Milbank Memorial Fund Quarterly/*Health and Society, Vol. 56, No. 3, 1978*

Prevention of Low Birth Weight and Pre-Term Birth

Literature Review and Suggestions for Research Policy

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INFANT and prenatal mortality[1] has greatly decreased during this century in developed countries. Despite this overall trend, there are great differences among countries and among groups within a country. An abundant literature shows that the socioeconomic status of the family or area in which the family lives explains most of the differences: the lower the status, the greater the mortality (Shapiro, Schlesinger, and Nesbitt, 1968; Niswander and Gordon, 1972; Kessner, Singer, Kalk et al., 1973; Department of Health, Education, and Welfare, 1972). The way in which socioeconomic status causes excess deaths is not known, although there are many theories.

Perinatal mortality and, to a lesser degree, infant mortality after the first week of life are dependent on the birth weight of the child: mortality is far greater in low birth weight children than in normal weight children. According to U.S. statistics for 1964–1966, low birth weight infants of different social classes have similar prognoses; the higher mortality in lower social classes is associated with a greater number of low birth weight infants (Department of Health, Education, and Welfare, 1972).

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[1]The following definitions are used in this article: *perinatal mortality* = number of deaths in period from the 28th week of gestation to the 7th day of life per 1000 live births; *neonatal mortality* = number of deaths during the first 28 days of life per 1000 live births; *infant mortality* = number of deaths during the first year of life per 1000 live births; *pre-term birth* = birth after less than 37 completed weeks of gestation; low birth weight = birth weight less than 2500 g.

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Low birth weight may result from premature delivery (pre-term infants), or poor intrauterine development (small-for-date infants). The highest mortality rate is found in pre-term infants, although small-for-date children have somewhat increased mortality rates as compared with normal birth weight infants (Shapiro, Schlesinger, and Nesbitt, 1968; Yerushalmy, van den Berg, Erhardt et al., 1965). Data from the United States and England show that about half the low birth weight infants have gestations of 37 weeks or over and that almost half the infants born before the 37th week weigh more than 2500 g (Shapiro, Schlesinger, and Nesbitt, 1968; Yerushalmy, van den Berg, Erhardt et al., 1965; Brimblecombe, Ashford, and Fryer, 1968). Therefore, pre-term and low birth weight groups overlap only partly. Despite this, in this article we consider low birth weight as indicating prematurity, since most vital statistics provide only birth weight, and even where gestation age is obtained it is generally unreliable. Additionally, analyses made by Susser, Marolla, and Fleiss (1972) of data from several populations show that birth weight explains 90% of the variance in perinatal mortality and suggest that prognosis for perinatal death can be made almost as well from birth weight alone as from an index of birth weight and gestational age. This may be due to the fact that the mortality rate for small-for-date infants or infants less than 37 weeks but over 2500 g is small compared to that for pre-term infants weighing less than 2500 g.

Frequency of Low Birth Weight Infants in the United States, Finland, and Sweden

We have obtained recent data on the frequency of low birth weight infants in three countries (United States, Sweden, and Finland). We chose these countries because U.S. perinatal and early neonatal mortality rates in the 1950s and 1960s have been compared unfavorably to those in Scandinavia. Figure 1 shows the percentage of all live born infants who were of low birth weight, and Fig. 2 shows the percentage of all infants (including fetal deaths) who were of low birth weight. These figures indicate a much greater percentage of low birth weight infants in all low birth weight groups in the United States than in Finland and Sweden. (Different weight groups were

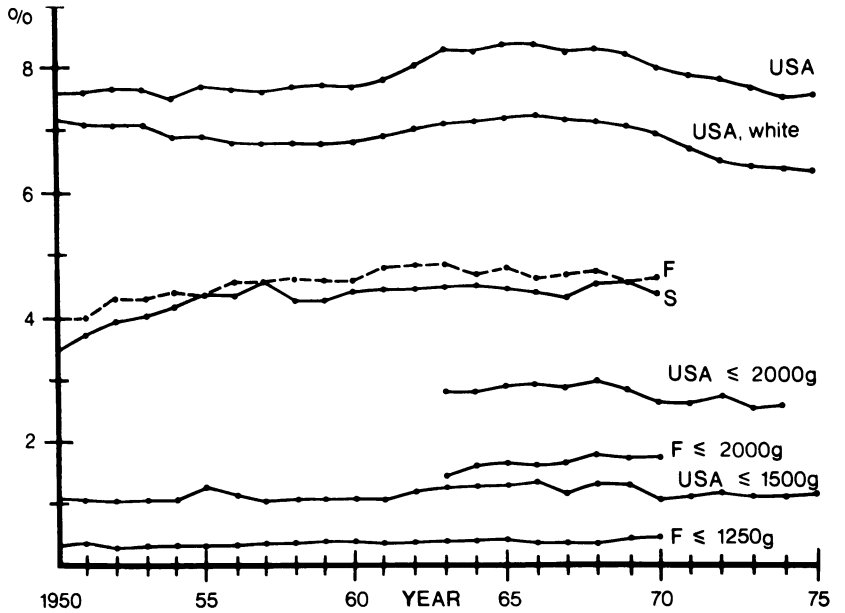

FIG. 1. Percentage of live born infants weighing under 2500 g of all live born infants in the United States (USA), Finland (F), and Sweden (S) during 1950–1975. *Sources:* Department of Health, Education, and Welfare, 1953–1976; Department of Health, Education, and Welfare, 1975, 1976; Finnish National Board of Health, 1951–1974; 1977; Sveriges Officiella Statistik, 1953–1976. *Note:* In the Finnish data, births in the weight group 1251–2000 g derive only from mothers registered at maternity health centers; however, this includes 97.2%–99.9% of all mothers.

used, as the countries group their data differently. For Sweden, no reliable data by detailed weight groups were available.)

The differences in the proportion of low birth weight infants is reflected in differences in the neonatal and perinatal mortality: Finland and Sweden show lower perinatal and neonatal mortality rates than the United States (Fig. 3). Geijerstam's (1969) data from 1964 show that the difference in neonatal mortality between the United States and Sweden decreased from 42% to 12% when the Swedish mortality rate was calculated applying U.S. incidence of low birth weight infants and Swedish weight-specific mortality.

However, there was no evident decline in the proportion of low birth weight infants in any of the weight groups or in any of the countries until the 1970s when the proportion of low birth weight infants started decreasing in the United States. Therefore, the decline in

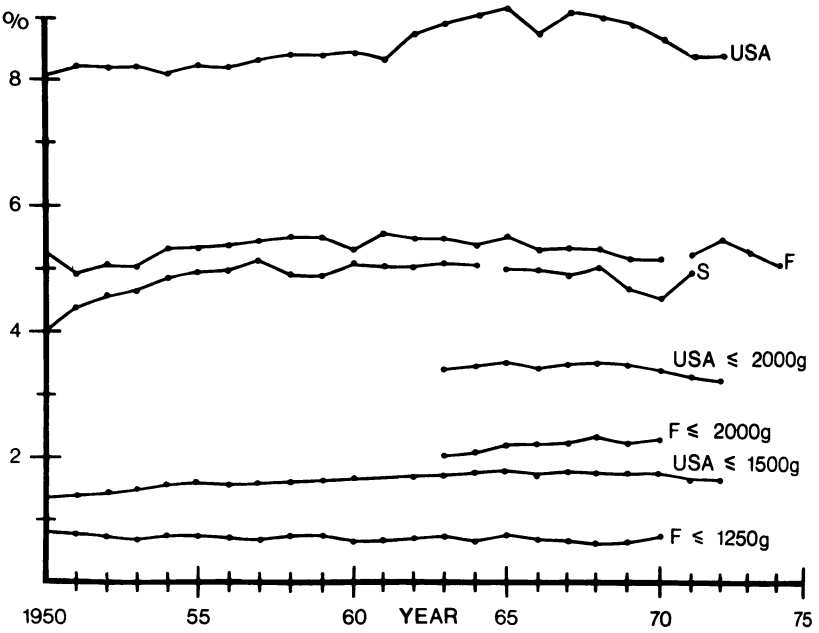

FIG. 2. Percentage of infants (both live and stillborn) weighing under 2500 g of all born infants in the United States (USA), Finland (F), and Sweden (S) during 1950–1974. Sources and Note, see Fig. 1.

mortality in the last two decades in these three countries must be due to factors other than changes in the frequency of low birth weight infants. In Finland and Sweden the perinatal mortality steadily decreased during the 1950s and 1960s even though the proportion of low weight births remained the same. In the United States there was a plateau in mortality rates from the mid-1950s to the mid-1960s, accompanied by, at most, a small increase in the proportion of low birth weight infants, so that perinatal mortality was higher than in Sweden and Finland by the end of the 1960s.

In all three countries the decline in fetal deaths was greater than the decline in neonatal mortality. The reported late fetal death ratio (number of fetal deaths after 28 weeks, gestation per 1000 live births) was lower in the beginning of the 1950s in the United States than in Sweden and Finland, but there was no further decline in the 1960s. In Sweden and Finland the fetal death ratio continued to decrease during this period so that by the 1970s the fetal death ratio was somewhat lower than that in the United States.

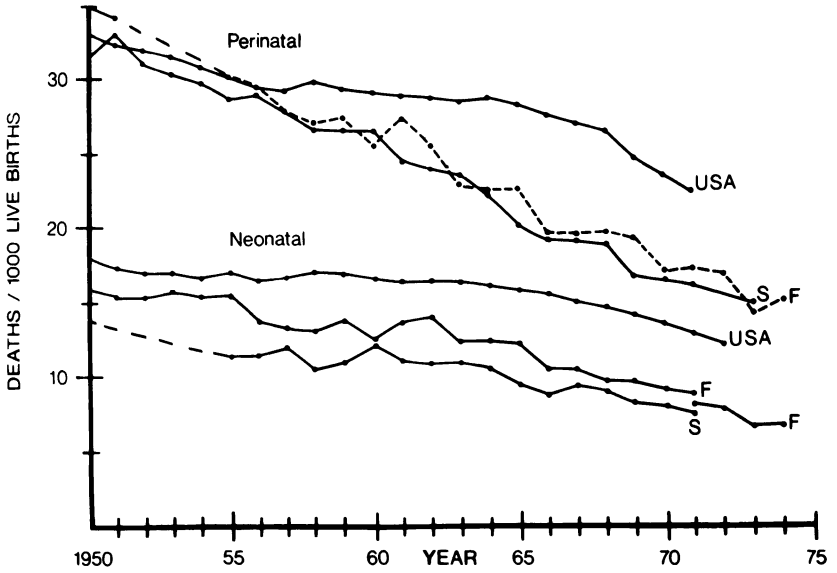

FIG. 3. Perinatal mortality and early neonatal mortality (deaths under 1 week of age per 1000 live births) in the United States (USA), Finland (F), and Sweden (S) during 1950–1974. *Sources:* Department of Health, Education, and Welfare, 1953–1976; Finnish National Board of Health, 1977; Sveriges Officiella Statistik, 1953–1976; United Nations, 1957; Shapiro, 1976.

Geijerstam's (1969) analysis for the years 1947-65 shows that the progress made in Sweden from 1947–65 in lowering the perinatal mortality rate was mainly due to a drop in the late fetal death rate together with some decrease in the early neonatal death rate of infants weighing more than 2500 g. The prognosis for live born infants weighing less than 2500 g in 1965 was about the same as in 1947. In Finland the trend during 1963–73 was different in that the prognosis for small live born infants did improve; our calculations show that the total perinatal mortality decreased by 39% (from 22.5 to 13.8 deaths per 1000 live births) and the perinatal mortality of low birth weight infants decreased by 48% (from 360.6 to 188.1 deaths per 1000 live born infants weighing less than 2500 g) (Finnish National Board of Health, 1951–1974; 1977). The decrease in perinatal mortality of low birth weight infants was a result both of a decline in still births (by 50%) and in mortality under one week of life (by 46%).

Even though there has been a decline in all components of infant mortality (Pharoah, 1976; Shapiro, 1976), the changes in the mor-

tality rate in each of the different groups of low birth weight infants and the effects of the change in one group on the mortality in another (*e.g.*, in fetal deaths on neonatal deaths) are largely unexplored. It is possible that infants who previously would have died *in utero* are now born alive but with low birth weight.

Prevention of Low Birth Weight and Pre-Term Birth

As the analysis from Finland and Sweden suggests, perinatal mortality can be decreased without decreasing the frequency of low birth weight; this is accomplished by preventing fetal deaths and by improving the prognosis for both low birth weight and normal birth weight infants. However, in countries that have already achieved a low perinatal mortality, further progress in reducing mortality may require reducing the prematurity rate. Preventing prematurity has the additional advantage of eliminating both the traumatic separation of mother and child and the subsequent greater morbidity.

Analysis of the Literature

To determine the possibilities for prevention, we searched the literature for proposed causes of low birth rate and pre-term delivery, and preventive strategies that could be implemented within existing social and medical systems. As is the case with perinatal mortality, the frequency of low birth weight infants varies within countries as well as among them. In the United States, low birth weight is more frequent among primiparae, non-white mothers, mothers from lower social classes, mothers with less education, and those of short stature (Shapiro, Schlesinger, and Nesbitt, 1968; Niswander and Gordon, 1972; Kessner, Singer, Kalk, 1973; Department of Health, Education, and Welfare, 1972). These factors are highly intercorrelated. The strong correlation between social class and low birth weight suggested that social changes abolishing social inequities would be most efficient in preventing low birth weight and pre-term birth. However difficult this might seem to accomplish, there might be some changes that could be made within the existing system to reduce the overwhelming impact of social class by influencing the mechanisms by which it has its effect.

In our search, rather than use the arbitrary definitions of pre-term and low birth weight infants, we considered all terms describing

suboptimal gestation ages and birth weights. We reviewed all measures that hindered the attainment of the optimum gestation age and weight as determined by the Medical Center of the University of Colorado in 1958–68; this optimum was a gestation of 39 to 41 weeks and a birth weight of 3250 to 3500 g (Lubchenco, Searls, and Brazie, 1972).

We did not include in our review:

1. Studies that attempted to regulate fertility by contraception and abortion, as effective as they might be in preventing low birth weight.
2. Studies from undeveloped countries. As the causes for low birth weight and pre-term birth apparently vary from one country to another and with the passage of time, we considered only literature from developed countries published within the past 20 or 30 years, because of its greater relevance to the United States.
3. Studies on prenatal care that did not specify the nature of the care provided. The components of prenatal care vary from place to place, and it is possible that some items are beneficial but others harmful.
4. Studies that merely described the relationship between screening of high-risk mothers and low birth weight and pre-term births. The nature of the care provided was what was important, rather than the impact of a general program of "screening."
5. Studies in languages other than English, German, Scandinavian, or Finnish.

Study 1: Proposed Causes of Low Birth Weight and Pre-Term Birth

Many causes for low birth weight and pre-term birth have been postulated. Table 1 gives those most frequently proposed. The first column contains factors suited to primary prevention; the arrows show some of the postulated relationships among the categories. If these causes were arrayed by mechanism of action, fetal hypoxia would be the most frequent intermediary.

Estimates of the significance of each factor based upon its frequency and associated risk are given in Table 2. Attributable risk

TABLE 1

Classification of Proposed Causes for Low Birth Weight and/or Pre-Term Birth

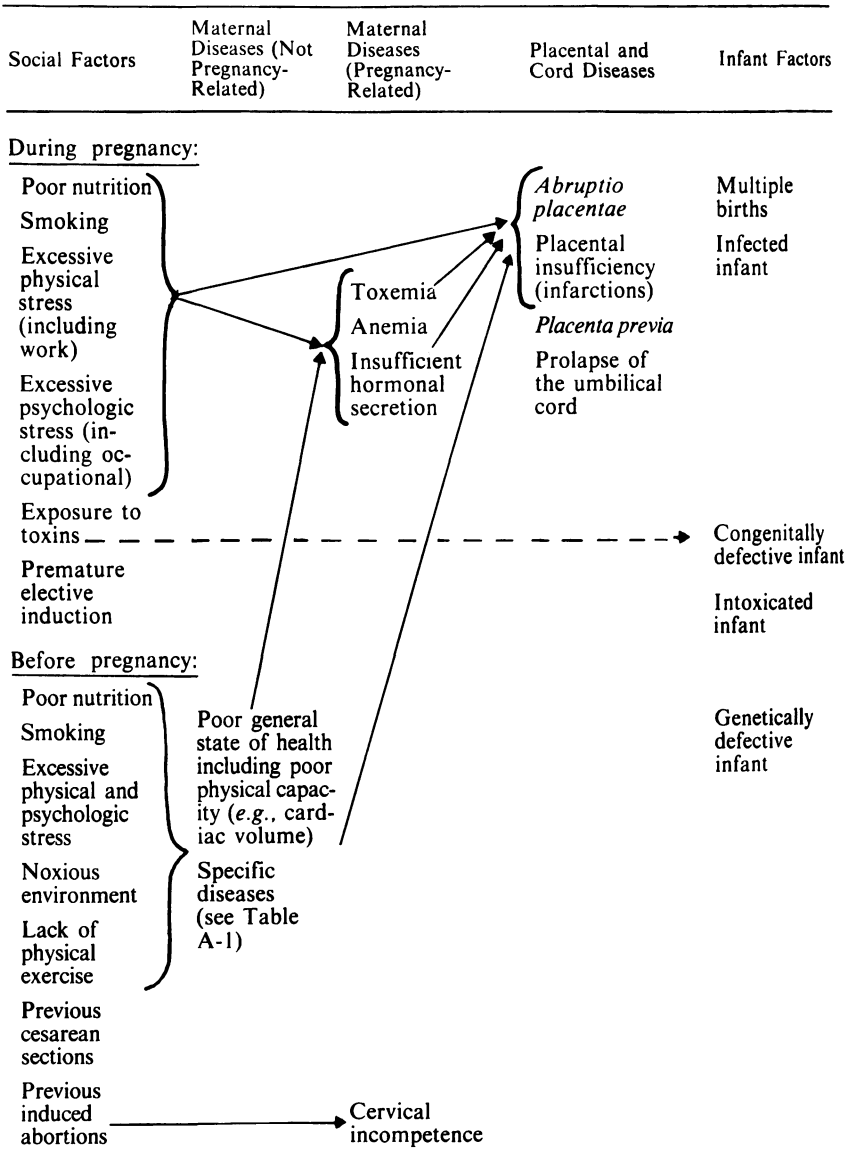

TABLE 2
Percentages of Low Birth Weight and Pre-Term Infants Attributed to Different Factors*

Medical and Social Factors	Frequency Among Pregnant Women		Low Birth Weight Infants		Pre-Term Infants
	White	Non-White	White	Non-White	White
Maternal diseases (not pregnancy-related):†					
(Niswander and Gordon, 1972);	12.0	11.0	7.7	3.8	
(Ontario Perinatal, 1967)	20.0		20.0		
Maternal diseases (pregnancy-related):					
Toxemia (Shapiro et al., 1968;	1.2	2.8	0.68	0.75	
(Butler and Alberman, 1969)	11.0		14.0		6.4
Anemia Hb < 9 (Kaltreider and Johnson, 1976)		1.7		1.1	
Hb < 11 (Ontario Perinatal, 1967)‡	24.0		1.4		
Incompetent cervix (Niswander and Gordon, 1972)	0.34	0.36	2.6	1.5	
Placental diseases:					
Abruptio placentae (Niswander and Gordon, 1972)	2.4	1.9	6.5	4.9	
Placenta previa (Niswander and Gordon, 1972)	0.77	0.56	2.8	1.7	
Prolapse of cord (Niswander and Gordon, 1972)	1.1	0.78	0.74	0.59	
Infant factors:					
Multiple births (Butler and Alberman, 1969)	2.4		14.5		10.0
Congenitally or genetically malformed infant (Page, 1967)§	0.81		1.5		
Social factors:					
Smoking (Meyer et al., 1976)	43.0		30.0		11.0
Poor nutrition during pregnancy**					
(Niswander and Gordon, 1972)	90.0	88.0	65.0	57.0 of term	
Poor physical condition††					
(Unnerus, 1959; Räihä and Kauppinen, 1963;	11.0		29.0		
Terris and Gold, 1969)		11.0?		11.0	
After rest was implemented (Räihä and Kauppinen, 1963)	11.0		5.0		

*For the method of calculation and description of studies, see Appendix A.
†The sum of different diseases. The individual diseases are given in Appendix A.
‡Excludes those 28% whose Hb was unknown.
§Infants with major malformations.
**Less than highest weight gain (35 lbs or more). Only pregnancies lasting more than 37 weeks were included.
††Heart volume less than 500 ml or 370 ml/m^2 body surface.

(percentage of the total low birth weight or pre-term infants attributable to the specific factor) was calculated or obtained directly from epidemiologic studies. The method of calculation and description of the studies are given in Appendix A. Unfortunately, risks could not be calculated for some of the factors listed in Table 1, because no studies could be found for them.

Table 2 should be interpreted with caution. The percentages attributable to the factors were counted by comparing the risk in women who had the condition to the risk in those who did not. There was insufficient information in the literature to permit calculation of risks that were standardized to other risk factors. Additionally, it was difficult to define which factors should be standardized. Often it was not known whether the other factor was a spurious correlator or a mechanism through which the factor of interest operates (or *vice versa*). In interpreting Table 2, the following reservations pertain. 1) The increased risk need not mean that the factor is a causal one; the increased risk may be due to correlations of the factor to true causal factors. For example, the higher risk of anemic patients need not mean that anemia is a cause of low birth weight, but that anemia is more frequent among women who, for other reasons, have low birth weight infants. 2) Some of the factors are probably mechanisms through which the other factors operate. For example, it may be that *abruptio placentae* is a factor through which smoking has its effects. 3) It is presumed that even the actual causative factors probably cluster in certain pregnant women. When the factors are considered one by one, many low birth weight infants are counted several times. 4) The frequency of the risk factors and the magnitude of the risk vary from area to area. The percentages in Table 2 were derived mainly from American, English, and Canadian studies. Even though studies covering a wide range of populations were sought, generalizations outside the study populations might be inappropriate. 5) The contributions made by individual factors to low birth weight are not necessarily the same as their contributions to infant mortality or morbidity. For example, the percentage of low birth weight infants attributable to smoking is 30%, but the contribution to perinatal mortality is only 6% (Meyer, Jonas, and Tonascia, 1976). 6) The risks attributable to maternal diseases were obtained from populations in which many of the mothers were treated for their diseases. In populations not receiving prenatal care, the attributable risk might be higher.

To illustrate the magnitude of the problem, the risks due to different maternal diseases were summed, even though we recognized that they probably did not act independently. In the American study, about 8% of the low birth weights in white infants and 4% in black infants resulted from maternal diseases not primarily related to pregnancy. In the Canadian study, 20% of the low birth weights were attributable to these diseases. The difference is probably due to the following factors. 1) The Canadian study included more diseases, some of them quite frequent. This resulted in more frequent double counting of the same low birth weight infants. 2) The Canadian study made comparisons to women with none of the diseases listed, whereas the American study made comparisons to women not having the specific disease under consideration. Thus, attributable risk could be expected to be greater in the Canadian study, as the comparison group had a lower risk than the comparison group in the American study.

If the percentages in Table 2, excluding the social factors, are summed, 40% to 50% of the low birth weights in white infants and 30% in black infants can be attributed to maternal and placental diseases or infant-related conditions. But as discussed above, simple adding of the different attributable risks greatly magnifies the importance of the maternal and placental diseases and infant-related conditions. Their total contribution is undoubtedly considerably under 40%. Additionally, even though the causes of maternal diseases or placental and infant-related diseases are poorly known, evidence suggests that social factors are important in their etiology. The determinants of the majority of low birth weight and pre-term birth must therefore be sought among the social factors, such as those listed in Table 1.

It is interesting to compare these results to hospital data in Baltimore, Maryland, in the period 1926–1945 (Eastman, 1947). In these data, where the rate of low birth weight infants averaged 11.7%, maternal diseases accounted for 16%, placental diseases 8%, congenital defects 2%, and multiple pregnancy 12%. Each infant was assigned only one cause and was therefore counted only once. Other studies done before the 1950s also concluded that no "obstetrical cause" could be found about in half of the premature births (Räihä, 1968).

Unfortunately, the data on social factors, except for smoking, are scant. Even in the case of nutrition, where much has been

published regarding its relationship to birth weight, most of the studies concerned small or selected populations, and it was not possible to estimate the general frequency of nutritional deficiency and associated risk. Weight gain during pregnancy, which does not necessarily reflect adequacy of diet, was used as a proxy for nutritional adequacy. Data of sufficient scope were found only for term infants. The frequency of small-for-date infants would theoretically be reduced by 65% (whites) or 57% (non-whites) if the rates of small-for-date infants for all women were the same as for women with the highest weight gain. However, weight gain is associated with other factors. For example, Thomson and Billewicz (1961) reported that intake of nutrients increased with increasing stature, and taller and heavier women were generally from a higher social class. On the other hand, Davies, Gray, Ellwood et al. (1976) reported that non-smokers gained significantly more weight than smokers, and that a large part of the effect of maternal smoking is mediated through maternal weight gain.

We found no study that examined the relationship of physical fitness to frequency of low birth weight or pre-term infants. As a substitute, the correlation between low birth weight and absolute heart volume was used, even though this measure is recognized as unsatisfactory.

Study 2: Interventions to Prevent Low Birth Weight and Pre-Term Births

Evaluating the significance of factors causing low birth weight and pre-term infants on the basis of correlation studies is fraught with problems. As stated above, the different factors are highly intercorrelated, and some are intermediates in the causal pathways of others. In practice, a factor is considered etiologic if altering it affects the frequency of low birth weight or pre-term infants. For our analysis of preventive strategies, we sought studies in which one or more of the factors listed in Table 1 were purposefully changed. We excluded from this search the maternal, placental, and infant diseases listed in Table 1 (except for anemia, inadequate hormone levels, and cervical incompetence), on the assumption that efficient treatment would certainly decrease their impact on birth weight and pre-term delivery if the means of treatment or prevention were known. We also excluded iatrogenic causes, as the definition of an iatrogenic cause implies

that abolishing it is followed by decrease in low birth weight or pre-term birth frequency. We therefore concentrated on studies that described the effectiveness of interventions to ameliorate the social factors and certain selected diseases (anemia, hormonal deficiency, cervical incompetence); we also considered the effectiveness of labor inhibitors.

To be included in our analysis of preventive strategies, an additional requirement was made that the study had to have an adequate control group. Studies published from January, 1930, to May, 1977, were included (Table 3 and Appendix B). No intervention studies were found for some factors, and very few were found for some others. The imbalance in the number of intervention studies is evident: research has centered on drug therapy (iron, vitamins, and labor inhibitors), despite the fact that drug therapy is associated with only a small reduction in the rate of low birth weight and

TABLE 3
Number of Intervention Studies Aiming to Prevent Low Birth Weight or Pre-Term Birth*

Intervention Strategy	No. of Controlled Studies	Studies Without Obvious Drawbacks Impeding Conclusions		Probability of Medical Side Effects†
		(No.)	Intervention Beneficial (No.)	
Prevention and therapy of premature labor by drugs	16	11‡	2‡	++
Prophylactic administration of iron and/or vitamins (only)	15	8	0	+
Completing diet by high-quality food or artifical protein diets plus iron and vitamins	3	0	–	+
Health education on diet	2	1	1	VS
Health education on smoking	1	1	0	VS
Hospital rest in twin pregnancies	1	0	–	+
Prevention of premature labor by cervical suture in twins	1	0	–	+
Physical exercise and diet before pregnancy, decreasing physical stress or psychological stress during pregnancy, etc.	0	–	–	VS
Total	37	20	3	

*The studies are listed in Appendix B. – = denominator is 0.
†VS = very small; + = small; ++ high or moderate.
‡The cells exclude trials in which two active drugs but no placebo were compared.

prematurity (Hemminki and Starfield, 1978a; 1978b). In contrast, other areas have been neglected.

The imbalance in the number of interventions directed toward the different factors is even more apparent, if the side effects of the interventions are considered. (The costs were not estimated, because empirical data were not available.) Estimates of the number and seriousness of the side effects (Table 3) are based either on qualitative data in the literature or on common sense, and are therefore imprecise. For example, stoppage of smoking has few detrimental side effects. In contrast, drug treatment to prevent premature labor may have serious side effects. The largest number of studies has been devoted to evaluating interventions with the greatest likelihood of side effects.

Why has there been this marked unevenness in the types of interventions studied? It may be because it is easier to find reports on drugs than on other types of interventions, since these reports are usually published in journals while others are not, being circulated only locally and not adequately indexed. It is also possible that the effect of these other factors has been assessed by outcome measures other than birth weight or maturity, such as morbidity and mortality. However, the studies encountered in our literature search that dealt with mortality and morbidity usually also contained data on birth weight and/or length of gestation, and thus would have been included in our review.

Undoubtedly, it is easier to conduct clinical trials on drugs than on exogeneous factors such as physical exercise before pregnancy. Perhaps the best explanation involves the way in which clinicians and clinical researchers see their roles. Drugs and the treatment of physical complications are customary areas of interest. Diet, exercise, work conditions, and psychological stress are not seen as primary responsibilities of physicians, and seldom are physicians educated about them.

The finding that there are very few experiments that evaluate social factors does not mean that there has been no research at all or that the factors are not appreciated. For example, there have been epidemiologic studies clarifying the associations between smoking and prematurity (deHaas, 1975) and nutrition and prematurity (Terris, 1966; Bergner and Susser, 1970; National Academy of Sciences, 1970a, 1970b). However, for the other factors—effect of psychologic stress and physical stress (such as stressful work), effect

of pre-pregnant physical exercise, and effect of (moderate) exercise and rest during pregnancy — even epidemiologic studies of their association with prematurity are scant despite their potentially great importance.

Are such studies needed if the relationship between a factor and prematurity appears to be obvious? We think so, for the primary reason that the presumed cause may not be the real cause, but only correlated with it. Moreover, it cannot be assumed that an intervention presumed to be beneficial will not have unanticipated side effects. A vivid example is the recommendation to drink milk during pregnancy, directed at combating the effects of suboptimal nutrition, a clear correlate of low birth weight, and therefore presumed beneficial. However, a large proportion of women, especially nonwhites, have lactose malabsorption (Paige, Bayless, and Graham, 1973); malabsorption is also suspected to hamper the absorption of other nutrients. Thus, an intervention directed at removing a well-accepted cause of low birth weight may be beneficial in theory but detrimental in practice.

Recommendations

Special attention should be given to factors of possible etiologic significance in initiating premature labor and low birth weight, and about which little research has been done. These factors are physical exercise and diet before pregnancy, physical and psychologic stress during pregnancy, and diet. The definition of good diet is difficult, however, due to the high degree of food processing, chemical contamination, and food impurities, and the changing concept of healthy food. A possible alternative approach could be to determine the effect of a diet that does not contain foods widely suspected to be harmful, such as sugar. First priority should be devoted to seeking and preventing the causes of prematurity. Without such information, reducing the incidence of prematurity depends upon the availability of interventions to detect and delay onset of labor, whatever its cause. Unfortunately, the effect of those medical interventions, and others such as induction of labor, on birth weight and gestation age have not yet been adequately investigated.

Whether studies should be observational or experimental depends on the amount of knowledge of the specific factor and the

feasibility of the research. In experimental studies, the intervention should be designed so that, if found efficacious, it can be easily applied in an ordinary clinical practice.

As the possibility of different types of interventions is large, research should be directed toward measures thought to be beneficial to health in general. Then, even if the interventions do not prove useful in improving pregnancy outcome, they should be likely to benefit the mother in the long run and less liable to be harmful. When these criteria are used, research on psychologic factors, extent of social and financial security, and the role of exercise, diet, and smoking become increasingly important.

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Appendix A: Method of Calculating Attributable Risks

THE POPULATION ATTRIBUTABLE RISKS shown in Table A-1 were calculated as follows:

$$\text{percentage} = 100 \times \frac{b\left(\frac{R_1}{R_2} - 1\right)}{b\left(\frac{R_1}{R_2} - 1\right) + 1},$$

TABLE A-1
Attributable Risks in Population Due to Maternal Diseases (Not Pregnancy-Related)

Disease	Black*	White*	All Pregnancies†
Organic heart disease	0.76	2.1	0.87
Tuberculosis	0.08	0.03	0.13
Pneumonia	0.02	0.26	
Bronchial asthma	0.28	0.44	
Diabetes	0.08	0.23	0.94
Hyperthyroidism	0.19	0.53	
Glomerulonephritis	0.14	0.30	0.59‡
Kidney-urinary bladder infection + fever	0.71	0.85	2.27
Leiomyoma	0.35	0.06	0.11
Psychosis or neurosis	0.69	1.3	0.41§
Alcoholism	0.15	0.43	
Drug habituation	0.11	0.30	
Neurologic diseases	0.11	0.28	
Cholelithiasis	0.05	0.14	
Hepatitis	0.03	0.22	
Appendicitis	0.06	0.23	
Virus infections			1.20
Shock or fright			1.08
Syphilis			0.28
Hyperemesis			0.52
Other chronic illness			3.27
Other acute illness			2.72
Surgical operation			1.83
Physical injury			1.12
Cervical lesion			0.48
Uterine anomaly			0.82
Vaginal infection			1.17
Total	3.8	7.7	19.81

*Niswander, et al, 1972.
†Ontario Perinatal Mortality Study Committee, 1967.
‡Chronic renal disease.
§Under psychiatric care.

where b = proportion of mothers with the factor; R_1 = rate of low birth weight or pre-term infants among mothers with the factor; and R_2 = rate among mothers without the factor. In the case of toxemia (Shapiro, Schlesinger, and Nesbitt. 1968) and heart volume (Unnerus, 1959; Terris and Gold, 1969) instead of R_1/R_2, the relative risk of the case-control study was calculated (a'd'/c'b': see MacMahon and Pugh, 1970, pp. 270–71).

The effect of weight gain (Niswander and Gordon, 1972) was counted by applying the low birth weight rate in the group that gained the most weight to the rate in all weight gain groups.

The following studies were included:

Niswander and Gordon, 1972. Twelve teaching hospitals in the United States, 1959–1965. About 19,000 single white births and 20,000 single black births. Only those diseases in which the rate was increased were included. R_2 = rate among mothers without the particular disease.

Ontario Perinatal Mortality Study Committee, 1967. pp 177, 185. Ten teaching hospitals, Ontario, Canada 1960. About 26,000 single births. R_2 = rate among the mothers without any of the diseases studied.

Shapiro, Schlesinger, and Nesbitt, 1968. pp 95, 326. Upstate New York 1960–62, number of births not given. Toxemia was defined as pre-eclampsia, eclampsia and hypertension.

Butler and Alberman. 1969. pp. 50–355. England and Wales 1959, births during one week. Toxemia was defined as moderate or severe pre-eclampsia.

Kaltreider and Johnson, 1976. Baltimore, U.S.A., one hospital 1955–60, about 8600 births, in which mother's Hb was known (=98%).

Page, 1966. pp. 44–52. California, U.S.A., 1961–1962, about 116,000 births.

Meyer, Jonas, and Tonascia. 1976. The figures are means of five different epidemiologic studies done in the United States, Canada and England in 1960's.

Unnerus, 1959. Helsinki, Finland 1958, about 800 births. Case control study.

Räihä and Kauppinen, 1963. Helsinki, Finland, 1959–61, about 12,000 births.

Terris and Gold, 1969. New York, U.S.A., about 1967, one hospital, about 300 births. Case control study. Since the study did not give the frequency of the condition, the attributable risk was calculated using the figure given in the study of Räihä and Kauppinen (1963).

Appendix B: Intervention Studies listed in Table 3

Prevention and Therapy of Premature Labor by Drugs

Briscoe, C.C. 1966. Failure of Oral Isoxsuprine to Prevent Prematurity. *American Journal of Obstetrics and Gynecology* 95: 885–886.

Castren, O., Gummerus, M., and Saarikoski, S. 1975. Treatment of Imminent Premature Labour. Acta Obstetrica Gynecologica Scandinavica 54: 95–100 (Two interventions).

Dieckmann, W.J., Davis, M.E., Rynkiewicz, L.M., and Pottinger, R.E., 1953. Does Administration of Diethylstilbestrol During Pregnancy have Therapeutic Value? *American Journal of Obstetrics and Gynecology* 66: 1062–1081.

Ferguson, J.H. 1953. Effect of Stillbestrol on Pregnancy Compared to the Effect of a Placebo. *American Journal of Obstetrics and Gynecology* 65: 592–600.

Fuchs, F., and Stakemann, G., 1960. Treatment of Threatened Premature Labor with Large Doses of Progesterone. *American Journal of Obstetrics and Gynecology* 79: 172–176.

Ingemarsson, I. 1976. Effect of Terbutaline on Premature Labor. A Double-Blind Placebo-Controlled Study. *American Journal of Obstetrics and Gynecology* 125: 520–524.

Johnson, J.W.C., Austin, K.L., Jones, G.S. et al. 1975. Efficacy of 172-Hydroxyprogesterone Caproate in the Prevention of Premature Labor. *The New England Journal of Medicine* 293: 675–680.

Lauersen, N.H., Merkatz, I.R., Tejani, N. et al. 1977. Inhibition of Premature Labor: a Multicenter Comparison of Ritodrine and Ethanol. *American Journal of Obstetrics and Gynecology*. 127: 837–845.

LeVine, L. 1964. Habitual Abortion: A Controlled Study of Progestational Therapy. *Western Journal of Surgery, Obstetrics and Gynecology* 72: 30–36.

Mathews, D.D., Friend, J.B., and Michael, C.A. 1967. A Double-Blind Trial of Oral Isoxuprine in the Prevention of Premature Labour. *The Journal of Obstetrics and Gynaecology of The British Commonwealth* 74: 68–70 (Two interventions).

Walters, W.A.W. 1977. A Trial of Oral Ritodrine for the Prevention of Premature Labor. *British Journal of Obstetrics and Gynaecology* 84: 26–30.

Watring, W.G., Benson, W.L., Wiebe, R.A. et al. 1976. Intravenous Alcohol — A Single Blind Study in the Prevention of Premature Delivery: A preliminary report. *Journal of Reproductive Medicine* 16: 35–38.

Wesselius-deCasparis, A., Thiery, M., Yolesian, A. et al. 1971. Results of Double-Blind, Multicentre Study With Ritodrine in Premature Labour. *British Medical Journal* 3: 144–147.

Zlatnik, F.J., and Fuchs, F. 1972. A Controlled Study of Ethanol in Threatened Premature Labor. *American Journal of Obstetrics and Gynecology* 112: 610–612.

Prophylactic Administration of Iron and/or Vitamins

Baumslag, N., Edelstein, T., and Metz, J. 1970. Reduction of Incidence of Prematurity by Folic Acid Supplementation in Pregnancy. *British Medical Journal* 1: 16–17.

Dieckmann, W.J., Adair, F.L., Michel, H. et al. 1944. Calcium, Phosphorus, Iron and Nitrogen Balances in Pregnant Women. *American Journal of Obstetrics and Gynecology* 47: 357–368.

Elias, H.L. 1936. A Clinical Study of the Influence of Vitamin B Supplements 2: On Maternal Health During Gestation and Labor. *Journal of Pediatrics* 8: 352–361.

Fletcher, J., Gurr, A., Fellingham, F.R. et al. 1971. The Value of Folic Acid Supplements in Pregnancy. *The Journal of Obstetrics and Gynaecology of the British Commonwealth.* 78: 781–785.

Fleming, A.F., Martin, J.D., Hahnel, R. et al. 1974. Effects of Iron and Folic Acid Antenatal Supplements on Maternal Haematology and Fetal Well-being. *Medical Journal of Australia* 2: 429–436.

Giles, P.F., Harcourt, A.G., and Whiteside, M.G. 1971. The Effect of Prescribing Folic Acid During Pregnancy on Birth Weight and Duration of Pregnancy. A Double-Blind Trial. *Medical Journal of Australia* 2: 17–21.

Hillmann, R.W., Caband, P.G., Nilsson, D.E. et al. 1963. Pyridoxine Supplementation During Pregnancy. Clinical and Laboratory Observations. *American Journal of Clinical Nutrition* 12: 427–430.

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quirements During Pregnancy. *Journal of the Royal College of General Practitioners* 26: 228–230.

Willoughby, M.L.N. 1967. An Investigation of Folic Acid Requirements in Pregnancy II. *British Journal of Haematology* 13: 503–509.

Completing Diet by High-Quality Food or Artificial Protein Diets + Iron and Vitamins

Ebbs, J.H., Tisdall, F.F., and Scott, W.A. 1942. The Influence of Prenatal Diet on the Mother and Child. *The Milbank Memorial Fund Quarterly* 20: 35–46.

Higgins, A.C. 1973. Montreal Diet Dispensary Study. *In Nutritional Supplementation and the Outcome of Pregnancy.* pp. 93–110. Washington: National Academy of Sciences.

Tompkins, W.T., Mitchell, R.McN., and Wiehl, D.G. 1955. (Op. cit.)

Health Education on Diet

Berry, K., and Wiehl, D.G. 1952. An experiment in Diet Education During Pregnancy. *The Milbank Memorial Fund Quarterly* 30: 119–151.

Cameron, C.S., and Graham, S. 1944. Antenatal Diet and Its Influence on Still-Births and Prematurity. *Glasgow Medical Journal* 142: 1–7.

Health Education on Smoking

Donovan, J.W. 1977. Randomised Controlled Trial of Anti-Smoking Advice in pregnancy. *British Journal of Preventive and Social Medicine* 31: 6–12.

Hospital Rest in Twin Pregnancies

Weeks, A.R.L., Menzies, D.N., and Boer, de, C.H. 1977. The Relative Efficacy of Bed Rest, Cervical Suture and No Treatment in the Management of Twin Pregnancy. *British Journal of Obstetrics and Gynaecology* 84: 161–164.

Prevention of Premature Labor by Cervical Suture in Twins

Weeks, A.R.L., Menzies, D.N., and Boer, de, C.H. 1977. (Op. cit.)

Preparation of this report was supported in part by the Robert Wood Johnson Foundation; USDHEW Grant 5 P50 HS01964 from the National Center for Health Services Research to The Johns Hopkins University Health Services Research and Development Center; USDHEW Grant RR05445 from the Biomedical Research Support Branch Division of Research Facilities and Resources to The Johns Hopkins University School of Hygiene and Public Health; and the Finnish-Norwegian Medical Foundation.

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