Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity?

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BACKGROUND: The effects of contraception on subsequent fecundity are yet to be substantiated. METHODS: A total of 2841 consecutive pregnant women in Hull and Sheffield completed questionnaires inquiring about time to pregnancy (TTP), contraceptive use, pregnancy planning, previous pregnancies, age and lifestyle characteristics of each partner. Outcome measures were mean TTP, conception probability and odds of subfecundity after discontinuing each contraceptive method. RESULTS: TTP following long-term combined oral contraceptive (COC), short-term intrauterine device (IUD) or any duration of injectable use were 2.0-, 1.6-, 3.0-fold longer than TTP after condom use, respectively. Within 6 months of discontinuing COC or injectable use, conception probabilities were 0.86 and 0.34, respectively, whereas those relevant to other methods were not significantly different. All levonorgestrel intrauterine system (IUS) users conceived within 1 month. Relative to condoms, odds of subfecundity after COC, injectable and short-term IUD use were 1.9, 5.5, 2.9, respectively. The effect of COC and injectables was stronger with long-term use, in older, obese or oligomenorrhoeic women. Similar results were obtained after adjustment for potential confounders. CONCLUSIONS: A significant reduction in fecundity occurs after COC, IUD or injectables, which is dependent on the duration of use. The effect of COC and injectables is evident in women with a potentially compromised ovarian function. Use of progesterone-only pills or IUS is not associated with a significant effect.

Key words: contraception/fecundity/fertility/lifestyle/time to pregnancy

Introduction

In general, the majority of couples desire to have children, though many delay this stage until they have established themselves in a relationship and a career (Chen and Morgan, 1991; Martin, 2000). To embark on many years of contraception, not knowing what effect this can have on the ability to conceive can cause concern. Young women may approach contraception with an ambivalent attitude because of this underlying desire to guarantee and prove their fertility (Trussell et al., 1999). Also for those using contraception to space their pregnancies, the impact on later fertility is a key determinant of their contraceptive behaviour and represents an essential part of the contraceptive counselling.

A huge literature on the efficacy and safety of various contraceptive methods already exists (Vessey et al., 1982; Hannaford and Kay, 1998; World Health Organization Scientific Group, 1998; Beral et al., 1999; Hannaford, 2000) while the effects of the modern and new methods on subsequent fertility are yet to be substantiated. Such effects may be viewed as a spectrum extending from contraceptive failure to impaired fertility. Contraceptive failure may reflect a high fecundity of the couple or a reduced efficacy of the contraceptive method or may reflect the couples’ inadequate contraceptive knowledge, their fear of side-effects or their belief that they are less fecund to the extent of using unreliable methods for contraception or using effective methods inconsistently (Milsom et al., 1991; Jones and Forrest, 1992; Baird et al., 1994; Rosenberg et al., 1995; Olsen et al., 1998; Peterson et al., 1998; Ranjit et al., 2001). On the other hand, while the immediate return of fertility after discontinuing barrier contraception is to be expected, the effect of hormonal contraception and of the intrauterine contraceptive devices, which have multiple contraceptive effects, on future fertility is less certain (Whitelaw, 1967; Vessey et al., 1978). In addition, the effect of all the methods on future fertility may be compounded by other factors such as the individual and lifestyle characteristics of the couples.

This study aimed to evaluate the impact of each of the commonly used contraceptive methods on subsequent fecundity as measured by the time to pregnancy (TTP) and the conception rates for users of each method after discontinuing contraception, before and after adjustment for the effects of the
individual and lifestyle factors. The effect of the duration of contraceptive use, overall and for the individual methods, was also evaluated.

Materials and methods
A survey was conducted in Hull and East Yorkshire and Sheffield. Consecutive women attending the antenatal clinics were asked to self-complete a questionnaire inquiring about their TTP (the interval of exposure to unprotected intercourse from discontinuing all birth control methods till conception), contraceptive use (methods, duration and behaviour), pregnancy planning, previous subfertility, pregnancies, gynaecological disease and surgery. Other questions included the individual and lifestyle characteristics of either partner such as age, weight, height, smoking, alcohol consumption, coffee/tea intake, recreational drug use and coital frequency. The postcode linked to the questionnaires was used as an indicator of living standard (Sloggett and Joshi, 1998; Noble et al., 2000).

The questionnaire was validated in a way similar to that used for earlier questionnaires (Hassan and Killick, 2003a,b; Hassan and Killick, 2004). An independent assessor interviewed women in the clinic after self-completing the questionnaire to ensure that they had understood exactly what information was required from each question. Another group was asked to complete the questionnaire on two occasions, 2 weeks apart, to ensure that their answers were consistent. Approval was obtained from the Local Research Ethics Committees in both centres. No conflicts of interest existed. The response rate (ratio of returned questionnaires to the distributed ones) was >98% and the sample included 2841 completed questionnaires.

Data analysis was carried out using SPSS (Statistical Package for Social Sciences). The outcome measures were the mean TTP, conception rate (CR) and odds ratio (OR) of subfecundity (TTP >12 months) after discontinuing each contraceptive method compared with that after condom use, overall and in relation to duration of use. The effect of contraceptive duration on subsequent TTP for each method was studied. CR in 6, 12 and 24 months after discontinuing each method and the OR of subfecundity relative to condom use were calculated, overall and for short and long-term use. Regression analysis was used to adjust for potential confounders (e.g. both partner’s age, weight, smoking and alcohol consumption, tea/coffee intake and recreational drug use as well as parity, coital frequency, menstrual pattern and age at menarche).

Results
Of the 2841 women in the study, 183 did not report TTP and 389 suffered contraceptive failures. Of the remaining 2269 women, 1460 (64.3%) conceived in 6 months rising to 1780 (78.4%) by the end of the first year, and 489 couples (21.6%) were subfecund. The combined oral contraceptive pill (COC) was the most frequently used method (COC alone: 40.7%, dual method: 14.5%), then condom 18.7%, progestosterone-only pills (POP) 4.6%, intrauterine device (IUD) 3.1%, injectables 3.0%, levonorgestrel intrauterine system (IUS) 0.7%, implant 0.2%, while 13.7% denied using contraception. The mean contraceptive duration was 43.5 months overall, but COC and POP use was significantly longer than the injectables, IUD or condoms use. The duration varied from <12 months (31.4%), 1–2 years (19.9%), 2–4 years (19.6%) to >4 years (29.1%).

Two-thirds of IUD, condom, injectables, IUS and implant use was short term whereas 60% of COC use was >2 years. There were significant differences in the individual and lifestyle characteristics of women and partners by the used contraceptive method (Table I). Mean TTP after stopping contraception was found to vary significantly with the preceding contraceptive method and its duration of use. These effects remained significant after adjustment for the effects of potential confounders. Compared with condom use, TTP after discontinuing COC use was 1.7-fold longer, that after IUD removal was 1.6-fold longer, whereas TTP of former injectable users was 3.0-fold longer (adjusted values: 2.0–2.2–3.9-fold respectively) (Table II). Implant users (n = 4) had TTP 2.6-fold longer than TTP of
condom users. All IUS users (n = 13) conceived within 1 month after removal but after adjustment this was not significantly different compared with condom use. TTP after stopping POP use was not significantly different than that after condom use, regardless of the duration of use. Those who denied using contraception had TTP 5-fold longer than TTP of condom users (Table II). Compared with condom use, the effect of COC on TTP was more evident with long-term use (2.0-fold), IUD effect was limited to short-term use (1.6-fold), implant effect was restricted to short-term use (3.4-fold) and that of the injectables was significant with short- and long-term use (2.4, 4.0-fold) (adjusted values: 2.7, 1.6, 3.0, 2.0 and 6.0 respectively) (Table III).

There was a significant progressive increase in subsequent TTP with increasing duration of previous contraceptive use [mean TTP (CI): 4.6 (3.9–5.3), 5.6 (5.0–6.1), 6.9 (5.9–8.0) and 9.2 (8.0–10.3) months after contraceptive use for <1, 1–2, 2–4 and >4 years respectively]. The effect of contraceptive duration on subsequent TTP was found to be significant only with COC or injectable use (Figure 1B and E) and their effects remained significant after adjustment for potential confounders. The effect of duration of IUD use on subsequent TTP was not significant overall, but its use for <1 year was associated with a significantly longer TTP compared with longer-term use (Figure 1D). TTP after long-term condom or POP use was not significantly different from that after short-term use. All IUS users (n = 13) conceived within 1 month of removal regardless of the duration of use (Figure 1A, C and F).

Within 6 months of stopping contraception, the CR were 81.5% after condom use, 70.1% after COC, 73.7% after POP,
76.8% after IUD, down to 27.4% after the injectables, whereas only 25% of implant users (n = 4) had conceived. Within 12 months, the CR increased to 91.3, 83.8, 94.7, 87.8, 51.6 and 50.0% respectively (Figure 2). Compared with condom use, the relative probability of conception in 6 and 12 months respectively decreased to 0.86 (0.8–0.9) and 0.92 (0.9–0.96) after discontinuing COC use, and 0.34 (0.2–0.5) and 0.57 (0.4–0.7) after stopping the injectables (P < 0.001, each). In all, 6.5 and 9.7% of previous COC and injectable users took >2 years to conceive compared with 2.6% of condom users [OR = 2.5 (1.3–4.9) and 3.8 (1.4–10.0), P = 0.003 and 0.01]. While probabilities of conception after stopping POP, IUD or implants were not significantly different.

Odds of subfecundity after stopping contraception varied with the contraceptive method and duration of use. Relative to condom use, OR of subfecundity after discontinuing COC, injectable and implant use were 1.9 (1.3–2.6), 5.5 (3.7–8.4) and 5.7 (2.0–16.0) respectively (adjusted values: 2.8, 15.4 and 9.3) (Table IV). Considering the duration of use, the effect of COC was limited to long-term use [OR = 1.9 (1.1–3.5)], implant effect was limited to short-term use [OR = 13.3 (4.9–36.3)] and injectables effect was significant with short- and long-term use [OR = 6.2 (2.7–14.2) and 6.7 (3.5–12.6)] (adjusted values in order: 3.9, 41.9, 8.1, 52.8) (Table V). The effect of IUD use was not significant overall but short-term users were 2.9-fold (1.1–7.6) more likely to be subfecund relative to condom users (adjusted 4.4) whereas none of the long-term users (n = 26) was subfecund (Table V). POP users were not more likely to be subfecund than condom users regardless of duration of use. None of the short-term POP users (n = 21) and none of the IUS users (n = 13) was subfecund. Those who denied using contraception were 6.1-fold more likely to be subfecund than condom users (adjusted 21.2) (Table IV).

The effects of COC and injectables, but not the other methods, on later fecundity were found to amplify in older women, obese women and those with menstrual disturbances. Compared with condom users, subsequent TTP of previous COC users was 1.0-fold, 1.7-fold and 2.5-fold in women aged <25, 25–34 and >35 years (P = 1.0, < 0.001, < 0.001) respectively. OR of subfecundity after COC use in these age groups in order were 1.5, 1.9 and 2.8 (P = 0.8, 0.003, < 0.001). In the same groups, TTP after injectable use was 2.1-, 3.3- and 3.8-fold longer than after condom use (P = 0.02, < 0.001, 0.04). Thin and obese previous COC users had a subsequent TTP 1.6- and 2.1-fold longer than condom users (P < 0.001, 0.02) and OR of subfecundity 1.8 and 4.3 (P = 0.003, 0.02) respectively. Their counterparts of previous injectable users had a subsequent TTP 2.7- and 5.5-fold longer and OR 5.2 and 12.2 (P < 0.001 each). Past menstrual disturbance in COC and injectable users was associated with later TTP 2.0- and 3-fold (P = 0.003, 0.01) and OR of subfecundity 2.5 and 5.9 (P = 0.01, < 0.001)
later fertility is lacking and most of the previous studies relate to old contraceptive methods no longer in use, e.g. high-dose COC (Goldman and Dale, 1971; Philipp, 1972; Janerich et al, 1976). To study the effect of previous contraceptive use on subsequent fecundity, we used time to current pregnancies (Juul et al, 1999) in order to avoid recall problems of the retrospective studies and avoid recruitment and follow-up difficulties in studies of pregnancy planners (Templeton et al, 1990; Joffe et al, 1995; Joffe, 1997; Hjollund et al, 1999). It should be remembered that studies of current pregnancies excluding those who failed to conceive or gave up the pregnancy attempt and fecundability estimation based on such studies is inaccurate (Basso et al, 2000; Jensen et al, 2000; Juul et al, 2000). Apart from a minority of IUD cases complicated with infection and tubal damage, the reversible contraceptive methods are not expected to have a sterility effect (Vessey et al, 1981; Fraser and Weisberg, 1982; Cramer et al, 1985) and such selective sampling is not expected to have a significant

### Table IV. The effect of previous use of each contraceptive method on the subfecund proportions and odds ratios (OR) of subfecundity after discontinuation of contraception, compared with condom use

<table>
<thead>
<tr>
<th>Contraceptive methods</th>
<th>% and OR of subfecundity after each contraceptive method relative to condom use</th>
<th>% and OR of subfecundity after each contraceptive method relative to condom use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before adjustment</td>
<td>After adjustment*</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Condom (n = 389)</td>
<td>34 (8.7)</td>
<td>1.86 (1.3–2.6)</td>
</tr>
<tr>
<td>COC (n = 928)</td>
<td>150 (16.2)</td>
<td>0.60 (0.2–1.6)</td>
</tr>
<tr>
<td>POP (n = 76)</td>
<td>4 (5.3)</td>
<td>1.00 (0.7–2.7)</td>
</tr>
<tr>
<td>IUD (n = 82)</td>
<td>10 (12.2)</td>
<td>5.54 (3.7–8.4)</td>
</tr>
<tr>
<td>Injection (n = 62)</td>
<td>30 (48.4)</td>
<td>0.00 (0.0–0.6)</td>
</tr>
<tr>
<td>IUS (n = 13)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Implant (n = 4)</td>
<td>2 (50.0)</td>
<td>5.72 (2.0–16.0)</td>
</tr>
<tr>
<td>&gt;One (n = 32)</td>
<td>60 (18.1)</td>
<td>2.07 (1.4–3.1)</td>
</tr>
<tr>
<td>None (n = 236)</td>
<td>174 (53.4)</td>
<td>6.11 (4.4–8.6)</td>
</tr>
</tbody>
</table>

Statistical tests: χ² and binary logistic regression model; P values: for OR of subfecundity following the use of each contraceptive method relative to condom use; statistical significance: P < 0.05.

*Adjustment in a general linear model for: women’s age, parity, weight, smoking, alcohol consumption, tea/coffee intake, drug use, menstrual pattern and men’s age, smoking, alcohol consumption, drug use and coital frequency.

CI = confidence interval; COC = combined oral contraceptive; POP = progesterone-only pills; IUD = intrauterine device; IUS = levonorgestrel intrauterine system.

### Table V. The effect of each contraceptive method in relation to the duration of use on the subfecund proportions and odds ratios (OR) of subfecundity after discontinuation of contraception, compared with condom use

<table>
<thead>
<tr>
<th>Contraceptive methods</th>
<th>Subfecund proportions and OR of subfecundity before adjustment</th>
<th>Subfecund proportions and OR of subfecundity after adjustment*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term use</td>
<td>Long-term use</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>OR (CI)</td>
</tr>
<tr>
<td>Condom</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>COC</td>
<td>7.7</td>
<td>1.55 (0.8–3.2)</td>
</tr>
<tr>
<td>POP</td>
<td>0.0</td>
<td>–</td>
</tr>
<tr>
<td>IUD</td>
<td>14.6</td>
<td>2.93 (1.1–7.6)</td>
</tr>
<tr>
<td>Injection</td>
<td>30.8</td>
<td>6.15 (2.7–14.2)</td>
</tr>
<tr>
<td>IUS</td>
<td>0.0</td>
<td>–</td>
</tr>
<tr>
<td>Implant</td>
<td>66.7</td>
<td>13.33 (4.9–36.3)</td>
</tr>
<tr>
<td>&gt;One method</td>
<td>18.8</td>
<td>3.76 (1.8–7.7)</td>
</tr>
</tbody>
</table>

Short-term use: <2 years; long-term use: >2 years; statistical tests: χ² and binary logistic regression model; P values: for OR of subfecundity following the use of each contraceptive method relative to condom use; Statistical significance: P < 0.05.

*Adjustment in a general linear model for: women’s age, parity, weight, smoking, alcohol consumption, tea/coffee intake, drug use, menstrual pattern and men’s age, smoking, alcohol consumption, drug use and coital frequency.

CI = confidence interval; COC = combined oral contraceptive; POP = progesterone-only pills; IUD = intrauterine device; IUS = levonorgestrel intrauterine system.

Discussion

A contemporary literature on the effect of contraception on later fertility is lacking and most of the previous studies relate to old contraceptive methods no longer in use, e.g. high-dose COC (Goldman and Dale, 1971; Philipp, 1972; Janerich et al, 1976). To study the effect of previous contraceptive use on subsequent fecundity, we used time to current pregnancies (Juul et al, 1999) in order to avoid recall problems of the retrospective studies and avoid recruitment and follow-up difficulties in studies of pregnancy planners (Templeton et al, 1990; Joffe et al, 1995; Joffe, 1997; Hjollund et al, 1999). It should be remembered that studies of current pregnancies excluding those who failed to conceive or gave up the pregnancy attempt and fecundability estimation based on such studies is inaccurate (Basso et al, 2000; Jensen et al, 2000; Juul et al, 2000). Apart from a minority of IUD cases complicated with infection and tubal damage, the reversible contraceptive methods are not expected to have a sterility effect.
effect. The questionnaire was designed for women to respond during clinic waiting time, a key factor in the overwhelming response, which would ensure that this sample is truly representing the pregnant population. Regression analysis was used to adjust for the effect of potential confounders. Two statistical approaches were used: firstly by comparing the mean TTP, then by comparing the conception rates and calculating odds of subfecundity after each contraceptive method. Condom was used as a reference method for comparison purposes, as it is not expected to have a lasting effect on fertility, unlike other methods that have multiple contraceptive effects.

A modest significant decline in fecundity after stopping COC use was found. Mean TTP of previous COC users was 3 months longer, the OR of subfecundity was doubled and they were 2.5-fold more likely to take >2 years to conceive, compared with condom users. The overall effect is similar to that shown by studies of high-dose COC (Pardthaisong and Gray, 1981; Linn et al., 1982; Vessey et al., 1986) and the residual effect of COC use on fertility seems to be dose-independent. Similar to other studies (Papiernik and Rozenbaum, 1975; Harlap, 1979; Weissberg, 1982; Harlap and Baras, 1984; Sperroff, 1989; Bracken et al., 1990) the effect of COC use, compared with condom use, was more evident in older women and those who had weight or menstrual disturbances, i.e. those with potentially compromised ovarian function. The negative effect of previous COC use on subsequent fertility could probably be due to transient persistence of ovarian suppression or anovulation, particularly in susceptible women (Hull et al., 1981a; Thomas and Forrest, 1983). In clinical terms, however, and apart from cases of low ovarian function, this and other studies show that the effect of previous COC use on subsequent fertility is trivial (Portuondo et al., 1979; Lahteenmaki et al., 1980; Hull et al., 1981b; Huggins and Cullins, 1990; Hassan et al., 1994; Chasan-Taber et al., 1997).

The above results, which showed a progressive decline in subsequent fecundity after stopping fertility could probably be due to transient persistence of ovarian suppression or anovulation, particularly in susceptible women (Hull et al., 1981a; Thomas and Forrest, 1983). In clinical terms, however, and apart from cases of low ovarian function, this and other studies show that the effect of previous COC use on subsequent fertility is trivial (Portuondo et al., 1979; Lahteenmaki et al., 1980; Hull et al., 1981b; Huggins and Cullins, 1990; Hassan et al., 1994; Chasan-Taber et al., 1997).

The above results, which showed a progressive decline in subsequent fecundity after stopping COC use, do not agree with the results of the study by Farrow et al. (2002), in which they suggested that previous prolonged use of oral contraception is associated with improved fecundity. There are several possible explanations for this difference. First, in the study by Farrow et al. unintentional pregnancies were excluded. Short-term contraceptive users are more likely to have experienced an unintentional pregnancy, and this was mirrored in the relatively small proportion of short-term users (<2 years) analysed in their study (18.0%) compared with short-term users in our sample (51.3%). An unintentional pregnancy may reflect high fecundity, and exclusion of these unintentional pregnancies means that short-term users would mistakenly seem less fecund compared with long-term users. We felt that inclusion of these would be practically more reflective. Second, less fertile women are less likely to use an effective contraceptive method such as COC, especially in the long-term. Consequently long-term users would appear relatively more fertile due to self-selection. Third, long-term contraceptive users are relatively older and hence less likely to persist in trying for pregnancy than short-term users. Consequently, potentially subfertile long-term contraceptive users are more likely to be excluded from studies of pregnant samples than short-term users, and long-term users may appear more fecund than short-term users, another source of selection bias. Therefore, we felt that, in order to assess the effect of duration of use of each contraceptive method, we should control for these and other biasing factors by using groups of condom users with matched durations of use for comparison purposes (Tables III and V). No such comparisons between COC use and the use of other contraceptive methods have been made in the study by Farrow et al. Finally, in the study by Farrow et al., early pregnancies were excluded and no differentiation between the use of COC or POP, which have been shown to have different effects on subsequent fecundity, was made.

Similarly, previous use of the injectables was associated with a significant reduction in subsequent fecundity (Schwallie and Assenzo, 1974; Ellinas, 1977; Fraser, 1982; Kaunitz, 1996). Mean TTP was 3-fold longer, conception rate was halved and odds of subfecundity increased to 5.5-fold relative to condom use. The delay in the return of fertility after injectable use was >1 year (Kaunitz, 1998) and in this study was even longer with prolonged use, in older women, obese women and those with menstrual disturbances. This cannot entirely be explained by delayed clearance of the residual drug from the body (Pardthaisong et al., 1980; Pardthaisong, 1984). As with previous COC use, the effect of the injectables on subsequent fertility could at least partly be due to residual ovarian suppression after stopping use (Saxena et al., 1980; Garza-Flores et al., 1985). These results apply to depot medroxyprogesterone acetate, the only injectable contraceptive currently licensed for long-term use in the UK. Studies investigating previous use of other injectables, e.g. norethisterone enanthate (Otherby et al., 1984; Indian Council of Medical Research, 1986) and Cyclofem (Bassol and Garza-Flores, 1994; Bahamondes et al., 1997) did not show a detrimental effect on later fertility.

Only short-term IUD use was associated with a negative effect on later fecundity in this sample. Compared with condom use, short-term IUD users had 1.6-fold longer TTP and were 2.9-fold more likely to be subfecund, but none of the long-term users was subfecund. This effect may be explained by occurrence of events for which IUD use was prematurely removed, whereas, unlike other studies (Bratt, 1987; Gupta et al., 1986; Tietze, 1968; Anwar et al., 1993; Doll et al., 2001). All IUS users in this study conceived within 1 month of its removal, whereas, unlike other studies (Belhadj et al., 1986;
Sivin et al, 1987; Diaz et al, 1987; Andersson et al, 1992; Sivin et al, 1992; Glasier, 2002), previous implant use was associated with a significant negative effect on subsequent fecundity. These results, however, should be interpreted with caution in view of the small numbers studied (13 and four respectively). The results of this study, like those of previous studies (Chi, 1993; Perheentupa et al, 2003), indicate that previous POP use is not associated with a detrimental effect on subsequent fertility. Those who denied past use of contraception in this sample had a significantly reduced fecundity. This could be explained by prior knowledge of their reduced fertility (26.3%) or their very sporadic coital frequency (29.5%).

Based on the above results, it appears that the contraceptive methods that act principally by ovarian suppression such as COC and the injectables might have a transient residual negative effect on subsequent fertility, particularly in the women who already have potentially compromised ovarian function. In such women, other methods, e.g. POP, provide effective means of contraception without a significant impact on later fertility. However, COC users should be reassured that the effect on later fertility is small. Further studies involving large numbers of IUS and implant users, in order to ratify their effects on later fecundity, are warranted.

Acknowledgement

We are grateful to Dr Fiona Fairlie, Consultant Obstetrician and Gynaecologist at Sheffield Teaching Hospitals, for help with recruitment of subjects.

References


Submitted on August 8, 2003; accepted on October 1, 2003

Contraceptive use: the impact on subsequent fecundity