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Delayed cord clamping and improved infant outcomes

Enough evidence exists to encourage a routine change in practice

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Cord clamping and cutting is a common procedure but little agreement exists among doctors about the optimal timing. Cord clamping takes place in the third stage of labour, which is defined as the period from expulsion of the fetus to the expulsion of the placenta. Early clamping in term babies is sometime between 10 seconds and one minute after birth, whereas delayed clamping is between two minutes after birth and cessation of cord pulsations. In the linked randomised trial, Andersson and colleagues compare the effects of early versus delayed cord clamping on infant iron status at 4 months of age in a European setting.

Management of the third stage of labour has typically focused on women and prevention of postpartum haemorrhage. A systematic review published in 2000 found that active management involving the use of oxytocics, early cord clamping, and controlled cord traction was superior to expectant management in terms of maternal blood loss. For this reason, early clamping was accepted into obstetric practice without much consideration.

Another systematic review published in 2008 studied the effects of different cord clamping times on maternal blood loss and found that delayed clamping poses no additional threats to women. These results should have paved the way for a more liberal approach to delaying clamping in uncomplicated term deliveries. Yet immediate clamping and cutting of the umbilical cord continues to be a routine part of the active management package. Recently published surveys among obstetricians and midwives in the United Kingdom show that more than 95% of respondents clamp before two minutes and pass the baby off as quickly as possible.

Immediately after a baby is born placental blood continues to flow in the direction of the child as long as he or she is positioned up to 10 cm above the level of the placenta. The additional blood volume transferred to the infant after birth is called placental transfusion. For a term infant, placental transfusion increases the total volume of blood by about 30%. Within a few hours the additional plasma is lost to the circulation, leaving a high red cell mass. This is broken down in the first two months of life and the iron is re-used or stored.

In the 1970s, paediatricians recommended early cord clamping, because of fears that over-transfusion caused polycythaemia, hyperviscosity syndrome, or hyperbilirubinaemia. However, a recent high quality meta-analysis of randomised controlled trials from the past 15 years convincingly showed that delayed cord clamping in full term neonates for a minimum of two minutes is beneficial to the newborn, and that this benefit extends into infancy. Benefits include improved haematological status—measured as haematocrit value, ferritin concentration, and stored iron—and a clinically important reduction in the risk of anaemia. An increase was seen in polycythaemia, but it seemed to be benign. No significant differences were seen between delayed and early cord clamping in the risk of neonatal jaundice. Because many of the included trials were from resource poor countries with a high prevalence of infant anaemia, the applicability of delayed clamping in developed countries was questioned.

Andersson and colleagues present a well designed and executed randomised controlled trial on the timing of cord clamping in 400 infants in Sweden, a country with a low prevalence of iron deficiency anaemia. The study found that delayed cord clamping significantly improved iron status and reduced the prevalence of anaemia and iron deficiency at 4 months of age. No significant difference was seen in adverse effects between the groups.

Although paediatricians think that early cord clamping is needed in infants who require immediate neonatal resuscitation, these cases are exceptions. Most newborn infants do not require resuscitation—immediate drying and keeping them warm is all that is needed. Less than 10% of newborns need help to start breathing at birth (stimulation, positioning, clearing the airway), and about 1% need extensive resuscitation. When respiratory efforts are absent or inadequate despite initial stabilisation, inflation breaths by mask.
ventilation are the priority. The earliest time to assess whether these inflation breaths are successful is about 60 seconds after delivery. All these steps can be done while the umbilical cord is intact (see figure). Immediate cord clamping to enable resuscitation away from the mother could deprive the infant of much needed extra blood volume, and the resulting hypovolaemia might adversely affect tissue perfusion. Furthermore, as long as the uterus is not contracting and the placenta has not been detached, the infant may still receive oxygen via the intact placental-fetal circulation.

No evidence is available on whether infants deprived of placental blood have poorer neurodevelopment than those who receive placental transfusion. This is why Andersson and colleagues emphasise the importance of exploring the long term effects on health of delayed and early cord clamping. The time to cord clamping should therefore be documented for all future births, especially in studies with a neurodevelopmental end point.

The balance of maternal risks and infant benefits of delayed cord clamping now clearly favours the child. How much more evidence is needed to convince obstetricians and midwives that it is worth while to wait for three minutes to allow for placental transfusion, even in developed countries? Andersson and colleagues’ study is convincing enough to encourage a change of practice.

Competing interests: The author has completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
The linked meta-analysis of randomised trials by van den Hoek and colleagues assesses whether the potential of statins to lower the risk of infections noted in observational studies is causal.\(^1\) Data were pooled from 11 eligible clinical trials of statins relative to placebo, all of which had at least 100 patients who were treated for at least a year. The trials studied 30 947 patients, of whom 4655 reported an infection—2368 in the statin group and 2287 in the placebo group. This new analysis—the strongest to date on this subject—showed no benefit of statins on the occurrence of infection (relative risk 1.0) or death as a result of infection.

These findings might seem surprising. They are in stark contrast to the favourable associations—greater than 60% reductions for some infection outcomes—reported in pooled analyses of mainly observational studies,\(^2\) which were also supported by mechanisms by which statins could theoretically reduce infection.

However, observational studies have reported improvements in other outcomes with statins (including bone health, cognition and Alzheimer’s disease, and colorectal cancer), which were also refuted in randomised trials. How can reversal of such sizeable benefits arise repeatedly for statins specifically, and preventive drugs in general (for example, hormone replacement therapy)?

There are several relevant factors. Firstly, indication bias: statins are given to people with high cholesterol, and such people have a lower risk of infection, including hospital admission for influenza and pneumonia (Health Maintenance Organization sample).\(^3\) Whether or not the association is causal, statin use is a proxy for higher cholesterol before (and often despite) treatment, and the protective associations this bears. Similar indication bias also applies to the associations between statins and bone health and protection from colorectal cancer.

Secondly, healthy tolerator effects: adverse reactions to statins, which promote non-adherence or non-use,\(^4\) are fostered by unfavourable physiological states, which both correlate with and produce worse health.\(^5\) Unhealthy people will therefore be less likely to take statins, which would also contribute to an apparent benefit of statins in observational studies.\(^6\)

Thirdly, healthy user effects are pivotal for preventive drugs in general. Adherence to drugs, including preventive drugs, is linked to better conscientiousness, mood, and cognitive function,\(^7\) all of which are predictors of better outcomes. Consequently, people with the “adherent phenotype” fare better not as a result of the drugs they are adherent to. One trial showed that people with high adherence to placebo had significantly lower all cause mortality than those with low adherence (15% v 28%).\(^8\)

Large associations between people who use preventive drugs and better outcomes would be expected through such effects. Their presence has no material implications for whether the causal effect of the drug is positive, negative, or neutral. Thus, van den Hoek and colleagues’ findings should not be surprising. The question should not be: why do findings depart from those of observational studies, but how might findings depart from the “truth”?

Indeed, caveats to van den Hoek and colleagues’ findings remain; these are based on generalisability, bias, effect modification, and time course. Generalisability can be questioned because participants in randomised controlled trials do not reflect real world users—in particular, such trials tend to exclude groups most likely to have adverse effects when taking drugs (such as older people and those with comorbidities taking multiple drugs).\(^9\)

With regard to publication and presentation bias, only 11 of the 632 statin trials identified were included.\(^3\) Many studies did not report infection outcomes, and most authors declined to provide the omitted information when approached. What might missing studies show? Most large statin trials are industry funded, and industry support is strongly associated with publication and presentation of favourable findings, and non-publication of unfavourable ones. The effect estimated from published studies could be biased: “reality” could be less favourable than published trials suggest—that is, worse than neutral. (However, investigators might simply have not shared the requested information because this is uncompensated work.)

Another caveat is effect modification—average effects need not reflect effects for all users. Statins have multiple mechanisms that could increase or decrease infection differentially in different groups, as is evident for other outcomes.\(^10\) The propensity of statins to reduce or increase oxidative stress and associated outcomes differs according to the dose and the individual.\(^11\) Their impact on infection could vary similarly and be influenced by individual characteristics.

The final caveat when interpreting the current results relates to duration of use and timing relative to onset of infection. The meta-analysis assesses incident infection with chronic use of statins. Some of the effects of statins precede lipid reduction,\(^11\) and acute effects of starting or stopping statins after infection (or high risk event) could be different.\(^11\)

The best evidence now says that statins do not reduce infection. There is more to learn. But for now, statins should not be used to forestall infection or its consequences.

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Impact of staging on mortality is unclear, and liver biopsy remains the definitive method

Non-alcoholic fatty liver disease includes several stages—from simple steatosis to non-alcoholic steatohepatitis with inflammation, progressive fibrosis, and ultimately cirrhosis. In clinical practice the diagnosis of non-alcoholic fatty liver disease is based on increased echogenicity on ultrasound and raised liver enzymes (alanine aminotransferase or aspartate aminotransferase); staging requires a liver biopsy. The risk of complications after liver biopsy is justified by the prognostic information gained: simple steatosis has a small, if any, effect on mortality, whereas non-alcoholic steatohepatitis has repeatedly been associated with increased mortality, primarily from cardiovascular disease, but also from liver disease.1 2

It is unclear whether non-alcoholic steatohepatitis is an independent risk factor for cardiovascular mortality or whether the association can be explained by the higher prevalence of the metabolic syndrome. The linked cohort study by Lazo and colleagues uses data from the NHANES III (Third National Health and Nutrition Examination Survey) 1988-94 cohort, which is ideally placed to answer this question.3 The authors describe cause specific mortality for patients with simple steatosis or non-alcoholic steatohepatitis—defined as ultrasonographic signs of steatosis with or without raised liver enzymes. However, the study raises as many questions as it answers. This is because it found no increase in mortality in either of the non-alcoholic fatty liver disease subgroups, even before controlling for these patients’ higher prevalence of cardiovascular risk factors.

How many US citizens develop non-alcoholic fatty liver disease in their 40s or 50s, and how many have this disease in their 40s but it later resolves? The answers to these questions are unknown but crucial to the interpretation of the current study. The participants without steatosis had a mean age of 41.4 years at baseline and were followed for a median duration of 14.5 years. Deaths before age 56 years were uncommon, so it is likely that only a few deaths occurred shortly after the baseline examination. The implication is that a substantial number of decedents could have developed non-alcoholic fatty liver disease after the baseline examination.4 Similarly, in some patients, non-alcoholic fatty liver disease could have been present at baseline but resolved during follow-up—although this was probably less common, because the prevalence of this disease increases with age.5 Overall, the risk that decedents were classified as not having non-alcoholic fatty liver disease when they did (or vice versa) is high, so the true impact of this disease on mortality could have been severely underestimated.

In addition, Lazo and colleagues distinguished simple steatosis from non-alcoholic steatohepatitis on the basis of raised liver enzymes even though a liver biopsy is required. The authors acknowledged this fact, but the resulting misclassification cannot explain the fact that mortality was not raised in either of the two non-alcoholic fatty liver disease subgroups.

Non-alcoholic fatty liver disease is common, and there is an obvious public health interest in its effects. Lazo and colleagues’ study might therefore have a considerable impact if it were true that patients with non-alcoholic fatty liver disease do not have increased mortality despite their higher prevalence of the metabolic syndrome. However, because of the study’s limitations and because the findings do not concur with existing evidence by failing to associate the metabolic syndrome with increased mortality, the results should be interpreted with caution. Moreover, no human studies are available to support or refute Lazo and colleagues’ hypothesis.6 Current clinical practice should therefore continue.7

How then can the prognostic impact of non-alcoholic fatty liver disease be determined? Randomised studies are impossible, so the strongest evidence will come from large population based cohort studies such as the current one. The next step would be to conduct a study with repeated ultrasound scans of study participants to allow for the fact that non-alcoholic fatty liver disease can develop and resolve after the baseline examination.

With regard to staging, the current study underlines that raised liver enzymes alone are no substitute for the prognostic information gained from a liver biopsy. A recent systematic review of progress in non-invasive staging of non-alcoholic fatty liver disease found that no method has gained widespread clinical use.7 Hopefully, future large cohort studies—many of which are currently being conducted in Europe and the United States—will contribute to progress in this area by offering participants several non-invasive examinations, such as clinical observations, serum biochemistry, biomarkers, imaging, and transient elastography. Such studies might identify a combination of tests that can separate patients with simple steatosis with no effect on mortality from those with an increased risk of death. Although such a combination may not be a method for diagnosing non-alcoholic steatohepatitis, it may provide comparable amounts of prognostic information and be of equal clinical value.

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Prognosis and staging of non-alcoholic fatty liver disease

Stages of disease range from simple steatosis, non-alcoholic steatohepatitis with inflammation, progressive fibrosis, to cirrhosis
A meta-analysis found that childhood maltreatment was associated with a lack of response or remission during treatment for depression

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Two large scale, well conducted studies have recently been added to the substantial literature on the health correlates of violence against women and children. The first was a population based survey of 6451 Australian women, in which more than a quarter of participants disclosed at least one lifetime experience of gender based violence. Consistent with many other studies, it found a strong dose-response association between the number of forms of such violence and the odds of any of the mental health conditions assessed.

The finding is hardly surprising. Why wouldn’t experiencing violence be associated with poor mental health outcomes? But the strength of the associations is sobering. Even having experienced only one form of gender based violence doubled or tripled the odds of each of the mental health conditions assessed. And having experienced three to four types increased the odds for any lifetime mental disorder to 11, and the odds for attempted suicide to almost 15. The attributable risk is astonishingly high after putting together the high prevalence of such violence and the strong association with poor health outcomes. Yet decades after these types of associations were first recognised, only a minority of clinicians regularly incorporate violence assessments into their practices, even when seeing patients with mental health concerns.

The authors carefully note the limitations of this well conducted study and conclude that further research is needed to establish a causal relation between gender based violence and health. But is that really what is needed? It is unlikely that the reason most clinicians do not ask about violence is that they are waiting for stronger data to confirm the association between violence and health.

Clinicians have to make choices about how to use the precious few minutes they have with each patient. Focusing on violence as something that can be screened for and fixed can devalue the many other clinical uses of information about lifetime violence experiences. And in the face of strong competing demands, clinicians can fail to recognise one of the strongest risk factors for poor health outcomes or one of the most important keys to understanding patients.

The second study offers a more nuanced example of the potential value of information about violence, and the potential danger of misusing that information. It includes two separate meta-analyses. Firstly, a meta-analysis of 16 epidemiological studies found that childhood maltreatment was associated with an increased risk of developing recurrent and persistent depressive episodes. What does this mean for clinical practice? On the one hand, prognostic information is very important. On the other, will this finding reinforce negative stereotypes about the “broken” nature of “victims” of violence or lead to yet an even greater sense of futility? Hopefully, this information will help healthcare professionals better understand and empathise with patients who may have more difficult courses of depression and it might lessen the inclination to blame or dislike the patient for not responding to treatment. Or perhaps it will help providers appreciate the strength it takes for patients to manage depression with a background of childhood maltreatment.

Next, a meta-analysis of 10 clinical trials found that childhood maltreatment was associated with a lack of response or remission during treatment for depression, whether with antidepressants, psychotherapy, or a combination of the two. This finding may have important implications for treatment choices. But again, caution is needed. One of the reasons for recommending that clinicians ask about violence in patients with depression is that it will help them better predict who will need more than just a prescription for an antidepressant. The greatest difference in response rates between patients with and without a history of childhood maltreatment were seen in those trials in which the intervention combined antidepressants with psychotherapy, so it could be argued that combined treatment should not be offered to patients with a history of abuse. However, none of the psychotherapy programmes used in the interventions dealt with violence or abuse. In fact, several of the papers made a clear distinction between the therapy programmes used in the intervention and other forms of treatment used to tackle trauma experiences. Providers need to ask about lifetime experiences of violence so that patients can be referred to treatments that actually tackle the effects of violence. It cannot be assumed that mental health therapists will automatically deal with the problem of violence. The failure of psychotherapy programmes to do so may explain the poor outcomes seen in clinical trials.

There is ample evidence that violence is bad for people’s health. More research is needed to understand how to prevent violence and to help guide treatment decisions about its health consequences. In the meantime, clinicians should ask about lifetime experiences of violence because the optimum management of depression or other mental illness depends on understanding the underlying risk factors.

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E-cigarettes vaporise nicotine in ways that enable it to be inhaled

Electronic cigarettes (e-cigarettes), cigarette shaped products that vaporise nicotine in ways that enable it to be inhaled, have become increasingly popular in the past few years.\(^1\)\(^2\) E-cigarettes are a potentially more attractive substitute for smoking than low toxin smokeless tobacco because the nicotine is delivered by puffing, as when smoking a cigarette. A range of products are now on the market, with new improved ones promised, and—something almost unheard of in tobacco use—self organising groups of users (who call themselves “vapers” because they inhale vapour, not smoke)—who are advocating for these products and sharing their experiences.\(^3\)\(^4\) Opposition has come from some health groups, either for pragmatic reasons or because they are opposed to any recreational use of nicotine.

Medical journals including the BMJ have called for more research or regulation (or both),\(^5\)\(^6\) with the main difference being whether this should occur before allowing the products on to the market,\(^7\) or accepting that they might continue to be allowed.\(^8\)\(^9\)

People who argue that research is needed first focus primarily on the risks—the lack of research on product safety and on the efficacy of e-cigarettes as cessation aids or as substitutes, and concern about them being a potential gateway to nicotine dependence for the young. These concerns have motivated some countries, such as Australia, to ban commercial sales.

Those who want them to be allowed now have focused on the potential of these products to serve as the centrepiece of a harm reduction strategy, with the argument being that e-cigarettes can drive down smoking faster than relying solely on a cessation oriented approach, because substitution is easier to achieve than abstinence. They also propose that these products cannot conceivably be as harmful as cigarettes and are probably much less harmful. They recognise that regulation will be needed to manage the risks, and that this will take time to work out because it is not appropriate to regulate these products as therapeutic goods.\(^2\)

The United Kingdom and United States seem set to follow this more relaxed approach. A recent recommendation to this effect has come from the UK government’s behaviour insights team,\(^9\) a unit within the Cabinet Office. In the US, this approach has been forced by the courts recently ruling that e-cigarettes should be regulated as tobacco products because they make no therapeutic claims and are thus subject to far less regulation before being marketed than would otherwise be the case.\(^3\)

How should the arguments be weighed up? Safety concerns have been raised, but the bulk of products tested showed no evidence of acute problems with safety.\(^2\) Clearly, all such products should comply with existing rules covering chemicals that are allowed for human consumption. It is not possible to predict what the long term effects might be, but—on the basis of research with other low toxicant nicotine products—the risks will probably be far lower than for smoked tobacco. It is also not known what proportion of smokers will use e-cigarettes rather than normal ones and what proportion will use them long term. The more e-cigarettes are used, the more smokers will be drawn away from smoking, but with the increased risk of substantial uptake by nicotine abstinent ex-smokers and those who have never used nicotine (mainly adolescents). Currently, there is no evidence of undesirable uptake, but it will be important to monitor trends so that action can be taken if it does occur. It will therefore be important to try to distinguish uptake in young people who would have smoked from uptake in those who would otherwise not have used nicotine.

The risk of undesirable use might rise if these products are marketed aggressively. This could happen if big consumer product companies were to buy into the market. These products should be subject to the same restrictions on advertising and promotion as other tobacco products, with changes (probably easing of restrictions) made only after careful consideration of the implications. That is not to say that no additional restrictions should be made now. A case can be made for controlling bulk sales of the nicotine solution on safety grounds,\(^5\) perhaps with the nicotine being sold only in ready to use cartridges.

Currently it seems that these products pose no serious immediate risk. On balance, by allowing the products to be sold the UK seems to be taking the approach with the greatest potential public health benefit. The approach also creates real incentives to conduct research and to consider more appropriate regulation. The alternative of waiting for the research may end up essentially as prohibition, if no one is sufficiently motivated to do the work.

However, allowing these products does not mean that health groups should actively promote them. Health professionals should begin with evidence based strategies and promote these first. However, health professionals should be able to suggest to smokers who are unable or unwilling to use or continue to use effective aids to quit, and who are interested in e-cigarettes, that these are a better option that continuing to smoke. And although it is better not to use any form of nicotine long term, if patients must, e-cigarettes are a lower risk option than continuing to smoke.

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Electronic cigarettes (e-cigarettes), cigarette shaped products that vaporise nicotine in ways that enable it to be inhaled, have become increasingly popular in the past few years.\(^1\)\(^2\) E-cigarettes are a potentially more attractive substitute for smoking than low toxin smokeless tobacco because the nicotine is delivered by puffing, as when smoking a cigarette. A range of products are now on the market, with new improved ones promised, and—something almost unheard of in tobacco use—self organising groups of users (who call themselves “vapers” because they inhale vapour, not smoke)—who are advocating for these products and sharing their experiences.\(^3\)\(^4\) Opposition has come from some health groups, either for pragmatic reasons or because they are opposed to any recreational use of nicotine.

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