Incorrect conclusions about unpublished pharmaceutical research

In a *CMAJ* news article,[1] David Juurlink states that "there is no obligation on a manufacturer to publish the results of a study," and that he "only sees the evidence that the companies let come to light."

Pharmaceutical companies should not be blamed automatically for the failure to publish an article once a study is complete. Often, these papers are submitted for publication and are rejected by peer-reviewed journals. There are a number of potential reasons why a journal may reject a paper. Peer reviewers may have a bias against a particular drug, company or the entire pharmaceutical industry. Reviewers may think that the quality of the research is inadequate or that there are problems with how the paper is written. In such situations, the paper is usually revised and resubmitted, either to the same journal or to a different one.

Many journals are motivated by impact factor which, from a business standpoint, is completely understandable. Impact factor is a measure of how many times a journal's published articles are cited.[2] This measure can dictate how good a journal is perceived to be and can lead to increased readership and revenue. This concern over impact factor may lead journal editors to reject a study if they believe that study will not increase their journal's impact factor. I suggest that negative or failed studies are most likely to fall into this category. Thus, a negative study may go unpublished because of a journal's business priorities and not because a pharmaceutical company is withholding data. Unfortunately, this gives the appearance that there is an overrepresentation of positive studies and an underrepresentation of negative studies when the literature is subsequently reviewed.

Any study done in the United States, including most clinical trials with Canadian sites, must be registered with www.clinicaltrials.gov. All pharmaceutical companies must post study results within a reasonable period of time following study completion. Also, some companies require researchers to post study results on public websites. Not adhering to these rules can result in huge financial penalties. Companies risk a decline in stock price if they are accused of not publishing results, and therefore they have much to lose from not publishing even negative studies.

Readers should not assume that nonpublication in a journal automatically equates to the purposeful withholding of data.

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Induction of labour

Mishanina and colleagues[1] have reported that the risk of cesarean delivery associated with induction of labour was 12% lower than with expectant management in a systematic review and meta-analysis encompassing 157 randomized controlled trials (RCTs). Although this study presents a wide-reaching review of trials related to this topic, we are concerned that it sends a message that risks associated with all inductions are equal.

The trials included in the review were highly varied in terms of the indications for induction that were studied. The methods of induction were also not standardized with various methods of pharmacological and mechanical induction carried out. The majority of RCTs included in the review also contained a mix of both nulliparous and multiparous parturients in their study cohort and individual examination of these groups may have yielded different results.

Furthermore, the range of institutional cesarean delivery rates across the trials included in the study was not addressed, and rates of prelabour cesarean delivery were also not examined.

Settling the argument of induction versus expectant management will be difficult. A large-scale RCT where participants are matched according to parity and indication for induction, and have standardized management for both spontaneous and induced labours is lacking in the literature. The challenges in design and implementation of such a trial are apparent; however, we feel it is misleading to encourage clinicians to apply the findings of the present study to all patients regardless of maternal baseline characteristics and the indication for induction.

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Reference

1. Mishanina E, Rogozinska E, Thatthi T, et al. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ* 2014;186:665-73.

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The most serious outcome of cesarean delivery is maternal death. Landon and colleagues[1] documented a 1 in 3000 risk of maternal death associated with nonemergency cesarean delivery. Mishanina and colleagues[2] state that induction had no impact on maternal death. This unqualified statement implies that maternal deaths were reported for all 157 studies and all 31 085 study participants. Only 20 of the 157 studies included (12.7%) reported occurrences of maternal death. The authors don't show the number of study participants upon which their conclusion about maternal

death is based. However, if the number is 12.7% of 31 085 (3948), this number is too small to obtain significance.

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The authors respond

We thank Hehir and colleagues[1] for their interest in our systematic review.[2] In response to their comment that not all inductions are equal and that the rate of cesarean delivery following induction compared with expectant management would be expected to be different for different indications for induction, baseline characteristics, methods of induction, parity and institutional cesarean delivery rates, we would like to draw their attention to the extensive subgroup analyses reported in Table 3. The relative risks for cesarean delivery depend on a wide variety of characteristics, including method of induction, indication for induction, gestational age, definition of induction, cervical status, pregnancy risk and parity. For some of these characteristics, we have precise evidence, because a relatively large number of trials reported results by the characteristics, but for others we do not have sufficient information. The results of meta-regression exploring the impact of factors such as patient's characteristics, induction methods and definition of induction are provided in Appendix 6, available at: www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130925/-/DC1. Unfortunately, the included trials did not report the institutional or prelabour cesarean delivery rates, so we were unable to evaluate these.

We also thank Slome Cohain[3] for her interest in our systematic review. There were 2568 cesarean deliveries in the expectant management groups from a total of 15 119 participants in the 157 trials, and the rates varied from 0% to 60%, with a mean of 19.4% and a standard deviation of 13.03%. There were 2384 cesarean deliveries in the induction groups from a total of 15 966 participants, and the rates varied from 0% to 50%, with a mean of 16.5% and a standard deviation of 11.05%.

We agree that the most serious outcome of cesarean delivery is death, which is why we specifically looked for it as one of the outcomes. This analysis was limited by the data published. The 20 trials that reported maternal deaths evaluated results for 4689 women, 2387 in the induction group and 2302 in the expectant management group. There was one death in each group, giving a crude overall mortality rate of 1 in 2345. The most we can say is that there was no difference in the maternal mortality rates in the two groups, and the rates were very low. An extremely large trial or meta-analysis of individual patient data from current trials (obtaining data on maternal mortality where it is not published) could aim to address the question of whether induction is associated with mortality.

Evidence-based medicine encourages a combination of the current best evidence with clinical acumen and the preferences of the patient. Ignoring current evidence would deprive women of the knowledge needed in decision-making concerning labour induction.

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3. Slome Cohain J. Induction raises maternal mortality [letter]. *CMAJ* 2014;186:1246-7.

***CMAJ* 2014. DOI:10.1503/cmaj.114-0078**

Thank you for saying this

In response to the *CMAJ* article by Lipscombe and colleagues,[1] I argue that the idea that slavish adherence to a specific number makes for better outcomes is untenable. The biochemical markers of diabetes and its complications are continuous variables. Treating someone who is 5'1" as short and someone who is 5'2" as tall is, of course, nonsense.

Parameters must be seen as a gestalt, not as rules, especially if there are substantial (nondiabetic) comorbidities. We are treating people, not numbers.

With respect to "marketing disguised as philanthropy," I am delighted to see this called out in public, and conflict of interest as well.

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***CMAJ* 2014. DOI:10.1503/cmaj.114-0080**

Otitis media and Bell palsy

I read the article by deAlmeida and colleagues[1] and found it very informative. It is generally accepted that most cases of Bell palsy are related to virus-induced inflammation of the facial nerve; however, there are a few cases which are related to acute otitis media, which is often bacterial.[2] As an anesthetist, I have seen situations where urgent myringotomy brought about rapid resolution of early Bell palsy. I mention this to remind the front-line physician that such a situation is possible.

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