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OUTCOME OF PREGNANCY IN MOTHERS GIVEN BROMOCRIPTINE

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1 Information has been obtained on the outcome of 448 completed pregnancies in mothers who had been given bromocriptine at some stage in the early weeks of pregnancy.

2 The frequencies of spontaneous abortions, twin pregnancies and malformations have been compared with those reported for 'normal' populations.

3 Based on this limited material, we conclude that the use of bromocriptine to restore fertility in hyperprolactinaemic women is not associated with an increased risk of abortion, multiple pregnancy or the occurrence of malformations in the infants.

Introduction

Previously infertile women treated with bromocriptine for hyperprolactinaemic conditions may become pregnant (Thorner, Besser, Jones, Dacie & Joves, 1975; Franks, Jacobs, Hull, Steele & Nabarro, 1977). In most cases medication continues after conception until the patient is aware that she is pregnant or until pregnancy is confirmed. There is no evidence from animal investigations that bromocriptine has a harmful effect on the fetus when given to dams in non-toxic doses. Nevertheless, it is important to know if the outcome of human pregnancies is adversely affected by bromocriptine medication in the early weeks. This paper provides information on the results of 448 pregnancies in women who received bromocriptine for some period into their pregnancies.

Methods

Bromocriptine is marketed in some countries and is undergoing clinical trial in others. The medical research departments of Sandoz affiliated companies in different countries have endeavoured to keep track of all pregnancies occurring in bromocriptine-treated patients. Clinicians are advised to stop medication as soon as pregnancy is diagnosed, and to follow the course of pregnancy carefully. They are requested to report the occurrence of pregnancy to us, using a simple form. At the end of pregnancy they should send a second form giving information on the outcome, with details of any abnormal results. If this second form is not sent spontaneously, Sandoz staff request the information from the clinician shortly after the estimated date of delivery. Clearly we are unable to cover all cases of mothers who become pregnant under bromocriptine treatment. We feel, however, that the data obtained reflect a fair sampling of the population 'at risk'. Any bias would be in favour of over-reporting of malformations, as most bromocriptine-induced conceptions occur in subfertile women who are anxious to conceive, and therefore are particularly alert to the possibilities of an abnormal outcome.

Results

The 448 pregnancies yielded 369 live births. The findings are summarized in Table 1. In the majority of cases, bromocriptine was given to treat hyperprolactinaemic conditions, such as amenorrhoea/galactorrhoea or ovarian insufficiency. In 70 cases pituitary tumour was reported as the primary diagnosis. (The effects of bromocriptine therapy on possible development of pituitary tumours in pregnancy will be reported elsewhere.) Three pregnancies occurred in acromegalic patients.

Information is available on the dosage of bromocriptine used from 422 patients (94%). The mean daily bromocriptine intake was 5.9 mg (range 1–35 mg).

Data are available on the duration of treatment in pregnancy from 360 patients (80%). Table 2 shows the distribution of this factor. The mean duration of bromocriptine administration after conception was 27.4 days.

Seventy-nine pregnancies ended in abortion. Of these, 49 were spontaneous. In the 21 patients who had abortions induced, the reasons given were: pituitary tumour, acromegaly, amenorrhoea/galactorrhoea, Chiari-Frommel syndrome, missed abortion (six cases – included here, not under

'spontaneous' heading), social grounds, or unknown. In the nine remaining abortions reported, the following conditions pertainedG three extrauterine pregnancies, three intrauterine deaths (at 20, 24 and 30 weeks), one premature delivery at 20 weeks, one twin-birth at 24 weeks, one hydatidiform mole. Table 3 shows the lack of a clearcut relationship between the duration of bromocriptine therapy and the day of spontaneous abortion, for those cases where these factors are known. The mean interval between ceasing medication and abortion is 37.7 days (range 5–80 days).

Of the 369 pregnancies resulting in live births, six were twin-births, the remainder being single-births. This gives an overall frequency of twin-births of 1.6%. If the abortion at 24 weeks is included as a twin pregnancy, the frequency of known twin pregnancies is 1.9%.

Malformations were seen in eleven infants. This corresponds to 2.9% of total births. There were two major malformations (0.5%) and nine minor aberrations (2.4%). Details are given in Table 4. No distinct pattern of malformations is apparent.

The mean birth weight of 363 live births (98% of the collective) was 3180 g (range 1000–4730 g). The mean duration of pregnancy was 38.5 weeks (range 32–42 weeks). The premature delivery rate (birth weight below 2500 g) was 10.1%.

Discussion

Obviously our information is not as detailed or complete as we should like. This is largely due to logistic problems – cases have been collected from

Table 1 Summary of data on clinical indications, children born and abortions

Total number of pregnancies = 448; total number of children born = 375

	Indication for bromocriptine treatment	*Children born*					*Abortions*			
		Total number of births	*Twin births*	*Major malformation*	*Minor malformation*	*Other findings*	*Total abortions*	*Spontaneous*	*Induced*	*Others*
1	Idiopathic amenorrhoea/galactorrhoea	199	4	1[1]	5[2]	2[3]	53	36	12	5[4]
2	Post partum amenorrhoea/galactorrhoea	32	—	—	—	1[5]	2	1	1	—
3	Post-pill amenorrhoea/galactorrhoea	17	—	—	1[6]	—	2	1	—	1[7]
4	Infertility, anovulatory cycles, luteal insufficiency	32	—	—	1[8]	—	10	7[9]	—	3[10]
5	Polycystic ovaries	4	—	—	—	—	2	—	2	—
6	Premenstrual syndrome	8	1	—	—	—	—	—	—	—
7	Pituitary tumour	62	1[11]	1[11]	2[12]	—	8	4	4	—
8	Acromegaly	2	—	—	—	—	1	—	1	—
9	Gigantomastia	3	—	—	—	—	—	—	—	—
10	No data given	10	—	—	—	—	1	—	1	—
	Total	369	6	2	9	3	79	49	21	9

[1] Pulmonary artery atresia.
[2] One syndactyly; one small deformity of ear-lobe; one congenital inguinal hernia; one talipes; one single umbilical artery.
[3] One death of premature infant (28–30 weeks) with no abnormalities; one naevus (not counted as malformation, disappeared after 13 weeks).
[4] Two extrauterine pregnancies; one hydatidiform mole; one intrauterine death (at 24 weeks); one death of premature infant at 20 weeks.
[5] Cerebral haemorrhage (?birth injury).
[6] Congenital dislocation of hip.
[7] Death of premature infant at 20 weeks.
[8] Syndactyly.
[9] One abortion after riding accident.
[10] One extrauterine pregnancy; one twin pregnancy, born week 24, died after 0.5 h, no anomalies; one intrauterine death at 30 weeks.
[11] Twin-birth (33 weeks) with renal agenesis in one child.
[12] One cleft palate; one congenital dislocation of hip.

twenty-four different countries, and the forms used were deliberately kept as simple as possible, to encourage cooperation from clinicians. Also no results have yet been obtained on infants later in life.

In spite of these drawbacks, we can compare our results in two ways – firstly with the data for a 'normal' population, and secondly with those from a population with a similar pathological background, i.e. infertile mothers rendered fertile with the help of other agents.

The incidence of spontaneous abortions in mothers taking bromocriptine was 10.9%. A recent detailed study of the course of pregnancy in over 13,500 cases yielded a 9.7% incidence of abortion (Report of German Research Council, 1977). However, 70% of these cases were only taken into the study between the eighth and twelfth week of pregnancy, i.e. after some potential candidates might have dropped out due to abortion. The figure of 9.7% is therefore regarded by the authors as probably artificially low. On the other hand, our bromocriptine patients were followed carefully from the first missed menstrual period, so that presumably all spontaneous abortions were detected. It should be noted, however, that apart from the possibility that one or more of the patients where pregnancy was terminated might have aborted spontaneously, in nine additional cases abortion would almost certainly have been inevitable – three extrauterine pregnancies, three intrauterine deaths, two premature deliveries (one twin birth), one hydatidiform mole. This gives an overall frequency of 12.9%. (If we include the missed abortions the overall frequency reaches 14.3%). Comparable incidences for spontaneous abortion reported after restoration of fertility using menopausal gonadotropin, chorionic gonadotropin or clomiphene citrate range from 11 to 25% (Ahlgren, Källen & Rannevik, 1976; Kase, 1973; Spadoni, Cox & Smith, 1974; Thompson & Hansen, 1970).

Table 2 Duration of foetal exposure

Duration of bromocriptine treatment into pregnancy (days)	*Number of cases*
0–7*	27
8–14	29
15–21	89
22–28	86
29–35	45
36–42	36
43–49	20
50–56	11
More than 56	17

*Day 0 taken as probable day of conception, *or* first day of last menstrual period-plus-13 days. It must be emphasised that in some cases the data here are unexact.

Table 3 Time from treatment-end to abortion

Interval between ceasing bromocriptine and abortion (days)	*Number of cases*
0–7	2
8–14	4
15–21	1
22–28	5
29–35	8
36–42	1
43–49	6
50–56	5
57–64	3
More than 64	3

It might be asked whether cessation of bromocriptine in early pregnancy could lead to hormonal changes which would promote abortion. As Table 3 reveals, the time interval between ceasing medication and abortion shows great variability in the 38 cases where these data are available. We conclude that stopping bromocriptine medication does not increase the risk of spontaneous abortion.

The observed frequency of twin pregnancies in our collective (1.6–1.9%) is not higher, in a statistical sense, than the normal population frequency of roughly 1 per 85 pregnancies = c.a. 1.2% (Report of German Research Council, 1977). The 95% confidence intervals for the binominal distribution assumed applicable to the rate of twin pregnancies overlap considerably. Multiple pregnancies with clomiphene therapy are well known, and even in Ahlgren's series twins occurred more frequently (7/141 = 5%) (Ahlgren *et al.*, 1976). After human menopausal gonadotropin, the multiple pregnancy rate has been reported to reach 30% (Kase, 1973).

The mean birth weight (3181 g) corresponded to that observed in normal pregnancies of 38.5 weeks duration (Documenta Geigy, 1977). The premature delivery rate (10.1%) is probably above that encountered in a normal population. However it is not higher than the rate quoted for pregnancies achieved under unfavourable maternal circumstances (Käser, Friedberg, Ober, Thomsen & Zander, 1967). Certainly our figures do not indicate that bromocriptine therapy leads to cervical insufficiency as has been suggested by Jürgensen & Taubert (1977).

Malformations (major and minor) occurred in our bromocriptine series in 2.9% of patients. Smithells (1976) cites a frequency of 2.7% spontaneous malformations for a collective of over 600,000 control patients. After reviewing the world literature covering 20 million births, Wilson (1973), citing Kennedy, concludes that the frequency of individuals with some degree of congenital defect at birth almost certainly exceeds 2%; indeed more intensive studies in about half a million infants yielded a mean rate for defective

Table 4 Summary of abnormal infants

			Bromocriptine therapy			Pregnancy		Child			
Country	Age (years)	Clinical indication	Total (weeks)	Pregnancy (days)	Dose (mg/day)	Duration (weeks)	Course	Sex	Weight (kg)	Malformation	Remarks
NL	23	Amenorrhoea galactorrhoea (idiopathic)	31	21	5.0	38.5	Uncomplicated	F	2.38	Pulmonary atresia	Diagnosed postmorten
NL	25	Amenorrhoea galactorrhoea (idiopathic)	?	24	5.0	39	Uncomplicated	F	3.22	Bilateral talipes	Same mother as above
NL	28	Amenorrhoea galactorrhoea (idiopathic)	5	21	5.0	38	Uncomplicated	F	2.88	Syndactily, absent terminal phalanges in 1 toe, 2 fingers	First child (clomiphene pregnancy) had talipes
NL	28	Amenorrhoea galactorrhoea (idiopathic)	8	15	5.0	40	Uncomplicated	F	4.10	Auricular appendage	
GB	23	Chromophobe pituitary adenoma	17	42	5.0	32	Antepartum haemorrhage, twins	M M	1.70 2.00	1. Absent kidney cystic degeneration of other 2. High blood urea at birth, but no anomalies	Diagnosed post-mortem Normal at 18 months
GB	34	Amenorrhoea galactorrhoea (pituitary tumour)	8	12	10.0	34	Uncomplicated	F	2.8	Small cleft palate	Mother treated by Yitrium-90 implant-ation
CH	34	Amenorrhoea galactorrhoea (idiopathic)	4	52	5.0	41	Uncomplicated	M	4.2	Congenital inguinal hernia	Hernia repaired at 2 months
NL	23	Oligomenorrhoea	7	36	5.0	41.5	Uncomplicated	F	2.86	Syndactily both hands and feet	Progesterone and oestradiol for first 16 weeks of pregnancy
S	25	Pituitary adenoma	5.5	21	5.0	41	Uncomplicated	M	3.02	Congenital dislocation of hip	
AUS	31	Secondary amenorrhoea, galactorrhoea	18	49	5.0	40	Uncomplicated	F	2.89	Congenital dislocation of hip	
GB	28	Galactorrhoea	4	?	2.5	40	Uncomplicated	M	2.58	Single umbilical artery	

NL Netherlands; GB Great Britain; CH Switzerland; S Sweden; AUS Australia

individuals of 4.5%. It is well known that such figures depend on the thoroughness of the examinations of the infants, the age at which such examinations are done and, obviously, whether quite minor aberrations such as a pigmented naevus are included under the heading minor malformations or not. Based on our present data, we conclude that the incidence for congenital malformations in infants born to bromocriptine-treated mothers lies within normal limits. On the other hand, if ovulation is induced in anovulatory patients with clomiphene or with natural gonadotropins, increased frequency of malformations has been reported.

Ahlgren and his colleagues (1976) reported eight major abnormalities in 148 births related to clomiphene therapy, i.e. an incidence of 5.4%; additional infants had minor anomalies. A 5.5% incidence of anomalies was reported in 62 pregnancies following induction of ovulation by human menopausal gonadotropin (Spadoni *et al.*, 1974). Other workers, however, report no increased frequency of anomalies with these forms of therapy (Kase, 1973; Hack, Brish & Seer, 1970). It is known that correct dosage of clomiphene can reduce the frequency of multiple births, and a similar dose-related factor may operate for malformations.

Of the eleven malformations in our series, two were considered major and nine minor. Although such a classification can be criticized for being arbitrary, it can be of help in putting the problem in perspective; minor aberrations are not incompatible with a normal life, and can usually be corrected surgically. The pattern of malformations reported for bromocriptine mothers corresponds closely with the commonest types occurring in a 'normal' population, i.e. heart and great vessels, central nervous system, facial cleft, dislocation of hip, talipes, urinary tract (Report of German Research Council, 1977). Absence of a specific type or types of malformation, and the overall low incidence, allows us to conclude that bromocriptine does not exert a teratogenic effect in man.

In spite of these satisfactory results, our knowledge of possible adverse effects of bromocriptine therapy on the unborn child is incomplete. Obviously we require more cases and a longer period of follow-up (even years) before we can state with certainty that there is no risk attached to maternal use of bromocriptine. Nevertheless, the drug may now be used to restore fertility in previously subfertile or sterile women in the knowledge that it can be stopped as soon as pregnancy is diagnosed, without an increased risk of inducing abortion or of a malformation occurring in the infant.

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