1962; Drillien, 1964; Smallpeice and Davies, 1964). Our methods seem to prevent symptomatic hypoglycaemia without the need for repeated laboratory monitoring of the blood glucose level.

The reason for *maintaining* very large energy intakes was to prevent an interruption in brain growth with consequent possible permanent reduction in brain capacity (Dobbing, 1968). During drip feeding the reduction in handling of the small infants lowers the risk of cross-infection, diminishes the loss of energy due to cooling, and saves valuable nursing time. Feeding the smallest infants is the most time-consuming task of the staff of a special care unit, producing considerable tension at times, especially when staff is depleted. There were no insuperable difficulties in managing this trial in spite of several changes in nursing staff. Our unit is staffed mainly by pupil midwives, as in many other district hospitals, and these methods have been dictated by necessity as well as providing better medical care.

COMPARISON OF MILKS

Although this trial was designed to determine the physical and biochemical safety of large volume intakes, the differences in weight gains between the different groups are of interest. The weight gains on human and SMA-S26 milk were similar throughout the trial period. In the first week for all patients the weight gain on half-cream Regal milk was significantly greater than on SMA-26 (Tables IV and V). The infants in the half-cream Regal group received the highest mineral load, and this may have been responsible for the larger weight gains in the first two weeks, although Davidson *et al.* (1967) showed that variations in the mineral content of feeds over a wide range had no effect on weight gains.

It has been traditional for many years to follow the dictum of Levine (Gordon *et al.*, 1947) that breast milk is inadequate for babies of low birth weight. Hence a valuable link between mother and infant in the early days is denied to many of these infants all over the world, with a grave risk of rejection or even child abuse. In our unit mothers are encouraged to provide breast milk for their infants and have been grateful for the satisfaction of feeling that they are playing a vital part in the care of their infants. In fact, there is a high incidence of established breast-feeding of babies of low birth weight in our unit.

The results of this trial show that human milk is an adequate food for infants of low birth weight provided that a sufficient daily intake is maintained. SMA-S26 has been shown to be a safe and satisfactory milk feed if breast milk is not available. How-

ever, our experience suggests that half-cream cows' milk preparations in these large volumes cannot be recommended unreservedly as a safe alternative.

We thank Miss M. A. Woodward, superintendent midwife, and Sisters J. Ryans and J. Burley, who were in charge of the special care unit and without whose valuable co-operation this study could not have been completed. We are indebted to Michael Curwen for advice on planning this study and to Mr. G. L. Draper of the department of social medicine, Oxford University, for help with the statistical analysis. We thank Dr. N. E. France for the postmortem examinations and Miss T. Cotgrove and Dr. B. Levin for the biochemical estimations. We are indebted to John Wyeth and Brother Ltd. for defraying part of the cost of the investigation.

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References

- Babson, S. G. (1970). *Journal of Pediatrics*, 77, 11.
- Bachra, B. N., Dauer, A., and Sobel, A. E. (1958). *Clinical Chemistry*, 4, 107.
- Bartrop, D., and Oppé, T. E. (1970). *Lancet*, 2, 1333.
- Buetow, K. C., and Klein, S. W. (1964). *Pediatrics*, 34, 163.
- Combes, M. A., and Pratt, E. L. (1961). *American Journal of Diseases of Children*, 102, 610.
- Cook, R. C. M., and Rickham, P. P. (1969). *Journal of Pediatric Surgery*, 4, 599.
- Daily, W. J. R., Klaus, M., and Meyer, H. B. P. (1969). *Pediatrics*, 43, 510.
- Davidson, M., Levine, S. Z., Bauer, C. H., and Dann, M. (1967). *Journal of Pediatrics*, 70, 695.
- Davies, P. A., and Russell, H. (1968). *Developmental Medicine and Child Neurology*, 10, 725.
- Day, R. L., Caliguiri, L., Kamenski, C., and Ehrlich, F. (1964). *Pediatrics*, 34, 171.
- Dobbing, J. (1968). In *Applied Neurochemistry*, ed. A. N. Davison and J. Dobbing, p. 287. London, Oxford University Press.
- Drillien, C. M. (1964). *Growth and Development of the Prematurely Born Infant*, p. 304. Edinburgh, Livingstone.
- Gordon, H. H., Levine, S. Z., and McNamara, H. (1947). *American Journal of Diseases of Children*, 73, 442.
- Gosset, I. H. (1960). *Lancet*, 1, 87.
- Gruenwald, F. M. (1966). *American Journal of Obstetrics and Gynecology*, 94, 1112.
- Hey, E. N., and Katz, G. (1970). *Archives of Disease in Childhood*, 45, 328.
- Laurence, B. M., and Smith, B. H. (1962). *Lancet*, 1, 589.
- Robinson, R. J. (1966). *Archives of Disease in Childhood*, 41, 437.
- Scopes, J. W., and Ahmed, I. (1966). *Archives of Disease in Childhood*, 41, 407.
- Smallpeice, V., and Davies, P. A. (1964). *Lancet*, 2, 1349.
- Valman, H. B., Brown, R. J. K., Palmer, T., Oberholzer, V. G., and Levin, B. (1971). *British Medical Journal*, 4, 789.
- Widdowson, E. M. (1969). *Journal of the Royal College of Physicians of London*, 3, 285.
- Young, W. F., Poyner-Wall, P., Humphreys, H. C., Finch, E., and Broadbent, I. (1950). *Archives of Disease in Childhood*, 25, 31.
- Ziegler, E. E., and Fomon, S. J. (1971). *Journal of Pediatrics*, 78, 561.

Crohn's Disease and Pregnancy

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British Medical Journal, 1972, 3, 550-553

Summary

This paper reports the outcome of 60 pregnancies in 40 women, all of whom had concomitant Crohn's disease. Detailed analysis of pregnancy rates in Crohn's disease supports in outline the hypothesis that some patients with bowel symptoms may be rendered temporarily subfertile by the activity of their bowel complaints. In contrast there is little or no evidence of any adverse

effect during pregnancy on mother or child. Most pregnancies went normally to term and, if anything, Crohn's disease tended to improve during the period of confinement.

After delivery, however, over 40% of patients suffered a relapse of Crohn's disease. Such a situation might well constitute a logical indication for the administration of corticosteroid therapy.

Introduction

Numerous authors have suggested that the occurrence of an inflammatory bowel disorder and pregnancy in the same patient carries an extremely unfavourable prognosis (Barnes and Hayes, 1931; Blair and Allen, 1962; Boreham and Saltau,

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1970; Heyworth *et al.*, 1970; Imrie, 1970; Schofield *et al.*, 1970). Indeed, patients with ulcerative colitis or Crohn's disease have on occasion been advised *not* to become pregnant in view of the apparent risks involved, while in other instances the presence of an inflammatory large-bowel disease has been cited as an indication for termination of an existing pregnancy. Some years ago we showed that in respect of ulcerative colitis such gloomy forebodings were quite unfounded (de Dombal *et al.*, 1965). In the present paper we examine the state of affairs in relation to Crohn's disease.

Patients and Method

The association between Crohn's disease and pregnancy was studied in all 332 patients seen and treated for Crohn's disease at the General Infirmary, Leeds, up to the beginning of 1969. The diagnosis of Crohn's disease was made during life in most cases on the basis of the histopathological criteria outlined by Morson (1968). All but five of the patients were traced and the survivors reviewed in 1969, the follow-up of this series being therefore just under 99% complete.

The vast majority of the surviving patients were reviewed by means of a personal interview in which a thorough review of the case notes was carried out in the presence of the patient. Where details were lacking in the recorded case histories they were amplified by the patient. Occasionally patients who could not attend for personal interview answered a detailed postal questionnaire instead. The results were transferred to specially designed forms, and thence to a small computer (Mathatronics Biostatistician 848) for further analysis.

Altogether some 171 female patients were eventually accepted into the survey. In many instances, however, Crohn's disease did not develop until after the child-bearing period of life, and such patients were excluded from the analysis. Also excluded from consideration was a smaller group of young patients who developed Crohn's disease while under the age of 15 and who up to the time of their review had neither married nor had the opportunity to bear children. This left a total of 86 women who developed Crohn's disease while still physically capable of bearing children and who had the opportunity to do so during the time covered by the survey.

Findings

OVERALL INCIDENCE OF PREGNANCY

Of the 86 women studied only 40 actually became pregnant during the survey period (the total number of pregnancies was 60 and the number of children conceived 61). The remaining 46 patients although married and apparently anxious to have children did not do so during the time of their follow-up by us. The fertility rates according to the site of Crohn's disease are shown in Table I. A higher proportion of patients with large-

TABLE I—Fertility Rates in the 86 Patients related to Site of Crohn's Disease

Site of Disease	Fertile		Subfertile		Total	
	No.	%	No.	%	No.	%
Large bowel	5	33.3	10	66.7	15	100.0
Small bowel	12	50.0	12	50.0	24	100.0
Large and small bowel ..	23	48.9	24	51.1	47	100.0
Total	40	46.5	46	53.5	86	100.0

bowel disease as opposed to small-bowel disease were apparently subfertile, but the difference was not statistically significant.

However, one interesting finding from the present series of patients was that *after surgery* the chance of a patient becoming pregnant in any given year (see Table II) is only marginally less than that of the general population. This is an important ob-

TABLE II—Fertility Rates before and after Surgery for Crohn's Disease

	Woman-years	No. of Pregnancies	qx/yr*
Time observed before surgery	599	27	0.045
Follow-up after surgery	463	33	0.071
Population of West Riding conurbation†	325,000	31,125	0.093

* Probability of pregnancy in any single given year.

† Females (aged 15-45 years) from Registrar General's figures for 1962.

servation, because it implies that women with Crohn's disease are rendered temporarily subfertile by the activity of their bowel disorder rather than infertile, as suggested by Fielding and Cooke (1970).

EFFECT OF CROHN'S DISEASE ON PREGNANCY

Two aspects of this situation were analysed. Firstly, we assessed the chance of bearing a live child (Table III). The results were reassuring in that 53 (88%) of the pregnancies resulted in the delivery of a live child (in one case in the delivery of healthy twins). There were three stillbirths and four abortions, although one abortion was performed therapeutically together with sterilization. The other aspect analysed was the incidence of abnormal births and complications of pregnancy. There were relatively few of these, and they are listed in Table IV.

TABLE III—Outcome of the 60 Pregnancies in Association with Crohn's Disease

	No.	%
Full-term normal delivery	53	88.3
Miscarriage 1st trimester	3	5.0
Stillbirth	3	5.0
Termination and sterilization	1	1.7
Total	60	100.0

TABLE IV—Complications in the 60 Pregnancies

	No.	%
Nil	53	88.3
Toxaemia*	2	3.4
Retained placenta	1	1.7
Placenta praevia	1	1.7
Breech delivery	1	1.7
Mongol child	1	1.7
Twins	1	1.7
Total	60	100.0

* One of these patients also developed tetany, and this pregnancy terminated in both maternal and fetal death.

EFFECT OF PREGNANCY ON CROHN'S DISEASE

The status of Crohn's disease at the time of conception in each instance is shown in Table V. Over half of the pregnancies (34; 56.7%) began at a time when the patient's bowel trouble

TABLE V—Status of Crohn's Disease at Conception in the 60 Pregnancies

	No.	%
Not begun	3	5.0
Present but inactive	34	56.7
Mild	14	23.3
Moderate	7	11.7
Severe	1	1.7
Unknown	1	1.7
Total	60	100.0

was inactive. This applied to patients both before surgery and after surgery. When one considers that in the former group only 20% of patient-years are spent in full remission of symptoms it is difficult to avoid the conclusion that active Crohn's disease managed conservatively militates against conception.

The overall effect of pregnancy on Crohn's disease is shown in Table VI. In the great majority of cases pregnancy made little difference to the activity of the patient's disease. Indeed, there was even a slight trend indicating that pregnancy is more often associated with an improvement in the patient's condition than with a relapse of symptoms (Table VII). Overall in some 33.3% of pregnancies the first trimester was marred by symptoms of

TABLE VI—Overall Effect of Pregnancy on Crohn's Disease in the 60 Pregnancies

	No.	%
No change	44	73.3
Improved	9	15.0
Relapsed	6	10.0
Unknown	1	1.7
Total	60	100.0

TABLE VII—Percentage of Patients with Active Disease in Each Trimester and in the Postpartum Period (60 Pregnancies)

	Medical Follow-up (27 Pregnancies)	Surgical Follow-up (33 Pregnancies)	Overall
Trimester { 1st	44.0	22.6	33.3
{ 2nd	29.2	20.0	24.1
{ 3rd	32.0	23.3	27.3
Postpartum	84.6	40.0	60.3

Crohn's disease, in 24.1% the second trimester, and in 27.3% the third. Table VII also indicates the figures separately for patients on conservative management alone and patients after surgery. The surgical group fared very much better, in keeping with our earlier findings (de Dombal *et al.*, 1971).

Both surprising and alarming was the proportion of patients with active disease in the three months after delivery (see Tables VII and VIII). Overall 40.0% of the patients experienced a relapse in symptoms after delivery; in the group on conservative management alone nearly 60% did so. This set of data parallels that which we earlier obtained for ulcerative colitis (de Dombal *et al.*, 1965).

TABLE VIII—Course of Crohn's Disease within Three Months after Delivery, as Percentage of Group Involved

	Before Surgery (27 Pregnancies)	After Surgery (33 Pregnancies)	Total (60 Pregnancies)
Relapse	59.3	24.2	40.0
No relapse	37.0	72.7	56.6
Unknown	—	3.0	1.7
Died	3.8	—	1.7

Discussion

An association between Crohn's disease and pregnancy has been reported on a number of occasions (Jones and Saltau, 1958; Blair and Allen, 1962), and there have been two large-scale reviews on the subject (Crohn *et al.*, 1956; Fielding and Cooke, 1970). Essentially this association of conditions poses three questions: (a) Does Crohn's disease predispose to subfertility? (b) Does Crohn's disease carry any particular dangers to mother and child? (c) What effect does pregnancy have on Crohn's disease?

On the second of these points Crohn *et al.* (1956) and Fielding and Cooke (1970) seem in complete agreement, concerning the lack of effect of Crohn's disease on mother and child. Our own data confirm their general impression that Crohn's disease has very little effect on the course of most pregnancies, in that the list of complications in Table IV is unremarkable and about 90% of all pregnancies went to term with the eventual delivery of a normal healthy child. This is about the national average, as reported by Baird (1950) and Howkins (1962).

One nagging doubt from our own series remains, however, and this concerns the fact that three pregnancies ended in still-birth after apparently proceeding normally into the third trimester. This is more than one might expect and must cause a

note of caution before one can agree unreservedly with the opinions from the New York and Birmingham reports. Even so, the added risk, if any, must be small—much smaller, for example, than that postulated by Heyworth *et al.* (1970) and Schofield *et al.* (1970)—and it seems clear that the vast majority of pregnancies in patients with Crohn's disease do proceed quite normally to term.

But are women with Crohn's disease subfertile? Here opinion is divided, for Crohn *et al.* (1956) concluded that fertility was not impaired by Crohn's disease, while Fielding and Cooke (1970) came to precisely the opposite conclusion. From our own data we are inclined to agree more with the latter point of view—that there is some impairment of fertility associated with Crohn's disease. Yet our findings are far less striking in this respect than those of Fielding and Cooke, and in particular we did not find the clear-cut difference between large-bowel and small-bowel disease these authors showed in the Birmingham series of cases.

Three other points emerge from the present data. Firstly, women tend to become pregnant while their Crohn's disease is in remission. Secondly, we were impressed by the fact that a number of these patients had been advised against pregnancy specifically on the ground of their Crohn's lesions; they were thus "infertile" because they were in practice taking contraceptive precautions. Finally, and most important of all, it appears that *after surgery* these patients became pregnant almost as often as other women in the population at large (see Table II).

Are contraceptive precautions justified? Here there is a major difficulty. Any assessment of the effect of pregnancy on Crohn's disease is valid only if the data concerning pregnant women are compared with data from patients who are *not* pregnant; and this both Crohn *et al.* (1956) and Fielding and Cooke (1970) failed to do. Furthermore, our own studies showed a pronounced difference in the symptomatic course before and after surgery, so that for any valid analysis to be made such cases must be considered in two separate groups.

The data in Tables V to VIII and those in the Chart show quite clearly that the patient with Crohn's disease does not face any major additional gastrointestinal risk during the period she is pregnant. Indeed if anything the symptoms are most likely to

Proportion of patients in each trimester and in postpartum period with active Crohn's disease. "Expected" proportions are calculated from analysis of data for females aged 15-45 years in a series of 332 patients (de Dombal, 1972).

improve during a pregnancy than to relapse. But after delivery relapse of bowel symptoms is common, confirming a trend indicated by Fielding and Cooke (1970). Indeed, on conservative management alone such a relapse is the rule rather than the exception.

MANAGEMENT OF PREGNANCY IN PATIENTS WITH CROHN'S DISEASE

From previous work and from the present study an overall pattern emerges which enables some broad recommendations to be made about the management of such patients. Firstly, one must expect a proportion of women with Crohn's disease to be subfertile, though experience indicates that this is more likely to be related to the activity of the bowel complaint than any permanent anatomical lesion. Next, patients who inquire about the dangers of pregnancy in Crohn's disease may be broadly reassured; and certainly there is no ground whatsoever for regarding Crohn's disease as an indication for termination of pregnancy or sterilization. During pregnancy itself one may expect that the symptoms of Crohn's disease will either remain static or even improve, though patients should be carefully followed up for at least three months after delivery, since a high proportion will experience a relapse of symptoms at this time.

As regards the details of such postpartum management the indications for surgery have been dealt with elsewhere but in the present context it is worth noting that this may be the one situation where steroids may be of value in the management of Crohn's disease. Following our earlier similar findings in a survey of 465 patients with ulcerative colitis (de Dombal *et al.*, 1965) we carried out a small-scale trial and were able to link in one or two cases a relapse of symptoms with a sharp drop in the

level of serum cortisol (de Dombal, 1966). It would thus seem logical to try the effects of systemic corticosteroid therapy in this comparable situation vis-à-vis Crohn's disease.

We are grateful to the physicians and surgeons of the Leeds General Infirmary for permission to study patients with Crohn's disease admitted under their care. One of us (I.L.B.) was supported by a grant from the board of governors of the United Leeds Hospitals, which we also acknowledge with gratitude.

References

- Baird, D. (1950). In *Combined Textbook of Obstetrics and Gynaecology for Students and Practitioners*. Edinburgh, Livingstone.
- Barnes, C. S., and Hayes, H. M. (1931). *American Journal of Obstetrics and Gynecology*, 22, 907.
- Blair, J. S. G., and Allen, N. (1962). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 69, 648.
- Boreham, P. F., and Saltau, D. H. K. (1970). *British Medical Journal*, 2, 541.
- Crohn, B. B., Yarnis, H., and Korelitz, B. I. (1956). *Gastroenterology*, 31, 615.
- de Dombal, F. T. (1966). Unpublished observations.
- de Dombal, F. T. (1972). Unpublished data.
- de Dombal, F. T., Watts, J. McK., Watkinson, G., and Goligher, J. C. (1965). *Lancet*, 2, 599.
- de Dombal, F. T., Burton, I. L., and Goligher, J. C. (1971). *British Journal of Surgery*, 58, 805.
- Fielding, J. F., and Cooke, W. T. (1970). *British Medical Journal*, 2, 76.
- Howkins, J. (1962). In *Shaw's Textbook of Gynaecology*, 8th ed. London, Churchill.
- Heyworth, B., Basu, S., and Clegg, J. (1970). *British Medical Journal*, 2, 364.
- Imrie, A. H. (1970). *British Medical Journal*, 2, 299.
- Jones, S. R. L., and Saltau, D. H. K. (1958). *Journal of Obstetrics and Gynaecology of the British Empire*, 65, 811.
- Morson, B. C. (1968). In *Ulcerative Colitis*, by J. C. Goligher, F. T. de Dombal, J. M. Watts, and G. Watkinson. London, Baillière Tindall and Cassell.
- Schofield, P. F., Turnbull, R. B., and Hawk, W. A. (1970). *British Medical Journal*, 2, 364.

Influenza and Infant Mortality

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British Medical Journal, 1972, 3, 553-556

Summary

Early neonatal mortality in England and Wales in the second quarter of 1970 after a major influenza epidemic was slightly but significantly higher than in the corresponding quarter of the previous year. An increase was also noted in the first quarter of 1970. Analysis of infant mortality and an index of influenza prevalence over the past quarter-century indicates that similar increases occurred in relation to four of the other five major influenza epidemics during the period, the exception being the "Asian 'flu" epidemic of the autumn of 1957. It is suggested that the increased mortality in 1970 was the consequence of an increase in the prematurity rate, but we have no evidence to indicate whether the effect is specifically due to the virus or is nonspecific in nature.

Introduction

In his annual report for 1970 the chief medical officer of the Department of Health and Social Security noted that infant

mortality had increased in comparison with the previous year; this was remarkable as only once previously, in 1951, had such an increase occurred in the past 25 years. As in 1951, it was the neonatal death rate that was most affected in 1970, and Sir George Godber pointed out that both 1951 and 1970 were years when a major epidemic of influenza had occurred. It had been suggested in the past that maternal influenza could give rise to congenital abnormalities but, he concluded, an association had not been clearly proved. Nevertheless, the coincidence linking the infant mortality rates of 1951 and 1970 merited further investigation (Department of Health and Social Security, 1971).

In this paper we analyse data for England and Wales derived from the Registrar General's annual reviews and quarterly returns. We also discuss mortality data from the official records of certain other countries and records of birth weight from a number of local health authorities.

England and Wales 1969 and 1970

Comparison of the infant mortality rates for 1969 and 1970 shows that only the early neonatal death rate increased in 1970, from 10.33 to 10.61 per 1,000 live births. The stillbirth rate and late neonatal and postneonatal death rates in 1970 were all lower than in the previous year. Furthermore, this increase in the early neonatal rate occurred predominantly in the second (June) quarter (from 9.88 per 1,000 live births in 1969 to 10.77 in 1970), although there was also a rise (from 10.26 per 1,000 to 10.56) in the rate for the first (March) quarter.

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