September 27, 1957. The jaundice had cleared by October 29, and since that date no physical illness has been reported.

The patient was investigated in May, 1958, when the following tests of liver function were recorded: serum bilirubin, 0.4 mg. per 100 ml; serum alkaline phosphatase, 46.7 K.A. units; bromsulphthalein retention, 13.8%. Needle biopsy of the liver on March 9, 1958, showed a considerable increase in fibrous tissue in the portal tracts, with slight cellular infiltration. Bile-duct proliferation and abnormality of parenchymal cells were not observed (Fig. 4).

Discussion

Chlorpromazine is of such recent introduction that enough time has not yet elapsed for the ultimate prognosis in all patients who develop jaundice to become clear. The present investigation indicates that restoration of normal liver histology or function, or both, may be long delayed. If permanent changes were to ensue, the original, cholangiolytic, type of lesion is of a nature that could lead to biliary cirrhosis. Myres *et al.* (1957) have observed such a case; one year after the onset of chlorpromazine jaundice, biliary cirrhosis, confirmed by liver biopsy, was present and portal hypertension was also noted. Twenty patients who had apparently recovered from chlorpromazine jaundice were studied by Kelsey *et al.* (1955), and early cirrhotic changes were reported in two cases. Eleven of the 20 cases, however, had previously suffered from diseases which could have involved the liver, and, as other drugs had been used in the two cases mentioned, the authors could not be certain that chlorpromazine was solely responsible.

Sensitization reactions to chlorpromazine within the liver are believed by Shay and Siplet (1957) to occur in 25% of patients who receive the drug, and are ascribed by them (Shay and Siplet, 1958) to the presence of the chlorine atom at the carbon-2 position in the promazine molecule. Such reactions are characterized by a cellular reaction within the portal tracts.

Needle biopsy of the liver was carried out by Sims *et al.* (1955) in 18 patients prior to chlorpromazine treatment and again at its conclusion. No patient became jaundiced, and biochemical tests of liver function remained normal. Four patients developed the characteristic hepatic lesions. A similar investigation was performed by Bartholomew *et al.* (1958) on 25 patients, two of whom became jaundiced. Of 16 patients in whom the pre-treatment liver biopsies had been normal, five developed the typical histological changes. The incidence of liver reactions to the drug is therefore much higher than the frequency of clinical jaundice would indicate.

When a history of previous chlorpromazine administration is not obtained from the jaundiced patient, extrahepatic biliary obstruction may be thought responsible and laparotomy performed. Surgical intervention for diagnostic purposes constitutes an additional hazard to the patient, and had been found necessary in 17.5% of a series of cases collected by Brick and Buckley (1957). Chlorpromazine jaundice is of intrahepatic cholestatic type, and in this variety Popper and Schaffner (1957) think that surgical procedures are apt to result in parenchymatous liver injury.

Chlorpromazine is a drug which is potentially toxic to the liver, as well as to leucopoietic and other tissues. When it occurs jaundice can be prolonged, and histological changes take place in the liver in a proportion of patients who do not develop jaundice. Sensitive tests of liver function may remain abnormal for long

periods after jaundice. Restoration of normal liver architecture may be long delayed, and permanent liver damage, though probably rare, has been reported. Despite its excellent general utility, these considerations suggest that chlorpromazine should be given to patients only when absolutely essential and if a less toxic drug of similar pharmacological action is not available.

Summary

Two patients who had chlorpromazine jaundice six months and one year previously have been studied by means of liver-function tests and needle biopsy. In both cases there were persistent histological changes, but biliary cirrhosis was not observed; in one case liver-function tests remained abnormal. The ultimate prognosis of chlorpromazine jaundice is discussed, and it is suggested that, since the drug is potentially toxic, it should not be used without careful consideration.

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ECTOPIC GESTATION

A STUDY OF A DECADE OF ABERDEEN CASES

BY

D. V. I. FAIRWEATHER, M.B., M.R.C.O.G.

*First Assistant, Department of Midwifery and Gynaecology,
University of Durham*

*Lately Registrar, Aberdeen Maternity Hospital and
Aberdeen General Hospitals*

Ectopic gestation remains a condition which exercises the diagnostic ability of the surgeon to the full, and occasional deaths still occur.

The object of this study has been to investigate the symptomatology, aetiological or predisposing factors, and prognosis of the condition. It is based on an analysis of the case records of all patients admitted within the decade 1946 to 1955 to the surgical and gynaecological wards of all the hospitals in the city of Aberdeen, and in whom the diagnosis of ectopic gestation was confirmed. (All the extrauterine pregnancies were situated in the tube, with one exception where it occurred in the ovary.)

The Investigation

There were 224 ectopic pregnancies in 215 patients, since the condition recurred in nine. Fifty-two cases were treated in the surgical wards and the remaining 172 in the gynaecological wards. Of the 215 patients, 127 resided within the city boundary, and they have been used to study the epidemiology of the condition.

A general analysis of the whole series was first made, with the following results.

Age Variation.—The youngest patient in the series was aged 17 and the oldest 43 years.

Parity.—As can be seen from Table I, 65% of the women were multiparous. This agrees with the findings

TABLE I.—Distribution of 224 Cases by Parity

First pregnancy	65	(29%)
Second "	54	(24%)
Third "	51	(23%)
Fourth "	22	(10%)
Fifth or later pregnancy	19	(8%)
No. detail	13	(6%)

of Crawford and Hutchinson (1954), who state that two-thirds of all ectopic gestations occur in women who have already been pregnant at least once.

Symptomatology.—The most consistent symptom was pain (99%), whilst bleeding occurred in 71%. Pain was slightly more common than bleeding as the first symptom. The incidence of shock was higher in the cases treated in the surgical than in the gynaecological wards (27% compared with 9%), and blood transfusion was also given more frequently (55% compared with 24%)—a finding that is due to the fact that severe cases are more often sent to the surgical wards. The cases occurred with equal frequency in the left and the right tube.

Recurrence Rate.—Of the 215 patients 16 had had a previous ectopic gestation (nine during the 10 years under review and seven before 1946), a recurrence rate of 7.4%. Published figures for the recurrence rates vary from 3.5% (Miller, 1940) to 9% (Henderson and Bean, 1950).

Mortality.—The death rate was 2.2% (5 out of 224 cases). It was 1.6% for city residents only. In a comprehensive review, Crawford and Hutchinson (1954) found death rates varying from 0 to 2.9%. Table II

TABLE II.—Five Maternal Deaths in Aberdeen

No.	Year	Ward	Age	No. of Pregnancy	Cause of Death
1	1946	Surgical	22	1	Transfusion reaction.
2	1947	"	31	4	Uraemia
3	1951	"	31	Not known	Paralytic ileus
4	1953	Mixed	34	"	Infection. Deep-vein thrombosis. Pyaemia
5	1955	Surgical	30	1	Undiagnosed—ruptured Air embolism following blood transfusion

Mortality rates:—2.2% of all cases; 1.6% of city residents only.

indicates the circumstances of each death. Two deaths were directly related to blood transfusion (Nos. 1 and 5). In two others (Nos. 3 and 4), delay in making a diagnosis was an important factor. In Case 4 death occurred from intra-abdominal haemorrhage without operation; in No. 3 pyosalpinx was diagnosed and conservative treatment given for 26 days, death occurring soon after laparotomy.

Epidemiological Study of City Resident Cases

Incidence.—In calculating the incidence of ectopic gestation, the 122 cases occurring in married women resident within the boundaries of the city of Aberdeen were related to the total legitimate births occurring in the same period. In the decade under consideration there were 31,821 legitimate births in city patients; the incidence of ectopic pregnancy was therefore 1 in 260, or 3.8 per thousand births. Peel (1955) quotes an incidence of 1 in 300 (3.3 per thousand births), and Johnson (1952) 1 in 126 (8 per thousand). (In the latter series 50% of the population was negro, amongst whom

ectopic pregnancy is known to be more common.) The extremes quoted vary from 3.3 (Schumann, 1921) to 9.5 per thousand (Beacham *et al.*, 1948). Even allowing for differences due to errors in sampling technique, it would appear that the incidence is definitely related to the type of population under survey. The high incidence in negro populations may be related to a high incidence of salpingitis.

Age/Parity Distribution.—The incidence in primigravidae and multiparae by age is shown in Table III. The incidence increases steadily with age, especially in primigravidae.

TABLE III.—Aberdeen Married City Patients. Incidence by Age

Age:	-24		25-29		30-34		35-39		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Primigravidae	16	0.25	12	0.38	7	0.60	4	0.78	39	0.35
Multiparae	10	0.23	25	0.36	22	0.40	17	0.44	74	0.36

No detail of parity in 9 cases.

Subsequent History of Primigravidae with Ectopic Pregnancy

An attempt was made to interview personally the 39 city primigravidae who had had ectopic pregnancies in the decade under review, but only 24 could be traced.

At interview, details of further pregnancies were noted, and where none had occurred an attempt was made to find out whether the sterility was voluntary or involuntary. The patients seemed very willing to talk freely and discuss their problems. In only one case had any attempt been made to postpone further pregnancy, and this was because of social and domestic circumstances. All wanted further pregnancy, and those who had failed to conceive again were rather overanxious. In some cases of failure fridity appeared to be developing, and in two cases there were definite indications that the home and married life were breaking up.

Of the 24 interviewed, 12 (50%) had achieved one or more additional pregnancies; in two cases it was a second ectopic gestation. Both women were in the age group 30-34 at the time of the first ectopic pregnancy.

Table IV shows that the prognosis for further pregnancies becomes poor over the age of 30. In the 30-34 age group, two out of the three further

TABLE IV.—Analysis of Interviews by Age at Time of First (Ectopic) Pregnancy

	Age:		-24		25-29		30-34		35+		Total
			No.	%	No.	%	No.	%	No.	%	
Interviewed			8		7		5		4		24
Further pregnancy			5		4		3		0		12

pregnancies were recurrent ectopics; the third patient, who had a normal pregnancy, was delivered by caesarean section (as a precautionary measure).

The low fertility subsequent to the ectopic pregnancy might be due to late marriage, and the results were therefore analysed by the patient's age at the time of marriage. Of the 24 patients, 21 married before the age of 30. The incidence of subsequent pregnancy was the same in those married before 25 and in the 25-29 age group—about one-half. None of the three women who were over 30 at the time of marriage had a further pregnancy. The patient's age at the time of marriage does not appear to be important in the prognosis for further pregnancy in this series.

Finally, the interval between marriage and the first (ectopic) pregnancy was investigated to find whether

relative infertility was a factor. It is apparent from Table V that of the 12 patients who had no further pregnancy adequate explanation was found in 5: one had proved tuberculosis of the tube; one had bilateral salpingectomy performed at the time of operation; one had hydrosalpinx of the remaining tube; in one

TABLE V.—Analysis of Interviews by Years Married Before (Ectopic) First Pregnancy (Figures in Parentheses Indicate Age at Time of First Ectopic Pregnancy)

Years	Interviewed	Further Pregnancies	No Further Pregnancy
<1	3	2 had 2 (20-24) 1 .. 3 (20-24)	—
1-2	3	1 .. 2 (20-24) 1 .. 1+1 abortion (25-29)	1 (25-29)
2-3	8	2 had 1 (25-29)	1 tuberculous salpingitis } (20-24) 1 bilat. salpingectomy } 1 hydrosalpinx } 1 (30-34) 2 (40-44)
3-4	2	1 had 2 (20-24) 1 .. ectopic after 2 years (30-34)	—
4-6	3	1 had 1 after 3 years (30-34) 1 had ectopic after 3 years (30-34)	1 salpingitis (25-29)
6+	5	1 had 1 after 18 months (25-29)	1 (25-29) (trying only 6 months) 1 (30-34) 1 (35-39) 1 (40-44)

salpingitis was found at subsequent laparotomy; and one had been trying for only six months for further pregnancy. Of the remaining seven where no lesion could be demonstrated, one was in the 25-29 age group, two were in the 30-34 age group, one was in the 35-39 age group, and three were in the 40-44 age group. Six of the seven were thus over 30, and three of the seven had been married for over six years before the first pregnancy was achieved.

It appeared, therefore, that in younger women who failed to have a further pregnancy there was evidence of a pathological lesion of the tube in almost every case. The majority of the younger women, however, had a successful pregnancy following the ectopic pregnancy, the reason for the original ectopic pregnancy being apparently a temporary defect of some kind in the reproductive mechanism.

The women who failed to conceive again despite the absence of any obvious lesion in the pelvis were mostly over 30 years of age, and as a result had probably become rather infertile.

Discussion

Aetiology.—About two-thirds of patients with ectopic pregnancy have had one or more previous intrauterine pregnancies. In some cases resultant sepsis, more particularly salpingitis, may have been an important predisposing factor, although there is not always a clear clinical history of this. The most novel finding in the present investigation has been that the incidence of ectopic pregnancy increases steadily with the age of the mother, particularly in primigravidae. Seventy-five per cent. of the primigravidae had been married for more than two years before the ectopic pregnancy occurred, suggesting some degree of infertility. It is not easy to explain how age operates. It may lead to a general lowering of the functional efficiency of the sex hormones, uterus, and tube, or to a defect in the ovum itself. On the other hand, physical changes such as uterine or tubal fibrosis or minor degrees of

endometriosis may be present. In the younger women, definite pathological conditions, especially of the tube, are often the cause. This is in line with the fact that, in populations with a low standard of living and a high incidence of gonococcal and tuberculous salpingitis, tubal pregnancy is relatively common in young women.

Conclusion

As can be seen from the analysis presented, the younger the patient the better the prognosis.

Bender (1956) found that another pregnancy occurred in 44% of cases of tubal pregnancy (made up as follows: another ectopic pregnancy, 7%; a live child, 32%; an abortion, 5%). The conception rate was 54% in women under 30 and 34% in those over 30. The outcome of the subsequent pregnancy was unaffected by whether or not the patient had had an intrauterine pregnancy prior to the ectopic pregnancy. These findings are confirmed in the present study.

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COMBINED LOCAL AND GENERAL ANALGESIA FOR CATARACT OPERATIONS

BY

JOHN IVES, M.B., B.S., F.F.A.R.C.S.

Senior Anaesthetist to the Croydon Group of Hospitals

"He now put his head betwixt his forelegs, and raising it slowly again he fell over on his side. His eye immediately became fixed. . . ."

Charles Waterton made these observations in 1812, describing his first experiment on a "medium-sized dog" with "wourali poison" (Aldington, 1949). It was not until 1947 that ocular akinesia by curare was used in eye surgery. Five years later Kirby (1952), who introduced the method, reviewed his experience with it in nearly 600 cases. His conclusions were that the relaxation during cataract surgery produced by curare, after sedation, analgesia, and local anaesthesia, is superior to, and has not been produced by, that induced by any other agent and that it is one of the pleasing features of the akinesia of curare that the surgeon can work efficiently and expeditiously and in a most delicate manner when he and the patient are relaxed.

Kirby's work stimulated others, many of whom were enthusiastic. Cordes and Mullen (1951), after using curare in 85 cases, finally came to the conclusion that curare should be used in every case of cataract extraction, for once the patient has squeezed and extruded vitreous it is too late for any relaxation-producing measures.

Barraquer Moner (1953), of Barcelona, summarizing his experience of 1,500 cases, said that the direct results of the excellent akinesia and hypotension produced by