Survival after extremely preterm birth

Viability is not determined solely by gestational age

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RESEARCH, p 1221

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Last week proposals in the UK to lower the 24 week deadline for abortion were rejected in the House of Commons. Decisions involving late abortion and the care of extremely preterm infants often result from strongly held beliefs rather than evidence. To a large extent this is understandable as these decisions are personal. However, when moral judgments are imposed on those holding different views and when the rights of the infant, be it to life or death, are in danger of colliding with those of parents and society the need for evidence is paramount.

In the linked study, Field and colleagues compare survival figures for two adjacent time periods, 1994-9 and 2000-5, for infants born at a gestational age of 22 weeks to 25 weeks and six days in a geographically defined region of the United Kingdom, the former Trent health region.[1] During this 12 year period, there was no change in the number of extremely preterm infants who were alive when born but died before admission to a neonatal unit. Survival to discharge significantly improved for infants born at 24 and 25 weeks but not for those born at 23 weeks. No babies born at 22 weeks' gestation survived in either period.

Data like these that describe temporal trends in geographically defined populations are important. Single centre studies are confounded by selection bias and tend to overestimate the likelihood of survival. The improved survival over time of more mature preterm infants shows how important it is to base decisions on as contemporaneous data as possible.

The upper gestational age limit for abortions in the UK remains at 24 weeks, although there is no age limit if the infant would be severely impaired if born alive or if the physical or mental health of the mother would be at serious risk were the pregnancy to continue. Of the 193 700 abortions that were recorded in 2006, 2% were at 20 weeks' gestation or over.[2] The UK Abortion Act 1967 was amended in 1990 to lower the age limit from 28 to 24 weeks, a change that was influenced by the Royal College of Obstetricians and Gynaecologists' report Fetal Viability and Clinical Practice (1985), which noted significant improvements in the survival of infants born preterm.[2]

The discussion continues to centre on the notion of "viability." However, other factors influence survival and health outcomes. Directives on the care that should be offered to extremely preterm babies should not be based primarily on gestational age because of biological variation and differing ethical perspectives.[3]

A recent study in the United States shows that outcomes can be predicted more accurately by considering four factors—sex, exposure to antenatal steroids, single or multiple birth, birth weight—in addition to gestational age.[4] Improved brain imaging and other prognostic investigations enable more informed discussion between parents and clinicians about withdrawal of intensive support in the face of the prospect of major impairment, another real but often unquantified influence on survival.[5] Thus, the care of the late second trimester fetus and the extremely preterm infant should not be determined solely by consideration of viability based on gestational age.

Field and colleagues' data are in keeping with other geographically defined population studies from the UK (EPICure), Belgium (EpiBel), Denmark, Finland, France (EPIPAGE), the Netherlands, Norway, Sweden, and Australia.[6] The new data are noteworthy, however, because they extend to 2005 and provide information that is among the most up to date available.

The assessment of health outcomes in large geographically defined populations has been severely limited by the costs and complexity of acquiring data. Epidemiological surveys have traditionally been conducted as single exercise research studies. They are expensive, funded for a limited period, and take a long time for data to be processed, analysed, and published.

Data for the Trent neonatal survey are collected by dedicated personnel and entered into a research register. Applying such robust but labour intensive methodology over many years is practical only when dealing with relatively small populations, in this case 16 hospitals and 55 000 births. A challenge for the coming years must be to harness emerging healthcare technologies to enable speedier entry of national health outcomes into the public domain.

In the UK this possibility is within our grasp. After a Department of Health review in 2003, neonatal services were organised into clinical networks with shared management and coordinated care pathways.[7] This led to the development of electronic neonatal records that are now used by about three quarters of the 180 neonatal units in England.[8] These records hold high quality standardised data on every admission to a neonatal unit; they support day to day clinical care, management, and commissioning; and they provide instant access to a full clinical record by the receiving hospital when a baby is transferred.

The potential provided by these electronic records to move the ascertainment of neonatal health outcomes out of the research arena and into routine NHS processes is

being looked at by the Neonatal Data Analysis Unit.[8] The unit was formed to support and develop the use of electronic clinical data for audit, service evaluation, surveys, and research. It is only with information on appropriately case mix adjusted outcomes in near contemporaneous cohorts that parents, clinicians, and governments will be able to make truly informed decisions.

1 Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. *BMJ* 2008; doi: 10.1136/bmj.39555.670718.BE.
2 House of Commons Science and Technology Committee. *Scientific developments relating to the Abortion Act 1967*. 2007. www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/1045/1045i.pdf.
3 Nuffield Council on Bioethics. *Critical care decisions in fetal and neonatal medicine: ethical issues*. 2006. www.nuffieldbioethics.org/fileLibrary/pdf/CCD_web_version_22_June_07_(updated).pdf.
4 Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; for the National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity: moving beyond gestational age. *N Engl J Med* 2008;358:1672-81.
5 Cuttini M, Nadai M, Kaminski M, Hansen G, de Leeuw R, Lenoir S, et al. End-of-life decisions in neonatal intensive care: physicians' self-reported practices in seven European countries. EURONIC Study Group. *Lancet* 2000;355:2112-8.
6 Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261-9.
7 Department of Health. *Neonatal intensive care review: strategy for improvement*. 2003. www.dh.gov.uk/en/Consultations/Closedconsultations/DH_4073174.pdf.
8 National Audit Office. *Caring for vulnerable babies: the reorganisation of neonatal services in England*. 2007. www.nao.org.uk/publications/nao_reports/07-08/0708101.pdf.

Smoking cessation in primary care

Evidence does not support routine use of combination therapy with nortriptyline

RESEARCH, p 1223

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In the linked paper, Aveyard and colleagues report a pragmatic randomised controlled trial (RCT) of nortriptyline for smoking cessation.[1] The study randomised 901 smokers to a standard regimen of nortriptyline or placebo, and all participants were given the option of using nicotine replacement according to their preference ("pragmatic therapy"). The National Health Service stop smoking service provided group support in seven weekly sessions. The primary end point of the study was prolonged abstinence at six months. Nortriptyline plus nicotine replacement showed a modest but non-significant effect compared with placebo plus nicotine replacement at six months (relative risk 1.4; 95% confidence interval 1.00 to 1.98). This effect size is similar to that reported in a Cochrane systematic review and meta-analysis of two RCTs of nortriptyline for smoking cessation (n=318; odds ratio 1.48; 0.87 to 2.54).[2-4] The results of the meta-analysis were also not significant, and significant heterogeneity occurred between studies.

Some of the major strengths of this research are its apparent methodological quality and large sample size, and it provides a substantial amount of new material for future meta-analyses of nortriptyline for smoking cessation. In particular, the sample size for the meta-analysis of combination nortriptyline will have increased at least fourfold compared with what has been published to date. These extra data should reduce statistical heterogeneity and provide greater statistical power to detect a modest effect of treatment if it exists, given the similarity between the effect size estimate of the present study and the existing pooled estimate from the most recent Cochrane review. This similarity supports the quality of the present study and suggests that the effect size estimate is close to the true value.

The study also highlights how little research has been published on combination treatments for smoking cessation. As the authors note, Cochrane systematic reviews and meta-analyses[4 5] have identified only two RCTs of combination nortriptyline,[2 3] and data indicating greater efficacy of nicotine replacement plus bupropion compared with nicotine replacement alone are derived from just one RCT.[6] Furthermore, few published studies have compared the benefit of combining two or more types of nicotine replacement therapy with individual treatments,[7] and we are not aware of any published trials of varenicline plus other pharmacotherapies for smoking cessation.[8] In fact, evidence based guidelines from the World Health Organization,[9] the NHS,[10] and the US Public Health Service (USPHS)[7] do not recommend combination bupropion therapy, and only the USPHS guideline explicitly recommends combination nicotine replacement therapy.[7]

Aveyard and colleagues are correct in concluding that on the basis of these results nortriptyline should not be routinely added to nicotine replacement therapy for smoking cessation. Moreover, although the contraindications for nicotine replacement are relatively few, those for nortriptyline are greater, so that combination therapy may not be appropriate for all. However, to date, more evidence supports a modest effect of combination nortriptyline than any other combined treatment for smoking cessation.

More research is needed to examine the relative efficacy of combined treatments for smoking cessation because even modest increases in the efficacy of drugs currently available to primary care doctors are likely to have a large effect on public health. For example, after the introduction of nicotine replacement therapy, the US Centers for Disease Control and Prevention estimated that attempts to quit smoking in the United States increased from around one million to seven million each year,[11] and the widespread use of this treatment in the US was projected to increase the number of ex-smokers by hundreds of thousands each year.[12]

Another important contribution of Aveyard and colleagues' study is the use of a pragmatic methodology. Compared with conventional RCTs—which are often funded by the drug industry and based in tertiary centres—the methodology provides a more realistic assessment of drug use and reflects the shared decision

making practices of primary care practitioners in the community. Patients' experiences with drugs in "real world" clinical practices are particularly relevant. Ultimately, primary care doctors rely on clinical judgment and experience to weigh the risks and benefits of a drug such as nortriptyline and to identify subgroups for whom it is contraindicated, such as people at risk for suicide, or for whom it may confer advantages, such as people with mild depression. The pragmatic approach may make doctors more confident that they can generalise results to real world practice, with perhaps greater potential to affect standards of care. Thus, pragmatic designs should be considered in future studies, particularly once efficacy has been established in more traditional RCTs.

If we had an established standard of care for use of combined treatments, such as nortriptyline plus nicotine replacement, given the dramatic benefits of smoking cessation on reducing mortality, even a modest increase in efficacy relative to nicotine replacement alone (consistent with results from the present study) would be expected to prevent millions of premature deaths worldwide over time.

1 Aveyard P, Johnson C, Fillingham S, Parsons A, Murphy M. Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial. *BMJ* 2008; doi: 10.1136/bmj.39545.852616.BE.
2 Hall SM, Humfleet GL, Reus VI, Munoz RF, Cullen J. Extended nortriptyline and psychological treatment for cigarette smoking. *Am J Psychiatry* 2004;161:2100-7.
3 Prochazka AV, Kick S, Steinbrunn C, Miyoshi T, Fryer GE. A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. *Arch Intern Med* 2004;164:2229-33.
4 Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007;(1):CD000031.
5 Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008;(1):CD000146.
6 Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-91.
7 Fiore MC. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA* 2000;283:3244-54.
8 Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2007;(1):CD006103.
9 Raw M, Anderson P, Batra A, Dubois G, Harrington P, Hirsch A, et al. WHO Europe evidence based recommendations on the treatment of tobacco dependence. *Tobacco Control* 2002;11:44-6.
10 Raw M, McNeill A, West R. Smoking cessation guidelines for health professionals. A guide to effective smoking cessation interventions for the health care system. Health Education Authority. *Thorax* 1998;53(suppl 5 Pt 1):S1-19.
11 Burton SL, Gitchell JG, Shiffman S. Use of FDA-approved pharmacologic treatments for tobacco dependence—United States, 1984-1998. *MMWR Morb Mortal Wkly Rep* 2000;49:665-8.
12 Shiffman S, Gitchell J, Pinney JM, Burton SL, Kemper KE, Lara EA. Public health benefit of over-the-counter nicotine medications. *Tob Control* 1997;6:306-10.

Increasing drug resistant tuberculosis in the UK

Control depends on a global perspective, not solely on local strategies

RESEARCH, p 1231

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Tuberculosis has resurged in the United Kingdom over the past two decades, with 8000 cases being reported in 2006.[1] Previous reports have indicated a stable proportion of drug resistance in people with tuberculosis in the UK from 1993 to 1999.[2] In the linked paper, Kruijshaar and colleagues present an updated analysis of trends in drug resistance in tuberculosis cases in the UK.[3]

Kruijshaar and colleagues report an increasing proportion of isoniazid resistance (from 5% to 6.9%) and modest increases in the proportions of rifampicin resistance (1.0% to 1.2%) and multidrug resistance (0.8% to 0.9%).[3] However, the true burden of drug resistant tuberculosis is better shown by the incidence of resistant cases, rather than the proportion of cases that are resistant.[4] Although the increase in the proportion of resistant cases is modest, when combined with the rising incidence, the increase in numbers of resistant cases is greater than would be assumed by looking at proportions alone.

Globally, the incidence of tuberculosis may be showing early signs of decline, albeit with important regional variations.[5] Yet the incidence of multidrug resistant tuberculosis increased to an estimated 0.5 million cases in 2006.[6] In addition, extensively drug resistant strains have now been reported in at least 45 countries,[6] with two cases in the UK. Although the greatest impact will be in those settings with the highest tuberculosis and HIV burden, this must serve as a wake up call for global control of tuberculosis in all countries.

The central approach to the control of tuberculosis from the World Health Organization's Stop TB programme is the routine detection and treatment of smear positive cases.[7] In addition, the Global Plan to Stop TB advocates several other approaches, including intensified case finding for earlier detection of active tuberculosis, provision of isoniazid preventive therapy for HIV coinfected patients, and tuberculosis infection control in healthcare and congregate settings.[7] The potential impact of some of these approaches on the control of tuberculosis is being investigated currently; for example, in the cluster randomised trials and mathematical modelling of the Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE; www.tbhiv-create.org).

Recent efforts have revitalised research into new diagnostics for tuberculosis, some of which identify Mycobacterium tuberculosis and give isoniazid and rifampicin sensitivities within 24 hours.[8] These will greatly reduce the time that patients are treated with inappropriate regimens, with direct implications for the health of patients and onward transmission.[9] Treating patients with regimens that contain insufficient drugs to which the strain is sensitive will promote further resistance. New drugs are urgently needed for multidrug resistant strains, which currently require 18-24 months of treatment, and for extensively drug resistant strains, which are difficult to treat at all.

Kruijshaar and colleagues found that multidrug resistance was four times more common in people with a history of tuberculosis than in those without. Combined with the low degree of clustering of multidrug resistant strains, this may mean that transmission of resistant

strains is uncommon and not a major concern. However, the increase in isoniazid resistance in London was largely caused by an outbreak of more than 300 cases.[3] Among the multidrug resistant cases, 73% had no history of tuberculosis. This suggests that most multidrug resistant cases were not caused by failure of previous treatment (acquired resistance), but by infection with a multidrug resistant strain (primary resistance). The low degree of clustering may be the result of transmission from multidrug resistant cases originating outside the UK.

High transmission of resistant tuberculosis has been shown in other settings—for example, the extensively drug resistant epidemic in Tugela Ferry, South Africa, which saw a high degree of nosocomial transmission and mortality that included healthcare workers.[10] Such experiences demonstrate the need to intensify strategies to curb transmission of resistant strains.

Infection control must be rigorously enforced. In resource poor settings this need not be expensive. A study from Lima, Peru, found that opening doors and windows greatly increased the number of air changes per hour, even compared with mechanically ventilated rooms.[11] Mathematical modelling of the Tugela Ferry outbreak has shown that using available strategies to control nosocomial infection could prevent half of their extensively drug resistant cases over the next five years.[12]

Molecular epidemiology should be considered internationally as a public health tool and not limited to research settings. This would enable quicker identification of possible outbreaks and greater understanding of the global epidemiology of tuberculosis.

Drug resistant tuberculosis in the UK cannot be controlled solely with local strategies—a global perspective is needed. This is best summed up by the slogan of World Tuberculosis Day 2007—"TB anywhere is TB everywhere."

1 Kruijshaar ME, French CE, Anderson C, Abubakar I. Tuberculosis in the UK: annual report on tuberculosis surveillance and control in the UK 2007. London, Health Protection Agency, 2007. www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1204100459636?p=1158945066450.
2 Djuretic T, Herbert J, Drobniewski F, Yates M, Smith EG, Magee JG, et al. Antibiotic resistant tuberculosis in the United Kingdom: 1993-1999. *Thorax* 2002;57:477-82.
3 Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, et al. Increasing antituberculosis drug resistance in the United Kingdom: analysis of national surveillance data. *BMJ* 2008; doi: 10.1136/bmj.39546.573067.25.
4 Zager EM, McNerney R. Multidrug-resistant tuberculosis. *BMC Infect Dis* 2008;8:10.
5 WHO. *Global tuberculosis control: surveillance, planning, financing.* 2008. www.who.int/tb/publications/global_report/en/.
6 WHO. *Anti-tuberculosis drug resistance in the world: fourth global report.* 2008. www.who.int/tb/publications/2008/drs_report4_26feb08.pdf.
7 Stop TB Partnership and WHO. *Global plan to stop TB 2006–2015.* 2006. www.stoptb.org/globalplan/.
8 Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. *J Infect Dis* 2007;196(suppl 1):S15-27.
9 Dowdy DW, Chaisson RE, Moulton LH, Dorman SE. The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model. *AIDS* 2006;20:751-62.
10 Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;368:1575-80.
11 Escombe AR, Oeser CC, Gilman RH, Navincopa M, Ticona E, Pan W, et al. Natural ventilation for the prevention of airborne contagion. *PLoS Med* 2007;4:e68.
12 Basu S, Andrews JR, Poolman EM, Gandhi NR, Shah NS, Moll A, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. *Lancet* 2007;370:1500-7.

Reforming NHS dentistry

Equitable distribution of affordable dental services is still possible

ANALYSIS, p 1219

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The linked analysis article by Thomas and colleagues provides routine data on hospital admissions and case reports to support their assertion that "admissions for surgical drainage of dental abscess are a result of changes in the provision of primary dental care in the United Kingdom."[1] Are Thomas and colleagues correct in their assumption? What have been the effects of the "new contract"—launched in England and Wales in 2006—on NHS dentistry?

The new contract was perceived as a portal to a new era of NHS dentistry. No longer would the general dental practitioner be chained to the "treadmill" of a "fee per item" NHS service but would focus on the prevention of dental caries, periodontal disease, and oral malignancies, thereby allowing for a more stress-free working environment for dentists and patients. Dental educators, dental hygienists, and dental therapists were of central importance in the new contract as providers of expertise in oral health. The essence of the contract was to promote oral health and subsequently increase access to primary dental health care, with dental treatment being conceptualised as a safety net for those who slipped off the prevention high wire.

Funding for NHS dentistry also changed as commissioning was devolved to local primary care trusts. Primary care trusts were provided with government funding to ensure "a high quality NHS dental service and to improve oral health and address inequalities."[2] Primary care trusts were able to place dental surgeries where they were needed and provide dentists with a stable annual income based on an agreed number of complete patient treatments—known as "units of dental activity." The units of dental activity replaced the old fee per item (piece work) system, which had been considered as an incentive for more invasive and complex treatment.[3] A simplified charging system was introduced to help patients gain access to affordable NHS treatment. Thus, all the ingredients were in place to promote accessible and affordable primary dental care. The 2006 contract, the greatest reorganisation of dental services since the beginning of the NHS, was instigated with the best of intentions.

When reports of difficulties in accessing NHS dentistry and of deregistered NHS patients queuing outside new dental surgeries hit the headlines,[4 5] the government, the dental profession, and patient groups queried the ability of the new contract to fulfil its potential. Government called for expert opinion in its select committees,[6]

dentists called for renegotiation, and patient groups showed that despite the new contract the main barriers to NHS dental care remained—as before—costs, availability, and anxiety.[7] Most patients who had accessed NHS dental care considered the treatment they received to be of the highest standard.[7] So what went wrong?

To answer this question we must revisit "Options for Change,"[2] which set out the parameters for the 2006 contract. Primary dental care would be cash limited, with primary care trusts holding the budget. Dental premises—once a retirement nest egg—would no longer be sold with goodwill, thereby reducing dentists' perceptions of being independent health contractors. Nevertheless, this document made it clear that changes in primary dental care must be "evolutionary"[2] rather than revolutionary. The NHS would offer general dental practitioners the choice of various arrangements at different points in their careers rather than continuing with a "one size fits all" approach. Also the changes would not occur suddenly but would evolve over time.

But despite these intentions, a sudden change did occur in the way dentists were contracted and paid by the NHS. By April 2006, dentists were no longer remunerated on the fee per item basis but by a prescribed number of units of dental activity. As the new dental contract gathered speed, the government's sensitivity regarding professional anxieties slipped away and the profession's sensitivities for patients' anxieties were forgotten. Despite the fact that only 4% of dentists left the NHS,[3] it seemed to the public that dentists had abandoned their patients,[4 5] and stories of dental extractions with pliers,[8] and as reported by Thomas and colleagues, life threatening dental abscesses,[1] became the folklore of the new dental contract.

With this degree of misunderstanding between public, patient, the medical profession, and the dental professions are there any grounds for optimism? It would seem that there are some grounds for hope because the government has acknowledged the difficulties experienced by the dental profession, and the extent of culture change involved.[5] It has recognised that "The next stage is to move to a more flexible and creative process of local commissioning, based on developing services more fully to meet patient needs. This will require strong engagement locally with public and patient representatives, with dentists and dental teams, and with primary care trust professional executive committees. It is only through this process that primary care trusts and dentists will be able to realise fully the benefits of the reforms in supporting improvements in access, quality and oral health."[3] It seems that we may be at the start of an important dialogue between stakeholders, which will have the ability to give patients a better experience of equitable and affordable NHS dentistry.[9]

During the first year of the new contract it seemed that it would be impossible to supply an equitable distribution of affordable NHS dentistry to populations in England and Wales. However, by appreciating the problems faced by patients and the profession, which were exacerbated by the speed of reform, the government now recognises the need for better communication between stakeholders. This dialogue should pave the way to accessible NHS dentistry for all.

1 Thomas SJ, Atkinson C, Hughes C, Revington P, Ness AR. Is there an epidemic of admissions for surgical treatment of dental abscesses in the UK? *BMJ* 2008; doi: 10.1136/bmj.39549.605602.BE.
2 Department of Health. *NHS dentistry: options for change.* 2002. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4008017.
3 Department of Health. *NHS dental reforms: one year on.* 2007. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077238.
4 Murphy C. Dental care: why nobody's smiling. *BBC News.* 2007. http://news.bbc.co.uk/1/hi/health/7044872.stm.
5 Hawkes N. January sales or a queue for an NHS dentist? *Times* 2007 April 5. www.timesonline.co.uk/tol/news/uk/health/article1615073.ece.
6 House of Commons Health Committee. *Dental services. Written evidence: Vol II.* 2008. www.publications.parliament.uk/pa/cm200708/cmselect/cmhealth/289/289ii.pdf.
7 National Health Service. *Dentistry watch survey results.* 2007. www.tin.nhs.uk/sys_upl/templates/PT_Directory_RSS/PT_Directory_RSS_details.asp?id=121782&pgid=2467&tid=153.
8 Boseley S. Patients pull own teeth as dental contract falters. *Guardian* 2007 Oct 15. www.guardian.co.uk/uk/2007/oct/15/health.healthandwellbeing.
9 Cohen L. Converting unmet need for care to effective demand. *Int Dent J* 1987;37:114-6.

Type of HRT and risk of venous thromboembolism

Transdermal oestrogen may be safer than oral oestrogen

RESEARCH, p 1227

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The results of randomised studies have been fairly consistent in finding an increased risk of venous thromboembolism with oral hormone replacement therapy. The linked systematic review by Canonico and colleagues finds similar results.[1] The review combined data from both randomised and observational studies and found that the risk of venous thromboembolism doubled with oral hormone replacement therapy compared with placebo (pooled odds ratio 2.4, 95% confidence interval 1.9 to 3.0).

Results from the observational studies alone were then pooled to assess the risk of venous thromboembolism from different types of hormone replacement therapy and duration of use. No significant difference was seen between combined therapy and oestrogen only (2.6 v 2.2; P=0.45). Risk of venous thromboembolism was significantly higher during the first year of treatment with oral oestrogen (4.0 for a duration of less than one year; 2.1 for more than one year), and past treatment was not associated with an increased risk (1.2, 0.9 to 1.7). The results echo those from the women's health initiative study.[2 3]

Canonico and colleagues' review is timely and follows the recent publication of the final analysis of the Esther (estrogen and thromboembolism risk) study.[4] This case-control study, by some of the same authors of this week's review, added a further 67 cases of venous thromboembolism with transdermal

use to the 15 that have been reported in three previous studies.

Because no randomised data exist on the risk of venous thromboembolism with transdermal oestrogen, the relation between venous thromboembolism and the route of hormone replacement therapy was derived from these four observational studies. Transdermal oestrogen did not increase venous thromboembolism (pooled odds ratio 1.2, 0.9 to 1.7)—the upper 95% confidence interval for transdermal use was lower than the lowest 95% confidence interval for oral use. Risk of venous thromboembolism was not higher with transdermal oestrogen for women at higher risk of thrombosis who had either raised body mass index or prothrombotic mutations.

Oral oestrogens are associated with prothrombotic changes in factors involved in coagulation and fibrinolysis.[5] Canonico and colleagues point out that whereas transdermal oestrogen has no effect, oral oestrogen increases plasma prothrombin fragment 1+2, lowers antithrombin concentrations, and causes an acquired resistance to activated protein C. They conclude that transdermal oestrogen seems to have little or no effect on haemostasis.[1]

However, the effect of the route of administration may be influenced by the type of oestrogen. The contraceptive patch, which was designed to deliver a relatively low dose of ethinyl estradiol (20 µg daily), was unexpectedly found to produce 60% higher concentrations in the serum than an oral 30 µg pill.[6] A 450% increase in sex hormone binding globulin, a marker of high oestrogen exposure, has also been shown with use of the contraceptive patch.[7] In addition, two of the three postmarketing studies, comparing the patch with a 30 µg or 35 µg oral contraceptive, showed a doubling of risk of venous thromboembolism with transdermal delivery.[8 9]

Do different types of hormone influence the risk of venous thromboembolism? Conjugated oestrogens and estradiol were used in both the observational and the randomised trials that showed increased risk. Estradiol was also the oestrogen used in the randomised study that found increased recurrence in women with previous venous thromboembolism.[10] One observational study found no increase with esterified oestrogens.[5] Whether the risk of venous thromboembolism for combined hormone replacement therapy is influenced by the type of progestogen, as in the oral contraceptive pill, also needs further investigation. The Esther study suggested that non-pregnane derivatives were associated with an increased risk whereas micronised progesterone and pregnane derivatives were not.[4] Interestingly, the pregnane derivatives included medroxyprogesterone acetate, the progestogen in the combined arm of the women's health initiative study.

Do we have any data on the effect of transdermal oestrogen on other outcomes? The Papworth study, which randomised women with angiographically confirmed ischaemic heart disease to transdermal therapy or placebo, found no significant difference in rates of cardiac events in the transdermal group.[11] The million women observational study showed similar increased risks for transdermal and oral oestrogens with respect to breast cancer.[12]

What about the side effect profile of transdermal oestrogens compared with oral ones? The answer to this has been hampered by a lack of trials and by incomplete and non-standardised reporting.[13] Transdermal hormone replacement therapy also costs more.

As Canonico and colleagues conclude, we need further investigation into the association between venous thromboembolism and transdermal oestrogen. In the meantime, we can advise healthy menopausal women aged 50-59 that the risk of venous thromboembolism with oral preparations is about 11 additional cases per 10 000 women per year for combined therapy and two additional cases per 10 000 women per year for oestrogen only.[14] Because a dose response seems to exist, these absolute risks may be lower with lower doses of hormones.[5] Women with previous venous thromboembolism or a mutation affecting prothrombin should be offered alternatives to oestrogen.

1 Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008; doi: 10.1136/bmj.39555.441944.BE.

2 Curb JD, Prentice RL, Bray PF, Langer RD, van Horn L, Barnabei VM, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772-80.

3 Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SAA, Brzyski R, et al; for the WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-45.

4 Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the Esther study. *Circulation* 2007;115:840-5.

5 Smith N, Heckbert S, Lemaitre R, Reiner AP, Lumley T, Rosendaal FR, et al. Conjugated equine estrogens, esterified estrogens, prothrombotic variants and the risk of venous thrombosis in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2006;26:2807-12.

6 Van den Heuval MW, van Bragt AJM, Alnabawy AKM, Kaptein MCJ. Comparison of ethinyl estradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005;72:168-74.

7 White T, Ozel B, Jain JK, Stanczyk FZ. Effects of transdermal and oral contraceptives on estrogen-sensitive hepatic proteins. *Contraception* 2006;74:293-6.

8 Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007;109:339-46.

9 Clinical Trials. Boston collaborative drug surveillance programme. *Postmarketing study of ortho evra and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of EE in relation to non- fatal venous thromboembolism, ischaemic stroke and myocardial infarction.* 2006. www.clinicaltrials.gov/ct2/show/NCT00511784.

10 Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy—results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000;84:961-7.

11 Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study group. *BJOG* 2002;109:1056-62.

12 Beral V; for the Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the million women study. *Lancet* 2003;362:419-27.

13 Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes. *JAMA* 2004;291:1610-20.

14 North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause* 2007;14:168-82.