The second is the disappointingly large number of women who respond poorly to such therapy.

New approaches, such as the use of cytokines, antigestagens and relaxin continue to be explored and to these can now be added NO donors. A long-cherished dream of clinicians has been to achieve such a high degree of cervical ripeness before the onset of labour, that mothers only require a short period of myometrial contractions to complete cervical dilation. We might even dream of improving on spontaneous labour. In this regard NO donors, whether alone or in combination with other therapies, would seem to represent an exciting new prospect.

On the other hand, the clinical subjects which may yet offer the most fertile field of investigation are those who respond poorly to therapies which are usually highly reliable. There is, for instance, a hard core of mothers whose cervices stubbornly resist local application of PGE2. This suggests that while PGE2 may be a crucial component in cervical ripening perhaps, as Kelly (1994) has suggested, by dilating and increasing the permeability to leukocytes of the cervical vasculature, that effect may be futile in the absence of other factors, such as chemokines and neutrophils.

A clearer picture of the biology of cervical ripening is steadily emerging. Although the jigsaw is still far from complete, NO seems certain to be one of the pieces.

References
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The inflammatory mediator, nitric oxide (NO), formed by the action of nitric oxide synthase (NOS) has been implicated in a huge variety of physiological and pathological processes, both within the female reproductive system and beyond (Anggard, 1994; Norman and Cameron, 1996; Thomson et al., 1997a; Rosselli, 1997). A role for NO has recently been defined in ripening of both the human and guinea pig uterine cervix (Thomson et al., 1997b; Chwalisz et al., 1997). Cervical ripening, defined as an increased softening, distensibility, and effacement of the cervix, occurs physiologically prior to the onset of parturition in species such as the rat, guinea pig, sheep and human. The timing of such ripening requires careful regulation. In the human, failure of cervical ripening leads to a delay in the onset of labour, with an associated increase in Caesarean section and birth asphyxia. Conversely, premature cervical ripening may lead to preterm delivery, a condition associated with increased perinatal mortality and morbidity.

There are no data on the potential role of endogenous NO in physiological ripening of the human cervix. However, previous studies in the rat have suggested that cervical ripening is associated with an increase in NO production (Buhimschi et al., 1996; Ali et al., 1997). Cervix from labouring rats at term had a greater ability to generate nitrite (the breakdown product of NO) in culture, than cervix obtained either from non-pregnant or rats in mid-pregnancy. Moreover, cervix from labouring rats had greater concentrations of inducible NO synthase (iNOS) and bNOS protein and mRNA compared with rats in mid-pregnancy.

The paper by Chwalisz et al. (1997) is the first to demonstrate that application of NO donors induces cervical ripening in guinea pigs. We have also reported similar effects of NO donors on the human cervix (Thomson et al., 1997b). In the study by Chwalisz et al. (1997) 5 mg of the NO donor sodium nitroprusside administered twice daily to the guinea-pig cervical canal on day 42 and 43 post-coitum (term = day 67, post-coitum) increased cervical distensibility within 12 h of administration of the final dose of drug. These effects were comparable with those of the progesterone antagonist onapristone (10 mg), prostaglandin (PG) E2 (3 mg), or the prostaglandin analogue sulprostone (0.1 mg). Moreover, the effects of NO donors on cervical histology were similar to those associated with spontaneous cervical ripening at term with an inflammatory infiltrate and disruption of organization of collagen fibrils. There were no apparent effects of the NO donor on cervical dilatation. In our own study, primigravidae treated with either of the NO donors isosorbide mononitrate (40 mg) or glyceryl trinitrate (500 μg) applied in a single vaginal dose at 8–12 weeks gestation had significantly lower cervical resistance (determined by force required for cervical dilatation) within 3 h compared with a control group. In contrast to Chwalisz et al. (1997), we found that isosorbide mononitrate caused a small but significant increase in cervical dilatation. These studies clearly indicate that NO donors can induce cervical ripening in either early or mid-pregnancy when applied locally to either the guinea pig or human cervix. Further work is required to determine whether such cervical ripening effects also operate at term, which would have particular relevance for the control of labour in women.

Cervical ripening after nitric oxide

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If NO plays a role in the induction of cervical ripening, can manipulation of this effect be useful in clinical practice? Preterm cervical ripening is implicated in the mechanism of preterm delivery, and it is tempting to postulate that such premature ripening could be attenuated by inhibitors of NO synthesis. In pregnancy, however, NO appears to play an important role not only in uterine quiescence, but also in the maintenance of the feto-placental circulation (for review see Sladek et al., 1997). Unless a NOS inhibitor could be targeted exclusively at the cervix, the adverse effects at extra-cervical sites are likely to prohibit their in-vivo use in pregnancy. Furthermore, NO donors down-regulate vascular endothelial growth factor (VEGF), and inhibition could lead to enhanced vascular permeability which might also be detrimental to the mother (Tsurumi et al., 1997). A more attractive option is the use of NO donors to stimulate cervical ripening. There are two main indications for cervical ripening. Firstly, cervical ripening is used prior to suction termination in the first trimester to minimize the force required to dilate the cervix, and by inference the potential damage to the cervix, prior to uterine evacuation. Secondly, cervical ripening is initiated in the third trimester to facilitate induction of labour. Failure of cervical ripening in this situation increases the incidence of dysfunctional labour, and Caesarean section. At present, prostaglandins are the agents most commonly used for cervical ripening. However, they have significant side-effects, largely because of their concomitant stimulatory effect on myometrial contractility. In the first trimester, this myometrial activity causes abdominal pain and bleeding. At term, the myometrial activity induced following the administration of prostaglandins is associated with an abnormal fetal heart rate in 7% of pregnant women (Wing et al., 1995). The advantage of NO donors for cervical ripening may lie in their relative relaxant effects on the myometrium (Norman et al., 1997). NO donors may therefore be the ideal agents for cervical ripening; those which ripen the cervix with minimal side-effects and without inducing myometrial contractility. Our preliminary data in the first trimester indicates that the use of NO donors is associated with a lower incidence of abdominal pain and pre-operative bleeding, but a higher incidence of headache and a greater intra-operative blood loss compared with prostaglandins (A.J.Thomson, C.B.Lunan, M.A.Ledingham et al., unpublished). Further work is required to determine the efficacy and side-effect profile of NO donors in inducing cervical ripening. In human pregnancy, this work should proceed cautiously, in order to establish the safety of NO donors in the third trimester. If successful, however, NO donors could make a major impact on obstetric practice within the next 10 years.

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References