REFERENCES

1. Clapp MA, James KE, Bates SV, Kaimal AJ. Unexpected term NICU admissions: a marker of obstetrical care quality? Am J Obstet Gynecol 2019;220:395.e1–12.
2. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia (PA): Lippincott Williams & Wilkins; 2008.
3. Pearce N. Classification of epidemiological study designs. Int J Epidemiol 2012;41:393–7.
4. Klebanoff MA, Snowden JM. Historical (retrospective) cohort studies and other epidemiologic study designs in perinatal research. Am J Obstet Gynecol 2018;219:447–50.

 https://doi.org/10.1016/j.ajog.2019.08.031

Generalizability from well-designed RCTs underpin their scientific strength

Check for updates

TO THE EDITORS: A recent commentary by Nezhat et al[1] attempts to draw conclusions regarding the results of a prospective randomized study (Laparoscopic Approach to Cervical Cancer trial) that demonstrated lower disease-free survival in patients who undergo minimally invasive radical hysterectomy compared with the open approach.[2] In response, we aim to highlight how the fundamental principles of study design and analysis have been overlooked by Nezhat et al. The design strength of randomization in a well-conducted clinical study ensures that all factors, both measured and unmeasured, are balanced among the groups being compared and guarantees that comparisons give unbiased and consistent estimates of the true underlying differences.[3] Heterogeneity in surgical experience is inevitable; while being controlled for by randomization, it also preserves the generalizability of the result. Surgical volume, although potentially impacting on outcome, would, by randomization, be balanced between the groups and add strength to the external validity of the results, particularly because, contrary to the implication in the commentary, the volume was not uniformly distributed across the participating surgeons. Additionally, the Laparoscopic Approach to Cervical Cancer trial was indeed stratified by site (a surrogate for surgeon) and stage of disease.

The suggested multilevel adjustment by Nezhat et al[1] would be an exercise in statistical acrobatics that would provide a limited and confusing interpretation of the resulting analyses. Limitations include (1) the results being anchored to the choice of model(s) selected, the appropriateness of which are never evaluated, (2) the distribution of factors being adjusted in the trial having little resemblance to the distribution in the wider surgical population, (3) the assumption (incorrect) that all heterogeneity can be explained by statistical adjustment, (4) potential numeric non-convergence/instability in the fitting process, and (5) introduction of missing values in the analyses when some of the factors being adjusted for are missing.

A further advantage of randomization, aside from the scientific rigor in study design, is the ability to perform unadjusted analyses that rely only on minimal assumptions. Although this may provide conservative estimates, it is underpinned by a robust design and strong scientific principles and provides a clear interpretation of the study results. The suggested post-hoc adjusted analysis is 1 of many possible approaches and, as with multiple comparisons, the risk of the selection of that method of adjustment that would support preconceived views is always present. The basic principle of clinical research dictates that new standards of care and changes in patterns of practice should be supported by well-conducted and adequately powered randomized trials. ■

Kristy P. Robledo, PhD
Val Gebski, MStat
NHMRC Clinical Trials Centre
University of Sydney
Sydney NSW, Australia
kristy.robledo@ctc.usyd.edu.au

Pedro Ramirez, MD
The University of Texas M.D. Anderson Cancer Center
Houston, TX

The authors report no conflict of interest.

REFERENCES

1. Nezhat F, Ananth C, Vintzileos A. Two Achilles heels of surgical randomized controlled trials: differences in surgical skills and reporting of average performance. Am J Obstet Gynecol 2019;221:230–2.
2. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.
3. Gail M, Wieand S, Piantadisi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. Biometrika 1984;71:431–44.

 https://doi.org/10.1016/j.ajog.2019.08.037

REPLY

Check for updates

There is nothing scientific about surgical randomized controlled trials (RCTs) when investigators do not take into consideration differences in surgical skills in the performance of a new complex procedure and adjust for it or if they cannot ensure that the new procedure was performed appropriately.

Contrary to the claim of Robledo et al,[1] results from such faulty RCT designs are not generalizable. They opined that the randomization in the Laparoscopic Approach to Cervical Cancer (LACC) trial ensured balance among measured and unmeasured confounders between the 2 comparison groups.[2] We disagree. First, it is difficult for any surgical RCT to provide any such balance because it is impossible to blind or mask a surgical procedure or perform a "sham" surgery; the unblinded nature of surgical RCTs inevitably leads to an unmeasured observer bias. Second, Robledo et al assume that the surgeons had similar expertise or similar variation in expertise in performing both procedures. This assumption is unreasonable for a new complex surgical procedure such as minimally invasive radical hysterectomy.

As we explained in our Viewpoint article,[3] the LACC investigators had several choices to correct for differences in surgical skills; sadly, they did not follow any of the available choices so that the minimally invasive arm of the study was at a disadvantage. The RCT design could not have compensated for varied or suboptimal surgical skills and techniques in performing the minimally invasive procedure.

Robledo et al[1] characterized our suggestion of addressing surgical variability via individual center reporting, based on multilevel models, as "statistical acrobatics." Our suggestion is a pragmatic one. In their letter, they admitted that the surgical volume was not distributed uniformly across the participating surgeons and therefore centers. In the LACC trial, cervical cancer recurrences occurred in only 14 of the 33 centers.[2] Should the remaining 19 centers, which had no recurrences, change their practice based on the results of the 14 centers when surgical proficiency has not been taken into serious consideration in the performance of the minimally invasive radical hysterectomy? ■

Farr R. Nezhat, MD
Director of Division and Fellowship
Minimally Invasive Gynecologic Surgery and Robotics
Department of Obstetrics and Gynecology
New York University (NYU) Winthrop University Hospital
NYU Long Island School of Medicine
Mineola, NY
fn0250@aol.com

Cande V. Ananth, PhD, MPH
Division of Epidemiology and Biostatistics
Department of Obstetrics, Gynecology, and Reproductive Sciences
Rutgers Robert Wood Johnson Medical School
New Brunswick, NJ

Anthony M. Vintzileos, MD
Department of Obstetrics and Gynecology
New York University (NYU) Winthrop University Hospital
NYU Long Island School of Medicine
Mineola, NY

The authors report no conflict of interest.

REFERENCES

1. Robledo KP, Gebski V, Ramirez P. Generalizability from well-designed RCTs underpin their scientific strength. Am J Obstet Gynecol 2019;221:663.

2. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.

3. Nezhat FR, Ananth CV, Vintzileos AM. The two Achilles heels of surgical randomized controlled trials: differences in surgical skills and reporting of average performance. Am J Obstet Gynecol 2019;221:230–2.

 https://doi.org/10.1016/j.ajog.2019.08.036

Cerebroplacental ratio and estimated fetal weight, the 2 different yardsticks

Check for updates

TO THE EDITORS: We read with interest the work of Akolekar et al[1] and agree with the authors in that cerebroplacental ratio (CPR) as a stand alone measurement is unable to predict adverse perinatal outcome accurately, unless it incorporates extra information that is provided by estimated fetal weight (EFW), maternal characteristics, and future biochemical markers. In this regard, the accuracy of CPR has become a question of debate because the reported prediction ability for adverse perinatal outcome (APO) and intrapartum fetal compromise (IFC) by different groups presents notable variations. In our opinion, several aspects regarding the accuracy of CPR in the prediction of APO deserve to be commented.

Despite the reported low accuracy, CPR and middle cerebral artery Doppler, are the only ultrasonographic parameters that change before late-onset stillbirth[2] and placental abruption,[3] which confirms that fetal cerebral vasodilation, and not weight restriction, represents the initial answer to the late unbalance between placental supply and fetal demands. A phenomenon that is related more with subacute cardiorespiratory decompensation than with chronic nutritional disorder that causes progressive weight loss.

In addition, when dealing with CPR prediction, we should consider that the existence of a low CPR only reflexes a reduction of the placental reserve, which is translated into a higher possibility of abnormal cardiotocography. This might explain the reason that CPR performs better at predicting cesarean delivery for fetal compromise and worse at predicting severe APO with encephalopathy and extremely low fetal acidosis, because they probably are related more with severe and unpredictable intrapartum events that cannot be anticipated by means of prepartum hemodynamics.