CLOMIPHENE AND NEURAL TUBE DEFECTS

by

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THE aetiology of anencephaly and/or spina bifida (neural tube defects) is still obscure. Most investigators are now agreed on a multifactorial causation with an important genetic factor and a substantial environmental component. The genetic factor is probably polygenic, but the mechanism by which it acts remains unknown. Recently, drugs that stimulate ovulation, particularly clomiphene, have been implicated in the aetiology of neural tube defects (Dyson & Kohler, 1973; Sandler, 1973; Barrett & Hakim, 1973; Field & Kerr, 1974). Although six infants with anencephaly and/or spina bifida have been born to mothers receiving clomiphene, it is impossible on present evidence to conclude whether the malformation rate for neural tube defects is greater than would have been expected. This report describes four patients on clomiphene who produced a total of five infants each with a neural tube defect.

Case Reports

Patient 1. This patient was aged 20 years when first seen on November 29, 1971, because of secondary amenorrhoea. Since her menarche at age 19 years, she had had only one menstrual period (February, 1971). Clinical examination was normal except for hirsutes on the thighs and upper arms and poor breast development. The uterus was small, mobile, and anteverted. Skull X-rays, adrenal steroid excretion and thyroid function tests were normal.

Treatment by clomiphene, 50 mgms. daily for five days was commenced on March 27, 1973. A pregnancy test was positive on May 14, 1973. At examination on May 21, 1973 and on June 8, 1973 the size of the uterus corresponded to six weeks and eight weeks gestation respectively. From July 1973, the size of the uterus was always in excess of the period of amenorrhoea. On October 12, 1973, the size of the uterus corresponded to 32 weeks, whereas the interval since ovulation was 26 weeks. An ultrasonic scan confirmed gross polyhydramnios and the absence of a fetal skull. A transabdominal amniocentesis was carried out; the amniotic fluid alpha-fetoprotein level was 43.0 μg/ml. At 26 weeks gestation the mean amniotic fluid alpha-fetoprotein level is 3.15 μg/ml; and the 95th percentile 5.82 μg/ml (Nevin, Thompson & Nesbitt, 1974). A straight X-ray confirmed the presence of an anencephalic fetus. Five days later, following induction, the patient delivered a stillborn female fetus weighing 1134 g with anencephaly and a meningomyelocele.
Patient 2: This patient, aged 23 years was first seen in February 1972. She had a normal menarche, aged 11 years, with menstrual periods lasting 21 to 35 days. For six months after her marriage in April, 1969, she had been taking an oral contra-

ceptive. After stopping the pill, there was a three-month period of amenorrhoea. For the next two and a half years, she had been trying unsuccessfully to conceive. Clinical and pelvic examination was normal. The uterus was anteverted and of normal size. There was no histoligical evidence of cyclic activity in the endometrium. Tubal insufflation was normal. In addition, vaginal cytology on five occasions from September 13, 1972 to October 11, 1972, showed no evidence of oestrogenic fluctuation throughout the cycle or any indication that ovulation had occurred.

The following courses of clomiphene, each lasting five days, were started in 1973: —

March, 23	50 mg daily
May, 9	100 mg daily
June, 6	200 mg daily

The temperature chart indicated that ovulation had occurred on July 20, 1973, but a subsequent pregnancy test on August 1, 1973 was negative. She had a normal menstrual period on October 14, 1973. Further courses of clomiphene, each lasting five days was given on: —

March, 1974	400 mg daily
April, 1974	400 mg daily
June, 1974	400 mg daily

She had a normal menstrual period on June 14, 1974. She had had only two and a half days treatment of the last course of clomiphene. On July 31, 1974, the size of the uterus corresponded to 6 to 8 weeks gestation. A pregnancy test on August 1, 1974, was positive.

At 24 weeks gestation on December 18, 1974, she was admitted to hospital because of an intrauterine death. Following syntocinon induction, on December 19, 1974, she was delivered of a macerated male fetus, weighing 590 g with iniencephaly.
Patient 3: This patient who was born May 31, 1951, was married on February 6, 1970. Her first pregnancy on March 26, 1972 was a stillborn anencephalic female. There had been no history of clomiphene treatment during this pregnancy. In 1972 her second pregnancy ended in a spontaneous abortion at 10 weeks gestation. This pregnancy was followed by secondary amenorrhoea. The following courses of clomiphene, each lasting five days were given in 1973: —

March, 1973	50 mg daily
April, 1973	50 mg daily
May, 1973	50 mg daily

The temperature chart indicated that ovulation had occurred on May 23, 1973. The pregnancy progressed normally. On March 14, 1974, she delivered a female with microcephaly and an encephalocele. The infant died 30 minutes after birth.
Patient 4: This patient, aged 22 years, was first seen in 1968 because of irregular menses. Her menarche was at the age of 17 years. Examination did not reveal any

abnormality. The uterus was small and anteverted with a uterine cavity length of 2 inches. Histologically, the endometrium showed only proliferative phase.

She was married in 1970 and two years later was again seen because of irregular menses. In the last 8 months she had had only two menstrual periods. Skull X-ray, thyroid function tests and steroid analysis were normal. Clomiphene therapy, 50 mg daily for five days, was started on July 31, 1972, and this was increased to 100 mg daily for five days on August 3, 1972. The temperature chart suggested that ovulation had occurred on August 20, 1972. Pregnancy tests on September 11 and 18, 1972, were positive, but two subsequent tests (September 19 and 20) were negative. She began to stain vaginally on September 16 and, as this failed to subside, a dilatation and curettage was undertaken on September 22, 1972. Histologically, the endometrium showed decidual reaction.

A third course of clomiphene, 100 mg daily for 5 days was given on November 7, 1972. No further treatment was given until September, 1973, when she had a fourth course of clomiphene—100 mg daily for five days. The temperature chart suggested that ovulation had taken place on October 1, 1973. On November 5, 1973, the pregnancy test was positive. Spontaneous labour took place on June 23, 1974, and she delivered a female infant with microcephaly, frontal encephalocele, and a meningomyelocele. This baby died 3 hours later.

A fifth course of clomiphene—100 mg daily for 5 days was given on May 6, 1975. Slight vaginal bleeding occurred on June 28 and July 4, 1975. On July 11, 1975, the size of the uterus corresponded to 11 weeks gestation. On July 14, 1975, she had an episode of crampy low back pain, and two days later, fresh vaginal bleeding. The pregnancy terminated on July 19, 1975 in a spontaneous abortion; the fetus had anencephaly.

Discussion

The use of ovulation stimulation agents such as clomiphene in the management of infertility has become widespread. Until recently, the only problems encountered in the use of clomiphene has been the high incidence of multiple pregnancy, and a high rate of early abortion (Whitelaw, et al, 1970; Murray, et al, 1971; Hack, et al 1972). Within the past few years, it has been suggested that clomiphene may have a teratogenic action (Table). In 1973, Dyson and Kohler, described two patients who produced infants with anencephaly and spina bifida following treatment with clomiphene. Since this initial report, several similar observations have been reported (Sandler, 1973; Barrett & Hakim, 1973; Field & Kerr, 1974). To date there have been six patients on clomiphene who had infants with a neural tube defect (Table). The present paper describes four women receiving clomiphene who produced five infants with a neural tube defect; two had anencephaly and/or spina bifida; of the remaining three cases one had iniencephaly; another microcephaly and an encephalocele, and the fifth microcephaly, frontal encephalocele and meningomyelocoele. Interestingly, although clomiphene has been used extensively in the United States, there are no published reports suggesting a casual association of neural tube defects and clomiphene.

TABLE

Neural-tube Defects following Ovulation Stimulation by Clomiphene

Author	*Case*	*Previous Obstetric History*	*Sex*	*Birth Weight (g)*	*Description of Abnormality*
Dyson & Kohler (1973)	1	Primigravida	F	1030	Cervical spina bifida, anencephaly, kyphoscolosis of thoracic spine and mild bilateral hydronephrosis
	2	One spontaneous abortion	M	NR	Anencephaly
Sandler (1973)	1	Primigravida	M	936	Anencephaly and severe spina bifida
Barrett & Hakim (1973)	1	Four previous pregnancies; first a female anencephalic infant; and the other 3 normal female infants	M	NR	Anencephaly
Field & Kerr (1974)	1	One normal male while on clomiphene therapy	M	NR	Lumbar meningomyelocele
	2	Primigravida	F	—	Anencephaly
Present Authors (1975)	1	Primigravida	F	1134	Anencephaly and meningomyelocele
	2	Primigravida	M	590	Iniencephaly
	3	Two pregnancies; first a stillborn anencephalic infant; and the other a spontaneous abortion	F	1432	Microcephaly and encephalocele
	4	One spontaneous abortion while on clomiphene	F	NR	Microcephaly, frontal encephalocele and a meningomyelocele
			NR	NR	Anencephaly

NR=not recorded

However, several large series of women receiving ovulation stimulation agents for a variety of causes of infertility have been reported but without any indication of an increased incidence of neural tube defects or indeed any congenital abnormality among their offspring. Goldfarb, et al (1968) found no increase in the incidence of congenital abnormalities in the offspring of women on clomiphene. In 166 infants and 17 abortuses in their study, only two congenital abnormalities, both haemangiomas, were noted. In the series reported by Whitelaw, et al (1970) of 88 pregnancies which resulted in 67 livebirths, there was no mention of congenital abnormalities. However, of the 104 infants born to 86 women on clomiphene reported by Hack, et al (1972), six had congenital abnormalities. One infant had a double aorta, hypoplasia of the right arch and a preductile coarctation of left arch with a patent ductus arteriosus; another infant had absence of second and fifth

digits; two additional infants had congenital dislocation of the hip; and another two had pyloric stenosis. None of the 104 infants had neural tube defects. Although they concluded that the "incidence of congenital malformations did not differ significantly from that found in the general population", six of 104 infants with a congenital abnormality should not be dismissed lightly.

An alternate explanation for the association of anencephaly and clomiphene is that couples who have infants with neural tube defects are subfertile and, therefore, likely to receive ovulation stimulation agents (Dyson & Kohler, 1973; James, 1973, 1974). Several epidemiological surveys of anencephaly have shown a longer fallow interval or conception wait before the anencephalic birth than in controlled groups (Smithells, et al, 1964; James, 1974). James (1974) using the data of the British Perinatal Mortality Survey (1963) and taking only patients with no previous obstetric history showed the following: of 134 cases of anencephaly, in 74 cases the marriage to confinement interval exceeded the median of the distribution of the control group. He concluded that although this finding was not statistically significant, it did suggest that primiparous mothers of anencephalic infants have a longer marriage to conception interval. As there is an association between dizygotic twinning (due to double ovulation) and anencephaly, Elwood (1974) has suggested that perhaps clomiphene acts via a mechanism which increases the risk of both.

Couples who produce infants with anencephaly may be subfertile, not because they are less able to conceive, but because they have a high spontaneous abortion rate (Record & McKeown, 1950; Coffey & Jessop, 1958; James, 1974). Thus, among their pregnancies there is a higher proportion of recognised and unrecognised spontaneous abortion.

There is undoubtedly a need for more information on the relationship between fertility and neural tube defects. A prospective survey of women receiving clomiphene is being carried out and a complete ascertainment of families with an infant with a neural tube defect born 1971–1974 inclusive, has been undertaken to determine some of the parameters of fertility. However, it is also important not to ignore the possible teratogenic effect of clomiphene.

Summary

This paper describes four patients who had five infants with neural tube defects while receiving clomiphene for infertility. Of the five infants two had anencephaly and/or spina bifida; one had iniencephaly; another, microcephaly and an encephalocele; and the fifth, microcephaly, a frontal encephalocele and a meningomyelocele. The possible teratogenic effect of clomiphene is discussed but it is also suggested that anencephalic-prone-couples are subfertile and thus anencephalic births would be associated, but not casually, with the administration of drugs designed to alleviate infertility.

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