In this issue, Evidence-Based Medicine highlights and comments on a landmark randomised trial, the ACHOIS trial.\(^1\)

In this trial, Crowther and her colleagues enrolled 1000 pregnant women with mild gestational diabetes who were either informed of their diagnosis and received treatment (including individual dietary advice, instruction on self monitoring of blood glucose concentrations, and insulin therapy as needed) or informed that they did not have gestational diabetes, the higher rate of labour inductions, and insulin based health care. Some recent threads have included an explanation and history of Simpson's paradox, outcomes research, the impact of dishonest reporting of research on EBM, and of course, that perennial discussion about the relative merits of RCTs and observational studies. In the course of that thread Badri Badrinath pointed out the fascinating article by John Ioannidis (Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005 Jul 13;294:218–28), in which the law of initial results ("first results are always spectacular, and subsequent ones are mediocre") was tested using the results of subsequent research. The author found that "most of the observational studies had been contraindicated, or subsequent research showed substantially smaller effects, but most randomised studies had results that had not been challenged." Happy reading.

**EBM notebook**

How should clinicians interpret results reflecting the effect of an intervention on composite end points: should I dump this lump?

In this issue, Evidence-Based Medicine has a lively discussion of topics in evidence-based medicine. Here are some highlights:

1. **EBM notebook**
   - **Jottings:** This section features important points about statistical methods and confidence intervals. It mentions the importance of shifting from p-values to confidence intervals and from relative (RRR) to absolute measures (ARR, NNT) of effect.
   - **EBM notebook:** This section provides insights on interpretation issues, such as the implications of composite end points. It questions the use of multiple outcomes and discusses how these can influence the interpretation of study results. A continuing controversy is over the use of multiple outcomes.

2. **Highlights and comments:** These features discuss the ACHOIS trial, a landmark randomised trial designed to determine the extent to which aggressive treatment of mild gestational diabetes affects outcomes in the mothers (induction of labor and cesarean section) and in the infants (a composite of death, shoulder dystocia, bone fracture, and nerve palsy). The trial findings are statistically significant (p = 0.04) and indicate that clinicians changed their management practices.

3. **Importance to patients:** The importance of these results using numbers needed to treat (NNT) is highlighted. The absolute risk reduction in the composite end point was 3% (CI 7 to 29) women intensively managed, 1 additional infant will require admission to the neonatal nursery.

4. **Importance to clinicians:** Clinicians are encouraged to consider the implications of these results on patient care. The evidence suggests that screening and managing gestational diabetes, the higher rate of labour inductions, and insulin-based health care can improve outcomes. The trial findings support the use of intensive management for mild gestational diabetes.

5. **Conclusion:** The conclusions emphasize the importance of composite end points and the need for clinicians to interpret results accurately. The use of composite end points requires careful consideration of their implications for patient care.
parents would consider perinatal death more important than the other components.

Greene and Solomon,1 in an editorial accompanying the New England Journal of Medicine publication of the ACHOIS trial,2 cite the US Preventive Services Task Force summary of the evidence to note that “only a fraction of deliveries complicated by shoulder dystocia result in birth trauma, and, in most cases, such trauma (clavicular and humeral fractures and brachial plexus injuries) does not result in permanent injury”.

Thus, shoulder dystocia without birth trauma may be of less patient importance than the bone fractures and nerve palsies that result from birth trauma. In summary, we conclude there is a large gradient of patient importance across the components of the composite end point, with perinatal death as the most important and shoulder dystocia as the least important.

**DID THE MORE AND LESS IMPORTANT OUTCOMES OCCUR WITH SIMILAR FREQUENCY?**

The large gradient in importance between the components of the composite end point has alerted us to a potential problem. If the more important components occur less frequently than relatively unimportant components, our concern will rise further.

Five (0.95%) of patients perinatal deaths occurred in the control group (n = 524) and none in the intensive management group (n = 506) (RRR 100%, CI 20% to 100%); the corresponding figures for shoulder dystocia were 16 (3%) and 7 (1.4%) (RRR 55%, CI −6% to 81%), for bone fractures 1 (0.2%) and 0 (RRR 100%, CI −662% to 100%), and for nerve palsies 3 (0.6%) and 0 (RRR 100%, CI −30% to 100%). These data tell us that shoulder dystocia, the least important component of the composite end point, accounted for 77% of all events. The difference in events between treatment and control group (0.95% for perinatal death, 1.6% for shoulder dystocia, 0.2% for bone fractures, and 0.6% for nerve palsies) is somewhat similar, and the exclusive occurrence of death in the control group warrants notice. Yet again, however, half of the overall absolute reduction in risk of the composite comes from the reduction in the risk of shoulder dystocia.

The relative dominance of shoulder dystocia over the other components and the large gradient in patient importance across the component outcomes would suggest one should focus on the effect of the intervention on the individual component outcomes and dismiss the effect on the composite end point. There is, however, one more question to consider.

**ARE THE COMPONENT OUTCOMES LIKELY TO HAVE SIMILAR RELATIVE RISK REDUCTIONS?**

Similar risk reductions across the component outcomes would suggest that the investigators got the biology of the intervention right. In other words, similar effects across components support use of a composite. In this case, the intervention (including tight glycaemic control) should affect the causal pathways leading to perinatal death, shoulder dystocia, bone fractures, and nerve palsies in a similar way and to a similar extent. While the biological link between hyperglycaemia and shoulder dystocia and birth trauma is macrosomia (the intervention reduced the risk of macrosomia by 53%, CI 36% to 66%), how hyperglycaemia and macrosomia are linked to perinatal death remains unclear.

Strong inferences about uniformity of RRRs across individual outcomes come only from considering the point estimates and their confidence intervals. The reductions in risk of perinatal death, bone fractures, and nerve palsies were all 100%, while the RRR for shoulder dystocia was 55%. The paucity of events and resulting imprecision of the estimates of RRR for each of the component outcomes weakens any inferences about their similarity.

To review our answers to the 3 questions, parents will find perinatal death far more important than bone fractures and nerve palsy, and most will find shoulder dystocia less important than the other 3 components. All components occurred infrequently with shoulder dystocia occurring most frequently. The wide confidence intervals around the RRRs weaken any inference about their similarity, but there is no clear biological reason to expect these to be similar. These answers to our 3 questions suggest to us that the composite end point used in this trial is a suboptimal measure of the effect of this intervention (while appreciating the very considerable efforts that investigators went to document this effect!).

In considering how to apply this evidence in clinical practice, decision makers should therefore focus on the effects of the intervention on the components of the composite end point, particularly on the most important one: perinatal mortality. With only 5 perinatal deaths among 1030 births in the ACHOIS trial, is this enough evidence to justify a policy of screening for gestational diabetes and intensive treatment? Another clinical trial is ongoing in this area,3 and perhaps only a meta-analysis of these and other randomised trial evidence will offer sufficient data on individual component outcomes to draw confident inferences about the balance between a possible reduction in perinatal deaths and the currently much stronger evidence of an increase in induced labour and admission to a neonatal nursery.

**CONCLUSIONS**

When event rates are low, the use of composite end points in clinical trials allows investigators to reduce sample size and the duration of follow up. These advantages come at a price: the interpretation of the effect on the intervention is complicated, and the combined end point can be profoundly misleading. We hope Evidence-Based Medicine readers will find our questions helpful in deciding when to accept the effect of treatment on the composite as a valid measure of the effect of treatment and when to ignore the composite end point and focus on individual components.

Evidence-Based Medicine has recognised the importance of this issue. Henceforth, the journal will report the event rate for each component outcome when reporting on trials using composite end points. The welcome beginning to this policy is this issue’s report of the ACHOIS trial.
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