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Editorial

Hypertension and haemodynamics in pregnant women – is a unified theory for pre-eclampsia possible?

The problem

Hypertension in pregnant women is a serious global problem. It has not significantly decreased in prevalence over the last 50 years and currently affects approximately 13 million pregnant women annually [1, 2]. Complications of the condition include seizures, kidney impairment, pulmonary oedema, hepatic rupture or failure, antepartum and postpartum haemorrhage, maternal death and fetal growth restriction and neonatal death [3]. Left untreated, severe disease has a case fatality rate of ~20% [2].

Definition

Gestational hypertension is the term given to new-onset hypertension (≥ 140/90 mmHg) in pregnancy in the absence of end-organ damage. Pre-eclampsia is hypertension with evidence of end-organ damage usually occurring after 20 weeks' gestation [4]. Whilst there is no agreed international definition of pre-eclampsia, all groups agree that hypertension is a mandatory diagnostic feature. Progression from gestational hypertension to pre-eclampsia occurs in ~25% of women. Fetal and maternal complications in this group are similar to those of women with severe pre-eclampsia.

Classifications

Pre-eclampsia is sub-classified into gestational and severity categories [5].

Gestation

The gestational classification typically dichotomises the disease into that occurring ≥ 37 weeks (the majority) and that occurring < 37 weeks. Classification into 'early' (usually < 34 weeks) and 'late' (≥ 37 weeks) is also described, the period between 34 and 37 weeks being considered 'preterm' but not 'early'.

New-onset hypertension may also occur in the postpartum period. There is, however, significant uncertainty as to whether the condition is pre-eclampsia or solely associated with the various changes occurring around the time of birth that can lead to hypertension.

Severity

The clinical severity classification categorises women presenting with pre-eclampsia according to what is considered mild, (moderate) or severe disease, although attempts to classify it thus are hampered by difficulty defining severe disease and by the variable presentation. Whilst severe pre-eclampsia is often associated with preterm or early disease, mild disease may also occur at preterm and early gestations, whilst severe disease and death may occur in term women. There is much overlap between the groups [5]. Attempts to understand the pathophysiology are further hampered by the broad range of risk factors associated with pre-eclampsia, and the failure (so far) to identify a reliable predictive/diagnostic test.

Risk factors

Many risk factors exist for the development of pre-eclampsia [6, 7]. It is more common at high altitude, [8, 9] in women who are anaemic [6, 10, 11] and in those with antiphospholipid syndrome, where thrombosis and ischaemia are common complications [7]. It is more common in women having twins and triplets and in women with pre-existing diabetes or obesity. It is also more common in nulliparous women, who have not had a previous pregnancy to enable adaptive uterine musculature and vascular responses to occur. It is less common in some groups where high levels of calcium intake is common [12], and in smokers [13] (who also are known to have smaller babies [13]), and there is evidence to suggest that the disease is

also less common in women with placenta praevia where there is increased vascularity to the uterus and placenta [14].

Whilst risk factors for the development of the disease exist, prediction of which women will develop pre-eclampsia is difficult. Despite extensive international research efforts examining an extremely large number of different biological substances, currently there is no predictive or diagnostic test that is appropriate to use in all pregnant women and the investigated biological substances are usually found in other non-pregnant conditions, often in association with ischaemia.

The placenta

The placenta has been considered central in the aetiology of the disease, as case reports exist of women with gestational trophoblastic disease developing what was considered pre-eclampsia. The combination of valid alternative mechanisms for the development of hypertension in these women, such as hyperthyroidism, pain, infection, the presence of an ongoing pregnancy, the problem of disease definition, and a recent review of modern cases, cast considerable doubt on this assumed causative mechanism [15]. Furthermore, the disease does not uniformly involve the placental vasculature, especially in term disease [16]. The disease does not always affect fetal growth, with babies who are born at various gestations to pre-eclamptic women being both appropriately sized for gestational age and demonstrating signs of fetal growth restriction.

Prevention

Once women are pregnant, successful preventative strategies in selected groups of high-risk women include the administration of aspirin [17], calcium [12] and heparin [18]. For most women, however, the emphasis of recommendations is on regular antenatal monitoring, accurate and documented clinical observations and then acting appropriately with correct interventions for abnormal observations [3].

Treatment

Once hypertension is diagnosed, there is no effective treatment apart from delivery of the fetus. Antihypertensive agents may control the level of hypertension; however, once commenced they are rarely able to be weaned whilst the fetus is present. Magnesium sulphate is the treatment for seizures and reduces the likelihood of a seizure in women with pre-eclampsia; however, in itself it will not limit disease progression.

A unified theory

In the light of the heterogeneity present in almost all aspects of the disease, is it possible to generate a unifying theory that explains the development of pre-eclampsia?

Haemodynamics

Haemodynamic observations in pregnant women before the development of the clinical syndrome of pre-eclampsia are highly suggestive that the disease is a hyperdynamic state with increased cardiac output [19]. This is consistent with the observation of sympathetic nervous system and renin-angiotensin system involvement in women with gestational hypertension and pre-eclampsia [20], the role of the sympathetic nervous system in hypertension and heart failure in general [21], and the relationship between cardiac output and arterial pressure [22].

Haemodynamic observations at the time of diagnosis, before treatment interventions, compared with healthy gestationally matched women and before decompensation, are suggestive of an association with a preserved or increased systolic heart function [23]. Decompensation can occur, with both preserved and reduced ejection fraction heart failure. Reduced ejection fraction with and without heart failure in the face of extreme afterload suggests a tipping point for cardiac failure [24] with mechanisms similar to non-pregnant adults [25]. Abnormalities of diastolic function, left ventricular hypertrophy and pericardial effusions are common, suggesting chronic stress, and this may predispose to long-term cardiovascular risks. In non-pregnant adults, these changes are associated with myocardial fibrosis and lead to long-term problems [26].

Fetal oxygen demand and maternal oxygen supply

These haemodynamic observations, the continuing high prevalence of the condition, and common features in the high- and low-risk groups, suggest that pre-eclampsia may develop as the result of an adaptive maternal response to the oxygen demands of a developing fetus. It could be considered the result of a mismatch between the stimulus of fetal oxygen demand and the response of maternal oxygen supply. The conditions that lead to this may

be classified into three broad categories: (i) pre-placental (maternal factors leading to impaired oxygen delivery to the placenta); (ii) placental (altered function – including placental oxygen demands – or structure, leading to impaired oxygen transfer from the placenta to the fetus); and (iii) post-placental (fetal factors, leading to increased fetal oxygen demand).[a]

A mismatch may occur through the interactions of these conditions with pre-placental conditions impairing oxygen delivery to the placenta (such as anaemia, high altitude, cardiovascular disease, intermittent desaturation), placental conditions impairing oxygen transfer (such as poor placentation or other placental damage), or post-placental conditions increasing oxygen demand (such as multiple pregnancies, macrosomic fetus), with the combined contribution of each condition leading to the development of the common endpoint of hypertension (Table 1; Fig. 1).

The mismatched demand and supply leads to the production of byproducts of relative hypoxaemia (both vasoconstrictive and vasodilatory and varying from woman to woman), aimed at increasing oxygen delivery to the fetus and thereby inducing the observed maternal changes. The contributions from each of the three categories of conditions also differ from woman to woman, differ in each gestational period and differ within each woman from pregnancy to pregnancy, thereby accounting for the heterogeneity observed clinically and in research studies, and the absence of the discovery of a unique biochemical biomarker(s) for this condition (Table 1; Fig. 1).

[a]Delivery of oxygen ∝ cardiac output × content of oxygen, where content of oxygen = (haemoglobin concentration × haemoglobin saturation × 1.34 $ml.g^{-1}$) + (arterial oxygen partial pressure × 0.03 $ml.l^{-1}$)

Table 1 Conditions that alter fetal oxygen demand and maternal oxygen supply.

Conditions that alter the demand for oxygen by the growing fetus
Increased demand
Multiple pregnancy
Relative macrosomic fetus
Normal demand
Healthy balanced fetal size/physiology/anatomy
Decreased demand
Fetal growth restriction
Fetal origin
Placental origin unrelated to vascular blood supply
Maternal substance abuse (smoking); (reduced growth without a maternal response i.e. no hypertension)
Small for gestational age
Conditions that alter the supply of oxygen to the developing fetus
Increased supply
Placental adhesive disorders
Normal supply
Healthy balanced maternal size/physiology/anatomy
Decreased supply
Reduced oxygen content
Reduced haemoglobin (anaemia)
Reduced oxygen partial pressure (high altitude)
Obesity (nocturnal hypoxaemia/term pregnancy)
Reduced efficiency of oxygen delivery (abnormal cardiovascular function and/or structure)
Altered rheology (antiphospholipid syndrome)
Heart (pre-existing hypertension and/or systolic/diastolic dysfunction)
Regional vascular beds
Placenta
Abnormal placental structure or function impairing oxygen delivery
Absence of pseudovascularisation (early pregnancy)
Ageing placenta and apoptosis (late pregnancy)
Uterus (abnormal uterine vasculature leading to poor placental/uterine vessel interface)
Other (vascular disease, connective tissue disease, renal disease)

The unique human conditions of fetal growth

The growth and development of a fetus presents the unique physiological challenge of a condition of rapid, prolonged and continuous growth in a young person with a compliant vascular system, with minimal effects of ageing, with a large physiological reserve and under the influence of the gravitational effects of an upright posture. Furthermore, the stimulus of normal growth constantly changes from day to day for many months from early pregnancy. It necessitates

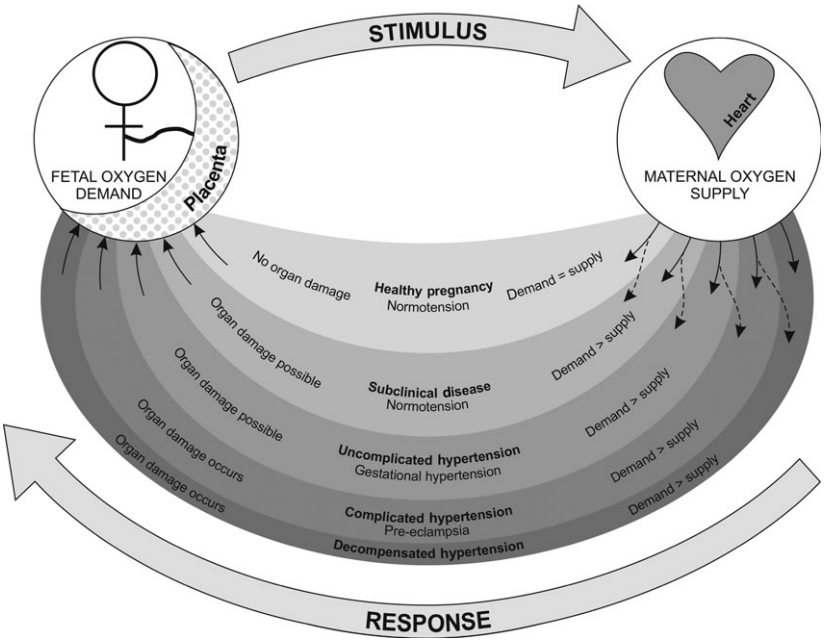

Figure 1 The constant stimulus and adaptive response (CSAR) model for the development of hypertension in pregnancy. At any time during pregnancy, due to imbalance between fetal oxygen demand and maternal oxygen supply, the woman may progress from healthy to sub-clinical disease and beyond (dashed arrows). The rate at which this occurs and the extent to which it progresses down the clinical pathway to decompensated hypertension depends on the pre-placental, placental or post-placental conditions, as well as when correction of the supply/demand imbalance occurs i.e. cessation of pregnancy.

a continual adaptive maternal response for an uncomplicated fetal and maternal pregnancy outcome and challenges the body to defend not only maternal cardiac output and oxygenation, but also the competing need of fetal growth, cardiac output and oxygenation.

The response commences with early pregnancy and implantation and appropriate vascularisation at the placental/uterine interface, and continues with ongoing fetal growth in the presence of the mechanical challenges of vascular compression and reduced cardiorespiratory reserve in advanced pregnancy. It is likely that appropriate oxygenation is necessary for all these steps [27]. These extreme conditions are not mimicked by any other process in humans. These conditions are also difficult to reproduce accurately in an animal model, especially if the haemodynamics before development of hypertension are hyperdynamic with increased cardiac output and increased flow to regional vascular beds, rather than the alternative view of vasoconstriction and reduced flow.

The unique response of each woman

In women who are able to maintain a sustained balanced oxygen supply to meet the changing metabolic demands of the fetus, pregnancy continues uneventfully. In women with a reduced capacity for oxygen delivery to the fetus, a response occurs in order to meet the fetus's demands. This initially leads to sub-clinical disease, which may include increased cardiac output and local vascular responses, with the aim of increasing fetal oxygen supply. This may lead to hyperperfusion of regional vascular beds in the absence of hypertension and in doing so, may create the conditions for vascular damage and clinical complications in the absence of hypertension i.e. seizures or haemolysis, elevated liver enzymes, low platelets (HELLP). Ongoing oxygen demand by the fetus then leads in a stepwise progression over varying lengths of time – dependent on the extent/burden of maternal and/or placental conditions – to hypertension alone, then to hypertension with end-organ dysfunction, and then to decompensation. With advancing disease progression and ongoing hypertension, negative feedback loops may lead to down-regulation of the sympathetic nervous and renin-angiotensin systems (Fig. 1).

Thresholds for the development of hypertension, the values of elevated blood pressure that define hypertension, and the gestation at which this occurs, may differ from woman to woman, depending on the combinations of her unique physiology and the interaction with her fetus both in size and function. The direct effects, as well as the responses including temporising measures to limit growth (primary and secondary responses, reflex responses and epiphenomena) of

individual regional vascular beds to flow and pressure, will also differ between women, depending on the contribution of pre-placental, placental and post-placental conditions (Fig. 1).

Implications

Viewing the development of pre-eclampsia, or more generally hypertension in pregnant women, as an adaptive process, consistent with the principles of integrative physiology in non-pregnant adults, and aimed at optimising fetal oxygen delivery, enables not only a framework for thinking about the mechanisms for the development of hypertension, but also a framework for treatment and risk reduction strategies.

An important implication is that once hypertension is established, treatment to prolong pregnancy is challenging because of the competing maternal safety requirements to decrease blood pressure and the fetal requirements for continuing growth and oxygenation.

Reduction in maternal blood pressure needs to occur without impairing oxygen delivery to the fetus. It also needs to maintain blood flow in remote maternal vascular beds such as the brain, kidney, gastrointestinal tract and liver. This balance is difficult, especially in severe disease where there are both primary and secondary vascular responses. Antihypertensive agents are commenced with little understanding of the cardiac output or regional blood flow distribution in the hypertensive woman, or of the drugs' effects on these physiological variables. Unless the reason(s) for the development of the hypertension (pre-placental, placental and post-placental conditions) are understood and the supply/demand problem is addressed, it is likely that some interventions will continue to have unpredictable and adverse effects in the woman, fetus or both. It is only by monitoring the haemodynamics of the disease and its treatments, at both clinical and research levels, that we will be able to ensure the safety and predictability of treatment interventions.

Treatments aimed at reducing circulating biological substances produced in women with pre-eclampsia are unlikely to reverse the response and may be deleterious, as these substances may be part of the adaptive response to maintain fetal oxygen delivery or part of a reflex or temporising response that protects the woman from ongoing or further damage. Such treatments currently lack scientific evidence and may potentially have adverse maternal or fetal consequences.

Research is needed into risk reduction strategies and early detection of changes focusing on:

1 Optimising oxygen delivery before and during pregnancy (maternal cardiovascular fitness, effective methods to achieve ideal body mass index [28], optimisation of chronic health conditions, calcium supplementation in appropriate groups).
2 Ensuring optimal blood oxygen content (determining optimal haemoglobin levels in pregnant women and treating anaemia accordingly, reducing periods of oxygen desaturation that may occur in obesity and in later pregnancy, perhaps through nocturnal continuous positive airway pressure delivery devices, and reducing chronic exposure to low partial pressure oxygen environments).
3 Ensuring optimal blood flow/rheology in at-risk women through the use of aspirin and heparin.
4 Enabling efficient materno-fetal transfer of oxygen (anticipating and managing deterioration in placental function with advancing gestation).
5 Reducing fetal oxygen demands (discouraging multiple pregnancies in assisted reproductive technologies).
6 Undertaking longitudinal studies throughout pregnancy and beyond, using echocardiography to quantify cardiac function and structure before, during and after the development of hypertension.

Reducing maternal and neonatal morbidity and mortality starts first with demystifying this common cardiovascular consequence of pregnancy through improving our understanding of the haemodynamic effects of the disease and its treatment in the clinical setting. There is an urgent need to apply the same standards of measurement in pregnant women as are used in non-pregnant adults with life-threatening cardiovascular disease i.e. the use of echocardiography to assist with clinical decision-making, measure

the effects of interventions and manage decompensated disease. Such demystification will lead to better informed counselling of women throughout the world, and perhaps even a less fascinating and historically outdated name given to hypertension caused by pregnancy.

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References

1. Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *British Journal of Obstetrics and Gynaecology* 2014; **121**(Suppl 1): 14–24.
2. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics Gynecology Reproductive Biology* 2013; **170**: 1–7.
3. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *British Journal of Obstetrics and Gynaecology* 2011; **118**(Suppl 1): 1–203.
4. National Collaborating Centre for Women's and Children's Health, 2011 Hypertension in pregnancy. The management of hypertensive disorders during pregnancy. National Institute for Health and Care Excellence Guideline 107 Issued August 2010, Modified 2011. http://www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf (accessed 16/06/2014).
5. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertension* 2013; **3**: 44–7.
6. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. *PLOS One* 2014; **9**: e91198.
7. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *British Medical Journal* 2005; **330**: 565.
8. Murray AJ. Oxygen delivery and fetal-placental growth: beyond a question of supply and demand? *Placenta* 2012; **33**(Suppl 2): e16–22.
9. Zhou J, Xiao D, Hu Y, et al. Gestational hypoxia induces preeclampsia-like symptoms via heightened endothelin-1 signaling in pregnant rats. *Hypertension* 2013; **62**: 599–607.
10. Kaupke CJ, Vaziri ND, Powers DR, Gonzales E. Erythropoietin in preeclampsia. *Obstetrics and Gynecology* 1991; **78**: 795–9.
11. Ali AA, Rayis DA, Abdallah TM, Elbashir MI, Adam I. Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala hospital, eastern Sudan. *BMC Research Notes* 2011; **4**: 311.
12. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2010; **8**: CD001059.
13. Ounsted M, Moar VA, Scott A. Risk factors associated with small-for-dates and large-for-dates infants. *British Journal of Obstetrics and Gynaecology* 1985; **92**: 226–32.
14. Adam I, Haggaz AD, Mirghani OA, Elhassan EM. Placenta previa and pre-eclampsia: analyses of 1645 cases at medani maternity hospital, Sudan. *Frontiers in Physiology* 2013; **4**: 32.
15. Soto-Wright V, Bernstein M, Goldstein DP, Berkowitz RS. The changing clinical presentation of complete molar pregnancy. *Obstetrics and Gynecology* 1995; **86**: 775–9.
16. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 2008; **51**: 970–5.
17. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* 2007; **2**: CD004659.
18. Rodger MA, Carrier M, Le Gal G, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. *Blood* 2014; **123**: 822–8.
19. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstetrics and Gynecology* 1990; **76**: 1061–9.
20. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia – a state of sympathetic overactivity. *New England Journal of Medicine* 1996; **335**: 1480–5.
21. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *European Heart Journal* 2012; **33**: 1058–66.
22. Guyton AC. The relationship of cardiac output and arterial pressure control. *Circulation* 1981; **64**: 1079–88.
23. Dennis AT, Castro J, Simmons SW, Permezel M, Royse CF. Haemodynamics in women with untreated pre-eclampsia. *Anaesthesia* 2012; **67**: 1105–18.
24. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. *Hypertension* 1991; **17**: 1072–7.
25. Jessup M, Brozena S. Heart failure. *New England Journal of Medicine* 2003; **348**: 2007–18.
26. Hill JA, Olson EN. Cardiac plasticity. *New England Journal of Medicine* 2008; **358**: 1370–80.

27. Fraisl P, Mazzone M, Schmidt T, Carmeliet P. Regulation of angiogenesis by oxygen and metabolism. *Developmental Cell* 2009; **16**: 167–79.
28. Centre for Maternal and Child Enquiries (CMACE)/Royal College of Obstetricians and Gynaecologists (RCOG) 2010. Joint Guideline: Management of women with obesity in pregnancy. http://www.rcog.org.uk/files/rcog-corp/CMACERCOGJointGuidelineManagementWomenObesityPregnancya.pdf (accessed 16/06/2014).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

S1. Additional references.

Editorial

Which supraglottic airway will serve my patient best?

How can we choose the 'right' device?

There are now so many supraglottic airways (SADs) available, and we need to decide which one to use. The laryngeal mask airway (LMA), introduced into clinical practice in 1988, has stood the test of time, and is now routinely used during general anaesthesia. Nevertheless, the original LMA has its limitations, and modified forms have been developed to address specific requirements, such as a more effective seal permitting positive pressure ventilation, and access to the gastrointestinal tract. In addition, the worldwide acceptance of the LMA has encouraged development of a large number of competitor SADs. Faced with such a choice, we need to match the right device with the right patient, in the hands of a practitioner with the right skills [1], instead of perpetuating the search for the holy grail (the ideal airway device) that will help all our patients. To do this, we should focus on becoming better at predicting which device will suit our specific patient's needs as we evolve towards an individualised treatment approach. In the era of evidence-based medicine, introduction of a new device into clinical practice must be justified first with scientific reasoning. In this and recent issues of *Anaesthesia*, such evidence is provided by way of three meta-analyses on the i-gel® [2–4] and one on the Ambu® AuraOnce™ [5].

When can a new device be introduced into clinical practice?

To choose the 'right' device from new products, we should first judge whether or not a new airway device is ready to be introduced into clinical practice. Cook [6], in his editorial of over a decade ago, has pointed out that many new devices have become commercially available with little or no prior evidence of their clinical efficacy and safety, and some of these untested devices do not perform to an acceptable standard. For example, some single-use laryngoscope blades [7] and single-use tube exchangers (bougies) [8] have been found to be inferior to conventional devices, and we should avoid using such devices. Cook has proposed a more formal, three-stage evaluation process for new devices [6], akin to development of drugs. In stage 1, devices are evaluated 'on the bench' and in specifically designed manikins; in stage 2, a rigorous pilot study takes place to determine whether the device is effective and safe; and in stage 3, the device is compared in a randomised controlled trial against the current gold standard device. The 'ADEPT' guidance, formulated by the Difficult Airway Society, recommends a minimum level of 3b evidence (a single case-control or historical-control study) to guide selection (or purchase) of airway devices [9].

We may be tempted to rely on manufacturers' preliminary trial results (industry reports) of device efficacy, but we need to await formal publications in scientific literature where there is some assurance of peer review, appropriate ethical conduct, statistical analysis and an opportunity for reader rebuttal [10].

