Infectious Disease and Perinatal Morbidity

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Excess perinatal morbidity and mortality continue to be major problems in developed and developing nations. Most perinatal deaths occur in infants born weighing <2500 g. Large expenditures of time, equipment, and personnel have led to striking reductions in neonatal mortality. However, rates of prematurity have not declined. Exploration of proven causes of prematurity and low birth weight suggests a role for infection that has hitherto not received sufficient attention. Women with symptomatic pyelonephritis, even when treated promptly, experience an excess of prematurity and perinatal death, and their children have lowered intelligence scores and neurologic scores. Women with asymptomatic bacteriuria experience higher rates of low birth weight and perinatal mortality, as well as symptomatic pyelonephritis, and these are preventable by screening and treatment during pregnancy. Recent evidence also suggests that genital mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis) are a cause of prematurity and that treatment of women colonized with these organisms results in significant reduction in prematurity rates.

INTRODUCTION

The unique role that Dorothy Horstmann has played in scientific progress has come from her capacity to synthesize laboratory evidence with the most precise use of epidemiologic methods. This skill and her unusual interpersonal talents are the ingredients of leadership, and it is this leadership, manifest in many contributions to the health of the community, that is a source of honor beyond the mere words that her devoted colleagues can muster. It is her devotion to the use of scientific method for the improvement of health that exemplifies her career and forces each of us, as we contemplate her achievements, to reexamine the many areas in which progress is needed to achieve still better health.

Few areas of medicine have received as much adverse comment and yet as little scientific attention as have perinatal morbidity and mortality in the United States. We are continually reminded that the United States ranks between fifteenth and twentieth in the world with respect to perinatal mortality and that this status has changed little over the past several decades in relation to that of other populations of the developed world, despite remarkable advances in neonatology [1,2]. These sobering figures require critical examination in order to determine where progress is needed. As a corollary, it is reasonable to expect that the lessons learned from attempts to reduce excess perinatal morbidity in the United States will be valuable to developing countries.

An analysis of a subject as complex as is perinatal morbidity and mortality re-
quires an initial segregation of certain portions of the problem even at the risk of oversimplification. Therefore, the following list comprises a series of general statements that provide a basis for recent speculations about newly acquired data and offer a possible rationale for preventive intervention.

1. The most important determinant of perinatal morbidity and mortality is the social class of the mother. The major reason that the United States compares unfavorably in international ranking is because of the high perinatal mortality rates in the less privileged segments of the American population [1,2].

2. Although obstetric care is a factor in reducing perinatal morbidity and mortality, and although less-privileged populations tend to receive less obstetric care than the more-privileged, critical analysis of the role of obstetric care suggests that only a relative minority of all instances of perinatal morbidity and a minority of high-risk pregnancies are recognizable during the course of pregnancy and, therefore, might be amenable to preventive intervention. Although obstetric services should be extended to provide each pregnant woman with the advantages of contemporary knowledge, it is unlikely that a major reduction of perinatal morbidity can be achieved at present by such care unless more information about prevention becomes available [1–4].

3. The most salient feature of the patterns of perinatal mortality is that the majority of infants that died in the neonatal and postnatal periods had birth weights of less than 2500 grams. This excess mortality in the small infant is as true in more-privileged as it is in underprivileged populations, and the adverse effect of being born small extends throughout the first several months of life [5]. This effect often goes unnoticed because mortality in postnatal data tends to be listed under cause-specific titles, so that malaria, respiratory, and diarrheal diseases are listed as principal causes of death. The uncommon susceptibility of small infants to these infections is widely recognized clinically but is rarely reflected in demographic statistics. Conversely, although infants who are heavier at birth are probably exposed to the same types of infectious agents, and, in underprivileged populations, undoubtedly have high infectious morbidity, their capacity to survive is greater than that of infants born small.

4. The mean weight at birth of infants in social class V (unskilled laborers) is approximately 80–100 grams less than the mean weight of infants born to mothers of social class I (professionals). Therefore, remarkably small differences in the weight of the newborn infants have profound effects on their capacity to survive in an environment that has substantial hazards. The small differences among birth weights of infants in the various social classes and, therefore, the small increases in birth weight that are the objective of preventive measures have generally not been appreciated [3]. On the other hand, most of the weight of the developing infant is acquired during the last weeks of pregnancy. Therefore, the factors interfering with birth weight exert their greatest influence during the last weeks before delivery, and these weeks are critical to development as well as to the degree of susceptibility to excess mortality and other morbidity.

5. Remarkable advances in neonatology have led to progressive declines in infant mortality in institutions that have been able to take advantage of these advances. The underlying fact, however, is that the number of babies born at low weights and numbers of premature deliveries have changed little in recent years [6]. Those infants that have been salvaged under high-risk conditions that might previously have led to death have a risk of 8 percent–15 percent of having serious developmental dif-
ficiencies for their entire lives [7]. The cost of neonatal intensive care is high, averaging at least $1000 a day in most institutions, and there is ample evidence that the length of stay in a neonatal intensive care unit is inversely proportional to birth weight of the infant. Despite the major advances of the past decades, repeated analyses of the problem have suggested that prevention of low birth weight is the most effective and economic intervention that can be contemplated. The neonatologist is necessarily concerned with the survival of each infant and has available an enormous range of technical facilities. Insufficient attention has been given to the corresponding need to investigate more effective ways of preventing these perinatal catastrophes.

PREVENTION OF PREMATURE DELIVERY

The problem of prevention of premature delivery is complicated by a number of features:

First among these is the inadequacy of present methods of predicting the high-risk pregnancy. Customarily, clinicians use factors such as age, race, blood pressure, past reproductive history, and presence or absence of excessive edema or proteinuria as indicators of high-risk pregnancies. Such indicators, however, have not generally been quantitatively analyzed, and it is well-known in obstetric clinics that they identify only a minority of the high-risk pregnancies that will actually occur.

We have attempted to quantitate the risk indicators using modern multiple regression methods. A list of thirty-five “predictors,” collected at the twentieth week of pregnancy, were analyzed; only a small number of these factors were significantly predictive of low birth weight. These were put into a multiple regression format as follows:

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\text{Birth wt. (oz)} = 0.2026 \times \text{maternal weight} + 7.73 \text{ (if white)} - 6.29 \text{ (if smoker)} - 0.2217 \times \text{lowest recorded systolic blood pressure} + 0.0517 \times \text{plasma volume} - 4592 \times \text{age} + 3.42 \times \text{no. live-born children} - 2.35 \times \text{no. live-born pregnancies} + 97.99.
\]

The multiple R for these predictors was approximately 0.4. Thus, only 16 percent of the variability in birth weight was explained through these measurements. Obviously many predictors remain to be identified.

Complicating the problem still further has been the complex problem of categorizing low-birth-weight infants. Although a large amount of epidemiologic data has been accumulated showing that low birth weight is still the best predictor of perinatal mortality, there are understandable attempts to define the categories of low birth weight more precisely. A variety of developmental scores and chemical analyses continue to be developed. None is as yet completely satisfactory.

Often overlooked is the interrelation between gestational age (although it is a poor measurement based upon memory or on measurements whose validity is still uncertain) and birth weight; the close relation between these two variables has been defined mathematically. Using the formulas of Goldstein et al. [7], it is possible to predict the extent of perinatal mortality and the subdivisions of prematurity in any large cohort of pregnant women simply because, in any group of low-birth-weight deliveries, a certain number will be small for gestational age, another group will be premature by gestational age, and so on, and yet the relative distribution within these subdivisions will occur with fairly regular frequency within any large cohort of pregnant women.
Similarly, low birth weight and perinatal mortality, as indicated above, tend to have a fairly fixed relationship. Thus, a sensitive indicator of the efficacy of intervention would be an effect on birth weight. After such an effect had been demonstrated, it would become economical and feasible to explore in larger populations the effects of intervention on both the various subdivisions of low birth weight and on perinatal mortality. The relation between perinatal mortality and low birth weight is such that it requires a study approximately eight to ten times larger to find significant effects on mortality than to find significant effects on birth weight. A strategy that seeks first to identify preventive approaches that alter birth weight would be an efficient first step, but would be useful only if it were followed by a larger study that securely established effects on immaturity, prematurity, and mortality. On the other hand, to design studies that would use these latter factors as end points, without earlier having established an effect on birth weight alone, would appear to be inefficient and expensive.

ROLE OF INFECTION ON OUTCOME OF PREGNANCY

Since antiquity it has been known that a febrile disease has a high likelihood of exerting an adverse effect on the course of a pregnancy. This observation has been confirmed in so many ways in the preantibiotic years that it no longer needs further documentation. With the advent of specific antimicrobial therapy, it was immediately apparent that the adverse effects of infections on the outcome of pregnancy could be greatly ameliorated. It was widely assumed, therefore, that the adverse effect of infections on pregnancy was completely overcome. However, the possibility that antimicrobial treatment brought about a reduction in risk, rather than an elimination of excess risk, was not explored systematically until relatively recently.

BACTERIURI A AND PREGNANCY

The studies on the effect of bacteriuria on the outcome of pregnancy demonstrated that when bacteriuric women developed symptomatic pyelonephritis of pregnancy and were treated promptly, they still had a high risk of low-birthweight deliveries and of perinatal mortality [8]. These demonstrations have received critical confirmation in the recent observations by Sever et al. [9] who analyzed the outcome of pregnancies having febrile complications among the 56,000 pregnant women who were participants in the National Maternal and Infant Health Study conducted in 17 obstetric centers throughout the United States. It was found that pyelonephritis of pregnancy contributed approximately five times as many febrile episodes during pregnancy as did other viral infections. Women diagnosed as having pyelonephritis of pregnancy were, of course, treated promptly by the obstetric staff. Nevertheless, these pyelonephritic pregnancies were associated with a striking number of low-birth-weight babies, increased perinatal mortality, and a variety of other perinatal morbid events such as anemia, toxemia, elevated blood pressure, and premature rupture of the membranes [9]. In addition, children born of mothers who had developed pyelonephritis during pregnancy and been treated had lower intelligence quotient scores at seven years of age than did the children of non-pyelonephritic mothers, despite correction for a variety of possible confounding factors such as age, race, social class, parity, and so on. Furthermore, children born of pyelonephritic mothers had lower motor function scores than did the others.

It is not clear whether detection of asymptomatic bacteriuria earlier in pregnancy,
thereby eliminating the risk of pyelonephritis, would have prevented these excess risks. All that is established at present is that the early detection of bacteriuria during pregnancy and its elimination virtually eliminate the risk of symptomatic pyelonephritis and that bacteriuric pregnancies are accompanied by an excessive risk of low birth weight and perinatal mortality, including stillbirth. Intervention to eliminate bacteriuria might have a beneficial effect on the other morbidities that accompany symptomatic pyelonephritis of pregnancy, but it would take a major study to establish the point. Such a study would be manifestly cost-efficient when the nature of the morbidity that is encountered in pyelonephritic pregnancies is considered. Whether such a study can be funded at present is uncertain, to say the least.

The awareness that subclinical as well as clinically apparent infections may alter the course of pregnancy has led to the search for other examples of this phenomenon. A chance observation made in our laboratory many years ago suggested that pregnant women who received tetracycline during pregnancy had substantially fewer low-birth-weight deliveries than did women who received a placebo [10]. (These studies were conducted before the effect of tetracycline on tooth staining was recognized and therefore were discontinued when the tetracycline effect became known.) A search for a possible explanation for the phenomenon led to an examination of the possible role of genital mycoplasmas on the outcome of pregnancy. A number of observations have been made in our laboratory and by other research groups suggesting a pattern that requires much more detailed study.

GENITAL MYCOPLASMAS AND LOW BIRTH WEIGHT

Initially it was demonstrated that approximately 80 percent of the pregnant women in the low-income population at a major municipal hospital were colonized with the two major genital mycoplasmas, *Ureaplasma urealyticum* and *Mycoplasma hominis*, together or separately [11]. Women colonized with these mycoplasmas delivered significantly smaller infants than women who were not colonized. Infants in a consecutive series studied by Klein et al. [12] were found to be colonized with genital mycoplasmas in inverse relation to birth weight; small infants were almost invariably colonized, and the large infants were much less frequently colonized. Infants born by cesarian section were not colonized. This observation suggested acquisition of colonization during passage through the birth canal and indicated an association between high levels of colonization, or of increased susceptibility to colonization, and low birth weight. A study of chorioamnionitis and vascular inflammation in placentas and umbilical cords indicated a significant association between such inflammatory changes in the membranes and vessels and the likelihood of colonization, particularly with *Ureaplasma* [13]. Kundsin et al. [14] demonstrated that when the chorion was cultured after delivery there was a substantially higher likelihood of isolating genital mycoplasmas from those pregnancies in which the infant received intensive care or those accompanied by perinatal mortality compared with full-term normal deliveries.

Most recently, by use of a newly developed mycoplasmacidal test, it has been found that rises in titers of antibodies to either or both of the genital mycoplasmas delineates a group of pregnancies with two- to threefold higher risk of low-birth-weight delivery than in pregnancies where such antibody rises are absent [15]. It appears from preliminary information that the excess risk of low-birth-weight delivery is found largely in women who have experienced rises in antibody titers to both genital mycoplasmas in the same pregnancy.
Concurrently, McCormack et al. have demonstrated in a double-blind study that those women receiving 1 g of erythromycin daily for six weeks during the third trimester of pregnancy have a striking reduction in the rate of low-birth-weight delivery, whereas women receiving the treatment during the second trimester have no significant reduction [15] over rates in women given a placebo. Presumably, the latter group became reinfected after treatment had stopped. At present, however, there is no proof that the effect of erythromycin is mediated exclusively, or at all, through an effect on genital mycoplasmas. This question is one for future research to address.

The conclusion that seems warranted is that genital mycoplasmas play a role in the outcome of pregnancy, particularly in low-income women, and that antimicrobial drugs alter favorably the outcome of pregnancy in low-income women. A few studies in private practice patients indicate that the rate of colonization with genital mycoplasmas is 50 percent, as opposed to 80 percent in low-income women. It is not yet known whether colonization with genital mycoplasmas in women with higher incomes has an effect on birth weight, or whether antibiotics have any effect on pregnancy.

Calculations of the effect of mycoplasmas on the outcome of pregnancy in the low-income population indicate that as much as half of the excess of low birth weight in this population (compared with the higher-income population), can be related to the rises in titers of antibody to genital mycoplasmas occurring during pregnancy.

OTHER PATHOGENS THAT MAY AFFECT PREGNANCY

Several other microorganisms of the genital tract have recently received attention. These include group B streptococci [16], *Chlamydia*, various anaerobes, and many other genital microorganisms. Space does not permit a review of the present status of these latter organisms in affecting the outcome of pregnancy.

The case for large-scale, carefully controlled observations that integrate the effects of these various organisms, determine whether they act separately or together, and explore the most effective preventive measures seems to be strong.

The circle becomes complete when we contemplate the role of Dorothy Horstmann in demonstrating how clinical trials should be conducted in large populations, for critically examining the implications of the data, and for providing to the medical world an appreciation of the significance of the results thereby obtained. Would that her expertise were available for the solution of the problems of the role of infection in the pathogenesis of perinatal morbidity and mortality!

REFERENCES

1. Abramowicz M, Kass EH: Pathogenesis and prognosis of prematurity. New Eng J Med 275:878-885, 938-953, 1001-1007, 1053-1059, 1966
2. Shapiro S, Schlesinger ER, Nesbitt REL Jr: Infant, perinatal, maternal and childhood mortality in the United States. Cambridge. Harvard University Press, 1968, 388 pp
3. Rush D, Stein Z, Susser M: Diet in pregnancy: a randomized controlled trial of nutritional supplements. New York, Alan R. Liss, Inc, 1980, 196 pp
4. Stanley FJ: Medical care of the fetus and the risk of prematurity. In The Epidemiology of Prematurity. Edited by DM Reed, FJ Stanley. Baltimore-Munich, Urban and Schwarzenberg, 1977
5. Mata LJ: The children of Santa Maria Cauque: a prospective field study of health and growth. Cambridge, MA, MIT Press, 1978, 395 pp
6. Alberman E, Benson J, McDonald A: Cerebral palsy and severe educational subnormality in low-birthweight children. Lancet i:606-608, 1982
7. Goldstein J: Birth weight, gestation, neonatal mortality and child development. In The Biology of Human Fetal Growth. Edited by DF Roberts, AM Thomson. London, Taylor and Francis, 1976, pp 81–102
8. Norden CW, Kass EH: Bacteriuria of pregnancy—a critical appraisal. Ann Rev Med 19:431–470, 1968
9. Sever JL, Ellenburg JH, Edmonds D: Urinary tract infections during pregnancy: maternal and pediatric findings. In Infections of the Urinary Tract. Edited by EH Kass, W Brumfitt. Chicago, University of Chicago Press, 1978, pp 19–21
10. Elder JA, Santamarina BAG, Smith S, et al: The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. Am J Obstet Gynecol 111(3):441–462, 1971
11. Braun P, Lee Y-H, Klein JO, et al: Birth weight and genital mycoplasmas in pregnancy. New Eng J Med 284:167–171, 1971
12. Klein JO, Bluckland D, Finland M: Colonization of newborn infants by mycoplasmas. New Eng J Med 280:1025–1030, 1969
13. Shurin PA, Alpert S, Rosner B, et al: Chorioamnionitis and colonization of the newborn infant with genital mycoplasmas. New Eng J Med 293:5–8, 1975
14. Kundsin RB, Driscoll SG, Pelletier PA: Ureaplasma urealyticum incriminated in perinatal morbidity and mortality. Science 213:471–474, 1981
15. Kass EH, McCormack WM, Lin J-S: Genital mycoplasmas as a cause of excess premature delivery. Trans Assoc Am Physicians 94:261–266, 1981
16. Baker CJ, Webb BJ, Kasper DL: The natural history of group B streptococcal colonization in the pregnant female. Am J Obstet Gynecol 137:39–42, 1980