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## Calcaneal fractures

### Surgery is no longer justified for most intra-articular displaced fractures

**Brigitte E Scammell** professor of orthopaedic sciences, Academic Orthopaedics, Trauma and Sports Medicine, University of Nottingham, Queen's Medical Centre, Nottingham, UK. [B.Scammell@nottingham.ac.uk](mailto:B.Scammell@nottingham.ac.uk)

Displaced fractures of the calcaneus, or heel bone, are a serious injury and the outlook for patients, who are typically young, remains poor. Usually due to a fall from a height at work or a road traffic incident, calcaneal fractures are often intra-articular and displaced, affecting primarily the subtalar joint. These fractures will heal if treated non-operatively, but patients can be left with persistent deformity, incongruent joint surfaces, and loss of alignment of the leg to the heel. A two year recovery, with a stiff, painful, deformed foot that will not fit into a normal shoe and osteoarthritis of the subtalar joint are common outcomes.<sup>1</sup>

Orthopaedic surgeons often fix these fractures internally to try to improve the final result. Does internal fixation work? In a linked paper, Griffin and colleagues report the results of a pragmatic, multicentre, randomised controlled trial comparing operative with non-operative care of closed, displaced intra-articular calcaneal fractures two years after injury.<sup>2</sup> They excluded open injuries and grossly displaced fractures, where surgery is absolutely indicated. Overall, they screened 2006 patients with calcaneal fractures, of whom a quarter (n=502) were eligible for randomisation. The trial was adequately powered, analysed according to intention to treat principles, and achieved 95% follow-up for the primary outcome, the Kerr-Atkins calcaneal fracture score (an injury specific measure of pain and function). But only 30% of eligible patients agreed to take part (151 of 502). Most refusals resulted from a preference for one or other treatment.

Griffin and colleagues found no significant difference in the primary or secondary outcomes (including heel width, hindfoot movement, walking speed, gait asymmetry, and general health) between treatment groups at two years, assessed by a blinded independent assessor (the patients wore thin socks to obscure any operative scar). The authors concluded that "operative treatment by open reduction and internal fixation is not recommended for these fractures." This seriously challenges current orthopaedic

practice, at least in the United Kingdom, where all displaced (>2 mm) intra-articular fractures are anatomically reduced and fixed with screws and plates, to facilitate early mobilisation of the joint and reduce the long term risk of osteoarthritis.

The new trial was conducted against a backdrop of great uncertainty as to whether surgical reconstruction of displaced intra-articular fractures of the calcaneum improves outcomes for patients. Conservative management is simple and consists of elevation, application of ice, range of movement exercises, splintage, and non-weight bearing for about six weeks. Surgery is expensive and invasive, requiring an inpatient stay of several days.<sup>3</sup> It has been rapidly adopted across the developed world since the 1990s, when computed tomography imaging improved the understanding of complex fracture patterns and better surgical approaches using well designed plates and screws facilitated safer surgery.<sup>4</sup> Most calcaneal fractures occur in developing countries, and here too surgery for these fractures is being enthusiastically adopted.<sup>5</sup>

#### Previous studies point in same direction

Uncertainty about management continues, despite a large multicentre Canadian trial of 424 participants showing no significant differences between surgical and conservatively treated groups at three years' follow-up.<sup>6</sup> However, participants were randomised before being enrolled, raising the possibility of selection bias, and there was incomplete follow-up. A 2013 Cochrane review, which included this and three much smaller single centre trials, concluded that "overall, there is insufficient high quality evidence relating to current practice to establish whether surgical or conservative treatment is better for adults with displaced intra-articular calcaneal fracture."<sup>7</sup> They asked for a definitive multicentre study.

The study by Griffin and colleagues has dealt with the criticisms of the Canadian study by avoiding selection bias, using patient centered and clinically relevant outcomes, and having 95% follow-up. The authors state, "We have clearly shown that surgery is ineffective," but most of their patients at two years had seriously impaired function with moderate pain and difficulty walking, so really no current treatment is effective.

Surgically treated patients had significantly more complications than controls treated conservatively (17/73 v 3/78; odds ratio 7.5, 95% confidence interval 2.0 to 41.8). Fourteen of the 17 surgical complications were surgical site infections, of which five necessitated further surgery (two for wound debridement, three for removal of hardware) and three of the complications necessitated a re-operation to remove prominent hardware.

But is this increased risk justified if surgery protects against subtalar arthritis that requires arthrodesis? Three patients needed subtalar arthrodesis after conservative management, compared with none after surgery. The Canadian study also reported significantly fewer arthrodesis procedures among surgically treated participants (7/206 v 37/218; relative risk 0.20, 95% confidence interval 0.09 to 0.44). So surgery may protect against early subtalar arthritis.

In the Canadian study most of the surgery was performed by one surgeon (73%), and on subanalysis one type of fracture (Sanders type 2) was found to benefit from surgery. In the more generalisable trial by Griffin and colleagues, 27 surgeons were involved, with an even spread of cases, and careful subgroup analysis showed no benefit of surgery. Thus it is possible that a surgeon with a very high volume for fixing calcaneal fractures could achieve better outcomes.

What should orthopaedic surgeons now advise patients with closed, displaced intra-articular calcaneal fractures? Despite the new trial, there are still some gaps in current knowledge.

Further meta-analysis may show that surgery offers protection against early subtalar arthrodesis in certain fracture subtypes. If so, then an eligible subgroup of patients might still consider surgery performed by a surgeon who does a high volume of calcaneal fracture fixations, but the trade-off is a higher risk of severe complications, especially infections.

For most patients, however, surgery for closed, displaced, intra-articular calcaneal fractures without gross displacement can no longer be justified. Conservative management is safer but equally ineffective.

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RESEARCH, p 10



[thebmj.com](http://thebmj.com)

- ▶ Editorial: Should HPV vaccine be given to men? (*BMJ* 2009;339:b4127)
- ▶ Editorial: HPV vaccination—reaping the rewards of the appliance of science (*BMJ* 2013;346:f218)
- ▶ Letter: Boys in the UK should be offered vaccination against human papillomavirus (HPV) (*BMJ* 2014;348:g3762)

## HPV vaccination

### What about the boys?

**Margaret Stanley** professor, Department of Pathology, University of Cambridge, Cambridge, UK

**Colm O'Mahony** consultant in sexual health and HIV, Countess of Chester NHS Foundation Trust, Chester, UK

**Simon Barton** clinical director HIV/genitourinary medicine and dermatology, Chelsea and Westminster NHS Foundation Trust, London, UK  
simon.barton@chelwest.nhs.uk

A year ago an editorial in *The BMJ* highlighted the limitations of HPV vaccination in the UK<sup>1</sup> and called for decisive action to maximise the public health benefits by thinking about vaccinating boys and some men. Similarly, a recent review by Stanley concluded, after consideration of cost effectiveness, that “failure to implement male vaccination looks like a missed public health opportunity.”<sup>2</sup> We therefore share the disappointment expressed by the Royal College of Surgeons’ cancer services committee about the lack of response to its concerns about the inequity of vaccinating only girls against HPV in the UK.<sup>3</sup>

To summarise, the UK vaccination programme initially opted for Cervarix, a bivalent vaccine against HPV types 16 and 18, which are associated with cervical cancer. The programme switched to the quadrivalent Gardasil (which also protects against genital warts caused by HPV types 6 and 11) in September 2012 but still vaccinates only 12-13 year old girls. Interestingly, new data show that at that age the immune response to these vaccines is excellent and that only two doses of either vaccine is sufficient for long lasting immunity, rather than the three required at older ages.

Australia was the first country to vaccinate girls, introducing a catch-up programme to age 26 years in 2007. Genital warts have a relatively short incubation period and, as predicted, within four years researchers reported a highly significant decrease in genital warts not only in young women but also in heterosexual men.<sup>4</sup>

These Australian data led public health leaders elsewhere to hope that vaccinating girls would create the herd protection required to also protect heterosexual men. However, the Australian experience may not translate to European countries, which have easier flow of populations across land borders. For example in Denmark, high coverage



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#### They'll thank us for it later

with the quadrivalent vaccine has been accompanied by a precipitous decline in genital warts in young women under 18, but little decline in warts in men has been detected so far.<sup>5</sup>

#### Oropharyngeal and anal cancers

It is easy to see why the vaccination programme was initially targeted at young women, who will benefit from a substantial reduction in cervical cancer and similar reductions in all forms of cervical dyskaryosis. This should lead to more a streamlined cervical screening programme and much less colposcopy and invasive treatment. However, the evidence is now conclusive that HPV also causes oropharyngeal cancers, with

most cases caused by HPV-16 and HPV-18, and this has the fastest rising incidence of any cancer (15% a year).<sup>2</sup>

An estimated 90% of cases of anal cancer in the UK are also linked to HPV infection. According to new figures

published by Cancer Research UK, anal cancer rates in the UK have increased by nearly 300% in the past 40 years.<sup>6</sup> Overall, rates have risen from 0.4 in every 100 000 adults in the mid-70s to 1.5/100 000 today. Anal cancer is still relatively rare and awareness of the disease is low, although the latest figures suggest that death rates have more than quadrupled since the mid-70s. Roughly six people now die every week from the disease in the UK.<sup>6</sup> In gay men who are infected with HIV, the incidence of anal cancer is even more alarming; rates of 107/100 000 have been reported in the US.<sup>7</sup>

Sexual health professionals in the UK have already called for the vaccination of young men who have sex with men in the hope of preventing mainly anal cancers and anal warts.<sup>8</sup> Realistically, for optimal effect the vaccine should be given at 12-13 years of age, and as only two doses may be given at this age, this strategy would also maximise cost effectiveness. However, young gay men may not declare themselves before their late teens, by which time they could have acquired several HPV types already. So an immediately implementable strategy would be to offer vaccination with three doses to all young gay men attending sexual health clinics, in the same way as they are currently vaccinated against hepatitis B.

Such a strategy would be seen to discriminate against young heterosexual men. There is also the potential that the successful “cervical cancer” vaccine programme could start to be portrayed as a programme for gay men, which could lead to confusion and have a negative effect on uptake overall.

The only sensible answer to these dilemmas is a gender neutral vaccination strategy in schools that gives two doses of the vaccine to all 12-13 year old boys and girls. Anything else is discriminatory, inequitable, less effective, and difficult to explain. Can the UK afford to do it? If the price is right, we can't afford not to.

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● PERSONAL VIEW, p 21

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- ▶ Research News: No evidence of cancer risk from folate supplements (*BMJ* 2013;346:f546)
- ▶ News: Taking folic acid at start of pregnancy seems to lower risk of cleft lip and palate (*BMJ* 2012;345:e4614)
- ▶ Editorial: Healthy eating in pregnancy (*BMJ* 2014;348:g1739)

## Folate and prevention of neural tube defects

Tracking red blood cell concentrations will help guide policy decisions about fortification

**Robert Clarke** reader in epidemiology and public health medicine [Robert.clarke@cts.u.ox.ac.uk](mailto:Robert.clarke@cts.u.ox.ac.uk)

**Derrick Bennett** senior statistician, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, UK

Neural tube defects are the most common disabling birth defect and can be reduced by 80% if women of childbearing age consume 400 µg of folic acid daily.<sup>1</sup> In the United Kingdom, where roughly 800 pregnancies are affected each year, the Scientific Advisory Committee on Nutrition recommends that all women planning pregnancy should take 400 µg folic acid daily as a supplement before conception and until the 12th week of pregnancy (or 5 mg daily for women with a previous pregnancy affected by a neural tube defect).<sup>1</sup>

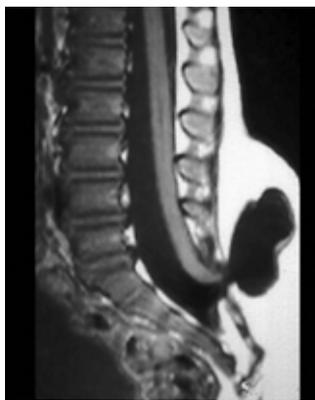
As half of all pregnancies are unplanned and less than a third of all women start taking folic acid before becoming pregnant,<sup>2</sup> voluntary folic acid fortification has been permitted in the United Kingdom (and elsewhere in most European countries), and mandatory fortification has been implemented in North America, South America, and Australia.<sup>1</sup> The relative efficacy and safety of voluntary and mandatory folic acid fortification programmes are uncertain.

The study reported by Crider and colleagues in *The BMJ* was designed to determine the optimal red blood cell (RBC) folate concentrations required to prevent neural tube defects.<sup>3</sup> The authors analysed data from two studies in non-fortified populations from two regions in China: a community intervention study testing folic acid supplementation to prevent neural tube defects that included 275 cases in 247 831 women treated with folic acid 400 µg daily<sup>4</sup>; and a population based randomised trial to evaluate the effects of folic acid supplementation in a subset of 371 women of reproductive age who provided RBC folate concentrations after treatment with 400 µg daily.<sup>5</sup>

The results show an inverse dose-response association of neural tube defect risks with RBC folate concentrations—participants with the low-

est red cell folate concentrations had the highest risk of neural tube defects (25.4 v 10/10 000 for 500 v 1200 nmol/L).<sup>3</sup> The authors defined the threshold for optimal RBC folate concentrations for prevention of neural tube defects as 1000 nmol/L. These results are concordant with the results of a previous study by Daly and colleagues in Ireland. Their study, which included 84 cases, reported a threshold of 906 nmol/L, above which the risk of neural tube defects was minimal.<sup>6</sup>

Applying the risk model developed from the Chinese data to population RBC folate concentrations in the United States, before and after fortification, Crider and colleagues showed that their predicted estimates for the prevalence of neural tube defects were concordant with the observed prevalence before and after fortification, confirming the validity of their model. Taken together, the Chinese, Irish, and US data indicate that RBC folate concentrations of about 1000 nmol/L or greater should be the population target for preventing neural tube defects. These findings are important and provide a clear target for RBC folate concentrations that should help guide the choice of population fortification strategies.



Target

ZEPHR/SPL

Traditionally, RBC folate concentrations have been viewed as a better measure of folate status than serum folate concentrations, as they reflect folate status throughout the cell's 90-120 day lifespan. However, red cell folate is unlikely to be a useful biomarker for individual women in the foreseeable future. Red cell assays are available only in specialist laboratories, whereas serum folate assays are readily available in most clinical laboratories, at least in developed countries, where they are widely used for measuring folate status in individual women.

Both tests can be useful for monitoring a population's response to changes in folate policies, and both should be included in nationally representative surveys of folate status such as the US National Health and Nutrition Examination Survey.<sup>7</sup> Data from this survey, reported by Crider and colleagues, suggest that with mandatory

**Chinese, Irish, and US data indicate that RBC folate concentrations of about 1000 nmol/L or greater should be the population target for preventing neural tube defects**

fortification, three quarters of the US population have adequate serum concentrations of folate and optimal RBC folate concentrations for preventing neural tube defects.<sup>3</sup> Data from Ireland, which operates a voluntary policy, paint a less healthy picture—median serum and RBC folate concentrations in one recent survey were about 17 nmol/L and 700 nmol/L, respectively, in non-supplement users and 30 nmol/L and 1000 nmol/L in supplement users.<sup>8</sup> Mandatory fortification in the United States (average daily dose of folic acid 0.14 mg) is associated with substantially greater population folate concentrations, which translates into a substantially lower risk of neural tube defects.<sup>9</sup>

### Mandatory beats voluntary

Moreover, voluntary folic acid fortification causes more extreme variation in folate status within populations (with low intakes in lower socioeconomic and ethnic minority groups and high intakes in users of high dose supplements).<sup>1</sup> Consequently, the Scientific Advisory Committee on Nutrition has called for mandatory fortification in the United Kingdom to replace voluntary fortification, together with guidance on high dose folic acid supplements, to increase the population folate concentrations while avoiding excessive intakes of folic acid.<sup>1</sup> Large trials of folic acid supplements at doses 10 times higher than the average extra intake after fortification provide reassurance that such a policy is likely to be safe.<sup>10-12</sup>

Population surveys of RBC folate concentrations, along with the optimum threshold confirmed by Crider and colleagues, will help to guide these policy decisions worldwide and allow public health leaders to monitor a population's response with the ultimate goal of reducing the incidence of largely preventable neural tube defects.

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● RESEARCH, p 11

Further research is definitely needed to examine the situation in developing countries, in disadvantaged populations, and in subgroups such as teenagers and women over 35 years of age

## Spacing babies

Small gaps look less harmful than big ones

**Julia Shelley** associate professor, School of Health and Social Development, Faculty of Health, Deakin University, Burwood 3125, NSW, Australia; and deputy director, Centre for Health through Action on Social Exclusion (CHASE), Faculty of Health, Deakin University [julia.shelley@deakin.edu.au](mailto:julia.shelley@deakin.edu.au)

An association between interpregnancy intervals of less than 18 months and an increased incidence of poor perinatal outcomes, including low birth weight, preterm birth, and small for gestational age infants, has been shown by strong and consistent findings over many years and in a wide range of countries. The same three poor outcomes have also been consistently associated with interpregnancy intervals of greater than five years. The strength and consistency of research findings, together with the proposal of several plausible mechanisms by which both short and long intervals could result in these poor outcomes, has led to the widely held acceptance that these associations are causal. As interpregnancy interval is a modifiable feature of pregnancy, public health organisations, including the World Health Organization, have recommended intervals of no less than two years between giving birth and another pregnancy.<sup>1</sup>

A recent article by Ball and colleagues seriously challenges this evidence.<sup>2</sup> By analysing several interpregnancy intervals for the same mother, rather than comparing intervals between different mothers, they show that short intervals (less than 18 months) are associated with very small, and possibly no, increase in risk of preterm, small for gestational age, or low birthweight births. Their findings do, however, reinforce the existing evidence linking increased incidence of small for gestational age and low birthweight births with interpregnancy intervals of five years or more ( $\geq 60$  months).

### Mothers as their own controls

The authors suggest that their findings are different because their within mother analyses control better for the unmeasured (or poorly measured) and unknown factors that confounded so many previous analyses. Mothers essentially act as their own controls. To further reinforce this point, Ball et al report findings from the same population in which analysis has been conducted in the more usual between mothers way.

The results of this approach closely mirror those of the many previous studies of interpregnancy interval and perinatal outcomes, including those of rigorously conducted systematic reviews and meta-analyses.<sup>3</sup>

Although these new findings indicate that public health messages and advice to women regarding interpregnancy intervals may need to be revised, it is too early to make that call. Public health policy should rarely, if ever, be based on a single study, and, regardless of the high quality of Ball et al's study, it represents only a single population in a single country, with the possibility that these results are due to chance rather than real. Whether the same associations would be found using the same analytical approach in other westernised, developed countries remains an open question.

Further research is definitely needed to examine the situation in developing countries, in disadvantaged populations, and in subgroups such as teenagers and women over 35 years of age, towards the extremes of reproductive age. Similarly, within mother analyses exploring maternal health outcomes are now needed, as are analyses investigating interpregnancy intervals that start with a pregnancy loss. Fortunately, no pressing need exists to revise public health messages for women. Little harm is likely to result from maintaining current advice about short intervals, and the correct messages about avoiding long intervals could be lost if we rush to revise advice.

In addition, recent research has linked closely spaced births with several outcomes that are unrelated to physiological attributes of the mother but may be related to the postnatal environment. Mental health disorders, problems with children's behaviour and development, and child abuse have been linked to short interpregnancy intervals,<sup>4 5</sup> although research remains sparse so far.

The findings of Ball et al's study remind us of the many limitations of traditional observational



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### Not spaced out

epidemiological research, although none of them is new and several have been discussed at great length previously. Meta-analysis of observational studies has frequently been criticised as potentially adding together the results of flawed studies,<sup>6</sup> a problem that was highlighted, for example, by the findings of the Women's Health Initiative trials evaluating hormone therapy for postmenopausal women.<sup>7</sup> These trials reported no reduction in coronary heart disease or osteoporosis, overturning decades of observational studies consistently supporting the value of hormone therapy for preventing these and a range of other problems. Residual confounding and the effect of unknown or unmeasured confounders ("known unknowns and unknown unknowns" to quote former US Secretary of Defense Donald Rumsfeld) is a problem that is often recognised but rarely dealt with, even though modelling has shown that small associations can be due entirely to such residual confounding.<sup>8</sup>

The argument that interpregnancy interval may not be the cause of poor perinatal outcomes surfaced in the early phases of research on this subject. As mentioned by Ball et al in their introduction Erikson and Bjerkedal presented data suggesting that mean birth weight was highly correlated for first and subsequent infants born to the same mother.<sup>9</sup> Why this observation, and its message regarding the contribution of maternal factors rather than interpregnancy intervals to poor perinatal outcomes, was lost from the subsequent examination of the role of interpregnancy interval may carry a warning for researchers to keep an open mind, especially regarding results that do not fit an established pattern.

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