JOURNAL CLUB

The pill, parity and cervical cancer risk

Two papers carried out by the International Agency for Research on Cancer (IARC) were published recently in *The Lancet* (2002). They aimed to investigate evidence of a link between long-term oral contraception (OC), increasing parity, human papilloma virus (HPV) and cervical cancer. These important papers address the growing suspicion that reproductive factors such as parity and contraception may affect the risk of cervical cancer. Certainly this is biologically plausible, since both pregnancy and combined oral contraception maintain the transformation zone on the ectocervix where it is exposed to co-factors such as HPV. Previous publications suggesting a link have been unable to exclude confounding factors such as sexual behaviour.

IARC pooled analysis of 10 case-control studies. These studies were performed in underdeveloped countries with high-risk populations for cervical cancer such as Morocco, Brazil, Peru, Paraguay and Colombia; with intermediate-risk populations such as Thailand and the Philippines; and low-risk populations such as Spain. The original case-control studies compared histologically verified cases of invasive cervical cancer and carcinoma in situ, with age-matched control women drawn largely from hospital populations. HPV was found in 1465/1561 women (94%) with invasive squamous cell cancer, 211/292 women (72%) with in situ cancer, 124/135 women (92%) with adenocarcinoma or adenosquamous carcinoma and 225/1916 (13%) control women. Statistical analysis was performed using unconditional logistic regression models and associations of exposures were assessed with likelihood ratios. Variables such as sociodemographic factors, sexual history, contraceptive use, smoking, lifetime history of cervical screening, history of sexually transmitted infection, and detailed obstetric history were ascertained by trained interviewers using a standardised questionnaire.

Effects of oral contraceptives on risk of cervical cancer in women with human papilloma virus infection: the IARC multicentric case-control study. Moreno V, Bosch FX, Munoz N, et al. *Lancet* 2002; **399(9312):** 1085–1092

This first paper aimed to investigate evidence of a link between cervical cancer, human papilloma virus (HPV) and long-term oral contraception (OC). Women were tested for presence of HPV DNA in cervical smears. HPV infection is now accepted as an important factor in the aetiology of cervical cancer. These papers therefore restrict their analyses to women who tested positive for HPV. A total of 1676 cases were included. Including HPV-negative women, who are essentially not at risk of cervical cancer, would have reduced the chances of detecting any genuine link between cervical cancer and OC use. There were only 255 controls, leaving the study vulnerable to selection bias. Around 90% of the HPV-positive women had high-risk HPV types. Restricting analysis to these women did not significantly alter the findings. Both squamous cervical cancer and carcinoma in situ were considered. Researchers analysed data using complex statistical models aimed at taking into account possible confounding factors such as age at first intercourse and age at first pregnancy.

An association between increasing duration of OC use and risk of cervical cancer and carcinoma in situ was identified. No association was found with age at first OC use. Use of OC for less than 5 years was not associated with increased risk of cervical neoplasia. Women with a total of 5 to 9 years of OC use had almost three times the risk of cervical neoplasia (odds ratio 2.82, 95% CI 1.46–5.42). Those women with more than 10 years of OC use had four times the risk of cervical neoplasia (odds ratio 4.03, 95% CI 2.09–7.79). The increased risk of cervical neoplasia appeared to persist for as long as 15 years after discontinuing OC. Use of OC itself did not appear to increase the chance of infection with HPV.

This study would appear to confirm a plausible association between OC and cervical cancer. Researchers focused on women deemed at high risk of developing cervical cancer because they were HPV-positive. These findings cannot therefore be explained away by higher risk sexual activity as has been done previously. It must be acknowledged, however, that there are a number of areas where bias may have been introduced. Recall bias is acknowledged in that women may not have accurately recalled previous use of hormonal contraceptive methods and some may have used progestogen-only methods. Only one HPV test was carried out, but persistence of HPV is thought to be an important factor in carcinogenesis. This study therefore could not distinguish those women who had only transient infection from those with persistent HPV. Although the findings are relevant for women in the developed world, most of the women in the study (apart from those from Spain) lived in countries in which there are no national cervical screening programmes. This study serves to underline the importance of attending for regular cervical screening smears. In this context, these findings need not affect women's contraceptive or reproductive choices. In discussion with women in the UK, it is important to stress the much lower rates of cervical cancer here, in addition to the many benefits of OC use and attending for routine cervical screening.

Reviewed by **Dr Kate Weaver,** MB ChB, DFFP
Career Grade Trainee, Family Planning, Edinburgh, UK

Role of parity and HPV in cervical cancer: the IARC muticentric case-control study. Munoz N, Franceschi S, Bosetti C, et al. *Lancet* 2002; **399(9312):** 1093–1101

This second paper looked at parity acting as a co-factor, with oncogenic strains of human papilloma virus (HPV), to cause neoplasia of the cervix.

The authors report a direct association between the number of full-term pregnancies and squamous cell cancer risk. A full-term pregnancy was defined as any pregnancy beyond 28 weeks gestation, regardless of outcome. Women with seven or more full-term pregnancies were almost four times more likely to develop squamous carcinoma or carcinoma in situ (odds ratio 3.8 95% CI 2.66–5.48) than nulliparous women, and were twice as likely to develop squamous carcinoma or carcinoma in situ (OR 2.3, 95% CI 1.6–3.2) than women who had only one or two term pregnancies. No significant association was found between risk of adenocarcinoma or adenosquamous carcinoma and number of pregnancies. Age at first pregnancy was also significant in that women with seven or more term pregnancies, who were younger than 17 years at first pregnancy, had a four-fold increase risk of cervical cancer as compared with women who had one or two term pregnancies and were older than 21 years at first confinement. The results suggest parity could act synergistically with other factors such as HPV to increase the risk of cervical cancer. There were very small numbers of caesarean section deliveries in the study populations and a protective effect of abdominal delivery over vaginal delivery could not be demonstrated. Several term pregnancies over a short time may be associated with increased risk of neoplasia. However, this study found no evidence to support this hypothesis. It is interesting to note that only pregnancies beyond 28 weeks were associated with an increased risk. The authors suggest that events in the second and third trimesters or related to delivery could be relevant. One possibility is that the increased levels of oestrogen and progesterone cause cervical ectropion and squamous metaplasia, which could render the cervix more susceptible to the oncogenic effects of HPV. Abortion seemed to be neutral or inversely associated with squamous carcinoma, although a genuine history of induced abortion can be hard to elicit and this result must be interpreted cautiously.

Reviewed by **Dr Ailsa Wyllie,** DFFP, MRCOG
Career Grade Trainee, Family Planning, Edinburgh, UK

Desogestrel-only pill and breastfeeding

Comparative study of the effects of a progestogen-only pill containing desogestrel and an intrauterine contraceptive device in lactating women. Bjarnadottir RI, Gottfredsdottir H, Sigurdardottir K, et al. *Br J Obstet Gynaecol* 2001; **108:** 1174–1180

This was a small study was carried out in 83 women aged between 18 and 40 years. The study was open and non-randomised because women had very strong preferences for postnatal contraception and were allowed to choose their preferred method. The study was described as group-comparative: women were included into two groups, either using 75 µg desogestrel-only progestogen pill or a copper intrauterine contraceptive device (IUD). The researchers aimed to look at the quantity and quality of breast milk in these two groups of women. In a small subset of women they also looked at the levels of etonorgestrel (the active metabolite of desogestrel) in breast milk and maternal serum. In addition researchers assessed infant growth and wellbeing until the age of 30 months. Women were included if they were fully breastfeeding (supplement feeds less than twice a week) and had a pre-pregnancy weight between 80% and 130% of ideal weight. All women had given birth to a healthy infant at a gestational age of 259–294 days weighing between the 10th and 90th centiles. A power calculation estimated that a sample size of 40 women in each group, desogestrel or IUD, was estimated to be able to identify a difference of 10% between treatment groups. During the study the observed drop-out rates were lower than the 25% expected. Five women withdrew from the desogestrel group due to headaches and vomiting, diminished lactation, mood changes, bleeding irregularity, or perceived increased sweating of the infant. One woman discontinued IUD use due to mild endometritis. The other nine

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women discontinued due to problems with compliance to the study. Although women were not randomised, statistical tests showed both groups were similar with respect to demographic details of women and infants. The results indicated there was no significant difference in mean volume of milk produced between the two groups. Milk volume was measured as pre- and post-feed infant weight, over 24 hours as is the standard method of assessment. The composition of milk was similar in both groups in terms of triglyceride, protein and lactose content. It was calculated that the suckling infant received a maximum of 0.01–0.05 µg/kg/day desogestrel. This accounts for 2.6–3.7% of the daily maternal dose. No significant differences were noted in weight, length and biparietal diameter up to the seventh cycle of treatment. When infants were followed up at 18 and 30 months there were no clinically relevant differences between the two groups. The authors conclude that 75 µg desogestrel progestogen-only pill is a safe and effective method of contraception for lactating women. Efficacy cannot be concluded from the study as pregnancy rates were not reported, however the authors refer to the effectiveness of the desogestrel pill from published data where desogestrel is known to inhibit ovulation and has a 12-hour window for missed pills. Bias may have been introduced due to the non-randomisation of women and also because neither patient nor researchers were blinded. It is unclear if laboratory staff were blinded. However, automated testing was used to identify milk composition. The safety of the desogestrel pill for lactating women has been demonstrated in this study.

Reviewed by **Dr Susan Brechin**, DFFP, MRCOG
Subspecialty Trainee in Sexual and Reproductive Health, The Sandyford Initiative, Glasgow, UK

Intrauterine device insertion following abortion

Insertion of an intrauterine contraceptive device after induced or spontaneous abortion: a review of the evidence. Stanwood NL, Grimes DA, Schulz KF. *Br J Obstet Gynaecol* 2001; **108:** 1168–1173

The purpose of this systematic review was to assess the safety and efficacy of immediate post-abortal intrauterine contraceptive device (IUD) insertion. The introduction clearly outlined potential benefits of immediate IUD insertion: providing immediate contraception when the woman's motivation is high, and the avoidance of the discomfort associated with insertion. Disadvantages of immediate IUD insertion may include: increased risk of perforation; increased risk of expulsion; increased risk of pelvic infection; and possibly reduced efficacy. The authors comprehensively and systematically reviewed randomised controlled trials (RCTs), in which at least one arm involved the insertion of an IUD immediately after spontaneous or therapeutic abortion. Databases searched included Medline; Popline, the Cochrane Controlled Trials Register and EMBASE. Of the 12 randomised trials identified, one was excluded due to non-randomisation, one was excluded as it did not identify the main outcomes of this review, and two were excluded due to design faults and unethical practice. Women of any age and gravity were included. All trials included had been carried out in the 1970s and 1980s. The two largest and most methodologically sound World Health Organization (WHO) studies, which included 4476 women-years of data, were both carried out almost 20 years ago in 1983. The IUDs used during these studies included the Copper 7, Lippes Loop and the Copper T220.

The following rates were obtained from the two WHO studies. Insertion of an IUD immediately following therapeutic abortion was associated with: perforation rates of 1 per 1000 insertions (3/2348 cases); expulsion rates of 7% (157 expulsions); failure rates of 2 per 100 woman years (this included 70 intrauterine and extrauterine pregnancies); and rates of pelvic infection (PID) of 0.4 per 100 woman years (12 cases of PID). Insertion of an IUD immediately following spontaneous abortion was associated with: perforation rates of 0.9 per 1000 insertions (1 in 1060 insertions); expulsion rates of 0.9% (128 expulsions); failure rates of 2 per 100 woman years (21 intrauterine pregnancies); and rates of PID of 0.2 per 100 women years (three cases of PID). The authors also noted that the risk of expulsion increased with increasing gestational age, with rates increasing 4.5-fold from first to second trimester abortion.

There were a number of factors that could have introduced bias. Many of the studies included were more than 20 years old and in that time clinical practice has changed. The IUDs used in these studies are not used today. Only one IUD included had doses of copper comparable to IUDs in use today which often contain 380 mm^2 of copper. This may affect the efficacy data presented since those devices with higher levels of copper have lower failure rates than do those with low doses of copper or inert devices. Problems interpreting the results from these studies to our present clinical practice may arise as a result of a number of factors. The majority of women included in the studies underwent surgical termination of pregnancy (STOP), rather than medical termination of pregnancy with prostaglandins (MTOP). This may influence the incidence of post-abortal infection in the study population. The authors concluded that IUD insertion immediate post-therapeutic or spontaneous abortion was safe and effective. Rates of pelvic infection (PID), one of the main outcomes measured, may differ in these older studies to the rates today. Rates of PID may be reduced by: increasing the numbers of women undergoing medical termination of pregnancy, thus avoiding uterine instrumentation; active screening for sexually transmitted disease pre-termination; and the use of prophylactic antibiotic policies. The rates of infection may increase, however, due to the increasing background rates of sexually transmitted infections (STIs), chlamydia and gonorrhoea in particular. Rates of expulsion, perforation, infection and failure were comparable to IUD insertion at other times. A follow-up appointment for an IUD check is essential. This study has highlighted the need for prospective studies of currently used copper devices, and indeed hormonal intrauterine systems.

Reviewed by **Dr Susan Brechin**, DFFP, MRCOG
Subspecialty Trainee Sexual and Reproductive Health, The Sandyford Initiative, Glasgow, UK

Mifepristone as a contraceptive agent

Daily low dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double blind randomized control trial of 2 mg and 5 mg per day for 120 days. Brown A, Cheng L, Suiqing L, et al. *J Clin Endocrinol Metab* 2002; **87:** 63–70

It has previously been demonstrated that antiprogestins have contraceptive potential. This current study is a double-blind randomised control trial (RCT) of daily mifepristone (2 mg versus 5 mg) for 120 days. It was conducted in Edinburgh (58 subjects) and Shanghai (40 subjects). In addition to examining effects on ovulation and bleeding, contraceptive efficacy was examined in a subgroup of 50 subjects who used it as their sole method of contraception. Both 2 mg and 5 mg of mifepristone suppressed ovulation (90% and 95%, respectively) and induced amenorrhoea in the majority of cycles (65% and 88%, respectively), although this was a more consistent finding with the 5 mg dose. Even in cycles in which ovulation did occur, the histology of the endometrium was such that it would be unlikely to support a pregnancy. Furthermore, there were no pregnancies amongst 50 subjects in over 200 months of exposure. Despite prolonged anovulation with continued oestrogen secretion, it is reassuring that end-of-study endometrial biopsies displayed no evidence of hyperplasia or atypia. Few side effects were reported and menses resumed within 3 weeks of cessation of treatment. Interestingly, Chinese subjects proved more sensitive to mifepristone as they experienced greater ovarian suppression and a higher incidence of amenorrhoea. This may be related to their lower body mass index (BMI) or dietary effects on the enterohepatic circulation of steroids. Importantly, this study provides medium-term data to support the potential of mifepristone (2 mg or 5 mg) as a daily contraceptive pill, by inhibiting ovulation and/or through effects on the endometrium. This oestrogen-free alternative to the progestogen-only-pill would also have the advantage of amenorrhoea. Larger studies of long-term duration are now needed.

Reviewed by **Dr Sharon Cameron**, MD, MRCOG
Lecturer/Subspecialty Trainee in Reproductive Medicine, University of Edinburgh, UK

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