Letters to the Editor

Oral contraceptives and diabetes mellitus: an update

There has long been interest in the possible relationship between oral contraceptive (OC) use and diabetes mellitus. In 1991, we reported our findings (in this Journal) on 45 women who had been referred to hospital for diabetes during follow-up in the Oxford-Family Planning Association (Oxford-FPA) contraceptive study. No association was found with OC use.[1] We nonetheless thought it would be of interest to comment briefly on the findings for this disease up to the time that individual follow-up of the study participants ceased in July 1994 (follow-up of cancer registrations and death notifications is still continuing).

The Oxford-FPA study methods have been described in detail elsewhere.[2] In brief, the study includes 17 032 white women who, when recruited between 1968 and 1974, were married and aged between 25 and 39 years. At entry, 56% were using OCs, 25% a diaphragm and 19% an intrauterine device. These women (save for certain subgroups – see Vessey and Painter[3]) were followed up annually and information was collected about changes in contraceptive methods, pregnancies and their outcome, hospital referrals and deaths. Women who at entry to the study reported that they were suffering from diabetes were excluded from the present analyses. There were 81 cases remaining. Only the first hospital referral (inpatient or outpatient) was taken into account in the analyses.

As expected, hospital referral was strongly positively related to age and body mass index (BMI). In addition, referral was three times as common in women of lower social class (IV–VI) as in women of upper social class (I–II), a difference only partly explained by BMI. Analyses of hospital referral rates in relation to OC use were therefore adjusted for age, BMI and social class.

Our first analysis compared women ever using OCs with those never doing so. The rate ratio was **0.8** with a 95% confidence interval (CI) ranging from 0.5 to 1.3. Rate ratios for hospital referral in relation to total duration of OC use were as follows (95% CIs are given in parentheses): *never used*, **1.0** (reference category); *1–48 months*, **0.9** (0.3–2.1); *49–96 months*, **0.7** (0.3–1.7); *97–144 months*, **0.9** (0.5–1.7); *145 months or more*, **0.6** (0.2–1.6). Corresponding rate ratios in relation to interval since last use of OCs were as follows: *never used*, **1.0** (reference category); *current–48 months*, **0.7** (0.3–1.4); *49–96 months*, **0.7** (0.3–1.7); *97–144 months*, **0.6** (0.2–1.5); *145 months or more*, **1.5** (0.7–2.8). The data were too few to enable analyses to be done by type of OC, but it should be noted that preparations containing 50 µg oestrogen made up 67% of OC exposure. OCs containing a greater amount of oestrogen provided only 2% of exposure.

We recognise the shortcomings of our data, which include the small number of affected women and the associated fact that only those referred to hospital with diabetes were identified. Nonetheless we believe that our case finding has been unbiased with respect to OC use. Furthermore, as we have pointed out previously,[1] if such a bias existed it might be expected to lead to hospital referral of more OC users than non-users.

In conclusion, the final results of the Oxford-FPA study with respect to diabetes mellitus offer further support to the view that OC use does not increase the risk of clinical diabetes mellitus, a finding in keeping with most other studies.[4–6]

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Increase in IUD expulsions

We write to raise awareness of an apparent increase in intrauterine device (IUD) expulsions noted since we started using the TT380 Slimline® in Autumn 2005.

As clinic policy we changed our preferred first-choice copper IUD to TT380 Slimline, mainly because of its 10-year licence compared to 8 years with the T-Safe® Cu380A. In early 2006 we noticed that a number of women were returning soon after insertion with either full or partial expulsion.

Two experienced doctors fit the majority of IUDs, either personally or as part of supervision for the FFPRHC Letter of Competence in Intrauterine Techniques (LoC IUT). We reviewed their IUD data from 1 January 2005 to 1 March 2006, choosing the dates to give roughly equivalent numbers of T-Safe Cu380A and TT380 Slimline insertions. We excluded insertions done by any other clinicians.

From the computer database we were able to identify those women who had not returned for follow-up and those who did not continue with the IUD. Only expulsions occurring in the first 3 months after insertion were included, although later expulsions also appear to be increased. We also noted an increase in women asking to have their IUD removed within the first 3 months. The results are shown in Table 1.

Table 1 *Summary of IUD fitting data*

Device	Total fittings (*n*)	No data (*n*)	No follow-up (*n*)	Expelled (refits) (*n*)
T-Safe® Cu380A	115	3	24	0
TT380 Slimline®	108	1	19	7 (4)
Nova-T® 380	15	1	2	0
GyneFix®	8		3	0
Mirena® (IUS)	196	2	39	2 (1)

IUS, intrauterine system.

Of the seven women who expelled the TT380 Slimline, four also expelled a replacement device. Similarly, of the two women who expelled the intrauterine system, one was known to have a fibroid uterus and also expelled her replacement device. None of the expelled devices had been fitted as part of LoC IUT training.

Although this is only a small observational study, we are concerned that this may be early evidence of a problem with the design of the TT380 Slimline. The plastic frame of this device seems to be softer and less springy than the T-Safe Cu380A and the discontinued, but similar, Ortho Gynae T380®. The TT380 Slimline takes longer to open fully post-fitting *in vitro*. We are careful to fit the device immediately after loading so the device is compressed within the tube for as little time as possible.

We value feedback from colleagues on their experience of using the TT380 Slimline.

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Liquid-based cytology

We very much welcome Dr Williams' commentary[1] in the July 2006 issue of the Journal on any advantage that liquid-based cytology (LBC) may offer and his critical analysis of the systematic review by Davey *et al*.[2] It is surprising that the favourable results of the large five pilots on LBC of England, Scotland and Wales were not included. Two recent publications from this country echo the LBC pilots as regards significant reductions in inadequate rates with LBC.[3,4]

Our positive experience at PathLinks with LBC are in line with these publications. PathLinks is a pathology network, which serves Greater Lincolnshire and Goole; the catchment population is approximately one million. The laboratory processes around 65 000 cervical cytology samples annually. PathLinks cytology service implementation of LBC began in June 2005, with one of the six PCTs converting every 6 weeks coinciding with training completion of a pathologist, a checker and three cytoscreeners. A total of 30 staff converted and provide the present service. Turnaround time just prior to conversion was 6 weeks. Presently this is 2 weeks, with around 90% of results being reported within a week. The inadequate rates were as follows: pre-conversion (April 2004–March 2005) 7.75%, during conversion (April 2005–March 2006) 4.9% and post-conversion 0.8%. The high-grade rates during these periods were 0.89%, 0.95% and 1.1%, respectively, suggesting concordance with the expectation of increased sensitivity of LBC. Our cytoscreeners have found the LBC slides to be 'clean' and easier to study as compared to conventional smears. Detection of endometrial cells is more frequent although this often causes diagnostic difficulty. Our cytoscreeners would be reluctant to return to interpreting conventional smears.

Whether the LBC can be made more cytoscreener-friendly is being explored by the NHS Health Technology Assessment Programme through the MAVARIC trial. Automated technology may make identification of abnormal cells easier. The computerised software will direct the cytoscreeners to probe some 20 locations on a slide rather than painstakingly scanning the whole slide. Furthermore, one of the machines (FocalPoint™) can sort the abnormal slides into quintiles. Up to 25% of the samples are likely to be classified as 'no further review' meaning that manual reading is not required. The MAVARIC trial set up in August 2005 compares two automated cervical screening technologies with manual screening. Cytology samples are randomly allocated to reading by manual screening alone or by one of the two automated technologies backed up by manual screening. The trial is expected to end in 2009 and the published results are due in 2011. Further uses of LBC are being actively researched. LBC lends itself to the hybrid capture technique for the human papillomavirus test[5] and for chlamydia screening.[6]

Williams[1] has already eloquently answered the question as to whether LBC offers any real advantage over the conventional smear technique. We agree that LBC is a very welcome technological tool in the screening programme and would encourage ongoing endeavours to explore how LBC can bring further benefits to women's health.

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Implanon® insertion

I was interested to read the articles in the July 2006 issue of the Journal regarding problems related to the Implanon® device.[1–4]

I recently inserted an Implanon device into the left arm of a 23-year-old, right-handed patient. The procedure went smoothly. Eleven days after the insertion the patient presented with a 3-day history of a red rash around the site of the implant. On examination she had a lymphangitis-type reaction extending proximally and distally from the site of the implant. She was otherwise well with no systemic symptoms. The patient was commenced on oral flucloxacillin.

Three days later the patient was reviewed. The erythema had resolved. A sclerotic vessel was palpable extending from just deep to the implant to the mid-forearm. It was not tender. The patient experienced some discomfort on full extension of the arm but as she was otherwise well had opted to leave the implant *in situ*. A diagnosis of thrombophlebitis was made.

I can find no mention of this complication in the product or FFPRHC literature. I wonder if others have also seen similar cases?

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Full-term pregnancy with Implanon® *in situ*

I write in regard to the letter on full-term pregnancy with Implanon® *in situ* by Drs Cooling and Pauli that appeared in the July 2006 issue of the journal.[1]

I had a similar experience when I fitted an Implanon in a patient who, in retrospect, was probably about 4 months pregnant. She gave a history of regular periods and was bleeding when I fitted it. She had not had unprotected sexual intercourse at all according to the history.

The patient then had amenorrhoea for several months and presented to her general practitioner with abdominal swelling and weight gain. She was obviously in advanced pregnancy (perhaps not the world's brightest!).

She was 36 weeks pregnant and the hospital contacted me to see if the Implanon should be removed. I could not see any reason for doing so at such a late stage. The patient delivered without problem and chose not to breastfeed. She at least now has effective contraception for a few years!

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1 Cooling H, Pauli H. Full-term pregnancy with Implanon® *in situ* (Letter). *J Fam Plann Reprod Health Care* 2006; **32**: 204.

Full-term pregnancy with Implanon® *in situ*

I read with interest the letter in the July 2006 issue of the Journal regarding a successful full-term pregnancy with Implanon® *in situ*.[1] I too have a patient who presented in similar circumstances and is continuing her pregnancy with the Implanon *in situ* as she would wish to use this method of contraception following her confinement.

After discussion with the patient and colleagues, it seemed that to leave the Implanon in place was an option. Time will reveal the outcome in due course.

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Full-term pregnancy with Implanon® *in situ*

The case of the full-term pregnancy with Implanon® *in situ* reported by Drs Cooling and Pauli in a recent issue of this Journal[1] raises several interesting issues.

First, *influence of pregnancy on Implanon*. As stated by the authors, the rate of release of the progestogen from the implant is likely to be unaltered in pregnancy. Also, the effects of the progestogen (both in terms of intended action and side effects) are likely to be overwhelmed by the massive increase in the placental production of progestogens.

Second, *influence of Implanon on pregnancy*. The authors correctly state that "progestogens in pregnancy have not been linked with fetal abnormality". This applies only to low-dose progestogen. High doses (>10 mg per day of norethisterone or equivalent) has been associated with masculinisation of the female fetus and hypospadias of the male fetus.[2] It is accepted that the dose of progestogen released by Implanon is low at 40 μg per day.[3]

Third, *timing of Implanon insertion*. The case in question is unique in that the Implanon was inserted after the critical period of organogenesis[4] (i.e. 10–12 weeks' gestation) when the susceptibility to teratogenic insults starts to decline. This is also the period when the luteo-placental shift becomes complete,[5] so that the placenta is now capable of detoxification. Thus, in the case described, the Implanon was effectively rendered inert, and its safety in this case cannot be extrapolated to exposure in early pregnancy. Pregnancy would continue to remain an absolute contraindication to Implanon insertion.

Fourth, *status quo*. The option of leaving the Implanon *in situ* has hardly any benefits apart from sparing the patient the minor inconvenience of removal and possible reinsertion, and negligible cost savings. Furthermore, the reason for the patient's satisfaction with Implanon needs to be explored. For example, the amenorrhoeic state may be incident on the pregnancy and not the Implanon. Hence, the patient's current experience with Implanon may not be predictive of her future response to the device.

Fifth, *primum non nocere*. It would seem biologically plausible that although low-dose progestogens have not proved to be teratogenic, zero exposure to exogenous progestogens would be the safest approach. Thus, the option of removing the Implanon would eliminate the potential for adverse effects.

Recommendation. The absence of a clear benefit coupled with a potential for harm would encourage me to advise the woman to have the Implanon removed. However, if after a full explanation of the implications she decides otherwise, I would accept her choice and support her through the pregnancy.

Postscript. A very dilute late afternoon urine sample could possibly explain the negative pregnancy test on the day of Implanon fitting. The initial pregnancy test could have been negative simply because it was too early: less than 3 weeks since unprotected sexual intercourse.[6] The interval between the two pregnancy tests has not been mentioned. If it is assumed that this is the standard practice of two negative pregnancy tests 3 weeks apart before initiation of any method of contraception, the patient is likely to have become pregnant about 8 weeks prior to Implanon fit.

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Reply

Dr Arunakumari identifies several important points. The negative urine pregnancy tests remain puzzling since the ultrasound scan performed at 27 ± 2 weeks would suggest the Implanon® was inserted when the patient was about 8 weeks pregnant (i.e. 6 weeks after conception). This means, however, that organogenesis would not have been complete by the time of insertion.

Dr Arunakumari is, of course, correct that pregnancy is a contraindication to use of Implanon. However, the issue in this case, as in Dr Melrose's case, is that removal and postnatal re-insertion of Implanon at this late stage in pregnancy subjects the patient to two extra