Cervical Cone Biopsy and Fertility

SIR,—Cone biopsy is widely regarded as a necessary and practically harmless procedure when abnormal and possibly precancerous cells are found in a cervical smear. There are many reports of successful pregnancy following this operation, and serious complications are rare.¹ Nevertheless, there is some anxiety about possible adverse effects from the numerous operations performed as a result of large-scale cervical cytology testing. In particular, a loss of subsequent fertility is sometimes feared.^{2,3} The following information, obtained a few years ago, may therefore be of interest.

Data were collected from a defined subgroup of women on whom a cone biopsy had been performed to see whether a prima facie case existed for suspecting a reduction in fertility. Those chosen were under age 41 and had had only one child before the biopsy; in this way it was hoped to select the group most likely to wish for further children. It was decided that a search for properly matched controls would be impracticable, since they would have to correspond in age, parity, time since last delivery, sexual activity, and use of contraceptives. For comparison Dr. J. A. Baldwin, of the Oxford Record Linkage Study, provided figures for age at first delivery of women in the area in 1963 and 1964; also the intervals between first delivery in 1963 and the last menstrual period prior to the second successful pregnancy. Also, the figure was available for the proportion of primiparae under age 41 who started a second pregnancy within two years of the first delivery.

Hospital records were examined from 289 women aged under 41 at the time of cone biopsy, covering the period 1963-9 inclusive. Of these, 55 had had only one child before operation. These did not differ from other primiparae in the distribution of their ages at first delivery. In nine cases cone biopsy was followed within six months by hysterectomy or tubal ligation and four subjects were lost to follow-up. There remained 42 in the study group who could be followed up for at least two years after cone biopsy. The number of successful pregnancies started within two years of biopsy was 16, or 34.8% of all those at risk including those lost to follow-up. At least four more have had babies at a longer interval after the operation and are therefore excluded from the above figure. For comparison, the figure for successful pregnancies started within two years of the first delivery in the general population of the Oxford area was 35.7%. Since the two years following first delivery are expected to give a higher figure than any subsequent two-year period, the performance of the women following cone biopsy appears good. Moreover, women in our series were chosen as having still only one child at the time of biopsy, which was performed in the whole series of 289 at the average age of 38; we are therefore dealing with a group weighted against high fertility. Seven women were attending for infertility before the cone biopsy was performed, and only one of these has failed to conceive afterwards. There was one recorded abortion in the two years following biopsy. (This patient conceived again within the two-year period and had a live child.) Full details of obstetric performance are not given here,

but will form part of the larger series to be reported by Chamberlain and Rogers.⁴ One caesarean section was performed owing to failure to dilate. Two babies are known to have weighed less than 2.5 kg, one being the smaller of a pair of twins.

We were intrigued by the fact that in those becoming pregnant after biopsy the mean interval from first delivery to biopsy was 55.9 months, yet the interval from biopsy to the last menstrual period prior to the second pregnancy was only 11.2 months. This at first suggested that cone biopsy may actually relieve infertility. There is, however, a bias caused by cone biopsy being done mainly on older women. Therefore when it is performed in the interval between a first and a second pregnancy it would naturally tend to be nearer to the date of the second.

Though small in number, our figures do not support the idea that cone biopsy causes any general reduction in fertility.

We are indebted to Dr. J. A. Baldwin for much help and advice and for supplying data from the Oxford Record Linkage Study; also to Professor Sir John Stallworthy and the staff of the Nuffield Department of Obstetrics and Gynaecology for their collaboration and for access to case-notes, most of which were initially sorted and analysed by Dr. R. P. Child. Fuller data and tables can be obtained by writing to the authors.

—We are, etc.,

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Cervical Injury and Prostaglandins

SIR,—Damage caused by forceful dilatation of the cervix uteri may result in spontaneous abortion and premature labour in a subsequent pregnancy.¹ It is therefore understandable that attempts should have been made (1) to introduce very early evacuation techniques requiring little or no dilatation, and (2) to study the stimulant effects of locally administered prostaglandins inducing dilatation, and possibly abortion, as a result of myometrial activity. Accordingly studies have been undertaken to promote a degree of dilatation by the insertion of prostaglandin pessaries before operation in an attempt to minimize operative trauma, but the applicability of this method for routine clinical use and the results obtained have been equivocal.^{2,3} On the other hand the local injection of a large dose of prostaglandins directly into the uterine cavity in patients sedated to minimize side effects may be a rational and effective alternative to surgery,⁴ and resultant cervical damage may be less.

While cervical damage may be considered to be an unlikely sequel to the induction of mid-trimester abortion, this is not necessarily the case. Cervical lacerations and fistulous communications between the vaginal fornix and lower uterine segment have been reported after the extra-amniotic injection of soapy pastes⁵ and the intra-amniotic injection of saline, urea, or prosta-

glandins.⁶ This may not be surprising since excessive uterine activity may be stimulated, particularly when intra-amniotic techniques are used, because supraoptimal doses may be inadvertently given to some patients in order to achieve abortion in a reasonable time in all subjects. It seems only likely that any specific patient in mid-pregnancy exhibits the similar features of "inducibility" which they acknowledge at term to indicate the likely length of induced labour and the optimum dose of oxytocic required—that is, the state of the cervix, etc. Obviously it would be preferable if the administered abortifacient dose could be related to some pretermination index indicating myometrial sensitivity, thereby minimizing over-stimulation.

Recently the intra-amniotic injection of prostaglandins (PGE₂ 5-10 mg; PGF₂α 20 mg) combined with urea (80 g) has been reported to be a particularly effective method, abortion resulting in a mean time of approximately 10 hours.⁷⁻¹⁰ While considerably lower doses of prostaglandins are required with this combined technique compared with those necessary when prostaglandins are injected alone, excessive myometrial activity may ensue. An example observed in a patient of advanced gestation after the injection of urea 80 g and PGF₂α 20 mg is shown in the figure. Until the dose

to be given can be related with sufficient accuracy to the potential "inducibility" of any given patient the lowest effective doses of abortifacient should be evaluated. Current studies in this department using intra-amniotic urea 80 g and PGE₂ 2.5 mg in 25 patients have not resulted in cervical injuries being observed at the time of evacuation of the uterus, which is now performed as a routine to prevent secondary haemorrhage occurring, even in those subjects in whom the abortion process appears complete.

Though extra-amniotic prostaglandin therapy may be associated with a lower incidence of cervical injury than are other methods, there are no comprehensive data on this matter and the recent practice of augmenting uterine activity by the use of an intravenous oxytocin infusion may provoke over-stimulation and cervical damage. Therefore there is a need to perform comparative studies into the effectiveness and side effects experienced with different techniques to establish which is the most rational way of dealing with this matter

with the minimum of sequelae.—We are, etc.,

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Meningococcal Disease

SIR,—In their interesting account of an outbreak of meningococcal disease in Devon (16 March, p. 50) Dr. D. M. Easton and his colleagues raise several points worthy of discussion.

They used a combination of penicillin, sulphonamides, and chloramphenicol in the initial treatment of most cases and suggest that if the low cerebrospinal fluid cell count in three of their cases "indicates only minimal inflammatory response in the meninges penetration of penicillin into the C.S.F. may be poor, so that the inclusion of chloramphenicol which passes well into the C.S.F. might be a beneficial addition to the treatment regimen." In meningococcal infection—especially of the fulminant type where relatively little involvement of the meninges is not uncommon—the major consideration is to deal with the systemic infection. Penicillin alone will do this adequately and, if inflammation of the meninges occurs will rapidly eradicate meningococci at that site without the need for the use of chloramphenicol.

The inclusion of sulphonamides in the treatment of meningococcal meningitis is of less certain help than formerly owing to the presence of resistant meningococci. Of the strains isolated in Scotland and forwarded to this laboratory for testing in 1973, 15% were fully resistant to sulphonamides. What is also of importance when considering prophylaxis is that in addition 51.5% of strains were partially resistant—that is, would not be eradicated from the nasopharynx by sulphonamide therapy. Hence if prophylaxis is to be used sulphonamides cannot be recommended.

This raises the question as to who should be protected and how. Firstly, I cannot agree with Dr. Easton and his colleagues that "family contacts should be screened and should all be given an adequate course of prophylactic treatment" if they imply that prophylaxis should be dependent upon screening. Screening will not pick up all carriers and in any case I would agree with Wenzel *et al.*¹ that it is the acquisition rate of meningococci that is important in terms of the dynamics of meningococcal infection, not the carrier rate. In other words, meningococcal disease is, like poliomyelitis, a "failure of carriage" (and it is interesting to note that in both these diseases asymptomatic infection leads to the production

of antibodies). Hence prophylaxis must be used early if at all and must cover the case contacts, not so much to eradicate carriage but to try to prevent acquisition leading to disease. There is no doubt that prophylaxis will abort epidemics, as has been shown in Africa² and in service camps in the U.S.A.³ but the problem is how this should be carried out in the face of sulphonamide resistance and the knowledge that penicillin will not eradicate meningococci from the nasopharynx of carriers.⁴ One approach might be to give penicillin in the hope of preventing disease (and maybe by reducing carriage rates to a low level to reduce the likelihood of acquisition by the non-carrier). However, there is evidence⁵ that penicillin not only will not eradicate carriage but will not prevent the onset of meningitis. The other approach is to give eradication treatment—for instance, using minocycline and rifampicin⁶ or rifampicin alone.⁷ Until reading the account of Foster *et al.*⁵ I might have conceded that in a family group penicillin, especially if given by injection, should be adequate, but I now feel that, as in an institutional outbreak where long-term carriage following inadequate prophylaxis could result in the seeding of the susceptible population once prophylaxis had been ended, eradication treatment should be considered. It would be interesting to hear the views of others on this important topic.

At one time the suggestion that family contacts should receive prophylaxis would not have been accepted because outbreaks in family groups were rarely reported, but in recent years outbreaks involving more than one member of a family have been reported⁸ and the experience in the Devon outbreak emphasizes that this can happen. Hence the urgency for reappraisal of the problem of prophylaxis is underlined.

Finally, Dr. Easton and his colleagues noted that group B meningococci predominated in their series. Were other groups isolated or were some strains either untyped or untypable?—I am, etc.,

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SIR,—Recent experience in Wigan supports the suggestion of Dr. D. M. Easton and others (16 March, p. 507) that there is a recrudescence of meningococcal disease, often with complications, in Britain. In the six months from October 1973 to March 1974 we treated 10 such patients compared with four in the corresponding period a year earlier. Their ages ranged from 5 months to 7 years. All had confirmed meningitis and in nine the presence of men-

ingococci was demonstrated bacteriologically. A petechial rash was noted in nine cases.

Two children died, a girl of 3 years with severe septicaemia and shock and a boy of 6 who had septicaemia and gross cerebral oedema with coning and superficial cerebellar haemorrhage. Two other children had brief convulsive episodes and a third who had prolonged convulsions went on to develop bilateral subdural effusions and has considerable residual brain damage. One child had definite arthritis of the right elbow joint and another a transient arthralgia affecting the left knee.

None of these children had any history of prior contact with meningococcal disease and their homes were scattered throughout the area served by this hospital.—I am, etc.,

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Misleading Discs

SIR,—The antibiotic discs described by Mr. D. F. J. Brown and Dr. J. B. Selkon (23 March, p. 573) are not the only ones to mislead.

Bacteria of the *Haemophilus* genus require one or both of two growth-promoting substances for normal growth on culture. These are haematin, designated the "X-factor", and coenzyme 1, designated "V-factor". Coloured paper discs marked X, XV, and V, impregnated with standard quantities of these substances, are commonly used as a simple screening method for preliminary recognition of *haemophilus* species. Recently a culture of *H. influenzae* appeared as only a fine ring of growth around an XV disc, but outside a zone 14 mm in diameter without any growth. It was almost invisible without a hand lens. Another *haemophilus* grew as a ring around a zone without growth surrounding both the X and V discs. Experimental cultures of pneumococci and streptococci also showed zones of inhibition around the X and XV discs. The discs were in date and stored dry at 4°C.

A similar phenomenon was observed some years ago. The paper dye was not to blame since control blank discs of the three colours were inactive, and it was assumed that the X-factor (haematin) solution used must have been inhibitory. The makers were informed and corrected the matter, but the difficulty now seems to have recurred.—I am, etc.,

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Clinical Diagnosis of Reye's Syndrome

SIR,—I entirely agree with the views expressed in the last paragraph of Dr. Ellen S. Kang's letter (16 March, p. 518). Having an abiding interest in Reye's syndrome^{1,2} may I develop her idea a little farther? I suggest that what she terms "toxic encephalopathy with fatty visceral changes due to a specific toxin" should be called the Reye-Bourgeois syndrome because it was the original intention of Reye *et al.*³ to place the entity of "encephalopathy with fatty degeneration of