

The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire

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Abstract. The aims of the study were to ascertain whether patients have similar a fertility rate to the background population in Leicestershire and whether they have a similar rate of congenital malformations compared to the background population in Leicestershire. Over 1400 patients were invited to participate with an overall response rate of 81% after three successive mailings. The response rate was similar for both sexes and between the disease groups. The crude infertility rate for the group was 21%. The mean number of children for the whole group was 1.7 ± 1.3 but both men and women with Crohn's disease had significantly less children than would be expected, (men with Crohn's disease 1.5, women with Crohn's disease 1.2). There were 39 children (2% of overall births) with congenital abnormalities reported by patients with inflammatory bowel disease and in 29 cases the parents reported taking sulphasalazine (Table 3). Although this figure compares well with the 1.8% reported congenital abnormality rate for Leicestershire within the patient group in this study congenital malformations were significantly related to sulphasalazine use, $z = 4.3$, $P < 0.0001$. In conclusion sulphasalazine not only as causes morphological abnormalities in spermatozoa but may increase the chances of having congenitally abnormal offspring amongst men with IBD. The effects of other 5-aminosalicylic acids have yet to be studied in detail.

Résumé. Le but de cette étude est de déterminer si les patients ont un taux de fertilité identique à celui du reste de la population du Leicestershire et s'ils développent un taux de malformations congénitales identiques à celui du reste de la population. Mille quatre cents patients ont été invités à l'étude, ce qui a permis d'obtenir un taux global de réponse de 81% après 3 envois postaux successifs du questionnaire. Le taux de réponse est analogue pour les deux

sexes et les différents groupes de patients. Le taux d'infertilité brute pour le groupe de patients était de 21%. Le nombre d'enfants moyen pour l'ensemble du groupe était de $1,7 + 1,3$ mais à la fois les hommes et les femmes atteints de maladie de Crohn avaient un nombre d'enfants significativement moindre que celui attendu (chez les hommes porteurs de la maladie de Crohn 1,5 et chez les femmes atteintes de la maladie de Crohn 1,2). Dans le groupe de patients atteints de maladies inflammatoires, on relève 39 enfants (2% de l'ensemble des naissances) atteints d'anomalies congénitales; chez 29 de ces derniers, les parents avaient pris de la sulfate salazine (Table 3). Bien que ces données soient analogues au taux de 1,8% d'anomalies congénitales rapportées chez l'ensemble des patients du Leicestershire, le taux d'anomalies congénitales est significativement dépendant de la prise de sulfate salazine ($z = 4,3$, $P < 0,0001$). En conclusion, la sulfate salazine entraîne des anomalies morphologiques des spermatozoïdes mais peut également augmenter le risque d'anomalies congénitales chez les descendants de patients porteurs de maladies inflammatoires de l'intestin. Les effets d'autres dérivés d'acide 5-amino-salicylique doit faire l'objet d'études détaillées.

Crohn's disease and ulcerative colitis commonly affect young people during their reproductive years. Whilst many studies [1–5] have investigated fertility in women with CD and UC and to a lesser extent in men [6–8], few have examined large numbers of such patients from the same community exposed to similar medical and surgical practice.

Women with Crohn's disease are thought sub-fertile and at risk of an early menopause [1–3]. This may be due to a combination of disease activity, advice against pregnancy and reluctance by the women themselves because of fear of reactivating their disease. Abstinence or reduced sexual activity as a result of pain, fear on incontinence and diarrhoea are also likely to play some role [9]. In contrast women with ulcerative colitis are not thought infertile [4, 5].

Whilst reduced fertility in men with IBD is widely recognised it is believed secondary to sulphasalazine therapy [10–14]. Within weeks of treatment there is a reduction in the number of sperm and their motility together with the appearance of large numbers of abnormal sperm including megalosperm. Few investigators consider these men to have other causes for reduced fertility [6]. However, it is possible that these seminal abnormalities may put the foetus at increased risk of congenital abnormalities but this has been disputed [6, 13, 14].

Our study reports the experience of nearly 1200 male and female patients with IBD in Leicester over a twenty year period. These patients were identified during rigorous epidemiological studies which used international diagnostic criteria [17] for both diseases [15, 16]. The aims of the study were to ascertain whether (i) Patients have a similar fertility rate to the background population in Leicestershire, (ii) Patients experience a delay in conception, (iii) IBD has an adverse effect on pregnancy and (iv) Patients have similar rates of congenital malformations to the background population. Comparisons were made with the available data from Leicestershire through the 1991 OPCS statistics.

Control population: The number of children born to patients with inflammatory bowel disease was compared to the expected figures calculated from data available from the 1991 OPCS data for Leicester regarding fertility and numbers of congenital offspring. This is the only data available for Leicestershire, a case-control study was therefore not undertaken as it would have proved very difficult and was less likely to have been more accurate. The healthy wives of men with inflammatory bowel disease also acted as controls.

Methods

Patients

Nearly 2,500 patients with IBD were originally identified from the data base in 1989 [15, 16]. Some 400 of these were cases in the Indian migrant community. The data exist in the form of a cardex and are not computerised. All patients subsequently had their cases notes reviewed and clinical, endoscopic, radiological and histological reports were double checked against agreed international diagnostic criteria for both ulcerative colitis and Crohn's disease [17]. This data base includes patients with both small and large bowel Crohn's disease as well as all types of ulcerative colitis including proctitis. Asian patients were not included in the study because of their documented poor response rates of such studies [18]. Of the European patients 1743 were thought alive at the commencement of this study, but 304 had either moved away ($n = 126$), died ($n = 138$) or were uncontactable ($n = 40$).

Methods

A questionnaire investigating the fertility of patients with IBD was developed from a previously validated proforma for collecting information on sexual dysfunction in patients with IBD [9]. The questionnaire was piloted on committee members of a local self-help organisation and after minor modification was sent to 1439 patients with IBD.

The questionnaire

The questionnaire sought details of marital status, duration of marriage and age at diagnosis. Patients were requested to record the total number of pregnancies and not conception's which took longer than 12 months. Details about miscarriages, stillbirths and terminations were also collected. Patients were asked about caesarian section and forcep procedures they had undergone. Enquiry was also made about significant illness or abnormality in offspring. Details of sulphasalazine use in temporal relationship to pregnancy were collected. Disease site and activity were not examined in this study. An important element of the study was the comparison of fertility before and after diagnosis. This is an established approach to investigate the effect of gastrointestinal disease on fertility and pregnancy [1, 19, 20].

Analysis

Analysis took place after three successive mailings of the questionnaire using Lotus spreadsheets, Student's t -tests and χ^2 . 100 patients were approached again six months later to check the reliability of the questionnaire.

Results

Response rate

Of the 1159 questionnaires returned, 1108 were completed but 51 patients refused to participate, usually because of advanced age. The total sample comprised 472 men (42%) and 636 women (58%), 439 patients had Crohn's disease (CD) (40%) and 669 had ulcerative colitis (UC) (60%). The overall response rate was 81% after three successive mailings. The response rate was similar for both sexes and between disease groups.

Representativeness of replies

280 patients failed to return the questionnaire after three successive mailings. There were no apparent differences between responding and non-responding groups in age (mean age of non-responders = 54.4 ± 15.8 , mean age of responders 52.2 ± 16.2 , $t = 2$, ns), sex or disease distribution. A range of patients with a range of disease distribution, severity and activity responded to the questionnaire. The sample is representative of people with IBD in Leicestershire.

Repeatability

10% (100 patients) of the responder group were selected at random and asked to complete the same questionnaire again six months later. The results were identical to the first mailing and included three women, pregnant during the first survey, who had successfully completed their pregnancies.

Fertility

The number of male and female patients with CD and UC who responded are recorded in Table 1 together with total numbers of live births before and after diagnosis. There were 1933 completed pregnancies (90.7% of total recorded pregnancies). The crude infertility rate for the group was 21%, for men with CD it was 27% and men with UC 24%, 60% of the men who were infertile admitted to taking sulphasalazine, where infertility was defined as failure to achieve conception. Women with CD had an infertility rate of 19% and for women with UC it was 15%. The mean number of children for the whole group was 1.7 ± 1.3 and for those aged 45 and under at the time of diagnosis it was 1.6 ± 1.3 . For Leicestershire the fertility rate or average number of completed pregnancies is 1.9 (21), if applied to our group you would expect 2050 live births compared with the observed 1933. Both men and women with CD had significantly less children than expected, but this was not so for patients with UC (Table 1).

All patient groups had significantly more children before diagnosis than after, (male CD, $z=24.4$, $P<0.0001$, female CD, $z=8.4$, $P<0.0001$, male UC, $z=17.9$, $P<0.0001$ and female UC, $z=12.7$, $P<0.0001$). 167 (7.8%) pregnancies ended in miscarriage ($n=161$) or stillbirth ($n=6$) and 33 (1.5%) pregnancies were terminated.

208 (23.8%) couples experienced a delay of more than twelve months in achieving conception for one or more of their children. In 69% of cases this was after diagnosis of IBD. In 58 families this delay was repeated for more than one pregnancy. 42 of the 49 men with CD who experienced such a delay did so after diagnosis and over half (22) reported taking sulphasalazine. 15 of the 26 men with UC who also experienced a delay did so after diagnosis and 8 of these men with UC also reported taking sulphasalazine. 39 of 53 women with CD who experienced a delay in achieving conception again did so after diagnosis and 21 of these women with CD reported taking sulphasalazine. 61 of 80 women with UC who experienced a de-

Table 1. Total numbers of patients and live births before and after diagnosis

	Males			Females			Grand total All groups
	Total	CD	UC	Total	CD	UC	
Patients	472	317	155	636	284	352	1108
Births before diagnosis	724	391	333	678	284	456	1402
Births after diagnosis	194	108	86	337	115	222	531
Totals	918	499	419	1015	337	678	1933
TPFR ^a	1.9	1.5	2.7	1.6	1.2	1.9	1.7

^a Total period fertility rate = average number of children over study period.

All patient groups had significantly more children before diagnosis than after. In particular men and women with Crohn's disease had significantly less children than would be expected

lay did so after diagnosis and 32 of them reported taking sulphasalazine.

Outcome of pregnancy

Women with CD had more miscarriages than women with UC, ($\chi^2=3.9$, $P<0.05$), they also had more forcep procedures than women with UC, ($\chi^2=7.1$, $P<0.01$). There were no differences in numbers of terminations or caesarian sections between these two groups, ($\chi^2=2.7$, ns and $\chi^2=0$, ns, respectively) (see Table 2).

Comparing the healthy wives of men with IBD to women with IBD, women with CD had significantly more miscarriages than the wives of men with CD, ($\chi^2=26.1$, $P<0.0001$). There was no difference between women with UC and the wives of men with UC, ($\chi^2=1.5$, ns). Women with CD also had significantly more caesarian sections and forcep procedures than the healthy wives of men with CD, ($\chi^2=38$), $P<0.0001$ and $\chi^2=9.3$, $P<0.005$ respectively). Women with UC had similar numbers of both procedures to the wives of men with UC, ($\chi^2=3$, ns and $\chi^2=1.6$, ns, respectively). There were slightly more terminations amongst women with UC when compared with wives of men with UC, ($\chi^2=5.5$, $P<0.05$). There were no such differences in the two CD groups, $\chi^2=3.7$, ns.

133 parents reported a significant illness amongst their offspring which included 21 children with IBD, 12 with coeliac disease and 74 with atopy. 52 parents also reported a congenital abnormality in their children including; major congenital malformations incompatible with life ($n=5$), other congenital malformations ($n=25$) childhood leukaemia ($n=5$), cleft palate ($n=4$), and congenital heart disease ($n=5$). 39 of these abnormalities occurred after diagnosis and in 29 cases parents reported a history of taking sulphasalazine (SAS) (Table 3).

The percentage of births with a serious congenital malformation was 2% which is comparable to the 1.8% reported for Leicestershire, ($z=0.7$, ns) [26]. Congenital

Table 2. The outcome of pregnancy in women with IBD compared with the healthy wives of men with IBD

	Female CD	Female UC	Wives male CD	Wives female UC
Miscarriage (spontaneous)	49	66	20	32
Termination (medical)	13	12	5	3
Forceps delivery	56	67	18	29
Caesarian section	22	43	10	19
Total no ^o pregnancies	379	719	541	461

Women with Crohn's disease had more miscarriages, forceps procedures and caesarian sections than the wives of men with Crohn's disease, $\chi^2=26.1$, $P<0.0001$.

Table 3. The distribution of serious congenital malformations among men and women with IBD in Leicestershire

	Male CD	Male UC	Female CD	Female UC	Total
Congenital malformat ^a	7	10	8	14	39
Took SAS ^a	6	8	5	10	29
% of total births	1.5	2.4	2.4	2.1	2
z value ^b	2.7	2.7	1	2.7	4.3
P-value ^b	0.05	0.05	ns	0.01	0.0001

^a Sulphasalazine.

^b Comparing proportion of parents who had a child with a serious congenital malformation and took SAS with those who had a child with a congenital malformation but *did not* take SAS, $z=2.7$, $P<0.05$.

Men with IBD who took sulphasalazine were more likely to have a congenitally abnormal offspring than those who did not take sulphasalazine.

malformations were significantly more common amongst parents who had taken sulphasalazine when compared to parents who had a child with a congenital malformation and had not taken sulphasalazine, ($z=4.3$, $P<0.0001$) (see Table 3).

Discussion

The response rate of the study was over 80%, and is probably representative of people with IBD in Leicestershire. Results were not analysed controlling for site of disease as many investigators believe this to be unimportant in relation to fertility [2, 6]. In a European study of fertility of 275 women with Crohn's disease localisation of disease had no effect on numbers of children born [6] although a study from Oxford suggested that infertility was associated with large bowel disease, but the numbers this suggestion was based on were very small, $n=6$ [2].

Young men with IBD wishing to have families are still likely to be prescribed sulphasalazine as first line therapy until they complain of infertility. Almost 25% of men with either Crohn's disease or ulcerative colitis had no children in our study which is 15% higher than the national average [6]. This may be secondary to sulphasalazine treatment [10–14] as 60% of these men reported taking it.

Crohn's disease

This study confirms the reduced number of children born to men with Crohn's disease reported by Burnell et al. in 1986 [6]. In this study the fertility of 70 men with CD was compared with a group of age matched controls. Men with Crohn's disease had a mean of 1.6 children compared with a mean of 1.9 in the controls. In the same study no correlation was found with either sulphasalazine or steroid ther-

apy. Men with Crohn's disease also demonstrated a significant drop in the number of births after diagnosis, which is also comparable with the Burnell study [6] where they also identified a threefold reduction in births after diagnosis.

Men with Crohn's disease (16%) also complained of a delay in achieving conception which although well recorded in women with Crohn's disease has not been previously reported in men [1, 2, 9].

Women with Crohn's disease had less children than the background population in Leicester (1.2), they have a higher level of infertility (19.4%) and take longer to conceive their families (24%). These findings compare well with other reports including a large European study investigating fertility and pregnancy in 275 women with Crohn's disease in 5 different countries [1]. In this study there was a significant reduction in births to women with Crohn's disease after diagnosis and a high number of women who failed to become pregnant despite no contraception [1]. A study from Oxford contradicted these findings and concluded that there was only a 12% involuntary infertility rate in 54 married women with Crohn's disease [2]. However, this study excluded patients advised not to become pregnant and patients who reported they did not wish to have a family, both factors likely to be affected by re-call bias.

Women with Crohn's disease had more miscarriages and caesarian sections than women with ulcerative colitis. They also had more miscarriages, forceps procedures and caesarian sections than the wives of men with Crohn's disease. Several studies have also reported an increased number of both miscarriage and stillbirths [2, 22–24]. Khosla et al. demonstrated 22 spontaneous abortions among 82 pregnancies in 44 married women with Crohn's disease but these were strongly biased by one woman having 9 successive spontaneous abortions [2]. Others associate a higher spontaneous abortion and still birth rate with either site of disease [23, 25], severity of the disease during pregnancy or CD presenting during pregnancy for the first time [23, 25, 26]. Steroids have also been implicated as a cause for an increased risk of stillbirths among women with asthma and rheumatoid arthritis [27, 28] and increased abortion and stillbirth rates, reduced litter sizes and reduced DNA synthesis in mice [7]. However, reports are more favourable concerning women with IBD and no such associations has yet been demonstrated [1, 2, 4]. It is perhaps not surprising that a structurally destructive disease which can cause severe perianal problems should lead to an increased miscarriage rate and a need for assisted delivery.

Whilst many studies have reported on the frequency of abnormal babies born to patients with IBD these have usually concentrated on female alone [2, 7, 22]. The impression is that there is no increased risk of congenital abnormalities [2, 22] in women with Crohn's disease although some investigators believe severe, untreated disease can have adverse effects on foetal development [7, 22]. Sulphasalazine has not been shown to affect the development of the foetus in women [1, 2, 7, 22], however this report casts serious doubt on this view. Men with a congenitally abnormal child were significantly more likely to have taken sulphasalazine, as were women with ulcerative col-

itis. This is the first study to suggest that the effects of sulphasalazine on sperm may lead to congenital abnormality in children. These findings are tentative but give cause for concern and need confirmation in further studies.

Ulcerative colitis

Patients with ulcerative colitis had comparable numbers of children to the background population in Leicestershire [21, 29]. However, 15% of patients experienced a significant delay in achieving conception, 9% of men with ulcerative colitis and 23% of women. These particular variables have not been studied in depth by other authors it is generally believed the fertility of patients with ulcerative colitis is normal [4, 5, 7, 22]. Whilst the fertility rate is normal in our study colitis does appear to influence some aspects of conception in ulcerative colitis.

The outcome of pregnancy in 352 women with ulcerative colitis in this study compares favourably with other centres reports [4, 5]. Willoughby and Truelove investigated 147 women with UC and concluded the outcome of pregnancy was essentially normal and that disease activity had to be severe and uncontrolled for an unfavourable outcome [4].

Once again men with ulcerative colitis who had a congenitally abnormal child were significantly more likely to have taken sulphasalazine. This was also the case in women with ulcerative colitis. It is possible that sulphasalazine interferes with foetal development. It is known to cross the placenta [30, 31] and again a large study is needed to confirm these findings.

Conclusion

Many male patients are still taking sulphasalazine and experiencing problems with fertility. Men and women with Crohn's disease have significant problems related to fertility which cannot be explained by drug treatment alone. Patients with ulcerative colitis have an essentially normal fertility but can experience delays in conception and reduced potential for pregnancy after diagnosis.

Sulphasalazine causes morphological abnormalities in spermatozoa [11] and may increase the chances of men with IBD having congenitally abnormal offspring. The effects of other 5-aminosalicylic acids have yet to be studied in detail.

Patients in the reproductive years with IBD should no longer be described sulphasalazine as first line therapy. Its effects on spermatozoa together with its possible association with congenital malformations are cause for concern.

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