

in patients with the atypical form of this disorder than in those with the typical form,<sup>4</sup> although fertility outcomes might be attributable to unidentified factors associated with the transplant procedure itself. The accompanying case<sup>1</sup> therefore emphasises the importance of recipient selection, not only for the purposes of the transplant but also for assisted reproductive procedures so that the recipient will obtain sufficient numbers of oocytes and embryos before transplantation. It also provokes key ethical questions about the need for guidance regarding balancing of the risks and benefits of ovarian stimulation and oocyte retrieval efforts to increase the number of transferable embryos before transplant, the possibility of using donor gametes and embryos in cases where the recipient's supply of embryos is exhausted, and the need for ongoing research to clarify safety and protocols to undertake in-vitro fertilisation in women post-transplant.

Another key set of complications exists, the occurrence and severity of which could only be speculated upon until recently. The transplant recipient in the report<sup>1</sup> developed pre-eclampsia and preterm contractions at 31 weeks and 5 days, and subsequently required steroids and preterm delivery by caesarean section. Whether these obstetric complications were due to the age of the donor, issues related to single kidney function, immunosuppression, or other factors is not yet clear. Moreover, although a livebirth following uterine transplant is a notable success, the effect of prematurity on the infant cannot be underestimated. In this case, the neonate needed only minimum support following delivery. However, the sequelae of prematurity are well documented.<sup>5</sup> Therefore, additional research will be necessary to establish whether the obstetric complications described in the report represent a set of events that will recur in all transplant recipients. Such data will only be obtained

from observations on other women who elect to undergo uterine transplant and pregnancy.

Finally, although Brännström and colleagues state<sup>1</sup> that they plan to remove the transplanted uterus to reduce the long-term risks of ongoing immunosuppression for the recipient, the decision to remove the uterus must be an informed and voluntary decision by the recipient. Although the recipient's partner might have input into her decision making, the choice to undergo further surgery with resultant removal of reproductive function can only be made by the recipient herself.

The successful birth of a child following a uterus transplant provokes a series of medical and ethical challenges, the breadth and depth of which have not yet been explored in the context of other transplanted organs. The unique aspects of uterine transplantation will need ongoing multidisciplinary analysis of the lead clinical and ethical issues for the donor, recipient, offspring, and other key stakeholders involved in this innovative family-building procedure.

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## Blood pressure in acute stroke: which questions remain?

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In ENOS, one of the largest randomised trials of blood pressure-lowering in acute stroke now published in *The Lancet*, Philip Bath and colleagues<sup>1</sup> assessed whether blood pressure could be safely lowered with a daily glyceryl nitrate patch for 7 days after acute stroke, and whether antihypertensive drugs should be continued or withdrawn. Blood pressure is increased in about 70% of patients with acute stroke and often falls spontaneously

over the next few days.<sup>2</sup> The potential causes of this transient rise include disturbed cerebral autoregulation, damage or compression of brain regions that regulate blood pressure, neuroendocrine disturbance, and non-specific mechanisms such as headache, urine retention, infection, and psychological stress.<sup>2,3</sup> There is also evidence, particularly in patients with intracerebral haemorrhage, that high post-stroke blood pressure

might be due to an increase in the hours or days before the event.<sup>4</sup>

Observational data have consistently shown that high blood pressure after acute stroke is associated with poor outcomes.<sup>5</sup> Raised blood pressure might increase cerebral oedema or haemorrhagic transformation in ischaemic stroke, or lead to haematoma expansion and rebleeding in intracerebral haemorrhage, but lowering of blood pressure might reduce cerebral blood flow and increase infarction or perihæmatoma ischaemia.<sup>2</sup> Indeed, some small trials of acute blood pressure-lowering after ischaemic stroke did suggest increased early mortality and worse functional outcome.<sup>6</sup> More recently, of the two previous largest trials of blood pressure-lowering in predominantly acute ischaemic stroke,<sup>7,8</sup> one reported an increase in stroke progression in patients treated with candesartan versus placebo and a worse functional outcome,<sup>7</sup> and the other reported no reduction in rates of death or disability with lowering versus discontinuation of any antihypertensive treatment.<sup>8</sup> A recent systematic review of these and 15 other randomised trials, including 13 236 participants, showed no effect of early blood pressure-lowering versus control on functional outcome, with some evidence of increased early mortality.<sup>6</sup> Practice has therefore been to tolerate high blood pressure in most patients who are not candidates for thrombolysis, although recent evidence that early reduction of high blood pressure after intracranial haemorrhage might improve outcome is changing clinical management of patients with this disorder.<sup>9</sup>

ENOS<sup>1</sup> was a multicentre, randomised, partial-factorial trial that enrolled patients within 48 h of acute ischaemic (83%) or haemorrhagic (16%) stroke with systolic blood pressure between 140 mm Hg and 220 mm Hg. 4011 patients with mean blood pressure of 167/90 mm Hg were randomly assigned to receive either transdermal glyceryl trinitrate 5 mg every day versus a matching patch without glyceryl trinitrate (placebo) for 7 days. Mean blood pressure was 7.0/3.5 mm Hg lower in those given glyceryl trinitrate than in those given no glyceryl trinitrate on day 1. Although adherence to treatment was very high, this difference was no longer significant by day 3, and there was no difference between the treatment groups in neurological deterioration, recurrent stroke, or death at 7 days, and no difference in the primary outcome of functional status (change in modified Rankin scale score) at 90 days.

Given previous concern about increased early progression of acute ischaemic stroke after treatment of hypertension, as reported in the SCAST trial (6% on candesartan vs 4% on placebo; risk ratio 1.47, 95% CI 1.01–2.13),<sup>7</sup> the absence of adverse effects with glyceryl trinitrate in ENOS is reassuring. ENOS also showed no adverse effect of glyceryl trinitrate on functional outcome in patients with acute stroke with severe symptomatic extracranial carotid stenosis, analogous with previous evidence that low blood pressure is only associated with an increased risk of recurrent stroke in the small subset of patients with bilateral severe stenosis or occlusion.<sup>10</sup>

The median time from stroke onset to randomisation in ENOS was 26 h, which is similar to the delay in previous large trials of blood pressure-lowering in acute ischaemic stroke.<sup>7,8</sup> However, blood pressure is highest in the first few minutes after stroke onset,<sup>4</sup> at which point any adverse pathophysiological effects might also be greatest. In the 273 (7%) patients recruited to ENOS within 6 h of stroke onset, allocation to glyceryl trinitrate did improve the primary outcome (OR=0.55, 95% CI 0.36–0.84). However, although this apparent subgroup-treatment effect interaction was significant, there was no evidence of any continuing interaction with increasing time beyond 6 h, and a more conservative analysis of the four equal 12 h periods would be non-significant. In the two previous large trials in acute ischaemic stroke, there was also no evidence of benefit in functional outcome in the subgroups randomised earliest.<sup>7,8</sup> Nevertheless, it remains possible that ENOS has identified a specific acute effect of glyceryl trinitrate, rather than a generic effect of early blood pressure-lowering, and some supporting evidence has been provided by a small previous pilot trial of ambulance initiation of glyceryl trinitrate in hyperacute stroke.<sup>11</sup> A large trial of this intervention by Bath and colleagues (the RIGHT-2 trial) is now funded and will address this question.

Investigators for ENOS also randomly assigned 2097 patients to continue versus stop their existing antihypertensive drugs. The only previous trial to have addressed this clinically important question did not show any harms from continuing drugs,<sup>12</sup> but was potentially underpowered. In ENOS, whether drugs were continued versus stopped had no significant effect on the primary outcome or on the risk of early deterioration at 7 days, but continuation did significantly worsen the Barthel index (<60) at 90 days and increased cognitive impairment



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in the subset of patients tested (1272 of 2095). Continuation also increased the risk of pneumonia, possibly related to aspiration. Risk of post-stroke cognitive impairment is strongly related to severity and complications of stroke,<sup>13</sup> and so this pattern of outcomes is plausible. Thus, although the primary outcome was not significantly adversely affected by continuation of drugs, the authors' conclusion that withholding blood pressure-lowering drugs after acute ischaemic stroke until patients are neurologically stable and treatment can be given safely is reasonable, and clinical guidelines will now need to make specific recommendations.

ENOS was a very well designed and executed trial, and outstanding questions relate mainly to how far the results should be generalised. Firstly, ENOS and almost all previous similar trials of acute blood pressure-lowering either excluded or recruited very few patients with transient ischaemic attack and minor stroke, although patients with these events now represent more than 70% of all referrals with acute cerebrovascular events in routine practice. Blood pressure-lowering a few days or weeks after transient ischaemic attack or minor stroke is known to be safe and effective to reduce long-term risk of major stroke, and early initiation of blood pressure-lowering drugs is associated with a low risk of recurrent stroke.<sup>14</sup> Therefore, any conclusions from the results of trials of acute blood pressure-lowering in major acute stroke should not be generalised to transient ischaemic attack and minor stroke.

Secondly, although ENOS included 629 patients with intracerebral haemorrhage and showed no improvement in functional outcome, consistent with the similar subgroup analysis of 274 patients with intracerebral haemorrhage in the SCAST trial,<sup>7</sup> this finding does not conflict with the non-significant benefits reported in the INTERACT trials in more than 3000 patients with intracerebral haemorrhage.<sup>9</sup> In these trials, blood pressure-lowering was started much earlier after the onset of stroke (mean time to randomisation was about 4 h) and treatment was more aggressive. It is hoped that future pooled analyses of data from all of these trials might cast further light on the interactions between these parameters and the effects of treatment in intracerebral haemorrhage. Thirdly, there remains uncertainty about the optimum early management of blood pressure in patients with acute ischaemic stroke who are candidates for thrombolysis. It is common

practice to avoid thrombolysis when systolic blood pressure is higher than 185 mm Hg because of an increased risk of symptomatic intracranial haemorrhage. The continuing ENCHANTED trial (NCT01422616) aims to assess whether intensive blood pressure-lowering (130–140 mm Hg target) improves outcomes compared with the guideline-recommended level of 180 mm Hg in patients eligible for thrombolysis in acute ischaemic stroke. Finally, there is evidence that variability of blood pressure in acute stroke is associated with a poor outcome, independently of mean blood pressure.<sup>15</sup> Future analyses of data from ENOS should establish the effects of glyceryl trinitrate on variability.

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## Scaling up antenatal corticosteroids in low-resource settings?

In hospitals in high-income and middle-income countries with universal access to special or intensive newborn care, antenatal corticosteroids are routinely given to mothers in preterm labour. A systematic review<sup>1</sup> of 21 randomised trials showed that antenatal corticosteroids accelerated fetal lung maturation, reduced respiratory distress, and cut neonatal deaths by 31%. Recently, international agencies have lobbied to make antenatal corticosteroids universally accessible to cut preterm deaths in poor countries. The authors of *Save the Children's State of the World's Mothers 2013* report<sup>2</sup> concluded that more than one million babies per year could be saved with four life-saving products, including antenatal corticosteroids, which are ready to be scaled up and would “reduce incalculable suffering”. A WHO global report and an analysis for the UN Commission on Life-Saving Commodities for Women and Children using the LiST tool estimated that up to 400 000 lives could be saved each year by antenatal corticosteroids in low-resource settings.<sup>3,4</sup>

We urged extreme caution with this policy, fearing that the balance of risks and benefits in poor populations could be very different from those in well nourished, wealthy populations with access to round-the-clock special newborn care.<sup>5</sup> Would mortality of preterm infants really fall in the absence of special care, and might maternal infection rates rise if steroids were widely used? Others responded that “no published data suggest a major risk of maternal infection with the use of antenatal corticosteroids”,<sup>6</sup> and that, contrary to our speculation, “antenatal corticosteroids are likely to have a greater effect [on mortality] in the absence of level 2 care, not a lesser effect”.<sup>7</sup> Critics further noted that “a one-off course of antenatal corticosteroids (<48 h) poses a very low risk of adverse effects”,<sup>8</sup> that the treatment is one of the UN Commission on Life-Saving Commodities' priority medicines for scale-up,<sup>9</sup> and that

“the evidence strongly supports giving a single, short course of corticosteroids to women at risk of preterm birth in hospitals everywhere, not just in high-income countries”.<sup>8</sup>

The results of Fernando Althabe and colleagues' excellent international, cluster randomised trial<sup>10</sup> of an intervention designed to increase the use of antenatal corticosteroid treatment in low-resource settings, reported in *The Lancet*, show that fears about the scale-up of antenatal corticosteroids were actually underestimated. The study population consisted of almost 100 000 pregnant women in six countries—Argentina (six clusters), Zambia (ten), Guatemala (ten), Belgaum, India (20), Nagpur, India (20), Pakistan (20), and Kenya (16). Compared with standard care, the use of a multifaceted intervention that included training in the identification of women at risk of preterm birth and increased use of antenatal corticosteroids was associated with an increase in overall newborn mortality of 12% (relative risk [RR] 1.12, 95% CI 1.02–1.22;  $p=0.0127$ ), in perinatal

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