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EDITORIAL

''Waste not, want not'', or the cost of doing the wrong thing☆,☆☆

''Waste not, want not'', ou o custo da opção errada

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In 1995, Sinclair pointed out that it had taken an inordinately long time to understand that we had synthesized adequate evidence on antenatal corticosteroids (ANCS) to prevent respiratory distress syndrome (RDS) and its complications in preterms.[1] Secondly, it then took even longer for the knowledge to be disseminated into practice. The dissemination problem was addressed by the NIH in a specific trial to enhance uptake of knowledge on ANCS by the obstetric community over 'standard' methods of teaching.[2] In that cluster randomized trial, a package of teaching interventions aimed at the high-risk perinatal caregivers improved the uptake of ANCS in target populations of mothers at risk of preterm delivery by 108%. Yet it appears that despite these two seminal 'wake-up calls' to the community – and despite the recommendations of key bodies such as ACOG[3,4] – the omission of ANCS continues to plague perinatal–neonatal medicine. For example, between 2005 and 2007 in California, Lee found that ''of 15,343 eligible neonates, 23.1% did not receive antenatal steroids in 2005–2007.''[5] Of these, a higher proportion of Hispanic mothers did not receive ANCS – 25.6%.[5] Disseminating this knowledge-based practice into poorly resourced or lower income countries has been even more challenging.[6,7]

In this issue of the *Jornal de Pediatria*, Ogata et al. re-emphasize the importance of the use of ANCS in the prevention of neonatal premature death, especially in the poor and middle-income countries.[8] To further convince the perinatal community, Ogata et al. performed a cost-analysis of the effects of ANCS on total hospital costs in Brazil – a middle-income country.[8] Ogata et al. have shown us that the potential cost reduction is still large in a very recent cohort. In surviving infants less than 30 weeks of gestational age, there was a 38% reduction in total costs, presumably driven by a 49% reduction in neonatal intensive care unit (NICU) length of stay.[8]

Previous cost-analyses on ANCS were performed in an earlier era,[9,10] but in developed and high-income countries. In the UK, Mugford applied expected odds of death derived from randomized trials[9] to the observed deaths in a UK hospital. This allowed them to estimate the anticipated improved survival, and thus the hospital costs per extra survivor. They found that in infants under 31 weeks of gestational age (GA), the actual cost per survivor would have been reduced by 10%. This was despite the projected increased survival rate – which would be expensive.[9] Similarly, modeling data from the USA showed projected cost-savings in 1995 with a minimum of $197,000 savings in hospital expenditure.[10] These data are from the 1990s. The findings of Ogata et al. strikingly confirm these earlier reports, but in a middle-income country.

A potential issue not fully clarified by any of the three studies[8–10] relates to possible misclassification of the exposure to ANCS. Specifically, mothers in the current study were classified as receiving treatment if they received any

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doses of the medication. In a very comprehensive population database in Nova Scotia (from 1988 to 2012), ''suboptimal exposure to ANCS'' (defined as less than 24 h or more than seven days before delivery) comprised 34% of deliveries.[11] Incomplete dosing in the ''treated'' group would potentially bias the observed effectiveness of ANCS toward the null, so the actual effect might be even higher than demonstrated here. Conversely, in the group who did not receive ANCS, there is the potential for confounding by indication: mothers who did not receive treatment may have been too sick, or proceeded to precipitous or complicated deliveries without any delay for corticosteroid administration. In this case, the non-treated infants might have been destined for worse outcomes, and the effect of ANCS would be over-estimated. In California, Lee did find that failure to receive ANCS was associated with such factors as fetal distress.[5] Interestingly, infants undergoing vaginal delivery (*vs.* cesarean) were also associated with non-ANS receipt.[5]

Another note of caution concerns the specific population that should be targeted in low- and middle-income countries. This issue has been thrown into recent considerable debate following the Antenatal Corticosteroid Treatment trial (ACT).[12] This cluster randomized clinical trial (RCT) in six low-to-middle income countries showed a higher 28-day neonatal mortality in all infants receiving ANCS (RR: 1.12; 95% CI: 1.02–1.22). However, the primary outcome of the trial was 28-day mortality in infants <5th percentile, which showed no statistically significant difference (RR: 0.96; 95% CI: 0.87–1.06). The secondary outcome of total mortality has of course received much attention, as the results stand in stark contrast to a meta-analysis on rates of neonatal death from RDS.[6] Mwansa-Kambafwile et al. pooled four trials in middle-income countries (total number of infants = 672) and showed a reduction in neonatal mortality [RR: 0.47 (0.35, 0.64)] which appeared to show even greater effect than that observed in developed countries (n = 3284 infants in 14 studies) [RR 0.79 (95% CI 0.65–0.96)].[6] In the ACT, eligibility was defined by use of a tape-measure of uterine height. It is possible that this led to mis-classification of infants, as suggested by Visser and DiRenzo.[13] It is further possible that infants at gestational ages of >34 weeks are less likely to benefit, due to the lower incidence of respiratory distress syndrome, but might still be exposed to as-yet-undefined risks of the medication. Indeed, such exposure was frequent in the Nova Scotia study noted earlier.[11] Moreover, ANCS should ideally be part of a continuum of best practices in the intrapartum and post-partum period, and suboptimal resuscitation or hygiene measures might adversely impact the effectiveness of antepartum treatment.

We should note that the lack of evidence penetration into practice remains a problem in parts of the world, despite both efficacy data from the 1990s[1] and the economic data for the same period.[9,10] Potential cost reductions are huge, and worthy of the obstetrician's and neonatologist's attention. Mangham et al. found an inverse relationship between both GA and BW, and the costs of hospitalization.[14] Total United Kingdom costs of newborn care for the extremely preterm were staggeringly high, at £ 94,740 (US$ 146,847) higher than a term survivor. Yet data on the economic aspects of health care on specific therapies is remarkably sparse, and what is available is of low methodological quality.[15,16] Moreover, data from large methodologically rigorous randomized controlled clinical trials can and should incorporate economic analyses.[17–19]

There remains resistance from some physicians to cost analyses, likely related to multiple factors including perceived infringement of autonomy and philosophical objections to 'limiting care.' However, given that resources for health care are constrained, particularly in low- and middle-income countries, it is essential that those resources are focused on the highest-yield therapies. Such therapies have an acceptable balance of costs and efficacy in improving outcomes, as summarized in the efficacy/cost ratio, or ''value equation.''[20] To that end, emphasis has recently been placed on eliminating practices that are costly while having poor evidence for effectiveness. This approach has been used in the ''Choosing Wisely'' campaign, in the United States and elsewhere, in which medical subspecialties identify lists of five practices that should be reconsidered.[21] Equally important, however, are those practices that have good evidence for efficacy but are not being used in all eligible patients. Such errors of omission, by foregoing improvements in outcome that would themselves reduce costs, are also wasteful. As shown by Ogata et al., antenatal corticosteroids are a prime example of such underused, but effective, therapies, and should be targeted in quality improvement initiatives in this setting.

Conflicts of interest

The authors declare no conflicts of interest.

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