In low risk pregnancies adverse events during labour that affect the development of the baby are rare. Most cases of cerebral palsy have antecedents in the antenatal period,[8] with only about 10% of cases having an intrapartum cause. The prevalence of perinatal mortality or cerebral palsy from intrapartum causes is about 0.8 per 1000 and 0.1 per 1000 respectively.[1] Most studies of electronic fetal monitoring were underpowered to detect these rare events and have concentrated on more immediate fetal outcomes. When perinatal mortality was studied no effect was seen. Nevertheless, the cardiotocograph continues to be an important document in many legal cases concerning cerebral palsy.

So the evidence is strongly against the routine use of electronic fetal monitoring. This is further reinforced by the publication last month of the Royal College of Obstetricians and Gynaecologists' guidelines on electronic fetal monitoring, which have been developed with the National Institute for Clinical Excellence.[1] This important document has brought together all the good evidence on electronic fetal monitoring. There are some important messages, which should affect practice on labour wards throughout Britain.

The chief recommendation is that intermittent auscultation is the most appropriate method of fetal monitoring for women in labour who are low risk. This allows the best compromise between assuring fetal safety and allowing the woman mobility and independence during labour. For auscultation to be successful it needs to be frequent, especially in the second stage of labour, and therefore requires one to one care of the woman. Unfortunately this is an ideal which may be impossible in hard pressed labour wards, where midwives are often in short supply. Ironically, there is good evidence that one to one care alone has a powerful effect on the labouring woman, reducing intervention.[8] The cardiotocograph can become a surrogate for this best quality care and has a major impact on the caesarean section rate.

If intermittent auscultation identifies a problem or the woman has major risk factors then electronic fetal monitoring should be used. The main problem then lies in interpreting the cardiotocograph trace. The guidelines address this at length and provide good criteria for identifying suspicious and abnormal traces. Another key recommendation is that all professionals involved in managing labour should have regular, continuing training in interpreting and storing cardiotocographs. This recommendation is in line with three recent Confidential Enquiries into Stillbirths and Deaths in Infancy, which have consistently recognised inadequate interpretation of the cardiotocograph as a prime cause of adverse events.[9–11] To prevent litigation trusts should act on this recommendation and ensure that such training is available free for all relevant staff.

The guidelines have also looked at other methods of testing fetal well being in early labour and of fetal monitoring, such as fetal pulse oximetry and fetal electrocardiography. These newer tools may be useful as an adjunct to electronic monitoring, but they are no more predictive of adverse outcomes. Research is needed to identify more specific tests of fetal well being that will allow us to identify babies at risk during labour without having a major impact on women. For now, it is important that electronic fetal monitoring should be used appropriately in high risk women and that intermittent auscultation is recognised as a valid form of management for most low risk cases.

Ros Goddard *specialist registrar in obstetrics and gynaecology*

Royal United Hospital, Bath BA1 3NG (ros_goddard@hotmail.com)

1 Royal College of Obstetricians and Gynaecologists. *The use of electronic fetal monitoring: the use and interpretation of cardiotocography in intrapartum fetal surveillance*. London: RCOG, 2001.
2 Neilson JP. Cardiotocography during labour. *BMJ* 1993;306:347-8.
3 Grant A. Monitoring the fetus during labour. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1989:846-82.
4 Thaker SB, Stroup DF, Chang M. Continuous electronic heart rate monitoring for fetal assessment during labor (Cochrane Review). *Cochrane Database Syst Rev* 2001;2:CD000063.
5 Grant A, O'Brien N, Joy MT, Hennessy E, MacDonald D. Cerebral palsy among children born during the Dublin randomised trial of intrapartum monitoring. *Lancet* 1989;8674:1233-6.
6 Ingemarsson I. Electronic fetal monitoring as a screening test. In: Spencer JAD, Ward RHT, eds. *Intrapartum fetal surveillance*. London: RCOG Press, 1993:45-52.
7 Mires G, Williams F, Howie P. Randomised controlled trial of cardiotocography versus Doppler auscultation of fetal heart at admission in labour in low risk obstetric population. *BMJ* 2001;322:1457-62.
8 Hodnett ED. Caregiver support for women during childbirth. *Cochrane Database Syst Rev* 2000;2:CD000199.
9 Maternal and Child Health Research Consortium. *Confidential enquiry in to stillbirths and deaths in infancy: fourth annual report*. London: MCHRC, 1997.
10 Maternal and Child Health Research Consortium. *Confidential enquiry in to stillbirths and deaths in infancy: fifth annual report*. London: MCHRC, 1998.
11 Maternal and Child Health Research Consortium. *Confidential enquiry in to stillbirths and deaths in infancy: seventh annual report*. London: MCHRC, 2001.

Preventing renal failure in the critically ill

There are no magic bullets—just high quality intensive care

Few doctors trained in the past 20 years have not learnt of the benefits of "low dose" dopamine in patients developing acute renal failure. The belief that low dose dopamine is beneficial was based on the physiological and pharmacological properties of dopamine and on personal anecdotes, but there is a lack of clinical trials, those available being of poor quality.[1] The recent publication of a high quality randomised, double blind, placebo controlled study[2] showing no benefit of "low dose" dopamine has, therefore, killed—or at least mortally wounded given that it takes time for cardiac surgeons to catch up—one of critical care's sacred cows.

In this study 328 patients (in 23 Australasian intensive care units) with an acute inflammatory response and early renal dysfunction (raised serum creatinine concentration or oliguria) randomly received a dopamine infusion (2 μg/kg/min) or placebo. The primary outcome variable, peak serum creatinine concentration during infusion, did not differ between the well matched groups. Moreover, there was no difference in any other variable studied, including

BMJ 2001;322:1437–9

requirement for dialysis. Indeed, urine output and use of frusemide did not differ, suggesting that dopamine was not even an effective diuretic. A possible criticism of the study is that the patients had already established renal dysfunction at time of entry, and some proponents of dopamine would argue that it is only likely to be of benefit if used as prophylaxis. However, the failure of dopamine to influence any study endpoint makes even this suggestion unlikely.

The results are actually not surprising. The weight of evidence has long been against the use of dopamine, especially as its adverse effects (inappropriate vasoconstriction, tachyarrhythmias, reduced respiratory drive, increased intrapulmonary shunt, altered immune and endocrine responses, and reduced splanchnic perfusion) are well recognised.[1] Low dose dopamine can no longer be considered to "do no harm and possibly do some good," as we were taught, and this study conclusively shows that dopamine has no role in preventing acute renal failure in critical illness.

If dopamine is out then what is in? The development of acute renal failure in hospital significantly increases a patient's risk of death (odds ratio for death 5.5 for contrast induced renal dysfunction[3]). When it occurs in intensive care in combination with acute respiratory failure, mortality exceeds 50% even in the best centres.[4] Prevention is therefore vitally important. Acute renal failure is generally associated with renal hypoperfusion often in association with severe sepsis or relative or absolute hypovolaemia or as a consequence of pump failure. Thus its prevention requires meticulous attention to the systemic haemodynamic disturbance, fluid balance, and the avoidance of nephrotoxins.

Invasive haemodynamic monitoring and optimum fluid management have never been studied in a prospective clinical trial, however, other than in those that have focused on perioperative management of high risk surgical patients. In this population the weight of the evidence seems to favour intensive haemodynamic monitoring with aggressive fluid therapy as a means of reducing overall morbidity and mortality.[5–7] In contrast, in the general intensive care unit population there is no evidence to support targeting any specific cardiac filling pressure or the use of any particular resuscitation fluid. Given the ready availability of mechanical ventilation and renal support (haemodialysis or filtration), we advocate generous fluid resuscitation in patients with oliguria and renal dysfunction. Access to the central venous pressure may help guide adequacy of resuscitation, but in patients with cardiac or respiratory disease measurement of pulmonary artery occlusion pressure may be more accurate. Both pressures can be influenced by factors other than blood volume, however, and interpretation of pressure traces is subject to considerable interobserver variability.[8] Hence modern monitoring techniques reporting circulatory volumes and lung water may in time be shown to be more useful. Fluid overload resulting in impaired pulmonary gas exchange should be avoided whenever possible, but if it does occur initial treatment is with high dose diuretics. Failure to respond suggests established acute renal failure and requirement for dialysis.

Optimisation of "preload" with adequate fluid resuscitation may not be enough. In critical illness renal perfusion pressure and renal blood flow develop a linear relation.[9] The vasopressor catecholamine norepinephrine has been shown in clinical studies of sepsis to increase renal blood flow and improve renal function.[10] Again, a lower acceptable limit for mean arterial pressure compatible with adequate renal perfusion is not defined. For most patients a level of 70 mm Hg is probably adequate, higher levels being needed in elderly people or those with hypertension. A good rule is to aim for the premorbid mean arterial pressure or seek the lowest pressure that maintains adequate end organ function. In cardiogenic shock or after cardiac surgery augmentation of perfusion pressure by intra-aortic balloon counterpulsation is also associated with improved renal function.[11] Raised intra-abdominal pressure is another factor that impairs renal perfusion despite normal or raised mean arterial pressure. Improvements in renal function often occur after decompressive laparotomy or drainage of tense ascites.[12]

What of pharmacological manipulations? Apart from avoiding nephrotoxins such as aminoglycosides and iodinated radiocontrast agents, there is little to recommend. Frusemide may induce diuresis and ease fluid management, but there is no evidence that promoting diuresis in acute renal failure improves outcome.[13] Similarly, there is no evidence to support the use of mannitol, a nephrotoxin, in high doses. A few new agents remain under investigation, but there is not yet enough evidence to recommend them.[14] In a small double blind, placebo controlled, randomised trial the free radical scavenger *N*-acetylcysteine attenuated the rise in serum creatinine concentration in patients with renal dysfunction receiving radiocontrast agents.[15] In our view, prevention of renal dysfunction in critical illness is simply a case of "back to basics": optimise volume and defend pressure.

Michael J O'Leary *staff specialist in intensive care*

St George Hospital, Kogarah, NSW 2217, Australia (M.OLeary@unsw.edu.au)

David J Bihari *associate professor in intensive care*

Prince of Wales Hospital, Randwick, NSW 2023, Australia

DB is a member of the medical advisory board of Pulsion Medical Systems, Munich, and a non-executive director of Pulsion Pacific Ltd, Sydney.

1 Burton CJ, Tomson CRV. Can the use of low dose dopamine for treatment of acute renal failure be justified? *Postgrad Med J* 1999;75:269-74.
2 ANZICS Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000;356:2139-43.
3 Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA* 1996;275:1489-94.
4 Nair P, Bihari D. Acute renal failure on the ICU in the 1990s—"anything goes"? *Intens Care Med* 1997;23:1193-6.
5 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993;270:2699-707.
6 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997;315:909-12.
7 Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ* 1999;318:1099-1103.
8 Komadina KH, Schenk DA, LaVeau P, Duncan CA, Chambers SL. Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. *Chest* 1991;100:1647-54.
9 Bersten AD, Holt AW. Vasoactive drugs and the importance of renal perfusion pressure. *Critical Care Medicine New Horizons* 1995;3:650-61.
10 Redl-Wenzl EM, Armbruster C, Edelmann G, Fischl E, Kolacny M, Weschler-Fordos A, et al. The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. *Intens Care Med* 1993;19:151-4.

11 Hilberman M, Derby GC, Spencer RJ, Stinson EB. Effect of the intra-aortic balloon pump upon postoperative renal function in man. *Crit Care Med* 1981;9:85-9.
12 O'Leary MJ, Park GR. Acute renal failure in association with a pneumatic antishock garment and with tense ascites. *Anaesthesia* 1991;46:796.
13 Shilliday IR, Quinn KJ, Allison MEM. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomised study. *Nephrol Dial Transplant* 1997;12:2592-6.
14 Gesualdo L, Grandaliano G, Mascia L, Perota G, Schena FP. Acute renal failure in critically ill patients. *Intens Care Med* 1999;25:1188-90.
15 Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;343:180-4.

Glucosamine for osteoarthritis: magic, hype, or confusion?

It's probably safe—but there's no good evidence that it works

People with joint pain, including those with osteoarthritis, are consuming large quantities of glucosamine as a result of a huge volume of recent media coverage on its possible value. Reviews and leading articles in medical journals have variously labelled it a magical new treatment,[1] criticised the "hype,"[2] or, more commonly, been non-committal.[3] Perhaps we are just confused.

Glucosamine is a sugar, a sulphated aminomonosaccharide, one of the constituents of the disaccharide units present in articular cartilage proteoglycans. In vitro work has shown that it can alter chondrocyte metabolism, and this is the rationale usually given for its use in osteoarthritis.[4] However, it is unclear whether oral glucosamine can reach chondrocytes in vivo,[3] and in addition to the oral compound (the commonly available form), injectables and local preparations have been subjected to clinical trial.[5–8] The most appropriate dose and route of administration remain unknown. We do not even seem to know how to classify it: is it a drug, a food supplement, a nutriceutical, or a complementary therapy?

Osteoarthritis is a heterogeneous and poorly understood condition. It is a common, age related cause of pain and physical disability in older people. In clinical practice any regional joint pain in an older person may be labelled as due to osteoarthritis, a concept reinforced by the almost ubiquitous radiographic changes.[9] However, the origin of pain caused by osteoarthritis is unclear, and regional joint pain in older people is often due to periarticular lesions or referred pain rather than articular problems.[10] Recent work also confirms that there is little relation between the severity of the radiographic changes and the severity of symptoms.[11]

There is confusion about what we are trying to do when we treat people with osteoarthritis, epitomised by the glucosamine literature. A reasonable objective is the reduction of pain, stiffness, and other symptoms that arise from a joint as a result of osteoarthritis, with the plausible goal of a secondary reduction in disability. But why should we expect an agent that affects articular cartilage to have any effect on symptoms? There are no nerves in articular cartilage.[10] In addition, examination of the glucosamine literature shows that investigators have used several different patient related outcome measures, often mixing up different domains of outcome. An agent that affects cartilage might conceivably affect the radiographic changes of osteoarthritis, but why should we want to try to alter the radiographic changes when there is no relation between their severity and the clinical expression of the disease?[11]

Nevertheless, a race is on among pharmaceutical companies to find agents that do alter the radiographic progression of osteoarthritis, in the belief that this will be followed by proof that this results in less long term morbidity and fewer joint replacements. That concept remains to be proved, though a recent report in the *Lancet* suggests that glucosamine and its makers may have won the race.[5]

So how good is the evidence that glucosamine alters either the symptomatic expression of osteoarthritis or its radiographic progression? Actually, not very good. Indeed, something amusing seems to be happening as a result of our evidence based approach to new therapies. Glucosamine may become the first agent about which we have more published systematic reviews, editorials, meta-analyses, and comments than we do primary research papers. Our literature search identified nine reviews (and many editorials and comments), but only 24 primary studies (three of which were on combined therapies that included glucosamine). Other overviews, including a Cochrane systematic review, are in the pipeline. Perhaps we could have got away with examining other peoples' reviews, but we have studied most of the trial publications as well.

We agree with McAlindon et al[12] and Delafuente,[13] who complain that most of the primary studies are poor and most of the trials too small. To be fair, the reviews and meta-analyses are dominated by trials done several years ago, many of which were particularly poor, and the quality of more recent studies is clearly better. But we have two additional concerns about the existing evidence. Firstly, much of the research is sponsored by companies making glucosamine. Company sponsorship affects the likelihood of positive results in trials of non-steroidal anti-inflammatory drugs,[14 15] and the same bias will probably exist with glucosamine. We identified 12 trials with clear involvement by a company producing the product: all these trials gave positive results. Nine other studies reported positive findings but we could not ascertain the source of funding. Conversely, of the three trials that reported a negative effect, only one reported commercial funding. Secondly, most reviews have not been able to take account of the possible effects of publication or language bias.[12 16 17] So, though much of the research points to glucosamine being a safe and effective treatment for osteoarthritis, problems with bias and quality mean that these results must be treated with caution.

We conclude that there is more confusion and hype than magic about glucosamine. The rationale for its use is unclear, the best dose and route of administra-

BMJ 2001;322:1439–40