Letters to the Editor

The Journal welcomes letters to the editor. If found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with Journal style. All letters that reference a recently published Journal article are sent to the original authors for their reply. If no reply is published, the authors have not responded by date of publication. Send letters to Paul M. Fischer, Editor, The Journal of Family Practice, 519 Pleasant Home Rd, Suite A-3, Augusta, GA 30907-3500, or Fax (706) 855-1107.

ACYCLOVIR THERAPY

To the Editor:

We appreciate Dr Clover's editorial response[1] to our recent article[2] concerning gestational acyclovir therapy, and we agree with his note of caution, particularly with respect to primary genital herpes infections during the third trimester. As we discussed, use of acyclovir in this situation is not clear-cut, but because this is a serious condition, acyclovir therapy might be considered.

As Clover mentions, the treatment of third trimester primary genital herpes with acyclovir presents a therapeutic dilemma. On the one hand, it may decrease maternal antibody response, depriving the fetus of transplacental immunoglobulins that may protect against disseminated neonatal herpes simplex virus (HSV).[3] On the other hand, limited prospective data[4,5] indicate that late-onset primary genital herpes infections are associated with extremely high rates of prematurity, growth retardation, neonatal herpes, and even fetal death. While caution is needed, acyclovir therapy appears justifiable during primary genital HSV infections in the third trimester. This view is held by leading authorities.[3,5,6] We do not advocate third-trimester use of acyclovir simply to shorten the course of the disease or to promote rapid healing of lesions.

Clover's remarks about the limitations of the Acyclovir in Pregnancy Registry also merit comment. First, the 600 total cases (425 first-trimester cases) reported to the Registry do not attest to "the low exposure rates"[1] during pregnancy, as Clover asserts; they more likely represent underreporting. In fact, an estimated 7500 live births each year experience gestational exposure to acyclovir.[7] Second, Clover is concerned that this data set is too small to detect anything but "a major increase in total birth defects or a single specific pattern of birth defects."[1] A recent update[8] of the Acyclovir in Pregnancy Registry published by the Centers for Disease Control and Prevention states that the sample size is sufficient to detect at least a twofold increase over the 3% background rate of birth defects. Furthermore, the update notes that human teratogens tend to cause specific, recognizable birth defect patterns. While this data set has limitations, it is the most comprehensive source of information related to intrapartum acyclovir. We therefore encourage readers to consider its use in advising pregnant patients and to notify the Registry of all prenatal acyclovir exposures.

John G. Spangler, MD, MPH
Julienne K. Kirk, PharmD
Mark P. Knudson, MD, MSPH
Department of Family and Community Medicine
Bowman Gray School of Medicine
Winston-Salem, North Carolina

References

1. Clover RD. Acyclovir: how often should it be used? J Fam Pract 1994; 38:121–3.
2. Spangler JG, Kirk JK, Knudson MP. Uses and safety of acyclovir in pregnancy. J Fam Pract 1994; 38:186–91.
3. Brown AZ, Baker DA. Acyclovir therapy during pregnancy. Obstet Gynecol 1989; 73:526–31.
4. Nahmias A, Josey W, Naib Z, et al. Perinatal risks associated with maternal genital herpes simplex infections. Am J Obstet Gynecol 1971; 110:825–37.
5. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987; 317:1246–51.
6. Brown ZA, Watts H. Antiviral therapy in pregnancy. Clin Obstet Gynecol 1990; 33: 276–89.
7. Andrews EB, Yankasakas BC, Cordero JF, Schoeffler K, Hampp S. Acyclovir in pregnancy registry: six years' experience. Obstet Gynecol 1992; 79:7–13.
8. Centers for Disease Control and Prevention. Pregnancy outcomes following systemic prenatal exposure to acyclovir. MMWR 1993; 42:806–9.

The preceding letter was referred to Dr Clover, who responds as follows:

Determining the appropriate use of acyclovir can be a challenging task for clinicians, especially when there is a lack of well-designed prospective studies. I appreciate Dr Spangler's letter to help clarify some of the points that I had made in my editorial.[1] Clinicians need to be aware of both the benefits and risks of a given treatment. Dr Spangler and associates adequately described the potential benefits of acyclovir treatment in pregnancy in their original article.[2]

Although primary genital herpes infections in the third trimester of pregnancy are associated with poor perinatal outcomes, I am not aware of any published prospective study that shows that the use of acyclovir decreases these poor perinatal outcomes. While Brown and colleagues[3–5] suggest the use of acyclovir for late primary herpes infections, they also clearly state that acyclovir should be used with caution. I hope future studies that address this important issue will be performed. Until then, many of the benefits and risks remain theoretical.

As stated previously, I strongly support reporting to the Registry to expand this data set. However, the present data set has significant limitations, and physicians need to be cognizant of these limitations when advising patients about the use of acyclovir during pregnancy. The article from the Centers of the Disease Control and Prevention[6] mentioned by Spangler and colleagues states that the potential limitations of this data set include "differential reporting of outcomes, losses to follow-up, underreporting, and small sample size." Thus, the representativeness of the sample is in question. If there are 7500 live births each year that had gestational exposure to acyclovir, then this data bank suffers from very significant underreporting. I caution the acceptance of this number (7500 births per year with gestational exposure to acyclovir) as being completely accurate since it is unpublished marketing-research data and the methodology used to collect this data has not undergone the rigors of peer review. Furthermore, the total number of live births per year in the United States in 1991 was 4,111,000.[7] Even if this 7500 figure is correct, this exposure represents an exposure rate of 2 per 1000 live births. This "low exposure rate" makes it difficult to perform a prospective study at a single site, thereby emphasizing the importance of all physicians' reporting all such cases to the registry.

The CDC report[6] suggests that the current sample size should detect a twofold increase in birth defects. I would argue that a twofold increase is a significant increase. Moreover, in doing these calculations, certain assumptions were made which may or may not be correct.

For example, it is assumed that adequate exposure to acyclovir occurred in every case, yet dosage and length of exposure undoubtedly varied. It combines women who were receiving relatively low suppressive doses of medication with those who were receiving high-dose intravenous acyclovir. I would suggest that combining this wide variety of drug exposure limits the interpretation of the data set, especially if there is any chance that dose-dependent toxicity might exist.

Richard D. Clover, MD
The University of Texas
Medical Branch at Galveston

References

1. Clover RD. Acyclovir: how often should it be used? J Fam Pract 1994; 38:121–3.
2. Spangler JG, Kirk JK, Knudson MP. Uses and safety of acyclovir in pregnancy. J Fam Pract 1994; 38:186–91.
3. Brown AZ, Baker DA. Acyclovir therapy during pregnancy. Obstet Gynecol 1989; 73:526–31.
4. Brown ZA, Vontver LA, Benedetti JK, et al. Genital herpes in pregnancy: risk factors associated with recurrences and asymptomatic viral shedding. Am J Obstet Gynecol 1985; 153:24–30.
5. Brown ZA, Watts H. Antiviral therapy in pregnancy. Clin Obstet Gynecol 1990; 33: 276–89.
6. Centers for Disease Control. Pregnancy outcomes following systemic prenatal exposure to acyclovir. MMWR 1993; 42: 806–9.
7. US Department of Health and Human Service. Health United States 1992. Washington, DC: US Department of Health and Human Services, Public Health Service, 1992. DHHS publication No. (PHS) 93–1232.

GDM SCREENING

To the Editor:

Although the objective of Dr Stephenson's review[1] is not stated, the author introduces the review by listing seven criteria suggested by Cadman et al[2] used in the assessment of community screening programs. The author's review focuses on criteria 2, 3, and 4. Regarding the "burden of illness" issue, the author fails to address the issue of the impact on perinatal mortality if *no* testing for gestational diabetes mellitus (GDM) is performed. Whether the seminal papers of O'Sullivan et al[3] and Pettitt et al[4] were overlooked or considered and discarded, their omission is a critical deficiency of any review.

These series indicate that if the diagnosis of carbohydrate intolerance during pregnancy is not made, the perinatal mortality rate will be four times or more greater than the rate seen in carbohydrate-tolerant subjects. The author reports observations regarding macrosomia as it relates to GDM. While acknowledging that many studies did reveal a higher incidence of macrosomia in infants of women with GDM, the author notes that the mean birthweight of infants of mothers with gestational diabetes mellitus was 3466 g as compared with 3336 g for infants of nondiabetic women, and concludes that the clinical significance of this 130-g difference is unknown.

The significance of a 130-g difference is debatable and really is not the clinical point. The significance of a ≥20% incidence of infants >4000 g and a 25% to 35% incidence of large-for-gestational age (LGA) infants is clear. This significantly higher incidence can be decreased to the normal rate (10%) with the achievement of mid- and late-pregnancy euglycemia.[5] The author asks and answers affirmatively the important question: Is a macrosomic infant at an increased risk compared with a normal-weight infant? Unless GDM is recognized, steps cannot be taken to reduce the incidence of LGA and macrosomia and the concomitant increased incidence of shoulder dystocia and cesarean section.

Lastly, regarding the "burden of illness" issue, the long-term implications of gestational diabetes to the woman and her offspring are well recognized,[6] but unfortunately they are not discussed in this review.

Stephenson's contention that there have been no prospective randomized control studies of the efficacy of the treatment of gestational diabetes disregards the work of Langer et al.[5] Regarding "effective treatment," I would agree with the author that large-scale, prospective, randomized studies evaluating the effectiveness of various treatment recommendations for GDM would be preferable. Nevertheless, the author's unwillingness to consider any study that is not "pure" in its experimental design seems unnecessarily rigid. Many centers' experiences, both published[7] and unpublished, have convincingly demonstrated that current perinatal management results in significant improvement in perinatal outcome as compared with nondiabetic pregnancies and perinatal mortality rates comparable to those of the nondiabetic population.

Larry M. Cousins, MD
Director of Maternal-Fetal Medicine
Mary Birch Hospital for Women
San Diego, California

References

1. Stephenson MJ. Screening for gestational diabetes mellitus: a critical review. J Fam Pract 1993; 37:277–83.
2. Cadman D, Chambers L, Feldman W, Sackett D. Assessing the effectiveness of community screening programs. JAMA 1984; 251:1580–5.
3. O'Sullivan JB, Charles D, Mahan CM, Dandrow RV. Gestational diabetes and perinatal mortality rate. Am J Obstet Gynecol 1973; 116:901–4.
4. Pettitt DJ, Knowles WC, Baird HR, Bennett PH. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians [abstract]. Diabetes Care 1980; 3:458–64.
5. Langer O, Anyaegbunam A, Brustman L, Divon M. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. Am J Obstet Gynecol 1989; 161: 593–9.
6. Cousins L, Baxi L, Chez R, Coustan D, Gabbe S, Harris J, et al. Screening recommendations for gestational diabetes mellitus. Am J Obstet Gynecol 1991; 165: 493–6.
7. Jacobson J, Cousins LM. A population-based study of maternal and perinatal outcome in gestational diabetic patients. Am J Obstet Gynecol 1989; 161:981–6.

The preceding letter was referred to Dr Stephenson, who responds as follows:

The purpose of the article[1] was to decide whether universal screening for gestational diabetes mellitus was justifiable through the application of specific criteria for screening programs, using critical appraisal data techniques.[2] The difference from other reviews is that studies cited were reviewed from a methodological perspective. The result was that methodological problems prevented clear conclusions supporting universal screening.

The two papers mentioned, O'Sullivan et al[3] and Pettitt et al,[4] were considered and rejected on methodological grounds. The O'Sullivan study compared 187 women with gestational diabetes recruited as part of another study over an 8-year period in the 1960s. They were

compared with a systematically selected control group picked over a 15-month period starting in 1967. They were not matched to the gestational diabetic group on any confounding variables, such as gestational age, maternal age, obesity, and socioeconomic status. It may well be these variables that caused the perinatal mortality rate of 6.4% in the women with gestational diabetes, not the presence of gestational diabetes per se.

The Pettitt et al study was done in a very atypical population, Pima Indians, who have 19 times the incidence of non–insulin-dependent diabetes compared with the general US population. In the study, there certainly is an association between third-trimester 2-hour plasma glucose and perinatal mortality rate. But association does not necessarily mean causation. Applying the rules of causation,[2] although there is an odds ratio of 9.9 for perinatal mortality rate when blood glucose ≥160 mg/dL is compared with blood glucose ≤160 mg/dL (data from Table 1), this is based on a case-control approach, which is subject to many biases. There is a dose-response curve, but again none of the confounding variables mentioned above were controlled for in determining the strength of association. This allows no firm statement based on this study as to causation.

The question of macrosomia as an outcome in gestational diabetes mellitus is critical. As noted in the review, the incidence of macrosomia varies in gestational diabetes, but macrosomia is an *intermediate* variable that needs to be clearly linked to maternal and neonatal outcome. The evidence of that linkage is not as clear because studies are generally retrospective, so that differences in prenatal care and intrapartum management and other confounding variables between groups may cause the differences seen.

There is certainly an increased cesarean section rate in mothers with gestational diabetes mellitus. What is unclear is whether this is anticipatory on the part of the physician or secondary to the intrapartum problems encountered during labor. Similarly, the whole area of long-term maternal and neonatal outcome is fraught with methodological problems and is in need of a thorough critical review.

The last point about therapy is that although therapy clearly reduces birthweight, the real question that needs answering is whether the infant is better off. Until methodologically sound studies of therapy that look beyond intermediate variables are done, this question is not answerable.

This insistence on evidence is based on a belief in the minimum school of medicine.[5] In this school, the prevention of harm is paramount, and good-quality evidence of benefit and lack of harm is essential before action. Finally, although in my opinion one cannot currently justify universal screening, the review does not conclude that the converse is true. We are in the middle and need to step back and look at the foundations before continuing to decorate a house built on a shaky foundation.

Michael J. Stephenson, MB ChB
Stonechurch Family Health Centre
Hamilton, Ontario

References

1. Stephenson MJ. Screening for gestational diabetes mellitus: a critical review. J Fam Pract 1993; 37:277–83.
2. Sackett DL, Haynes RB, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. Toronto/Boston: Little, Brown, 1985.
3. O'Sullivan JB, Charles D, Mahan CM, Dandrow RV. Gestational diabetes and perinatal mortality rate. Am J Obstet Gynecol 1973; 116:901–4.
4. Pettitt DJ, Knowles WC, Baird HR, Bennett PH. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians [abstract]. Diabetes Care 1980; 3:458–64.
5. Stephenson MJ. Gestational diabetes mellitus [editorial]. Can Fam Physician 1993; 39:745–8.

HEALTH CARE ETHICS

To the Editor:

At face value, I should be happy with the report by Brody and Alexander[1] on the ethical foundations of the Clinton health care plan. I do not find it reassuring, however, because apparently the majority of ethicists on the Clinton ethics panel approve of physician-assisted suicide.[2]

This means that the "values" behind the Clinton plan are not traditional or Hippocratic values but instead reflect newer trends in medical ethics, which use utilitarian and economic values for life and death decisions.[3]

In this world of bioethics, one cannot assume that words mean what they seem to mean. For example, does "personal responsibility" mean that we, as a society, have the responsibility to care for the vulnerable, or does it mean that we, as individuals, have the responsibility to forgo medical treatment because the high cost will be a burden to society?[4]

Does "wise allocation" mean giving money to preventive care, or does it mean health care guidelines that would deny any treatment for the retarded and handicapped because it is "futile"—ie, will not make them "normal"?

Does "professional integrity" mean that if a bureaucrat decides care is not warranted, we will treat the patient anyway, or does it mean obeying the bureaucrat?

Does "individual choice" mean the right to choose medical treatment when the treatment is denied under government guidelines? And, if payment for medical treatment is denied, does "individual choice" include the right to "physician-assisted suicide"?

One simply cannot ignore the implications of the growing effort by Brody and others to legalize assisted suicide[5] and the possibility that it will be encouraged by a government bureaucracy in the name of economics.

A recent *Detroit News* editorial noted this connection in a Michigan court decision that legalized "physician-assisted suicide" by using the notorious 1927 *Buck v Bell* Supreme Court decision that mandated forced sterilization of the unfit.

As the editorial observed: "Indeed, if *Buck v Bell* is still considered a legitimate decision, it can be used to justify having the government decide whether it likes your quality of life—and move to end it, whether you like it or not, on grounds that your continued existence 'saps the strength' of the state. It can't happen here? It already has."[6]

N.K. O'Connor, MD
Nanty Glo, Pennsylvania

References

1. Brody H, Alexander G. Ethics and health care reform. J Fam Pract 1994; 38:192–4.
2. International Anti-Euthanasia Task Force Update: Clinton Administration Health Care Ethics Panel: Vol. 7: May, June 1993: 1–2.
3. Pelligrino ED. Medical ethics: entering the post hippocratic era. J Am Board Fam Pract 1988; 1:4:230–7.
4. Etzioni A. First: cut the paperwork. Responsive Community: Fall 1993:4–6.
5. Brody H. Assisted suicide: a challenge for

family physicians. J Fam Pract 1993; 37: 123–4.
6. Editorial. Three generations of imbecils. Detroit News 1993 Dec 16:20A.

The preceding letter was referred to Dr Brody, who responds as follows:

Dr O'Connor raises a number of good questions regarding ethical values in health care reform. I hope, however, she is not suggesting that a litmus test of ethical purity ought to have been applied to those serving on the ethics working group of the Health Care Reform Task Force, by which any of us who have defended physician-assisted suicide would have been excluded.

The thrust of the value statements previously reported is that a physician of integrity must perform the role of patient advocate, and no bureaucratic arrangement should prevent the physician from serving in that role (even though, in some individual cases, there may be other defensible reasons why a patient ought not to receive the care that the physician and the patient both want). Patients should be encouraged, especially through preventive care and health education, to take responsibility for those aspects of their own health that are under their control, but that does not mean that anyone would be denied care simply because it is costly or because that individual was somehow seen as a "burden" to society. Persons with disabilities should receive care that promotes their health and improves their ability to function, and standards applicable to so-called normal persons should not be used as an excuse to deny them beneficial care. All persons would have the right to seek care that is not included under the standardized benefits package, but they would not necessarily have the right to reimbursement for that care.

The ethics working group tried to identify moral values that are widely shared within our society and, therefore, could serve as a solid ethical foundation for a reformed health care plan. Therefore, divisive and controversial issues such as physician-assisted suicide and abortion were not addressed in these discussions.

As a tangential point, I support physician-assisted suicide in some very limited circumstances, but I do not accept the existence of a constitutional right to physician-assisted suicide. I therefore reject the reasoning of the Michigan judge, whose reference to the infamous case of *Buck v Bell* is quite justly condemned in the editorial to which Dr O'Connor refers.

Howard Brody, MD, PhD
Michigan State University
East Lansing, Michigan

Tips from Practice

Do you have a practical solution to a common problem faced by family physicians? If so, share it with fellow readers of *The Journal of Family Practice*.

"Tips from Practice," a regular feature in *The Journal*, is a forum for the exchange of practical tips from family practice. "Tips" should be 250 to 500 words in length, typed, and double spaced. Authors of "Tips" that are accepted for publication will receive a copy of *Current Medical Diagnosis & Treatment*, an annual publication of Appleton & Lange.

"Tips from Practice" should be addressed to *The Journal of Family Practice*, 519 Pleasant Home Road, Suite A-3, Augusta, GA 30907.