Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis

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BACKGROUND: Opinion remains divided as to whether finding endometriotic lesions in the absence of adhesions has an adverse effect on the likelihood of conception. METHODS: This was a retrospective study of 192 fully investigated infertile couples, followed up for up to 3 years following laparoscopy. Women studied were ovulating, <40 old years and their partners had normal sperm parameters. All 117 women with unexplained infertility and 75 with minimal/mild endometriosis without adhesive disease were managed conservatively. RESULTS: Women with endometriosis were found to have a lower probability of pregnancy compared with women with unexplained infertility (36% versus 55%; P < 0.05). Other factors adversely associated with pregnancy were primary infertility, smoking and longer duration (>3 years) of infertility. However, the effects of duration of infertility and primary infertility were not observed to be statistically significant for women with endometriosis. CONCLUSIONS: The findings, although undertaken in a select population undergoing laparoscopy, suggest the likelihood of pregnancy is reduced in infertile women with minimal/mild endometriosis compared with those infertile women with a normal pelvis. Duration of infertility and a previous history of pregnancy are important in predicting the likelihood of pregnancy in women with no obvious cause for their infertility (unexplained), whilst the relationship may be more complex in women with minor endometriosis.

Key words: endometriosis/inferility/laparoscopy/pregnancy/unexplained

Introduction

Differences in opinion exist as to whether minor endometriosis is associated with infertility (Mahmood and Templeton, 1989; Olive and Schwartz, 1993; Wardle and Hull, 1993; Thomas, 1995; Bergqvist and D’Hooghe, 2002). Even its presence as a disease entity has been questioned (Koninckx, 1994). In the absence of anatomical lesions preventing tubal or ovarian function in women with minimal/mild endometriosis (American Fertility Society, 1985), many women with these minor visible lesions, when infertile, have been labelled as having unexplained infertility (Hull et al., 1985; Ronnberg, 1990; Berube et al., 1998a).

The findings of a randomized controlled trial (Marcoux et al., 1997) showed improved natural conception rates following surgical treatment of visible endometriotic lesions. The findings suggest that the presence of visible minor lesions alone may have an adverse effect on natural conception; however, this was in contrast to the findings of another randomized trial that failed to show any significant benefit from surgery (Parazzini et al., 1999). Evidence from some IVF studies suggests less favourable outcomes in women with high-grade endometriosis (Arici et al., 1996; Azem et al., 1999; Barnhart et al., 2002). These data suggest an adverse further effect in the presence of endometriosis, notwithstanding circumventing natural conception with IVF treatment.

The undefined causes affecting fecundity in normal couples diagnosed as having subinfertility in the presence or absence (unexplained infertility) of endometriosis found at laparoscopy makes precise treatment difficult. If differences in these two groups of women (unexplained and minor endometriosis) are established, this may help distinguish the two groups as separate entities that may require different management approaches.

Two groups of infertile women were studied: those with unexplained infertility and those with endometriosis in the absence of any pelvic adhesions or ovarian cysts. The current study attempts to determine whether there are differences in the probabilities of natural conception between women with unexplained infertility and those with minimal/mild endometriosis, but otherwise unexplained infertility. Our hypothesis was that the probabilities of conception in these two groups would be similar, as shown by others (Berube et al., 1998). Pursuit of other plausible differences and confounders is important; we therefore controlled for the influence of
Variables known to affect the likelihood of conception over time such as the woman's age, duration of infertility, type of infertility (i.e. primary or secondary) and smoking.

Patients and methods

Local research ethics committee approval was obtained for the study. This was a retrospective study of infertile women who attended the Reproductive Medicine Clinic at St Michael's Hospital in Bristol between 1985 and 1995. The clinic is run as a subspecialty service dealing with infertile couples referred by General Practitioners in the Bristol area and tertiary care to couples referred by specialists in Bristol, the South West of England and parts of South Wales. All couples studied had a diagnostic laparoscopy for assessment of tubal patency, fibrosis, distortion or the presence of endometriosis or pelvic adhesions. If tubal patency was not confirmed at the time of laparoscopy, this was attempted by hysterosalpingography. Couples who had a distinct cause of infertility such as ovulatory dysfunction with no index of pelvic disease would not have had a routine laparoscopy, and some others conceived before laparoscopy was necessary or arranged. Although different clinicians carried out the laparoscopies over this period of time, each clinician employed the same technique because they were trained and supervised initially by one of two consultants (Professor M.G.R. Hull and Mr P.G. Wardle) prior to being allowed to assess the pelvis independently. All clinicians undertaking laparoscopy were accredited specialists or experienced senior trainees. Findings were recorded in a standardized way and no surgical therapy was undertaken to treat any endometriosis found at this time. Biopsies were not taken; therefore, the diagnosis of endometriosis required one or more lesions to be visually identified at laparoscopy as defined by the revised American Fertility Society classification for endometriosis (American Fertility Society, 1985). In women found to have endometriosis, only those with minor lesions referred to as minimal/mild endometriosis by the revised American Fertility Society classification were studied. To avoid any adverse influence of anatomical factors, women with adhesive disease or cysts were also excluded.

For the purposes of this study, women were included if menstruation in four of five spontaneous menstrual cycles had a duration of 21–35 days irrespective of cycle variability. Ovulation was investigated by estimation of serum progesterone concentration in the mid-luteal phase, which was retrospectively confirmed (by the patient ringing the clinic) to be within 5–10 days of the onset of menstruation. A progesterone level of 30 nmol/l (9.4 ng/ml) or greater was taken to indicate a normal ovulatory cycle, as previously established by the observation of untreated conception cycles (Hull et al., 1982b). Semen analysis was considered normal if the sperm concentration was ≥20 × 10^6/ml with normal motility ≥50% and normal morphology ≥30% (WHO, 1992). The post-coital test (PCT) was used as a screening test for coital and ejaculatory competence, mucus receptivity and sperm function. This test was carried out by instructing couples to have intercourse at mid-cycle, preferably when they recognized the typical pre-ovulatory mucus secretion, 6–18 h before the test, as described by Hull et al. (1982a). A PCT was considered favourable if one or more progressively motile sperm was seen per high power field.

The women with unexplained infertility satisfied the criteria of having a normal pelvis, partner’s normal sperm function and normal ovulatory cycles as described above. The women with endometriosis included in this study fulfilled the criteria as those with unexplained infertility, the only difference being the presence of minor endometriosis at laparoscopy. The factors explored in this study were history of previous pregnancy by the couple (primary or secondary infertility); duration of infertility and age of the woman at the time of laparoscopy; frequency of intercourse; and whether the woman was a smoker or not. All couples had a minimum of 1 year duration of infertility. The effect of duration of infertility was analysed in two ways: initially women were divided into four groups: <3, 3–3.9, 4–4.9 and ≥5 years of infertility; later they were dichotomized into groups of <3 years or ≥3 years of infertility, both at the time of laparoscopy. The frequency of intercourse was divided into women who had intercourse once or less a week and those who had intercourse twice or more a week. A woman was said to be a smoker if she admitted to any smoking at the time of initial consultation. The effect of age was analysed in two ways: the first one dividing women into three groups: <30, 30–34 and 35–39 years, and as a continuous variable (range 21–39 years). The duration of follow-up from laparoscopy was censored at 3 years and women who were 40 years or older were excluded from the analysis. However, women who were 40 years were included provided their laparoscopy was undertaken when they were under the age of 40 years. All women were managed expectantly as treatment of these conditions at the time was considered to be of doubtful benefit (Hull et al., 1985; Hull, 1992).

Following laparoscopy, a 3-year duration of follow-up was sought to assess fertility outcome. If the follow-up details of the woman were not available in her infertility records or if the duration of follow-up was shorter than 3 years, women were sent a questionnaire to obtain details on whether and when they conceived, and if they had any form of further treatment. For the patients who conceived, the time interval of interest was from the date of diagnostic laparoscopy to the last menstrual period before conception. For the patients who did not conceive, the time interval of interest was until the time of the last follow-up or correspondence with the patient. For analytical purposes, the patients who did not become pregnant were censored at this time. Pregnancy was defined by a positive pregnancy test and confirmed by the presence of an intra-uterine gestation sac by ultrasonography. A live birth was defined as a pregnancy known to go beyond the 24th week of pregnancy.

Statistical methods and analysis

Time to outcome may be affected by a number of factors. Analyses of these factors provide concomitant information that may improve the description and interpretation of the data. Although the (univariate) log rank test used in this study was useful for comparing time-to-pregnancy or live birth curves between two or more groups and taking into account
differences in follow-up times and drop outs, to allow adjustment for other factors (multivariate analysis), a series of Cox’s proportional hazards regression models (Cox, 1972) were used.

**Results**

Three hundred and twenty-six women with all grades of endometriosis were identified, of whom 92 women had minimal/mild endometriosis in the absence of adhesions or cysts. One hundred and forty-four couples with unexplained infertility were also identified following a normal laparoscopy. Of all these women with either minor endometriosis or unexplained infertility, those aged 40 years or more (at the time of laparoscopy; n = 18), those with partners with sperm dysfunction or incomplete data (n = 22) were excluded. Subsequent analysis is therefore based on 192 infertile women: 117 women with unexplained infertility and 75 infertile women with endometriosis. There were 52 and 43 drop-outs before the full 3 years of follow-up was completed for the unexplained and endometriosis groups, respectively (accounted for using Kaplan–Meier curves). The revised American Fertility Society classification (American Fertility Society, 1985) scores for the infertile women with endometriosis ranged from 1–10, with a median score of 4.

Both groups of infertile women had very similar characteristics (Table I). While there were no differences in the proportion of women having miscarriages or ectopic pregnancies in the two groups, univariate analysis using Kaplan–Meier curves revealed that infertile women with endometriosis had a lower chance of conceiving compared with women with unexplained infertility over a 3-year period (log rank test P = 0.048; Figure 1A; Table II). A similar, but non-significant (P = 0.105), trend was observed for live births (Figure 1B). Analysis of factors in relation to pregnancy and live birth rates are shown in Tables III and IV, but the focus in the following sections will be on probability of pregnancy, as this was the primary outcome we sought to evaluate.

For the 192 women overall, factors other than laparoscopic findings emerged as having statistically significant adverse effects on the likelihood of conception (Table III). These were a history of no previous pregnancy (primary infertility), prolonged duration of infertility (in particular 3 years or more) and a history of smoking. There was a trend of decreased chance of conception with increasing age, but neither this nor frequency of intercourse was significant in this analysis. The overall composition of the two groups of women were similar in respect of these other ‘risk’ factors (Table I), initially suggesting to us that controlling for these would not explain our observed group difference. Our preliminary multivariate analysis, however, using Cox proportional hazards models, suggested some statistical interaction between the diagnostic groups and other factors, i.e. the effects of some of the factors were different between the two groups.

To simplify the picture initially, we show in Table IV results of separate analyses carried out for the two diagnostic groups. The frequency of intercourse was omitted from all models since it was not significant throughout. Age was included here as a continuous variable and the duration of infertility was dichotomized into <3 or ≥3 years on the basis of our preliminary analysis. Risk ratios (RRs) and 95% confidence Intervals (CIs) are shown for binary variables; an RR <1 indicates a reduced chance of pregnancy/live birth. Primary infertility was statistically significant only for unexplained infertility (Table IV). Although for both groups of infertile couples those with a prolonged (≥3 years) duration of infertility fared worse, the effect was less marked and not significant for those with endometriosis. The woman’s age was not found to be a significant determinant in endometriosis, but was significant for unexplained infertility; outcome was poorer with increasing age. While only 26% of women were smokers, this was confirmed to be a significant factor in reducing the chance of pregnancy in both groups.

In view of possible interactions, it was necessary to compare the outcomes for the two groups when different factors were operating within them. For example, women with unexplained infertility fared better as a whole; however, their outcome was worse if they had primary infertility and were older. As such, analysis of whether older women with primary infertility still fare better than those with endometriosis was required. In general if the interaction is significant, the main effects of the variables do not have a simple interpretation, because the effect of each depends on the level of the other variable. However, if interaction is not significant it is best to remove it from the model.

<table>
<thead>
<tr>
<th>Table I. Clinical characteristics of untreated infertile women studied</th>
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<td>---------------------------------------------</td>
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<tr>
<td>Median age at laparoscopy [years (range)]</td>
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<tr>
<td>Median duration of infertility [years (range)]</td>
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<tr>
<td>Primary (couple) infertility [n (%)]</td>
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<tr>
<td>Primary (male) infertility [n (%)]</td>
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<tr>
<td>Primary (female) infertility [n (%)]</td>
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<tr>
<td>Intercourse &lt;2 per week [n (%)]</td>
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<tr>
<td>Smokers [n (%)]</td>
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aMann-Whitney U-test.
bContinuity-corrected χ²-test.

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To address this, we fitted Cox models (Cox, 1972) to all 192 cases that allowed for differences between the two diagnostic groups and interactions between the group difference and all the other factors. Interactions with duration and smoking were found to be non-significant and were removed, in a backward-stepwise manner, from models, pregnancy and live birth (minimum \(P = 0.191\)). The interactions with couples’ infertility (arising because the effect of primary infertility was more marked in the group with unexplained infertility) were retained (\(P = 0.032\) and \(P = 0.056\), respectively, for pregnancy and live birth). The age interaction was similarly retained despite being non-significant (\(P = 0.129\) and \(P = 0.122\), respectively) since the age coefficients were so different for the separate groups (Table IV).

In the combined models, smoking was associated with a significantly reduced chance of pregnancy and live birth [Table V (A)]. Prolonged duration of infertility of \(\geq 3\) years was similarly associated with a reduced chance of pregnancy/live birth. The effect of primary infertility was significant only for unexplained infertility for both pregnancy and live births (Table V; \(P < 0.001\)), but not for endometriosis (\(P = 0.621\) and \(P = 0.690\), respectively; comparisons are not shown in Table V). For unexplained infertility, the estimated coefficients for age in relation to pregnancy and live birth \([-0.083 (SEM 0.036), P = 0.021\]; and \(-0.109 (SEM 0.039), P = 0.006\), respectively\), suggested that across these women, the chances of pregnancy and live birth fell overall by \(~56\%~\) and \(~66\%~\) per 10 years increase of age. The coefficients for endometriosis were not significant \([0.035 (SEM 0.069), P = 0.605; and 0.019 (SEM 0.072), P = 0.789\), respectively\]. This suggested the relationship with age was different for the two groups. But the interaction suggested by the data in Table IV was, however, not found to be statistically significant. To reconcile this, we chose to ignore the latter on the basis that the test for interaction,
which is a test for a difference between the two slopes, is generally more difficult. In the same analysis, Table V (B) shows model-estimated RRs according to diagnostic group (unexplained/endometriosis) and primary/secondary infertility, calculated at two arbitrary ages: the median/mean age of this cohort (31 years) and the maximum age (39 years). All the results shown adjust for effects of smoking and duration of infertility. At age 31 years, couples with unexplained and secondary infertility (the reference category) fared best. Subjects with endometriosis did worse, even if they had secondary infertility. By the age of 39 years, however, any advantage of unexplained, secondary infertility over endometriosis was lost.

**Discussion**

The findings of the present study suggest that infertile women with minor endometriosis have a reduced chance of natural conception compared with those with otherwise unexplained infertility. The groups studied represent women not with
infertility, but with varying degrees of involuntary subfertility, particularly as all investigations were normal apart from those with the finding of visible minor lesions of endometriosis. Nonetheless, these women are recognized to have a reduced monthly probability of conception (fecundity) in view of their duration of infertility being at least 1 year. This study, unlike previous ones, explores putative associations with regards to the likelihood of conception and controls for biologically plausible confounding factors. All women studied were managed expectantly, in other words did not have surgical or medical treatment at the time of their laparoscopy because such treatment was considered to be of doubtful benefit (Hull et al., 1985; Hull, 1992). This practice has since been reconsidered in light of recent publications (Marcoux et al., 1997; Parazzini et al., 1999), but was not addressed in the present study.

While other studies have also shown that infertile women with endometriosis have lower fecundity compared with women with unexplained infertility (Collins et al., 1983; 1984a, 1995; Snick et al., 1997), they were based on all severity grades of endometriosis. Although one of these studies (Collins et al., 1995) distinguished women with mild forms of endometriosis, only crude estimates of pregnancy were provided. One of the other studies (Snick et al., 1997) also studied women managed conservatively. These authors observed the highest probability of pregnancy in women with unexplained infertility, which was higher than that observed in the present study. This perhaps reflects differences in the study populations with regards to duration of infertility and the fact that follow-up in the present study started from laparoscopy, and not from registration as in the other study (Snick et al., 1997).

Fecundity rates in women with minimal or mild endometriosis and unexplained infertility were compared by the Canadian Collaborative Group on endometriosis (Berube et al., 1998a). In that study fecundity rates were lower in women with endometriosis but did not reach statistical significance. Their study, however, included women with adhesions and excluded those with non pigmented red or vesicular lesions, which may account for the differences found in our study, as may the short duration of follow up of only 6 months employed in their study compared with our attempted 3 years of follow-up. There was a high drop-out rate before completion of 3 years follow-up. This was particularly proportionally higher in the endometriosis group and could have accounted for the lower probability of pregnancies observed in this group, despite our attempts to account for this using survival methods of analysis with Kaplan–Meier curves.

It is also possible that the criteria used by the Canadian study (Berube et al., 1998) for the diagnosis of sperm dysfunction did not exclude all men with male factor infertility, because it was based on motile counts only. In order to exclude subtle male factor infertility, the present study was restricted to couples in whom standard infertility investigations, including PCTs, exposed no apparent factors that were responsible for their subfertility. PCTs are prognostic indicators for the likelihood of pregnancy (Hull et al., 1982a; Snick et al., 1997; Glazener et al., 2000). Our findings, however, are corroborated by the findings of a study of similar women undergoing ovulation induction and artificial insemination (Omland et al., 1998). In that study pregnancy rates were also reduced in women with minor endometriosis, and could reflect differences in pathogenesis and aetiology for the two groups (Omland et al., 1998). While the probability of pregnancy was the primary outcome, the probability of live birth was studied as well. Examination of the time-to-live-birth curves (Figure 1) reveals divergence between unexplained infertility and endometriosis, which mirrors that of pregnancy. Nonetheless, this was a non-significant finding, but may reflect the fact that other factors affect outcome of pregnancy and determine whether live birth, miscarriage or ectopic pregnancy occurs. Because of the lower number of live births compared with pregnancies, the study may have been underpowered to account for this.

The results of investigation in the couples studied were normal; as such, the present study is limited in trying to attribute a cause to their subfertility and can only explore associations. Although the two groups studied were very similar, the independent relationships of these characteristics to the chance of pregnancy were explored. A woman’s age is recognized as an important factor affecting fertility (Collins et al., 1995; Akande et al., 2002), especially when infertility is

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Pregnancy [RR (95% CI)]</th>
<th>P-value</th>
<th>Live birth [RR (95% CI)]</th>
<th>P-value</th>
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<tr>
<td>(A)</td>
<td></td>
<td></td>
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<tr>
<td>Duration of infertility</td>
<td>&lt;3years*</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>≥3years</td>
<td>0.35 (0.21–0.59)</td>
<td>&lt;0.001</td>
<td>0.36 (0.20–0.63)</td>
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<td>Smokers</td>
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<td>0.27 (0.12–0.60)</td>
<td>0.32 (0.14–0.73)</td>
<td>0.32 (0.14–0.73)</td>
<td>0.591</td>
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<tr>
<td>(B)</td>
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<td>Unexplained</td>
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<td>0.001</td>
<td>1</td>
<td>&lt;0.001</td>
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<td>Primary infertility</td>
<td>0.22 (0.12–0.42)</td>
<td>&lt;0.001</td>
<td>0.24 (0.12–0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometriosis (at median age 31 years)</td>
<td>Secondary infertility</td>
<td>0.26 (0.11–0.62)</td>
<td>0.002</td>
<td>0.29 (0.11–0.74)</td>
<td>0.009</td>
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<td>Primary infertility</td>
<td>0.21 (0.10–0.43)</td>
<td>&lt;0.001</td>
<td>0.24 (0.11–0.51)</td>
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<td>Endometriosis (at maximum age 39 years)</td>
<td>Secondary infertility</td>
<td>0.68 (0.16–2.88)</td>
<td>0.599</td>
<td>0.81 (0.17–3.90)</td>
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<td>0.53 (0.13–2.20)</td>
<td>0.385</td>
<td>0.66 (0.14–3.05)</td>
<td>0.591</td>
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</tbody>
</table>

*Reference categories.
unexplained (Collins and Rowe, 1989), as was found in the present study. This may imply that although the majority of these women were young (mean age 31 years), there may be an enhanced decline in fecundability in this group of women. However, the decline with age was not present amongst women with endometriosis, an observation that is difficult to explain, but which may reflect the fact that only younger women (<40 years), who are known to have a better chance of conception, were studied. Furthermore, the usual distinction of couples with secondary infertility having a more favourable prognosis (Collins et al., 1984a) was not found to be the case amongst women with endometriosis in the current study, thus implying some other unaccounted adverse influence on fecundity in these women, perhaps related to the presence of lesions. These findings also imply that the relationship with age was different for the two groups.

Current theories for diminished fertility in women with minor endometriosis have been explored by our group and are likely to include oocyte dysfunction or the surrounding milieu being suboptimal (Akande et al., 2000; Cahill, 2002; Trinder and Cahill, 2002). The findings also confirm those of our previous studies using the IVF model in both natural (Cahill et al., 1995) and stimulated (Hull et al., 1998) cycles. Further evidence of poor oocyte quality, and thus reduced implanting ability of embryos, is strengthened by studies showing no adverse effect on implantation rates in women with endometriosis using donated oocytes (Sung et al., 1997), and recipients of oocytes from donors with endometriosis may result in lower implantation rates (Garrido et al., 2002). The present study’s findings are further corroborated by recent evidence of reduced conception rates in women with endometriosis as shown by a meta-analysis examining studies using the in vitro model (Barnhart et al., 2002).

Given that human beings are inefficient reproducers, the chance of natural conception depends in part on adequate exposure to cycles in which this is likely to occur (Evers, 2002). The present study showed that with 3 years or more of infertility the likelihood of conception was much reduced, adjusting for and irrespective of the woman’s age. In such couples there would seem to be a real but unidentified cause of infertility. However, contrary to published data (Collins et al., 1984b; Hull et al., 1985; Hull, 1992), the effect of prolonged duration of infertility in women with minor endometriosis was less than that observed in women with unexplained infertility, and was not significant. These findings are also difficult to explain, but may suggest that the effect of duration of infertility is dependent on the cause, or that the presence of the endometriotic lesions is a sign of an underlying factor that adversely affects fertility. Therefore, a hypothesis could be proposed that ‘in clearly defined causes of infertility the chance of pregnancy would be unrelated to duration of infertility’. This remains to be tested. Another explanation may be that in these women endometriosis worsens with time, further reducing their monthly fecundity. This would only apply if fecundity is related to endometriosis in a dose–response manner.

Previous suggestions that prolonged duration of infertility itself may be a precursor of endometriosis in the absence of other causes (Pepperell and McBain, 1985; Moen, 1991) was not supported by the findings of the present study, nor the findings in another case–control study (Berube et al., 1998b). It is not possible, however, to discount the possibility that women with unexplained infertility may actually have atypical or subtle endometriotic lesions (Nisolle et al., 1990), which may be associated with an adverse effect on fertility. This does not diminish the observation in the present study of the unfavourable effect on fertility found in women with visual endometriotic lesions. The present study was on a selective infertile population therefore may not apply to all normal women with minor endometriosis. This warrants further study, as does the concept of localized pelvic endometriotic lesions being a cause rather than the effect of a systemic process. Until more data show direct evidence that the endometrial implants alone alter reproductive ability, the issue will remain controversial (Haney, 1993).

The relationship between endometriosis and infertility is unclear. This study in women undergoing laparoscopy suggests, however, that minor endometriosis may be associated with a reduction in fertility. A causal effect was not explored and can only be addressed by basic scientific research. In this study, the duration of a couple’s infertility and secondary infertility were of less importance in determining likelihood of pregnancy for infertile couples with endometriosis, but the relationship with age was more complex.

Acknowledgements

We would like to acknowledge the contribution of the late Professor M.G.R.Hull during the initiation of this study, who sadly was not able to see it to completion due to his untimely death.

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Submitted on January 9, 2003; resubmitted on August 22, 2003; accepted on September 16, 2003.