Bacterial vaginosis and preterm delivery

Bacteria may contribute to lung disease in neonates

EDITOR,—Phillip E Hay and colleagues' report on abnormal bacterial colonisation of the genital tract and preterm labour.¹ The association between infection and preterm labour has been widely reported, with the genital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*) often being implicated.² Many of the preterm infants need ventilation, and a considerable number develop chronic lung disease. In our unit in 1993 there were 84 survivors of ≤ 30 weeks' gestation, of whom 41 developed chronic lung disease. The aetiology of this disease is multifactorial, with gestation and positive pressure ventilation being the most important determinants.

In a pilot study of the incidence of ureaplasma and mycoplasma infections the endotracheal secretions of all intubated neonates of ≤ 30 weeks' gestation ($n=63$) were examined weekly from birth while the neonates remained intubated. Sixteen of the infants were positive for one or both organisms, with 11 yielding positive results on the first culture. Fifteen (94%) of these 16 infants with positive cultures went on to develop chronic lung disease whereas only 18 (38%) of the 47 infants for whom culture yielded negative results developed the disease ($P<0.001$). There were no significant differences between the two groups in gestation, birth weight, and duration of positive pressure ventilation.

These data agree with data from the United States.³ It has been suggested not only that these organisms induce preterm labour but that their presence in the lungs causes a low grade inflammatory response, increasing the need for ventilation and hence increasing the degree of damage done by the ventilator, resulting in chronic lung disease. The presence of an inflammatory response in the development of chronic lung disease from the respiratory distress syndrome is well recognised,⁴ and we have found an association between high levels of the cytokine interleukin-8 (as a marker of inflammatory response) on day 2 of life and subsequent chronic lung disease (J McCollm, N McIntosh, unpublished observations).

We have started an intervention study looking at the relation between infection, acute inflammatory response, and chronic lung disease and the effect of early treatment with erythromycin. Chronic lung disease has a high mortality and morbidity, and any intervention that reduces its incidence and severity will have important implications in neonatal care.

AJLYON
N MCINTOSH
R ILIES
P W ROSS

Neonatal Unit,
Stimpson Memorial Maternity Pavilion,
Edinburgh EH3 9EF

- 1 Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994;308:295-8. (29 January.)
- 2 Cassell GH, Waites KB, Watson H-L, Crouse DT, Harasawa R. *Ureaplasma urealyticum* intrauterine infection: role in prematurity and disease in newborns. *Clin Microbiol Rev* 1993;6: 69-87.
- 3 Cassell GH, Waites KB, Crouse DT, Rudd PT, Canupp KC,

Priority will be given to letters that are less than 400 words long and are typed with double spacing. All authors should sign the letter. Please enclose a stamped addressed envelope for acknowledgment.

Stagno S, et al. Association of *Ureaplasma urealyticum* infection of the lower respiratory tract with chronic lung disease and death in very-low-birth-weight infants. *Lancet* 1988;iii:240-5.

- 4 Robertson B. The evolution of neonatal respiratory distress syndrome into chronic lung disease. *Eur Respir J* 1989; 2(suppl):33-7.

Little evidence of causal association

EDITOR,—Phillip E Hay and colleagues report an association between bacterial vaginosis in early pregnancy and subsequent late miscarriage and preterm delivery.¹ Although a causal effect has yet to be shown, many people have quoted previous studies with similar findings²—and will no doubt quote this study—as evidence that bacterial vaginosis in asymptomatic women should be treated.

Bacterial vaginosis often has an identifiable underlying cause. It can be associated with the presence of an infection such as *Chlamydia trachomatis* infection, which itself has been associated with adverse outcome of pregnancy.³ In non-pregnant women the vaginal flora may alter cyclically, and bacterial vaginosis is uncommon in prepubertal girls and postmenopausal women; this suggests that hormonal changes may result in alteration of the vaginal flora. Other women find that unprotected sexual intercourse precipitates symptoms. There is no good evidence that bacterial vaginosis is a sexually transmitted disease, and it has been suggested that semen, by altering the pH of the vagina, can lead to an alteration in the flora. We note that in Hay and colleagues' study the presence of sperm in the Gram stained slides was recorded, although any correlation between this and the presence of bacterial vaginosis was not reported.

It is conceivable that hormonal factors or frequent sexual intercourse, or both, could precipitate preterm labour; certainly, women known to be at risk of miscarriage are commonly advised not to have intercourse in the early stages of pregnancy, and women at term are often encouraged to have intercourse to try to precipitate labour (although scientific evidence supporting this advice is lacking). The finding of increased prostaglandin concentrations in the cervical mucosa of pregnant women with bacterial vaginosis⁴ has led to the postulation of a mechanism by which bacterial vaginosis could provoke preterm labour. It is equally conceivable, however, that coitus could stimulate both production of prostaglandin and bacterial vaginosis. Thus bacterial vaginosis could be a marker of risk rather than a cause of adverse outcome of pregnancy.

Because of this the results of controlled interventional studies, such as the one currently being undertaken by Hay and colleagues, should be awaited and the risks and benefits of intervention established before a potentially large number of asymptomatic women are treated, especially

during pregnancy, when the use of drugs should be minimised.

CECILIA J F PRIESTLEY
A NAGESWARAN
JYOTI DHAR

Department of Genitourinary Medicine,
Royal Hallamshire Hospital,
Sheffield S10 2JF

- 1 Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994;308:295-8. (29 January.)
- 2 Gravett MG, Hummel D, Eschenbach DA, Holmes KK. Preterm labour associated with subclinical amniotic fluid infection and bacterial vaginosis. *Obstet Gynecol* 1986;67: 229-37.
- 3 Ryan GM, Abdella TN, McNeeley SG, Baselski VS, Drummond DE. Chlamydia trachomatis infection in pregnancy and effect of treatment on outcome. *Am J Obstet Gynecol* 1990;162:34-9.
- 4 Mardh PA. The definition and epidemiology of bacterial vaginosis. *Rev Fr Gynecol Obstet* 1993;88:195-7.
- 5 Platz-Christensen JJ, Brandberg A, Wijkvist N. Increased prostaglandin concentrations in the cervical mucosa of pregnant women with bacterial vaginosis. *Prostaglandins* 1992;43:133-4.

Spurious link may lead to overtreatment

EDITOR,—Phillip E Hay and colleagues confirm¹ the well known and highly significant relation between previous preterm delivery and preterm delivery.^{2,3} It has been inferred from this relation that an underlying factor leads to preterm delivery in the index case and recurs with the occurrence of further preterm deliveries. Consequently it is surprising that the authors did not publish an analysis of their data on primiparous singleton pregnancies and show the association between bacterial vaginosis and preterm labour in these pregnancies.

Hay and colleagues' work shows that the association between previous preterm delivery and preterm delivery ($P<0.001$) is much greater than the association between preterm delivery and bacterial vaginosis at the initial antenatal visit ($P=0.04$). Unusually, previous preterm delivery and bacterial vaginosis were considered to be independent predicting variables; this is surprising because bacterial vaginosis, which is a chronic recurrent condition, is postulated to be a causative factor in repeated preterm labour. If bacterial vaginosis is truly predictive of preterm delivery the logistic regression analysis should be expected to show that preterm delivery is more strongly associated with bacterial vaginosis than previous preterm delivery as bacterial vaginosis will be a factor occurring in index cases but previous preterm delivery will not.

These findings therefore question whether bacterial vaginosis is implicated as a cause of preterm delivery. The assumption that bacterial vaginosis leads to preterm labour will lead to a false sense of security among those mothers who do not have bacterial vaginosis as well as to unnecessary antibiotic treatment in mothers with bacterial vaginosis.

ANN YOONG

St Mary's Hospital,
Manchester M13 0JL

- 1 Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994;308:295-8. (29 January.)
- 2 Kaminski M, Goujard J, Rumeau-Rouquette C. Prediction of low birth weight and prematurity by a multiple regression analysis with maternal characteristics known since the beginning of pregnancy. *Int J Epidemiol* 1973;2:195-204.

- 3 Hobel CJ, Youkeles L, Forsythe A. Prenatal and intrapartum high risk screening. *Am J Obstet Gynecol* 1979;135:1051-6.
- 4 Guzik DS, Daikoku NH, Kaltreider DF. Predictability of pregnancy outcome in preterm delivery. *Obstet Gynecol* 1984; 63:645-50.
- 5 Holbrook RH Jr, Laros RK, Creasy RK. Evaluation of a risk scoring system for prediction of preterm labour. *Am J Perinatol* 1989;6:62-8.

Authors' reply

EDITOR,—A J Lyon and colleagues mention interesting data that they, in common with others, have obtained about the association between neonatal infection and genital mycoplasmas and chronic lung disease. It seems reasonable to speculate that the existence of these organisms in a neonate at least partially reflects bacterial vaginosis in the mother since both organisms are associated with bacterial vaginosis—*Mycoplasma hominis* more strongly than the ureaplasmas. On the assumption that this is the case, giving antibiotics that are active not only against the ureaplasmas but against the other bacteria found in bacterial vaginosis seems prudent.

Our responses to the concerns of Ann Yoong and of Cecilia J F Priestley and colleagues are as follows. We are continuing to look at our data, and in our current analysis there are 238 primigravidae. Four of the 197 women with normal (grade I) flora delivered before term compared with one of the nine with grade II flora and five of the 32 with grade III flora. Thus, as for other women with abnormal flora, primigravidae with grades II and III flora were significantly more likely to have a preterm delivery (odds ratio 6.7 (95% confidence interval 1.35 to 35.05); $P < 0.01$ (Fisher's exact test)).

We do not agree with Priestley and colleagues that bacterial vaginosis often has an identifiable underlying cause, and, as we pointed out, sexually transmitted infections, including those due to *Chlamydia trachomatis*, were rare in our pregnant population. We agree with Yoong that bacterial vaginosis is a chronic recurrent condition, but only in some women, not in all. We have seen women with bacterial vaginosis who miscarried and then, in a subsequent pregnancy with a normal vaginal flora, proceeded to term. In the initial analysis, however, only 25 women had a history of preterm birth, so it is difficult for us to draw conclusions about them. Nor does the strong association between bacterial vaginosis and late miscarriage or preterm birth enable us to prove causation.

We have been conscious throughout our work that the condition might be merely a marker for an underlying change, perhaps hormonal, that causes preterm birth, as Priestley and colleagues mention. That is why current investigations involving treatment of bacterial vaginosis in pregnant women are important. At the moment, if a doctor is aware that a pregnant woman has bacterial vaginosis it seems reasonable to discuss the condition and treatment with her, but we are not formulating a policy that would lead to unnecessary antibiotic treatment. Indeed, only if controlled trials of antibiotic treatment are shown to reduce the incidence of premature delivery would we recommend screening and treatment in pregnancy.

Finally, Yoong worries about generating a false sense of security in women with normal flora. Crude univariate analysis in our study shows that 96% of women with normal flora go to term compared with 83% of women with bacterial vaginosis. If this produces a false sense of security in women with normal flora we believe it to be misplaced.

P E HAY

Department of Genitourinary Medicine,
St George's Hospital,
London SW17 0RE

R F LAMONT

Department of Obstetrics and Gynaecology,
Northwick Park Hospital,
Harrow, Middlesex HA1 3UJ

D TAYLOR-ROBINSON

MRC Sexually Transmitted Diseases Research Group,
St Mary's Hospital,
London W2 1NY

Haematuria clinics

Cystoscopy of little value in children

EDITOR,—In the editorial on haematuria clinics, Philip Marazzi and Roger Gabriel do not refer explicitly to children under 15 years old.¹ It would be unfortunate if unwary readers assumed, by default, that the problems of diagnosis and management in children are similar to those in adults; they are not.

Surgically remediable causes of haematuria in children are generally confined to the upper urinary tract and can be diagnosed by ultrasonography combined with plain abdominal radiography.² Bladder causes are rare and cystoscopy is generally unnecessary,^{3,4} yet paediatric nephrologists still see children referred with haematuria in whom cystoscopy has yielded normal results.

Once urinary tract infection, surgical causes, and rare medical disorders have been excluded most children with haematuria will be found to have a glomerulopathy. The most common causes are IgA nephropathy, Alport's syndrome, and thin membrane nephropathy,² but incompletely resolved poststreptococcal nephritis and unrecognised Henoch-Schönlein nephritis, with minimal rash, are occasional causes. The haematuria in thin membrane nephropathy and in girls with Alport's syndrome is usually only microscopic and should not be dismissed as necessarily benign.

When haematuria is persistent, familial, or accompanied by proteinuria or granular casts, renal biopsy will be required to determine the cause, and processing for immunofluorescence and electron microscopy is crucially important.² Not all patients, however, need a biopsy, at least immediately, and selection demands the skill and experience of a paediatric nephrologist, to whom these children are best referred.

R H R WHITE

Department of Nephrology,
Children's Hospital,
Birmingham B16 8ET

- 1 Marazzi P, Gabriel R. The haematuria clinic. *BMJ* 1994;308: 356. (5 February.)
- 2 White RHR. The investigation of haematuria. *Arch Dis Child* 1989;64:159-65.
- 3 Glasgow EF, Moncrieff MW, White RHR. Symptomless haematuria in childhood. *BMJ* 1970;iii:687-92.
- 4 Bullock N. Asymptomatic microscopic haematuria. *BMJ* 1986;292:645.

Open access is useful if rapid treatment is available

EDITOR,—Haematuria is often worrying for patient and doctor alike; it is the single most important symptom in urological practice. It should be taken seriously and investigated promptly to exclude an underlying malignancy. In this context, the concept of haematuria clinics¹ has become popular over the past 15 years. With the advent of flexible cystourethroscopy all the necessary investigations can be completed relatively quickly. Undoubtedly the provision of "rapid" haematuria diagnostic services will allay patients' anxieties, and there may be an associated survival benefit. The effectiveness of haematuria clinics was the subject of a recent review that concluded that such a service may result in an improvement in prognosis.² This also depends, however, on being able to provide rapid treatment after diagnosis.

We established an open access haematuria clinic 14 months ago and recently published the results.³ There is little point in running such a service if communication with general practitioners is inadequate. We encourage referrals by fax or telephone and see all patients within one week of referral. If the general practitioner has already sent urine specimens for microbiological and cytological examination then the diagnostic work up is finished within 24-36 hours of the patient being

seen in the clinic. Patients should undergo flexible cystoscopy only in a sterile theatre environment; therefore theatre time and space have to be available. A disadvantage of flexible cystoscopy is that biopsy specimens of suspicious areas cannot be obtained for histological examination. A concern that tumours might be missed that would be diagnosed with conventional rigid cystoscopy seems to be unwarranted.⁴ In addition, cystological examination of the urine is mandatory and, in particular, is a key investigation in carcinoma in situ of the bladder. Finally, the ability to provide such a service depends heavily on support services.

Two issues remain unresolved. Firstly, to avoid swamping such a service a sensible referral policy from primary care needs to be established and encouraged. Secondly, precisely what constitutes an appropriate diagnostic protocol varies among patients and remains a matter for debate.

M A W MILLER
M S NATHAN
R J MORGAN

Royal Free Hospital,
London NW3 2QG

- 1 Marazzi P, Gabriel R. The haematuria clinic. *BMJ* 1994;308: 356. (5 February.)
- 2 Nathan MS, Naseem MS, Morgan RJ. Same day haematuria diagnostic service. *Journal of One Day Surgery* 1993;3(2):12
- 3 Britton JP. Effectiveness of haematuria clinics. *Br J Urol* 1993;71:247-52.
- 4 Walker L, Liston TG, Lloyd-Davies RW. Does flexible cystoscopy miss more tumours than rod-lens examination? *Br J Urol* 1993;72:449-50.

Human gonadotrophin preparations

Patients can't afford new drug

EDITOR,—Recently, a drug company launched a new gonadotrophin preparation and at the same time discontinued its previous product, which itself had been hailed as a major breakthrough on the basis that preparations containing low concentrations of luteinising hormone or follicle stimulating hormone alone were considered better at inducing ovulation. What concerns us is the sudden discontinuation of a product that many specialists had previously been encouraged to use. Though we believe in the advantage of preparations containing low luteinising hormone concentrations or follicle stimulating hormone alone,^{1,2} we are concerned for patients seeking treatment of infertility as many have to pay for their drugs.

We run a busy fertility clinic offering simple treatments such as superovulation with intra-uterine insemination,³ transvaginal ultrasound monitored egg release and insemination (follicles are lanced to ensure ovulation), and direct oocyte transfer, a modification of gamete intrafallopian transfer (GIFT).^{3,4} These are carried out as outpatient procedures, offering couples the opportunity of active management locally (reducing the stresses of travel). Without the costly fertility drugs, these three treatments would be much less effective,² and would give us substantially less than the 10-15% delivery rates per cycle that we currently achieve.

Our patients currently pay between £200 and £400 per cycle for their drugs. Now that the follicle stimulating hormone preparation (the mainstay of our fertility programme) has been replaced with purified follicle stimulating hormone at twice the price some couples will effectively be barred from further active management of their infertility. Some couples will elect to be treated with an older preparation containing high concentrations of luteinising hormone, simply because it is cheaper. This is ironic because the drug company previously claimed this older preparation to be less effective than the follicle stimulating hormone preparation it has now discontinued.