Current Issues in Perinatal Epidemiology

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The main national data sources for perinatal epidemiology are birth and death certificates, yet routinely linked birth and death certificate data are still not available in the U.S. Completeness and quality of the reporting of perinatal events should be considered in examining trends over time and between jurisdictions. The U.S. has experienced a marked decline in its infant mortality rate, but only a very modest decline in the rate of low birth weight. Research must focus more on studies of pre-term labor, rather than low birth weight, which include children who are undergrown or who are born too early and who, therefore, may represent different etiologies. Sensitive hormonal tests may provide more precise estimates of the rate of very early fetal loss. Management of labor and delivery and of the high-risk newborn have undergone marked changes during the last 15 years, and yet clinical trials have not played a major role in the evaluation of these changes. The difference in reproductive outcomes between whites and blacks, especially in the rate of low birth weight, have persisted and are not understood. Data bases are becoming available for intergenerational studies to determine whether nature or nurture accounts for this difference.

This report highlights several topics which are of importance to the field of perinatal epidemiology and relate to major public health problems. Perinatal epidemiology differs from other areas in being more dependent on vital records and less dependent on census estimates. This is because county of birth and fetal death provide better denominators than the census can.

PROBLEMS ASSOCIATED WITH DATA COLLECTION

The main national data sources are birth and death certificates obtained from state or local jurisdictions or nationally by the National Center for Health Statistics (NCHS), national surveys conducted by the NCHS, e.g., the National Natality Survey of 1980, the National Study of Family Growth, which addresses fertility issues, and the National Infant Mortality Survey (NIMS) of 1980. While a number of states link birth and death certificates, such linked data are not available nationally. The recently completed National Infant Mortality Survey of 1980 which involved collaboration between the National Center for Health Statistics, the Centers for Disease Control, and state agencies is the latest attempt at providing linked records. Linked birth and death certificates have been available in Norway routinely since 1967 and in Sweden since 1976, but not in the United States. This represents an important gap in data sources required by the perinatal epidemiologist.

There still exist substantial problems in the completeness and quality of reporting of perinatal events. For instance, it now appears that the apparent increase in the rate of low birth weight among blacks in the early to mid-1960s was the result of underreporting of live births in the 1950s at a time when many births still occurred at home [1].
The shift to higher rates of hospital births resulted in better and more complete reporting in the 1960s. That these problems are still with us is supported by McCarthy's report in the late 1970s of a 20 percent rate of underreporting in hospitals of live births under 1,500 grams [2]. This study involved all hospitals in one state. We do not know whether we can generalize to other states.

Another difficulty is that states vary in their requirements for fetal death reporting. Six states mandate reporting of all fetal deaths irrespective of gestational age. These states have a substantially higher fetal mortality ratio than states which require only reporting of fetal deaths above 20 weeks. This difference suggests that the requirement to report all fetal deaths also results in more complete reporting of fetal deaths above 20 weeks as compared to states which require only reporting of fetal deaths above 20 weeks [3]. Recently attention has been called to a marked variation in the proportion of live births under 500 grams reported by different jurisdictions in this country [4]. Since live births under 500 grams are almost never viable, major differences in the reporting of such very low-weight live births can substantially affect neonatal mortality rates. U.S. whites in 1980 had a rate of live births under 500 grams of .07 percent and U.S. blacks of .23 percent (Table 1). Artifacts in the data are suggested by the range of values among jurisdictions. In whites this varied from a low of .05 percent in Alabama to a high of .12 percent in Maryland. For blacks the range was considerably greater, showing a low rate of .11 percent in Missouri and a high rate of .42 percent in Washington, D.C.

Washington, D.C., had a rate of births among blacks of less than 500 grams which was 83 percent higher than that of the United States, 27 percent higher than the next highest states, which were Michigan and Maryland, and 162 percent higher than Mississippi and Alabama. In 1985, 20 percent of all infant deaths to residents of Washington, D.C., weighed less than 500 grams. Among states the variation in the contribution of live births under 500 grams to neonatal mortality varies from 5 to 24 percent. Part of the high neonatal and infant mortality rate in Washington, D.C., can be reasonably ascribed to the more complete reporting of live births under 500 grams. This situation is certainly not unique for Washington, D.C. In Detroit the rate of live births under 500 grams went up from .23 percent in 1976 to .43 percent in 1981 [5]. During this period the infant mortality rate changed very little from 22.8 in 1976 to 21.9 in 1981.

To look at changes over time in infant mortality without considering this substantial increase in reporting of live births under 500 grams, all of which die during the first few days of life, does not address the complexity of what has actually taken place. One simple way of handling this problem would be to add another infant mortality rate which excludes live births under 500 grams from the numerator and denominator. If we do this for Detroit for 1976 and 1981, this revised and more restricted infant mortality rate would have been 20.5 in 1976 and 17.3 in 1981. There could also be differences over time and between jurisdictions in the classification of live births as opposed to fetal deaths. WHO recommends that any infant showing signs of life, irrespective of weight or gestational age, be reported as a live birth. Some have advocated that this problem can be circumvented by using perinatal mortality. States with the underreporting of live births under 500 grams presumably may report these as fetal deaths; however, the incompleteness in the reporting of fetal deaths in some states, as stated earlier, remains problematic. As reporting of live births at the lower
end of viability improves, we might observe an increase in neonatal mortality as a result of better reporting.

INFANT MORTALITY

This country, in common with other countries of the developed world, has experienced a dramatic decline in its perinatal and infant mortality rate during the last decades. This decline is observed both for whites and blacks (Table 2). The rate of decline for the decade of the 1970s was approximately 4.5 percent per year and according to provisional data has slowed down to around 2 percent [6]. Final 1984 infant mortality rates, however, show a decline of 3.4 percent which is a greater reduction than suggested from the provisional rates [7].

LOW BIRTH RATE

In contrast to this marked reduction in infant mortality in the United States, there has been very little change in the rate of low birth weight [8]. Approximately 6.7

| Year | White | Black |
|------|-------|-------|
| 1950 | 29.2  | 43.9  |
| 1960 | 26.0  | 44.3  |
| 1970 | 20.0  | 32.6  |
| 1975 | 16.1  | 26.2  |
| 1976 | 15.2  | 25.5  |
| 1977 | 14.1  | 23.6  |
| 1978 | 13.8  | 23.1  |
| 1979 | 13.1  | 21.8  |
| 1980 | 12.6  | 21.4  |
| 1981 | 11.9  | 20.0  |
| 1982 | 11.5  | 19.6  |
| 1983 | 11.2  | 19.2  |
| 1984 | 10.8  | 18.4  |

*Per 1,000 live births
percent of all live births in the United States weigh less than 2,500 grams. These low birth weight babies account for approximately 70 percent of deaths during the first year of life. Since 1970, the reduction in the rate of low birth weight has been only about 15 percent (Table 3). Clearly, immense progress has been made to keep low birth weight and very low birth weight babies alive, but surprisingly little progress in preventing low birth weight births.

Low birth weight is a useful predictor of infant mortality. Birth weight contributes more to the prediction of mortality than gestational age, except for gestational ages of 37 to 42 weeks, where gestational age makes more of a contribution to the prediction of mortality [9].

Low birth weight includes children who are born too early, i.e., are truly premature, or who are undergrown, i.e., intrauterine growth retarded or small for gestational age, or both. These conditions may represent different etiologies. Coming back to the modest reduction in the rate of low birth weight since 1970, a simple disaggregation of low birth weight into pre-term and term low birth weight shows that most of the improvement has been in term low birth weight and very little, if any, in pre-term low birth weight [8] (Table 4). This result is also observed in the trends in the rates of very low birth weight, i.e., children weighing less than 1,500 grams, most of whom are premature. There has been no change in the rate of live births under 1,500 grams since 1970 (Table 3).

There are marked variations in rates of low birth weight among different populations. In some developing countries, the rate may be three to four times higher than in the industrial world. Most of this excess is due to an increase in intrauterine growth retardation and not in pre-term delivery [10]. This is an important point since the prevention of intrauterine growth retardation requires different interventions than if the excess were due to pre-term delivery.

Epidemiological research has mainly focused on risk factors associated with low birth weight and very little on risk factors associated with pre-term delivery. The reasons for this are obvious. Birth weight is readily available and reported on birth certificates. For the use of pre-term delivery as an outcome, gestational age estimates are based upon the interval between reported date of the last menstrual period and the date of delivery. A high proportion of birth certificates report gestational ages unknown. In addition, gestational age estimates are frequently erroneous. Surrogate measures of gestational age have recently been developed based upon ultrasound use during pregnancy. Various measures of fetal growth as obtained by ultrasound correlate well with gestational age and therefore can be used as substitutes in instances where there are marked discrepancies between estimated gestational ages and other indicators of fetal size such as fundal height. Pediatricians have also come up with measures of neonatal maturity, based upon an examination of the newborn, which correlate reasonably well with gestational age and which are now used frequently as substitutes for gestational age (Dubowitz score). Since ultrasound is frequently used during pregnancy, it should aid investigators in obtaining reliable gestational age estimates on large-scale populations of pregnant women, especially in some European countries where a large majority of women have early ultrasound. In order to move this field forward it is important in our studies to state hypotheses to be tested clearly and, to paraphrase Leon Gordis, "the hypotheses should be biologically plausible" [11]. If the aim of epidemiological investigations is to identify etiologies, our studies must
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TABLE 3
Live Births, According to Race and Selected Characteristics: United States, Selected Years 1970–81
(Data are based on the National Vital Statistics System.)

| Race and Selected Characteristics | % of Live Births per Year |
|-----------------------------------|--------------------------|
|                                   | 1970 | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 | 1981 |
| Total                             |      |      |      |      |      |      |      |      |
| Birth weight                      |      |      |      |      |      |      |      |      |
| 2,500 grams or less               | 7.94 | 7.39 | 7.26 | 7.07 | 7.11 | 6.94 | 6.84 | 6.81 |
| 1,500 grams or less               | 1.17 | 1.16 | 1.15 | 1.13 | 1.17 | 1.15 | 1.15 | 1.16 |
| Whites                            |      |      |      |      |      |      |      |      |
| Birth weight                      |      |      |      |      |      |      |      |      |
| 2,500 grams or less               | 6.84 | 6.26 | 6.13 | 5.93 | 5.94 | 5.80 | 5.70 | 5.67 |
| 1,500 grams or less               | 0.95 | 0.92 | 0.91 | 0.89 | 0.91 | 0.90 | 0.90 | 0.90 |
| Blacks                            |      |      |      |      |      |      |      |      |
| Birth weight                      |      |      |      |      |      |      |      |      |
| 2,500 grams or less               | 13.86| 13.09| 12.97| 12.79| 12.85| 12.55| 12.49| 12.53 |
| 1,500 grams or less               | 2.40 | 2.37 | 2.40 | 2.38 | 2.43 | 2.37 | 2.44 | 2.47 |

Distinguish between intrauterine growth retardation and pre-term delivery; the use of low birth weight defeats that purpose. Almost 50 percent of low birth weight births are 37 gestational weeks and above and therefore are not pre-term births. Investigations need to focus on factors associated with the onset of pre-term labor and its prevention. The hypothesis that infection of the genitourinary tract is associated with an increased risk of low birth weight or premature labor has been the subject of many investigations over the past 25 years, but only recently has it been subjected to a truly large-scale randomized clinical trial. Clinicians report success with attempts to teach women to recognize early signs of premature uterine contractions in order to improve the diagnosis of premature labor at a time when it may be easier to arrest. Tocolytics have come into widespread use in an attempt to arrest premature labor, with as yet uncertain results. Opportunities to test these hypotheses are excellent and should be

TABLE 4
U.S. Incidence of Low Birth Weight and Term- and Pre-Term Low Birth Weight Infants by Race, 1970 and 1980

| Race | Year  | % Reduction |
|------|-------|-------------|
|      | 1970  | 1980        |             |
| White |       |             |             |
| Low birth weight | 6.34 | 5.28 | 16.7 |
| Term low birth weight | 3.09 | 2.33 | 24.6 |
| Pre-term low birth weight | 3.24 | 2.95 | 9.0 |
| Black |       |             |             |
| Low birth weight | 12.86 | 11.60 | 9.8 |
| Term low birth weight | 5.79 | 4.93 | 14.9 |
| Pre-term low birth weight | 7.07 | 6.66 | 5.8 |

Low birthweight indicates a birthweight of 2,500 grams or less; term, at least 37 completed weeks of gestation; pre-term, under 37 completed weeks of gestation.
undertaken. When gestational age estimates are suspect or unreliable, it is better to focus on very low birth weight (<1,500 grams) as a separate group in etiological studies since most of these children are pre-term.

EARLY FETAL LOSS

The study of early fetal loss is of great interest to many. It may be a useful end-point for studies of environmental effects. In addition to the early fetal loss in clinically recognized pregnancies, there is an unknown proportion of fetal loss very early in pregnancy, before the pregnancy has been clinically recognized. The recent advent of sensitive tests of specific hormones associated with pregnancy, particularly human chorionic gonadotropin (hCG), which can be detected as early as seven days after presumed conception, may permit an accurate estimate of the rate of fetal loss in subclinical pregnancies.

In a recent study a highly specific and very sensitive assay of hCG was used on a sample of women who wanted to become pregnant and provided daily urine samples for evaluation [12]. A preliminary analysis of a subset of this population provided a rate of fetal loss of subclinical pregnancies of around 22 percent. Here, of course, the problem is one of confirmation. Pregnancies are diagnosed by hormonal assay, and sequential testing over time identifies women with hormonal levels which have returned to baseline values. They presumably have suffered a fetal loss. At present I am not aware of any confirmatory test of pregnancy by testing for products which are uniquely related to pregnancy. Schwangerschaftsprotein, which is a protein derived from the placenta, may fit that description, although it cannot be measured until a few days after implantation [13].

The recognition that a high proportion of early fetal losses represent chromosomally abnormal fetuses has called into question the use of fetal loss of less than 20 weeks' gestation as a summary outcome measure. Even for chromosomally normal fetuses lost early in pregnancy, the event of the expulsion of the fetus and the time when it occurs is not a useful variable for investigation. The critical variable is the time of the fetal death and not the time of expulsion of the dead fetus. It has been shown that the rate of fetal loss after eight weeks in pregnancies in which the fetuses were viable by ultrasound at eight weeks is rather low and on the order of around 3 to 4 percent [14]. Studies of clinically diagnosed pregnancies, followed prospectively, report a rate of early fetal loss of between 8–12 percent. Since pregnancies are generally not clinically recognized until the second missed menstrual period, this rate of loss is past eight weeks' gestation. Most of these losses, therefore, are fetuses who have died before the eighth week of gestation. The time of exposure in studies of fetal loss must therefore be geared to the period when the fetus was known to be alive (by ultrasound) or, failing that, to the first six to eight weeks of pregnancy.

ASSESSING CLINICAL MANAGEMENT TECHNIQUES

Fetal surveillance and management of labor and delivery have undergone marked changes in recent years. Electronic intrapartum fetal monitoring of the fetal heart in conjunction with the monitoring of uterine contractions and fetal scalp sampling to measure pH and pO₂ have become routine in the management of labor and delivery of high-risk pregnancies. According to the National Natality Survey of 1980, 47.2 percent of all pregnancies had electronic fetal monitoring during labor and 29.3
percent of women report at least one ultrasound during pregnancy [15]. These technologies have added substantially to the cost of providing prenatal care. Their efficacy has been judged almost exclusively on the basis of the experience gained by those using this technology. Clinical trials have not been used in their evaluation until very recently. There are three clinical trials of electronic fetal monitoring that have been done in this country. They were of insufficient size and therefore had inadequate power to measure efficacy [16,17,18]. More recently the Perinatal Epidemiology Unit in Oxford, England, conducted a major clinical trial of electronic fetal monitoring in Dublin [19]. This trial included about 13,000 women. No differences were seen in rates of Cesarean sections, which were 2.4 percent for electronic fetal monitoring and 2.2 percent for routine care (a rate of Cesarean section only about one-tenth the rate in this country and reflecting a substantially different approach to the management of labor and delivery than in the U.S.). The perinatal mortality rate was the same; however, there was a twofold increase in neonatal seizures and persistent neurological signs in the group without electronic fetal monitoring, which was shown to be related to duration of labor. Clinical trials of the routine use of ultrasound have been done in Norway, but not here [20]. Again the trials of the use of ultrasound in Norway had rather limited power.

Another marked change in obstetrical management is reflected in the rise in Cesarean section rates in the U.S. [21]. The use of Cesarean section has increased from 5.7 percent in 1970 to 21.2 percent in 1984 (Table 5). Several indications have contributed to this marked increase. One example is breech presentation. In 1970, 11.6 percent of breech presentations were delivered by Cesarean sections. This number increased to 26.7 percent in 1974, to 60.1 percent in 1978 and was reported to be 79.8 percent in 1984. This result is a remarkable change and yet it is based exclusively on clinical experience. Now some investigators are questioning the various indications for Cesarean sections on the basis of observational data, especially for breech presentation. The dictum, once a Cesarean section always a Cesarean section, results in a further increase in the rate of deliveries by Cesarean section because of the increase in the rate of primary Cesarean section. Now this dictum is also being challenged.

Obstetrical practice in this country has been influenced extensively by the increase in malpractice suits facing obstetricians. The desire to have an objective record of the status of the fetus before and during labor and delivery undoubtedly has increased the use of various tests of fetal well-being and monitoring and this testing in turn has resulted in more aggressive management of labor and delivery, including the use of Cesarean section. The fear of malpractice suits will make it more difficult to develop clinical trials of obstetrical management and delivery in the U.S. An extensive survey, about ten years ago, of the 50–60 leading perinatal obstetricians in this country revealed that most of them felt that a clinical trial of fetal monitoring in high-risk pregnancies could not be done either because it was ethically not defensible or increased the probability of litigation or both. More than 50 percent declined the use of clinical trials in this field, even for low-risk pregnant women, for similar reasons [22]. Clinical trials in this area which attempt to use perinatal or neonatal mortality as end-points, moreover, require enormous sample sizes. Since the risk of perinatal mortality in the average pregnant woman is probably no more than one percent, or possibly even less, sample sizes of the order of 20,000 or more are necessary for adequate power. The importance of clinical trials to the field of obstetrics is increasingly recognized, and, despite the stated reservations, this field will see a
considerable upswing in the use of clinical trials as a means of evaluation of efficacy and safety.

High technology has likewise entered the field of neonatal care, also referred to as neonatal intensive care. The success in improving the rate of survival of very low birth weight children, i.e., children weighing less than 1,500 grams or even less than 1,000 grams, is remarkable and much of it can be attributed to neonatal intensive care, which was pioneered at Yale about 25 years ago. Most of the technology and therapies used in neonatal intensive care have not been subjected to evaluations by randomized clinical trials. The absence of clinical trials in this field is particularly remarkable in view of the fact that in the 1950s a randomized clinical trial of controlled oxygen administration identified oxygen as a risk factor of retrolental fibroplasia [23].

LOW BIRTH WEIGHT

Low birth weight does not always mean a higher risk of neonatal or perinatal mortality. The well-known differences among the sexes offer a good example. Girls, on the average, weigh less at birth than boys and have a higher rate of low birth weight, but a lower rate of neonatal mortality. The birth weight distribution of girls is slightly shifted to the left of boys. Blacks and whites differ in their birth weight distribution as well, but the difference is not a mere shift to the left. For a given birth weight, up through around 3,000 grams, blacks experience a lower perinatal mortality than whites. Blacks therefore have a lower birth weight-specific perinatal mortality than whites for birth weights up to about 3,000 grams and a higher rate than whites above 3,000 grams. To compare in birth weight-specific mortality populations which differ in their underlying birth weight distribution, simple adjustment is not sufficient. Wilcox and Russell have demonstrated that the black/white differences in perinatal mortality are not explained by a mere shift of the birth weight distribution of blacks to the left of that of whites [24]. He distinguishes two components to the birth weight distribution: the predominant Gaussian distribution and the residual distribution of small infants. For blacks, the residual distribution at the left tail of the birth weight distribution reveals a considerable excess in very low birth weight births as compared to whites. Blacks have a rate of low birth weight which is about twice as high as whites, but their rate of very low birth weight (1,500 grams or less) is nearly three times as high. When the race-specific predominant birth weight distributions are plotted relative to their own means, blacks are found to have a higher mortality throughout. About two-thirds of the excess perinatal mortality in blacks is due to the large residual distribution of small infants and about one-third to the higher mortality in the predominant distribution.

| Year | %   |
|------|-----|
| 1970 | 5.7 |
| 1974 | 9.1 |
| 1978 | 14.7|
| 1984 | 21.2|

*As reported by Commission on Professional Hospital Activities

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**TABLE 5**

| Year | %   |
|------|-----|
| 1970 | 5.7 |
| 1974 | 9.1 |
| 1978 | 14.7|
| 1984 | 21.2|

Rates of Cesarean Sections in the U.S.A., 1970–1984

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The reasons for the marked differences in the birth weight distribution of blacks vs. whites are not understood. Most of the difference remains even after adjusting for some of the major risk factors of low birth weight such as maternal education, age, parity, maternal pregnancy weight, weight for height, use of prenatal care services, medical and obstetrical complications, and differences in smoking and alcohol consumption [25].

A woman’s birth weight is related to the birth weight of her offspring. She has a threefold increased risk of delivering a low birth weight child if she weighed between four and six pounds at birth as compared to eight or more pounds at birth [26,27]. Since there are twice as many low birth weight mothers among blacks, this fact could explain some of the black/white difference. The effect appears to operate through intrauterine growth and not pre-term delivery; at least this is what the evidence currently available suggests. Since both mother’s and father’s birth weight contribute to fetal size, some of this effect may well be genetic in nature. These questions can now be addressed through intergenerational studies. There are a number of fairly detailed data sets available of pregnancies and births from the 1950s and early 1960s in this country, the United Kingdom, and other European countries, which include information on many of the known risk factors of low birth weight. Linkage of these data sets to pregnancy and pregnancy outcome data of the present generation should provide excellent opportunities to determine whether nature or nurture accounts for this unresolved and puzzling difference in birth weight distribution.

SUMMARY

There are still many opportunities for research in perinatal epidemiology and important public health issues in maternal and child health which need to be addressed. The complexities of this field are immense and challenging. It provides for stimulating interactions with people from many different disciplines and its research crosses two, and now possibly three, generations. As a lifelong student of this field, I have found it easy to sustain my enthusiasm.

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