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Cone biopsy shortens the cervix and is associated with preterm birth in later pregnancies

Research question Does vaginal ultrasonography help predict preterm birth among women who have been treated for cervical intraepithelial neoplasia?

Answer Possibly. Vaginal ultrasonography may help predict preterm birth among women who have had loop electrosurgical excision.

Why did the authors do the study? Some evidence exists that treatments for cervical intraepithelial neoplasia, such as cone biopsy, are associated with preterm birth. If so, a shortened cervix could be to blame. These authors wanted to find out if measuring the cervix in mid to late pregnancy could help predict preterm birth among women who have had cervical procedures.

What did they do? They compared three groups of pregnant women: 132 who had had loop electrosurgical excision, cold knife conisation, or cryotherapy for cervical intraepithelial neoplasia, 63 who had had a spontaneous preterm birth, and 81 who had had neither. The authors measured the women's cervices by using vaginal ultrasonography between 24 and 30 weeks of pregnancy and followed them up until the birth. They looked for differences in cervical length and incidence of preterm birth between the three groups and then did a multiple logistical regression analysis to find out which cervical procedures were independently associated with preterm birth. Finally, they estimated the predictive value of a short cervix for preterm birth among women who had had loop electrosurgical excision.

What did they find? Women who had had any cervical procedure had a shorter cervix mid-pregnancy than low risk controls (mean length 3.54 cm, 3.69 cm, 3.75 cm among women with loop excisions, cold knife conisation, and cryotherapy compared with 4.21 cm among controls; $P<0.05$ for all procedures). Women with a previous preterm birth also had a shorter cervix (3.78 cm).

The two types of cone biopsy, but not cryotherapy, were independently associated with preterm birth (odds ratio 3.45 (95% CI 1.28 to 10) for loop excision and 2.63 (1.28 to 5.56) for cold knife conisation). Among women with a previous loop electrosurgical excision, a cervix less than 3 cm on vaginal ultrasonography predicted preterm birth with a positive predictive value of 53.8% (7/13) and a negative predictive value of 95.2% (59/62). The authors were unable to estimate the predictive value of vaginal ultrasonography for women who had had cold knife conisation because of the small size of their sample.

What does it mean? These data add to growing evidence of a link between cone biopsy and preterm birth and are reassuring for women who have had cryotherapy. The strongest findings were for women who had had loop electrosurgical excision, whose risk was three times higher than that of controls. Measuring the cervix of these women in pregnancy may be useful, if only because women with a cervix over 3 cm long seem unlikely to deliver early. Note, however, that the authors had no data on social class and were unable to account for the effects of this important confounder.

Crane JMG, et al. Transvaginal ultrasonography in the prediction of preterm birth after treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2006;107:37-44

Editor's choice

Count the harms

Hippocrates may not have foreseen the complexities of modern medicine, but 24 centuries ago he (or whoever wrote the Hippocratic Oath) set down a fundamental rule for all clinicians and researchers—"first do no harm." This rule has special resonance this week as we explore over-diagnosis in breast cancer screening, and the evolving clinical trial nightmare at Northwick Park.

Three weeks ago an editorial in the *BMJ* concluded that despite limitations, breast cancer screening does save lives (*BMJ* 2006;332:499-500). But in the same issue of the journal we published an analysis by Karsten Juhl Jørgensen and Peter Gøtzsche of the letters inviting women for screening (*BMJ* 2006;332:538-541). None of the letters mentioned the major harms of screening, and the authors concluded that organisers of screening programmes have a serious conflict of interest in wanting high uptake, which compromises their ability to provide balanced information about benefits and harms. That same week we also published "online first" Sophia Zackrisson and colleagues' 15 year follow-up from the Malmö trial of screening for breast cancer, which concluded that 10% of cancers detected by screening in women aged 55-69 are over-diagnosed.

This week we pull these strands together, along with letters selected from among the rapid responses to all three pieces (p 727). The total picture is far from reassuring. As Zackrisson et al explain (p 689), their 10% figure is a conservative estimate, since some of the women in the control group also had mammography. In a letter, Gilbert Welch and colleagues suggest that the more relevant figure is 24% since, based on the Malmö data, this is the chance that a screen detected cancer represents over-diagnosis (p 727). Their higher figure is more in line with Gøtzsche's estimate of 30% (p 727). Whatever the figure, or the reasons for it (pp 678, 691 and 727), there seems little doubt among our contributors that over-diagnosis is real and substantial. As Michael Baum relates, his unaddressed concerns about the UK's screening programme, which he helped to set up, led him to resign from the programme committee (p 728). He and Hazel Thornton (p 728) endorse Gøtzsche's concerns about conflicts of interest and the "fobbing off" of women with unbalanced, insufficient information.

Lack of proper information may prove to be at the heart of events that have left six young men seriously ill in hospital after the "first in man" trial of the monoclonal antibody TGN1412 (p 683). Michael Goodyear asks what lessons can be learned from this catastrophe (p 677), and Kate Mandeville describes her own experiences as a clinical trial volunteer (p 735). Questions are mounting about the trial, and they need answering. An inquiry by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) will not be enough, since this body may itself be implicated in mistakes that were made. There must be a full public inquiry if we are to prevent something like this happening again.

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