EDITORIALS

Vaginal Birth after Cesarean Revisited

Michael F. Greene, M.D.

The U.S. total cesarean delivery rate has risen from 4 percent of deliveries in 1950 to 26 percent in 2002.[1] Concerned about the rising rate of cesarean deliveries, and noting that 98 percent of women with a prior cesarean section delivered by repeated cesarean section, a National Institutes of Health Consensus Development Task Force in 1980 recommended that "properly selected" women should be encouraged to labor and deliver vaginally after a prior cesarean delivery.[2] U.S. obstetricians and their patients were slow to respond to this call, but by the end of the 1980s, the rate of vaginal birth after prior cesarean delivery was clearly on the rise. However, after peaking at 28.3 percent in 1996, the rate fell steadily to 12.6 percent in 2002 in the wake of reports of uterine ruptures and their catastrophic consequences.

The decline in the U.S. rate of vaginal birth after prior cesarean delivery was well established by the time a large study from Washington State was published in 2001.[3] That study of more than 20,000 women with a single prior cesarean delivery compared the risk of uterine rupture among women who underwent elective repeated cesarean delivery with that among women with spontaneous onset of labor and attempted vaginal delivery from 1987 to 1996. The rate of uterine rupture associated with the spontaneous onset of labor was significantly higher than that associated with repeated cesarean delivery without labor (5.2 per 1000 vs. 1.6 per 1000). Among the 91 women with uterine rupture, there were five perinatal deaths (5.5 percent), as compared with a perinatal mortality rate of 0.5 percent among women who did not have uterine rupture.

Subsequently, Smith et al. reported a large study including all singleton deliveries with cephalic presentation in Scotland from 1992 to 1997.[4] Among women with one or more prior cesarean deliveries, the perinatal mortality rate was significantly higher among those who attempted labor than among those who delivered by planned repeated cesarean section (12.9 per 10,000 vs. 1.1 per 10,000).

A strength of population-based studies that report results for an entire state or country is that they report "real world" results achieved across a wide spectrum of patients and patient care settings for very large numbers of subjects. However, they have been retrospective, have lacked consistent prespecified definitions of outcome measures, and have relied on vital records or administrative databases that have the potential for incomplete ascertainment and misclassification. Furthermore, women and providers who choose to attempt vaginal delivery may be different in important ways from those who choose elective repeated cesarean delivery. Smaller studies from individual centers that have better data quality by means of direct access to patient records have not had adequate power to address uncommon outcomes such as perinatal death. An assessment prepared in 2003 for the U.S. Agency for Healthcare Research and Quality regarding the practice of vaginal birth after cesarean delivery noted that "patients, clinicians, insurers, and policymakers do not have the data they need to make truly informed decisions about appropriate delivery choices following one of the most common surgical procedures performed on women."[5]

In this issue of the *Journal*, Landon et al. report the results of a large, observational multicenter study comparing maternal and perinatal outcomes of elective repeated cesarean delivery with those of trial of labor after prior cesarean delivery.[6] There are several features of this study that make it unique. The primary outcomes are reported for more than 33,000 women selected from among nearly 46,000 women with singleton gestations and a history of

prior cesarean delivery. Women with clear indications for cesarean delivery, such as malpresentation and placenta previa, were excluded. Trained study nurses collected the data prospectively, directly from patients' medical records, according to standardized and prespecified definitions. All the participating institutions were academic medical centers in the United States. The data are recent (1999 through 2002) and contemporaneous with the current (July 1999) recommendation of the American College of Obstetricians and Gynecologists that a provider capable of performing an emergency cesarean delivery should be "immediately available" during a trial of labor for a woman who has had a prior cesarean delivery.[7] Thus, the results presented are, arguably, "as good as they can get" in the United States.

Women in the vaginal-birth group and the cesarean-delivery group were significantly different in many ways before the index birth. Those who underwent a trial of labor were more likely to have had a prior vaginal delivery, a prior successful vaginal delivery after a cesarean delivery, smaller babies, and only one prior cesarean delivery (94 percent). These characteristics made the women good candidates for successful vaginal births, with a low risk of adverse outcomes. The risk of uterine rupture was 0.7 percent in the group undergoing a trial of labor, slightly higher than, but consistent with, the rates in prior studies.[3,8] In contrast to a meta-analysis, which found increased risks of transfusion, febrile morbidity (fever above 100.6°F [38.1°C] for more than six hours), and hysterectomy among women undergoing elective repeated cesarean delivery, the current study found reduced risks of transfusion and endometritis, no difference in the risk of hysterectomy, and a lower risk of composite "maternal complications" with elective repeated cesarean delivery as compared with a trial of labor.

Among term infants, there were two intrapartum fetal deaths among the women undergoing a trial of labor and none among the women undergoing elective repeated cesarean delivery. There were 12 cases of hypoxic–ischemic encephalopathy among the infants of the women attempting labor, and none among the women undergoing elective repeated cesarean delivery. Noting that elective repeated cesarean delivery is usually performed at 39 weeks of gestation, and recognizing that fetal deaths before this gestational age may have prompted (rather than resulted from) a decision to attempt labor, the authors considered only those deaths that occurred after 39 weeks of gestation as possible consequences of the mode of delivery. Combining these cases with cases of hypoxemic–ischemic encephalopathy and neonatal deaths to represent "poor perinatal outcomes" associated with the chosen method of delivery, there would need to be 588 elective repeated cesarean deliveries to prevent one poor perinatal outcome.

There remain no randomized trials to compare a trial of labor with elective repeated cesarean delivery for women with a prior cesarean delivery. Previous data are inconsistent regarding the maternal risks of elective repeated cesarean delivery, but results from the current study are very reassuring regarding these risks. Remaining issues of concern are the increased risks of placenta previa and placenta accreta for pregnancies subsequent to elective repeated cesarean delivery. These are difficult to quantitate. Adding the present data to those available from other observational studies, the consistent result is that elective repeated cesarean delivery is associated with less perinatal risk than is a trial of labor. It is unlikely that a randomized trial would yield results substantially different from the accumulated data.[9,10] Furthermore, it is doubtful that we can substantially better these results by improving the selection of patients for a trial of labor or by improving the conditions under which trials of labor are conducted.

Some people will consider the estimated 588 cesarean deliveries needed to prevent a severe adverse perinatal outcome to be a reasonable number, whereas others will consider the perinatal risks associated with a trial of labor small and well worth taking for the benefit of a vaginal delivery. Ultimately, risk, like beauty, is in the eye of the beholder.

From the Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston.

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Oral Mucositis — The Search for a Solution

Adi A. Garfunkel, D.M.D.

The oral cavity is a complex environment composed of tissues with different origins, structures, and functions. Moreover, a myriad of commensal bacteria, fungi, and viruses populate the mucosa, connective tissue, salivary glands, taste buds, bones, and teeth of the mouth. This environment is disrupted in oral mucositis (Fig. 1), a serious complication of high-dose chemoradiotherapy that affects up to 75 percent of patients who undergo hematopoietic stem-cell transplantation[1] and 77 percent of patients with head and neck cancer who receive such treatment.[2]

Numerous studies in animals and humans have tried to find a means of preventing and treating oral mucositis. In this issue of the *Journal,* Spielberger and coworkers[3] report the use of the recombinant keratinocyte growth factor palifermin for this purpose. Keratinocyte growth factor has a beneficial effect on mucositis in mice given chemoradiotherapy[4] and in human recipients of hematopoietic stem cells who received etoposide, cytarabine, and melphalan.[5] In these patients, pretreatment with keratinocyte growth factor reduced mucosal atrophy and weight loss, accelerated mucosal regeneration, decreased ulceration, and improved survival through a gene-mediated effect on growth and differentiation.[6] In addition, it ameliorated graft-versus-host disease.[7] The finding by Spielberger et al. that the incidence of febrile neutropenia was significantly lower in the palifermin group than in the group given a placebo (75 percent vs. 92 percent, $P<0.001$) is important and accentuates the key role played by the oral mucosal barrier in the prevention of sepsis. All the patients were given filgrastim, a recombinant granulocyte colony-stimulating factor that prevents bacteremia with gram-negative bacteria or α-hemolytic streptococci that originate in the oral cavity; such organisms cause 25 to 50 percent of cases of septicemia in patients treated with chemotherapy.[8]

Spielberger et al. do not comment on the results of cultures of the oral mucosa or describe protocols used to reduce the population of local pathogens.[9] Only prophylactic acyclovir was given to all patients. Since acyclovir is considered to be highly effective in preventing mucosal injury by herpes simplex virus 1 and reducing systemic infection with streptococci,[10] it may well have increased the effect of palifermin. The World Health Organization laconically describes grade 4 oral mucositis as "ulcers" and an "inability to swallow fluids"; for patients, however, it causes excruciating pain, for which there is no objective means of measurement. The suffering caused by severe oral mucositis is a major problem that requires a better solution than treatment with opioid analgesics. The pain and dry mouth of oral mucositis should receive the same attention as the associated tissue changes and infections. One of the primary end points of phase 3 trials of the treatment of this complication should be a reduction in pain in the ulcerated area. Indeed, Spielberger et al. found that patients receiving palifermin used significantly lower cumulative doses of morphine equivalents and for fewer days than did placebo recipients and had only minor adverse effects, such as rash.

Studies of other treatments have provided only

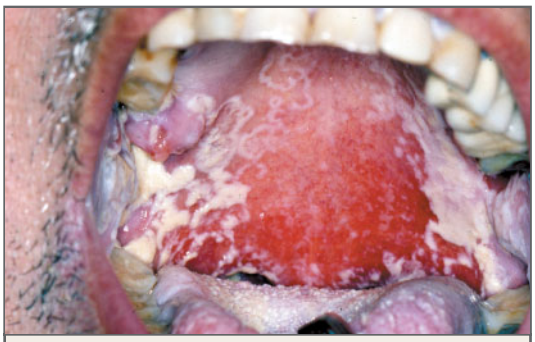

Figure 1. Oral Mucositis after Chemoradiotherapy in a Patient with Leukemia, Who Was Later Treated with Bone Marrow Transplantation.