

Clinical Studies Without Patients

To the Editor:

In the recent article, "The septate uterus: a review of management and reproductive outcome" by Homer, Li, and Cooke (1), the authors state that "The absence of Bcl-2 results in failure of regression of the septum." This was in reference to Dr. Lee's original article (2) on Bcl-2, in which he localized this antiapoptotic protein to the müllerian tract. He demonstrated using immunostaining, the existence of Bcl-2 in the embryonic endometrium and the absence of this protein in normal embryonic uterine septum, suggesting its role in protecting these cells from apoptosis. Although this does not answer all the questions about apoptotic events, the evidence stands as a proposed mechanism for apoptotic events in the development of the müllerian system. Using this knowledge, we would logically expect women with septate uteri to have Bcl-2 present in these septum and not its absence, as stated in this article. Although I understand the limitations of Bcl-2 as a predictor of apoptosis and the possibility of a false negative with immunostaining assays, an understanding of this reference and the proposed role of Bcl-2 in apoptosis are important.

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References

1. Homer H, Li Tin-Chiu, Cooke ID. The septate uterus: a review of management and reproductive outcome. *Fertil Steril* 2000;73:1-14.
2. Lee DM, Osathanondh R, Yeh J. Localization of Bcl-2 in the human fetal müllerian tract. *Fertil Steril* 1998;70:135-40.

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To the Editor:

The authors present a review of contemporary literature addressing the management of the septate uterus (1). Although the literature citations are comprehensive, the quality of the evidence and strength of the recommendations deserve explicit emphasis in a contemporary, evidence-based environment, a shortcoming cited by the authors in their summary of clinical results. The literature is composed largely of observational studies, rendering these recommendations weak at best. But the issues are more complex than a lack of randomized, controlled trials, and the data are even more suspect when several other issues are considered. Two ad-

ditional points (and the questions they imply) are relevant to the critical analysis of this literature. These include the lack of a standard, quantitative definition and diagnostic criteria for a septate uterus (what is normal?) and the observations that reproductive outcomes tend to improve in this setting without intervention (what happens when nothing is done?). These issues have been addressed in the past by our predecessors on both sides of the Atlantic. Their thoughts and insights provide an interesting background against which contemporary management may be evaluated.

A critical need for standardized definitions of a normal and an abnormal uterine cavity has long been recognized. In 1958, David Hay suggested that the features to distinguish a normal and an abnormal hysterosalpingogram were unknown and issued a challenge that practitioners forge more quantitative and exact definitions (2). The intention was to provide a means of comparison and eventually reliable indications for intervention. In 1962, Pendleton Tompkins, editor of *Fertility and Sterility* from 1950 to 1952, reinvigorated the debate and suggested that these abnormalities be viewed on a spectrum from clearly normal to clearly abnormal (3). He suggested that the case for or against intervention rested on subtle distinctions. No debate can be mustered, for example, for configurations at either end of the spectrum. However, earnest haggling and debate certainly are appropriate to sort out normal from abnormal for those configurations in between. Tompkins set forth a system of classification based on curvature of the fundus to differentiate septate from arcuate from normal uterine cavities. In so doing, Tompkins had hoped to establish what configuration(s) required therapy and what might well be neglected benignly and function normally. The challenge remains, and we continue to use relatively subjective standards to differentiate normal from abnormal: what may be septate to one examiner may be arcuate to another.

The second issue turns on the likely improvement in outcomes regardless of intervention. In 1960, M. M. White noted that reproductive outcomes in patients with müllerian abnormalities improved with repeated pregnancies regardless of intervention (4). White's observations have been substantiated in several observational studies describing favorable outcomes both in untreated populations and when compared in treated and untreated populations (5). These studies, although provocative, unfortunately lack sufficient power to yield firm conclusions but lend credence to White's observations that improvement may be expected when no intervention is taken. These data suggest that there may be

some cases that in fact are amenable to intervention and resection of the septum and others that will function perfectly well without any surgery. Surgery may not be the answer to every case of a septate uterus.

What is needed for resolution are well-designed, prospective, randomized trials including untreated controls and rigid definitions that enable accurate comparisons. These needs remain unchanged over some 40 years of clinical observation. The authors offer a valuable reference and comprehensive review describing appropriate indications for intervention based on the literature available. In our evidence-based environment, some stipulation of the quality of evidence attached to the recommendations would be useful to the reader to clarify the strength or confidence of the recommendations and to perhaps include in counseling a patient with these complex abnormalities.

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References

1. Homer HA, Li Tin-Chiu, Cooke ID. The septate uterus: a review of management and reproductive outcome. *Fertil Steril* 2000;73:1-14.
2. Hay D. Diagnosis and significance of minor defects of uterine abnormality in relation to pregnancy. *J Obstet Gynecol Br Emp* 1958;65:557-61.
3. Tompkins P. Comments on the bicornuate uterus and twinning. *Surg Clin North Am* 1962;42:1049-62.
4. White MM. Uteroplasty in infertility. *Proc R Soc Med* 1960;53:1006-9.
5. Letterie GS. Septate, arcuate, bicornuate and didelphic uteri. In: Letterie GS. *Structural abnormalities and reproductive failure: effective techniques for diagnosis and management*. Malden (MA): Blackwell Science, 1998:139-76.

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Reply of the Authors:

We thank Dr. Letterie for his comments regarding our paper and fully appreciate the divergent opinions concerning the management of the septate uterus. These are the very circumstances where in-depth analysis of the relevant evidence is essential to produce useful, working guidelines. Guidelines have been shown to improve the process of care and improve outcomes for patients and are meant to represent the best practice based on available evidence. We too lament the absence of randomized controlled trials in this particular arena of reproductive medicine. Although it is acknowledged as being the gold-standard quality of evidence on which to base recommendations, it seems unlikely that we will ever have the benefit of its guidance on this issue. This is related in no small part to the relative rarity of the condition that would entail coordinating a multicenter trial to generate sufficient participants. In addition, we are all only too aware of the despair and grief that enshrouds couples with reproductive difficulties (such as recurrent miscarriages) and their understandable hesitancy to consent to the

potential of being part of a "no-treatment" arm if intervention offers even a small chance of benefit.

The link between treatment benefit and the quality of evidence on which it is based must take into account the type of treatment involved and any attendant morbidity. Clearly, interventions associated with significant risk of morbidity or mortality (such as transabdominal metroplasty) would demand the backing of the highest quality evidence. We have highlighted the relative safety of hysteroscopic metroplasty under laparoscopic guidance (1). This does not imply that all cases of a uterine septum demand intervention or that minimal access surgery is risk-free and, as we have outlined, there are some series suggesting no reproductive impedance in women with this uterine abnormality (2, 3). Nevertheless, as we have delineated, there are subgroups of women in whom obstetric success is jeopardized and for whom the evidence (observational though it might be) is overwhelmingly in favor of septal resection.

The issue of well-defined diagnostic criteria remains unresolved. Unfortunately, medicine is not a precise science, and much of its practice depends on the subjective clinical acumen of its providers: at which precise point, for instance, does mild endometriosis become moderate? Diagnosis and classification of uterine abnormalities are no exception. On review of the embryologic development of the müllerian system it will be appreciated that septal defects form a continuum from almost nonexistent (the arcuate uterus) to divisions that extend to the cervix and beyond (on this point, we thank Dr. Rychlik for his astute clarification of the role of Bcl-2). We believe that the problem lies not with "what is normal?" but rather "what degree of abnormality is clinically significant?" This is where the patient's history is an important guide. Bearing this in mind, and as long as fundal notching is not of a sufficient degree to prohibit safe hysteroscopic surgery, precise classification may ultimately not prove to be a major stumbling block. Results suggesting an adverse effect of the arcuate uterus and improved outcome after hysteroscopic metroplasty lend credence to this (4).

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References

1. Homer HA, Li Tin-Chiu, Cooke ID. The septate uterus: a review of management and reproductive outcome. *Fertil Steril* 2000;73:1-14.
2. Ashton D, Amin HK, Richart RM, Neuwirth RS. The incidence of

- asymptomatic uterine anomalies in women undergoing transcervical tubal sterilization. *Obstet Gynecol* 1988;72:28-30.
3. Simon C, Martinez L, Pardo F, Tortajada M, Pellicer A. Mullerian defects in women with normal reproductive outcome. *Fertil Steril* 1991; 56:1192-3.
 4. Mancaglia L, Tantini C. Hysteroscopic treatment of septate and arcuate uterus. *Gynaecol Endosc* 1996;5:151-4.

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Editorial Comment

Clinical Studies Without Patients

Performing randomized controlled trials (RCTs) for the management of septate uteri may always be a "gedanken-experiment." Admittedly, RCTs and frequentist statistics are valuable inferential tools, but it is important to note that growing numbers of alternative approaches for the design and analysis of outcome studies have been pouring into the literature. The reasons for this are multifold. Newer computational methods to take advantage of the advancements in computing power have been developed in the past decade.

At the same time, the gurus of evidence-based medicine have begun to realize that some clinical problems, because of ethical and technical issues, defy the methodologic constraints of RCTs. Simulation studies, computer modeling, and Bayesian analysis have become commonplace for analyzing the daily probabilities of conception, declining sperm counts, etc. More and more one may read an article and note that the methodology seems alien.

A recent article published in the Journal of the American Medical Association looking at the value of seven different intervention strategies in patients with breast cancer and BRCA1/2 mutations is a good example of this methodologic trend (1). If you don't look carefully while reading this article, you will assume that this is a typical retrospective or cohort study of a large number of women with unilateral breast cancers, who have had different interventions and have been followed for life expectancy. You are slightly confused when you are unable to find the exact numbers of patients that were studied ($n = ?$). Finally, it dawns on you that this is a "clinical study without patients," and the only n values are the numbers of simulations. Probabilities for each of the interventions (tamoxifen, contra lateral mastectomy, oophorectomy, or combinations of all three) are taken from published studies.

The model simulates the natural history of these hypothetical cohorts of women with unilateral breast cancer who have been selected for one of the interventional strategies. Computer simulations are performed for women from each of the several prognostic groups as defined by several variables (age at onset, family history, lymph node status, and BRCA1/2 penetrance). These simulations, worked out by

repetitive computer analysis, estimate the gain in life expectancy to be anticipated by each of the secondary cancer prevention strategies. These simulations include various hypothetical combinations of all three prophylactic measures. The authors refer to the simulation methodology as the Markov state transitional model. The results tend to be expressed as ratios and proportions. This method uses all available published information and is the biostatistician's answer to highly sophisticated clinical judgment.

Editors of scientific journals are especially sensitive to the increased use of Bayesian inference, simulations, and computer modeling because they must find a special subset of biostatisticians who can review submissions that use these methods. One reservation concerning the study under discussion is that so many subgroups are analyzed that it may increase overall type I error rates.

In the final analysis the techniques are especially valuable for the design and analysis of studies in which the disorder is infrequent and/or the outcome is many years removed. Medical decision making is becoming more and more complex as the number of variables that impact an outcome are increasing. Fortunately, the methodology to analyze those variables is on the rise (2).

The Markov simulation or a combination of this approach with others might prove to be valuable in studies of mullerian anomalies as discussed by the correspondents. Perhaps someday the clinical judgment of the astute physician, who has literally "neuroxed" the literature and experienced the topic (uterine anomalies) will be restored in rank close to probability analysis, Markov simulations, Markov chain Monte-Carlo Methods, and computer modeling. The physician may have a distinct advantage—the ability or courage to be skeptical—an uncommon trait for most computers.

Michael O'Donnell in a wonderful viewpoint article in the Lancet provided similar thoughts when he indicated that most of the troubles in the world seem to be generated by people who have the courage of their convictions. Many of us and computers might fall into this category. O'Donnell stated further that perhaps we need to hear more from those who have the courage of their doubts (3).

Paul G. McDonough, M.D., Editor, Letters

References

1. Schrag D, Kuntz KM, Garber JE, Weeks JC. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. *J Am Med Assoc* 2000;283:617-24.
2. Lilford RJ, Thornton JG, Brauholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995;311:1621-5.
3. O'Donnell M. Evidence-based illiteracy: time to rescue "the literature." *Lancet* 2000;355:489-91.

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