

## Crohn's disease and pregnancy.

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**SUMMARY** Infertility and the outcome of pregnancy has been examined in 112 married women with Crohn's disease who were below the age of 45 years. Fifty four patients were available for study. The infertility rate (12%) was similar to that seen in the general population. Patients who had active disease at the time of conception continued to have symptoms and they mostly failed to go into satisfactory remission despite therapy. Furthermore, there was a high rate (35%) of spontaneous abortion in this group. In contrast, patients whose disease was in remission at the time of conception had a normal pregnancy and, in the majority, the Crohn's disease remained quiescent.

Crohn's disease may begin in early adult life and therefore may coexist with the reproductive years of many of the women who develop the disease. It has been suggested in the past that the occurrence of Crohn's disease and pregnancy in the same patient carries an unfavourable prognosis and patients have at times been advised not to become pregnant because of the apparent risks involved.

This study reports the experience of patients with Crohn's disease attending the Gastroenterology Clinics at the Radcliffe Infirmary and subsequently at the John Radcliffe Hospital, Oxford, during a 20 year period 1962-1981. The design of the study was similar to that previously reported for ulcerative colitis<sup>1</sup> and four major questions have been asked. (1) Do patients with Crohn's disease have normal fertility? (2) Does Crohn's disease affect the outcome of the pregnancy? (3) Does pregnancy make the Crohn's disease worse? (4) Does medical treatment for Crohn's disease have serious side effects on the mother or the child?

### Methods

#### PATIENTS

During the period under survey, a total of 112 married women below the age of 45 years attended the Crohn's Disease Clinic at Oxford. Of these 112 patients, 58 were excluded for the following reasons: (1) The family was completed before the diagnosis of Crohn's disease (n=49); (2) Moved to another

country and could not be traced (n=3); (3) Had a hysterectomy before the onset of Crohn's disease (n=1); (4) Moved to another area and could not be traced (n=5). The remaining 54 patients were all personally interviewed in order to obtain details of their disease and their obstetrical history. These were obtained by using a standard set of questions in the presence of the complete case notes.

### Results

#### FERTILITY

Of the 54 patients interviewed, 44 had conceived and 10 had not. Of these 10, the infertility was voluntary in four patients (two patients did not wish to have a family, and the other two had been only recently married, and did not want children until later). The other six had involuntary infertility. Of these, four couples had been investigated and no cause of the infertility has been found. The site of the disease in these six patients was: small intestine 0; large intestine 2; small and large intestine 4. Thus the majority of patients had both small as well as large intestinal disease and there was no patient without colonic disease who was infertile.

Fourteen of the 54 patients had been advised at some stage in their lives not to have children because of Crohn's disease. In all cases the advice was given after they had at least one child, so that in this survey there was no patient who was childless as a result of being advised not to have children.

In six of these 14 patients, the advice against pregnancy was given by the patients' own doctor. In the remaining eight patients, hospital consultants had advised them not to have children, these

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consultants being seven physicians and one obstetrician.

#### EFFECT OF CROHN'S DISEASE ON PREGNANCY

During the 20 year period under review, there were 82 pregnancies among the 44 married women who had conceived.

Table 1 shows that in 80 completed pregnancies there were 56 normal live births. Among these, there were three babies of low birth weight (less than 2.5 kg), but they subsequently developed normally.

Two of the women were still pregnant at the end of the period of this study and in both the pregnancy was proceeding uneventfully. Only one child was abnormal at birth – he had congenital heart disease but is now doing well at school without any need for surgery. One child was born normally but then developed acute lymphoblastic leukaemia and died at the age of 18 months.

Spontaneous abortion occurred during 22 pregnancies. This was strongly biased, however, by one woman who had nine abortions. There was no apparent cause for these abortions and this patient was in long term remission as far as the Crohn's disease was concerned.

There was one stillbirth, for which no cause was found. There were no perinatal deaths, apart from this stillbirth.

If the pregnancies are analysed in more detail to take account of the state of the Crohn's disease at the time of conception, it is seen that of the six cases in whom conception occurred when the disease was severely active, spontaneous abortion occurred in three (Table 1). In 14 patients, conception occurred when the disease was mildly active, and of these there was one stillbirth and four spontaneous abortions. Overall, therefore, 20 patients conceived when the disease was active, and of these there were only 12 normal live births.

Fifty four patients conceived when the Crohn's disease was in remission, and there were 36 live births in this group, but as stated previously this was

biased by the woman who had had nine successive abortions.

One woman had the first attack of Crohn's disease in the first trimester of her pregnancy and had a normal delivery. Seven patients had the first attack of Crohn's disease in the puerperium. In all cases, the Crohn's disease followed the birth of normal babies.

#### EFFECT OF PREGNANCY ON THE CROHN'S DISEASE

This is probably best studied using the classification used by Abramson,<sup>2</sup> which was first used when assessing the effect of pregnancy on ulcerative colitis.

Patients are divided into four categories: (1) Patients with established Crohn's disease who were quiescent at the time of conception. (2) Patients with active Crohn's disease at the time of conception. (3) Patients who developed Crohn's disease for the first time during pregnancy. (4) Patients who developed Crohn's disease for the first time in the puerperium.

Table 2 shows the data from the patients classified in this way.

In 52 of the 80 completed pregnancies, conception occurred when the Crohn's disease was in remission. Of these 52 patients, 44 remained in remission during the pregnancy and puerperium. In the remaining eight patients relapse occurred, in seven in the first trimester and in the puerperium in one patient.

Overall, therefore, pregnancies conceived when the Crohn's disease was in remission were likely to stay in remission and when relapse occurred they were most likely to occur in the first trimester. In contrast with earlier reports, there was no increased likelihood of relapse in the puerperium.<sup>3</sup>

When pregnancy occurred in patients with active Crohn's disease, however, the outcome was less favourable. Twenty patients conceived when the Crohn's disease was clinically active and 13 of them remained in relapse or got worse as the pregnancy progressed. Once again, in contrast with earlier

Table 1 *Effect of Crohn's disease on the outcome of pregnancy*

	Normal	Congenital abnormality	Spontaneous abortion	Stillbirth	Still pregnant	Total
Mildly active at conception	9		4	1		14
Severely active at conception	3		3			6
First attack in pregnancy	1					1
First attack in puerperium	7					7
Crohn's disease in remission at conception	36	1	15*		2	54
Total	56	1	22	1	2	82

\* Nine of these occurred in a single patient

Table 2 *Effect of pregnancy on the course of Crohn's disease during the pregnancy*

State of Crohn's disease		Total
1 In remission at conception	Remission maintained	44
	Relapse: 1st trimester	7
	2nd trimester	52
	3rd trimester	
Puerperium	1	
2 Clinically active at conception	Remission	3
	Better	4
	Same	6
	Worse	5
	Worse in puerperium	2
3 First attack in pregnancy		1
4 First attack in puerperium		7
Total		80

reports, the chances of relapse were not increased in the period immediately after the delivery.

Only one patient had the first attack of Crohn's disease during the pregnancy: this occurred in the first trimester and the symptoms continued during the pregnancy. The result of the pregnancy was a normal delivery.

Seven patients had the initial attack of Crohn's disease in the puerperium. Of these, two had severe disease subsequently.

#### EFFECT OF MEDICAL TREATMENT

There were 52 patients whose disease was in remission at the time of conception. Table 3 shows the outcome of these pregnancies in relation to therapy with sulphasalazine. It can be seen that the abortion rate was less in the group on treatment but this difference can largely be explained by the one patient with nine abortions who was not on sulphasalazine.

The only congenital abnormality occurred in a patient who was not taking any maintenance therapy. The only case of pathological jaundice, defined as jaundice requiring medical treatment, occurred in a patient who was not on maintenance treatment.

Taking the patients whose Crohn's disease was clinically active at some stage during the pregnancy, the treatment that they received and the outcome of the pregnancy is shown in Table 4. Two babies were

jaundiced but this was mild, did not require medical treatment, and was considered to be physiological.

#### Discussion

The four questions mentioned in the Introduction can be answered to some extent by this study. These answers, however, must be assessed in the light of the fact that this is a retrospective study and the patient numbers are relatively small.

#### FERTILITY

Women with Crohn's disease have an infertility level slightly more than that of the general population. The overall rate of involuntary infertility was 12% compared with a rate of 10% for the general population.<sup>4</sup> The infertility rate in women with Crohn's disease, however, appears to be double that associated with ulcerative colitis.<sup>1</sup> Crohn<sup>5</sup> considered that fertility was not impaired by Crohn's disease. Subsequent reports have come to the opposite conclusion, however. Fielding and Cooke<sup>6</sup> reported that 25 out of 77 married women were infertile (33.4%). De Dombal *et al*<sup>3</sup> found that 53.5% of their married women were either infertile or subfertile.

In this study the incidence of infertility was much lower than in these previous studies. Probably the most important single reason for this was the exclusion of patients who were infertile because they were taking contraceptives. De Dombal *et al*<sup>3</sup> mentioned that a number of their patients who were said to be infertile were in fact on contraceptives, but these patients were not excluded from the analysis.

No patient without colonic disease was found to be infertile. This finding is similar to the other reports published.<sup>6</sup>

#### OUTCOME OF PREGNANCY

There were 56 normal live births in 80 completed pregnancies (70%). This is a lower percentage than in most previous series, their average rate being 84.7%.<sup>7</sup> The major reason for this is probably the bias introduced by the patient who had nine successive abortions. She accounted for just over 40% of the total number of abortions in the entire

Table 3 *Effect of sulphasalazine on the outcome of pregnancy in patients whose disease was in remission*

	Normal	Congenital abnormality	Abortion	Stillbirth	Pathological jaundice	Total
Maintenance therapy with sulphasalazine	11		3			14
No maintenance therapy	24	1	12	1		38

Table 4 Effect of sulphasalazine on the outcome of pregnancy in patients with active disease

	Normal	Congenital abnormality	Abortion	Stillbirth	Jaundice	Total
No treatment	5	0	4		1	10
Sulphasalazine only	6			1		7
Local steroids only	1		2			3
Oral steroids only	2					2
Sulphasalazine and steroids	4		1		1	6

study. Further analysis concerning the result of the pregnancy provided some encouraging results. There were only three babies of low birth weight (less than 2.5 kg), and these three then developed normally. This incidence of babies of low birth weight is similar to that occurring in the general population.<sup>8</sup> Moreover, there was only one stillbirth and one congenital abnormality in the series. This low incidence of congenital abnormalities has also been reported in previous studies.<sup>7</sup> Among the 20 patients who conceived when their Crohn's disease was active, there were 12 live births (60%). Of the 54 patients who conceived when their disease was in remission, there were 36 live births (67%). Once again there was a bias introduced because one patient who was in prolonged remission had nine successive abortions while she remained in remission.

Therefore there is the suggestion that women are more likely to have a normal live delivery if they conceive when their Crohn's disease is in remission, than if they do so when their Crohn's disease is active.

#### EFFECT OF PREGNANCY ON CROHN'S DISEASE

If the Crohn's disease is in remission at conception, it is likely to stay in remission during the pregnancy. Forty four out of 52 patients who conceived when in remission remained in remission during the pregnancy (84%). This compares well with the results obtained in all patients with inactive Crohn's disease. For example, in the National Cooperative Crohn's Disease Study,<sup>9</sup> about 80% of such patients remained in remission after a follow up of nine months.

Therefore if a woman conceives when the Crohn's disease is in remission, she is just as likely to stay in remission as a non-pregnant woman. If a relapse does occur it is most likely to occur in the first trimester. This pattern is similar to that seen in patients with ulcerative colitis.<sup>1</sup>

If the patient had clinically active Crohn's disease at the time of conception, she is likely to have continuing problems with the Crohn's disease during that pregnancy. Only seven out of 20 patients (35%)

who conceived when their Crohn's disease was clinically active went into remission or had even a slight improvement during that pregnancy.

Crohn's disease occurring for the first time in the puerperium was not found to be necessarily associated with a more severe course. In the present series, only two out of the seven patients whose disease started in the puerperium have subsequently had severe disease.

In contrast with previous reports,<sup>3,6</sup> this study found no evidence that Crohn's disease is likely to relapse during the puerperium. Therefore, these results support Fielding's contention<sup>7</sup> that corticosteroids should not be given during the puerperium as prophylaxis.

#### EFFECT OF TREATMENT

There was no maternal mortality in this series and there was no evidence that either mother or baby were harmed by sulphasalazine or corticosteroid therapy. It is not completely certain whether corticosteroids in pregnancy predispose to abortion or congenital abnormalities.

In this study the only patient who had a child with a congenital abnormality did not receive either sulphasalazine or corticosteroids during her pregnancy.

It is known that sulphasalazine and its main metabolites cross the placenta and therefore they could displace unconjugated bilirubin from binding sites on albumin.<sup>10</sup> There is thus a theoretical risk of causing kernicterus. In practice, however, this risk does not seem to occur. In this study, the only patient whose baby had a severe jaundice requiring treatment was not on sulphasalazine which conforms with experience of other studies.<sup>1,3,6</sup>

#### Conclusions

Patients who have active Crohn's disease should be advised not to conceive as their disease is likely to remain active during the pregnancy. For patients with inactive disease, however, there appears to be little risk to the course of the pregnancy or of the Crohn's disease itself. If patients require treatment

for Crohn's disease during pregnancy, both sulphasalazine and corticosteroids may be safely prescribed.

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