even in cases of adequate tumor resection, long term follow up has shown a high recurrence rate after surgery⁽²¹⁾. Therefore, medical therapy appears to be appropriate as a primary treatment in almost all hyperprolactinemic infertile patients.

Antenatal care of hyperprolactinemic patients is more or less the same as for general pregnancy. Prolactin lowering agents should be discontinued as soon as pregnancy is diagnosed. Prophylactic medical treatment has been recommended in early studies⁽²²⁻²⁴⁾. Today, this practice is no longer advocated because of the low incidence of tumor complications during pregnancy and the availability of effective medical treatment if such complications occur as discussed earlier.

In our opinion, visual field determination may not be necessary in every antenatal visit especially in women with functional hyperprolactinemia and patients with microprolactinoma. Careful

advice to the patients about the risk, signs and symptoms of tumor complications should be done. Finger test performed by an obstetrician or midwives at each antenatal visit may be adequate for screening of visual impairment in patients with no complaint. Only those who had headache or visual symptom were subjected for visual field determination. This policy will cause less interference in busy ophthalmologic clinics. During pregnancy some authorities suggested periodic serum prolactin determination^(5, 22, 25). However, the clinical value of this practice has not been proven. The maternal prolactin levels seem not to be predictive of any tumor complications^(20, 25, 26). It also causes a lot of expense. We, therefore, do not follow serum prolactin levels during pregnancy.

In the past, breast feeding was also a controversial issue. During early postpartum, suckling has a marked stimulatory effect on prolactin secretion⁽²⁷⁾. This physiological effect caused concern and some authors advised against breast feeding especially in patients with prolactinomas^(28, 29). Experience gained from later studies revealed that breast feeding does not cause deteriorious effect on prolactinoma^(9, 20). There is therefore, no reason to withhold the patient from the advantages of breast feeding. Most of our patients could breast feed normally.

Summary

In conclusion, this study supports the policy of medical treatment of hyperprolactinemic infertile women without prior surgery and/or radiotherapy

except in patients who had a large prolactinoma with suprasella extension. After pregnancy is confirmed the drug should be discontinued. The patients should be carefully informed about the risk, symptoms and signs of tumor complications that might occur during pregnancy. Regular antenatal visits should be performed as usual. Should tumor complications occur, reinstitution of prolactin lowering agent is usually effective. Surgery is limited to those who fail medical treatment. Induction of labor may be considered if pregnancy is near term. After delivery, the patient should be advised to breast feed like other mothers.

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