Induction of labour is carried out worldwide for a broad range of maternal and fetal indications, so as to improve pregnancy outcomes. Oral misoprostol has been widely discussed as a method of labour induction. It is recommended for this indication by the World Health Organization (WHO), the International Federation of Gynecology and Obstetrics (FIGO), and the Society of Obstetricians and Gynaecologists of Canada (SOGC).\(^1\)\(^-\)\(^3\) A systematic review comparing misoprostol with Foley catheter and dinoprostone induction agents suggests that ‘oral misoprostol for the induction of labour is safer than vaginal misoprostol and has the lowest rate of caesarean section’.\(^1\)\(^-\)\(^3\) A recently completed UK National Institute of Health Research (NIHR) funded network and cost-effectiveness analysis included 31 induction regimes evaluated in 611 trials with over 100 000 trial participants. Titrated low-dose oral misoprostol was identified as likely to be the most cost-effective method, and also had a favourable safety profile.\(^5\)\(^-\)\(^6\) Sublingual or buccal misoprostol had significantly higher rates of hyperstimulation. This recent evidence is in contrast with the current National Institute for Health and Care Excellence (NICE) guidelines that do not recommend the use of misoprostol, citing that misoprostol is not intended for labour induction, and that accurate concentrations and reliable drug delivery cannot be guaranteed given that low-dose formulations are not available.\(^7\)

‘Oral misoprostol’, however, is not a single entity and systematic reviewers have struggled to cope with the wide variation in protocols (Table 1). Published randomised trials have a wide variety of misoprostol doses (20–200 \(\mu\)g) and frequency of administration (1–6 hourly). Some protocols use a single dose for the whole induction period, whereas others escalate the dose until the desired effect is achieved. Some use misoprostol purely for cervical ripening and replace it with an oxytocin infusion once membrane rupture is feasible, whereas others use oral misoprostol continuously until delivery. But the variation doesn’t stop there. Until recently there was no commercially produced low-dose misoprostol tablet, and so clinicians developed their own ways of preparing and administering the intended dose. Some practitioners divided the small and notoriously crumbly 200- or 100-\(\mu\)g tablets into fragments. Others made up 1-\(\mu\)g/ml solutions by dissolving tablets in tap water. It is only recently that commercially available 25-\(\mu\)g tablets have become available (Cipla, India; Azanta A/S, Denmark), but these are not yet widely available.

Is there evidence to suggest that any of these protocols are superior? Subgroup analyses of some important clinical outcomes show a clear dose effect. For example, when comparing oral misoprostol with dinoprostone, the rate of hyperstimulation increases as the initial dose rises from 25 to 200 \(\mu\)g.\(^4\) It would therefore appear that there are safety benefits of using doses of 20–25 \(\mu\)g, even if they may result in a slower induction process. This is supported by a systematic review of just the studies that used 20–25 \(\mu\)g of oral misoprostol, which found lower caesarean section and lower hyperstimulation rates compared with standard induction methods.\(^5\) And whereas in previous studies researchers have been forced to either use cut 200-\(\mu\)g tablets or solution, high-quality 25-\(\mu\)g tablets are now available. Findings from a non-inferiority randomised controlled trial (RCT) of oral misoprostol 50mcg versus Foley catheter for induction of labour showed equivalent safety and effectiveness,\(^9\) whereas misoprostol tablets (25 \(\mu\)g) has recently been found to be more an effective than Foley catheter when given orally in a large Medical Research Council (MRC) labour induction study.\(^10\)

The use of regimens in which misoprostol is given every 2 hours is supported by pharmacokinetic studies that show that oral misoprostol reaches its peak serum level within 30 minutes, but that its half-life is only 90 minutes as misoprostol acid is rapidly metabolised by the liver and...
excreted by the kidneys. With oral misoprostol sustained uterine activity is achieved in 90 minutes and the duration of action is approximately 2 hours. The 4–6 hourly dosage regimens have stemmed from an incorrect assumption that the oral pharmacokinetic data is the same as that for vaginal doses.

It remains untested whether the low dose of oral misoprostol will perform better if titrated to clinical response, and whether there are benefits of continuing its use through to the end of labour. Most studies have used oxytocin to continue with the induction process once cervical ripening is complete. There is no question that there are considerable logistic and safety challenges with both approaches, particularly in low-resource settings.

Oxytocin infusions are notorious for causing hyperstimulation, especially when, as in many parts of the world, they are used without electronic rate controllers. In settings where labour ward staff numbers are very limited, an oxytocin infusion can run unsupervised for many hours without a member of staff checking on its rate or effect on uterine contractions. In contrast, a titrated oral dose of misoprostol needs to be regularly administered by a trained member of staff, a factor that forces some kind of regular clinical assessment and stops the induction process in the absence of staff. So there may also be organisational and safety benefits to the use of low-dose oral misoprostol over oxytocin in low-resource settings. This is supported by a recent randomised trial of oxytocin versus oral misoprostol 20-μg solution given every 2 hours, which found no difference in major outcomes, but reduced rates of hyperstimulation in the misoprostol group. This advantage of low-dose oral misoprostol is in agreement with a network meta-analysis that we recently conducted assessing induction of labour methods.

What is the way forward? Although off-label drug use remains essential in pregnancy (for example with betamethasone for fetal lung maturation), clinicians continue to worry about using an off-label drug when labelled alternatives are available. The development or import of a commercially available 25-μg tablet licensed for labour induction would therefore be a major advance and would provide a definitive protocol. Until that time we recommend the use of 25-μg tablets or solution used every 2 hours. It appears to be safe to use it up to the time of birth rather than simply for cervical ripening; however, use of this ‘extended’ protocol should include close observation and the use of acute tocolytics when hyperstimulation is suspected. There are no direct comparisons of the extended protocol with the standard regimen, nor of the stepped increase in misoprostol dose up to 50 μg. However, they appear to be safe and effective in studies in which they have been used. More research is required into ways of reducing adverse outcomes in high-risk groups (nulliparous women or those with a scarred uterus), potentially using a combination of mechanical and uterotonic methods.

Ideally, formal pharmacokinetic studies would help to clarify the differences between tablets and oral solution, and to establish the optimal frequency of the lowest effective dose. Regrettably, such studies are unlikely to be supported by pharmaceutical companies as misoprostol is too expensive for the market.

Table 1. Published trials of labour induction using low-dose (<50 μg) oral misoprostol

| Initial dose (μg) | Formulation | Dosing interval (hours) | Max. single dose μg (vol.) | Continued in active phase? | References |
|------------------|-------------|-------------------------|---------------------------|---------------------------|------------|
| 5                | Titrated low-dose solution | 1 | 20 (20 ml) | Not stated | Dodd 2006a,14 |
| 10               | Titrated low-dose solution | 4 | 20 (20 ml) | No | Majoko 200215 |
| 20               | Titrated low-dose solution | 1 | 50 (50 ml) | No | Rouzi 201416 |
|                  |             | 80 (40 ml) | No | Srouza 201317 |
|                  |             | 40 (40 ml) | No | Thaisomboon 201218 |
|                  |             | 60 (60 ml) | Yes, only if augmentation required | Cheng 200819 |
| Fixed low-dose solution | 2 | 40 (40 ml) | Yes, only if augmentation required | Hofmeyr 200120 |
|                  |             | 40 (40 ml) | Yes | Dallenbach 200321 |
|                  |             | 20 (20 ml) | Yes | Dodd 200622 |
|                  |             | 20 (20 ml) | No | Moodley 200323 |
| Fixed low-dose solution | 2 | 25 (25 ml) | No | Aalami-Harandi 201324 |
| Tablet           | 2           | 50         | Yes | Bricker 200825 |
|                  | 3           | 25         | Yes | De 200626 |
|                  | 4           | 100        | No | Henrich 200827 |
|                  | 25          | No         | No | How 200128 |
|                  | 72          | 25         | No | Kipikasa 200529 |
| Fixed low-dose solution | 1 | 30 (30 ml) | No | Zvandasara 200830 |

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cheap to justify the investment. Also, the association of misoprostol with termination of pregnancy does not help, despite the fact that its uterotonic properties are life-saving in many low-resource settings. Whether public funders in high-resource settings will rise to the challenge remains to be seen. A large study of a combination of titrated low dose oral misoprostol followed by oxytocin in active phase of labour versus titrated oral misoprostol alone given until birth seems an obvious way forwards.

Disclosure of interests
Full disclosure of interests available to view online as supporting information.

Contribution to authorship
ZA had the original idea for the article. The first draft was written by ADW, with KN contributing research on the doses used. All authors contributed with further editing written by ADW, with KN contributing research on the doses used. All authors contributed with further editing.

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