The power of meta-analysis to address an important clinical question in obstetrics

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I realized the value of meta-analyses when I wrote my first one.[1] I had dedicated much of my professional life to discovering if cerclage was a helpful or harmful procedure. My bias was that it was too simplistic to think that a stitch around the cervix could save lives. Come on! I thought the most probable future of cerclage was to end up soon as the leeches did, in medical history books.

But first I needed to research it. My interested started back in 1994 through 1995, the first year of my fellowship. With my mentors Drs Kuhlman and Wapner, we were looking at our first transvaginal ultrasound (TVU) cervical length (CL) measurements, beginning to correlate them with preterm birth (PTB),[2,3] and having absolutely no clue on how to stop the process we had noticed. Others were doing much better research on the same issues.[4] Long before a meta-analysis, clinicians must have a serious clinical question, a well-defined study population, and an intervention with potential for benefit.

My first oral presentation at the Annual Meeting of the Society for Maternal-Fetal Medicine (SMFM), then called Society of Perinatal Obstetricians, in 1997, was a comparison of manual vs TVU CL examinations.[5,6] My second SMFM oral, in 1999, was a retrospective comparison of 42 cases of cerclage compared to 24 cases of no cerclage in women with singleton gestations and a short cervix.[7,8] The results were disappointingly negative. Cerclage seemed to cause no harm, and no benefit. After my oral presentation, Dr Iams came to the bottom of the podium, graciously congratulated me, and we both realized how little we knew. His assumption—benefit—, and mine—maybe harm—, might both be wrong…

So I embarked on a randomized controlled trial (RCT). Over 5 trying years, we at Jefferson were able to enroll 61 singleton gestations with short cervix to cerclage or no cerclage. The results: negative again, no harm and no benefit.[9] In the meanwhile, our colleagues Rust et al,[10] Althuisius et al,[11] and To et al[12] reported on 3 more related RCTs. The largest ones, by To el al[12] and Rust et al,[10] were negative too. Only the smallest of the 4 RCTs, by Althuisius et al,[11] seemed to be able to show benefit from cerclage. Three RCTs[9,10,12] against one.[11] Overall the evidence did not seem in favor of cerclage.

The friendly interactions we investigators of the RCTs had at many meetings convinced us to share our individual databases, to put all our data together. Our 4 RCTs[9-12] were not exactly identical, but were pretty similar indeed. Suddenly, instead of dealing with a few dozen cases, we all together could look at 607 singleton gestations with short CL randomized to cerclage or no cerclage.[1]

There is not much more exciting to me professionally than looking at the statistical results of analyses of clinically meaningful questions, such as this one about cerclage. Suddenly, while overall the results were negative, when we looked at singletons with a short CL *and* a prior spontaneous PTB (SPTB), we found a 39% significant decrease in PTB.[1] Was there now in 2005 a light at the end of the tunnel I entered first in 1994, when I started my fellowship? The power of meta-analysis was beginning to reveal itself.

Luckily, the hero to rescue us all was coming. John Owen and his colleagues, based also on these contradictory but slightly hopeful results, had obtained a grant from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to do a new, much larger RCT, to evaluate cerclage in exactly this subgroup where benefit seemed to exist: singletons with a prior SPTB and a short CL. He was gracious enough to invite me to join this party.

About 7 years after his grant was submitted, with >300 women randomized, he got his χ^2 results: the *P* value for the primary outcome of PTB <35 weeks was .09[13]: close to making cerclage a winner, but not quite there yet. And to think that we had discussed several times whether to stop at 300, or before, or to recruit more. The trial—and the money—was over. But we did have lots of evidence—statistically significant!—that cerclage was preventing PTB: the incidences of PTB <24 weeks and <37 weeks, perinatal mortality, and the survival curves all pointed to significant benefits for cerclage.[13] John's and our frustration was palpable. Was this once again an issue of just not having studied enough women?

So I asked John and the NICHD to put all our data together. Now we had 5 RCTs.[9-13] They were gracious to agree and collaborate. All authors of the 5 RCTs agreed to provide patient-level data, ie, their databases, to make the meta-analysis as good as it could be. When I looked at the cumulative results, there was indeed a *significant* 30% decrease in PTB, and a *significant* 36% decrease in neonatal morbidity and morbidity.[14] We had gone from 66 retrospectively ascertained, heterogenous, probably mismatched nonrandomized women in 1999,[7,8] to 504

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singleton gestations all with a prior SPTB and all with a short CL <25 mm in 2011.[14] The estimation was that 6500 children would be saved from death annually with this policy in the United States alone.[14] About 17 years has elapsed from when I had first gotten interested—and indeed passionate—in answering this issue. Collaboration and persistence paid off.

Soon after the publication of this meta-analysis,[14] the Royal College of Obstetricians and Gynecologists (RCOG)[15] in 2011, SMFM[16] and the American Congress of Obstetricians and Gynecologists[17] both in 2012, and the Society of Obstetricians and Gynecologists of Canada (SOGC)[18] in 2013 all issued guidelines suggesting cerclage is associated with benefits in this particular group of women, and should be considered and offered in this clinical scenario of singleton gestations, prior SPTB, and TVU CL <25 mm <24 weeks. I was astounded that all our years of work as a team of researchers and the power of meta-analysis led to worldwide recommendation for a major change in practice.

Of course it's true that a meta-analysis is only as good as the RCTs it contains. Pooled results incorporate the biases of individual studies and embody new sources of bias, mostly because of the selection of studies and the inevitable heterogeneity among them. It is also true that a large high-quality RCT often has more meaningful conclusions than a meta-analysis including poor-quality studies.[19,20] In fact, about a third of the time, the results of a meta-analysis are not confirmed by the subsequent large RCT.[20] The importance of doing a properly powered RCT in the first place cannot be overemphasized.

On the other end, meta-analyses can be "the best form of evidence to inform decision making."[21] But to do so, they need to be properly performed. Guidelines for how to perform a meta-analysis are published and widely available.[22] Some highlights are included here, but many more steps are required. First of all, proper selection of which RCT to include is paramount. Second, heterogeneity needs to be investigated and managed. Third, proper meta-analysis methods should be followed. Fourth, individual patient-level data should be sought. Fifth, the meta-analysis should be registered before analysis. Doing a proper meta-analysis is a complex and lengthy task.[21,22]

So, after >20 years of evidence-based hard and fulfilling work, a few words of advice. First, when you study something, try to study it in an RCT if you can. Second, try to include in your RCTs as many women and/or fetuses as possible. Third, collaborate! And when you put your clinician hat on, and try to evaluate if something (an intervention) works or not, please look at all the best data. And looking at all the best data means looking at a meta-analysis of the RCTs. The RCOG, SOGC, and other experts and societies rank meta-analyses of RCTs as the best level of evidence (A+, or I-A, respectively),[15,18] even above that of a single RCT.

If you are doing and publishing good-quality RCTs and good quality meta-analyses of RCTs, or at least reading them and having them lead your clinical decisions, you should be praised and proud of yourself. Women and children will continue to benefit from ever more RCTs and meta-analyses of RCTs on pregnancy-related issues. ■

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