Antenatal Betamethasone Compared With Dexamethasone (Betacode Trial): A Randomized Controlled Trial

To the Editor:

The randomized control trial reported by Elimain and colleagues[1] supports retrospective reports[2,3] of equal effectiveness of betamethasone compared with dexamethasone to reduce the risk of respiratory distress syndrome. However, they raise concern that there is a statistically significant greater risk of high-grade intraventricular hemorrhage (Grade III/IV) with the use of betamethasone.

Their report lacked a piece of information that would be helpful for the reader to better assess their findings. The gestational age at delivery was not provided. Gestational age has an influence on intraventricular hemorrhage. As pointed out in the accompanying editorial by Murphy, the greater than 40% incidence of respiratory distress syndrome in both treatment groups leads one to "assume that a very high proportion of women gave birth preterm."[4] As well, the mean birth weight of the two treatment groups (1983 g and 2036 g) would also suggest this.

Of the three eligible groups of patients for enrollment (preterm labor with intact membranes, preterm premature rupture of membranes, and anticipated delivery for fetal or maternal indications between 24 and 33 weeks and 6 days) the reader is only certain that all of the patients in the last category delivered prematurely.

Because the authors have the information, it should have been presented along with an analysis of any statistical significance to any difference in gestational age at delivery between the groups.

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Financial Disclosure
The author has no potential conflicts of interest to disclose.

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Antenatal Betamethasone Compared With Dexamethasone (Betacode Trial): A Randomized Controlled Trial

To the Editor:

In the article by ElImian et al,[1] on page 27, under Materials and Methods, the authors state, "We conducted a randomized, double-blind, placebo-controlled trial . . . ." I searched the Results section but was unable to find the placebo data. Were those data published elsewhere?

Daniel M. Strickland, MD
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Financial Disclosure
The author has no potential conflicts of interest to disclose.

Antenatal Betamethasone Compared With Dexamethasone (Betacode Trial): A Randomized Controlled Trial

To the Editor:

I was disappointed that both an original research article[1] and an editorial[2] discussing reduction in preterm neonatal morbidity and mortality both maintained a focus on the use of corticosteroids without reference to the documented[3–5] efficacy of intraamniotic thyroxine. The potential benefits of thyroxine were not promulgated for reasons that are unclear, and a significant therapeutic agent was overlooked.

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Financial Disclosure
The author has no potential conflicts of interest to disclose.

In Reply:

We appreciate the editorial by Dr. Murphy that accompanied our original article and the valuable comments and questions raised by Drs. Campbell, Strickland, and Wallach. We indeed have information with respect to the concerns raised. Only women who delivered preterm (ie, less than 37 weeks) and their neonates were included in our analysis. However, note that the proportion of women who subsequently delivered at term did not differ between groups. There were no differences in the mean gestational age at delivery between neonates exposed to betamethasone and those exposed to dexamethasone (32.87±1.3 compared with 32.85±1.3, P=.88). Similarly, the interval from randomization to delivery did not differ between the groups. With respect to grades III/IV intraventricular hemorrhage, our study did not find a statistically significant difference between the groups. On the subject of placebo, women in the betamethasone group received 12 mg of betamethasone at 0 and 24 hours and a similar-looking placebo at 12 and 36 hours, whereas women in the dexamethasone group received 6 mg of dexamethasone at 0, 12, 24, and 36 hours. In essence, placebo was given only to women in the betamethasone group, such that all study subjects received four intramuscular injections at the same interval. Finally, we are not sure that information about the efficacy of intraamniotic thyroxine has any place in our original article; however, thank you for the information. Our group as well as other investigators will surely take note of your comments.

Andrew Elimian, MD
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The High Cost of Free Lunch

To the Editor:

I read with great consternation the commentary by Wall and Brown[1] entitled, "The High Cost of Free Lunch." It is a well-written and well-documented paper. The authors describe marketing strategies and goals of the pharmaceutical industry. Doctors and patients are bombarded by advertising in person, in the press, on television, and on the Internet. New information is constantly conveyed to physicians, and this often happens during launches, lunches, dinners, or other social gatherings. In South Africa, ethical rules are applied and reinforced by the Medical Council, and continuing professional development points are earned for listening to advertising during suppers. I personally feel offended by the idea of prescribing any management with which I am not familiar or is not registered by a reputable licensing body such as our Medicine Control Council or the U.S. Food and Drug Administration (FDA). Advertising works on the medical profession equally efficiently on any other profession or person. Doctors, however, do not make a profit on their prescription, but health maintenance organizations (HMOs), pharmacies, and pharmaceutical companies do so. Lunches bring us together and pens remind us of certain prescriptions, but the authors missed the whole point of professional advertising. Health maintenance organizations have their formularies, preferred providers, and limitations based on price, quantity related incentives, rebates, and fixed fees, while insurance companies and clinics offer and pay for the cheapest drug or the drug with highest profit margin. Advertising to the public makes prescribing consumer driven. In South Africa, pharmacists can change a doctor's prescription, while in clinics and to HMO patients the doctor can only prescribe what is allowed from a formulary. Why did the authors pick on free lunches and doctors? Why was this paper published by a reputable, peer-reviewed journal? The motives of the reviewers for publishing such a one-sided article is intriguing.

The authors performed a superficial and biased analysis of one aspect of advertising and competition. Their analysis was incomplete, and they did not conclude with any positive thoughts which might protect and help doctors and patients on how to decide which management to use. There was no positive input or advice on how to protect the public against unethical advertising and competition. I see no place for superficial, incomplete, subjective, vindictive, and aimless commentaries in leading, peer-reviewed journals.

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REFERENCE

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Financial Disclosure
The author has no potential conflicts of interest to disclose.

The High Cost of Free Lunch

To the Editor:

The article by Wall and Brown provides food for thought on a topic that can spark a lively debate among health care professionals. No physician wants to think he/she can be influenced about important decisions by what the authors refer to as a "bribe." Their examples of medical universities banning free meals and suggestion that all physicians avoid such inducements from pharmaceutical companies will not solve the problem. Medical university bans on free meals or gifts only affects what occurs on campus and only for residents and faculty physicians. It will not impact pharmaceutical company sponsorship of off-campus evening social events, educational conferences, or contact with physicians in private practice. This is a feel-good approach that only covers up and does not solve the problem.

Even if there was universal proscription of a free lunch, I think a more powerful influence on physician-prescribing practice is evolving. As the authors mention, there is an "explosive increase in direct-to-consumer advertising of prescription drugs." Television and internet advertisements targeting patients have the potential to replace the free lunch. If media advertisement provides patients with more objective data that seems compelling to them, then physicians might feel more obligated to satisfy their patients than please a pharmaceutical representative.

Bribery (money or favors, as described by the authors) is an innate part of our culture from childhood. Parents (and children) use food in exchange for good behavior. Adults use bribery for social and personal benefit all the time. Politicians entice the electorate with a promise of nirvana, and the electorate

Financial Disclosure
Dr. Campbell serves on the Board of Directors for the Hartford County Medical Society (Hartford, CT).

promises votes to get what they want from their elected officials.

The focus on solving the cost of the free lunch should be on teaching physicians how to make decisions based on objective data. Medical universities should develop meticulous guidelines that will allow for the provision of food, etc, by pharmaceutical companies when they seek contact with physicians to advertise their product. Teaching faculty and residents in training should receive education about ethics and decision making as it pertains to influence on prescribing practice. This is the basis upon which good example and practice can be developed and become a part of a physician's practice.

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1. Wall LL, Brown D. The high cost of free lunch. Obstet Gynecol 2007;110:169–73.

The High Cost of Free Lunch

To the Editor:

I have been in private practice 29 years. During that time, drug samples have always been provided by salesmen for my patients. I have given these out when appropriate, and I do not believe my prescribing habits have been affected by the type of samples available in my closet. The patients have certainly benefited from the free medicine.

In the last 29 years, the number of pharmaceutical company–supplied lunches in my office has increased. My employees are happy to eat the free meal. I spend 10 minutes with the drug representative in the office at any given time and eat the lunch they provide also. I do not believe that this has ever affected my prescription habits. I have, on occasion, changed my prescribing habits based on scientific information provided during these lunches, but this was based on the information, not on the lunch. My employees, who make no decisions as to the type of drugs written, save money by not buying their lunches that day and look at this as a benefit of their job.

For some time, I spoke at dinner meetings for several pharmaceutical companies for which I was paid a reasonable amount of money. This had a direct effect on my prescribing habits and also, theoretically, affected the habits of the other physicians at the meeting. When I realized how much this was affecting my prescribing practices, I stopped.

I find it disturbing that physician organizations choose to criticize those parts of pharmaceutical sales which directly benefit the patient (free samples) and those that benefit office employees (free lunches) but do not address that part of pharmaceutical sales that have the greatest effect on individual prescription practice: the fees paid to physicians to speak at dinner meetings.

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Financial Disclosure
Dr. Rankin was a paid speaker for Warner Chilcott (Rockaway, NJ).

The High Cost of Free Lunch

To the Editor:

I recently read the comments of Drs. Wall and Brown.[1] I agree that this issue remains bothersome. There is always the issue of appearance of impropriety if a physician receives a gift from a pharmaceutical or similar representative. The use of samples may be problematic in steering trial of medications toward the newer and more expensive drugs (since only those are sampled).

However, I think that interaction between physicians and representatives can be risk-neutral and positive in many ways.

1) One byproduct of the physician-representative interaction is sampling. Although these involve more expensive drugs, it remains a real benefit for patients.
2) I may be revealing my naivete, but I feel that, if I can sort through nonstraightforward illnesses and difficult personalities of patients, I can select which medication to use. I greatly appreciate samples of Levaquin (levofloxacin, Ortho-McNeil, Raritan, NJ), yet I feel using the 5-day levofloxacin pack for initial sinusitis treatment is criminal. My patients get high-dose amoxicillin routinely. I attended company-sponsored speaker training for Ketek in Chicago, yet subsequently never spoke for (and rarely use) the drug because of its lack of endorsement for sinusitis.
3) One hopes that physicians retain some academic skill to use when reviewing literature in journals and in maintaining healthy skepticism regarding studies provided by the pharmaceutical representatives.

When kept in appropriate context and limits, it seems that these practices may fall under the heading of professional or business courtesies. It enhances office morale if we get an occasional treat for our staff to be taken to lunch by the representatives. I can personally take or leave all of this, yet I find (again, within reason) work and life are nicer with a few niceties thrown in.

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Financial Disclosure
Dr. Randall attended company-sponsored speaker training for Ketek (Sanofi-Aventis, Bridgewater, NJ).

REFERENCE

1. Wall LL, Brown D. The high cost of free lunch. Obstet Gynecol 2007;110:169–73.

In Reply:

We thank the correspondents for their interest in our commentary. We are not surprised that physicians continue to deny–in spite of evidence to the contrary–that drug company lunches and promotional materials are highly effective tools for altering their prescribing behavior.[1]

Pharmaceutical companies exist to sell drugs, not provide education. Pharmaceutical sales representatives visit doctors to market drugs and to influence the prescription-writing habits of physicians. Residency training programs are choice targets because the earlier prescribing habits can be influenced, the greater the long-term sales gain.

The argument is often made that free samples benefit patients; however, these samples are not "free." The cost of sample medications is a cost of doing

business built into the marketing budgets of drug companies. Virtually all samples are expensive, patent-protected medications provided to drive sales of those products. Notice how fast "free samples to benefit patients" disappear when the sample drug goes generic. A pharmaceutical company that wants to make drugs more readily available to the poor cuts prices across the board; samples are irrelevant. Furthermore, a large percentage of sample drugs provided to physician offices is actually used by the office staff, by doctors themselves, and by their friends and relatives rather than by indigent patients.

Free lunches are not "free." Free lunches are provided to doctors as a quid pro quo for granting access to sales representatives. "Free lunch" for the office staff buys sales representatives access to the physicians who write prescriptions.

Dr. Rankin recognizes that his being paid a speaker's fee influenced his prescription-writing habits; it is unfortunate he does not recognize that a free lunch has the same intent. That the letters have mentioned other abuses (eg, speakers' fees to physicians, direct-to-consumer advertising, off-campus social events, kickbacks to pharmacies, special deals for hospital formularies, etc) does not undermine the conclusions of our article; rather, it underscores that the pharmaceutical companies have enormous, wide-ranging, powerful, and worrisome influence on the practice of medicine.[2,3]

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Cost-Effectiveness Analysis of Strategies for the Surgical Management of Grade 1 Endometrial Adenocarcinoma

To the Editor:

Similar to Cohn et al,[1] we recently published a cost-effectiveness analysis comparing two treatment paradigms for endometrial cancer using empiric data from a population-based study in Canada: 1) surgical staging, with selective adjuvant radiotherapy, and 2) simple hysterectomy with a more liberal policy for adjuvant radiotherapy.[2] In our analysis, the most cost-effective strategy for grade 1 cancer was simple hysterectomy. We acknowledge that the absolute costs for radiotherapy and surgery are substantially different between Canada and the United States; however, relative costs are similar.[1,2] The data used by Cohn et al are predominantly from retrospective, single-institution studies of surgical staging alone or prospective studies of intermediate/high-risk, early-stage endometrial cancer. These data may not be representative of women with grade 1 cancer in the general population to which their analysis is intended to apply. The majority of these women present with low-risk disease, and they do well with simple hysterectomy and observation alone.[3]

Important details of Cohn et al's model are missing, including the overall proportion of patients with "clinical" stage I and the proportion of these patients who received whole pelvic radiation therapy/brachytherapy. These assumptions, when applied to the general population, may have a significant impact on costs. A recent report of the largest randomized trial comparing treatment strategies in endometrial cancer (Medical Research Council–A Study in the Treatment of Endometrial Cancer [MRC-ASTEC]) (Orton J, Blake P, on behalf of ASTEC/EN.5 collaborators. Adjuvant external beam radiotherapy (EBRT) in the treatment of endometrial cancer: results of the randomised MRC ASTEC and NCIC CTG EN.5 trial [abstract]. J Clin Oncol 2005;25[suppl 18S]:5504) did not identify a survival benefit for either surgical staging or adjuvant pelvic radiotherapy. As a result, utilization of adjuvant pelvic radiotherapy may be reduced for grade 1 patients, even in the absence of surgical staging.

We congratulate the authors for their important work in evaluating various treatment strategies for grade 1 endometrial cancer. As the debate on surgical staging continues, cost-effectiveness analyses provide valuable information when confronted with uncertainties relating to treatment. As more data become available on outcomes from different surgical and adjuvant radiotherapy practices, it will be important to refine model assumptions and update this analysis.

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Mark Carey
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In Reply:

We appreciate the interest shown by Kwon et al in our cost-effectiveness analysis of the various strategies of the management of grade 1 endometrial cancer[1] and agree that their contribution to the literature on this topic[2] is critical in optimizing the management of patients with this disease. Importantly, there are substantial differences in our reports and, in particular, the fact that our study "group" was a hypothetical group of women with

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grade 1 endometrioid adenocarcinoma of the endometrium compared with Kwon's patients with clinical stage I and II endometrial cancer managed in Canada. Kwon et al point out that the outcomes of our "patients" with grade 1 endometrial cancer were predicted based on our own tertiary institutional data and not that from the community of clinicians that provide endometrial cancer care (such as general surgeons and obstetrician–gynecologists). While we acknowledge that only a small percentage of women with endometrial cancer in the United States are managed by gynecologic oncologists (Partridge EE, Jessup JM, Donaldson ES, Taylor PT, Randal M, Braley P, et al. 1996 Patient care evaluation study of cancer of the corpusuteri. The National Cancer Data Base, American College of Surgeons [abstract]. Gynecol Oncol 1999;72:445), we are unaware of any data supporting that patients with grade 1 endometrial cancer in a university hospital in the United States have any different epidemiologic, biologic, genetic, or pathologic characteristics from those managed by a gynecologist outside of a tertiary care center in Canada.

Kwon et al also point out that we did not report the proportion of patients with "clinical" stage I endometrial cancer or the proportion of those patients who received pelvic radiotherapy. In our model, we hypothesized that 87% of patients who underwent hysterectomy without lymphadenectomy were diagnosed with clinical stage I disease, and of those, 70% were observed and the remainder were treated with adjuvant pelvic radiotherapy. We believe that these assumptions are both sound and conservative. Furthermore, we performed a sensitivity analysis where the percentage of patients diagnosed with clinical stage I endometrial cancer and the rate of prescription of adjuvant radiotherapy in this situation were varied. Despite adjusting for such uncertainties, routine comprehensive staging without adjuvant radiotherapy remains the most cost-effective strategy for the management of women presenting with grade 1 endometrioid adenocarcinoma. We ultimately hope that all women diagnosed with endometrial cancer, including those with grade 1 tumors, will be offered comprehensive surgical staging.

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Laparoscopic Findings and Pelvic Anatomy in Mayer-Rokitansky-Küster-Hauser Syndrome

To the Editor:

We wish to draw attention to the 18 cases of Fedele et al[1] where magnetic resonance imaging revealed "tiny fibrous cavitated structures with a diameter of a few millimeters [localized] in the retrovesicorectal space," and interpreted as "possible remnants of Gartner's duct."

In 1989, we observed pelvic peritoneal pockets with associated urinary and reproductive tract anomalies in 18 of 54 (33%) of patients. One patient had Mayer-Rokitansky-Küster-Hauser syndrome.[2]

Of special interest, Faulconer[3] noted that "marked variations in the site of the müllerian groove [indicated] that the formation of the müllerian duct is potentially the function of a wide area of specialized epithelia at the cranial end of the Wolffian body." Examining classic cases of Mayer-Rokitansky-Küster syndrome, Ludwig[4] stated that "only the initial [cranial] segment of the müllerian duct . . . is an independent formation," ie, independent of the Wolffian duct.

Given Faulconer's observations and given Ludwig's theory of development of the cranial end of the müllerian duct independent of the Wolffian duct and given the presence of a müllerian choristoma far removed from the influence of the Wolffian ducts,[5] is it possible that the tiny fibrous "cavitated" structures in the retrovesicorectal space might represent rudimentary duplications of the cranial end of the primary müllerian system, formed independently of the Wolffian duct?[2]

Would the authors consider examining the "cavitated" structures for histologic evidence of endometrial glands and stroma, estrogen and progesterone receptors, and *HOX* genes, as well as incubating sections with monoclonal antibodies specific to Wolffian cell antigens?[6] Was there histologic evidence of adenomyosis, endosalpingiosis, peritoneal, tubal, or ovarian endometriosis?

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Financial Disclosure
The authors have no potential conflicts of interest to disclose.

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In Reply:

We thank Dr. Batt and colleagues for their interest in our work and the stimulating embryologic observations. Indeed, Rokitansky syndrome, together with other müllerian anomalies, presents several unusual embryogenetic aspects. In particular, with regard to the magnetic resonance imaging (MRI) findings of tiny cavitated structures in the vesico-rectal space, our hypothesis about their embryologic origin seems fully sustainable. In our paper, as in our previous one,[1] we theorized a Wolffian origin because they had the anatomic site and some radiologic characteristics in common with Gartner paravaginal cysts. We agree that a histological evaluation might give a certain response. However, all patients in the present series were operated upon with the Vecchietti technique without the dissection of the vesicorectal space and, therefore, without the possibility of removing such structures. Since we are presently operating upon some patients with the Davydov technique, modified with the use of laparoscopy instead of laparotomy, we will have the chance of obtaining anatomical samples for histological evaluation of such structures.

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