Pre-eclampsia and increased cardiovascular risk

Guidelines for primary prevention of cardiovascular disease are appropriate for all women

PICTURE PARTNERS/ALAMY

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Cardiovascular disease is the leading cause of death in women.[1] Although its incidence is declining in men, this is not the case in women.[2]

Pre-eclampsia is a novel cardiovascular risk marker. Pre-eclampsia increases both the long term risk of cardiovascular disease and the risk that it will occur earlier. This has been shown consistently over time, in different settings, and for coronary and cerebrovascular outcomes. The magnitude of the risk for cardiovascular disease in women with previous pre-eclampsia is similar to that of dysplipidaemia.[3] Risk seems to be greater for pre-eclampsia than for gestational (or "pregnancy induced", non-proteinuric) hypertension. Risk is also greater for early-onset pre-eclampsia and for pre-eclampsia associated with placental complications (such as stillbirth or small for gestational age infants).[4] Two papers in this week's *BMJ* assess the link between pre-eclampsia and cardiovascular disease.[5 6]

In the first paper, Bellamy and colleagues summarise the consistency and strength of the association between pre-eclampsia and long term risk of cardiovascular disease.[5] They confirm the dose-response relation between severe pre-eclampsia (more severe hypertension or pre-eclampsia of earlier onset) and cardiovascular disease, as well as between gestational hypertension and long term hypertension.

The underlying link between pre-eclampsia and cardiovascular disease is unclear. Although pre-eclampsia may initiate endothelial damage, it is thought to be more likely that pre-eclampsia and cardiovascular disease have a common pathogenesis rooted in shared risk markers. Women with previous pre-eclampsia more often have the metabolic syndrome or its components (such as overweight or obesity, dyslipidaemia, hypertension, or insulin resistance).[7] In the second paper, Magnussen and colleagues provide support for a shared pathogenesis between cardiovascular disease and pre-eclampsia.[6] In their linkage study of Norway's medical birth registry and a Norwegian population based study of cardiovascular risk markers, they found significant associations (after adjustment) between pre-eclampsia and higher waist circumference, systolic blood pressure, diastolic blood pressure, and non-fasting total cholesterol before pregnancy.[6]

Despite the important attributable risk of cardiovascular disease associated with pre-eclampsia, the absolute risk over the short term is low.[8] Bellamy and colleagues show that in the 10-15 years after pre-eclampsia, the risk of cardiovascular disease and death is low (hypertension 21.9%, ischaemic heart disease 0.2%, stroke 0.2%, venous thromboembolic disease 0.3%, death 1.4%). Given these low short term risks, few women with previous pre-eclampsia are likely to have absolute values of lipids, blood pressure, or blood sugar that are above intervention thresholds, according to existing guidelines.

What should clinicians do for women who have had pre-eclampsia? Firstly, we must recognise that these women are still young, their absolute risk of cardiovascular disease is low over the short term, and their risk will evolve over subsequent decades. As such, we have an opportunity for primary prevention, especially as cardiovascular disease is largely preventable. In a large multinational study, 90% of the risk of a first myocardial infarction was accounted for by nine potentially modifiable risk markers: smoking, dyslipidaemia, hypertension, diabetes, abdominal obesity, psychosocial factors, inadequate consumption of fruits and vegetables, insufficient regular consumption of alcohol, and lack of exercise.[9]

Secondly, although guidelines on thresholds and targets for the treatment of hypertension, diabetes, and dyslipidaemia rely heavily on estimates of short term cardiovascular risk, those thresholds and targets vary widely.[10] Global assessment tools for cardiovascular risk (like Framingham) have limited applicability to young women. Limitations include errors in the risk estimate at the extreme ranges and omission of traditional (for example, obesity) or novel (for example, microalbuminuria) risk markers of cardiovascular disease.[11]

In terms of action, several possibilities exist. If we consider earlier screening for traditional risk markers of cardiovascular disease or lower treatment thresholds and targets (or both), no evidence is currently available to guide our decision making. If we consider following existing recommendations for screening or treatment (or both), we have a large body of evidence showing that a heart-healthy diet and lifestyle decreases cardiovascular risk.[1] Such advice is applicable to all women—regardless of risk of cardiovascular disease—and it is probably the most appropriate initial intervention for women with previous pre-eclampsia.

Unfortunately, simply advising people to undertake a healthier lifestyle is not enough to change their behaviour. However, women might be more receptive if they have had a complicated pregnancy. Perhaps we could tailor the advice to women with newborns and young

children. We know that the new mothers' caregiving role is one of the most commonly reported reasons for lack of activity among women,[12] and this extends to the presence of other (older) children in the household.[13]

We should ask women about their pregnancy experience. Women with a history of pre-eclampsia (or gestational hypertension) should have their risk of cardiovascular disease actively assessed at three to six months postpartum. They should pursue a heart-healthy diet and lifestyle. All of these women should probably be screened early for traditional risk markers of cardiovascular disease, and they should be treated, at a minimum, according to published guidelines. Future research must investigate whether targeting women with previous pre-eclampsia identifies a population that is more receptive to lifestyle changes or one that should have their traditional cardiovascular risk markers treated earlier and more aggressively (or both).

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Antibiotics for respiratory tract infections in primary care

Most infections can be managed by watchful waiting

RESEARCH, p 982

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Prescribing antibiotics for community acquired respiratory tract infections in primary care involves balancing the risk of missing pneumonia or serious complications on the one hand and treating infections unnecessarily on the other. Recent studies have shown that using antibiotics causes resistance among respiratory pathogens in individuals.[1 2] These studies were needed to confirm earlier studies showing an association between antibiotics and resistance at population level and to support prescribing campaigns to combat resistance by optimising antibiotic use.[3] But, although optimising the use of antibiotics seems to reduce resistance, it might increase the risk of complications.

In this week's *BMJ*, Petersen and colleagues assess whether antibiotics protect against serious complications of common respiratory infections.[4] They identified 3.36 million episodes of respiratory tract infection recorded between 1991 and 2001 in the UK General Practice Research Database and determined whether complications were less common in people who were prescribed antibiotics than in those who were not.[4] They found that in the month after the original diagnosis, pneumonia after upper respiratory tract infection, quinsy after sore throat, and mastoiditis after otitis media were rare in people not prescribed antibiotics, at 11/10 000, 14/10 000, and 5/10 000 patients, respectively. Prescription of antibiotics was associated with a small absolute reduction in risk for these serious complications. In contrast, the risk of pneumonia in the month after the diagnosis of chest infection was high and substantially reduced by antibiotic prescription (244/100 00 *v* 66/10 000 patients); the protective effect was greatest in people aged 65 and over.

Although this is one of the better studies to examine the effect of antibiotic prescribing on rare complications of common respiratory tract infections, a major confounding factor is that sicker patients and those more likely to have adverse outcomes were offered antibiotics more often. The findings might have been more meaningful if the participating general practitioners had low rates of antibiotic prescribing for the four conditions studied. But, according to the database used, upper respiratory tract infection, sore throat, otitis media, and chest infection or lower respiratory tract infection were four of the five main indications for prescription of antibiotics. Antibiotics were prescribed in 44.2%, 64.3%, 62.5%, and 82.2% of cases, respectively, between 1998 and 2001,[5] and the figures were even higher before 1998.[6]

Randomisation eliminates the problem of confounding but, as Petersen and colleagues state, randomised controlled trials generally lack the power to study rare events, and participants may not be representative of those seen in routine practice. Nevertheless, according to meta-analyses of randomised controlled trials in people with colds or upper respiratory tract infections,

antibiotics are not effective.[7] A possible exception is a subgroup of people (20%) with positive nasopharyngeal culture for *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. However, no rapid point of care tests are currently available to detect these organisms.

Acute rheumatic fever and acute glomerulonephritis are rare in industrialised countries. In people with sore throat, antibiotics slightly improve symptoms and reduce the risk of suppurative complications, such as quinsy.[8] A recent randomised controlled trial in children with sore throat found no effect of penicillin on the duration of sore throat and lacked power to detect a protective effect. The trial stated that each complication identified was successfully treated without referral to hospital.[9] According to a meta-analysis of individual patient data from children with acute otitis media, antibiotics are effective in children with otorrhoea (21%) and in those under the age of 2 years with bilateral infections (20%).[10] No cases of mastoiditis were found in children denied antibiotics. In people with acute bronchitis or chest infections, antibiotics modestly reduce cough.[11] The reduction in mean days with impaired activities and days feeling ill did not reach significance, and neither did the increase in adverse events. The largest trial to date included 807 people with acute uncomplicated lower respiratory tract infections offered immediate or delayed amoxicillin, or no treatment, and it found little difference in resolution of symptoms.[12]

In summary, the available evidence does not provide clinicians with the guidance they need to prescribe antibiotics effectively for common infections in primary care, except maybe for acute otitis media. For lower respiratory tract infections in particular, clinicians cannot be confident about identifying who will benefit from antibiotics and who will not.

GRACE (genomics to combat resistance against antibiotics in community acquired lower respiratory tract infections in Europe; www.grace-lrti.org), a network funded by the European Commission, is currently undertaking research across Europe to provide answers to these questions. Together with spin offs like TheraEDGE, an integrated platform enabling microbiological diagnosis of lower respiratory tract infections in primary care, GRACE could mould the future management of this condition in primary care.[12]

Simultaneously, the European Centre for Disease Prevention and Control in Stockholm is preparing for an annual European antibiotic resistance day, starting in 2008. This might act as a catalyst for further reductions in antibiotic prescriptions in the member states. In anticipation of this, it might be worth while establishing a surveillance system to monitor complications, to run alongside two existing European surveillance systems (EARSS (www.rivm.nl/earss) and ESAC (www.esac.ua.ac.be)).

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Community acquired MRSA in Europe

Is less common than in the US but spread must be actively controlled

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Infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) were originally identified only in hospital settings. But new strains of MRSA have emerged and are now an important cause of community acquired infection worldwide,[1] and they often affect patients with no risk factors for acquiring a strain of hospital origin. A study just published estimates that 94 360 invasive MRSA infections occurred in the United States in 2005, primarily but not entirely related to health care.[2] In the study's surveillance sample, 58.4% of cases were defined as having community onset (cases with a healthcare risk factor but with a culture obtained ≤48 hours after hospital admission) and 13.7% were community associated (meaning that they started outside hospital and were not associated with health care).

Many isolates of community acquired MRSA produce Panton-Valentine leucocidin (PVL), a toxin that is not detected in MRSA infections associated with health care. The toxin destroys leucocytes and causes extensive tissue necrosis. The prevalence of PVL positive community acquired MRSA varies greatly between continents. In the United States, 50% of patients with skin and soft tissue infections seen in emergency departments test positive for PVL

positive MRSA.[3] In Europe, the prevalence is generally lower, at around 1-3%,[4] but a few countries, such as Greece, have reported a much higher prevalence.[5] The risk of a wider spread through Europe is therefore a possibility. Moreover, PVL positive strains of community acquired MRSA are increasingly isolated in cases of hospital acquired infection in countries such as the US and Greece.[5 6]

Most cases of community acquired MRSA are caused by a few specific clones, which are defined by molecular criteria that designate sequence type. The main European clone, with sequence type 80, has been detected in almost all European countries, including the most northern parts of Europe, where MRSA strains are rare in hospitals.[7] One of the most prevalent clones in the US, designated USA300, belongs to sequence type 8, while the South West Pacific clone sequence type 30 is prevalent in Asia and Oceania.[7] Some clones have spread all over the world to become pandemic. For instance, the USA300 clone has been introduced into Europe by travellers from the US and is now spreading sporadically.[8]

Even young healthy people without risk factors can be infected with community acquired MRSA,[2] usually directly through close contact with someone who has a skin infection. Behavioural risks for infection include use of injected drugs, poor personal hygiene, and the presence of open wounds or minor abrasions (for example, from shaving). Indirect contact with contaminated objects—such as towels, soap, bed linen, clothes, sports equipment, and wound dressings—seems to be another route of transmission. Epidemics of community acquired MRSA have occurred in members of "closed populations," such as household members, competitive athletes, military recruits, jail inmates, men who have sex with men, and children in schools or childcare centres.

Community acquired MRSA usually manifests itself as skin and soft tissue infections. It tends to produce larger abscesses that need to be drained more often than abscesses caused by PVL negative methicillin sensitive *S aureus*. Life threatening invasive infections such as necrotising pneumonia, necrotising fasciitis, and sepsis-like syndromes have been reported too.[9 10] Necrotising pneumonia, which has a case fatality rate as high as 75%, often occurs after infection with a flu virus.[9] The conjunction of both potential pandemics (flu virus and community acquired MRSA) could represent a health disaster.

Uncomplicated community acquired MRSA infections of skin and soft tissue are managed primarily by incision and drainage of fluctuant lesions.[11] Antibiotic treatment has only a moderate effect on clinical outcome and some authors have suggested limiting antibiotic treatment to patients with a suboptimal response to surgery.[11] In countries with a high prevalence of community acquired MRSA, empirical treatment regimens consisting primarily of vancomycin, co-trimoxazole, or clindamycin are worth trying.[7] Linezolid is an option for oral or intravenous treatment of infections caused by clindamycin resistant isolates.

When PVL contributes to the severity of infection, misuse of oxacillin—the mode of action of which could lead to overproduction of this toxin—might exacerbate tissue necrosis.[12] Drugs that shut down ribosomal translation of proteins in *S aureus*, such as clindamycin and linezolid, decrease production of PVL.[12] The ability of community acquired MRSA strains to acquire resistance to other antimicrobials, however, will almost certainly pose a longer term challenge.

Hygiene measures have proved to be successful in controlling community acquired outbreaks and should be taught more extensively in the community, as they are in hospital settings. Patients with community acquired MRSA infections of soft tissue should be counselled on the importance of hand hygiene, of not sharing personal items such as towels, and of appropriate wound care. Decolonisation of patients and contacts—for example, using topical mupirocin applied nasally—may prevent the spread of community acquired MRSA, especially within closed communities.[13] Adequate prevention of spread is currently the only way to stop *S aureus* conquering the world with epidemics of virulent antibiotic resistant clones.

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Surgery for disc disease

New evidence supports its use in selected patients

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Spinal surgeons have striven to underwrite their surgical practice by sound evidence from clinical trials, yet data of adequate quality have not always been available. This has led to clinical dilemmas with respect to the simplest of questions, such as when should surgery be recommended for acute disc prolapse and, in degenerative disc disease, whether surgery is more effective than extended non-operative treatments? Recent trials answer these questions.

The authors of the 2007 Cochrane review of surgical interventions for lumbar disc prolapse[1] conclude that surgical discectomy for carefully selected people with sciatica provides faster relief from the acute attack than conservative management. However, it was unclear whether surgery had any positive or negative effects on the natural history of the underlying disc disease. This conclusion was based primarily on one unblinded study published in 1983,[2] in which around a quarter of people treated conservatively crossed over to surgery (although there was an intention to treat analysis). Patient and observer ratings showed that discectomy produced significantly better relief of low back pain and sciatica than conservative treatment at one year, although these differences were not maintained at four and 10 years. Importantly, the trial also showed that postponing surgery to further assess clinical progress delayed recovery but did not cause long term harm. Discectomy was highly cost effective, at around $29 000 (£14 600; €21 500) per quality adjusted life year gained.[3] However, neither this trial, nor two other trials,[4 5] considered the optimal timing of surgery.

This matter is dealt with in a recently published randomised trial of 283 people who had had severe sciatica for six to 12 weeks. This trial compared early surgery (mean 2.2 weeks) with prolonged conservative treatment and surgery if needed (mean 18.7 weeks).[6] Outcomes at one year were similar in both groups, but pain relief and perceived recovery were faster for people who had early surgery. This suggests that there is a case for avoiding delay in surgery, although people with a mild motor deficit who choose not to have surgery will probably not develop a progressive deficit.[7]

Two year data from the multicentre US spine patients outcomes research trial (SPORT) are also now available.[8] This trial was designed to assess the relative efficacy and cost effectiveness of surgical and non-surgical approaches for treating the three most common conditions for which spinal surgery is performed—disc herniation, degenerative spondylolisthesis (vertebral slip forwards of one lumbar vertebra on another with an intact neural arch), and spinal stenosis (degenerative narrowing of the spinal canal). Data from 501 people with disc herniation were reported.[8] Although high rates of crossover (surgery was performed in only half of people assigned to it and in just under a third of the non-surgical group within three months) led to inconclusive results in the intention to treat analysis, the as treated analysis showed strong, statistically significant advantages of surgery on all outcomes for up to two years of follow-up. Back pain improved in both non-operative and surgical groups, but the improvement was significantly greater in people who had surgery. The result was consistent for all herniation locations and morphologies.

In total, 607 people were enrolled in the degenerative spondylolisthesis and spinal stenosis cohort.[9] One year crossover rates were high in the randomised group (about 40% in each direction), and an intention to treat analysis found no statistically significant effects for primary outcomes. However, as treated analysis for both cohorts combined showed significant advantages for surgery at one year, which diminished only slightly by two years. Symptoms improved quickly (as early as six weeks) in patients who had surgery. Greater improvements in spinal function and patient satisfaction were also seen at two years in people treated surgically included in the third arm of the SPORT trial (spinal stenosis without degenerative spondylolisthesis versus non-operative treatment).[10]

These results are encouraging and generally in line with those from a randomised trial published earlier this year that included people with and without degenerative spondylolisthesis.[11] What the studies do not adequately look at is the extent of spinal fusion, if any, that should accompany decompression of the spine to relieve symptoms from spinal stenosis and nerve root compression. Recent data from a randomised controlled trial in Edinburgh suggest that people with foraminal stenosis and single level degenerative disc disease may be better treated by decompression alone, with the proviso that further surgery may be needed at a later date.[12] If the surgeon does elect to proceed to fusion then stabilisation of the spine by pedicular instrumentation has been shown to promote a higher fusion rate, but with marginal benefit in terms of clinical outcome.[13]

Spinal surgeons have been particularly proactive in the past five years in publishing randomised trials. These latest trials support the common practice of early referral by the primary care doctor of people with acute sciatica who are "failing" non-operative treatment. A surgical option should also be explored for people with progressive lumbar spinal stenosis. The ongoing challenge for surgeons is to produce evidence that supports or discredits new technical advancements in minimal intervention surgery, disc arthroplasty, and procedures to correct spinal deformity. These technologies are generally driven by commercial interests and at a premium cost to health providers. They should be introduced to spinal centres, where they can be tested rigorously against other available treatments. Producing this evidence within a reasonable time frame will require multicentre collaboration as used in the SPORT trial

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Hepatitis B vaccination

The BMA adds its voice to the call for universal childhood immunisation in the UK

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Hepatitis B virus is a substantial threat to global health, with 360 million people chronically infected and more than 500 000 deaths each year from fulminant hepatitis, cirrhosis, and liver cancer.[1 2] After a call by the World Health Organization for the global introduction of vaccine prevention programmes by 1997,[3] 82% of countries in the world had introduced universal hepatitis B immunisation by 2005, and at least 55% of the world's children are now receiving three doses of the vaccine.[4]

To date, the United Kingdom has not offered universal immunisation, so most of its citizens are susceptible to infection. At the June 2007 annual representatives meeting, the BMA voted in favour of adding its voice to those of other expert groups in the UK calling upon the Department of Health "to introduce the hepatitis B vaccine into the childhood schedule without further delay."

The main argument against introducing universal immunisation is the relatively low incidence of disease in the UK compared with other countries.[5] However, 180 000 people in the UK are chronically infected with hepatitis B virus and can transmit infection to the unvaccinated population. Furthermore, the huge global burden of infection means that growing travel and migration in the 21st century put the UK population at risk of exposure to hepatitis B from abroad. Indeed, 3.3% of legal migrants to the UK are thought to be chronically infected, further adding to the pool of transmitters.[6 7]

Almost 1300 new cases of acute hepatitis B infection occur each year in the UK.[7] Moreover, 7700 new cases of chronic hepatitis B infection are detected each year, with huge cost to the National Health Service. Only 300 of these infections are acquired in the UK, however, and the remainder of cases are identified in people who entered the UK from countries with a high prevalence of the disease.[8]

Up to one third of people at risk of infection are difficult to identify.[7 9] As many as 40% of infections are acquired perinatally or in childhood, and infection at this age is far more likely to result in chronic carriage of the virus than infection in adulthood.[7 10] This makes early childhood an important target for prevention programmes. Fortunately, the hepatitis B virus can be controlled and, possibly, eventually eliminated by immunisation with highly effective vaccines.[11] Indeed, countries that have introduced universal childhood immunisation in the past 15 years now have a new generation of adolescents and young adults among whom transmission is being interrupted.

A key component of the UK targeted immunisation strategy is preventing perinatal transmission of hepatitis B virus to infants of mothers who are found to be infected during antenatal screening. Some studies have shown high uptake of screening, and one found that 92% of babies exposed perinatally receive their vaccination within 48 hours of birth and 86% complete a three dose course.[12] To improve coverage of children at risk, the favoured approach by the UK Joint Committee on Vaccination and Immunisation[5] is to extend the current targeted programme to families with at least one parent from a country with high prevalence. However, the committee rightly noted that "selective programmes can be difficult to implement." Furthermore, such an approach stigmatises people from particular groups and wrongly suggests that hepatitis B is not a concern for the rest of the population.

So, unfortunately, targeted strategies alone do not protect the population against hepatitis B, as it is impossible to reach all those who will be exposed. The easiest and cheapest way to implement universal immunisation is to add hepatitis B vaccine to the current UK primary immunisation schedule in early infancy using a hexavalent vaccine (against diphtheria, tetanus, pertussis, *Haemophilus influenza* type b, polio, and hepatitis B). This would avoid both extra visits to the doctor and more injections for the infant.

This approach is already widely used in Europe to prevent childhood hepatitis B infection, and a cohort of immune individuals will eventually reach adulthood. The addition of one more antigen to the current pentavalent combination vaccine should have little, if any, effect on the cost of the primary immunisation schedule. However, although universal immunisation of infants could eventually prevent new cases beyond the neonatal period, the high rate of chronic carriers in migrants to the UK means that a targeted neonatal screening programme is still needed to prevent perinatal transmission for the foreseeable future.

At this time, infant immunisation alone is insufficient to limit the transmission of hepatitis B virus, because of ongoing transmission among the non-immune adult population and the difficulty in identifying and reaching people at risk. For this reason, the current targeted programme aimed at high risk groups (injecting drug users, prisoners, etc) needs strengthening to reduce the burden of new infections until those in a universal immunisation programme reach adulthood.

The recent proposal to introduce vaccination for human papillomavirus vaccine in pre-adolescents next year (to prevent cervical cancer) could provide a vehicle for implementing a concomitant adolescent hepatitis B programme (to prevent liver cancer). This would generate a cohort of immune individuals more quickly than universal infant immunisation alone and hasten the control of the hepatitis B virus in the UK.

All references are in the version on bmj.com