

Mean arterial pressure and prediction of pre-eclampsia

Is better than diastolic or systolic pressures in low risk women, but is still only moderately effective



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RESEARCH, p 1117

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Competing interests: None declared.

Provenance and peer review: Not commissioned but revised to incorporate linked research paper; externally peer reviewed.

BMJ 2008;336:1079-80

doi: 10.1136/bmj.39555.518750.80

Pregnancies complicated by pre-eclampsia, chronic hypertension, or both, are at significantly increased risk of adverse outcomes. For most women, the assessment of blood pressure and urinalysis form the mainstay of routine antenatal care. In the recently published report by the Confidential Enquiry into Maternal and Child Health (CEMACH), pre-eclampsia or eclampsia was the second most common cause of direct maternal mortality in the United Kingdom between 2003 and 2005.¹ Although no intervention has been proved to prevent pre-eclampsia, much attention in recent years has focused on improving our ability to predict this common complication.

The accompanying meta-analysis by Cnossen and colleagues examines the relation between early pregnancy blood pressure values and subsequent development of pre-eclampsia.² In low risk women, mean arterial pressure in the second trimester was a better predictor of pre-eclampsia than systolic blood pressure or diastolic blood pressure. The predictive strength of mean arterial pressure was moderate (area under the receiver operating characteristic curve 0.76), however. The positive and negative likelihood ratios of a second trimester mean arterial pressure of ≥ 90 mm Hg were 3.5 and 0.46. Increases in systolic blood pressure and diastolic blood pressure over baseline showed poor predictive accuracy. The best predictor of pre-eclampsia in a widely defined “high risk” group was a diastolic blood pressure ≥ 75 mm Hg at 13-20 weeks’ gestation, although the predictive value was limited (positive likelihood ratio 2.8, negative likelihood ratio 0.39).

Pre-pregnancy and antenatal risk assessments are the most widely used and simplest means of predicting subsequent pre-eclampsia. Although taking a careful family history and medical history (for obstetric events, hypertension, renal disease, or thrombophilia) can help to stratify the risk of hypertensive disorders of pregnancy, history alone will identify fewer than half the women who later develop pre-eclampsia.³ Doppler ultrasonography of the uterine arteries at 20-24 weeks’ gestation, to detect abnormal trophoblast invasion, predicts about 40% of subsequent pre-eclampsia, although its success in predicting severe early onset pre-eclampsia approaches 80%.³ Recently, several predictive biochemical markers—including placental growth factor, soluble fms-like tyrosine kinase-1 (sFlt-1), plasma protein 13, and pregnancy associated plasma protein-A (PAPP-A)—have been evaluated, but none is currently in routine clinical use.⁴

Several measurements of blood pressure—including systolic blood pressure, diastolic blood pressure, pulse, mean arterial pressure, and 24 hour ambulatory pressure—have been studied in early pregnancy as predictors of pre-eclampsia.⁵ In Cnossen and colleagues’ meta-analysis, mid-trimester mean arterial pressure was the best predictor of pre-eclampsia in low risk women, but—as the authors concede—the low positive likelihood ratio makes it unlikely that this measure would have a clinical effect in isolation.² Furthermore, the ability of blood pressure measurements in early pregnancy to predict severe pre-eclampsia, which has the highest attendant risk of fetal growth restriction and perinatal mortality, was limited.

Traditionally, the criteria used to define pre-eclampsia have lacked consistency and have overemphasised diastolic blood pressure. This is because, historically, systolic blood pressure has been thought to be very variable in pregnancy.⁶ However, awareness of the importance of systolic blood pressure in pregnancy has improved, and currently both the International Society for the Study of Hypertension in Pregnancy and the working group of the national high blood pressure education program in the United States define pre-eclampsia as either systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, with associated proteinuria after 20 weeks’ gestation.⁷⁻⁸ Proteinuria is usually detected with urine dipstick testing and confirmed by a 24 hour collection. A recent review in the *BMJ* of spot protein:creatinine ratios in pregnancy found this to be a reasonable “rule-out” test, although 24 hour testing should still be used to accurately measure proteinuria.⁹ Diastolic only thresholds are still recommended for diagnosis in the community in the UK; this may be reasonable for pragmatic reasons, to avoid confusion arising from multiple end points.¹⁰

A clear distinction must be made between diagnostic and treatment thresholds. Anecdotally, hospital based midwifery and medical staff tend to reference only the diastolic blood pressure (“her blood pressure is on 90”), even in treatment decisions in patients with established pre-eclampsia. This trend is supported by findings from the CEMACH report and surveys of UK obstetric practice.¹⁻¹¹ Increasingly, automated blood pressure devices are being used in pre-eclampsia, and these devices may underestimate systolic blood pressure and overestimate diastolic blood pressure.¹² As such, many authorities recommend using the mean arterial pressure in severe pre-eclampsia protocols, with 125 mm Hg being the most commonly used cut-off point.

Stroke is a catastrophic, albeit relatively infrequent, complication of hypertensive disorders of pregnancy. However, intracranial haemorrhage—the biggest cause of death in women who die from pre-eclampsia or eclampsia—has been rising, not falling, in recent years.¹ The single major failing in clinical care of pre-eclampsia according to CEMACH is inadequate treatment of systolic hypertension.¹ In a recent review of haemorrhagic stroke in pregnancy, systolic blood pressure was ≥ 160 mm Hg immediately before the event in 96% of cases.¹³ In contrast, only 21% and 13% of patients had pre-stroke diastolic blood pressures of ≥ 105 mm Hg and ≥ 110 mm Hg. Thus, life threatening intracranial haemorrhage can occur despite only modest increases in diastolic blood pressure.

The most effective and clinically useful method to predict subsequent pre-eclampsia continues to evolve using historical, clinical, biophysical, and biochemical modalities. Early pregnancy mean arterial pressure measurements are simple to do and can be done in both community and hospital settings, but with only a modest predictive ability. A more comprehensive model of treating pre-eclampsia is needed, as are increased awareness and consistent reporting of systolic hypertension and appropriate management of both systolic blood pressure and diastolic blood pressure.

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Reducing blood pressure in people of different ages

Absolute benefit increases with age and management of overall cardiovascular risk

In the accompanying paper, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) compares the effects of different regimens for reducing blood pressure in different age groups.¹ The meta-analysis found that across 31 trials of more than 190 000 randomised patients, the reduction in blood pressure with various antihypertensive drugs was independent of the patients' ages.

Previous large scale prospective observational studies and meta-regression analyses have highlighted the role of reducing blood pressure for preventing cardiovascular complications in patients with hypertension.²⁻⁵ The new BPLTTC analysis shows that the relative risk reduction of a cardiovascular event with tighter blood pressure control occurs irrespective of the patient's age.¹

One potential limitation of the BPLTTC analysis is that the age difference between younger and older patients was only about 15 years, and that 65 years was the arbitrary cut off between younger and older patients. However, subsidiary analyses with age fitted as a continuous variable provided better statistical power and reassurance that moderate or large age related effects had not been missed.¹

The BPLTTC analysis provides strong support for the use of blood pressure lowering drugs in elderly patients with hypertension.¹ Because the absolute risk of cardiovascular events is higher in older patients than in younger ones, for a similar relative risk reduction in blood pressure, far fewer patient-years of treatment are needed to prevent one major cardiovascular event in an elderly person. This is especially true in the presence of additional risk factors, such as male sex or a history of previous cardiovascular complications.

In older patients (≥ 60 years) with isolated systolic hypertension (≥ 160 mm Hg), antihypertensives reduced systolic blood pressure on average by ~ 10 mm Hg compared with placebo.⁶ The number of patients needed to treat for five years to prevent one major cardiovascular complication was as low as 18 in men (38 in women), 19 at 70 years or more (39 at 60-69 years), and 16 in patients with previous cardiovascular complications (37 in patients without such a history).⁶

The recently published hypertension in the very elderly trial proved that lowering blood pressure in very old patients (≥ 80 years) with

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Competing interests: JAS has acted as a consultant for drug companies and received funding for studies or travel from AstraZeneca, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Pfizer, and Sigma-Tau.

Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2008;336:1080-1

doi: 10.1136/bmj.39560.541725.80

systolic hypertension (≥ 160 mm Hg) or diastolic hypertension (90-109 mm Hg) to below 150 mm Hg systolic pressure and 80 mm Hg diastolic pressure reduced the incidence of fatal and non-fatal stroke by 30%.⁷ Fatal stroke declined by 39% and all-cause mortality by 21%. These results dispelled the suspicion that the benefit of antihypertensives in the very elderly in terms of preventing stroke might come at the cost of higher mortality.⁷⁻⁸ To prevent one death, only 40 very elderly people had to be treated for two years.

An age oriented strategy in the choice of first line antihypertensive drugs is appealing because it translates certain physiological and pharmacological principles into clinical practice. Examples are the decrease in the activity of plasma renin with age or the age related increase in postsynaptic α adrenoceptor mediated and calcium influx dependent vasoconstriction.

The recently revised British guidelines propose the use of angiotensin converting enzyme inhibitors in people below 55 years and diuretics or calcium channel blockers in older people.⁹ The BPLTTC analysis did not specifically investigate whether the age related blood pressure lowering activity of angiotensin converting enzyme inhibitors or other inhibitors of the renin system differed from that of diuretics or calcium channel blockers.

In the antihypertensive and lipid lowering treatment to prevent heart attack trial,¹⁰ the mean follow-up systolic blood pressure was 2 mm Hg higher in the lisinopril group than in the chlorthalidone group for all participants, 4 mm Hg higher in black people, and 3 mm Hg higher in those 65 years or older. These findings suggest that ethnicity and age have differential effects on the blood pressure lowering efficacy of antihypertensive drugs and therefore support current guidelines.⁹⁻¹¹

The British and European guidelines emphasise overall cardiovascular risk rather than hypertension as an isolated risk factor.⁹⁻¹¹ They favour a global approach, with the use of charts for stratifying risk based on additional risk factors, target organ damage, or associated conditions, such as diabetes mellitus or a history of cardiovascular or renal disease.⁹⁻¹¹ This approach is justified on the basis that hypertension, hypercholesterolaemia, and smoking account for around 85% of the cardiovascular risk that can be modified. The Cholesterol Treatment Trialists Collaboration found that the proportional reduction ($\sim 20\%$) in major vascular events per mmol/l decrease in serum low density lipoprotein cholesterol was similar in people above and below 65 years, but as for blood pressure, the absolute benefit of lowering cholesterol increased with age.¹² Interventions targeted at multiple risk factors hold great potential for efficient prevention of cardiovascular complications.

The BPLTTC analysis strongly supports the early and aggressive management of hypertension, irrespective of age.¹ Clinicians should be aware that

The BPLTTC analysis strongly supports the early and aggressive management of hypertension, irrespective of age



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similar proportional reductions in risk across the age range translate into much higher absolute benefit in older patients than in younger ones,⁶⁻⁷ and that antihypertensive treatment should be embedded within the management of global cardiovascular risk.⁹⁻¹¹ The BPLTTC analysis did not exclude the possibility that angiotensin converting enzyme inhibitors and other inhibitors of the renin system given as first line treatment in older people might be less efficacious than diuretics or calcium channel blockers.¹

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Increasing diversity among clinicians

Is politically correct but is costly and lacks evidence to support it

ANALYSIS, p 1111

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Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2008;336:1082-3

doi: 10.1136/bmj.39569.609641.80

UK medical students tend to come from higher socioeconomic classes,¹ perhaps not surprisingly, as social class correlates with intellectual ability.² As part of the UK government's widening participation initiative, there is a push to increase the proportion of students from lower socioeconomic classes (as well as mature students, those from minority racial groups, and disabled people) in higher education. Two underlying principles exist for medicine in particular. The first, social justice, aims to ensure fair access to a degree course that is the gateway into the medical profession.³ The second is the belief that a diverse population of doctors can better serve a diverse population of patients.⁴ To help promote widening participation, the Higher Education Funding Council for England and the Department of Health have provided funding to medical schools for projects such as outreach schemes at local schools and innovative degree programmes.⁵

In the accompanying article, Garlick and Brown describe the six year extended medical degree programme (EMDP) at King's College London.⁶ The first two years of the conventional medical curriculum is spread over three years, which allows for more academic and pastoral support. It is open to students from low achieving state schools in inner London. Most of these schools have exam results below the national average, so the authors argue that A level results may not be an accurate reflection of the true academic potential of these students. However, that ignores the large detailed study by the Higher Education Funding Council for England, which found that the aggregate performance of a student's school performance does not predict a student's subsequent university performance.⁷ Successful applicants were given a standard offer of CCC at A level, after going through an extended interview and a mental agility test. However, a recent paper found aptitude tests to be less useful than A levels as university selection tools, with no added value for the UK context.⁸

Nevertheless, the EMDP selection process has resulted in a more diverse student population. Only 31% of EMDP students are from middle class families compared with 76% on the conventional course at King's College London, and 91% of EMDP students are from ethnic minorities compared to 51% of "conventional" students. These figures provide evidence that widening participation to some extent achieves wider access, although white working class students are still notably absent. The diversity of this population of medical students should also translate into a more diverse population of doctors—the EMDP's overall retention rate is 90%, and its first cohort graduated successfully in 2007.

The logical next step is to question the second assumption underlying the widening participation initiative. Can a more diverse population of doctors

better serve a diverse population of patients? At the very least, the assertion that patients require or expect doctors of the same ethnicity, sex, and social class as themselves (white patients demanding white doctors would probably prompt claims of racism) is an uncomfortable one. Widening participation targets narrowly defined segments of society—lower socioeconomic groups and people who are geographically disadvantaged (those who live in inner city or rural areas). Do patients from these populations have better health outcomes when they are cared for by doctors with similar backgrounds? Are they more satisfied? We do not know.

Even if, through faith, we accept that a more diverse population of doctors better serves a diverse patient population, the awkward question of whether doctors selected through the widening participation initiative will end up serving disadvantaged patient populations remains. The best way to investigate this would be to follow the career paths of graduates from the widening participation scheme.⁹ An alternative is to look at the current population of doctors to see whether doctors from disadvantaged backgrounds are more likely to serve disadvantaged populations. Using this method, a study in the United States found that black doctors cared for more black patients than other doctors and Hispanic doctors cared for more Hispanic patients.¹⁰ Black and Hispanic doctors also cared for poorer patients.

This raises a potential conflict between the two premises of widening participation. If social justice in the form of fair access into the medical profession is the primary concern, no one should complain if widening participation graduates end up in private practice. But this would also mean a failure of the second premise, as disadvantaged patients are not benefiting.

Garlick and Brown conservatively estimate the total costs of the EMDP to be £190 000 (€240 000; \$375 000) each year. Is this money well spent? They conclude that "widening participation students need considerable extra academic and pastoral support if they are to be successful," and the pass rate is still lower than for conventional entrants. Their study has no control group, however, so it does not show that the extra support is needed.

A recent study from St George's, University of London, suggests the contrary.¹¹ Thirty five "adjusted criteria" students (with A level grades between BBC and ABB) performed as well as conventional students (given the standard A level offer of AAB). The adjusted criteria students did not receive additional support, but the comparison is limited because the average A level grades of EMDP students are lower—CCC in the first four years of the scheme and BBC in the recent two years—and small sample sizes mean that statistical power is low.

Intangible costs must also be considered. A quota system has effectively been set in place at King's College London. Four hundred medical school places are available each year; 50 are reserved for the EMDP and are inaccessible to the conventional applicant. The quest for social justice involves sacrificing equality of opportunity, where all applicants are treated uniformly.⁹⁻¹² This may be noble as we cannot afford to be complacent about injustice. But in seeking to understand unfairness we need to admit that it will never be eradicated from society, and an elite will arise in lower socioeconomic groups. So is it worth our while to widen participation, particularly if this risks reducing standards? Political ideology says yes, but the evidence is pending and the costs are rising fast.

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Preventing child deaths

New report emphasises the need to review the circumstances of death

NEWS, p 1089

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Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2008;336:1083-4

doi: 10.1136/bmj.39576.499907.80

There is no question that preventing child mortality should be a priority for all, and this is indeed so in the United Kingdom.¹ With this objective, the Confidential Enquiry into Maternal and Child Health (CEMACH) has recently conducted a comprehensive review of the deaths of all children aged from 28 days to 17 years and 364 days in Wales, Northern Ireland, and three regions of England (South West, North East, and Midlands).² This review pre-empts the mandatory review of all child deaths by local safeguarding children boards in England from 1 April 2008.

The aims of the review were to identify and collect core data on all deaths in the five targeted CEMACH regions for the calendar year 2006, to review a subset of these deaths with a focus on identifying avoidable factors, and to consider a national application of the methods. The review undertook a quantitative analysis of a core sample of 957 child deaths. A subset of 126 deaths was selected for closer scrutiny by a series of 41 multidisciplinary panels. These panels were a crucial and critical component of the review process.

The success of the review was dependent on the collaboration of a large number of people and organisations. In particular, the authors should be commended for their collaboration with young people. Increasingly, child health organisations are consulting with young people to provide greater insights into the nature, causes, and potential preventability of such deaths.

The review identified preventable factors for mortality, but because it was not a case-control study the results cannot necessarily be applied to a wider population. These factors were not detected from the core dataset or from the medical certificates but from the findings of the multidisciplinary panel review. The panel considered relevant information

describing circumstances surrounding death. Information from death certificates was inaccurate or insufficient in about a third of the cases reviewed.

The report identified cases of high quality care and cases where, despite the best care and services, the child still died. The most worrying cases were those in which the attending healthcare practitioners did not have the competencies, or systems were not in place, to enable accurate diagnosis or treatment or to facilitate efficient communication. In such circumstances, the inability to identify serious illness in the child and start timely and appropriate treatment were identified as factors in the child's death. The report also found that particular effort is needed to improve the detection and follow-up of children with mental health problems.

The review recommended the development of a mechanism for the national application and review of the common dataset. It emphasised the importance of disaggregating data so that patterns and trends of mortality in minority and socially or economically deprived populations can be identified. It was acknowledged that systems and expertise for the collection and review of neonatal deaths were already in place and should be used in future planning.

The report found examples of both high quality and substandard primary health care and emphasised the importance of ensuring the maintenance of paediatric skills among general practitioners. Primary prevention, in particular timely and complete immunisation, is vital in preventing child deaths and serious illness.

Mechanisms for reviewing child deaths exist in many jurisdictions throughout the world. These mechanisms vary in structure and function depending on the practices already in place, including existing legislative frameworks, cross jurisdictional relations, and collaborative

frameworks. Efficient communication and collaboration between a range of agencies have been widely identified as key factors in effective review of child deaths.

Generally, the literature shows that teams who review child deaths are multidisciplinary and include child protection workers, police, public health workers, medical personnel, mental health personnel, and prosecuting authorities. This shift towards multidisciplinary review teams and local ownership has tended to occur in countries where review processes have previously been more accusatory than investigative.

In Australia, all states and territories except Western Australia have a process for timely review of the deaths of all children who die in their jurisdictions. Many of these processes are supported by legislation to allow pertinent documents to be obtained and to protect the information gathered by the child death reviews. However, mechanisms for determining a score for the “preventability” of a death and avoidable factors are not well developed, although some states and territories are moving to develop such a score. A recent initiative by the commissioner for children in New South Wales has seen the establishment of a National Child Death Review Group, primarily to determine a core dataset for deaths and national consistency in such elements as key definitions.³ Priority has been given to the accurate identification of minority populations within the child death registries, particularly indigenous Australians, to enable differing causes, patterns, and trends in child mortality, systemic problems, and areas of crucial need to be identified.⁴

In 2005 an important comparative study of case reviews and approaches to child deaths across 16 countries was completed.⁵ It concluded that comparing countries with different traditions, policies, and processes is difficult, so that models cannot easily be transferred across international borders. An earlier study in the United States of 58 child fatality review teams found that an increasing number of teams collect data and publish reports on the internet, which allows teams to share resources.⁶

Reviews of child deaths must be rigorous and they should collect timely, standardised, and precise data on all child deaths. Such reviews, combined with appropriate epidemiological research, may help to decrease child mortality—as has been the case with sudden infant death.⁷ Parents and other carers must also be given feedback and an improved understanding of why their child died.



GEOFF VAROSKY/FOTOLIA

Reviews of timely, standardised precise data, combined with epidemiological research, could reduce child deaths

Future research should incorporate investigations of the medical factors, social factors, environmental conditions, and other circumstances of those who die during childhood compared with those who do not, including primary care and hospital contacts. Coding systems of the cause of death should be clinically relevant and independently validated. Timely and ongoing review will require committed and appropriate funding, leadership, cooperation, effective communication, adequate trained staff in all departments and agencies, and the necessary supporting legal framework.

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