Reviews Analyses

Bulletin of the World Health Organization, **65** (5): 663–737 (1987)

Determinants of low birth weight: methodological assessment and meta-analysis

M. S. KRAMER[1]

It is generally recognized that low birth weight can be caused by many factors. Because many questions remain, however, about which factors exert independent causal effects, as well as the magnitude of these effects, a critical assessment and meta-analysis of the English and French language medical literature published from 1970 to 1984 were carried out. The assessment was restricted to singleton pregnancies of women who lived at sea level and who had no chronic illnesses. Extremely rare factors were also excluded, as were complications of pregnancy. In this way, 43 potential determinants were identified. A set of a priori *methodological standards were established for each potential determinant. Studies that satisfactorily met (SM) or partially met (PM) these standards were used to assess the existence and magnitude of an independent causal effect on birth weight, gestational age, prematurity, and intrauterine growth retardation (IUGR).*

A total of 921 relevant publications were identified, of which 895 were successfully located and reviewed. Factors with well-established direct causal impacts on intrauterine growth include infant sex, racial/ethnic origin, maternal height, pre-pregnancy weight, paternal weight and height, maternal birth weight, parity, history of prior low-birth-weight infants, gestational weight gain and caloric intake, general morbidity and episodic illness, malaria, cigarette smoking, alcohol consumption, and tobacco chewing. In developing countries, the major determinants of IUGR are Black or Indian racial origin, poor gestational nutrition, low pre-pregnancy weight, short maternal stature, and malaria. In developed countries, the most important single factor, by far, is cigarette smoking, followed by poor gestational nutrition and low pre-pregnancy weight. For gestational duration, only pre-pregnancy weight, prior history of prematurity or spontaneous abortion, in utero *exposure to diethylstilbestrol, and cigarette smoking have well-established causal effects, and the majority of prematurity occurring in both developing and developed country settings remains unexplained.*

Modifiable factors with large effects on intrauterine growth or gestational duration should be targeted for public health intervention in the two settings, with an emphasis on IUGR in developing countries and prematurity in developed countries. Future research should focus on factors of potential quantitative importance for which data are either unavailable or inconclusive. In developing countries, the most important of these for intrauterine growth are caloric expenditure (maternal work), antenatal care, and certain vitamins and trace elements. For prematurity, especially in developed countries, factors deserving further study include genital tract infection, antenatal care, maternal employment and physical activity, and stress and anxiety.

[1] Associate Professor, Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Faculty of Medicine, 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada.

INTRODUCTION

What is low birth weight?

In both developed and developing countries, birth weight is probably the single most important factor that affects neonatal mortality, in addition to being a significant determinant of post-neonatal infant mortality and of infant and childhood morbidity (*1*). Thus, birth weight has long been a subject of clinical and epidemiological investigations and a target for public health intervention. In particular, considerable attention has been focused on the causal determinants of birth weight, and especially of low birth weight (LBW), in order to identify potentially modifiable factors.

Low birth weight is defined by WHO as a birth weight less than 2500 g (before 1976, the WHO definition was less than or equal to 2500 g), since below this value birth-weight-specific infant mortality begins to rise rapidly (*2–5*). However, plots of the cumulative frequency distribution of birth weight show two different normal distributions and 2000 g has been suggested as a lower cut-off point (*6*).

Birth weight is governed by two major processes: duration of gestation and intrauterine growth rate. LBW is thus caused by either a short gestation period or retarded intrauterine growth (or a combination of both). Prematurity is usually defined as a gestational age of less than 37 weeks. Although intrauterine growth retardation (IUGR), which is also referred to as "small-for-gestational-age" or "small-for-dates," has no generally accepted standard definition, the following are commonly used: birth weight less than 10th (or 5th) percentile for gestational age; birth weight less than 2500 g and gestational age greater than or equal to 37 weeks; and birth weight less than 2 standard deviations below the mean value for gestational age.

Birth weight and gestational age each have an important effect on fetal and neonatal mortality (*7–9*). Both types of LBW infants have an increased risk of developing cerebral palsy, although prematurity appears to carry a greater risk (*10*). Premature infants, especially those weighing less than 1500 g (also called very-low-birth-weight infants), have a far greater risk of developing hyaline membrane disease, apnoea, intracranial haemorrhage, sepsis, retrolental fibroplasia, and other conditions related to physiological immaturity. On the other hand, IUGR infants are far more likely to exhibit growth deficiencies (*11–13*), which appear to be permanent (*14*). Short stature can lead not only to lowered self-esteem, but can also impair physical working capacity, a sequela of special importance in developing countries, where individual and societal welfare may depend on the ability to carry out manual labour. Subtle neurocognitive deficiencies may also be more common in IUGR infants (*14, 15*).

At least two different subtypes of IUGR can be distinguished: "disproportional" or "wasted" IUGR infants with relatively normal length and head circumference for their gestational age, but who are thin, with low weight-for-length and skinfold measurements; and "proportional" or "stunted" IUGR infants with proportional reductions in weight, length, and head circumference (*16, 17*). The distinction, which may be related to an earlier and more persistent impairment in growth in the stunted group, appears to be prognostically important. "Wasted" IUGR infants exhibit greater postnatal catch-up growth and less severe cognitive deficits than those who are stunted (*18*).

Thus, the clinical importance of LBW may depend on its type: prematurity or IUGR; "wasted" or "stunted" IUGR. It may also depend, however, on the primary cause. As Habicht et al. (*19*) have emphasized, the association between LBW and mortality, morbidity, and performance does not necessarily mean that eliminating a given cause will result in lower morbidity or mortality or improved performance. For example, an infant who has IUGR as a result of an intrauterine rubella infection will have a much poorer prognosis than another of similar birth weight who is small because his mother is short.

How common is low birth weight?

The overall public health importance of LBW is determined not only by the risks for subsequent morbidity and mortality, but also by how frequently it occurs, i.e., its prevalence in a given population. The best available global estimates of mean birth weight and the prevalence of LBW were produced by WHO in 1979 (*20*) and updated to 1982 (*21*) (Table 1). Of the 127 million infants born in the world in 1982, 20 million (16%) were estimated to weigh less than 2500 g, and over 90% of these infants were born in developing countries, a function not only of the higher birth rate in these countries but also of their much higher prevalence of LBW.

The lowest birth weights were reported for Asia, with mean values ranging from about 2700–2800 g in the Indian subcontinent to 3200–3300 g in China and Japan, and corresponding LBW rates of 30–40% and 5–6%, respectively. In West Africa, the range of mean birth weight was 2800–3000 g with an LBW rate of 10–20%, while in North Africa, the corresponding values were 3200–3300 g and 5–15%. The range of mean birth weights was 2900–3100 g with an LBW rate of 10–18% in Central America and, respectively, 3100–3300 g and 9–12% in South America. The highest birth weights were reported

Table 1. Mean birth weights and low birth weight (LBW) prevalence by country[a]

Country	Mean birth weight (g)	LBW (%)
North America		
Canada	3327	6.0
USA	3299	6.9
Europe		
Czechoslovakia	3327	6.2
France	3240–3335	5.6
Federal Republic of Germany	3356	5.5
Hungary	3144–3162	11.8
Italy	3445	4.2
Norway	3500	3.8
Sweden	3490	4.0
United Kingdom	3310	7.0
Latin America		
Brazil	3170–3298	9.0
Chile	3340	9.0
Colombia	2912–3115	10.0
Guatemala	3050	17.9
Mexico	3019–3025	11.7
Africa		
Egypt	3200–3240	7.0
Kenya	3143	12.8
Nigeria	2880–3117	18.0
Tunisia	3210–3376	7.3
United Republic of Tanzania	2900–3151	14.4
Zaire	3163	15.9
Asia		
China	3215–3285	6.0
India	2493–2970	30.0
Indonesia	2760–3027	14.0
Iran	3012–3250	14.0
Iraq	3540	6.1
Japan	3200–3208	5.2
Malaysia	3027–3065	10.6
Pakistan	2770	27.0

[a] See: WORLD HEALTH ORGANIZATION. The incidence of low birth weight: a critical review of available information. *World health statistics quarterly*, **33**: 197–224 (1980); and WORLD HEALTH ORGANIZATION. The incidence of low birth weight: an update. *Weekly epidemiological record*, **59**: 205–211 (1984).

for North America and western Europe (mean birth weight, 3300–3500 g; LBW rates, 4–8%).

Unfortunately, most of the studies upon which these data are based do not distinguish between prematurity and IUGR. In most developing countries the majority of infants are born at home, women are often unsure of the date of their last menstrual period, and investigators are generally content with accurate birth weight measurements on a defined population. However, analysis by Villar & Belizan (*17*) of data from 11 different regions in developed countries and 25 areas in developing countries indicates that in the former most LBW is due to IUGR, whereas in developed countries (especially those with the lowest LBW rates) most is due to prematurity. Differences in the IUGR rates of developing and developed countries are far greater than those for prematurity, with relative risks of 6.6 and 2.0, respectively.

What are the causes of low birth weight?

The causes of LBW have been the focus of a vast number of investigations over the last few decades, and with the general availability of fairly accurate infant weighing devices, birth weight and its determinants have come under intense global scrutiny. As a result, it is now acknowledged that many factors can influence the length of gestation or the rate of intrauterine growth, i.e., that the causality of LBW is "multifactorial". None the less, there is considerable confusion and controversy about the factors that have independent effects on LBW as well as the quantitative importance of those effects. One of the reasons for this has been a failure to distinguish between IUGR and prematurity. Thus if the causal determinants differ for IUGR and prematurity the results of a study of the principal etiological determinants of LBW in a country where most cases arise from IUGR will probably differ from those of a similar study in another country where most LBW infants are premature.[a] Secondly, a given factor might affect the middle or upper range of the birth weight or gestational age distribution but not those infants identified as IUGR or premature. Furthermore, changes in mean birth weight may be important even if there is no change in the LBW rate, since the lowest infant mortality is associated with birth weights of 3500–4000 g (*2*, *3*, *5*), and any increase in the proportion of birth weights below 3500 g might increase infant mortality. There is great diversity, some investigators reporting on mean birth weights and gestational ages and others on the rates of LBW, IUGR, or prematurity, and this could explain some of the discrepant findings.

[a] Within certain populations, IUGR and prematurity rates may be closely linked. For example, Spiers & Wacholder (*22*) have reported correlation coefficients >0.70 for IUGR and prematurity rates for defined age and parity categories of White women in North Carolina and Washington State. For North Carolina Black women, on the other hand, the correlation was low and statistically not significant. These findings suggest that the determinants of IUGR and prematurity may overlap in some groups.

Perhaps the most important reason for the discrepant findings has been the failure to distinguish markers or associated factors from true causal determinants. Many of the potential determinants are highly associated and their effects are thus mutually confounded. Failure to control for confounding variables can lead to erroneous associations between a factor and IUGR or prematurity. For example, anaemia is highly associated with undernutrition, and if insufficient maternal caloric intake is a true cause of IUGR, failure to control for such intake will produce an association between anaemia and IUGR. Anaemia, however, may merely be a marker of poor maternal nutrition, and not a true causal determinant of IUGR. Thus if anaemia has no independent effect on intrauterine growth, routine use of iron supplements during pregnancy will have no impact on the rate of IUGR.

Finally, the large number of factors that could theoretically influence birth weight indicates that each of them may have a rather small individual impact. Unequivocal demonstration that such small effects are statistically significant requires the use of large sample sizes as well as control for confounding and other non-random sources of variation. Unfortunately, readily available and reliable sources of data on large sample sizes for defined population groups, such as birth certificates in most developed countries, often lack key clinical information, e.g., height, pre-pregnancy weight, gestational weight gain, and smoking and drinking habits. Conversely, most clinical studies carried out in single hospitals or clinics are often quite satisfactory for measuring potentially important variables, but the sample sizes are usually insufficient to detect small effects, and may also be unrepresentative.

Fortunately, however, a few large cohort studies have been carried out that adequately meet both criteria: examples include the British Perinatal Mortality Survey of 1958, the U.S. Collaborative Perinatal Project carried out in the 1960s, and the British Births Survey of 1970. Other large cohort studies have been aimed at assessing specific factors, e.g., gestational caloric intake (*23*). Also, randomized clinical trials have enabled the impact of factors that are susceptible to experimental intervention to be measured, without usually requiring adjustment for potential confounders.

What more do we need to know about the causes of low birth weight?

Despite the profusion of studies over the last 20 years that have investigated the causes of low birth weight, the conclusions are often controversial; a methodological critique and synthesis may therefore be helpful. Such an approach should address the following ten questions:

—What are the factors that should (or should not) be considered as possible determinants?
—For each factor, what methodological criteria should be satisfied by studies designed to assess its impact?
—How well do existing studies of each factor measure up to these criteria?
—If the best available information for each factor is considered, what factors have an independent effect on gestational age, prematurity, birth weight, and IUGR?
—If a factor has an independent effect on gestational age, prematurity, birth weight, or IUGR, what is its magnitude?
—Is there evidence of interaction among causal factors or between causal factors and other important variables?
—By considering the prevalence of each of the identified causal determinants in different population groups, what is the quantitative, population-based contribution of each to gestational age, prematurity, birth weight, and IUGR?
—Towards which potentially modifiable determinants should clinical or public health interventions be aimed in order to prolong gestational duration or improve intrauterine growth?
—For which potential determinants are the data inconclusive?
—How should future research on inconclusive factors be improved in order to permit better definition of their respective roles?

This article attempts to answer these questions based on data published in English and French from 1970 to 1984.

METHODS

Literature search

The literature search was accomplished as follows. The subject catalogue of the WHO library was first searched for monographs or books published since 1970 dealing with birth weight, gestational age, LBW, prematurity, IUGR, and their determinants. A similar search was carried out for review articles cited in *Index Medicus* over the same period. These were supplemented by a MEDLINE computer search covering the years 1982–84. Finally, a "snowball" procedure was used, whereby the references cited in each article or book chapter located were scrutinized for further reports published since 1970, each of which was further examined for relevant references, and so on. No attempts were made to obtain copies of

research theses, internal institution reports or newsletters, or proceedings of congresses.

Each report that contained data that had a bearing on the association between one or more factors and either intrauterine growth or gestational duration was assessed as described in the following section. Many studies of LBW, however, reported data related to extraneous factors that were not the primary focus of the particular investigation. For example, a study of the effects of maternal cigarette smoking during pregnancy might also contain data on age, parity, or socioeconomic status. In many instances, such data, particularly if drawn from a large and methodologically well-designed study, are often more valuable sources of these "secondary" factors than other investigations where such factors are the primary focus.

Use of such an assessment procedure considerably increased the number of sources of data on each factor, and the number of reports examined for all the factors was therefore much greater than the number of individual studies. The method, although iterative and time-consuming, nevertheless maximized the information examined and increased the validity and precision of any conclusions drawn.

No claim is made for the completeness of the literature survey. Many articles containing potential determinants of prematurity and IUGR have probably not been included, especially those in less frequently cited sources and those published between 1970 and 1975. Within these limitations, however, the search method was reasonably comprehensive and relatively objective.

Choice of factors for assessment

Because the number of factors that might influence the duration of gestation or intrauterine growth is almost limitless, criteria were required to define the boundaries of the assessment. In order to focus on causal determinants in previously healthy individuals, data for women with underlying chronic illnesses were not considered. Also, in order to standardize the potential for the delivery of oxygen to the fetus, pregnancies among women living at high altitude were excluded. Compared with singleton pregnancies, multiple pregnancies are subject to additional restrictions in intrauterine growth (*24*) and these were also not considered. The assessment was therefore restricted to reports of singleton pregnancies among women not living at high altitude who had no underlying chronic illness.

A further limiting criterion was the potential public health impact of a factor, which depends on both the magnitude of its effect, e.g., the number of grams of birth weight attributable to it or the relative risk of IUGR, and its prevalence in the population. Extremely rare (low-prevalence) factors are thus likely to have little impact on a whole population even if they are associated with huge risks of prematurity or IUGR. Although such factors are of great importance to the individual women concerned, as well as to those who care for them during pregnancy, they are not responsible for a significant portion of the variation within population groups or for differences between two or more groups. An example is congenital malformation of the genital tract: although 30% of women with such malformations may give birth to LBW infants, their prevalence (0.13% and 0.31% in two large series) is so low that they account for only a trivial portion of LBW in the population (*25*, *26*).

The final group of factors that were excluded may be more controversial and were related to medical complications during pregnancy. Many investigators who studied the causes of prematurity or IUGR have included conditions such as toxaemia, pregnancy-related hypertension, abruptio placentae, placenta previa, and premature rupture of the membranes. These conditions should properly be considered, however, as intermediate *outcomes* of pregnancy (*27*). Thus, for example, if genital infection leads to premature rupture of the membranes, and hence to premature labour and delivery, control for premature rupture will diminish, and perhaps even eliminate, the significant effect of infection.

The following 43 "factors" (or groups of factors) therefore remained for assessment:

A. *Genetic and constitutional factors*
- —Infant sex.
- —Racial/ethnic origin.
- —Maternal height.
- —Maternal pre-pregnancy weight.
- —Maternal haemodynamics.
- —Paternal height and weight.
- —Additional genetic factors.

B. *Demographic and psychosocial factors*
- —Maternal age.
- —Socioeconomic status (education, occupation, and/or income).
- —Marital status.
- —Maternal psychological factors.

C. *Obstetric factors*
- —Parity.
- —Birth or pregnancy interval.
- —Sexual activity.
- —Intrauterine growth and gestational duration in prior pregnancies.
- —Prior spontaneous abortion.
- —Prior induced abortion.
- —Prior stillbirth or neonatal death.

—Prior infertility.
—*In utero* exposure to diethylstilbestrol.

D. *Nutritional factors*
—Gestational weight gain.
—Caloric intake.
—Energy expenditure, work, and physical activity.
—Protein intake/status.
—Iron and anaemia.
—Folic acid and vitamin B_{12}.
—Zinc and copper.
—Calcium, phosphorus, and vitamin D.
—Vitamin B_6.
—Other vitamins and trace elements.

E. *Maternal morbidity during pregnancy*
—General morbidity and episodic illness.
—Malaria.
—Urinary tract infection.
—Genital tract infection.

F. *Toxic exposures*
—Cigarette smoking.
—Alcohol consumption.
—Caffeine and coffee consumption.
—Use of marijuana.
—Narcotic addiction.
—Other toxic exposures.

G. *Antenatal care*
—First antenatal care visit.
—Number of antenatal care visits.
—Quality of antenatal care.

Method of assessment

Two different methods of assessing the data are tenable. The first approach is unrestricted meta-analysis, by which all studies containing data that have a bearing on a given factor are analysed statistically as independent units. No prior selection is made; instead, an average effect for each factor is computed by weighting the magnitude of the effect reported in each study by the corresponding sample size. The total variance of individual effect magnitudes is then analysed to determine what proportion can be accounted for by sampling variation (the amount of variation expected to occur by chance under the null hypothesis that each study sample is drawn from a hypothetical population having a single effect magnitude). Only if considerable variance remains unexplained by sampling error are the studies themselves examined for differences in design and methodological rigour. In the second approach, *a priori* methodological standards are established for studies of each factor. Those that satisfactorily conform to the standards are then examined to yield a "best estimate" of the significance of the given factor and the magnitude of its effect.

The method actually used was a hybrid of both approaches. The "pure" meta-analytical procedure was rejected for a variety of reasons. Firstly, it can be assumed that failure to control for mutually confounding effects can lead to erroneous inferences about both statistical significance and effect magnitude. Thus poorly controlled studies will generally overestimate the magnitude of effects and the overall variance in effect magnitudes will be larger than that due to sampling variation alone under the null hypothesis that they are equivalent.

Furthermore, it is reasonable to establish methodological criteria for selecting studies for quantitative analysis. Just as individual studies select their subjects on defined demographic and clinical characteristics, an analysis of the results of a group of studies should also establish limits of eligibility. What meta-analysts rightly object to is the exclusion of studies *after* examining their reported results (*28*). *A priori* criteria, however, better focus the assessment and also render more manageable the statistical analysis.

Secondly, pure meta-analysis is best suited to assess the differences in means or proportions and correlation coefficients. However, for LBW, most of the effect magnitudes are either represented by regression coefficients (from multiple linear regression analyses of birth weight or gestational age) or by the relative risks of prematurity or IUGR, all of which are not easily treated using currently available meta-analytical techniques.

The following meta-analytical principle was, however, retained: the use of effect magnitudes weighted for sample size. For two studies of comparable methodological rigour, but different sample sizes, the effect magnitude reported in the larger study is more precise, i.e., less subject to sampling variation, and should, therefore, be weighted more heavily in estimating the overall magnitude of the effect.

The assessment procedure used can be outlined as follows:

—Methodological standards were established *a priori* for studies of each candidate factor listed in Table 2 (see pp. 670–1). The first four standards involve general aspects of research design: definition of the target population and study sample; description of study participation and follow-up rates; clear demonstration of the appropriate time sequence between the factor and outcome; and the use of an experimental design.

The remaining standards relate to potentially confounding variables that require control and are further described in the discussion of the individual factors.

—Studies that satisfactorily met (SM) or partially

met (PM) the standards were selected for further analysis. Studies classified as SM generally fulfilled the majority of the predetermined criteria, although perfect conformity was not required, while those classified as PM gave some attention to rigorous design and analysis but fulfilled less than half of the pre-set criteria. Since the specific standards differed for each factor, a study with data on two or more factors might well receive two or more different ratings. Also, ratings could differ even for a single factor according to the different outcomes under study (e.g., prematurity or IUGR).

—Based on the studies selected for further analysis, each factor was assessed for its independent causal effect on birth weight, gestational age, prematurity, and IUGR. An independent causal effect was taken to have been demonstrated if, on the basis of the combined evidence, the effect magnitude on any of these four outcomes was greater than zero and sampling variation could be excluded ($P<0.05$). If a factor had an independent effect on gestational duration (gestational age or prematurity), only those SM or PM studies that adjusted for gestational duration were used to assess the effects on birth weight. Of course, the definition of IUGR automatically includes gestational age. Where an effect on gestational duration was ruled out, however, LBW (<2500 g) was accepted as a proxy for IUGR.

—If a factor produced a causal effect, the difference attributable to that factor (number of grams of birth weight or weeks of gestation) was extracted. This difference could have been a difference in means from a randomized trial or matched cohort study, an adjusted difference obtained from an analysis of covariance, or a regression coefficient (slope) from a multiple linear regression analysis. For the rate of prematurity or IUGR, the corresponding effect magnitude extracted was the relative risk (or from case–control studies, the odds ratio) adjusted for potential confounders either by matching, the Mantel–Haenszel procedure, or a multiple logistic regression analysis.

It should be noted that the definitions of prematurity and IUGR varied among the studies. A "standard" definition for prematurity of less than 37 weeks gestational age and for IUGR of less than 10th percentile (of an appropriate standard) birth weight for gestational age was used. Studies that used slightly different definitions (e.g., ⩽37 weeks, ⩽36 weeks, or <38 weeks for prematurity; and <5th or <3rd percentile or ⩽−2 birth weight standard deviations for gestational age, or ⩽2500 g birth weight plus gestational age ⩾37 weeks for IUGR) were accepted under the assumption that the relative risks for prematurity or IUGR would not vary greatly as a result. The population-specific IUGR rates discussed below (under Synthesis, see p. 717), however, are based on the full-term LBW definition (<2500 g and ⩾37 weeks).

—The extracted values for the contribution of prematurity and IUGR to birth weight (in grams) and to gestational age (in weeks) as well as the relative risk (or odds ratio) were weighted using the study-specific sample sizes to arrive at a best estimate of these four effect measures for each factor.

—Using the available estimates for the prevalence of each demonstrated causal factor in different population groups, etiologic fractions (EFs) were calculated for prematurity and IUGR. EF is sometimes referred to as the population attributable risk and is calculated using the procedure described by Levin (*29*):

$$\mathrm{EF} = \frac{P(RR-1)}{P(RR-1)+1}$$

where P is the prevalence of the factor in the given population group and RR is the relative risk (or odds ratio).

The results of these steps are discussed under each factor in the following section.

FACTOR ASSESSMENT

Literature search

The literature search using the combined procedure described above identified a total of 921 publications. Of these, 895 (97.2%) were successfuly located and reviewed. As shown in Table 3, considerably more

Table 3. Number of publications located by year, 1970–84

Year	No. of publications
1970	32
1971	52
1972	41
1973	44
1974	38
1975	50
1976	47
1977	45
1978	69
1979	73
1980	83
1981	85
1982	72
1983	73
1984	91
Total	895

Table 2. Methodological standards used to assess published studies of 43 causal factors

Factor	Population sample	Participation follow-up	Cause vs. effect	Experimental design	Race/ethnicity	Height	Pre-pregnancy weight	Maternal birth weight, gestational age	Age	Socioeconomic status	Stress, anxiety	Parity
A. Infant sex[a]												
Race/ethnicity	×	×			—	×[b]	×[b]		×	×[b]		×
Maternal height	×	×			×	—	×[b]		×	×		
Pre-pregnancy weight	×	×			×	×[c]	—		×	×		
Haemodynamics	×	×	×[c]			×	×		×			
Paternal size	×	×			×	×	×		×	×		
Other genetic factors	×	×				×[b]	×[b]			×		
B. Maternal age	×	×			×	×	×		—			×[c]
Socioeconomic status	×	×			×[c]	×	×		×	—		×
Marital status	×	×			×[c]	×	×		×	×[c]		×
Psychological factors	×	×	×[b]		×				×	×	—	×
C. Parity	×	×			×				×[b]	×		—
Birth interval	×	×	×[b]		×					×		×
Sexual activity	×	×	×[c]						×	×		
Prior birth weight, gestational age	×	×				×	×	×				×
Prior spontaneous abortion	×	×					×					×
Prior induced abortion	×	×										×
Prior deaths	×	×										×
Prior infertility	×	×					×					×
In utero diethylstilbestrol	×	×					×	×			×	×
D. Gestational weight gain	×	×	×		×	×	×		×[d]	×		
Caloric intake	×	×	×	×	×	×	×		×[d]	×		
Physical activity	×	×				×	×		×[d]	×		
Protein	×	×	×	×[b]	×	×	×		×[d]	×		
Iron, anaemia	×	×	×	×[b]	×	×	×		×[d]	×		
Folate, vitamin B_{12}	×	×	×	×[b]	×	×	×		×[d]	×		
Zinc, copper	×	×	×	×[b]	×	×	×		×[d]	×		
Calcium, phosphorus, vitamin D	×	×	×	×[b]	×	×	×		×[d]	×		
Vitamin B_6	×	×	×	×[b]	×	×	×		×[d]	×		
Other nutrients	×	×	×	×[b]	×	×	×		×[d]	×		
E. General morbidity	×	×	×[c]				×			×		
Malaria[e]	×	×		×			×			×		×
Urinary tract infection	×	×							×	×		×
Genital tract infection[f]	×	×	×[b]	×					×	×		×
F. Cigarette smoking	×	×			×		×		×	×	×	
Alcohol use	×	×			×		×		×	×	×	
Caffeine, coffee	×	×			×		×		×	×	×	
Marijuana	×	×			×		×		×	×	×	
Narcotic addiction	×	×			×		×		×	×	×	×
Other toxic exposures	×	×			×				×	×	×	
G. First antenatal visit	×	×	×[c]	×	×		×		×	×		×
No. of antenatal visits	×	×	×[c]	×	×		×		×	×		×
Quality of antenatal care	×	×		×	×		×		×	×		×

[a] Infant sex should be unconfounded with other factors. Thus, PM and SM ratings were not assigned for studies of this factor.

[b] Standard must be met to receive SM rating.

[c] Standard must be met to receive PM or SM rating.

[d] Parity was accepted as a proxy for maternal age as a control variable in assessing these factors.

Birth interval	Prior LBW, pre-maturity	Prior spon-taneous abortion	Ges-tational weight gain	Caloric intake	Maternal work	Protein	Iron, anaemia	Genital tract infection	Smoking	Alcohol	Ante-natal care	Treatment
×			×[b, g]	×[b, g]	×			×	×	×	×	
			×[g]	×[g]								
			×[g]	×[g]					×			
									×	×		
									×	×		
			×[g]	×[g]					×	×	×	
×			×[g]	×[g]				×	×	×	×	
×			×[g]	×[g]				×	×	×	×	
									×	×		
×								×	×	×		
—	×											
								×				
	—		×[g]	×[g]					×	×		
		—	×[g]	×[g]					×	×		
								×	×	×		
	×	×							×	×		
								×				
			—		×	×			×	×		
				—	—				×	×		
				×					×	×		
			×[c, g]	×[c, g]					×	×		
			×[c, g]	×[c, g]					×	×		
			×[c, g]	×[c, g]			×[c]		×	×		
			×[c, g]	×[c, g]					×	×		
			×[c, g]	×[c, g]					×	×		
			×[c, g]	×[c, g]					×	×		
			×[c, g]	×[c, g]					×	×		
									×	×		×
			×[g]	×[g]	×							×
								×				×
								—				×
									—	×		
									×[b]	—		
									×[b]	×[b]		
									×[b]	×[b]		
									×[b]	×[b]		
									×	×		
									×	×		
									×	×		
									×	×		

[c] Control for rural versus urban residence was an additional standard for studies of malaria.

[f] Control for microorganisms other than the one under investigation was an additional standard for studies of specific infectious agents.

[g] Either gestational weight gain or caloric intake was accepted as a control variable in assessing these factors.

Table 4. Number of publications containing data that had a bearing on the 43 candidate factors

Factor	No. of publications
A. Genetic and constitutional factors	
Infant sex	66
Racial/ethnic origin	67
Maternal height	79
Maternal pre-pregnancy weight	74
Maternal haemodynamics	13
Paternal height and weight	6
Additional genetic factors	5
Subtotal	310
B. Demographic and psychosocial factors	
Maternal age	144
Socioeconomic status	113
Marital status	37
Maternal psychological factors	30
Subtotal	324
C. Obstetric factors	
Parity	120
Birth or pregnancy interval	26
Sexual activity	10
Intrauterine growth and gestational duration in prior pregnancies	27
Prior spontaneous abortion	37
Prior induced abortion	41
Prior stillbirth or neonatal death	24
Prior infertility	5
In utero exposure to diethylstilbestrol	8
Subtotal	298
D. Nutritional factors	
Gestational weight gain	61
Caloric intake	41
Energy expenditure, work, and physical activity	34
Protein intake/status	32
Iron and anaemia	42
Folic acid and vitamin B_{12}	27
Zinc and copper	16
Calcium, phosphorus, and vitamin D	8
Vitamin B_6	4
Other vitamins and trace elements	12
Subtotal	277
E. Maternal morbidity during pregnancy	
General morbidity and episodic illness	12
Malaria	4
Urinary tract infection	16
Genital tract infection	50
Subtotal	82
F. Toxic exposures	
Cigarette smoking	121
Alcohol consumption	35
Caffeine and coffee consumption	12
Use of marijuana	7
Narcotic addiction	14
Other toxic exposures	12
Subtotal	201
G. Antenatal care	
First antenatal care visit	26
Number of antenatal care visits	27
Quality of antenatal care	21
Subtotal	74
Overall total	1566

publications per year were located from 1978 onwards than during 1970–77. This probably reflects an increased interest in LBW and its causes, but may be an artefact of the search procedure. Although the majority of reports originated from developed countries in North America and western Europe, a large number also came from developing countries in Africa, Latin America, and south-east Asia, as well as from India. The number of publications for each of the 43 factors included in the assessment is shown in Table 4.[b]

Each of the 43 factors is assessed individually under the headings outlined above. In each case the discussion is divided into two parts: a brief background of possible biological mechanisms and the methodological standards used to evaluate the pertinent studies identified by the literature search, followed by the results of the assessment.

A. *Genetic and constitutional factors*

1. Infant sex

Background. The sex of the fetus is probably the easiest of the factors to evaluate. The sex ratio (the proportion of males is slightly higher than that of females) appears to be constant in different population groups and seems not to co-vary with the other factors analysed. By definition, confounding variables must be associated with the "exposure" factor (here, infant sex) and, independently of exposure, with the outcome. Since infant sex is not associated with any of the other factors being assessed, its relationship to gestational duration and intrauterine

[b] A list of all studies assessed for each of the 43 factors, along with their respective ratings (SM, PM, or neither), is available on request from the Nutrition Unit or the Maternal and Child Health Unit, World Health Organization, 1211 Geneva 27, Switzerland.

growth should be unconfounded. Study participation and drop-out rates should also be unrelated to sex. Furthermore, sex assignment should not be subject to measurement error or bias. No methodological standards are therefore required to study the effect of infant sex beyond an adequate description of the study sample. Thus, no SM or PM ratings were assigned for this factor, and all studies containing data on male–female differences in gestational age, prematurity, birth weight, or IUGR were included in the analysis.

The magnitude of the effect of sex on intrauterine growth, however, depends on the ultimate potential for such growth. Population groups that have birth-weight distributions shifted to the left (e.g., developing countries) exhibit smaller sex differences in birth weight, i.e., population group is an effect modifier, since the effect of the infant's sex on birth weight differs for individuals from different groups. Thus for birth weight the data should be analysed separately for populations with different birth-weight distributions. Since there is no reason, however, to expect a difference in the *relative* weight of male and female fetuses in different population groups, IUGR rates should not show such effect modification, and separate analysis is not required.

Results. Data on infant sex and its relationship to one or more of the outcomes were found in 66 studies. Practically all these studies concluded that the sex of the infant had no effect on gestational age or prematurity; however, males had a higher birth weight and lower risk of IUGR. Owing to small sample sizes, not all of the birth weight or IUGR differences were statistically significant.

Only two studies reported a statistically significant sex difference for gestational age or prematurity. Meyer et al. (*30*) found an adjusted rate for gestational age (<38 weeks) of 9.2% for males and 8.1% for females ($RR=1.14$) among 51 490 births in Ontario in 1960–61. Also, Hingson et al. (*31*) reported the opposite sex effect (partial correlation coefficient = +0.064) among 1690 women in Boston. Since many studies with equally large or larger samples found no sex difference in gestational duration, the results reported by Meyer et al. and Higson et al. may be due to sampling variation, especially in view of the small differences noted.

Only one study (*32*) reported a statistically significant difference in birth weight that favoured females; however, the larger study (*31*), of which this formed a part, found the opposite effect.

In assessing the magnitude of the birth-weight difference attributable to sex, consideration must be given to the population group. For example, in 15 studies on non-poor populations in developed countries (total sample size, 100 100), the sample size-weighted sex difference was 126.4 g; however, in 19 studies in developing countries (including two studies of poor urban Blacks in the USA), the comparable difference was 93.1 g, based on a total sample size of 47 341.

Nine studies provided data on the relative risk for LBW. Since, in the absence of gestational age differences, this should be similar to the relative risk for IUGR, the relative risks were weighted by the respective sample sizes (for the eight studies reporting sample sizes) to yield an overall estimate of 1.19 for the risk of IUGR in females versus males. In the ninth and largest of these studies, based on a large representative sample of total births in the USA in 1976 (*33*), there was no indication of the sample size, but the relative risk for LBW was 1.19. The three largest studies (*30*, *33*, *34*) reported relative risks of 1.19, 1.18, and 1.20, so we can be quite confident in assigning a relative risk of 1.19. If it is assumed that females constitute 48.5% of births, the etiologic fraction is given by:

$$EF = \frac{0.485(1.19-1)}{0.485(1.19-1)+1} = 0.084\ (8.4\%)$$

The results for infant sex are summarized in Table 5.

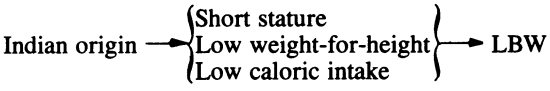
2. *Racial/ethnic origin*

Background. This factor focuses on whether true *genetic* differences exist in intrauterine growth or gestational duration between different racial or ethnic groups. That mean birth weights and LBW rates (mostly IUGR) differ across population groups is evident both from comparisons between countries and regions (see Introduction) and from large surveys in countries with an ethnically heterogeneous population, such as the USA (*33*, *35–37*). In view of the large cultural (environmental) differences between

Table 5. Results of the assessment of infant sex

Outcome	Effect
Gestational age	0 weeks
Prematurity	
Relative risk (for females)	1
Birth weight	
Developed country (male-female difference)	126.4 g
Developing country (male-female difference)	93.1 g
IUGR	
Relative risk (for females)	1.19
Etiologic fraction	8.4%

different ethnic groups, however, it is likely that differences in age or parity, maternal height and weight, socioeconomic status (education, occupation, or income), nutrition, potentially harmful habits (smoking and drinking), antenatal care, birth interval, and infection could explain a large part of the observed differences in birth weight. Isolation of a genetic effect of racial/ethnic origin thus requires control for these other variables. The methodological standards for this factor are shown in Table 2 (pp. 670–1). Studies were given an SM rating if in addition to fulfilling more than half of these standards they had also at least controlled for socioeconomic status, height, pre-pregnancy nutritional status, and either caloric intake or weight gain during gestation. These control variables are perhaps not correctly described as confounders, however, since some of them may represent intermediate outcomes of racial/ethnic factors. For example, if Indian women have smaller babies *because* they are shorter and thinner and consume fewer calories during pregnancy, their racial/ethnic origin may be an indirect cause of LBW and the true causal pathway may be as follows:



Proper statistical demonstration of such a causal pathway would require the use of path analysis. Although formal path analysis has not been applied to the study of race and LBW, the above causal pathway is consistent with accepted biological mechanisms and principles. Thus even if no genetic effect exists independently of these intermediate variables, racial/ethnic origin might still be an indirect cause of LBW. Nevertheless, if data on such variables are available, the indirect effect can be disregarded in apportioning birth weight deficits to various determinants.

Results. A total of 67 studies were located that had a bearing on the effects of racial or ethnic origin. Eight of these were rated as SM and 27 as PM. Because of other likely confounding differences between countries, to say nothing of the practical difficulties involved in international cooperative studies, virtually all of the reports compared groups within a single study country. Most dealt with White, Black, and Hispanic groups in the USA; White, West Indian, and Asian (mostly Indian or Pakistani) groups in the United Kingdom; Chinese, Indian, and Malaysian groups in Malaysia and Singapore; European, North African, and Middle Eastern groups in Israel; and French, North African, and West Indian groups in France.

Only one SM study had a bearing on the effect of racial/ethnic origin on mean gestational age or the rate of prematurity: compared to Whites, Berkowitz (*38*) reported a significantly decreased risk of prematurity among New Haven Blacks, but gestational age was determined by physical examination (Dubowitz score) rather than by the date of the last menstruation.

In the eight pertinent PM studies, the results were inconsistent. For example, in Ontario, Meyer et al. (*30*) found a slightly increased risk of prematurity for mothers who were born outside Canada and Europe; however, such mothers represented an ethnically mixed group, and the results are thus difficult to interpret. Weiner & Milton (*39*) reported a significant negative association between gestational age and Black race in Baltimore, USA. Similarly, Garn et al. (*40*) and Garn & Bailey (*41*) found that the gestational age distribution had been shifted to the left and that there was a higher rate of prematurity among Blacks than among Whites who participated in the U.S. Collaborative Perinatal Project; however, several important confounding variables were not controlled, and those that were controlled were considered only one at a time. In Paris, Kaminski et al. (*42*) reported an increased prematurity rate among West Indian and North African immigrants compared with that of native French women. A more recent study by Mamelle et al. (*43*), however, reported no significant effect of ethnic origin in two regions of France with large North African immigrant populations. Also, Hughes et al. (*44*) reported no differences in gestational age among Indians, Malays, and Chinese in Singapore, and similar results were obtained by Davies et al. (*45*) for Indians and Caucasians in Leicester, England.

There therefore appears to be no significant independent effect of racial or ethnic origin on duration of gestation. The number of methodologically rigorous studies is meagre, however, and future carefully controlled, large studies might detect small effects, especially between Blacks and Whites in the USA.

Four SM studies from the USA have a bearing on differences in mean birth weight among Blacks and Whites; three of them found a significant difference in favour of Whites, as did all four PM studies. Based on the only SM study (*46*) that provided quantitative data on the effect, Blacks exhibit a decrease of 108 g in birth weight. In a larger PM study (*47*), the reported deficit of 164 g for Blacks is likely to be an overestimate confounded by differences in maternal size, gestational weight gain, and smoking and drinking habits. It is of interest that another PM study of a large representative sample in the USA (*33*) found *higher* birth weights for Blacks than Whites for gestational ages less than 36 weeks, with a reversal thereafter. This suggests either a genetic difference in the intrauterine growth curve or an environmental factor that has a predominant impact during the last four weeks of gestation.

In an SM study from Israel, Yudkin et al. (*48*) found that women of North African ethnic origin had babies whose birth weight averaged 74 g higher than those of Western, Israeli, or Asian origin. However, in a PM study from Israel, Palti & Adler (*49* reported slightly lower birth weights for children of mothers of North African origin than those from Europe or the USA, but that North African birth weights were 143 g higher than those from Israel and 154 g higher than those of Asian origin.

The best data comparing birth weights of babies born to mothers of Indian or Pakistani origin and those of native Caucasians come from studies carried out in the United Kingdom. Unfortunately, control of confounding factors in these studies was insufficient to produce an SM rating. Of the five PM studies, all reported lower birth weights for Indian mothers (range, 100 g to 322 g). Because lower stature, weight-for-height, and gestational weight gain in Indians are likely to account for some of these differences in birth weight, the reported values are probably too large. Although it appears that part of the birth-weight deficit in Indians may have a genetic basis, this conclusion is not at all certain, and the magnitude of the deficit, if it exists, is likely to lie closer to 100 g than 300 g.

The possible birth-weight deficit in infants of Indian ethnicity is further supported by a PM study from Singapore (*44*). Here, the mean birth weight was lower for babies born to mothers of Indian origin than for those born to Malaysian or Chinese mothers, but in this instance also incomplete control for important potential confounding variables precludes definitive inferences.

Finally, one PM study (*50*) indicated higher birth weights among one tribe of North American Indians (Sioux) in north-western Ontario than among the general Canadian population, despite the lower socioeconomic status of this group. Mean birth weights were 107 g higher for males and 245 g higher for females, but incomplete control for confounding by other factors and the absence of other relevant studies of North American Indians prevent a more definitive conclusion.

Only one SM study was located that dealt with the ethnic effects on the risk of IUGR (or, since no ethnic differences in gestational age have been unequivocally demonstrated, of LBW) (*51*). In this study, a statistically significant adjusted odds ratio of 1.39 was reported for Blacks in Boston, USA. An increased risk in American Blacks was also found in five of six PM studies that contained pertinent data, but the magnitude of the risk reported is likely to be exaggerated by uncontrolled confounding differences between Blacks and Whites. If a relative risk of 1.39 is used and it is assumed that Black births constitute 16.5% of total births in the USA (*52*), the etiologic fraction for Blacks can be estimated as:

$$EF = \frac{0.165(1.39-1)}{0.165(1.391)+1} = 0.060$$

No SM studies that have a bearing on the relative risk of IUGR in other ethnic groups were found. PM studies on Israeli immigrants, Indians and Pakistanis living in the United Kingdom or south-east Asia, and North American Indians are consistent with the above-mentioned effects on birth weight. Thus the risk of IUGR appears to be elevated in Indians and Pakistanis and reduced in North-African Sephardic Jews and North American Indians, but residual confounding prevents an accurate estimate of the magnitude of these changes in risk.

In summary, despite the large number of studies that have a bearing on racial/ethnic differences in intrauterine growth, few have been of sufficient methodological rigour to permit estimates of an independent genetic contribution. Although it seems clear that Blacks, Indians, and Pakistanis have lower birth weights than European and North American Whites and that certain ethnic groups (e.g., North African Jews and North American Indians) are prone to larger babies (Table 6), the extent to which such ethnic differences are due to anthropometric differences, maternal nutrition, and intake of toxic substances during pregnancy has not been controlled enough to permit estimates of any independent genetic effects.

Table 6. Results of the assessment of racial/ethnic origin

Outcome	Effect
Gestational age	0 weeks
Prematurity	
Relative risk for all ethnic groups	1
Birth weight	
North American Blacks	−108 g[a]
Indians, Pakistanis	↓[b]
North African Sephardic Jews	↑[b]
Amerindians	↑[b]
IUGR	
Relative risk for North American Blacks	1.39
Etiologic fraction ($P = 0.165$)	6.0%
Indians, Pakistanis	↑[b]
North African Sephardic Jews	↓[b]
Amerindians	↓[b]

[a] Based on North American Caucasian standard.

[b] These increased (↑) and decreased (↓) risks represent general trends, but available data do not permit a quantitative estimate.

3. Maternal height

Background. A mother's height during pregnancy is determined by three factors: her genetic potential for growth; her state of skeletal maturity; and the effect of environmental influences during the period of skeletal immaturity. These factors differ in their modifiability. Genetic potential is presumably fixed, but delayed child-bearing among young adolescents and, over the long term, general improvements in nutrition might be achieved by interventions.

Maternal height could affect intrauterine growth through either genetic or environmental (physical) mechanisms. Part of the mother's genetic potential would be passed on to the fetus, and any deficit in her stature, regardless of its etiology, could impose physical limitations on the growth of the uterus, placenta, and fetus. On the other hand, there is no obvious biological mechanism whereby height could affect gestational age or prematurity.

There is no *a priori* reason to expect an effect caused by difference in height among different population groups. Diminished maternal height may well be one of the causes of the increased rate of LBW in many developing countries, whether caused by a true difference in genetic potential or prior stunting during the mother's childhood. However, because tall women are heavier and consume more calories than short women, and because pre-pregnancy weight and gestational nutrition may independently affect birth weight, these are potential confounders and should be controlled in assessing the independent effect of height. Another potentially important confounder is age, since adolescents who have not completed their growth will be shorter, on average, than more physiologically mature women, and because adolescence may also be independently related to birth weight or gestational age.

In ethnically mixed populations, height effects may be confounded by those due to true genetic differences in intrauterine growth or gestational duration. Racial/ethnic origin thus requires control. Finally, socioeconomic status is another important confounding variable that should be controlled, because women of lower socioeconomic status tend to be shorter than those of higher status and may be prone to impaired fetal growth or earlier delivery independent of their shorter stature.

The methodological standards appropriate for maternal height are shown in Table 2. An SM rating required control for pre-pregnancy weight in addition to meeting more than half of the overall standards.

Results. Seventy-nine studies were identified that contained data that had a bearing on the effect of maternal height on birth weight, gestational age, IUGR, or prematurity. Of these, 18 satisfactorily met (SM) the methodological standards described above, while an additional 17 partially met (PM) them. The assessment is based on these 35 studies, with priority given to those rated SM.

Only four SM or PM studies (total sample size, 7189) investigated the effect of maternal height on gestational age or prematurity, and these were unanimous in concluding that neither was affected by height. Thus control for gestational age is not required in studies of the effect of maternal height on birth weight (IUGR accounts for gestational age, by definition).

Of the 15 SM studies that reported mean birth weights, 10 found a statistically significant positive correlation with maternal height, while the five studies that reported no significant effect were based on relatively small sample sizes. Based on the eight SM studies that contained sufficient data, the effect on birth weight, weighted for sample size, was 7.8 g per centimetre maternal height (total sample size for the eight studies, 52 371).

Although among different population groups or subgroups there were no apparent differences in the effect of maternal height on birth weight, few studies from developing countries received an SM or PM rating. Niswander & Jackson, however, reported very similar effects of maternal height for the Whites and Blacks who participated in the U.S. Collaborative Perinatal Project (*53*). Results from less well-controlled studies (those rated neither SM nor PM) generally showed consistent maternal-height effects in different population groups. Thomson, for example, reported similar slopes for plots of birth weight against maternal height in several developed and developing countries (*54*).

Assessing the effect of maternal height on the relative risk for IUGR is statistically less straightforward, because such calculations usually require that both the exposure (height) and outcome (IUGR) be measured on a categorical (usually dichotomous) scale. Since height is measured on the continuous centimetre scale, the measurement is usually categorized (e.g., <150 cm or $\geqslant 150$ cm) in order to calculate relative risk. Alternatively, multiple logistic regression analysis can be used to measure the effect of a given difference in height (e.g., 10 cm) on the risk of IUGR.

The three SM studies with data on IUGR reported a significant inverse relationship between maternal height and the risk of IUGR, but in only two was the relative risk either calculated or calculable. Scott et al. studied 488 IUGR infants and 367 appropriate-for-gestational-age controls (*55*). They found that a difference between the mean height of the control mothers (162.2 cm) and this value minus 1 standard deviation (155.7 cm) was associated with a relative risk for IUGR of 2.03. In the much larger study by Meyer et al. (*30*), women <158 cm had an adjusted

relative risk of 1.18 for delivering a LBW infant compared with women of average height (158–172 cm). Oddly, women of height ⩾173 cm also had a slightly elevated risk.

Of the four PM studies that investigated IUGR, three found that low maternal height was a significant risk factor, but only for the large study by Fedrick & Adelstein (*56*) could a relative risk be calculated: women <157.5 cm had a relative risk of full-term (⩾37 weeks) LBW of 1.54 compared with women of average height (157.5–167.5 cm). A combination of the results from the two large SM and PM studies (*30*, *56*) gave a sample-size-weighted estimate for the relative risk of IUGR associated with a maternal height <157.5–158 cm of 1.27. Although no study that reported on LBW or IUGR in developing countries received an SM or PM rating, less well-controlled studies consistently found that the rates were lower for taller women.

To estimate the etiologic fraction, let us assume that maternal height follows a normal distribution and compute the prevalence of women of height <158 cm in three hypothetical population groups: a developed country (C_1) with mean height 162 cm, a developing country (C_2) with a mean height 156 cm, and a developing country (C_3) with a mean height 152 cm (e.g., India). The proportion (P) of women with heights below 158 cm are first calculated as follows, using the theory of the normal curve, assuming a standard deviation of 6 cm in all three cases:

$$C_1\colon Z_1 = \frac{158-162}{6} = -0.67; P_1 = 0.25$$

$$C_2\colon Z_2 = \frac{158-156}{6} = +0.33; P_2 = 1-0.37 = 0.63$$

$$C_3\colon Z_3 = \frac{158-152}{6} = +1.00; P_3 = 1-0.16 = 0.84$$

The corresponding etiologic fractions are then given by:

$$EF_1 = \frac{0.25(1.27-1)}{0.25(1.27-1)+1} = 0.063$$

$$EF_2 = \frac{0.63(1.27-1)}{0.63(1.27-1)+1} = 0.145$$

$$EF_3 = \frac{0.84(1.27-1)}{0.84(1.27-1)+1} = 0.185$$

In populations with a high prevalence of short stature, low maternal height therefore accounts for a sizeable proportion of IUGR infants. Once again, however, these calculations are based on the assumption that the relative risk is constant in different population groups. Although data are consistent with this assumption, new studies or refined analyses of existing data would be required to substantiate it. The results for maternal height are summarized in Table 7.

Table 7. Results of the assessment of maternal height

Outcome	Effect
Gestational age	0 weeks
Prematurity	
Relative risk for height <157.5–158 cm	1
Birth weight	7.8 g/cm
IUGR	
Relative risk for height <157.5–158 cm	1.27
Etiologic fraction for:	
$P=0.25$	6.3%
$P=0.63$	14.5%
$P=0.85$	18.5%

4. *Maternal pre-pregnancy weight*

Background. As with maternal height, maternal pre-pregnancy weight is influenced by both genetic and environmental factors. Even after correcting for stature, body weight is in part genetically determined, and genes that control adiposity or lean body mass could, theoretically, be expressed in the newborn. Even in the absence of such expression, however, maternal weight prior to conception reflects nutritional stores potentially available to the growing fetus.

Since heavier women are generally taller and have a greater caloric requirement than thinner women, isolation of the effect of maternal pre-pregnancy weight requires control for the confounding effects of maternal height and caloric intake (or gestational weight gain). Control for maternal height could be achieved either by using a weight-for-height index (e.g., body mass index, ponderal index, or relative weight), by stratifying the weight effect by height, or by including height as one of the independent variables, along with pre-pregnancy weight, in a multivariate analysis. Since teenagers recently past their menarche are likely to be thinner than older, physiologically more mature women, age should also be controlled.

Nicotine is a well-known appetite suppressant, and, all else being equal, women who smoke may be lighter than those who do not. Since cigarette smoking might also affect the outcome of pregnancy, it too needs to be controlled in the analysis. Finally, since weight is likely to co-vary with racial/ethnic origin and socioeconomic status, and since these factors may be linked to intrauterine growth or gestational duration independent of their relationship to weight,

these should also be controlled.

The methodological standards used to assess studies of pre-pregnancy weight are shown in Table 2 (pp. 670–1). In order to receive an SM or PM rating, the studies had to include some form of control for height. Also, only those studies were assessed that reported the effect of weight prior to conception, since weights measured during or after pregnancy include the effect of gestational weight gain. Most pre-pregnancy weights represent mothers' self-reports, usually obtained by interview during the course of antenatal care or immediately postpartum.

Results. Data on the effect of maternal pre-pregnancy weight were reported in 74 studies: 14 satisfactorily met (SM) the methodological requirements, while in another 13 they were partially met (PM).

Only one of the 14 SM and none of 13 PM studies included well-controlled data on the effect of pre-pregnancy weight on gestational age (*31*): pre-pregnancy weight was positively correlated with gestational age but only the r^2 and P values were reported, and the regression coefficient was not indicated.

The effect on prematurity has been reported more frequently, but here the categorization of pre-pregnancy weight (thin vs. normal, obese vs. normal) used in the calculation of relative risk differed considerably among the various studies. Three (*30*, *57*, *58*) of four SM studies and one PM study (*59*) reported a significantly elevated risk of prematurity among thinner women. In contrast, another PM study (*60*) found no reduction of risk for prematurity in grossly obese women compared with non-obese controls. Thus we can conclude that thin women have an elevated risk for delivery before 37 weeks, but that overweight women do not necessarily have a further reduction in prematurity over women of normal weight. The relative risk weighted for sample size, calculated using data from the three SM studies permitting such a calculation (*16*, *30*, *58*), was 1.25 for "light" women vs. women of average pre-pregnancy weight. The definition of "light" differed in the three studies; however, since most of the total sample size was from the study by Meyer et al. (*30*), this value should be considered to apply to women whose pre-pregnancy weight was less than 54 kg, compared with those of 54–61 kg.

Based on normally distributed pre-pregnancy weight with a constant standard deviation of 10 kg, three different population means (60 kg, 55 kg, and 50 kg) were used to calculate the following prevalences (P) of pre-pregnancy weight <54 kg, assuming a constant relative risk:

$$P_1 = p\left(Z < \frac{54-60}{10} = -0.6\right) = 0.27$$

$$P_2 = p\left(Z < \frac{54-55}{10} = -0.1\right) = 0.46$$

$$P_3 = p\left(Z < \frac{54-50}{10} = +0.4\right) = 0.65$$

The corresponding etiologic fractions are given by:

$$EF_1 = \frac{0.27(1.25-1)}{0.27(1.25-1)+1} = 0.063$$

$$EF_2 = \frac{0.46(1.25-1)}{0.46(1.25-1)+1} = 0.103$$

$$EF_3 = \frac{0.65(1.25-1)}{0.65(1.25-1)+1} = 0.140$$

Since pre-pregnancy weight appears to affect gestational age, or at least the risk of prematurity, gestational age should be controlled in assessing any effect on birth weight. The nine SM and 13 PM studies relating pre-pregnancy weight to gestational-age-corrected birth weight unanimously reported a significant positive correlation. The sample-size-weighted effect of 9.5 g birth weight per kg maternal pre-pregnancy weight was based on the results reported in four SM studies (total sample size = 27 323) that permitted such a calculation.

Finally, only two SM studies (*55*, *58*) and one PM study (*60*) specifically addressed the relative risk of IUGR. Unfortunately, these studies used different comparisons, as well as different definitions of IUGR. Only Scott et al. (*55*) reported a relative risk by pre-pregnancy weight, rather than by relative weight; based on a case–control study of 488 IUGR and 367 control infants, they estimated the odds ratio associated with a pre-pregnancy weight <49.5 kg as 1.84. The approximate etiologic fractions corresponding to the prevalences (P) of women of pre-pregnancy weight <49.5 kg for mean pre-pregnancy weights of 60 kg, 55 kg, and 50 kg are given by:

$$P_1 = p\left(Z < \frac{49.5-60}{10} = -1.05\right) = 0.15;$$

$$EF_1 = \frac{0.15(1.84-1)}{0.15(1.84-1)+1} = 0.119$$

$$P_2 = p\left(Z < \frac{49.5-55}{10} = -0.55\right) = 0.29;$$

$$EF_2 = \frac{0.29(1.84-1)}{0.29(1.84-1)+1} = 0.196$$

$$P_3 = p\left(Z < \frac{49.5-50}{10} = -0.05\right) = 0.48;$$

$$EF_3 = \frac{0.48(1.84-1)}{0.48(1.84-1)+1} = 0.287$$

Table 8. Results of the assessment of maternal pre-pregnancy weight

Outcome	Effect
Gestational age	?
Prematurity	
Relative risk for pre-pregnancy weight <54 kg	1.25
Etiologic fraction for:	
$P=0.27$	6.3%
$P=0.46$	10.3%
$P=0.65$	14.0%
Birth weight	9.5 g/kg
IUGR	
Relative risk for pre-pregnancy weight <49.5 kg	1.84[a]
Etiologic fraction for:	
$P=0.15$	11.9%
$P=0.29$	19.6%
$P=0.48$	28.7%

[a] Based on a single case-control study of 855 subjects.

The results of the assessment of maternal pre-pregnancy weight are summarized in Table 8. Caution is advised in drawing inferences for developing countries. Although thin women in these countries have been reported to have lower birth weights and prematurity and LBW rates, the methodological quality of these studies is generally poor and only one (*59*) received a PM rating, while none was rated SM. Furthermore, in developing countries "thin" is usually defined using a substantially lower weight or weight-for-height than in developed countries. The assumption of constant relative risks for pre-pregnancy weights below 54 kg or 49.5 kg, therefore, can neither be confirmed nor refuted from existing evidence.

5. *Maternal haemodynamics*

Background. Since adequate uterine blood flow depends, to some extent, on maternal haemodynamics, systolic and diastolic blood pressure or maternal plasma volume might be expected to have an association with birth weight. Demonstration of the effect of these factors should be based, however, on measurements taken before pregnancy to avoid confusing a determinant of body weight or gestational age with an intermediate *outcome* of pregnancy. Measurement of haemodynamic factors prior to conception was thus a required prerequisite for studies to receive either a PM or SM rating.

Additional methodological considerations (see Table 2) pertain to potential confounding factors. Since taller and heavier women both have higher blood pressures and give birth to heavier babies, maternal height and pre-pregnancy weight require control. Similarly, since blood pressure increases with age, age should also be controlled.

Results. None of the 13 reports dealing with the effect of maternal haemodynamic factors on gestational growth or duration related these outcomes to factors measured before the study pregnancy, and thus none received an SM or PM rating. In two reports (*61*, *62*), measurements were taken *after* the completion of pregnancy but neither controlled for the confounding effects of height, pre-pregnancy weight, or age. On the other hand, there is much better evidence of higher birth weights among women with hand and face oedema or with diastolic pressures of up to 90 mmHg *during* pregnancy, even after controlling for important confounders (*63–65*). Thus these appear to represent favourable markers, or prognostic signs, of good intrauterine growth. Demonstration of any causal effect of haemodynamic factors, however, must await their adequate study based on measurements taken *before* the study pregnancies actually begin.

6. *Paternal height and weight*

Background. Any contribution of paternal height or weight to gestational growth or duration must, of course, have a genetic basis. Because of assortive mating (the tendency of men and women of similar relative stature and weight to marry), maternal height and pre-pregnancy weight are important confounding variables that require control. Similarly, because weight usually increases with age, (maternal) age should also be controlled. Since in developed countries eating habits resulting in overnutrition are often linked to smoking and drinking habits (and secondarily, therefore, to such habits in wives), these too should be adjusted for. Finally, racial/ethnic origin and socioeconomic status are also associated with height and weight in men, and since these variables may be linked to gestational duration or growth independent of paternal size, they too require control.

Results. Only six reports were located (all from developed countries) in which paternal height or weight was studied in relation to birth weight or gestational age. These studies were generally of high methodological quality, however; two were classified as SM and three as PM. All of the studies focused on birth weight (usually adjusted for gestational age) and no data are available on gestational age, prematurity or IUGR. There is no reason, however, to suppose

an association between paternal size and gestational duration.

The five SM and PM studies that investigated paternal height reported a positive partial (adjusted) correlation with birth weight, but the results were statistically significant in only three studies, including the two largest (*66*, *67*). Based on the data from these five studies, the sample-size-weighted magnitude of the effect was estimated to be 1.6 g/cm.

Three of the studies reported on the effect of paternal weight, all of which adjusted for the effect of paternal height in addition to other potential confounders. The adjusted correlation with birth weight was positive in all three studies, but the result was statistically significant in only the two largest (*67*, *68*). The sample-size-weighted magnitude of the effect was 3.3 g/kg.

Thus, the effects of paternal size are considerably smaller than those of maternal size, which is exactly what we would expect, considering the important contribution of the mother's size and nutritional stores to the intrauterine environment. Since the assessment described here is entirely based on studies from developed countries, however, caution is advised in extrapolating the calculated effect magnitudes to populations in developing countries.

Although potential interactions with other factors have not often been investigated, Lazar et al. (*68*) reported a greater effect of paternal height on birth weight for women aged 18–21 years. Also, in a much smaller study, Winikoff & Debrovner (*69*) found a greater effect of paternal height on the offspring of thin women and a greater effect of paternal weight in heavy women.

7. Additional genetic factors

Background. A genetic tendency to produce offspring of low birth weight or gestational age might be expressed, in part, through the effects of racial/ethnic origin or parental size. However, there may be an additional genetic effect above and beyond the effects of race and parental size—the tendency for birth weight or gestational age to correlate across generations, or between siblings, after adjusting for differences in parental size and important confounding variables. It should be noted that in this respect racial/ethnic origin is controlled automatically, since the family groups analysed were usually racially homogeneous.

Parents who smoke or drink are probably more likely to have brothers, sisters, and children who do likewise. Thus maternal smoking and drinking are important confounders requiring control. Since socioeconomic status also has a strong inter-generational and familial correlation, it should also be controlled. The methodological standards applied to this factor are shown in Table 2 (pp. 670–1). Studies were required to control for both maternal height and weight in order to receive an SM rating.

Results. Five studies provided data on the familial correlation of gestational growth or duration. All were from developed countries; three were classified as SM and none as PM. Only one of the studies reported correlations between birth weight or gestational age of the father and those of the offspring (*67*). Although these correlations were significant and similar in magnitude to those between mother and offspring, they were not controlled for parental size or potential confounding variables.

One of the three SM studies compared both gestational-age-adjusted birth weight and prematurity in sisters and sisters-in-law of mothers of IUGR and premature infants (*70*). This study reported that the sisters of mothers who had IUGR infants tend also to have babies of lower gestational-age-specific birth weight percentile than the sisters of mothers of premature infants. Also the sisters of mothers who had premature infants had a nonsignificantly greater risk ($RR=1.60$) of having premature offspring relative to the sisters of mothers who had IUGR infants. Since no such effects were observed for sisters-in-law, a familial tendency towards IUGR or prematurity may be expressed only in women. For a population in which 5% of mothers were themselves born prematurely, a relative risk of 1.60 corresponds to an etiologic fraction given by:

$$EF = \frac{0.05(1.60-1)}{0.05(1.60-1)+1} = 0.029,$$

i.e., only about 3% of the population's premature infants are attributable to maternal prematurity.

The other two SM studies both examined the relationship between maternal birth weight (without adjustment for gestational age) and offspring birth weight. Hackman et al. (*71*) reported a significant partial correlation between maternal birth weight and that of infants after controlling for a number of potential confounders using multiple linear regression. Since infant birth weight was not controlled for infant gestational age, however, and since "retrospective" (i.e., case–control) analysis indicated a univariate association between maternal birth weight and infant gestational age, it is not clear whether the effect of maternal birth weight represents maternal intrauterine growth, gestational duration, or (probably) a combination of the two.

Klebanoff et al. (*72*) found that maternal birth weight did not significantly affect either gestational age or prematurity upon univariate (unadjusted) analyses but had a significant effect on both birth weight and the risk of LBW. Compared with offspring of mothers with birth weights of 2724–3587 g,

those whose maternal birth weights were 1816–2679 g weighed 145 g less and had an odds ratio for LBW of 2.08, after adjusting for a number of confounders. The proportion of women whose birth weight was 1816–2679 g represented 0.126 of the study population included in the multivariate analyses. The etiologic fraction for this population corresponding to a risk ratio of 2.08 for IUGR is given by:

$$EF = \frac{(0.126)(2.08-1)}{(0.126)(2.08-1)+1} = 0.120$$

Thus, maternal birth weight might explain 12% of the IUGR in such a population. These results are unadjusted for maternal height, however, and mothers whose birth weight was in the lowest birth weight category (908–1771 g) gave birth to heavier infants than those who weighed 1816–2679 g at birth. Since these data are the only ones available on the size of the effect of maternal birth weight on infant birth weight or risk of IUGR, they should be regarded as highly tentative.

The overall assessment of this "factor" thus indicates a probable genetic effect for intrauterine growth and a possible effect for gestational duration. The magnitude of the genetic effect may be considerable but requires further study. Once again, it should be noted that the assessment of this factor is based entirely on studies from developed countries, and the importance of these effects in developing countries is therefore uncertain.

B. *Demographic and psychosocial factors*

1. Maternal age

Background. Pregnancy outcomes, including birth weight and gestational age, are generally less favourable among adolescents and women over 35 years of age; however, there is considerable controversy as to whether age itself is an independent determinant of either intrauterine growth or gestational duration. Age is closely associated with parity, which must therefore be controlled in attempts to isolate the independent impact of age. Furthermore, young adolescents (those within 1 or 2 years of menarche) have not completed growing, are likely to have a lower weight-for-height than older women, and may consume fewer calories and other nutrients. Because their pregnancies are often unwanted or unplanned, they are often late in seeking antenatal care. Increased cigarette smoking, alcohol consumption, and drug use among teenagers may also put them at risk. Also, in the USA at least, teenage mothers are more likely to be Black than older mothers. The methodological standards used to assess studies of the effects of maternal age are shown in Table 2. Control for parity was required to receive a PM or SM rating.

Not all of the above factors are true confounders, since a very young age may be an *indirect* cause of prematurity or IUGR through its effect on stature, weight, gestational nutrition, or cigarette, alcohol, or drug use. Indirect causal effects may be important, especially for very young age, because interventions aimed at delaying pregnancy in young adolescents might be more effective or more practicable than attempting to influence their height, weight, or gestational nutrition. None the less, in the present assessment I focus on the independent effect of age on intrauterine growth and gestational duration over and above these indirect effects. Although path analysis has not been used to investigate these relationships, it would probably be helpful in demonstrating the extent of such indirect causal effects (*73*).

Finally, because women over 35 years of age may exhibit impaired intrauterine growth or gestational duration, multivariate statistical models of the effect of age should contain a quadratic term for age (in addition to the usual linear term) if this is measured on a continuous scale. In this way, increases in the linear term with age (positive coefficient) would be countered, and perhaps even exceeded, by decreases in the quadratic term (negative coefficient).

Results. A total of 144 studies were located that had a bearing on the effect of maternal age on gestational age, prematurity, birth weight, or IUGR; 17 were classified as SM and 31 as PM. Two SM studies (*16*, *74*) found that age had no significant effect on mean gestational age, and one (*38*) reported no altered risk for prematurity. The absence of an independent effect on gestational duration was confirmed by three PM studies that reported no impact on gestational age and by only one of four PM studies that reported an altered risk of prematurity.

Of 12 SM studies that dealt with the association between maternal age and mean birth weight, only one (*48*) found a significant independent effect, which could easily have arisen by sampling variation. The largest and best of these studies (sample size, 31 604) detected no age effect (*75*). Similarly, none of the four SM studies reported a significant impact of maternal age on the risk of IUGR or LBW.

The absence of a direct causal effect of maternal age is not limited to developed countries. Although only a few studies that dealt with this factor originated from developing countries, several were of high methodological quality. For example, SM studies from both India (*76*) and Guatemala (*77*) reported no independent effect of age on birth weight.

The extremes of the maternal age spectrum ($\leqslant 16$ years and $\geqslant 35$ years) were examined separately. Because of the small number of such women, young teenagers or women over 35 years of age might have exhibited impaired intrauterine growth or gestational

duration that was not detected in the overall analysis for age effects. For young adolescents the data are clear: neither of two SM studies (*32*, *46*) showed independent deficits in birth weight; and none of four PM studies (*78–81*) demonstrated independent effects on gestational age, prematurity, birth weight, or IUGR. In contrast, for women $\geqslant 35$ years of age the situation is more complicated. Two SM studies indicated that increasing age may interact with other risk factors. Meyer et al. (*30*) found higher prematurity and LBW rates among women aged $\geqslant 35$ years only during their first and second pregnancies. Furthermore, Miller & Merritt (*16*) found no increase in prematurity or IUGR in older women who had no other risk factors, but increases in both (compared with women aged $\leqslant 34$ years) among those with other risk factors.

The results in five PM studies are conflicting. Both Legg et al. (*82*) and Eisner et al. (*83*) found significantly elevated LBW rates (gestational age was not controlled) among women aged $\geqslant 35$ years. Similar results were reported by DaVanzo et al. (*84*), who found, however, no significant deficit in mean birth weight. Neither age nor age squared (*2*) was significantly correlated with birth weight in the PM study by Quick et al. (*85*). Finally, Kaminski et al. (*57*) found an increased risk of LBW (without control for gestational age) but a *decreased* risk of prematurity among women aged $\geqslant 40$ years. Incomplete control for confounding in these five studies, as well as their inconsistent results, prevent definitive inferences about whether age $\geqslant 35$ years has any independent causal impact on intrauterine growth or gestational duration. The two SM studies (*16*, *30*), however, suggest that older women may be more sensitive to the adverse effects of other factors.

In summary, maternal age does not appear to be an important independent determinant of intrauterine growth or gestational duration. Although age, and particularly a very young age, may exert indirect effects by influencing height, weight, nutrition, cigarette smoking, as well as alcohol and drug abuse, no direct causal effect can be demonstrated. Older women may not be at increased risk because of their age alone, but age $\geqslant 35$ years may augment the impact of other risk factors.

2. *Socioeconomic status*

Background. For the purposes of this assessment, socioeconomic status encompassed mainly factors such as education (usually maternal), occupation (usually paternal), and family income. In contrast, only a few studies focused on related variables such as size of dwelling or number of persons per room. Since all these factors are highly intercorrelated, they will be considered together here.

Important variables that require control (see Table 2) include maternal age, parity, racial/ethnic origin (control required for PM or SM rating), height, pre-pregnancy weight, caloric intake (or gestational weight gain), cigarette and alcohol consumption, antenatal care, birth interval, and infection. As with maternal age, we are interested in the direct effect of socioeconomic status, independent of other factors. Women of low socioeconomic status in developed countries are more likely to be members of racial/ethnic minorities and may be more likely to smoke cigarettes, have shorter birth intervals, make less use of antenatal care, and have a higher incidence of systemic and genital tract infection. In developing countries, such women are likely to be shorter and thinner and to consume fewer calories and other nutrients during pregnancy. Thus the absence of an independent effect of socioeconomic status does not rule out its role as an indirect cause of prematurity or IUGR.

Results. A total of 113 studies were located that had a bearing on the effect of socioeconomic status on intrauterine growth or gestational duration; of these 10 were classified as SM and 37 as PM.

Among the SM studies, Polednak et al. (*74*) found that socioeconomic status had no independent effect on gestational age, whereas Berkowitz (*38*) reported an odds ratio of 5.50 for prematurity for Class V vs. Class I mothers. Among the seven PM studies with relevant data, none of three found a significant association between socioeconomic status and gestational age, while two of four reported an elevated risk of prematurity. Available information therefore indicates that socioeconomic status has no effect on mean gestational age. Although it might be possible to affect the risk of prematurity without significantly altering mean gestational age, the mixed results do not permit such an inference. Convincing demonstration of an independent effect of socioeconomic status on prematurity must, therefore, await well-controlled studies, or re-analyses of existing data.

Eight SM studies enable fairly confident conclusions to be drawn about the effect of socioeconomic status on birth weight and IUGR. Two of these studies (*55*, *86*) found no increased risk of IUGR (or LBW) for women of lower socioeconomic status, while none of the six studies that had a bearing on mean birth weight reported a significant association between socioeconomic status and birth weight. These results permit the inference that socioeconomic status has no independent effect on intrauterine growth. Although all of the SM studies were from developed countries, similar findings were also reported in three PM studies from developing countries (*84*, *87*, *88*).

It is, nevertheless, likely that low socioeconomic status may be a social "cause" of other nutritional,

toxic, anthropometric, or infectious factors that may themselves be causal determinants. As with maternal age, indirect causal effects may be important for intervention. The most easily modifiable aspect of socioeconomic status is maternal education, although, in the long term, family income could also be influenced. The potential importance of socioeconomic status is considered in the Recommendations section under public health interventions (see p. 723).

3. Marital status

Background. Marital status or, more broadly, parental cohabitation, is closely linked to socioeconomic status. In developed countries, however, "legitimacy" and parental cohabitation have become independent of education, occupation, and income, and often reflect life-style-based choices among the middle and upper social classes. Any effect on intrauterine growth or gestational duration thus might operate in the mother through a psychological mechanism, e.g., stress, independently of her socioeconomic status. Demonstration of an independent effect depends, therefore, on controlling for the same variables as for socioeconomic status, in addition to controlling for the latter itself. Control for racial/ethnic origin and socioeconomic status was required to receive a PM or SM rating (see Table 2).

Results. In total, 37 pertinent studies were located, of which three were classified as SM and 13 as PM. The three SM studies reported the following: Berkowitz (*38*) found that there was no independent effect of marital status on the risk of prematurity, and neither Kennedy et al. (*89*) nor Horon et al. (*46*) detected an effect on mean birth weight. Among the PM studies, Wiener & Milton (*39*) reported no significant effect on mean gestational age, and neither Papiernik & Kaminski (*90, 91*) nor Mamelle et al. (*43*) found a significant effect on the risk of prematurity. Three of five PM studies reported lower mean birth weights, while another three of seven reported an elevated risk of IUGR (or LBW) among single women; however, incomplete control of important confounding variables is a likely explanation in these cases.

In summary, the evidence that marital status (or cohabitation) is an independent determinant of either intrauterine growth or gestational duration is inconclusive. None of the SM or PM studies that had a bearing on this factor came from developing countries, however, and no firm conclusions can be drawn about its role there.

4. Maternal psychological factors

Background. Maternal psychological factors include stressful life-change events, anxiety, mental illness, and unwanted pregnancy. Anxiety might increase metabolic expenditure, leading to a lower gestational weight gain, and hence a smaller fetus, for a given caloric intake. Also, an anxiety-mediated change in catecholamine or hormonal balance could provoke pre-term labour. Higher levels of epinephrine and hydrocortisone are generally associated with anxiety, although these changes might be expected to decrease, rather than increase, uterine contractions.

In addition to difficulties in making valid and reproducible measurements of stress and anxiety, studies of the effect of these factors face several other methodological pitfalls—the major one being when the measurements were made. Postpartum studies of these factors are faced with the problem of deciding between cause and effect: did stress or anxiety cause a premature or growth-retarded baby or did the birth of a premature or IUGR infant lead to increased maternal anxiety or enhanced recall of prior stressful events? Studies should therefore either focus on objective, independently verifiable life events or measure stress or anxiety *before* the onset of labour or any pregnancy complications. Only studies conforming with this requirement were therefore considered eligible for an SM rating.

Potential confounding factors that should be controlled (see Table 2) include age and parity, since early and first pregnancies are more stressful and, independently, are associated with worse pregnancy outcomes; race, since membership of a racial/ethnic minority might produce increased anxiety and may also have a genetic effect on birth weight; cigarette smoking and alcohol consumption, since anxiety or stress may lead to smoking and/or drinking, which may have independent effects on intrauterine growth or gestational duration; psycho-pharmacological therapy among women with mental illness, since such therapy might adversely affect the fetus separately from any effect of the illness being treated; and socioeconomic status (or, as a proxy, height and prepregnancy weight), since important anthropometric determinants of birth weight or gestational age are likely to differ in women of different socioeconomic status, who may also differ in their exposure to stress and anxiety. Gestational weight gain, on the other hand, should *not* be controlled, because anxiety may increase caloric expenditure and thus reduce the weight gained for a given caloric intake.

Finally, investigations of the gestational effects of maternal psychological factors should attempt to identify variables that may act as effect modifiers. Primiparity, young age, and low socioeconomic status, as well as absence of social support, for example, might augment the adverse effect of stress, with obvious implications for preventive intervention.

Results. Data on the effect of maternal psychological factors on intrauterine growth or gestational

duration were located in 30 reports. Only two of these satisfactorily met (SM) the methodological requirements, while another 11 partially met (PM) the requirements. All of the SM and PM studies were from developed countries.

In the one relevant SM study (*92*) and the four pertinent PM studies, no effect was found on mean gestational age. In contrast are the data on the risk of prematurity. Here, the single SM study (*93*) found a higher mean number of recent "objective" stressful life events among women who delivered pre-term compared to those with full-term infants; most of these appeared to occur in the third trimester. A significant effect on the risk of prematurity was also reported in four PM studies, while two PM studies that reported no effect (*94*, *95*) did not assess the influence of stress or anxiety *per se*, but rather the risk associated with schizophrenia and other endogenous psychoses.

The magnitude of the increased risk is difficult to assess. Berkowitz & Kasl (*96*) reported an odds ratio of 2.0 for women with a high (versus those with a low) number of stressful life events, but only for women whose pregnancy was highly desired. Stress had no effect on women whose pregnancies were not highly desired. Although these results suggest an interaction between pregnancy desirability and life stress, data are based on postpartum interviews and it is thus difficult to separate cause from effect. Unfortunately, this is the only study that specifically examined effect modifiers for stress and anxiety. Mamelle et al. (*43*) found that mentally stressful work during pregnancy was associated with an odds ratio for prematurity of 1.8, but here work was confounded with physical exertion, posture, and other work-related variables.

In the one SM study (*93*) that had a bearing on intrauterine growth, no effect of stress was found. Similarly, seven PM studies reported that maternal psychological factors had no effect on gestational-age-adjusted mean birth weight, while two detected no increased risk of IUGR.

In summary, data from developed countries show no link between maternal psychological factors and intrauterine growth but a possible effect on pre-term delivery, although mean gestational duration does not appear to be affected. This suggests that stress and anxiety may provoke pre-term labour in some susceptible women; however, firm conclusions about such an effect, as well as its magnitude, must await further investigation.

C. *Obstetric factors*

1. Parity

Background. There is general agreement that pregnancy outcomes are more favourable for multiparae than primiparae; grand multiparity, however, is often believed to constitute a risk.

Several factors may confound the association between parity and intrauterine growth or gestational duration (see Table 2). In particular, primiparae tend to be younger than multiparae. Although age does not appear to have any independent effect on pregnancy outcome, young adolescents are likely to differ from older women in their height, pre-pregnancy weight, gestational nutrition, cigarette and alcohol consumption, and use of antenatal care. Control for age was therefore considered essential for an SM rating. Grand multiparity may also be associated with racial/ethnic origin, socioeconomic status, cigarette smoking, alcohol consumption, and genital infection. Thus control is also required for these factors. In addition, as mothers of high parity are likely to have had shorter intervals since their previous pregnancy, birth (or pregnancy) interval should also be controlled.

Because extremely high parity may also be associated with poorer outcome, the effect of grand multiparity should be examined separately. Multivariate statistical models of the effect of parity on birth weight or gestational age should ideally contain a quadratic term for parity, in addition to the usual linear term, when parity is expressed on a continuous scale. Finally, because age may modify the effect of parity, evidence should also be sought for an age–parity interaction.

Results. Data that had a bearing on the effect of parity were located in 120 studies; of these 25 were rated as SM and 31 as PM. Unfortunately, only a few of the SM and PM studies provided data on the effect on either gestational age or prematurity, and the findings do not permit confident inferences. Only one (*39*) of the three relevant SM studies (*39*, *74*, *92*) reported a significant association between parity and gestational age—the association was negative and of trivial magnitude (partial correlation coefficient = -0.02). On the other hand, an SM study by Mamelle et al. (*43*) reported a significantly lower risk of prematurity with increasing parity. Similar findings were reported in the SM study by Meyer et al. (*30*), at least for women $\geqslant 20$ years of age. The SM case–control study by Berkowitz (*38*), however, found no protective effect of multiparity on the risk of prematurity. Among the PM studies, the single study (*97*) that dealt with gestational age found no effect, and only one (*22*) of four relevant studies (*22*, *56*, *98*, *99*) reported a significant effect on the risk of prematurity.

Data on intrauterine growth are far clearer. Of 17 relevant SM studies, 12 reported that increasing parity increased the mean birth weight. Three of the five studies that did not detect such an effect involved sample sizes below 500, and the largest sample size of

the five was 2259 (*100*). Sixteen of 19 relevant PM studies also found that parity had a significant effect on birth weight. Based on data in the seven SM studies (total sample size, 83 501) permitting calculation of the magnitude of the birth-weight effect, the sample-size-weighted effect was 43.3 g per birth. For the two SM studies (*48*, *84*) that reported the adjusted difference in mean birth weight for multiparae versus primiparae, the sample-size-weighted difference was 82.7 g.

The risk of IUGR associated with primiparity can be calculated from four SM studies (*51*, *84*, *88*, *101*) (total sample size, 142 259); although not all these studies adjusted for gestational age, there is no unequivocal evidence that parity has an effect on gestational age. If it is assumed, therefore, that the relative risks for IUGR and LBW are equivalent, the sample-size-weighted risk ratio associated with primiparity is 1.23. The associated etiologic fraction in a population in which half the births are to primiparae can thus be calculated as:

$$EF = \frac{0.50(1.23-1)}{0.50(1.23-1)+1} = 0.103$$

Among the studies mentioned above, four SM (*76*, *77*, *84*, *88*) and one PM (*98*) originated from developing countries; the results were entirely consistent with those from developed countries, with the two largest studies (*84*, *88*) showing clear parity effects. The magnitude of the effects on birth weight and IUGR were also similar, and the sample-size-weighted effect magnitudes given above are based on a combination of SM studies from developed and developing countries. Because primiparity is less prevalent in developing countries, however, the etiological fraction for IUGR should be lower for a given relative risk. If it is assumed that one-third of the births in developing countries are to primiparae, the etiologic fraction can be calculated as:

$$EF = \frac{0.33(1.23-1)}{0.33(1.23-1)+1} = 0.071$$

The magnitude of the parity effect on birth weight should, however, be interpreted in the light of two complicating factors: the effect of grand multiparity; and a parity–age interaction. Although lower birth weights have frequently been reported for women of very high parity (>5 or 6), few studies have adequately controlled for confounding. However, among the three SM studies that addressed this issue, Peters et al. (*102*) found no fall-off in adjusted birth weight for a fifth or higher birth order in an analysis of data from the 1958 British Perinatal Mortality Survey or the 1970 British Births Survey. In contrast, Fabia (*103*) found a significant effect for both the parity (positive) and parity squared (negative) terms in a multiple regression analysis of a 10% sample of singleton births in Quebec in 1970–71; however, the reported regression coefficients indicate that birth weight would not begin to decrease until the 14th or 15th pregnancy. Finally, Philipps & Johnson (*104*) found a *positive* effect for the parity^2 term in a very small study (sample size, 47) in rural Wisconsin. Thus there appears to be no unequivocal evidence that high parity has an important independent deleterious effect on birth weight.

Data on a possible age–parity interaction were reported in one SM and six PM studies. The SM study by Meyer et al. (*30*) found that multiparity increased the risk of LBW (gestational age was not controlled) for women aged under 20 years, had little effect for those aged 20–34 years, and substantially decreased the risk for those aged $\geqslant 35$ years. Similar trends for birth weight, LBW, and IUGR were reported in the six PM studies (*22*, *33*, *56*, *83*, *105*, *106*). From the standpoint of the age–parity interaction the major risk groups are therefore young multiparae and older primiparae. Although it is difficult to quantitate the impact of this interaction, it might well be of importance in developing countries (and among underprivileged groups in developed countries) where repeat pregnancies during adolescence are common. It could also become important in developed countries where women's education and careers increasingly result in delayed childbearing.

The results of the assessment for parity are summarized in Table 9. The indicated effect magnitudes are overall estimates and thus do not take the age–parity interaction into account.

2. *Birth or pregnancy interval*

Background. A short interval since the previous birth might lead to poor pregnancy outcome. Nutri-

Table 9. Results of the assessment of parity

Outcome	Effect
Gestational age	?
Prematurity	?
Birth weight	43.3 g/birth[a]
Multiparae–primiparae difference	82.7 g[a]
IUGR	
Relative risk for primiparae	1.23[a]
Etiologic fraction for:	
$P = 0.50$	10.3%[a]
$P = 0.33$	7.1%[a]

[a] These figures are overall estimates that do not take into account the effect of age–parity interaction.

tional depletion would be the most obvious biological mechanism for such an effect, but inadequate physiological (e.g., hormonal) recovery could arise for other reasons. In any case, identification of an independent effect of birth interval on intrauterine growth or gestational duration requires adequate control for numerous other factors (see Table 2). Primary among these is length of gestation, and failure to control for this could lead to prematurity itself (and the corresponding lower birth weight) as the cause of a shorter birth interval. Use of either the *pregnancy interval* (the time between the previous birth and conception of the current pregnancy), rather than the birth interval, or appropriate life-table techniques, is thus required for studies that have a bearing on gestational age or prematurity, and only those that incorporated such control received a PM or SM rating. For studies on birth weight, use of pregnancy interval or adequate control for gestational age was required for an SM rating.

One important potential source of confounding is the outcome of the previous pregnancy. If the prior gestation resulted in a stillbirth or neonatal death, which is far more likely if the infant was premature or LBW, the mother will be at increased risk for *both* a shorter birth or pregnancy interval *and* a repeat premature or LBW pregnancy (see below).

Short intervals are more likely among grand multiparae, certain racial or ethnic groups, and the poor; thus parity, racial/ethnic origin, and either socioeconomic status or its important correlates (especially height, cigarette smoking, and alcohol consumption) also require adequate control. Pre-pregnancy weight should not be controlled, however, since any effect of close pregnancy spacing on intrauterine growth may act by depleting maternal fat stores.

Results. Twenty-six pertinent studies of birth or pregnancy interval were located, only five and seven of which were rated SM and PM, respectively. The major methodological weakness among studies assessed was the use of the birth interval (rather than pregnancy interval) without control for length of gestation. Thus, although many studies reported lower birth weights or increased LBW rates among women with short intervals, it is impossible to separate the effect of birth interval from the tendency for shorter pregnancy duration (i.e., prematurity) to produce shorter birth intervals.

Only the study by Papiernik & Kaminski examined the effect of pregnancy interval on gestational age or prematurity (*90*) and found no significant increase of short pregnancy intervals (< 1 year) among women who gave birth to premature infants. No control for confounding factors was used; however, another report by the same authors, rated as SM, showed no increased risk of LBW (prematurity and IUGR combined) for short pregnancy intervals after adequate multivariate control for confounding (*91*).

No effect of short birth interval was detected in two SM studies (*77*, *89*) and one PM study (*107*) that reported on gestational-age-adjusted birth weight. Another SM study (*108*) examined the effect of *pregnancy* interval on birth weight (unadjusted for gestational age). Although lower birth weights were observed for births following a pregnancy interval < 1 year, the same trend was recorded also for births to women that occurred *prior* to such a short interval. Since the effect was greatly diminished after correcting for stillbirths and postnatal deaths, the authors concluded that short pregnancy interval had no causal effect on birth weight and that the apparent association was due to rapid child replacement by women who were prone to prematurity or other causes of stillbirth or postnatal death.

The only large PM study (*109*) that examined whether there was an effect on true IUGR found none. Two SM reports studied the effect of pregnancy interval on the risk of LBW. The small study by Kaminski & Papiernik (*91*) describing the absence of effect on LBW, coupled with the finding of no bivariate effect on prematurity (*90*), indicates no association with impaired intrauterine growth. In a much larger SM study from the USA, Eisner et al. (*83*) found higher rates of LBW in women with shorter pregnancy intervals; the differences, though statistically highly significant, were associated with pregnancy intervals of < 6 months, which included only 3.8% of the total study sample. Furthermore, since no control was made for gestational age it cannot be determined whether the effect reported was on intrauterine growth or gestational duration.

All of the five PM studies that had a bearing on LBW found a significant effect, but four analysed birth interval, rather than the pregnancy interval, and none controlled for length of gestation.

In summary, the effect of birth (or pregnancy) interval on gestational duration has not been adequately studied. Although most of the better studies indicate no effect on intrauterine growth, the elevated risk for LBW reported by Eisner et al. (*83*) precludes a definitive conclusion. Even if the latter finding reflects an effect on intrauterine growth, the etiologic fraction for IUGR associated with pregnancy intervals < 6 months in the USA in 1974 was only 0.012 for Whites and 0.022 for Blacks, even with the higher odds ratios reported in the multiple logistic regression analysis (rather than the lower values from Mantel–Haenszel analyses). Thus it seems unlikely that short pregnancy intervals are an important cause of IUGR, at least in the USA. In the only SM study from a developing country, Mata (*77*) reported no effect of birth spacing on intrauterine growth, which is consistent with results from developed countries.

3. Sexual activity

Background. There are at least four biological mechanisms that could explain an association between sexual activity during pregnancy and premature labour and delivery:

—Semen contains relatively high concentrations of prostaglandins (*110*), which could lead to uterine contractions after absorption across the vaginal mucosa.
—Orgasm causes release of oxytocin, a stimulant of uterine contractions.
—Bacteria may reach the amniotic fluid after coitus, provoke infection, and thus precipitate pre-term labour (*111*).
—Nipple stimulation in late pregnancy causes release of oxytocin, which provokes uterine contractions (*112*).

The major methodological difficulty here relates to the normal decrease in sexual activity during pregnancy, especially the third trimester. Among women in Seattle, Solberg et al. (*113*) have documented decreases in the frequency of coitus, the proportion of coital acts resulting in orgasm, and the intensity of orgasm. Decreased coital frequency in late pregnancy has also been reported by Grudzinskas et al. (*114*) and Mills et al. (*115*) in studies from London and Jerusalem, respectively. Here again there is difficulty in distinguishing cause from effect. Women who deliver prematurely are likely to report more frequent coitus and orgasms because they have had a shorter time to experience the expected decrease in sexual activity that continues until term. Furthermore, postpartum interviewing of women, who may wish to "explain" why they have given birth prematurely, is prone to recall bias.

Thus, an objective comparison should use data on sexual activity collected prospectively during pregnancy. Also, the appropriate control group should be compared either in a cohort study (i.e., the incidence of prematurity among women with high versus low or varying frequencies of sexual activity) or as a case–control study (pre-term cases and full-term controls) in which controls are compared for sexual activity at the same point in gestation as the onset of labour in the cases. Only studies incorporating such control were considered eligible for a PM or SM rating.

Potentially important confounding factors (see Table 2) include any characteristics associated with sexual activity, on the one hand, and (independently) with pregnancy outcome, on the other. Age is one such characteristic, because the frequency of sexual activity is likely to vary with it. Since sexual activity is also likely to vary with socioeconomic status, either this or its risk factor correlates (such as height, weight, gestational nutrition, and cigarette and alcohol use) should also be controlled. Finally, since genital tract infection is linked to sexual activity, and may be a cause of prematurity, it also should ideally be controlled.

Results. A total of 10 studies provided data on the effect of sexual activity during pregnancy on pregnancy outcome. Eight of these reported on premature labour and delivery, while the two others dealt with known antecedents of prematurity (abruptio placentae and premature rupture of the membranes). One other report (*111*), which dealt with amniotic fluid infection and perinatal mortality, was excluded because of the uncertain link between such infection and prematurity. None of the studies reported the effects of nipple stimulation, and only two (*113, 115*) examined the effects of sexual activity on intrauterine growth. The major methodological weakness among the 10 reports was inability to distinguish between cause and effect. Although several reported an association between prematurity and frequency of coitus or orgasm, in most it was impossible to separate the normal higher frequency of sexual activity that occurred during the early part of gestation from a true causal effect of coitus or orgasm. Only one of the reports was rated SM, and none as PM.

One SM study (*116*) compared sexual activity among women who had had premature infants (cases) with full-term controls who were interviewed at the same gestational age; no association with frequency of either coitus or orgasm was found. Although the possibility of an effect should not be dismissed on the basis of one small study, however well controlled, it has to be concluded that convincing evidence has yet to appear.

4. Intrauterine growth and gestational duration in prior pregnancies

Background. Some women appear to have a tendency to repetitive prematurity or IUGR. Whether this represents merely the persistence of other risk factors or an inherent tendency is unclear. For example, if smoking leads to IUGR and a woman smokes in each of two consecutive pregnancies, she will be at increased risk for an IUGR infant in both pregnancies. Failure to control for other risk factors may thus lead to the fallacious conclusion of an "inherent tendency" for prematurity or IUGR. In addition to smoking, the important factors that require control include height, pre-pregnancy weight, gestational weight gain or caloric intake, and alcohol use. Furthermore, since women of higher parity are at a lower risk for LBW and also have had a greater opportunity to have a history of prior LBW infants, parity should also be controlled. Finally, since an inherent tendency to prematurity or IUGR may be genetic, it is not clear whether this operates independently of other genetic

factors, such as the mother's own birth weight and gestational age at birth, and thus these genetic factors should also be controlled. The methodological standards used in the assessment are listed in Table 2.

Ideally, control for the above factors should *precede* analysis; otherwise some of their effects may be erroneously ascribed to an inherent tendency for prematurity or IUGR. Any such tendency should be based on an explanation of variance (for gestational age or birth weight) or risk (for prematurity or IUGR) that remains *after* the effects of other factors have been accounted for. Thus, when multiple regression or other multivariate statistical techniques are used, other risk factors should be introduced first in the analysis. Stepwise or similar procedures underestimate the effects of other risk factors, because their effects will be diminished by the extent to which they are correlated with gestational age and birth weight or repetitive prematurity and IUGR in subsequent pregnancies. This type of "overcontrol" may have been responsible, for example, for the failure to detect effects, or the detection of smaller effects, in studies of other risk factors.

Results. Twenty-seven studies had a bearing on the effects of intrauterine growth or gestational duration in prior pregnancies. Four were rated SM and six as PM. None of these studies reported effects on mean gestational age, but two SM studies (*57*, *117*) and one PM study (*43*) found an increased risk of prematurity among women with a prior history of premature infants. For the two studies that permitted calculation of relative risks (*43*, *117*), the results were nearly identical (3.05 and 3.1, respectively), with a sample-size-weighted average of 3.08. If it is assumed that the population prevalence among multiparae for a history of prior prematurity is 5% and that the proportion of multiparae among women giving birth is 50%, the etiologic fraction for this factor can be calculated as follows:

$$EF = \frac{(0.05)(0.50)(3.08-1)}{(0.05)(0.50)(3.08-1)+1} = 0.049$$

One SM (*89*) and one PM study (*118*) found significantly lower gestational-age-adjusted birth weights among women with a prior history of LBW. Of these, Kennedy et al. (*89*) reported that such a history was associated with a decrease of 138.6 g in birth weight. Rush et al. (*118*) reported a decrease of 112.8 g for *each* prior LBW pregnancy; however, when other confounders were included in the multiple regression analysis, the increase in explained variance (r^2) was reduced. The effect magnitude (regression coefficient) from this latter analysis was not reported, but is undoubtedly less than 112.8 g.

Also, one SM (*55*) and one PM study (*119*) reported a significant effect of prior LBW on the risk of IUGR. Two additional studies (one SM (*89*) and one PM (*91*)) reported on the risk of LBW, but because gestational age was not controlled, the effect on intrauterine growth was confounded with that on gestational duration. From the data provided by Kaminski et al. (*119*) for heavy and light alcohol consumers, a Mantel–Haenszel relative risk for prior LBW of 2.75 was calculated for a total sample size of 5485. The corresponding etiologic fraction for a prior LBW rate of 8% and a multiparae rate of 50% is given by:

$$EF = \frac{(0.08)(0.50)(2.75-1)}{(0.08)(0.50)(2.75-1)+1} = 0.065$$

Scott et al. (*55*) reported an adjusted odds ratio of 7.98 for previous live births whose average birth weight was less than 1 standard deviation below the mean for gestational age. Because this estimate is based on prior intrauterine growth rather than LBW, it is not directly comparable to the value calculated from the data provided by Kaminski et al. Furthermore, the birth weight cut-off used does not correspond to the usual definition of either LBW or IUGR. Nevertheless, the etiologic fraction for this factor, assuming a 15% prevalence of this history among multiparae and a 50% rate of multiparae, is given by:

$$EF = \frac{(0.15)(0.50)(7.98-1)}{(0.15)(0.50)(7.98-1)+1} = 0.344$$

This value is very high, however, and should be interpreted with caution, especially in view of the small sample size ($n=855$).

All the SM and PM studies assessed were carried out in Europe and North America, and it is not known

Table 10. Results of the assessment of intrauterine growth and gestational duration in prior pregnancies

Outcome	Effect
Gestational age	?
Prematurity	
Relative risk for prior premature birth	3.08
Etiologic fraction for $P=0.05$ (multiparae rate = 50%)	4.9%
Birth weight	
≥ 1 prior LBW	−138.6 g[a]
IUGR	
Relative risk for ≥ 1 prior LBW	2.75[a]
Relative risk for average previous birth-weight-for-gestational age <-1 standard deviation	7.98[a]

[a] Based on the results of a single study.

whether similar effects on prematurity, birth weight, or IUGR occur also in developing countries. This is particularly important for birth weight and IUGR, because the much higher prevalence of LBW in developing countries, coupled with a higher rate of multiparity, suggests that many more mothers are exposed to this risk factor there and that the effect on population mean birth weight and etiologic fraction for IUGR could be substantial. With so many other causes of IUGR in developing countries, however, the relative risk due to an inherent tendency to IUGR may actually be lower than in developed countries, and the etiologic fraction may be no higher. This factor overlaps also with other genetic factors (see section on additional genetic factors, p. 680). Finally, since none of the studies that were assessed controlled for maternal gestational age or birth weight, the extent to which prior prematurity, LBW, or IUGR has an *independent* impact is unclear. The results for this factor are summarized in Table 10.

5. *Prior spontaneous abortion*

Background. Spontaneous abortion overlaps substantially with pre-term delivery. In particular, the distinction between late second-trimester abortion and prematurity has become progressively more blurred with the recent tendency towards increasing viability of infants born before 28 weeks of gestation. Thus second-trimester spontaneous abortion and prematurity should probably be considered as a continuum, rather than as two separate phenomena. The effect of a history of second-trimester abortion in prior pregnancies may therefore be the same as a history of prior prematurity. Potentially confounding factors that should be controlled are the same as those discussed under prior prematurity and are listed in Table 2.

Control for parity, however, requires further discussion. In particular, should women whose only previous pregnancy was a spontaneous abortion be compared with those who are pregnant for the first time, or with those who have had one previous pregnancy that resulted in a live birth? The answer depends on whether the improved outcomes associated with a second pregnancy arise because of conception and the physiological changes in early pregnancy or on the enhanced uterine blood flow and anatomical enlargement during late pregnancy. Whichever choice is made, the decision will affect the measured impact of the prior abortion history, since women with one previous live birth have better outcomes, on average, than primiparae.

One mechanism whereby prior spontaneous abortion might affect a current pregnancy is the use of dilatation and curettage (D and C) to remove retained products of conception. Cervical dilatation could lead to cervical "incompetence" and thus predispose to subsequent pre-term delivery. Thus, studies should indicate whether or not prior spontaneous abortions were followed by a D and C.

Results. Thirty-seven pertinent studies were located. Seven of these were rated as SM and the same number as PM. Two SM studies (*31*, *97*) reported that a history of prior spontaneous abortion had no effect on mean gestational age. One SM study (*117*), however, found a significantly elevated risk for prematurity. A similar risk for prematurity was reported by three PM studies (*120–122*), although one, a multicentre study by a WHO task force (*121*), found a significant effect in only one of three clusters of participating centres. A relative risk was given by Guzick et al. (*117*) and can also be calculated from the adjusted prematurity rates in the studies by Pantelakis et al. (*120*) and Schoenbaum et al. (*122*). The sample-size-weighted average relative risk for prematurity is 1.57. Insufficient data are available, however, to determine whether the risk for prematurity increases with the number of prior spontaneous abortions. If it is assumed that 10% of pregnant women (for primiparae and multiparae combined) have a history of prior spontaneous abortion, the etiologic fraction is given by:

$$EF = \frac{(0.10)(1.57-1)}{(0.10)(1.57-1)+1} = 0.054$$

Thus, since at least part of the excess risk associated with prior spontaneous abortion may be the same as that due to prior prematurity (only one SM (*117*) and one PM study (*91*) examined both effects simultaneously), and since both may be expressions of an underlying genetic tendency to early delivery, the contribution of prior spontaneous abortion to prematurity in the general population is quite small. Furthermore, the failure of virtually all studies to consider the role of post-abortion D and C

Table 11. Results of the assessment of prior spontaneous abortion

Outcome	Effect
Gestational age	0 weeks
Prematurity	
Relative risk for positive history	1.57
Etiologic fraction for $P = 0.10$	5.4%
Birth weight	0 g
IUGR	
Relative risk for positive history	1

makes it difficult to ascribe any increased risk of prematurity to the abortion itself.

Four SM studies and one PM study (*63*) reported no effect on gestational-age-adjusted birth weight, while another PM study (*123*) found no impact on the risk of IUGR. Although two reports of one SM study (*51*, *86*) and one (*121*) of two PM studies (*93*, *121*) found a significant effect on LBW, failure to control for gestational age indicates that the probable association was with prematurity rather than IUGR.

The reports of the assessment of prior spontaneous abortion are summarized in Table 11. Although there is no reason to expect that this factor is country-dependent, none of the SM or PM studies originated from developing countries, and caution is advised, therefore, in extrapolating the results to these countries.

6. Prior induced abortion

Background. Interest in this factor centres on whether cervical dilatation leads to chronic cervical changes (incompetence) that can predispose to subsequent pre-term delivery. Because of the greater dilatation that usually accompanies D and C, the main concern relates to this technique rather than to vacuum extraction. Thus both the method of induced abortion and the number of such abortions are important; and the degree of cervical dilatation used should ideally be considered as a mediating variable.

Control for parity presents the same problems for this factor as for spontaneous abortion. Studies of women whose only previous pregnancy resulted in induced abortion may find worse outcomes (especially for intrauterine growth) than those of women with one previous live birth; however, it is difficult to determine whether the effects are caused by the induced abortion or the difference in parity. Other potentially confounding factors are similar to those discussed previously for intrauterine growth and gestational duration in the sections on prior pregnancies and prior spontaneous abortion, with the addition of genital tract infection. The methodological standards used in assessing this factor are shown in Table 2.

Results. A total of 41 pertinent studies were located, seven of which were rated as SM and nine as PM. Neither of two SM (*31*, *97*) nor two PM studies (*124*, *125*) reported an effect of prior induced abortion on gestational age. One (*38*) of two relevant SM studies (*38*, *97*) found an increased risk of prematurity associated with induced abortion, as did only one of seven relevant PM studies (*120*). These results are in striking contrast to those of less well-controlled studies (those not judged as SM or PM), many of which reported a significant increase in prematurity. Two PM studies (*126*, *127*) provide evidence that D and C with dilatation over 12–13 mm may be associated with a greater risk of prematurity than D and C with lesser dilatation, vacuum extraction, or saline instillation; and prior induced abortion cannot, therefore, be completely ruled out as a risk factor for prematurity.

The data on intrauterine growth are clear. Neither of two SM (*31*, *97*) nor two PM studies (*124*, *125*) found that a history of prior induced abortion affected gestational-age-adjusted birth weight. Similarly, neither one SM study (*97*) nor two PM studies (*124*, *125*) detected any altered risk of IUGR; although in one of three SM studies and two of five PM studies that reported an effect on LBW, gestational age was not controlled, the effects, if real, may reflect prematurity rather than IUGR.

In summary, prior history of induced abortion has no apparent effect on intrauterine growth. Although most of the best evidence also shows no impact on gestational duration, D and C with extreme dilatation may increase the risk for subsequent prematurity. However, since this technique in general, and extreme dilatation in particular, are becoming less frequent practices for pregnancy termination, any effect this factor may have had in the past will probably be less relevant in the future. The SM and PM studies cited represent a fairly wide geographical distribution, including North America, western and eastern Europe, China (Province of Taiwan), Korea, and Israel, although none originated from developing countries.

7. Prior stillbirth or neonatal death

Background. A number of investigators have studied the effect of prior stillbirth or neonatal death on intrauterine growth or gestational duration in subsequent pregnancies. Most of them, however, have not adequately separated this effect from that of prior prematurity, LBW, or spontaneous abortion. Pre-term and severely growth-retarded fetuses have a vastly increased risk of being stillborn or of dying in the neonatal period. Furthermore, spontaneous delivery of a nonviable 25- or 26-week fetus may be termed variously stillbirth or second-trimester spontaneous abortion. Thus, prior LBW and spontaneous abortion should be controlled in measuring the independent impact of prior stillbirth or neonatal death.

Potentially important confounders are shown in Table 2. Control for parity is less problematic here, however, because a woman whose only previous pregnancy terminated in stillbirth or neonatal death should be compared with multiparae for subsequent pregnancy outcomes.

Results. A total of 24 relevant studies were located, of which four (all from developed countries) were rated SM and three PM. Only two studies (both SM) examined the effect of prior stillbirth or neonatal death on gestational duration. Meirik et al. (*97*) found no significant impact on gestational age, while Kaminski et al. (*57*) found an elevated risk for prematurity, although the magnitude and statistical significance of the relative risk were not reported. Meirik et al. (*97*) also found no significant effect on gestational-age-adjusted birth weight, and a PM study by Ganguly et al. (*123*) detected no increased risk for IUGR. The only SM or PM study to report a positive effect was that by Billewicz & Thomson (*63*) (rated PM), who found a lower mean adjusted birth weight in women with prior stillbirths, even after stratification for the weight of the stillborn. Incomplete control for other potential confounders, however, makes it difficult to attribute this effect to the history of stillbirth itself.

Three SM reports (*51*, *57*, *86*) (including two (*51*, *86*) based on the same study sample) and one PM study (*128*) found an elevated risk for LBW, but a failure to control for gestational age indicates that the effect may be on the risk for prematurity, rather than IUGR. Combining these findings with those of Kaminski et al. (*57*), we can conclude that prior stillbirth or neonatal death may augment the risk for subsequent prematurity.

None the less, of the four SM and three PM reports pertaining to this factor, only one (*57*) controlled for a prior history of LBW. The magnitude of the discriminant coefficient for subsequent prematurity associated with previous stillbirth in the last-mentioned study was small, and no corresponding *P*-value was indicated. Since it is likely that previous stillbirths and neonatal deaths represent severely premature or growth-retarded fetuses, any effect of these prior infant deaths is probably due to the mothers' inherent tendency for prematurity or LBW. For example, in the two reports by Linn et al. (*51*, *86*) the relative risks for prior stillbirth (3.03 and 2.63) were very similar to the relative risk for prior prematurity (2.75). In developed countries, therefore, prior stillbirth or neonatal death is probably a proxy for prior prematurity (or LBW) and not an independent determinant of gestational duration or intrauterine growth.

8. *Prior infertility*

Background. Certain hormonal factors that hinder becoming pregnant might also have an adverse influence on intrauterine growth or gestational duration. Here, the main confounding factor is genital tract infection, particularly salpingitis, since it causes infertility and there is a suspicion that it has an independent impact on pregnancy outcome. Congenital malformation of the uterus or fallopian tubes might also lead to both infertility and impaired pregnancy outcome, but its prevalence is very low.

Parity is another important confounder that requires control, since previously infertile women who become pregnant for the first time are appropriately compared with other primiparae, who are likely to have somewhat worse outcomes (especially intrauterine growth) than multiparae. Since thin women may have amenorrhea or hypo-ovulation, and also are at risk for smaller fetuses, pre-pregnancy weights should also be controlled. In the absence of data about genital tract infection, control for socioeconomic status or its risk factor correlates (cigarette and alcohol use, height, and gestational weight gain) could be used as a proxy. The methodological standards applied to this assessment are shown in Table 2.

Results. Only five studies examined prior infertility, and one each was classified as SM and PM. The SM study (*38*) found a significantly elevated risk for prematurity among women in New Haven who had not conceived, despite attempting for 12 or more months. In the PM study by Olsen et al. (*100*) a "delay" in conception of more than 6 months was associated with a significant decrease in adjusted birth weight among Danish women who delivered full-term singleton infants; however, whether the women studied were really attempting to conceive is not clear. Furthermore, most of the decrease in birth weight occurred among women with "delays" of 7–12 months. If these women are combined with those who had a delay of 1–6 months, in order to correspond more closely to the usual definition of infertility, no difference in birth weight was apparent for women with delays of $\geqslant 13$ months.

Neither of these two studies was controlled for genital tract infection, and Olsen et al. did not control for pre-pregnancy weight, although parity and other potential risk factors were controlled in both studies. In view of the paucity of information on prior infertility, and unresolved concerns about the adequacy of control for confounding, no definite conclusion can be drawn about its effect on pregnancy duration or intrauterine growth.

9. In utero *exposure to diethylstilbestrol*

Background. Women who had been exposed *in utero* (i.e., during their mothers' pregnancies) to diethylstilbestrol have a greatly increased prevalence of vaginal and cervical ridges, vaginal adenosis, and uterine malformations (*129*, *130*), which might well cause problems with either intrauterine growth or gestational duration. The major methodological difficulty in investigating the effect of exposure to

diethylstilbestrol is determining why the drug was prescribed to the women's mothers. Its use during pregnancy was discontinued in 1971 following report of an association with vaginal adenocarcinoma in female offspring (*131*, *132*). Prior to this, however, it was frequently used to "treat" women with a history of prematurity or spontaneous abortion, despite evidence from randomized trials that it was ineffective for this purpose (*133*). Because maternal LBW or prematurity may be an independent risk factor indicating an inherent (genetic) tendency towards prematurity (see above), the daughters of such women might inherit this independently of exposure to diethylstilbestrol. Control for this important confounding factor is thus important. Furthermore, since pre-pregnancy weight appears to be an independent risk factor for prematurity and may also have a genetic component, it should also be controlled. Parity is another important source of confounding, since women exposed to diethylstilbestrol might be less fertile or not wish to become pregnant as often, and thus might be over-represented among primiparae. Finally, anxiety (or its risk factor correlates, cigarette smoking and alcohol consumption) could be caused by knowledge of prior exposure to diethylstilbestrol and the risk of vaginal cancer, and strictly speaking, these factors should also be controlled.

Results. Eight pertinent reports, all from the USA, were located; one was rated as SM (*135*) and two as PM (*134*, *136*). One of the PM reports (*134*) later formed part of the larger and better-controlled SM report (*135*).

The reports by Herbst et al. (*134*, *135*) are particularly interesting, because the subjects were the female offspring of mothers who participated in a randomized, placebo-controlled trial of diethylstilbestrol in the early 1950s (*133*). Women in the exposed and control groups should therefore have been similar with respect to maternal LBW or prematurity and other heritable factors that could affect pregnancy risk.

In their SM report, Herbst et al. (*135*) found a significantly higher rate of LBW (and correspondingly lower rate of birth weights $\geqslant$2500 g) among exposed women than in the control group. The rate of full-term deliveries ($\geqslant$37 weeks gestational age) was significantly lower in the group exposed to diethylstilbestrol, thus indicating that the reported effect is probably on prematurity rather than IUGR. Furthermore, there was a significantly higher rate of adverse pregnancy outcomes (not considered separately for prematurity or LBW) among exposed women with cervical ridges, and a similar but non-significant trend in those with vaginal changes and those who were exposed before the 14th week of their mothers' gestation. The PM study by Barnes et al. (*136*) reported very similar findings, although the control group consisted of both non-exposed sisters and age-matched unrelated women, whose mothers presumably had fewer pregnancy problems. The women exposed to diethylstilbestrol tended to have a higher risk for prematurity, but the definition of prematurity used (birth weight $<$2500 g *or* gestational age $<$36 weeks) does not distinguish between IUGR and true prematurity. None the less, since the exposed women had a significantly higher risk of never having had a full-term live birth (birth weight $\geqslant$2500 g and gestational age $\geqslant$36 weeks), as well as a higher risk of spontaneous abortion, the result probably reflects an influence on prematurity, not IUGR. As in the study by Herbst et al. (*135*), women exposed to diethylstilbestrol who had cervical and vaginal structural defects tended to have higher "prematurity" rates. Furthermore, the exposed women with a history of "premature" delivery had significantly longer *in utero* exposures and a trend towards higher doses and exposure earlier in gestation than those without such a history, thus indicating a dose–response effect.

If it is assumed that the increased risks in the above studies by Herbst et al. and Barnes et al. reflect an effect on prematurity, the sample-size-weighted average relative risk is 2.25. It has been estimated that 1–1.5 million women were exposed to diethylstilbestrol prior to 1971 in the USA (*137*). Furthermore, if we take it that all of these are now of child-bearing age and that the total number of women of child-bearing age in the USA is about 40 million, the proportion of child-bearing women with a history of exposure to diethylstilbestrol is 1.5/40, or 3.75%. The etiologic fraction for the child-bearing population in the USA can then be calculated as:

$$\mathrm{EF} = \frac{(0.0375)(2.25-1)}{(0.0375)(2.25-1)+1} = 0.045$$

Thus, up to 4.5% of premature births in the USA could be attributable to *in utero* exposure to diethylstilbestrol, although this is probably an overestimate. Also, prematurity caused by this factor should become less frequent in the USA as exposed women age beyond their childbearing years, since few (if any) women today are given diethylstilbestrol during pregnancy. No studies were found that dealt with the effect of *in utero* exposure to diethylstilbestrol outside the USA.

D. *Nutritional factors*

1. Gestational weight gain

Background. Since maternal caloric intake and nutritional stores (mostly fat) are the sole source for

fetal energy requirements, weight gain during pregnancy would be expected to affect intrauterine growth. Gestational weight gain has four principal components: laying down of fat stores; growth of breast and uterine tissue; increased plasma volume; and growth of the fetus, placenta, and amniotic fluid (*138*). Only the first of these serves as an energy source to the growing fetus. None the less, a correlation might be expected between overall weight gain and birth weight. Since growth of the fetus, placenta, and amniotic fluid includes, and is largely determined by, fetal size, attempts to correlate gestational weight gain with birth weight should ideally subtract the birth weight and the weights of the placenta and amniotic fluid from the overall gestational weight gain.

Maternal energy stores are a major source of nutrients for the fetus, and pre-pregnancy nutritional status (as reflected in pre-pregnancy weight-for-height or skinfold thickness) should therefore be important. Not only might it confound the association between gestational weight gain and intrauterine growth (since the former may vary according to pre-pregnancy nutrition), but it is also a likely effect modifier of gestational weight gain. Thus we might expect an interaction between gestational weight gain and pre-pregnancy nutrition, such that for a given gestational weight gain thin women would derive a greater increase in birth weight than other women. In contrast, for women who begin pregnancy with large fat stores, gestational weight gain might have little if any effect on intrauterine growth.

Besides maternal pre-pregnancy weight and height, other potential confounders that require control include age (or parity), racial/ethnic origin, socioeconomic status, cigarette and alcohol use, and antenatal care, because each of these may co-vary with both gestational weight gain and pregnancy outcome (see Table 2). Finally, the length of gestation itself must be controlled, because women who deliver prematurely will have less time to increase their weight. In order to take this into account, gestational weight gain should be expressed as a rate (e.g., g/week) rather than a total weight. For assessments of intrauterine growth, overall gestational weight gain can be used if gestational age is controlled.

Results. Sixty-one pertinent studies were identified, 10 of which were rated as SM and 18 as PM. One SM (*31*) and one PM study (*139*) reported a significant positive effect of gestational weight gain on gestational age, and one SM (*16*) and one PM study (*38*) found that high gestational weight gain reduced the rate of prematurity. Of these four studies, however, only that by Miller & Merritt (*16*) expressed gestational weight gain as a rate (g/week). Hence it is not clear whether the reported association in the other three studies arose because the gestational weight gain had an effect on gestational duration or simply because women with shorter pregnancies had less time to gain weight. Miller & Merritt reported a higher rate of prematurity among White women who gained less than 227 g/week during the last two trimesters, but no effect was seen among Black women in the study, and no definitive conclusion can therefore be drawn. Most of the evidence, however, indicates that gestational weight gain has no effect on gestational duration.

Data for an effect on intrauterine growth are clearer. All seven SM studies reported that gestational weight gain had a positive effect on gestational-age-adjusted birth weight, and each of two SM studies (*16*, *55*) found a significant effect on IUGR. Of the SM studies, however, only two (*53*, *118*) permitted calculation of the effect of gestational weight gain on birth weight in g/kg. Niswander & Jackson (*53*) reported a positive effect among Blacks and Whites in the USA (21.1 g/kg and 19.0 g/kg, respectively), which was also similar to the value of 20.7 g/kg reported by Rush et al. (*118*) among Blacks in New York City. The sample-size-weighted average effect from these two studies is 20.3 g/kg. In another SM study, Horon et al. (*46*) reported that women with a gestational weight gain $\leqslant$9.1 kg had an adjusted birth weight that was 120.8 g lower than those with weight gains of 9.5–13.6 kg. It should be noted that these effect magnitudes may be overestimates, since none of the studies corrected for the weight of the products of conception. Although all the SM studies discussed above originated from developed countries, PM studies from Peru (*140*) and of poor urban New York City Blacks (*118*) reported similar results.

Quantitative estimates of the effect of gestational weight gain on the risk for IUGR can be derived from the two pertinent SM studies. The Mantel–Haenszel relative risk for IUGR associated with gestational weight gain $<$227 g/week for the combined data on Blacks and Whites in the study by Miller & Merritt (*16*) (IUGR includes both infants of low ponderal index and those who were short-for-dates) is 2.06. The adjusted odds ratio of 1.28 for IUGR determined by Scott et al. (*55*) related to women with gestational weight gains that were less than 1 standard deviation below the mean "net" gestational weight gain (minus fetal and placental weight) in the control group (9.0 kg), i.e., less than 4.3 kg. The gestational weight gain of 227 g/week reported by Miller & Merritt corresponds to a total gain of about 7 kg for a full-term pregnancy. If we assume an average total gestational weight gain in developed countries of 11 kg, and a standard deviation of 4.5 kg, both of the relative risks mentioned above pertain to the risk of IUGR associated with a weight gain about 1

standard deviation below the mean. The corresponding sample-size-weighted average relative risk is 1.98. Since women with a gestational weight gain less than 1 standard deviation below the mean value can be estimated, using the theory of the normal curve, to represent 16% of the population, this relative risk corresponds to an etiologic fraction of:

$$EF = \frac{(0.16)(1.98-1)}{(0.16)(1.98-1)+1} = 0.136$$

In a developing country with a mean gestational weight gain of 6 kg, the prevalence of gains <7 kg would be about 0.59, which corresponds to an etiologic fraction of:

$$EF = \frac{0.59(1.98-1)}{0.59(1.98-1)+1} = 0.366$$

It should be noted that the effects on intrauterine growth are average effects in women with adequate pre-pregnancy nutritional status and thus do not take into account the potential modification of the gestational weight gain by pre-pregnancy nutritional status. Studies of the effect of a given gestational weight gain among women of varying pre-pregnancy weight-for-height have virtually unanimously concluded that the two factors strongly interact. Miller & Merritt (*16*), for example, reported that IUGR rates increased among women of low gestational weight gain as their pre-pregnancy weight-for-height decreased. Similar results were reported in several PM studies of the effect on birth weight, including those by Winikoff & Debrovner (*69*) and by Naeye (*65, 141*). Thus it seems clear that undernourished women reap a greater benefit than other women from a given gestational weight gain.

This effect modification by pre-pregnancy nutritional status is of major importance in developing countries. The etiological fraction of 36.6% calculated above corresponds to a relative risk for IUGR of 1.98 for gestational weight gains <7 kg. Since a large proportion of pregnant women can be expected to be undernourished in these countries, the relative risk and the etiological fraction may actually be much higher. The results for this factor are summarized in Table 12.

Table 12. Results of the assessment of gestational weight gain

Outcome	Effect
Gestational age	0 (?) weeks
Prematurity	
Relative risk	1 (?)
Birth weight	
g/kg total gestational weight gain (well-nourished women)	20.3 g/kg
IUGR	
Relative risk for total gestational weight gain <7 kg (well-nourished women)	1.98
Etiologic fraction for:	
$P = 0.16$ (mean gestational weight gain = 11 kg)	13.6%
$P = 0.59$ (mean gestational weight gain = 6 kg)	36.6%

2. *Caloric intake*

Background. Maternal caloric intake during pregnancy is closely related to gestational weight gain; however, it is more purely nutritional than the latter, in that it is not "diluted" by the increases in plasma volume and breast and uterine size.

Compared with gestational weight gain, caloric intake has two main disadvantages, however, in assessing the effect of maternal energy supply to the fetus. Firstly, it takes no account of energy expenditure. Women who burn more calories will usually also consume more calories. Gestational weight gain, on the other hand, reflects net positive energy balance. Thus, measurement of the impact of caloric intake requires control for caloric expenditure. Secondly, it is difficult to measure caloric intake with validity and precision.

An important aspect of caloric intake, however, and one that distinguishes it from all the factors considered so far, is its susceptibility to experimental intervention. In particular, random assignment of caloric supplementation is feasible and provides the best methodological approach to assessing the effect of this factor, provided that caloric substitution and net caloric increase are taken into account.

For this factor, important potential confounders that require control (see Table 2) include intake of other nutrients (especially protein), which is highly correlated with caloric intake. Other confounding factors are similar to those discussed for gestational weight gain and include racial/ethnic origin, socioeconomic status, age (or parity), height, pre-pregnancy weight, and cigarette and/or alcohol consumption. The effect of caloric intake on gestational duration should be based on the daily intake (or total intake early in pregnancy) rather than total overall intake. Effects on intrauterine growth should either be based on a similar measure of caloric intake or should control for gestational age. Finally, as with gestational weight gain, we should seek evidence for effect modification by pre-pregnancy nutritional status.

Results. A total of 41 relevant reports were located, although several represented multiple reports of the same study. Thirteen were classified as SM and another 12 as PM. The results were very similar to those seen for gestational weight gain.

Only one (*142*) of the five relevant SM reports found a significant association between caloric intake and gestational age, but this was inconsistent with the results of two previous reports of the same study of caloric supplementation in Guatemala (*143*, *144*). Delgado et al. (*142*) also reported a significant reduction in prematurity with increasing caloric intake, but no such effect was detected in randomized trials of caloric supplementation in China (Province of Taiwan) (*145*) or New York City (*146*). Stein et al. (*23*) concluded that Dutch mothers exposed during the Second World War to severe famine in the first trimester were more likely to deliver prematurely, but a simultaneous increase in first-week deaths in non-famine cities led them to postulate an interaction with antenatal maternal infection. Thus, although definite conclusions cannot be drawn, most of the evidence suggests that maternal caloric intake has no effect on gestational duration. The absence of an effect on gestational age in two PM studies (*147*, *148*) adds additional weight to this evidence.

The data on birth weight indicate a significant effect, provided the mother is not well nourished prior to pregnancy. Two of nine SM studies (*146*, *149*) reported no significant effect of maternal caloric intake on gestational-age-adjusted birth weight, and it seems likely that the majority of study mothers had adequate pre-pregnancy nutrition. In two SM reports of the caloric supplementation trial in China (Province of Taiwan) (*150*, *145*), the overall effect, although not statistically significant, was in the expected direction; however, since only 6.7% of the infants previously born to study mothers weighed less than 2500 g at birth, these Taiwanese women were probably well nourished prior to pregnancy. The remaining five SM reports, all of mothers of poor or borderline nutritional status, found a significant impact. Two SM reports of a supplementation trial in Bogotá, Colombia (*151*, *152*) also showed a clear trend—a statistically non-significant increase of 51 g in the supplemented group; however, stratification by pre-supplementation weight-for-height revealed a large (181 g) and statistically significant effect for thin women, compared with almost no effect (22 g) for those with adequate weight-for-height. Similarly, Prentice et al. (*153*) detected an effect of caloric supplementation only during the wet season in the Gambia, when most pregnant women have a negative energy balance. Analogous findings were also reported in a PM supplementation trial by Viegas et al. (*154*).

Data on the importance of timing of caloric intake are far from clear. The Dutch famine study (*23*) found that caloric *deprivation* was important only in the third trimester. The positive results in the Bogotá trial (*151*, *152*) were based on caloric *supplementation* during the third trimester. On the other hand, the study in Guatemala (*143*) suggests that total calories, including those given in the first two trimesters, have an impact, a result supported by a more recent supplementation trial in the Gambia (*153*).

There is also the possibility of effect modification by infant sex. In both the trials in Bogotá and China (Province of Taiwan), the effect of supplementation was greater among male than female infants; however, no such effect was seen in the trials in Guatemala or New York City (*146*) or in the Dutch famine study.

To quantify the effect of supplemental caloric intake on birth weight, we must stratify for pre-pregnant nutritional status. Many of the mothers in the trials in Guatemala, Bogotá, and the Gambia (wet season only) were at least moderately undernourished prior to supplementation. If calories taken at any time during pregnancy have the same impact on birth weight, the sample size-weighted effect from these three trials is 99.7 g/100 kcal/day. In other words, for each additional 100 kcal per day ingested throughout pregnancy, the birth weight will increase by about 100 g. We can calculate the effect for non-malnourished women using data from the high weight-for-height groups in Bogotá, the dry season in the Gambia, China (Province of Taiwan), and New York City (assuming that women received the lower protein "complements" for an average of 16 weeks and ignoring the results for women who received high-protein "supplement", which may have had a negative effect). In this way, the sample-size-weighted effect magnitude calculated is 34.6 g/100 kcal/day given throughout pregnancy, i.e., only about one-third of that for undernourished women.

The trials in Guatemala and the Gambia (wet season) both showed a significantly reduced risk of IUGR in women who received the supplements. In accord with the results for birth weight, supplementation produced a non-significant reduction in risk for better-nourished women during the dry season in the Gambia or in China (Province of Taiwan). Estimating the magnitude of the risk reduction is difficult, because of the different degrees of supplementation used in the various trials. For example, in Guatemala, a mean difference of 96 kcal/day (extended over 280 days of a pregnancy) approximately halved the relative risk for IUGR; and in the wet season in the Gambia, a net caloric supplementation of 216 kcal/day was associated with a relative risk of 0.17 for IUGR. If a linear relationship is assumed between the amount of caloric supplementation and the natural

Table 13. Results of the assessment of caloric intake

Outcome	Effect
Gestational age	0 (?) weeks
Prematurity	
Relative risk	1 (?)
Birth weight	
g/100 kcal/day supplement throughout pregnancy:	
Undernourished women	99.7 g/100 kcal/day
Well-nourished women	34.6 g/100 kcal/day
IUGR	
Relative risk for 100 kcal/day supplement throughout pregnancy:	
Undernourished women	0.47
Well-nourished women	0.82

logarithm of the relative risk, the approximate sample-size-weighted average is 0.47 for 100 kcal/day supplemented throughout pregnancy. With the same assumptions, we can calculate the sample-size-weighted relative risk associated with each 100 kcal/day supplement in well-nourished women to be 0.82, based on data from the trials in China (Province of Taiwan) and the Gambia (dry season).

The results for caloric intake are summarized in Table 13. It should be re-emphasized that the effects of caloric intake are not independent of those for gestational weight gain.

3. Energy expenditure, work, and physical activity

Background. This factor is of major interest in rural areas of developing countries, because women in such areas often engage in strenuous outdoor activities, even during pregnancy. Maternal work, however, could have an effect on pregnancy independently of its nutritional (energy) effect. In particular, physical exertion or upright posture might diminish uterine blood flow and thus hinder the supply of oxygen and nutrients to the fetus. This has been stressed by Briend (*155*, *156*) and is supported by experimental research in animals (*157*) and humans (*158*), although some contradictory evidence has been adduced (*159*). Postprandial physical exertion might also lead to reduced absorption of nutrients by shifting blood flow away from the gastrointestinal tract. Psychological stress is yet another mechanism whereby maternal employment might affect intrauterine growth or (especially) gestational duration. Finally, the possible beneficial or harmful effects of leisure-time physical activity also need to be considered, especially in developed countries, where women may continue to engage in sport and exercise during pregnancy.

The methodological issues (see Table 2) that are important for this "factor" vary depending on the particular aspect of maternal physical activity under consideration. If the focus is on energy expenditure or strenuous physical labour, studies should control for caloric intake, since the net balance of available energy, as reflected in the gestational weight gain, depends on both caloric intake and expenditure. Because women who burn more calories are also likely to eat more (if sufficient food is available), failure to control for caloric intake may yield spurious results. Other factors that require control include age (or parity), height, pre-pregnancy weight, racial/ethnic origin, and either socioeconomic status or its risk factor correlates.

In contrast, if the interest is on posture, fatigue, psychological stress, or aspects of maternal work not involving increased energy expenditure, caloric intake need not be controlled. Since the type of work may vary according to a woman's age, height, weight, racial/ethnic origin, and socioeconomic status, however, these factors still require control. Furthermore, if the focus is on stress- or anxiety-related aspects of work, any observed effect may add to and overlap with other sources of stress or anxiety.

Leisure-time physical activity is likely to co-vary with many of the same factors, but for different reasons. In developed countries, women who engage in such activity are more likely to be young, well-nourished, of high socioeconomic status, and less likely to be members of a racial minority. They are also far less likely to smoke or drink. Finally, since intensive sport or exercise entails significant energy expenditure, caloric intake should also be controlled.

Results. Thirty-four reports were identified that had a bearing on the effect of maternal work or physical activity, several of which were multiple reports of the same study; three reports (two studies) were classified as SM and 18 as PM.

It was often difficult to separate the effects of energy expenditure from non-energy-related work factors. In many of the reports from developed countries, for example, maternal work was studied as a dichotomous variable (e.g., paid employment versus no paid employment during pregnancy), with no attempt to distinguish different types of work in terms of physical exertion, posture, fatigue, or stress. In most studies from developing countries, on the other hand, the maternal work involved considerable caloric expenditure, in addition to any non-energy-related effects.

No SM reports assessed the effect of maternal work on gestational age. Two PM reports that used a single set of data from the Gambia (*160, 161*), however, found no significant effect. The evidence concerning prematurity is conflicting: the two SM studies of maternal employment, both from developed countries, arrived at different conclusions. Berkowitz et al. (*162*) found that working mothers had no elevated risk after adequate control for potential confounders, and that there were no bivariate associations between prematurity and physical position during work, lifting or carrying, weights of loads, frequency of lifting, number of hours worked, hours per week of housework, the use of housework assistance, climbing stairs, or hours per week of child care. On the contrary, light and moderate leisure-time physical activity was associated with a significantly reduced risk of prematurity. This was the only SM or PM study to examine this aspect of maternal physical activity. Mamelle et al. (*43*), on the other hand, reported an increased risk of prematurity among working women whose work involved tiring postures, industrial machines, physical exertion, mental stress, or a physically uncomfortable environment. Unfortunately, neither of these two studies controlled for maternal caloric intake.

Among the PM studies that had a bearing on prematurity, that by Kaminsky et al. (*57*) found no increased risk among women who said they had worked outdoors during pregnancy. Murphy et al. (*163*) reported no significant difference in prematurity rates between employed and unemployed women during pregnancy, although re-analysis of the same data by Williams (*164*) showed a significantly reduced risk among the employed women. Similarly, two reports of a single French study (*165, 166*) found a reduced risk of prematurity among working women, although those who worked more than 42 hours per week or worked in a standing position had an increased risk.

Thus, the available evidence permits no definite conclusions to be drawn on the effects of working during pregnancy on gestational duration. Upright posture and prolonged strenuous or stressful work activities may increase the risk for prematurity, and moderate leisure-time physical activity may reduce the risk, at least in developed countries, but further studies are required.

No SM reports were located that dealt with the effect of maternal work on intrauterine growth. Of 12 PM reports, seven found a significant reduction in birth weight among working women, including all six studies (four from developing countries) that controlled for gestational age. Three of the PM reports (*164–166*) found no evidence of increased risk of IUGR in working women, but all were from developed countries where maternal work does not generally require large energy expenditures. Incomplete control for potentially important confounding factors in these PM studies, however, precludes definitive inferences, even for heavy physical labour in developing countries. For example, several reports from the Gambia (*161, 167, 168*) document lower birth weights during the labour-intensive wet season, but this is confounded by lower food availability and higher malarial activity during this season. Similarly, Tafari et al. (*169*) found higher birth weights among Ethiopian women not exposed to strenuous work (housewives with domestic help or women with sedentary jobs) than among those who engaged in more demanding work (housewives without domestic help or women with strenuous jobs); however, these two groups were probably of different ages, parities, and socioeconomic status — none of which was controlled.

Finally, two PM reports provide some evidence of an important interaction between maternal work and maternal nutrition. Both Tafari et al. (*169*) and Naeye & Peters (*170*) found a greater reduction in birth weight that was attributable to maternal work for women with low pre-pregnancy weight and gestational weight gain.

In summary, the effect of maternal work on intrauterine growth is uncertain. Such an effect would nevertheless be consistent both with biological principles and with the evidence already examined concerning gestational weight gain and caloric intake, at least for work involving high energy expenditure. Increased effects in undernourished women, if confirmed, would identify a factor of major importance in developing countries, where women often continue strenuous physical work through pregnancy. Future studies should attempt to distinguish (whenever possible) between the effects of energy expenditure, posture, fatigue, and stress.

4. Protein intake/status

Background. Fetal growth cannot occur without a source of nitrogen and essential amino acids. What is not so clear, however, is whether and to what extent commonly occurring inadequacies in maternal protein status or intake can impair pregnancy outcome. Studies of this factor could relate intrauterine growth or gestational duration to one of the following aspects of maternal protein nutrition: existing protein nutriture, e.g., lean body mass or serum albumin concentration; protein intake, as measured by dietary recall or direct observation and analysis; or protein supplementation.

Here again an experimental design (protein supplementation) can be used to minimize the potential for confounding bias. In non-experimental studies, the potential for confounding by caloric, vitamin, and mineral intake is considerable, and these (especially

caloric intake) should be controlled in any attempt to isolate the effect of protein. Only studies that used an experimental design were eligible for an SM rating, and control for caloric intake (or gestational weight gain) was required to be rated SM or PM. Other important confounders are similar to those discussed for caloric intake (see Table 2). Finally, total serum protein concentration declines during pregnancy (*171*). Studies relating gestational duration to serum protein concentration should therefore either be based on measurements made very early in pregnancy or control for the gestational age at which the measurements were made.

Results. In total, 32 pertinent studies were located, of which only two were rated SM and six PM. The major methodological shortcoming was failure to control for the confounding effects of other nutritional variables, especially caloric intake. The evidence that has a bearing on gestational duration, though meagre, is clear: two SM (*144*, *146*) and two PM studies (*154*, *172*) found that protein supplementation had no significant effect on gestational age, and Rush et al. (*146*) detected no significantly altered risk for prematurity.

Two SM supplementation trials, one each in Guatemala (*144*) and New York City (*146*), found that protein supplementation did not have a significant effect on birth weight. Among the four PM supplementation trials, the study by Adams et al. (*173*) detected no difference in birth weight for women who received supplements. Also, Viegas et al. reported that protein supplementation during the second and third trimesters had no effect on unselected Asian mothers in the United Kingdom (*174*), but there was a significant increase in birth weight when similar supplementation was given during the third trimester to women with poor increments in triceps skinfolds (*154*). In the latter study, however, women who received only calorie supplementation had lower height, weight, and triceps skinfolds than those who received calories plus protein. Furthermore, among well-nourished women (those with adequate triceps skinfold increments), birth weight was *lower* for the group who received calorie and protein supplements, and the decrease was almost statistically significant. Thus it is difficult to attribute the higher birth weights in the undernourished women to the protein supplement. In the fourth PM supplementation trial (*172*) a significantly lower birth weight was found for women who received a supplement that provided, on average, 9.0 g/day of protein in excess of that consumed by the control group. The lack of an equicaloric group that received no protein supplements and incomplete control for confounding, however, make this result difficult to interpret. None the less, the possibility that protein supplementation can impair intrauterine growth cannot be dismissed. Rush et al. (*146*) noted a lower mean birth weight among mothers who received, on average, a protein supplement of 27.7 g/day above their normal intake, compared with those who received a calorie supplement only. Although the difference was not statistically significant for the overall group, it was for those mothers who delivered prematurely.

The two other PM studies that had a bearing on intrauterine growth are based not on trials of protein supplementation, but on correlational analyses. Metcoff et al. (*175*) found that neither maternal dietary protein, hair protein content, nor serum total protein at mid-gestation differed significantly for groups of women whose infants had adjusted birth weights, relative to the mean, that were low (< -1 standard deviation), average (-1 to $+1$ standard deviation), or high ($> +1$ standard deviation). In a multiple regression analysis, however, the 1-day dietary history of protein intake had a significant positive correlation with birth weight. In view of the numerous variables assessed, it is difficult to exclude chance as an explanation for this finding. In the other PM correlational study, Bhargava et al. (*176*) reported no significant association in Indian women between the concentration of maternal postpartum serum albumin and birth weight after stratification for height and postpartum weight.

In summary, the evidence does not support an important role for maternal protein intake or status in either gestational duration or intrauterine growth. The effect of extreme degrees of protein deficiency has not been studied. Although the presumed low prevalence of such extreme deficiency may diminish its global impact, its significance for individual mothers or certain severely malnourished subgroups remains to be assessed.

5. *Iron and anaemia*

Background. Despite increased maternal erythropoiesis during pregnancy, haemoglobin concentration falls progressively until about the 32nd week of gestation (*177*), owing to even greater increases in plasma volume. Anaemia, especially if severe, could impair oxygen delivery to the fetus and thus interfere with normal intrauterine growth or pregnancy duration. Iron deficiency, even without anaemia, might affect key enzymes (especially cytochromes) and thereby also lead to adverse pregnancy outcomes.

Because iron supplementation can be allocated experimentally, randomized trials (required for SM rating) provide the best methodological approach to minimize confounding in studies of this factor. Less rigorous designs include correlating dietary iron intake (determined by interview or direct observation) or blood haemoglobin concentration (or

haematocrit) with the subsequent outcome. Because haemoglobin levels fall during pregnancy, however, they should be measured very early in pregnancy, since otherwise, the effect is confounded with that of expanded plasma volume (see Maternal haemodynamics, p. 679). Moreover, the tendency of women who deliver prematurely to have higher concentrations of haemoglobin may obscure an effect unless the gestational age at measurement is controlled. As shown in Table 2, additional potentially important confounding variables are similar to those cited for other nutritional factors. Of particular importance is control for other nutrients, especially caloric intake (or gestational weight gain), and only studies that included such control were eligible for an SM or PM rating.

Results. Although 42 relevant studies were identified, none was rated SM and only five received a PM rating. The major methodological flaws were a tendency to correlate pregnancy outcome with haemoglobin concentration (or haematocrit) measured late in pregnancy or at delivery and a failure to control for caloric intake and other nutritionally related confounders.

Of the PM studies, only one (*178*) was a randomized trial of iron supplementation (60 mg/day). No effect was seen on either gestational age or birth weight, but the small sample size and high drop-out rate preclude definitive inferences. Furthermore, although the Australian women who participated in the trial were generally of low socioeconomic status, their mean haemoglobin concentration was 12.7 g/dl. Few of these women were likely to have been anaemic, and the findings are of little relevance for developing countries where the prevalence of iron-deficiency anaemia is high.

The other four PM studies (*31*, *123*, *175*, *179*) were observational (correlational) and were carried out in developed countries. None reported a significant effect of haematological status or iron intake on gestational-age-adjusted birth weight. One study (*31*) found a positive correlation between consumption of iron supplements and gestational age, but whether this refers to any supplementation, regardless of quantity, or is dose-related is unclear. None of the five PM studies examined the effect on prematurity or IUGR.

In summary, studies that have a bearing on the impact of iron or anaemia on intrauterine growth or gestational duration are particularly weak from a methodological standpoint. The few reasonably rigorous investigations do not indicate any significant effects, especially for birth weight; because none of these was carried out in a developing country, however, it cannot be ruled out that iron supplementation could be beneficial in countries with a high prevalence of iron-deficiency anaemia.

6. Folic acid and vitamin B_{12}

Background. The importance of both folic acid and vitamin B_{12} for DNA synthesis suggests that these micronutrients might play a role in intrauterine growth or gestational duration. Because of the potential for confounding by both nutritional and non-nutritional correlates of folate and vitamin B_{12} status, randomized supplementing trials represent the soundest methodological approach for elucidating the possible roles of these factors. Use of an experimental design was thus considered necessary for studies to receive an SM rating.

For observational studies, confounding variables that require control are similar to those for other nutritional factors (Table 2). Among the nutritional confounders, caloric intake (or gestational weight gain) and iron status are the most important (control for both were required for a PM or SM rating), even though the role of iron is uncertain (see previous section), since calorie and iron deficiency often occur together with folate deficiency. Finally, because blood levels of folic acid and vitamin B_{12} usually decline progressively during normal pregnancy (*171*), studies that use vitamin levels should either be based on measurements taken very early in pregnancy or controlled for the gestational age at the time of measurement.

Results. Twenty-seven studies with data that had a bearing on the effects of folic acid or vitamin B_{12} (four studies reported on both) were located. Five SM and four PM studies concerned folate, all but one of which (*175*) were supplementation trials. Only one SM supplementation trial (*180*) and one PM observational study (*181*) examined the role of vitamin B_{12}.

Three SM (*182–184*) and two PM studies (*178*, *185*) from developed countries investigated the effects of folate on gestational age. Only one of the PM studies (*185*) found a significant impact, with a mean gestational age of 40.7 weeks for women who received folate supplements and 39.9 weeks for those who received no supplement. The longer-than-expected mean gestational age for the supplemented group, coupled with a drop-out rate of nearly 50% and a failure to show equivalence of prognostically important variables (i.e., lack of bias) among those who completed the trial suggest the need for cautious interpretation. No SM or PM studies reported on the effect of folate on prematurity rates. The bulk of evidence, therefore, suggests that folate (or at least folate supplementation) has no effect on gestational duration, and this is supported by the absence of an effect among women with low serum folate levels prior to supplementation (*183*).

Data on intrauterine growth (i.e., birth weight, since no SM or PM studies reported on IUGR) are

less clear. Three SM clinical trials from developed countries (*182*, *183*, *186*) found that folate supplementation had no effect. One of these (*183*) reported no effect for women with low serum folate concentrations prior to supplementation. In contrast, a fourth SM supplementation trial (*184*) reported an increase in mean birth weight of 407 g for women who received folate and iron supplements versus those who received iron alone. This result applied to only 36 well-nourished Danish women, although it was claimed that the subjects' deliveries in early June, following a winter and spring when uncooked green vegetables were in short supply, argue for a seasonal folate deficiency. None the less, the small sample size, coupled with the very high mean birth weight (3610 g) in the folate-supplemented group, as well as absence of random treatment assignment, indicates the need for cautious interpretation of these results.

In the fifth SM supplementation trial (*180*), a beneficial effect of folate on birth weight was conditional on prior nutritional status. Large positive effects (a difference in mean birth weight of 340 g) were seen in 183 South African Bantus whose diets were deficient in folic acid, while no significant benefit was observed in 172 well-nourished Whites.

Results were conflicting in the four PM studies, including three supplementation trials (*178*, *185*, *187*) and one correlational study (*175*). Of these, only Iyengar (*187*) and Blot et al. (*185*) found that folate had a positive effect on birth weight, and once again, large drop-out rates, with their potential for confounding bias, vitiate the reported results. The trial reported by Iyengar (*187*) was the only PM study from a developing country (India).

The evidence supporting an important role for folic acid in intrauterine growth is weak; however, a beneficial effect on folate-deficient populations cannot be entirely ruled out. Randomized trials of folate supplementation, incorporating methodologically rigorous procedures and efforts to maximize follow-up, would seem to be warranted in such populations, especially in developing countries.

Only one SM study (*180*) investigated the role of vitamin B_{12}. No difference in birth weight was seen in either Bantu or White South African women who received supplementations of folic acid and vitamin B_{12} versus those who received folic acid alone. No evidence was presented, however, that either of these groups was prone to vitamin-B_{12} deficiency, and thus the relevance of the findings for populations with diets deficient in vitamin B_{12} (e.g., strict vegetarians) is uncertain. Finally, the PM observational study by Roberts et al. (*181*) found no association between serum concentrations of vitamin B_{12} (determined upon registering for antenatal care) and birth weight after stratification for ethnic origin, even among vegetarian Asian immigrants with low levels of vitamin B_{12}. The available high-quality data are thus meagre, but the vitamin does not appear to play an important role in intrauterine growth. Although neither of these two studies measured gestational age, the absence of any effect on birth weight unadjusted for gestational age also argues against an impact on gestational duration.

7. Zinc and copper

Background. Maternal zinc status could affect intrauterine growth or gestational duration in one of two ways. Firstly, zinc is a cofactor for several key enzymes, including carbonic anhydrase and DNA polymerase. In particular, reduced activity of DNA polymerase as a result of zinc deficiency could lead to impaired DNA synthesis and, therefore, fetal growth. Secondly, there is evidence for a low-molecular-weight peptide in amniotic fluid that has zinc-dependent broad-spectrum antibacterial activity (*188*). Moreover, the amniotic fluids of African women, whose diets are often deficient in zinc, have lower antibacterial activity, which is restored to normal upon addition of zinc (*189*, *190*).

Copper is also a cofactor for certain essential enzymes, including cytochrome oxidase, monoamine oxidase, and L-ascorbate oxidase. Copper deficiency *per se* is very rare, however, in the absence of severe intestinal malabsorption. The major clinical manifestations of copper deficiency in humans include anaemia, neutropenia, central nervous system degeneration, and skeletal defects. A primary effect on intrauterine growth or gestational duration is not strongly suggested from either animal or human studies.

The methodological issues for copper and zinc are similar to those discussed for other nutritional factors (Table 2). Thus randomized supplementation trials provide the most rigorous approach, and only studies that used an experimental design were rated SM. Observational studies of dietary intake or blood or tissue levels of zinc or copper should control for the important potential confounders outlined previously, particularly caloric intake or gestational weight gain (required for an SM or PM rating) and pre-pregnancy nutritional status. Zinc levels decrease progressively during gestation, while those of copper gradually increase (*191*). Thus, studies that correlate the levels of these elements with pregnancy outcome must either measure them very early in gestation or control for the gestational age at which the measurements are taken.

Results. Sixteen pertinent reports were located. Of these, 13 were concerned with zinc and nine with copper, while six included data on both. The methodological quality of most studies was poor. Only one

study of zinc (*192*) received an SM rating, while three PM reports contained data that had a bearing on both zinc and copper.

Hunt et al. (*192*) carried out a placebo-controlled, double-blind randomized trial of zinc supplementation in Los Angeles among 213 low-income women of Mexican descent with zinc-deficient diets. No differences in mean birth weight, prematurity, or IUGR rates were seen among those who received zinc supplements versus those who received a placebo. The three PM reports, all observational studies from North America, confirmed the negative findings reported by Hunt et al. and also found that copper had no effect. Crosby et al. (*193*) found no significant correlation between mid-gestational plasma zinc or serum copper concentrations and birth weight after adjusting for a number of important confounding variables. In a later report of the same study, Metcoff et al. (*175*) confirmed these negative results for a larger sample. Finally, Gibson & DeWolfe (*194*) found no difference in the zinc or copper concentrations in the hair of normal, premature, and IUGR Canadian neonates. Thus, although methodologically rigorous studies are few, the available data suggest that neither zinc nor copper has an important impact on intrauterine growth or gestational duration. Randomized trials of zinc supplementation in populations with clinical evidence of zinc deficiency would, however, be required to rule out such an impact.

8. *Calcium, phosphorus, and vitamin D*

Background. Calcium, phosphorus, and vitamin D are metabolically related in bone formation, parathyroid function, gastrointestinal absorption, and renal excretion. Calcium is important not only for development of the fetal skeleton, but also for neuromuscular function and blood coagulation. Phosphorus is laid down with calcium (as phosphate salts) in bone and serves an essential role (as high-energy phosphates, phospholipids, and nucleic acids) in intermediary metabolism. Vitamin D and its hormonal metabolites are of vital importance in regulating calcium homoeostasis. Because phosphorus is ubiquitous in all natural foods, isolated dietary phosphorus deficiency is virtually unknown. However, dietary deficiencies in calcium and vitamin D occur commonly among strict vegetarians, and the effects are exaggerated among those who also receive inadequate exposure to sunlight. The major mechanisms whereby deficiencies in these factors could affect intrauterine growth or gestational duration are by impairing fetal skeletal development, and thus reducing growth, or by altering membrane permeability and excitability, which could lead to premature uterine contractions and subsequent delivery.

Methodological requirements for these factors are similar to those for other nutrients (see Table 2). Randomized supplementation trials in groups of women with low intakes of calcium or vitamin D and low exposure to sunlight are the preferred design. Observational studies of maternal dietary intakes or blood levels should control for the important confounding variables (especially caloric intake and prepregnancy nutritional status) discussed in previous sections. Since serum levels of all three nutrients fall during pregnancy (although phosphorus begins to rise again after 30 weeks), studies that correlate these levels with pregnancy outcome should control for the gestational age at which the levels are measured (*195*).

Results. A total of eight reports that examined the effect of calcium or vitamin D on intrauterine growth or gestational duration were identified. While no study dealt with phosphorus, its dietary ubiquity makes it a very unlikely determinant of the outcomes under assessment. Because of the intimate relationship between vitamin D and calcium, they were considered together. None of the eight reports received an SM rating, but three supplementation trials were rated PM.

Raman et al. (*196*) carried out a clinical trial of two different doses (300 and 600 mg/day) of calcium supplementation and a placebo among 273 Indian women of low socioeconomic status. Unfortunately, data were obtained for only 87 subjects. Although the authors claimed that "Infants born to mothers of the three groups were ... comparable with regard to their birth weight", the women in the placebo group actually had infants with a mean birth weight 200 g *higher* than either of the two calcium-supplemented groups, and re-analysis of the data using a two-tailed Student's *t*-test indicates that the difference is statistically highly significant ($P < 0.01$). Gestational age was not reported. Although the three groups of women who completed the trial had similar age, parity, and height, other potentially confounding variables were not examined. Moreover, since assignment of treatment was not randomized, it would be hazardous to conclude that calcium supplementation impairs fetal growth, especially in the absence of any obvious biological mechanism.

The other two PM reports (*197*, *198*) are based on a trial of third-trimester vitamin D supplementation among Asian immigrants in London. Although these two reports contain data on several different outcomes, those that have a bearing on birth weight and gestational age are identical. The trial was placebo-controlled, randomized, and double-blind, but the number of women lost to follow-up is not stated. Of the recipients who completed the trial, 59 received vitamin D and 67 placebo; no significant difference

was detected in birth weight or IUGR rate, although trends favouring both outcomes were found in the vitamin D-supplemented group (3157 g versus 3034 g mean birth weight; 15.3% versus 28.6% IUGR). The mean gestational age was 39.1 weeks and 39.3 weeks in the two groups, although this result is vitiated by the exclusion of women who delivered prematurely. The small sample size, coupled with the clinically important differences in birth weight and IUGR rate, indicate a high probability for Type II error. Moreover, in view of the lack of details about the number and characteristics of the women who were randomly assigned, inferences should be guarded.

In summary, data on the role of calcium and vitamin D in intrauterine growth and gestational duration are meagre and of generally poor quality. Although the best evidence does not suggest that they are important, more definite conclusions must await the results of future supplementation trials incorporating larger sample sizes and efforts to minimize losses to follow-up.

9. *Vitamin B_6*

Background. Vitamin B_6 (pyridoxine) has an important role in intermediary metabolism, serving as a cofactor (in its pyridoxal phosphate form) for aminotransferases and tyrosine decarboxylase. Animal studies demonstrate that vitamin B_6 deficiency during pregnancy can adversely affect the developing central nervous system of the fetus. The major concern in humans, besides its effect on the central nervous system, is a possible association between gestational vitamin B_6 deficiency and toxaemia (*199*, *200*). Because intake and blood levels of the vitamin are often low in pregnant women (*201*, *202*), even among those from middle- and upper-class backgrounds in developed countries (*203*), a causal association with toxaemia could well lead to impairment of intrauterine growth or gestational duration.

Isolation of the effect of vitamin B_6 requires adequate control for the many confounding factors already mentioned for other nutrients (see Table 2), and the randomized supplementation trial is the preferred study design. Observational studies that use blood levels of the vitamin should control for the gestational age at the time of measurement, since levels fall progressively during gestation (*171*). Only studies that controlled for caloric intake (or gestational weight gain) were rated SM or PM, and use of an experimental design was required for an SM rating.

Results. Only four studies were located on the effect of vitamin B_6 on intrauterine growth, all of which were from the USA; no studies reported on gestational duration. None of the studies were supplementation trials and none received an SM or PM rating; however, the three studies that presented numerical data (*103*, *202*, *204*) reported no significant effect on birth weight (*103*, *202*) or IUGR (*204*). The available data, although meagre and of poor quality, therefore do not suggest an important role for this vitamin, at least in the USA.

10. *Other vitamins and trace elements*

Background. A number of other vitamins and trace elements play important metabolic roles and thus should be considered as possible determinants of intrauterine growth or gestational duration. Among these are thiamine, riboflavin, niacin, vitamin A and other carotenoids, vitamins C and E, biotin, pantothenic acid, iodine, magnesium, manganese, chromium, and vanadium. Because deficiencies in any of these substances often occur simultaneously with those of other nutrients, isolation of their effects requires use of either single nutrient supplementation trials or rigorous control for the many potential confounding factors. Also, as with most of the nutrients considered earlier, blood levels usually decrease progressively during pregnancy, and studies that correlate blood levels with birth weight or gestational age should therefore control for the latter when the measurements are made. The methodological standards used are listed in Table 2.

Results. Twelve pertinent reports were located that examined the effects of one or more of the above-mentioned vitamins or trace elements. Two of the nine observational studies were rated PM, and these were serial reports of the same study (*175*, *193*). Only one of the PM studies was a supplementation trial (*205*). No study received an SM rating.

Thilly et al. (*205*) reported a placebo-controlled, double-blind randomized trial of iodized oil administered by intramuscular injection at a mean gestational age of 28 weeks to 671 pregnant women in an area in Zaire with highly endemic goitrous cretinism. Although no significant difference was seen in the mean birth weight of infants born to the two treatment groups (gestational age was not assessed), a statistically significant difference of 203 g was found in favour of iodine-supplemented mothers who had low urinary iodine concentrations (<5 μg/dl) prior to treatment. Unfortunately, the study has several important weaknesses that detract from its otherwise rigorous design. Firstly, it can be calculated from the data presented that for mothers who did not have low pretreatment levels of urinary iodine, supplementation reduced the mean birth weight relative to controls who received a placebo (2655 g and 2807 g, respectively). Secondly, birth weights were given for

only 295 (44%) of the original 671 trial participants. Not only were over half the women lost to follow-up, but the loss was proportionately higher (and statistically significantly so, according to the results of a χ^2 test) for the iodine-supplemented group. Also, no data were presented showing that the women who were followed up represented an unbiased sample of those originally randomly assigned to the treatment groups. Thus no inference can be drawn about the real effect of iodine supplementation in these women. Furthermore, since congenitally hypothyroid newborns are often large for gestational age and also have a tendency to above-average gestational ages, at least in the sporadic form of the disease (*206*), the likelihood that iodine supplementation would increase birth weight seems remote.

The other PM study (*175*, *193*) was an observational investigation that correlated maternal characteristics, dietary intake histories for calories and protein, and a large number of blood tests made at mid-gestation with subsequent birth weight, adjustment being made for numerous potential confounders. Blood levels of vitamin A, total carotenes, and vitamin C, *inter alia*, were measured. Although the earlier report (*193*) found a significant positive correlation between total carotene level and birth weight, this was no longer so in the later study (*175*), which was based on a larger sample (423 versus 182). Despite the obvious limitations of this approach, the data suggest that these three nutrients have no important impact on intrauterine growth.

In summary, the lack of reliable data on other vitamins and trace elements precludes any conclusions about their roles in intrauterine growth or gestational duration.

E. *Maternal morbidity during pregnancy*

1. General morbidity and episodic illness

Background. Common episodic illnesses and symptoms, such as upper respiratory infections, fever, nausea, vomiting, diarrhoea, headache, and anorexia, could affect intrauterine growth or gestational duration through any of three mechanisms. Firstly, such symptoms often result in decreased caloric intake, which, if prolonged, could lead to a reduction in the energy available to the fetus and, in women who have inadequate nutritional reserves, impair fetal growth. Secondly, the metabolic cost of maintaining febrile temperatures or of mounting appropriate host defences may reduce the energy available to the fetus, even with a constant dietary caloric intake. Finally, the infection or symptom could lead to diminished uterine blood flow or even spread to the placenta or amniotic fluid and hence interfere with intrauterine growth or precipitate premature delivery.

The major methodological difficulty in assessing the effect of maternal illness is the separation of cause from effect. This is especially true when illness is defined by symptoms, rather than by documented infection with particular viruses, bacteria, or other organisms. If symptoms such as headache, anorexia, and diarrhoea occur more frequently in women with abnormal pregnancies, it is difficult to know which causes which. In this respect, it is important that self-reports of illness or symptoms be collected prospectively, i.e., prior to delivery, in order to avoid recall bias. Only studies with prospective assessment of maternal morbidity were eligible for an SM or PM rating.

Episodic infections are more likely to occur among the poor, especially those living in close, crowded quarters. They may also be more likely to occur among women with low pre-pregnancy nutritional status, regardless of socioeconomic status. Respiratory symptoms occur more frequently among women who smoke, and those with heavy alcohol consumptions may be prone to a variety of symptoms such as headache and gastrointestinal upset. Thus, pre-pregnancy weight, smoking and alcohol consumption habits, as well as socioeconomic status should be controlled in any attempt to isolate the effect of episodic illness. On the other hand, caloric intake or gestational weight gain during or following maternal illness should not be controlled.

Finally, the effect of illness may be confounded by the treatment given. For example, if a medication is itself capable of affecting pregnancy outcome, the treatment, rather than the infection, may be responsible for the observed outcome. Thus medical treatment is another potentially confounding variable that requires to be controlled. The methodological standards used to assess studies of this factor are shown in Table 2.

Results. A total of 12 studies with data that had a bearing on this factor were located. Two were classified as SM (*77*, *207*) and one as PM (*31*). Both of the SM studies were carried out in rural regions of Guatemala, whereas the PM study was from Boston, USA.

The study by Lechtig et al. (*207*) used self-reported symptoms collected during home visits every two weeks. When grouped together, the symptoms of anorexia, headache, and diarrhoea were significantly associated with birth weight, adjusted for gestational age and a large number of potentially confounding factors. Since caloric intake was also controlled, these results indicate that at least part of the effect may operate through a mechanism other than by reducing the ingestion of calories. The magnitude of

the effect was −4.3 g per % of pregnancy days with illness. Since the study women had such symptoms during 10.4% of their pregnancy, on average, the mean effect of this factor per pregnancy was a decrease in birth weight of 44.7 g.

The other SM report was Mata's cohort study (*77*) of 465 pregnancies that occurred in 203 women in the rural Guatemalan village of Santa Maria Cauqué, and is based on mothers' self-reports of "illness" during regular antenatal care visits. The association between maternal illness and birth weight was observed in a bivariate analysis, but in a multiple linear regression that involved terms for first, second, and third trimester illnesses *and* total illnesses in pregnancy, in addition to gestational age and a number of potential confounding variables, only third-trimester illness was significantly negatively correlated with birth weight. The size of the effect was a reduction in birth weight of 80.8 g. Since caloric intake or third-trimester weight gain was not controlled, this effect, if real, might have been mediated by a reduction in dietary intake.

In the PM study by Hingson et al. (*31*), multiple regression analyses for both gestational age and birth weight included "history of maternal illnesses" and many other independent variables, including most of the relevant confounders. Although no effect was seen on gestational-age-adjusted birth weight, maternal illnesses did have a significant negative correlation with gestational age. It is unclear, however, what kind of illnesses or symptoms were included or whether they occurred during, rather than before, pregnancy. Moreover, in view of the large number of independent variables examined, a partial correlation of the magnitude observed (−0.086) might well have arisen by chance alone, and the reported effect on gestational age is difficult to interpret.

In summary, there is little available information on the effect of episodic maternal illness on intrauterine growth, and almost none on pregnancy duration. The few pertinent rigorous studies suggest that, at least in rural developing countries, such illness may be associated with an impaired fetal growth, on average, of 45 g per birth. However, whether such an association represents a causal effect of maternal illness on fetal growth, or merely a marker for problem pregnancies, is not clear at present. Future prospective studies using sensitive microbiological and serological techniques to monitor pregnant women could provide answers for definable infections, although not for symptoms that are not attributable to documented infection.

2. *Malaria*

Background. In areas that are endemic for malaria, the prevalence of parasitaemia is higher among pregnant than nonpregnant women, especially among primiparae (*208–210*). This may arise because pregnancy causes a hormonally mediated inhibition of antimalarial immunity (*211*), but, regardless of its mechanism, it is suspected that maternal malaria has a deleterious effect on the fetus. Besides the metabolic and other possible physiological consequences of fever and systemic maternal illness (see previous section), the malarial parasite appears to have a predilection for the placenta, and heavy placental infestation may interfere with circulation in the placenta. The end result would be a growth-retarded fetus or, perhaps, a tendency to premature delivery. Since placental parasitaemia may occur in 40% or more of all pregnancies in endemic areas (*211*), maternal malaria could be a major determinant of intrauterine growth or gestational duration.

Owing to the greater exposure to mosquitos, malaria is more common in rural than in urban settings, even within endemic regions. Also, since socioeconomic status and other rural–urban differences may be associated with pregnancy outcome, these should be controlled as potential confounding factors. Malarial activity varies seasonally, with higher prevalences during wetter months. Since food availability (as reflected in gestational weight gain or caloric intake) and maternal work may also exhibit seasonal variations in rural areas, these (or season) should also be controlled. The greater susceptibility of primiparae to malaria and the tendency of such women to have lower birth weights also indicate a need to control for parity. Antimalarial treatment begun early in pregnancy should also be controlled since it may obscure a detrimental effect of infection.

Finally, because pre-pregnancy nutritional status might alter susceptibility to the disease, pre-pregnancy weight-for-height or skinfold thickness should, ideally, also be controlled. The best research design to control for all of the above factors would be a placebo-controlled randomized trial of malarial prophylaxis during pregnancy in an endemic area. Table 2 lists the methodological standards applied to studies of maternal malaria.

Results. Only four studies were identified that examined the effect of maternal malaria. None used an experimental design (e.g., trial of prophylaxis) and although none was classified as SM, two received a PM rating. The two PM studies will be discussed in chronological order.

In the Solomon Islands, MacGregor & Avery (*212*) demonstrated that the mean birth weight increased and the LBW rate decreased during the period 1969–71, and that these changes occurred simultaneously with the introduction of a DDT spraying programme for mosquito control. Prior to this, birth

weight on Malaita island was 147 g, on average, lower than that on islands that had already been sprayed. On Malaita, spraying resulted in a sharp drop in malarial prevalence, a corresponding increase of 165 g in mean birth weight, and a concomitant fall in the LBW rate from 20.5% to 11.8%. The changes were even more dramatic among primiparae. The LBW rate discrepancy with other malaria-controlled areas virtually disappeared over the same time period. Although the use of historical controls makes it impossible to rule out simultaneous improvements in nutrition or other factors that might have led to the observed changes, the most likely explanation appears to be a reduction in maternal malaria.

In a large study (sample size 6427) from the Gambia, McGregor et al. (*213*) found an average decrease in birth weight of about 170 g for women with placental malaria, even after stratifying for residence, parity, and infant sex. Increased placental infection was documented during the wet season, but no attempt was made to control for the seasonal lower food availability and higher work loads.

Neither of the above-mentioned studies presented data on gestational duration, and it is therefore not clear whether the effect on birth weight was mediated by impaired fetal growth or an increased tendency to premature delivery. However, a less well-controlled study (*208*), which also found lower birth weights in malaria-infected mothers, reported no effect on mean gestational age. Although the absence of control for confounding in the latter study precludes inference of a significant birth-weight effect, the findings suggest that the impact of maternal malaria on birth weight operates by impairing intrauterine growth.

In the absence of SM studies, it is difficult to estimate the magnitude of the effect of malaria on birth weight. In their study, MacGregor & Avery (*212*) report a 147-g deficit in birth weight and an an etiologic fraction for IUGR of 42% in a hyperendemic area (Malaita island). The 170-g deficit among women with placental malaria reported by McGregor et al. (*213*) was associated with a 20.2% placental malaria rate. The overall effect in a population with this rate of placental infection would thus be 170×0.202 or about 34 g per pregnancy. In populations with 40% placental infections, the attributable impact of malaria would rise to 68 g. These estimates are considerably lower than those suggested by the data for the Solomon Islands.

Thus, although the magnitude of the deficit cannot be estimated with precision, maternal malaria does not appear to impair intrauterine growth; however, this conclusion is far from definitive, and data from a randomized trial of malarial prophylaxis would be useful to clarify the situation. None the less, with the available evidence, it might be difficult ethically to justify such a trial in malaria-endemic areas. Selective administration of routine prophylaxis (either chloroquine or, in chloroquine-resistant areas, pyrimethamine–sulfadoxine) to pregnant women, along with monitoring of birth weights and IUGR rates in areas with and without such prophylaxis, should be a high priority.

3. Urinary tract infection

Background. Bacterial infection of the urinary tract could spread to the placenta and amniotic fluid (*214*), thereby affecting gestational duration and possibly precipitating premature labour and delivery. Such an infection, if chronic, might interfere with fetal growth by inducing hypertension and secondary uterine vascular changes. Any effect of maternal urinary tract infection may depend, however, on its site and severity. Thus, severe pyelonephritis might be expected to have a greater impact than asymptomatic bacteriuria.

One important potential source of confounding (see Table 2) is genital tract infection. Any association between urinary tract infection and pregnancy outcome might be confounded by concomitant genital tract infection unless the latter is controlled, since the risk of both these infections increases with sexual activity. Also, since urinary tract infection is likely to vary with age, parity, and socioeconomic status (*215*), these variables should also be controlled. Finally, medical treatment for urinary tract infection requires control, both because successful treatment may obscure an effect of infection and because the treatment itself might conceivably affect the outcome. For asymptomatic bacteriuria, the methodologically preferred design would be a placebo-controlled randomized trial of antibiotic treatment, but this would be unethical in women with symptoms.

Results. A total of 16 relevant reports were located, all from developed countries. The one SM study and three PM studies were from the USA or the United Kingdom. The major methodological weakness was a failure to control for confounding factors.

The SM study was a placebo-controlled clinical trial of tetracycline among 281 pregnant women with asymptomatic bacteriuria and 279 controls matched for age, parity, and race (*216*). Treatment assignment, though not randomized, resulted in groups that had similar histories of prior abortion and smoking, in addition to the matching variables. Analysis of the data indicates no significant difference between the tetracycline and placebo groups for mean gestational age (38.5 versus 38.3 weeks, respectively), mean birth weight (3087 g versus 3125 g), or LBW rate (11.3% versus 10.3%). In contrast, the authors' analysis not only ignores the experimental treatment assigned but fails to control for confounding differences among the groups. The

absence of any treatment effect by experimental groups constitutes strong evidence against any impact of asymptomatic bacteriuria on either intrauterine growth or gestational duration.

The three PM studies provide conflicting information. Brumfitt (*217*) reported no significant difference in mean birth weight or LBW rate between 235 treated and 178 untreated (placebo) patients with bacteriuria and ruled out confounding by age, parity, or socioeconomic status. Differences in racial/ethnic background and smoking habits were not controlled, however, and neither the type of treatment nor the method used to assign it was described.

In the analysis by Sever et al. (*218*) of data from the U.S. Collaborative Perinatal Project, 1370 women with *symptomatic*, culture-proven urinary tract infection were pair-matched by age, race, medical institution, socioeconomic status, and gestational age to women free of such infection. The relative risk for LBW associated with urinary tract infection any time during gestation was 1.40 ($P<0.001$); the risk was also significant for infection during the second or third trimesters. In the absence of precise data on gestational age, however, it is unclear whether the observed effect on LBW reflects impaired fetal growth or prematurity.

Finally, a case–control PM study by Berkowitz (*38*) found an elevated risk of prematurity associated with second- or third-trimester urinary tract infection, but this was not statistically significant. The small number of women with the infection, however, suggests the possibility of a Type II error.

In summary, the evidence is weak that maternal urinary tract infection affects either intrauterine growth or gestational duration. The data reported by Elder et al. (*216*) argue strongly against any impact of asymptomatic bacteriuria, and even if we accept the findings of Sever et al. (*218*) on symptomatic urinary tract infection, the relative risk of 1.40 and a 3.4%-prevalence of symptomatic urinary tract infection among women in the U.S. Collaborative Perinatal Project give an etiologic fraction of:

$$EF = \frac{(0.034)(1.40-1)}{(0.034)(1.40-1)+1} = 0.013$$

Urinary tract infection would, therefore, account for only about 1% of LBW in a population similar to that in the Perinatal Project. Data are insufficient to determine whether more severe infections of this type, such as symptomatic pyelonephritis, might carry a greater risk, but since they occur less commonly, they are unlikely to have an important impact on a population-wide scale.

Further data would certainly be useful in drawing more definitive inferences. In particular, the clinical trial of antibiotic treatment of asymptomatic bacteriuria (*216*) published in 1971 bears repeating. Current information, however, suggests that urinary tract infection is probably not a major determinant of intrauterine growth or gestational duration, at least in developed countries. Nevertheless, in developing countries, both the effect and prevalence of gestational urinary tract infection merit increased attention.

4. Genital tract infection

Background. Maternal genital tract infection might precipitate pre-term labour and delivery, while chronic low-grade infection could interfere with intrauterine growth. We are not concerned here with the well-described effects of transplacentally acquired infection of the fetus with rubella, syphilis, cytomegalovirus, and toxoplasmosis, since their rarity argues against any important role as population-wide determinants of birth weight or IUGR. Rather, of interest is the colonization or infection of the genital tract with organisms such as *Chlamydia trachomatis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Gardnerella vaginalis*, *Trichomonas vaginalis*, *Candida albicans*, and a variety of anaerobic bacteria. Some of these organisms are normal vaginal flora, and all of them can frequently be cultured from samples taken from pregnant women. Thus any effect of these organisms on pregnancy outcome would have considerable significance. That such may indeed be the case was first indicated by data in the study reported by Elder et al. (*216*) cited in the previous section. In addition to a placebo-controlled trial of tetracycline among pregnant women with asymptomatic bacteriuria, 279 nonbacteriuric women who were also treated with the drug gave birth to infants of greater mean gestational age than those who received a placebo. Genital tract infection was not specifically studied, however, as a possible explanation for these findings.

Several mechanisms could account for the effect of genital tract infection on gestational duration, and one hypothesis concerns the role of the high level of esterified arachidonic acid in the amnion and chorion. Both leukocytes and many of the commonly occurring vaginal microorganisms produce phospholipase A, the enzyme that hydrolyzes esterified arachidonic acid. The liberation of free arachidonic acid appears to be the rate-limiting step in the synthesis of prostaglandins, which (particularly prostaglandin E and $F_{2\alpha}$) may play a major role in initiating labour. Alternatively, spread of vaginal organisms to the fetal membranes might have a direct weakening effect, resulting in their premature rupture and onset of labour.

Here, the most important methodological issue is the temporal relationship between infection and the onset of labour. For example, the association between prolonged rupture of membranes and chorioamni-

onitis is well established, but it is likely that the ruptured membranes permit passage of vaginal organisms. Evidence that the organisms can *cause* membrane rupture would require documentation of membrane or amniotic fluid infection prior to rupture or proof that women harbouring a certain organism in their vagina or cervix earlier in their pregnancy were at greater risk for subsequent membrane rupture and premature labour. This is particularly important for prematurity, because a threatened premature delivery is often treated with tocolytics to delay delivery as long as possible and, hence, maximize fetal (especially lung) maturity. The long period between membrane rupture and delivery in such cases provides ample opportunity for *secondary* invasion by microorganisms. Thus, documentation that infection preceded membrane rupture and labour, or at least that infection rates did not rise with increasing intervals between membrane rupture and delivery, was required to receive an SM rating.

Potentially confounding factors that require control (see Table 2) are similar to those discussed for urinary tract infection and include any medical treatment given for genital tract infection. Because the vagina contains a large number of potentially pathogenic organisms, several of which appear to be associated with one another, studies of the effect of a given organism need to control for the others.

Results. In total, 50 reports were located with data that related to the impact of genital tract infection on intrauterine growth or gestational duration or their known clinical precursors (premature rupture of membranes and premature labour). These included 23 reports that had a bearing on "general" (i.e., all organisms considered together, rather than separately) infection of amniotic fluid, chorioamnionitis, or endometritis; 11 and 12 reports, respectively, on *M. hominis* and *U. urealyticum*; four reports each on *C. trachomatis* and *Neisseria gonorrheae*; three each on *Listeria monocytogenes* and group B *Streptococcus*; two on *T. vaginalis*; and one each on *C. albicans* and a variety of other bacteria and viruses. Almost all originated from developed countries.

Only four reports were classified as SM and six as PM. The major methodological weakness was uncertainty as to whether infection preceded rupture of membranes or onset of labour. This was a particular problem for studies of amnionitis and general infection; none of these studies received an SM rating and only one was rated PM. The other principal shortcoming was a failure to control for the confounding effects of parity (or age), socioeconomic status, presence of other microorganisms, and treatment. The reports rated SM or PM are discussed here.

The data on *M. hominis* infection suggest that this organism has no effect on either intrauterine growth or gestational duration. In an SM study by Ross et al. (*219*), positive cervical cultures for *M. hominis* were not associated with significant differences in either gestational age or gestational-age-adjusted birth weight. Similarly, the SM study by Harrison et al. (*220*) found no association between positive cervical cultures and either prematurity or LBW (nor, by inference, IUGR). Among four PM studies, those by Braun et al. (*221*) and Harrison et al. (*222*) found no association between positive cultures for *M. hominis* and gestational age or birth weight. A PM study by Kass et al. (*223*) reported no significant difference in prematurity or LBW rates but higher mean birth weights among women with positive cultures for either *M. hominis* or *U. urealyticum* who were treated with erythromycin. The difference in birth weight was evident only among women treated in the third trimester who complied with a full 6 weeks of therapy (less than 25% of the total participants), and the overall results were not presented according to the species of organism. It is difficult, therefore, to implicate *M. hominis* as a cause of lower mean birth weight in this study. Finally, a PM study by Minkoff et al. (*224*) found no association between positive vaginal cultures and either prematurity or LBW.

Data on infection with *U. urealyticum* are less clear. The two SM studies by Ross et al. (*219*) and Harrison et al. (*220*) indicate no association between positive cervical cultures and subsequent gestational age, prematurity, birth weight, or LBW (IUGR). On the other hand, a more recent SM report by Kundsin et al. (*225*) demonstrated a statistically significant association between risk of prematurity and positive placental cultures for *U. urealyticum*. Because such cultures were obtained at birth, however, there is no assurance that infection preceded prematurity. For example, onset of preterm labour may have led to attempts to delay delivery after membrane rupture, thus leading to secondary placental invasion from the cervix or vagina. No association was seen, however, between culture positivity and the interval between membrane rupture and delivery in women with intervals <48 hours, and this was not changed by restricting the analysis to deliveries that occurred within 48 hours of membrane rupture. The relevant PM studies are the same as those cited for *M. hominis*. The small study by Harrison et al. (*222*) detected no effect on gestational age or birth weight, while Minkoff et al. (*224*) found an elevated risk of premature *labour*, but not premature delivery or LBW. Braun et al. (*221*) reported no impact on gestational age, but a significantly lower mean birth weight among culture-positive women. Finally, the results of Kass et al. (*223*) indicate no significant effect on prematurity or LBW, but any impact on birth weight is clouded by methodological difficulties.

Two SM studies that have a bearing on *C. trachomatis* infections report conflicting results. Martin et al. (*226*) found that women with positive cervical cultures did not exhibit significantly increased prematurity or LBW risk but a significantly reduced mean gestational age; however, significant differences in mean birth weight were not controlled for gestational age, and possible confounding by infection with other organisms was also not controlled. Harrison et al. (*220*) found no association between positive cervical cultures and subsequent prematurity or LBW, but reported a significantly elevated LBW rate among culture-positive women with serological evidence of *C. trachomatis* infection. This association with LBW was not controlled for gestational age, however (and thus might represent prematurity, rather than IUGR), and the confounding effects of socioeconomic status or its risk-factor correlates were not considered.

Other organisms and infection categories were each treated by one PM report. Edwards et al. (*227*) found that an elevated risk for prematurity, but not IUGR, was associated with positive cultures for *N. gonorrheae*, but the results were not controlled for other microorganisms or for the effect of the treatment given. Minkoff et al. (*224*) found that an elevated risk for both prematurity and LBW was associated with positive vaginal cultures for *Bacteroides* species. No such associations were seen with *Staphylococcus aureus* or *S. epidermis*, non-specific vaginitis, *C. albicans*, group B *Streptococcus*, *Enterococcus*, or several other bacteria. Incomplete control for confounding and the large number of organism-outcome associations argue for caution in interpreting the observed effect for *Bacteroides*. Finally, in Cape Town, Woods et al. (*228*) reported no association between placental inflammation and birth weight among full-term infants of "coloured" racial origin and ruled out confounding by maternal age and nutritional status (but not by socioeconomic status or its correlates). This was the only one of 23 studies of "general" (i.e., not microorganism-specific) chorioamnionitis that received an SM or PM rating.

In summary, the evidence linking genital infection to intrauterine growth or gestational duration is not compelling. For most organisms, insufficient reliable data are available; however, for *M. hominis* the inference of no association appears well supported. Of particular interest are possible associations between *U. urealyticum* or *C. trachomatis*, and prematurity. The data are far from convincing for either organism and appear particularly weak for *C. trachomatis*, whose relatively low prevalence (ranging from zero among women from a sample of high socioeconomic status in the United Kingdom (*219*) to 6.7% and 8.0%, respectively, in two groups of low-to-mid socioeconomic status in Seattle (*226*) and Tucson (*220*)) suggests that it is unlikely to be a major cause of prematurity. Even doubling the relative risk for prematurity, combined with a prevalence of 5%, would lead to an etiologic fraction of only :

$$EF = \frac{0.05(2-1)}{0.05(2-1)+1} = 0.048$$

Infection involving *U. urealyticum*, however, is far more common. For example, Ross et al. (*219*) found prevalences of 42.7% and 34.6% among, respectively, Caucasian and Asian mothers in the United Kingdom, whereas the overall rate among women of lower socioeconomic status in Tucson reported by Harrison et al. (*220*) was 72.3%. With a prevalence of 50%, doubling the risk of prematurity would be associated with an etiologic fraction (EF) of:

$$EF = \frac{0.50(2-1)}{0.50(2-1)+1} = 0.333$$

Thus a true association between *U. urealyticum* and prematurity might explain a substantial proportion of premature births, at least in developed countries. Further studies of the effect of this organism should receive the highest priority. In this respect, randomized trials of antibiotic treatment in women harbouring *U. urealyticum*, but free of other suspected pathogens, are likely to make the most significant contribution. Finally, much more information is required about the impact of genital tract infection, as well as its prevalence, in developing countries.

F. *Toxic exposures*

1. Cigarette smoking.

Background. Maternal cigarette smoking could affect intrauterine growth (and possibly gestational duration) through several mechanisms (*229*). The most likely mediators are carbon monoxide and nicotine. Carbon monoxide can interfere with oxygen delivery to the fetus in two ways: by displacing oxygen from haemoglobin, and by shifting the oxyhaemoglobin dissociation equilibrium to the left, so that less oxygen is released to the fetal tissues for a given partial pressure of oxygen (*230*). Nicotine is an appetite suppressant and is believed to result in rapid increases in maternal catecholamines and consequent uterine vasoconstriction (*231*). Tobacco smoke also contains cyanide compounds, and a third possible mechanism for a smoking effect involves cyanide-mediated interference with fetal oxidative metabolism (*232*).

Smoking is likely to co-vary with several other suspected risk factors, including alcohol consumption, age, pre-pregnancy weight, psychological stress and anxiety, racial/ethnic origin, and either socio-

economic status or its risk factor correlates (e.g., height, caloric intake, and genital infection). Isolating an effect due to smoking thus requires adequate control for these potential confounders. Since smoking may cause appetite suppression, caloric intake or gestational weight gain should not be controlled, unless focus is on direct causal effects only. Although cigarette smoking cannot be assigned experimentally, a randomized trial of anti-smoking counselling or therapy would be a methodologically methodologically attractive approach. Causal associations in observational studies are strengthened not only by adequate control for confounding, but also by prospective (i.e., pre-delivery) ascertainment of smoking history and demonstration of a dose–response effect between the number of cigarettes smoked and the study outcome. Table 2 lists the methodological standards used to assess studies of this factor.

Results. The effect of maternal cigarette smoking on intrauterine growth and gestational duration has been a fertile topic for investigation over the period assessed here. In total, 121 reports with pertinent data were located, although several represented re-analyses of the same study sample. All originated from developed countries. The overall methodological quality was considerably higher than those for most other factors; 40 were classified as SM and 33 as PM. Given the large number of methodologically superior studies, I shall discuss only the results from the 40 SM studies.

Of seven relevant SM studies, only two (*74*, *97*) found that cigarette smoking had a significant association (reduction) on gestational age, and in both cases the magnitude of the effect was small (-0.05 weeks for each cigarette smoked per day, or about 3.5 days for a woman who smoked 10 cigarettes per day (*97*).

Despite this questionable association with mean gestational age, maternal cigarette smoking does appear to increase the risk of prematurity. Of seven SM reports that examined this effect, five detected a significantly increased risk. This may be mediated, at least in part, by an increased risk of placenta previa and abruptio placentae (*30*). The two dissenting SM reports (*38*, *233*) were of a single case–control study that compared risks in women who smoked $\geqslant 10$ cigarettes/day versus those who smoked < 10 cigarettes/day; however, even this study reported a modest (though statistically nonsignificant) risk elevation in all three trimesters with increased smoking. Based on the four studies that permit calculation of the relative risk, the sample size-weighted average is 1.41 among smokers, for a total sample of 59 631. If the prevalence of 40% smokers reported in many studies from developed countries is used (*234*), this relative risk results in an etiologic fraction of:

$$\mathrm{EF} = \frac{(0.40)(1.41-1)}{(0.40)(1.41-1)+1} = 0.141$$

Although cigarette smoking may be uncommon in certain developing countries in Asia and Africa, it appears to be more frequent (about 20%) in several Latin American countries (*234*). A relative risk similar to that reported for developing countries in Europe and North America and a 20% prevalence result in an etiologic fraction of:

$$\mathrm{EF} = \frac{(0.20)(1.41-1)}{(0.20)(1.41-1)+1} = 0.076$$

Data on intrauterine growth are both abundant and clear, and for no other single factor (with the possible exception of infant sex) was there greater unanimity. Of 30 SM reports that examined the effect of smoking on birth weight, 28 found a significant deficit among smokers' infants and many of these also demonstrated dose–response relationships, with birth-weight impairments increasing with the number of cigarettes smoked per day. The only two dissenting reports were those by Zuckerman et al. (*32*) and Papoz et al. (*149*), the former of which was based on analysis of a subgroup from a larger SM study (*31*) that did find a significant effect on birth weight. The study by Papoz et al. (*149*) reported an effect on birth weight similar in magnitude to that observed in other studies, and the lack of statistical significance appears to be due to its relatively small sample size. The sample-size-weighted birth weight deficit for infants of mothers who smoked is 149.4 g, based on a total sample of 48 064. The per-cigarette estimated deficit is 11.1 g per cigarette per day.

The effect of smoking on birth weight appears to depend on the period in pregnancy when the mother smoked, and, in particular, is more marked for smoking during the last trimester. Butler et al. (*235*) found that smoking after the fourth month of pregnancy was critical in reducing birth weight. Consistent with this finding, three other SM studies (*149*, *236*, *237*) reported that women who stopped smoking during pregnancy gave birth to infants of similar birth weight to those who did not or those who stopped smoking before becoming pregnant. Perhaps the most convincing evidence is that of Sexton & Hebel (*238*), who reported a higher mean birth weight for infants born to smoking women who were randomly assigned to anti-smoking counselling after an average of 15-weeks' gestation.

Considerable debate has raged as to whether the effect of smoking on birth weight is mediated by appetite suppression or by an independent mechanism (*239*, *240*). Nicotine is an appetite suppressant, and some (but by no means all) studies have demonstrated lower gestational weight gains or caloric intakes for smoking mothers; however, even in these studies the

effect caused by smoking has persisted after controlling for nutritional differences, which indicates an impact above and beyond that of appetite suppression. Thus, smoking has a strong direct impact on birth weight in addition to its possible indirect appetite-suppression effect. Caloric supplementation may overcome part of the deficit in infantile birth weight caused by maternal smoking (*146*), but this may also occur with deficits from other causes, and does not indicate that the effect of smoking is primarily mediated by a nutritional mechanism.

Finally, all five SM studies that examined the effect reported a significant elevation in the risk of IUGR associated with maternal smoking. The two studies that permit calculation of relative risks (*16*, *55*) yield a sample-size-weighted relative risk of 2.42 for smoking mothers (sample size, 3592). If it is assumed that 40% and 20% of pregnant women, respectively, smoke in developed and developing countries, the etiologic fractions are given by:

$$EF_{developed} = \frac{(0.40)(2.42-1)}{(0.40)(2.42-1)+1} = 0.362$$

and

$$EF_{developing} = \frac{(0.20)(2.42-1)}{(0.20)(2.42-1)+1} = 0.221$$

Thus in populations where a sizeable proportion of women smoke during pregnancy, smoking has a major impact on IUGR; however, the figures should be interpreted cautiously for developing countries. Although there is no reason to expect a different biological effect (birth weight deficit or relative risk for IUGR) in such countries, confirmatory data would be useful.

Table 14. Results of the assessment of cigarette smoking

Outcome	Effect
Gestational age	~0 weeks
Prematurity	
Relative risk for smokers	1.41
Etiologic fraction for:	
$P = 0.40$	14.1%
$P = 0.20$	7.6%
Birth weight	
Relative risk for smokers	−149.4 g
g per cigarette per day	−11.1 g/cigarette/day
IUGR	
Relative risk for smokers	2.42
Etiologic fraction for:	
$P = 0.40$	36.2%
$P = 0.20$	22.1%

Even in developing countries where maternal cigarette smoking is rare, the use of wood and other biomass fuels for cooking and heating may result in indoor concentrations of carbon monoxide of 25–50 ppm (25–50 mg/litre) in poorly ventilated dwellings (*241*). Constant exposure to such levels of carbon monoxide would result in maternal carboxyhaemoglobin concentrations of 4–7% (*230*), which are roughly the same as those observed in women who smoke. However, women in most agrarian societies spend considerable time outdoors as well, so that their carboxyhaemoglobin levels would be expected to be lower. None the less, indoor smoke represents an important source of exposure to carbon monoxide in such countries.[c] No studies were located on the effect of such exposure on intrauterine growth or gestational duration.

The results of the assessment for cigarette smoking are summarized in Table 14.

2. *Alcohol consumption*

Background. Even in the absence of the full-blown fetal alcohol syndrome—consisting of growth retardation, cognitive defects, short palpebral fissures, and maxillary hypoplasia (*242*, *243*)—maternal alcohol consumption during pregnancy might adversely affect intrauterine growth. In experimental animals the fetal growth-inhibiting effect of alcohol has been amply demonstrated when high doses are administered, and the mechanism may involve fetal hypoxia (*244*) or decreased incorporation of amino acids into protein (*245*).

Women who take alcohol during pregnancy are likely to differ in other respects from those who do not. Confounding factors that require control are similar to those discussed for cigarette smoking (see Table 2). The most important of these, of course, is cigarette smoking itself, and control for this was required to receive an SM rating. Prospective data on alcohol consumption are probably necessary to avoid recall bias. Furthermore, since drinking is usually considered more socially pejorative than smoking, data on alcohol consumption are probably more reliable if collected by specially trained personnel during direct interview sessions, using a probing but structured format, rather than by routine clinical history or self-administered questionnaire. This is especially true for the *dose* of alcohol consumed. Also, a minority of women probably go through an entire pregnancy without even an occasional drink; hence, if threshold or dose–response effects exist,

[c] DE KONING, H. W. ET AL. *Biomass fuel combustion and health.* Unpublished document WHO/EHE/84.64. A condensed version was published in *Bulletin of the World Health Organization*, **63**: 11–26 (1985).

valid quantification of alcohol intake takes on considerable importance.

Results. In total, 35 pertinent reports were identified, of which 16 were classified as SM and six as PM. The proportion of methodologically rigorous studies was high, perhaps because most have appeared since 1980 and have recognized the importance of minimizing confounding bias, especially by cigarette smoking. Only one report (*246*) originated from a developing country, but this received neither an SM nor PM rating.

Data on gestational duration are conflicting. Of the three SM studies that reported on gestational age, only one found a significant association: Tennes & Blackard (*92*) reported a negative correlation between gestational age and total alcohol intake during pregnancy, although only 1.8% of study mothers consumed ⩾24.4 ml of absolute alcohol (slightly less than two "drinks") per day. In contrast, Rosett et al. (*247*) reported that even "heavy" (⩾1.5 drinks per day) maternal alcohol intake during pregnancy had no effect, whereas Hingson et al. (*31*) found no association with maternal drinking *during* pregnancy but a significant negative correlation with drinking *before* pregnancy. The data on prematurity are equally confusing. The SM study by Marbury et al. (*248*) found no significant elevation in the risk of prematurity among women who drank ⩾14 drinks per week, whereas in another SM study (*38*, *233*), a similar intake reached statistical significance only for consumption during the second trimester. The evidence that maternal alcohol intake has an important effect on gestational duration is, therefore, unconvincing, and the finding that alcohol seems, if anything, to prolong gestation in rats (*249*) is consistent with this conclusion.

By contrast, data showing a detrimental effect on intrauterine growth are more convincing, at least for higher doses of alcohol. Six of 10 relevant SM and all three relevant PM studies reported that significantly lower birth weights were associated with maternal alcohol consumption. Two (*31*, *32*) of the four SM studies that reported negative correlations are based on one study sample in which only 2.8% of the women consumed ⩾2 drinks per day. In another negative SM report (*92*) the proportion of such women was even lower. A fourth SM report (*250*) did not find a clearly significant association, but the results of the multiple regression analysis for alcohol were combined with those for coffee consumption, and the corresponding *P*-value was not indicated. All the SM or PM studies that included a sizeable number of women who consumed more than two drinks per day reported an effect on birth weight, whereas the findings of those with lower proportions of such women were mixed.

All three SM (*75*, *100*, *247*) and two PM studies (*119*, *251*) that provided specific data demonstrated significant dose–response effects. The findings indicate that consumption of ⩾2 drinks per day is associated with lower birth weight; in contrast, for lower consumption levels the data are conflicting. Using the data from the three SM studies (*75*, *100*, *252*) that permit calculation of the magnitude of the effect, we can estimate that the sample-size-weighted reduction in birth weight associated with consumption of ⩾2 drinks/day is 155.0 g (total sample size, 34 105).

The few available data indicate that exposure to alcohol during the late stages of pregnancy may be more important. For example, in the SM study by Little (*252*), the reported size of the alcohol effect was −90.8 g, −95.2 g, and −159.7 g birth weight per 28.35 g (1 ounce) absolute alcohol consumed before pregnancy, and during 0–4th month and 5th–8th month, respectively. Rosett et al. (*247*) found that heavy drinkers who stopped or reduced their alcohol intake before the third trimester had infants of similar birth weight to women who drank only moderately or rarely. Most of the SM and PM studies that reported significant birth weight effects used total or average consumption during pregnancy, however, and thus it cannot be inferred that alcohol intake during early pregnancy is of no consequence.

The evidence for an effect on IUGR is similar to that for birth weight. Three of four relevant SM studies and three PM studies found a significantly increased risk of IUGR among mothers who drank heavily, while in the one dissenting SM report (*248*), only 0.7% of the study women consumed ⩾2 drinks per day. Evidence of a significant dose–response effect was found in both SM (*75*, *247*) and both PM studies (*119*, *253*) that examined this aspect. From the two SM studies and one PM study that contained pertinent data, the sample-size-weighted relative risk for IUGR associated with ⩾2 drinks per day was calculated as 1.78 (based on a total sample size of 44 923).

Calculation of an etiologic fraction requires information on the prevalence of women who consume ⩾2 drinks per day during pregnancy. In North America, the proportion of such women ranges from 0.5% to 11%, with most studies reporting 2–3% (*254*). If the 3%-level is taken, a relative risk of 1.78 corresponds to an etiologic fraction of:

$$\mathrm{EF} = \frac{(0.03)(1.78-1)}{(0.03)(1.78-1)+1} = 0.023$$

Thus, drinking at this level plays a relatively minor population-wide role in causing IUGR. Furthermore, although alcohol consumption is increasing in many developing countries, it is generally lower than that in

developed countries (*255*) and thus is probably responsible for an even lower proportion of total IUGR (assuming a similar relative risk). However, certain population groups (e.g., North American Indians) may have higher prevalences of "heavy" drinking during pregnancy, and the corresponding etiologic fractions may be higher.

It should be emphasized that a totally safe "threshold" level of alcohol consumption may not exist. For example, the SM study by Mills et al. (*75*) demonstrated that infants born to women who consumed an average of less than 1 drink per day had a statistically significant deficit in birth weight of 14 g and a relative risk for IUGR of 1.11, compared to women who did not drink. Since 43.9% of the study sample consumed this level of alcohol, the associated etiologic fraction is given by:

$$EF = \frac{(0.439)(1.11-1)}{(0.439)(1.11-1)+1} = 0.046$$

Thus, although low levels of alcohol consumption may carry only a small increase in risk, the high prevalence of such women could have a measurable impact on the occurrence of IUGR in the population. As discussed above, however, most studies have not detected effects on birth weight or IUGR for low alcohol intakes, and the data reported by Mills et al. should therefore be interpreted cautiously.

The results of the assessment of the effects of maternal alcohol consumption are summarized in Table 15.

3. *Caffeine and coffee consumption*

Background. Caffeine is a potent inhibitor of phosphodiesterase, the enzyme responsible for the metabolic breakdown of cyclic AMP, and it has been demonstrated that caffeine clearance diminishes during the second and third trimesters of pregnancy (*256*). The resulting increased levels of cyclic AMP could either interfere with cell division or lead to catecholamine-mediated uterine vasoconstriction, with obvious consequences for fetal growth or (possibly) gestational duration. The major dietary source of caffeine is coffee; lesser amounts are also contained in tea, cola beverages, and chocolate. Because coffee and other foods may contain potentially harmful chemical agents other than caffeine, it should be emphasized that a significant association between, say, coffee consumption and IUGR does not necessarily implicate caffeine as the etiologic agent.

Table 15. Results of the assessment of alcohol consumption

Outcome	Effect
Gestational age	0 (?) weeks
Prematurity	
Relative risk for ⩾2 drinks/day	1 (?)
Birth weight	
⩾2 drinks/day	−155.0 g
IUGR	
Relative risk for ⩾2 drinks/day	1.78
Etiologic fraction for $P = 0.03$	2.3%

Coffee drinking is highly correlated with both cigarette smoking and alcohol consumption. Since these other practices both appear to have a deleterious effect on intrauterine growth, rigorous control for their confounding effects was essential for an SM rating. Other potential confounders are shown in Table 2 and include maternal age, racial/ethnic origin, pre-pregnancy weight, stress or anxiety, and socioeconomic status (or its other risk factor correlates).

Results. Of the 12 pertinent reports identified (all from developed countries), six were rated as SM and one as PM. The evidence from these seven reports is virtually unanimous that maternal caffeine or coffee consumption has no effect on either intrauterine growth or gestational duration. Neither of two relevant SM studies (*31*, *92*) reported a significant association with gestational age, and two others (*86*, *233*) detected no significant effect on the risk for prematurity. Also, three SM reports (*31*, *32*, *92*) and one PM report (*257*) found no effect on birth weight, while the SM study by Linn et al. (*86*) demonstrated no impact on IUGR. The only SM or PM study that did not clearly indicate the absence of an association was that by van den Berg (*250*), who reported the results of a multiple regression analysis for alcohol and coffee consumption taken together.

4. *Use of marijuana*

Background. Some animal studies indicate that administration of high doses of crude marijuana extract or its pharmacologically active ingredient, Δ^9-tetrahydrocannabinol, can impair intrauterine growth (*258*), although it is not clear whether this represents a direct toxic effect or is secondary to a drug-induced reduction in maternal food and water intake. Since use of marijuana by humans, at least in North America, is associated with a young age, low socioeconomic status, cigarette smoking, and alcohol consumption (*51*, *259*), isolation of its effect on intrauterine growth or gestational duration requires control for these confounders (control for smoking and alcohol were required for SM rating). Racial/ethnic origin, stress, and pre-pregnancy weight might also potentially be confounders, and ideally they too should be controlled (Table 2).

Results. In total, seven reports, all from North America, were identified that had a bearing on the possible effects of maternal use of marijuana. These studies were generally of a very high methodological standard and five were rated as SM and one as PM.

The SM studies by Tennes & Blackard (*92*) and Hingson et al. (*31*) did not detect a significant effect on gestational age. Similarly, neither the large SM study by Linn et al. (*51*) nor the PM study by Goodlin et al. (*260*) reported a significant association with prematurity, although the latter study was based on a very small sample size.

The evidence for an effect on intrauterine growth is also weak. Four SM reports provided data on gestational-age-adjusted birth weight. Of these, neither the study by Tennes & Blackard (*92*) nor that by Rosett et al. (*248*) found a significant association with use of marijuana. The two other SM reports (*31*, *32*), which are based on the same study sample, found a small statistically significant inverse correlation; however, the change in explained variance (r^2) was less than 0.01 in both reports, and in view of the large numbers of independent variables tested in the multiple regression analyses, the observed association might well have arisen by chance alone. Finally, the largest (sample size, 12 424) and best study (*51*) demonstrated that there was no increased risk of IUGR among women who used marijuana.

5. *Narcotic addiction*

Background. Maternal addiction to heroin or methadone might adversely affect intrauterine growth or gestational duration either by a direct toxic effect or by repeated withdrawal-induced episodes of fetal hypoxia (*261*). Because narcotic addicts are likely to differ from nonaddicts in terms of their cigarette smoking, alcohol consumption, racial/ethnic origin, socioeconomic status, age, genital tract infection, nutritional status, parity, and stress, it is essential to control for the confounding effects of these variables (control for smoking and alcohol was required for an SM rating) before testing for the independent effect of narcotic addiction. The methodological standards that applied to studies of this factor are listed in Table 2.

Results. In total, 14 studies were located that had a bearing on the effects of maternal narcotic addiction, and all were from urban areas in developed countries. Virtually all of these studies reported that infants born to addicts had lower birth weights than those born to nonaddicts, but since none adequately controlled for the important confounding effects discussed above, none received an SM or PM rating. To quote one recent study (*262*): "It is unclear from available clinical evidence whether growth impairment of infants born to narcotic-dependent women is related to the narcotic itself or to the adverse social, economic, and health factors commonly associated with addiction."

Thus, the available data permit no inferences as to the effect of narcotic addiction on either intrauterine growth or gestational duration. Re-analyses of existing data, using multivariate statistical techniques to control for the numerous sources of confounding bias, would probably be helpful in clarifying any independent causal impact of this factor. If future studies or analyses do demonstrate effects in addicted women, this factor could have a small, but not insignificant, population-wide impact in certain settings. Since the prevalence of narcotic addiction among pregnant women is about 2% in some large urban areas in the USA (*263*, *264*), tripling the relative risk for IUGR would result in an etiologic fraction of:

$$EF = \frac{(0.02)(3-1)}{(0.02)(3-1)+1} = 0.038$$

in such areas.

6. *Other toxic exposures*

Background. The possible deleterious effects on intrauterine growth or gestational duration of a number of other agents have also been studied. These include tobacco chewing, use of LSD and other psychoactive drugs, exposure to insecticides and environmental noise, as well as use of spermicides. Because exposure to these agents is likely to differ according to socioeconomic status, racial/ethnic origin, and age, and may co-vary with cigarette smoking, alcohol consumption, and psychological stress, these potentially confounding factors should be controlled in studies that attempt to isolate an effect of the suspected toxic exposure (Table 2).

Results. Two SM studies from India (*265*, *266*) examined the effect on birth weight of tobacco chewing or ingestion. Although neither controlled for alcohol consumption, nor is it clear whether Verma et al. (*266*) excluded women who smoked, both studies provided good control for other potential confounders and both demonstrated large birth weight deficits for infants born to tobacco-chewing mothers. Krishna (*265*) also showed a trend towards higher prematurity rates among exposed women, but socioeconomic status was the only confounding variable controlled in the analysis, and no test of statistical significance was reported. Moreover, for many categories of socioeconomic status and maternal-weight, birth weights were higher among exposed than non-exposed women who delivered prematurely, thus casting doubts about the accuracy of the gestational age assessments. In most categories with adequate sample sizes, the birth-

weight deficit found by Krishna was 100–200 g. The overall birth weight difference among the 70 matched pairs studied by Verma et al. (*266*) was 395 g, with an impressive dose–response effect for the daily quantity of tobacco consumed. Inadequate details about the matching criteria used, however, indicate that this value may be an overestimate.

In any case, if the 16.5%-prevalence of tobacco chewing among pregnant women reported by Krishna (*265*) is typical in India, a 200-g deficit in birth weight attributable to exposure would result in a population-wide reduction of 33 g in mean birth weight. The effect is probably due to nicotine or cyanide compounds in tobacco, and public health intervention to reduce this practice in India and other countries should receive high priority.

Two studies examined the effect of the use of LSD or other psychoactive drugs. The SM report of Hingson et al. (*31*) found no association with either gestational age or birth weight. A case–control PM study by Goodlin et al. (*260*) reported that 6% of 50 mothers with premature infants used LSD compared with none among 50 controls. Although the study claims that this difference is statistically significant at the $P<0.02$ level, re-calculation of the Fisher exact test using the data reported by the authors yields a nonsignificant P-value$=0.121$. Thus, taken together, the few available data do not indicate that use of LSD or other psychoactive drugs has a significant effect on fetal growth or gestational duration.

Five PM studies investigated the possible effects of environmental exposure to insecticides (especially DDT and other chlorinated hydrocarbons) or chemical wastes. For example, Vianna & Polan (*267*) reported a higher rate of LBW, but not of prematurity, among residents who lived near the Love Canal (a waste dumping site in New York State) in swale areas (shallow depressions lying along natural drainage pathways) during years of active chemical dumping around the canal; however, those living on streets abutting the canal did not exhibit an increased LBW rate. Furthermore, since it is difficult to implicate a specific chemical agent and there was inadequate control for potential confounding variables, definitive inferences cannot be drawn. In view of the widespread environmental exposure to insecticides and other chemicals, this "factor" requires further study.

Two PM studies, one from Japan (*268*) and another from the Netherlands (*269*), dealt with the possible effects on birth weight of maternal exposure to aircraft noise. In one city near Osaka airport, Ando & Hattori (*268*) found a 455-g difference in adjusted birth weight for infants born to mothers who lived in residences with the highest category of measured aircraft noise, compared with those who lived in the quietest residences (the partial correlation coefficient of this factor in a multivariate analysis was 0.09; no corresponding P-value was reported). Mothers' reports of aircraft or other noise, however, had no significant association with birth weight. These results are based on only 50.1% of the study subjects from one city and only 26.4% of the total study sample. Also the confounding effects of maternal smoking and drinking levels, infection, and nutritional status were not considered. The Dutch study (*269*) did not find a significant difference in mean birth weight reported by mothers who lived in residences with high versus low measured aircraft noise levels in six villages near Amsterdam airport. When the analysis was restricted to hospital births (only 32.4% of participants), a statistically significant birth-weight deficit of 69 g was seen, but no control was made for potential confounding factors. After adjustment for family income and infant's sex, the proportion of infants with birth weights <3000 g was significantly greater among women exposed to higher noise-levels who also delivered in hospital.

The low participation rates and inadequate control for confounding in these two studies prevent firm conclusions about the impact of aircraft or other sources of noise on intrauterine growth or gestational duration; however, the ubiquity of loud noise in industrialized societies, both at home and in the workplace, suggests the need for further study.

Finally, one SM study (*74*) investigated the effect on birth weight of maternal use of a spermicide after the last menstrual period. Multiple regression analysis among 302 such women showed a significant inverse correlation between birth weight and the month during which spermicide use was discontinued, but only for female infants. Nevertheless, the difference between males and females, coupled with the absence of control for alcohol consumption, genital tract infection, and gestational nutrition, indicates that the results should be interpreted cautiously. Further study seems warranted.

G. *Antenatal care*

1. First antenatal care visit

Background. Antenatal care could have a beneficial impact on intrauterine growth or gestational duration, either by diagnosis and timely treatment of pregnancy complications (such as toxaemia, gestational hypertension or diabetes, antepartum haemorrhage, or cervical incompetence) or by eliminating or reducing modifiable risk factors.[d] The results of the assess-

[d] It should be re-emphasized that this assessment of the impact of antenatal care pertains to women without underlying chronic disease. Obviously, antenatal care might have substantial benefits in women with complaints such as pre-existing diabetes or sickle cell anaemia, but such women were excluded from this assessment.

ment indicate that those risk factors that seem most amenable to such an impact include caloric intake, cigarette smoking, alcohol consumption, and malaria prophylaxis or treatment. Other modifiable determinants that may affect pregnancy outcome are maternal work and genital tract infection. The stage in pregnancy at which a woman is first seen for antenatal care might be of great importance, because the effects of many pregnancy complications and risk factors, if attended to early in gestation, could then be substantially mitigated.

One methodological difficulty in evaluating the potential impact of initial antenatal care is related to pre-term delivery and the now familiar cause-and-effect problem. Women who deliver prematurely will have had a shorter period before attending their first antenatal visit. This should not create a major problem if those who seek care in the first or early second trimester are compared in studies with those who do not. In many developing countries, however, and even among the poor in developed countries, women may not seek care until rather late in pregnancy, and thus premature labour and delivery may prevent them from receiving any antenatal care at all. Although this "prematurity artefact" should not affect an analysis of gestational-age-adjusted birth weight or IUGR, it would constitute a major bias in assessing the effect on gestational duration. The use of life-table techniques (survival analysis) would be one way of controlling for such bias. Studies that had a bearing on gestational duration were therefore considered eligible for an SM or PM rating only if they incorporated some procedure for reducing or eliminating bias from this source.

Women who begin antenatal care at a late stage in their pregnancy and those who never begin are likely to differ in prognostically important ways from those who seek early antenatal care: they are more likely to be young, primiparous, poor, members of a racial/ethnic minority, or undernourished, and may be more likely to smoke or drink. Any attempt to isolate an independent effect for antenatal care should, therefore, control for these confounding factors (Table 2).

Negative confounding is also possible for this factor. If women who seek early antenatal care are those who experience problems at an early stage of gestation, such use of antenatal care could either appear to be associated with worse outcomes, or a true beneficial effect of early care might be obscured. The reason why antenatal care is first sought thus becomes a source of confounding, and the best way of avoiding such "confounding by indication", as well as the other methodological pitfalls discussed above, would be to randomly allocate a group of women to early versus late antenatal care.

Results. In total, 26 pertinent studies were identified that had a bearing on the effect of first antenatal care. Also included are studies in which women who had no antenatal care were compared with those who had made one or more visits. Three of the studies were classified as SM and seven as PM. The major methodological weakness was a failure to control for the bias caused by the shorter time that women who deliver prematurely have to come for their first antenatal visit. Several of the better studies based their analyses on the Institute of Medicine's index (or a modification thereof) for the overall adequacy of antenatal care (*270*), which probably reduces (without entirely eliminating) this source of bias by taking duration of gestation into account. For the five PM studies that used such an index, however, the effect of first antenatal care was confounded with the number of visits and/or the quality of care. The other major weakness in some of the larger studies that were based on birth certificate data was incomplete control for confounding. Only three (*271–273*) studies originated from developing countries, and none of these was rated SM or PM.

Only one of the SM or PM studies examined the effect of first antenatal care on gestational duration. Using life-table analysis to control for the prematurity artefact, Terris & Glasser (*274*) in a PM study actually found a higher proportion of women who had not had their first antenatal visit by each month of gestation among mothers who gave birth to full-term infants of weight >2500 g than among mothers of premature infants. However, inadequate control for confounders and missing data on gestational age in about 16% of the matched pairs suggest the need for cautious interpretation.

Three SM studies (*32*, *74*, *89*) investigated the impact of first antenatal care on gestational-age-adjusted birth weight, but none found a significant effect. In contrast, two large PM studies (*47*, *85*) did report a significant increase in birth weight, but the effect of early antenatal care was inseparable from that of the number of visits, and control for confounding was incomplete.

Two large PM studies (*274*, *275*) reported a lower risk of IUGR associated with earlier antenatal care, but both were based on data obtained from birth certificates and were thus unable to control for the confounding effects of maternal nutritional status, smoking, or drinking. Finally, three large PM studies (*101*, *128*, *270*) found that early care significantly decreased the risk of LBW. None of these controlled for gestational age, however, and thus it is not clear whether the reported effect reflects intrauterine growth or gestational duration. Furthermore, all three studies combined the effect of first care with that of the number of visits and/or quality of care, and control for confounding was incomplete.

In summary, the evidence that early antenatal care

improves intrauterine growth or gestational duration is unconvincing. The best studies indicate no effect on birth weight, but larger studies with adequate information on and control for potentially important confounders would be required to rule out a small effect on birth weight or IUGR. It is also possible that "confounding by indication", whereby women with early pregnancy complications seek earlier care, might have obscured a beneficial effect. Only control for the reasons for beginning care, or far better, a randomized trial of early versus late antenatal care, would resolve this issue.

Finally, caution is advised in using the available evidence to draw inferences about the effect of early antenatal care in developing countries. All of the SM and PM studies assessed were from developed countries and were based, therefore, on generally healthy women who had perhaps less need for antenatal care. Although women from less favourable settings might derive a greater benefit from early care, demonstration of this must await the results of future well-controlled studies.

2. *Number of antenatal care visits*

Background. The biological and methodological issues for the number of antenatal visits are similar to those discussed for first antenatal care (see Table 2). Theoretically, the greater the number of contacts with health professionals who attempt to reduce or eliminate risk factors and treat pregnancy complications, the better the outcome should be. Because women who deliver prematurely have a shorter time for visits, control for this artefact is essential. Similar also is the possibility for negative "confounding by indication", since women whose pregnancy is proceeding normally without symptomatic complications may feel they require fewer visits.

Results. In total, 27 relevant studies were located. Only one of these was rated SM, while eight received a PM rating. Five of the reports, one of which (*88*) received a PM rating, originated from developing countries. Methodological weaknesses were very similar to those noted for first antenatal care. Five of the PM studies (*101*, *128*, *270*, *274*, *275*) based their analysis on a combination of number of visits with first antenatal care and/or its quality, and thus the effect of number of visits could not be isolated.

None of the SM or PM studies provided data on gestational duration. The SM study of Kennedy et al. (*89*) found that the number of antenatal visits had no effect on gestational-age-adjusted birth weight; however, two PM studies (*46*, *276*) did report that more frequent visits had a beneficial effect. Neither of these studies controlled for tobacco and alcohol use, although one (*46*) did control for maternal anthropometric and nutritional variables. The PM studies by Quick et al. (*85*) and Showstack et al. (*47*) also found beneficial impacts on birth weight, but the effects could not be separated from those of first antenatal care, and control for confounding was incomplete.

The PM study by Donaldson & Billy (*88*) reported a significantly lower risk for IUGR among women who had $\geqslant 6$ antenatal visits (versus those with $\leqslant 5$ visits) in four (Chile, Honduras, Sweden, and Thailand) of six study countries, but, once again, incomplete control for confounding hinders definitive inference. Lastly, the same three PM studies of LBW risks cited under first antenatal care (*101*, *128*, *270*) also found beneficial effects of more frequent care, but the same reservations discussed previously for these studies apply.

Thus, no firm conclusions can be drawn about the possible benefit of frequent antenatal visits on either intrauterine growth or gestational duration. Existing data are conflicting, control for important confounding factors is incomplete, and no study adequately measured and accounted for the potentially obscuring effect whereby women with difficulties in pregnancy seek more frequent care. As with early antenatal care, rigorous evaluation of this factor may require randomized clinical trials of frequent versus infrequent antenatal care visits. Further study is particularly warranted in developing countries because any beneficial effect of increased antenatal visits, if it exists at all, should be more evident in women from these countries.

3. *Quality of antenatal care*

Background. Quality of antenatal care comprises any qualitative attribute of the content (structure or process) of the care, including continuous versus episodic care, specialist versus generalist care, and the evaluation of antenatal care programmes targeted for specific at-risk groups (e.g., teenagers or the poor). Here, I have attempted to isolate the impact of these aspects of antenatal care from those associated with the timing of the first visit and the number of visits.

The methodological requirements for this "factor" are very similar to those already discussed for other aspects of antenatal care (see Table 2). The artefact caused by prematurity might be less important for the quality of antenatal care, however, unless women who deliver early have a lesser chance of being referred or recruited into special care programmes. Because motivation for participating in such programmes may be closely linked to other prognostically favourable factors, control for confounding is essential in attempts to evaluate their impact. Randomized allocation to special versus routine antenatal care is therefore the preferred study design.

Results. In total, 21 studies were located that had a bearing on the quality of antenatal care. These were generally of a higher methodological standard than those on the other aspects of antenatal care already discussed. Although only one study was classified as SM, 10 other studies received a PM rating. The principal weakness was inadequate control for potential confounders, especially those concerned with motivation in seeking special antenatal care programmes. Only one (*277*) of the studies originated from a developing country (Martinique) but received neither an SM or PM rating. None the less, several of the PM studies from developed countries reported on underprivileged, high-risk groups.

The SM study by Berkowitz (*38*) found a "borderline significant" odds ratio for prematurity of 2.1 among women cared for in a hospital obstetric clinic (presumably compared with those who received private service) after adjustment for socioeconomic status and a large number of other confounding factors, but this finding might have arisen by chance alone. A PM study by Sokol et al. (*278*) did find a significantly lower prematurity rate among Cleveland women enrolled in a Maternal and Infant Care Project, but the number of antenatal visits, which was not known, may have been higher among these women, and also control for confounding was incomplete.

In a PM study, Wilner et al. (*279*) reported no difference in gestational age, prematurity, birth weight, or IUGR for Boston women who received antenatal care from a pre-paid health maintenance organization compared with those who obtained traditional fee-for-service care. By contrast, Quick et al. (*85*) reported that in Portland, Oregon, such prepaid antenatal care resulted in significantly higher birth weights, even after controlling for first antenatal care and the number of antenatal visits. The effect on birth weight was unadjusted for gestational age, however, and the potential confounding effects of maternal smoking, drinking, and nutrition were not controlled. A similar beneficial effect on birth weight was reported in a PM study of a health maintenance antenatal care programme in southern California that stressed nutritional and anti-smoking counselling (*280*). Despite the content of the programme, however, the effect appeared to be mediated by a difference in gestational age, rather than intrauterine growth (LBW was not adjusted for gestational age). Moreover, potentially confounding factors were controlled only one at a time.

No studies provided data that permitted an assessment of the impact on IUGR, although six PM studies reported on LBW. Sokol et al. (*278*) found a significantly lower rate of LBW among women enrolled in a Maternal and Infant Care Project, but their finding of a similar difference for prematurity (see above) suggests that the observed effect was on gestational duration, rather than fetal growth. Peoples & Siegel (*128*) studied the impact of a similar project in rural North Carolina. After controlling for first antenatal care, number of visits, and several other confounders, they found that project mothers had a higher LBW rate. The reverse was seen, however, when the analysis was restricted to the high-risk group of non-White adolescents. In a more recent PM report from North Carolina (*281*), however, a targeted Improved Pregnancy Outcome Project did not lower LBW rates, even among poor Black teenagers.

Felice et al. (*282*) reported a lower LBW rate among adolescents who attended a special obstetric clinic, but the number of antenatal visits was not reported and thus may have confounded the results, while control for other confounders was also incomplete. Jekel et al. (*283*) also studied the impact of a special antenatal programme for high-risk adolescents: LBW rates were not statistically significant on their own, but when combined with infant Apgar scores and survival rates, the overall outcome was significantly better among programme women. Once again, however, number of antenatal visits and a variety of confounding factors may have biased the results.

Finally, two other PM studies (*101*, *270*) also reported beneficial impacts on LBW rates, but antenatal care was evaluated *in toto*, i.e., the quality was combined with first care and number of visits. Furthermore, incomplete control for gestational age and several important confounders further complicate interpretation of the results.

In summary, no definitive conclusions can be drawn about the impact of the quality of antenatal care. Many of the better studies do show a favourable effect for high-risk groups, and the results are generally more positive than those for the other two aspects of care assessed. Thus, the type of antenatal care may be more important than its early initiation or frequent visits. In view of the evidence linking certain modifiable factors (e.g., cigarette smoking and caloric intake) to intrauterine growth or gestational duration, antenatal care that focuses on these factors might indeed prove beneficial, but this requires further study.

SYNTHESIS

Methodological considerations

The quantity of research on the causes of LBW over the period 1970–84 is impressive. Two major limitations, however, have detracted from its quality: failure to distinguish the different types of LBW; and

inadequate attention to rigorous study design and statistical analysis.

The importance of the conceptual distinction between intrauterine growth and gestational duration is generally acknowledged. None the less, many population-based studies without access to adequate data on gestational age, especially those from developing countries, have continued to focus on LBW as if it were a single pathological entity. As should be evident from this review, the causes of prematurity and IUGR are often quite different. Since their prognoses also differ, little purpose is served by continuing to "lump" them together, and although the LBW rate may be useful as an overall health indicator, the contribution of much previous etiological research in this area has thus been limited.

IUGR may also require subclassification. The potential importance of distinguishing between "stunted" (proportional) and "wasted" (disproportional) IUGR, for example, has been recognized relatively recently (*16*, *17*). Few researchers have attempted to separate the causes of IUGR subtypes, despite theoretical indications that they may be quite different.

Research design and statistical analysis of data have also left much to be desired. Descriptions of study target populations, sampling procedures, and participation and follow-up rates have often been inadequate. Reproducibility and validity in the measurement of risk factors and outcomes have usually not received the attention they deserve. Furthermore, retrospective collection of data has often prevented establishment of the temporal sequence (cause versus effect) between certain suspected factors and pregnancy outcome. Also, few investigators have made use of randomized clinical trials for factors, e.g., specific nutrients and antenatal care, for which experimental designs are feasible. Finally, observational studies have often failed to measure and statistically control for the multiple variables that can confound the effect of a given factor or factors under study.

These methodological shortcomings have been particularly evident in studies from developing countries. Although this is understandable, in view of the sophisticated epidemiological and statistical techniques required (to say nothing of the necessary computer facilities), the unfortunate result is that we know least about the causes of LBW in the very populations where it is most common.

Intrauterine growth

Table 16 lists the 43 factors assessed for causal effects on intrauterine growth in developed and developing countries. Factors are grouped according to the strength of the available evidence, potential for population-wide importance (based on the effect magnitude and prevalence), and modifiability. A distinction is made also between factors with direct causal effects and those whose effects are indirect, i.e., factors that affect direct determinants but have no independent causal impacts. This distinction may not always be clear-cut, however. For example, maternal height and pre-pregnancy weight, though listed as direct determinants, may themselves be affected by the mother's intrauterine and postnatal growth, which depend, in part, on *her* mother's pregnancy and on subsequent nutritional and other environmental influences during childhood.

It must be re-emphasized that there is substantial overlap between several of the factors, i.e., their effects on intrauterine growth are not independent. Maternal birth weight and previous history of LBW may represent the mother's inherent (genetic) potential for intrauterine growth. Also, gestational weight gain and caloric intake are highly interrelated, since the latter is one of the major determinants of the former.

For those factors whose direct causal effects are clearly established, it may be useful to consider their *relative* importance in terms of their quantitative contribution to birth weight or IUGR in a given population group. Population-based effect magnitudes depend not only on the effect magnitude per individual, but also on the prevalence of the given factor among individuals in the population. Each of these components must be considered separately.

A factor's effect magnitude per individual is the attributable number of grams of birth weight or the relative risk of IUGR among women possessing that factor. What is the evidence that this magnitude differs substantially in different populations? With the notable exception of gestational weight gain and caloric intake, the evidence for such differential effects is meagre. As we have seen, a given weight gain or caloric intake will have a smaller effect on birth weight or IUGR in previously well-nourished than in clearly undernourished women. Although the effect of parity seems to depend on a mother's age (high parity is unfavourable for teenagers but favourable for older mothers), there is no indication that for an individual mother this interaction varies according to her population of origin.

No convincing evidence has been adduced that the effect per individual for other factors differs according to geographical location. For example, the birth-weight deficit due to primiparity is similar in Honduras, India, and New York City. Unfortunately, however, the paucity of rigorous methodological studies from developing countries hinders similar conclusions for other established causal determinants, including maternal height, pre-pregnancy weight, maternal birth weight and prior LBW history,

Table 16. Factors assessed for their effects on intrauterine growth in developed and developing countries[a]

Assessment	Developed countries	Developing countries
Causal effect ruled out with high probability	Maternal psychological factors Prior spontaneous abortion Prior induced abortion Prior stillbirth or neonatal death *In utero* exposure to diethylstilbestrol Iron and anaemia Zinc and copper Genital tract infection Caffeine and coffee consumption	—
Causal effect unlikely, but evidence insufficient to rule out	Marital status Sexual activity Prior infertility Protein status/intake Folic acid and vitamin B_{12} Calcium, phosphorus, and vitamin D Vitamin B_6 Urinary tract infection Use of marijuana First antenatal care visit Number of antenatal care visits	Marital status Maternal psychological factors Sexual activity Prior spontaneous abortion Prior induced abortion Prior stillbirth or neonatal death Prior infertility *In utero* exposure to diethylstilbestrol Protein status/intake Iron and anaemia Vitamin B_{12} Zinc and copper Calcium, phosphorus, and vitamin D Vitamin B_6 Urinary tract infection Genital tract infection Caffeine and coffee consumption Use of marijuana
Causal effect uncertain, but importance unlikely owing to small effect magnitude or low prevalence	Birth or pregnancy interval Strenuous maternal work Other vitamins and trace elements	Birth or pregnancy interval Heavy alcohol consumption Narcotic addiction
Causal effect established, but importance unlikely, owing to small effect magnitude or low prevalence	Paternal height and weight Malaria Heavy alcohol consumption	—
Causal effect established and important, but unmodifiable	Infant sex Racial/ethnic origin Maternal birth weight Parity Prior LBW history	Infant sex Parity
Causal effect established and important, but modifiable only over long term	Maternal height Socioeconomic conditions[b] General morbidity, episodic illness	Maternal height Socioeconomic conditions[b] General morbidity, episodic illness
Causal effect established, important, and modifiable over short term	Pre-pregnancy weight Very young maternal age[b] Maternal education[b] Gestational weight gain Caloric intake Cigarette smoking	Pre-pregnancy weight Very young maternal age[b] Maternal education[b] Gestational weight gain Caloric intake Malaria Tobacco chewing
Causal effect uncertain, but potentially important and modifiable	Maternal haemodynamics Narcotic addiction Environmental toxins and noise Quality of antenatal care	Maternal haemodynamics Strenuous maternal work Folic acid Other vitamins and trace elements Cigarette smoking and indoor smoke First antenatal care visit Number of antenatal care visits Quality of antenatal care

[a] Factors are grouped by strength of available evidence, potential for population-wide importance, and modifiability (order of presentation corresponds to that in the text).

[b] These factors have indirect causal influences on intrauterine growth, i.e., they affect direct determinants but have no independent causal impacts of their own. Socioeconomic status has been subdivided into maternal education and socioeconomic conditions because of the temporal differences required for their modification.

cigarette smoking, and alcohol consumption. In the absence of evidence to the contrary, we have assumed that individual effect magnitudes calculated for developed countries also pertain to other settings. As repeatedly emphasized, however, this assumption requires confirmation.

What does differ from one setting to another is the prevalence of the various determinants. Even if the effect of maternal cigarette smoking is the same in India and the USA, the prevalence of smoking among pregnant women is far higher in the latter country and so, therefore, is the population-based effect magnitude. Accordingly, a ranking of population-based effects must take setting into consideration.

In any population for which the prevalence of a factor is known, its approximate effect magnitude can be calculated using the information provided in the Factor Assessment (see p. 669). For example, to what extent do differences in maternal height explain the difference in mean birth weight between India and the USA? If we assume average heights of 152 cm and 162 cm, respectively, in these two countries, the lower average height among Indian women would be expected to result in a reduction in mean birth weight of 10 cm×7.8 g/cm=78 g (see Table 7). If we further assume that the respective prevalences of height <158 cm in India and the USA are 0.25 and 0.84, the etiologic fractions for IUGR would be 6.3% and 18.5%, respectively, i.e., low maternal height would be responsible for three times the proportion of IUGR in India as in the USA.

The relative importance of the factors with established direct causal impacts on IUGR were approximated using two "typical" settings: a rural population in a developing country where malaria is moderately endemic but pregnant women do not smoke; and a developed country in which 40% of the women smoke during pregnancy. The results are shown in the pie charts in Fig. 1 and 2, respectively, where the size of the sectors is proportional to the etiologic fraction for each of the indicated factors. "Developing" and "developed" hide a great deal of heterogeneity, of course—the IUGR pie chart for a poor urban or peri-urban population, for example, might be intermediate between that shown in Fig. 1 and 2. Low gestational weight gain has been combined with low caloric intake, and maternal LBW with prior history of LBW, to avoid overlap in their effects.

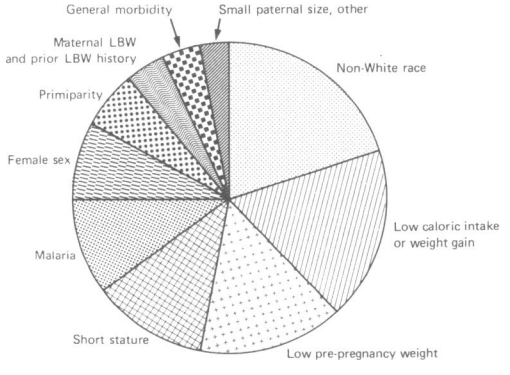


Fig. 1. Relative importance of established factors with direct causal impacts on IUGR (rural developing country).

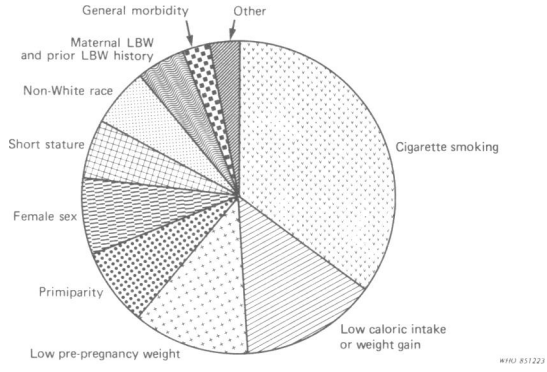


Fig. 2. Relative importance of established factors with direct causal impacts on IUGR (developed country).

Note should be made of the approximate nature of such a quantitative breakdown. In particular, the etiologic fractions for the "typical" rural developing country add up to over 100%. Since some of the determinants of IUGR are presumably unknown, the high total etiologic fraction is undoubtedly an overestimate, principally because the factors listed are not mutually exclusive, and the overall etiologic fraction associated with their joint distribution in any population will therefore be less than the sum of the etiologic fractions for the individual factors (*284*). Some of the estimates of the relative risk of factor prevalences may also be too high (due either to inappropriate extrapolation of the relative risk derived from developed countries or to inadequate control for confounding and thus residual overlap in the effects of several factors). One possible source of error is the etiologic fraction associated with non-Whites. Studies of racial/ethnic differences in intrauterine growth have not adequately controlled for differences in height, pre-pregnancy weight, and cultural differences in caloric intake. With the exception of IUGR for Blacks in the USA, the etiologic fractions attributed to race/ethnicity may

well be too large. The influence of poor gestational nutrition may also have been overestimated, since it is based on effect magnitudes demonstrated with caloric *supplementation* and ignores any metabolic adaptation to chronic undernutrition.

With due consideration of these methodological reservations, Fig. 1 and 2 none the less convey a good deal of useful information. If true racial/ethnic differences exist, these are probably responsible for a large proportion of IUGR in developing countries with high prevalences of Blacks or Indians. The other major factors in such countries are poor gestational nutrition, low pre-pregnancy weight, short maternal stature, and malaria. Of these five leading factors, gestational nutrition, pre-pregnancy weight, and malaria may be modifiable in the short term. Also, it may prove possible to improve short maternal stature through improved antenatal and childhood nutrition, but substantial increases in maternal height can occur only over generations.

In developed countries (Fig. 2), the most important factor appears to be cigarette smoking. This is followed by poor gestational nutrition, low pre-pregnancy weight, primiparity, female sex, and short stature. The three leading factors are all potentially modifiable, once again with obvious implications for public health intervention. Although the IUGR rate (defined as birth weight <2500 g and gestational age $\geqslant 37$ weeks) is lower than in developing countries, a large proportion of the fetal growth retardation may be preventable.

Another useful way to consider the quantitative importance of the determinants listed in Table 16 is to examine their respective contributions to the *difference* in IUGR rates between the populations of developing and developed countries. If we assume

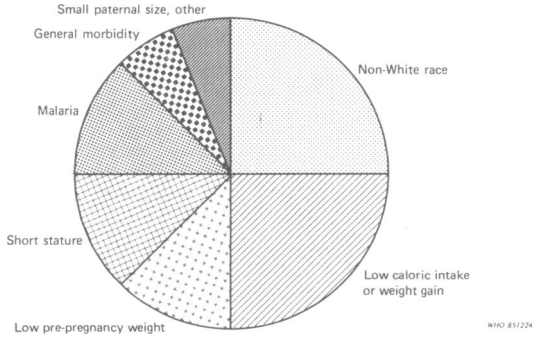


Fig. 3. Relative importance of established factors with direct causal impacts on IUGR in explaining the difference in IUGR rates in rural developing country and developed country.

Fig. 4. Relative importance of established factors with direct causal impacts on prematurity (rural developing country).

IUGR rates of 2% and 10%, respectively, which factors are most responsible for the differences? A rough estimate is indicated in Fig. 3, from which it can be seen that if gestational nutrition in developed and developing countries were the same and malaria were eradicated, more than one-third of the difference in IUGR rates would disappear.

Finally, it should be re-emphasized that the above treatment derives from those factors that seem likely to have an impact, based on data published from 1970 to 1984. Not only may some of the estimated effects be too large, especially in developing countries, but other factors may eventually be shown to play an important role, including those that are currently under suspicion (see Table 16), as well as those yet undiscovered. Prominent among factors currently suspected, but for which data are either nonexistent or inadequate, are strenuous maternal work, folic acid, cigarette smoking, and indoor smoke in developing countries, as well as maternal haemodynamics, antenatal care (especially its qualitative attributes), and environmental toxins and noise, which are of potential relevance in all settings.

Gestational duration

Table 17 lists the 43 factors assessed for causal effects on gestational duration, grouped in the same way as in Table 16. For those factors whose direct causal impacts are established, their approximate relative contributions to prematurity in the "typical" rural developing country and developed country are illustrated in Fig. 4 and 5, respectively.

In both settings, the majority of premature births remains unexplained. In part, this is a reflection of the far less intense research activity in studying gestational duration, as compared to intrauterine

Table 17. Factors assessed for their causal effect on gestational duration in developed and developing countries[a]

Assessment	Developed countries	Developing countries
Causal effect ruled out with high probability	Infant sex Maternal height Paternal height and weight Parity Iron and anaemia Caffeine and coffee consumption Use of marijuana	Infant sex Maternal height Paternal height and weight Parity Iron and anaemia
Causal effect unlikely, but evidence insufficient to rule out	Racial/ethnic origin Maternal haemodynamics Marital status Sexual activity Prior stillbirth or neonatal death Prior infertility Gestational weight gain Caloric intake Protein status/intake Folic acid and vitamin B_{12} Zinc and copper Calcium, phosphorus, and vitamin D Other vitamins and trace elements Malaria Urinary tract infection Alcohol consumption Narcotic addiction First antenatal care visit Number of antenatal care visits	Racial/ethnic origin Maternal haemdynamics Marital status Sexual activity Prior stillbirth or neonatal death Prior infertility Gestational weight gain Caloric intake Protein status/intake Folic acid and vitamin B_{12} Zinc and copper Calcium, phosphorus, and vitamin D Other vitamins and trace elements Malaria Urinary tract infection Alcohol consumption Caffeine and coffee consumption Use of marijuana Narcotic addiction
Causal effect uncertain, but importance unlikely owing to small effect magnitude or low prevalence	Birth or pregnancy interval Prior induced abortion Vitamin B_6 Other vitamins and trace elements	*In utero* exposure to diethylstilbestrol Birth or pregnancy interval Prior induced abortion Vitamin B_6
Causal effect well established, but importance unlikely, owing to small effect magnitude or low prevalence	—	—
Causal effect well established and important, but unmodifiable	Prior history of prematurity Prior spontaneous abortion	—
Causal effect well established and important, but modifiable only over long term	Socioeconomic conditions[b]	Socioeconomic conditions[b]
Causal effect well established, important, and modifiable over short term	Pre-pregnancy weight Very young maternal age[b] Maternal education[b] *In utero* exposure to diethylstilbestrol Cigarette smoking	Pre-pregnancy weight Very young maternal age[b] Maternal education[b]
Causal effect uncertain, but potentially important and modifiable	Stress and anxiety Maternal work General morbidity, episodic illness Genital tract infection Environmental toxins Quality of antenatal care	Stress and anxiety Maternal work Other vitamins and trace elements General morbidity, episodic illness Genital tract infection Cigarette smoking and indoor smoke Tobacco chewing, environmental toxins First antenatal care visit Number of antenatal care visits Quality of antenatal care

[a] Factors are grouped by strength of available evidence, potential for population-wide importance, and modifiability (order of presentation corresponds to that in the text).

[b] These factors have indirect causal influences on intrauterine growth, i.e., they affect direct determinants but have no independent causal impacts of their own. Socioeconomic status has been subdivided into maternal education and socioeconomic conditions because of the temporal differences required for their modification.

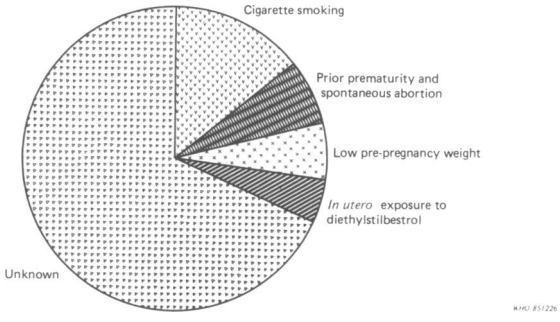


Fig. 5. Relative importance of established factors with direct causal impacts on prematurity (developed country).

growth. This has been particularly true in developing countries, where IUGR is a more common cause of LBW than prematurity, and where accurate gestational age determinations are often hampered by infrequent antenatal care visits and poor maternal recall of the date of the last menstrual period. In developed countries, however, the epidemiology of prematurity has recently received increased attention. This is appropriate, since most LBW in highly developed countries is now attributable to prematurity, rather than IUGR. Unfortunately, some of the factors that are currently under suspicion are difficult to study. These include stress and anxiety, maternal work, general morbidity and episodic illness, genital tract infection (especially due to *U. urealyticum*), and antenatal care. In developing countries, cigarette smoking, tobacco chewing, and exposure to indoor smoke are additional factors that may have important consequences for gestational duration but whose effects are unknown.

RECOMMENDATIONS

The recommendations that follow are divided into suggested public health interventions and priorities for future research. The former are based on those modifiable factors for which convincing evidence indicates a quantitatively important (direct or indirect) causal role, whereas the latter include studies of modifiable factors of potential quantitative importance but for which data are either unavailable or inconclusive (see Tables 16 and 17). The recommendations are considered separately for developing and developed countries, and for intrauterine growth and gestational duration.

Public health interventions

Interventions should be specific for the population concerned and aimed at quantitatively important modifiable determinants of intrauterine growth and gestational duration (Table 18). As we have seen, the quantitative importance of a factor is determined by its individual effect magnitude and prevalence; however, public health authorities also need to consider issues such as cost-effectiveness, cultural acceptability, and political feasibility, which must be assessed in planning any intervention programme.

In developing countries, the interventions likely to have the largest short-term impact on intrauterine growth include caloric supplementation before and during pregnancy, malaria prophylaxis or treatment (in endemic areas), and efforts to reduce maternal cigarette smoking and tobacco chewing (in countries

Table 18. Suggested public health interventions

	Developed countries	Developing countries
Intrauterine growth	Anti-smoking efforts Selective caloric supplementation before and during pregnancy Delayed child-bearing in young adolescents Improved maternal education Selective improvements in nutrition Selective improvements in socioeconomic conditions New vaccines to prevent communicable diseases	Caloric supplementation before and during pregnancy Malaria prophylaxis or treatment Anti-smoking efforts Efforts to reduce tobacco chewing Delayed child-bearing in young adolescents Improved maternal education General improvements in nutrition General improvements in socioeconomic conditions Improved sanitation and water supplies
Gestational duration	Anti-smoking efforts Selective caloric supplementation before pregnancy Delayed child-bearing in young adolescents Improved maternal education Selective improvements in socioeconomic conditions	Caloric supplementation before pregnancy Delayed child-bearing in young adolescents Improved maternal education General improvements in socioeconomic conditions

where these are common practices). Over the long term, general improvements in nutrition, living conditions, water supply, and sanitation should increase maternal height and reduce communicable diseases during pregnancy. Interventions could also be directed at one of the indirect causes of IUGR: very young maternal age and socioeconomic status. Although maternal age has no independent impact on intrauterine growth, girls within one or two years of their menarche are more likely to be short and suboptimally nourished than older women. More widespread use of contraception and selective abortion among young adolescents may thus have an indirect effect on IUGR by delaying pregnancy until they are taller and better nourished. In societies where women often marry and begin to bear children in their early teens, however, the cultural obstacles to such intervention may be considerable. Better maternal education may improve nutrition and reduce cigarette smoking, tobacco chewing, and other harmful practices during pregnancy. Over the long term, improvement in socioeconomic conditions would also be expected to produce favourable indirect effects.

Of the identified determinants of gestational duration in developing countries, few seem susceptible to remedy in the short term. However, increased pre-pregnancy weight, delayed childbearing among young adolescents, and maternal education would probably be beneficial. Also, improved socioeconomic conditions would be helpful but require far longer to achieve. Prematurity is probably a lower priority in developing countries than IUGR, since the latter accounts for the majority of LBW in such countries.

In developed countries IUGR (defined as birth weight <2500 g and gestational age $\geqslant 37$ weeks) is far less prevalent (in some developed countries it is probably $\leqslant 2\%$). Not only are LBW rates much lower (see Table 1), but most LBW babies are premature rather than growth-retarded. The major modifiable factor responsible for IUGR in such countries is cigarette smoking. Thus, successful efforts to convince mothers to stop or reduce their cigarette consumption would be expected to decrease the already low IUGR rate even further. Moreover, any beneficial effect on intrauterine growth that increases the proportion of babies with birth weights >3500 g should also reduce infant mortality and childhood morbidity. The randomized trial of anti-smoking counselling by Sexton & Hebel (*238*) suggests that such an approach can be effective.

Other public health interventions likely to have a short-term impact on intrauterine growth in developed countries include improved pre-pregnancy weight and maternal caloric intake, especially where nutrition is suboptimal for a substantial minority of the population. Although the effect of a given caloric intake appears to be less than in developing countries, caloric supplementation such as that provided by the Women, Infants, and Children (WIC) programme in the USA may indeed have an impact (*89*, *285*, *286*). Delayed child-bearing among young adolescents and improved maternal education might also yield additional favourable, if indirect, short-term effects. In addition, over the longer term, better nutrition, socioeconomic conditions, and prevention of communicable diseases, e.g., by means of new vaccines, should be beneficial.

As far as interventions to lower prematurity in developed countries are concerned, reduction in cigarette smoking should receive high priority. Improved pre-pregnancy nutrition, delayed childbearing among young teenagers, and improved maternal education (short term), as well as improved socioeconomic conditions (long term) should also be beneficial. As discussed below, further reductions in prematurity rates will depend on the ability to clarify the role of currently suspected, and to identify the as yet undiscovered, determinants of gestational duration.

It should be borne in mind that no matter how convincing the evidence that a given factor is causally related to intrauterine growth or gestational duration, there is no guarantee that its elimination or reduction will lead to lower infant mortality or childhood morbidity. Lower prematurity rates can be reasonably expected to reduce neonatal mortality because of lower incidence of conditions such as hyaline membrane disease, apnoea, and sepsis. Improved intrauterine growth, especially if begun early in gestation, could reduce subsequent short stature and enhance neurocognitive performance, but may not have a major impact on mortality.

Priorities for future research (see Table 19)

General recommendations. As discussed above, an active public health approach is indicated for those important and modifiable determinants of intrauterine growth and gestational duration whose role is clearly established. For other factors, however, a more restrained approach is probably called for, with the highest research priority given to modifiable factors of potential quantitative importance but for which current data do not justify large-scale public health interventions. A lower level of priority should be assigned to factors whose causal impact is uncertain but whose low prevalence, suspected small effect, or unmodifiable nature make them unlikely targets for future intervention. This is particularly true for developing countries. Developed countries with large financial resources, however, may wish to support research on such factors.

Those factors whose causal role is already well

Table 19. General recommendations for future etiologic research

1. Highest priority to modifiable factors of potential quantitative importance for which evidence of a causal effect is inconclusive.
2. Lower priority to factors of uncertain causal impact with low prevalence, suspected small effect, or fixed (unmodifiable) nature.
3. Lowest priority to known determinants. Population surveys to determine the prevalences of such determinants, as well as studies in developing countries aimed at defining their respective effect magnitudes, should however be encouraged.
4. General methodological improvements required:
   - —Separate consideration of gestational duration and intrauterine growth.
   - —Differentiation of subtypes of IUGR.
   - —Better description of target populations, sampling procedures, and study participation and follow-up rates.
   - —Assessment and reporting of reproducibility and validity of measurements.
   - —Prospective data collection whenever temporal sequences in question.
   - —More frequent use of randomized clinical trials.
   - —For observational studies, measurement and adequate statistical control for confounding factors.

established should receive the lowest research priority. The large-scale availability of both infant weighing devices and statistical software packages has led to an unprecedented profusion of small, poorly controlled observational studies of LBW and its determinants. The rationale behind this approach is often obscure. Rare are the authors who hypothesize the existence of a new factor or even a reason for suspecting that an already well-known factor might be more or less important in their study setting. Few if any of these studies have added to our understanding over the last decade, and the waste in terms of both financial resources and human effort has been considerable. Far more useful would be population-wide surveys of the prevalence of those risk factors already identified (e.g., cigarette smoking, tobacco chewing, alcohol consumption, malaria, and general morbidity) to assess their overall impact in the population surveyed. Furthermore, the effect magnitudes of several determinants, including racial/ethnic origin, maternal height, pre-pregnancy weight, paternal height and weight, maternal birth weight and gestational age, prior history of LBW and prematurity, prior spontaneous abortion, cigarette smoking, and alcohol consumption, are based almost exclusively on studies from developed countries. The assumption that effect magnitudes are similar in developing countries requires confirmation. Much of the needed information could probably be obtained by careful re-analysis of existing data and would not involve major commitment of human and monetary resources for new large-scale studies.

General methodological recommendations follow from comments made in the section on Synthesis (see p. 717). Firstly, gestational duration should be considered separately from intrauterine growth in all studies of LBW. This distinction requires valid and reproducible measurement of gestational age, preferably based on the date of the last menstrual period, determined *early* in the pregnancy. Future etiologic research should attempt to differentiate various subtypes, such as "stunted" (proportional) versus "wasted" (disproportional) IUGR, since their prognoses appear to differ. Such an approach requires careful measurement of birth length, preferably supplemented by that of head circumference and mid-arm circumference, and of skinfolds or other index of body fat.

Research design and statistical analysis also require improvement. Target populations, sampling procedures, as well as study participation and follow-up rates should be better described. Reproducibility and validity in the measurement of risk factors and outcomes should be assessed and reported to facilitate interpretation of both positive and negative findings. Wherever temporal sequences between suspected factors and pregnancy outcomes are open to question, data should be collected prospectively. Finally, randomized clinical trials should be used whenever feasible, and observational studies should measure and statistically control for potential confounding factors.

Factors requiring further study (see Table 20)

As discussed above, limited resources dictate that future etiologic research should focus on potentially important and modifiable factors for which evidence does not justify large-scale public health intervention. In developing countries, perhaps the most important of these factors that has a bearing on intrauterine growth is caloric expenditure (strenuous maternal work). Of course, the extent to which cultural forces in such countries would permit modification is

Table 20. Factors requiring further study

	Developed countries	Developing countries
Intrauterine growth	Maternal haemodynamics Narcotic addiction Environmental toxins and noise Quality of antenatal care	Strenuous maternal work Indoor smoke Folic acid Antenatal care (quantity and quality) Racial/ethnic origin[a] Malaria[a]
Gestational duration	Genital tract infection Maternal employment and physical activity Stress and anxiety General morbidity Quality of antenatal care	Genital tract infection Tobacco chewing Indoor smoke Maternal work General morbidity Anxiety and stress Antenatal care (quantity and quality)

[a] Research required to provide better estimate of effect magnitude.

unclear. Even if reduction in maternal work can be shown to result in larger babies, it is far from certain that families would be willing or able to forego the pregnant woman's contribution to productivity and financial stability. None the less, provision of nearby public water supplies, for example, could provide benefits in areas where pregnant women are obliged to carry heavy loads of water over considerable distances. The feasibility of specific interventions needs to be carefully considered for each setting, but the most fruitful approach for future research will probably be clinical trials of such interventions.

Another major priority for research in developing countries is the effect on pregnant women of indoor smoke (especially carbon monoxide). In view of the effect of maternal cigarette smoking and the prevalence of poorly ventilated stoves that burn wood and other biomass fuels, a deleterious effect on intrauterine growth seems likely among pregnant women who spend a large proportion of their time indoors.

Because some studies have shown that folic acid supplements have a beneficial effect, further randomized trials of women who have folate-deficient diets should be undertaken. Additional factors that require study in developing countries include antenatal care, the effects of other vitamins and trace elements, and maternal haemodynamics. Although evidence on iron deficiency and anaemia indicates that these have no significant effect on intrauterine growth, additional trials of iron supplements may be necessary to confirm this.

Research is also recommended for racial/ethnic origin and maternal malaria, two factors listed as "established" in Table 16. Although racial/ethnic origin appears to explain a significant proportion of the differences in intrauterine growth between developed and developing countries (see Fig. 3), the size of the attributable difference, and even its very existence, are far from certain. Even though race is obviously not a modifiable factor, clear delineation of its importance should receive high priority. This will require far better control for differences in height, weight, gestational nutrition, and toxic exposures than has been the case in studies to date. Re-analysis of existing data may provide much of the required information for this factor. Also, although it seems clear that placental malaria results in some degree of impairment of fetal growth, better data are required to determine the magnitude of this effect. Such data would permit more definitive conclusions about the overall impact of malaria on birth weight in endemic areas. As repeatedly emphasized, prematurity appears to be a lower priority than IUGR in most developing countries. None the less, suspected risk factors such as genital tract infection, tobacco chewing, indoor smoke, maternal work, general morbidity, stress and anxiety, and antenatal care merit further study.

In developed countries, etiologic research on intrauterine growth should focus on maternal haemodynamics, narcotic addiction, environmental toxins (particularly insecticides and other potentially hazardous chemicals) and noise, and antenatal care. Toxic environmental exposures cannot, for ethical reasons, be experimentally assigned, but future observational studies will require better control for potentially confounding variables. Antenatal care, on the other hand, can be studied using an experimental design, and emphasis should be placed on identifying those qualitative elements of care, e.g., nutritional or anti-smoking counselling, that really have an effect.

In view of its greater relative importance and largely unknown cause, prematurity should be the

main focus of etiologic research on low birth weight in developed countries. Several factors appear promising in this respect, including genital tract infection (especially that caused by *U. urealyticum*), maternal employment and physical activity, stress and anxiety, general morbidity, and antenatal care. All of these present formidable methodological obstacles that require carefully designed studies and statistical analysis. Randomized antibiotic trials should be undertaken of women who are colonized with *U. urealyticum* (or *C. trachomatis*) early in pregnancy. Also, randomized trials should help to identify those aspects of antenatal care that may reduce the risk of pre-term delivery. For the other suspected factors, experimental designs may not be feasible, and adequate study will require improvements in measurement, e.g., of posture, caloric expenditure, physical fitness, and stress, as well as careful control for confounding.

Finally, there is a need for studies to keep sight of infant and child mortality, morbidity, and functional performance, since birth weight and gestational age are important only insofar as they affect these outcomes. Most studies of determinants of intrauterine growth or gestational duration assume that they will automatically affect more "distal" health outcomes. That such is not always the case is clearly illustrated by infant sex. Newborn girls are significantly smaller than newborn boys but exhibit lower neonatal mortality, lower incidence rates for many infant and childhood diseases, and no impairment of subsequent neurocognitive performance.

Establishment of a direct link between a suspected risk factor and the "true" outcomes of mortality, morbidity, and performance requires the use of far larger sample sizes, and often a longer follow-up period than demonstration of an effect on LBW. While the practical difficulties must be acknowledged, future research in this area should attempt to establish such direct links whenever possible.

ACKNOWLEDGEMENTS

I am indebted to the following colleagues who participated in and helped me prepare for a workshop on low birth weight held at WHO, Geneva, 13–16 August 1985, for their many valuable comments and suggestions: Dr Olusola Ayeni, Dr Mark Belsey, Dr Djamil Benbouzid, Dr Manuel Carballo, Dr Richard Guidotti, Dr Jean-Pierre Habicht, Dr Wolfgang Keller, Dr A. Petros-Barvazian, Dr Alberto Pradilla, Dr Prema Ramachandran, Dr Zena Stein, Dr Nebiat Tafari, and Dr José Villar. Although they should not be held responsible for the content of this review, their contributions are gratefully acknowledged. Special thanks go to Ms Claire Sasportas, who coordinated the arduous library research and organized the bibliography. The entire staff of the WHO library, and especially Ms Faith Meakin, were extremely helpful in carrying out the computer literature search and locating references not held at WHO. Ms Cécile Gregory and Ms Maya Jalaleddine provided useful guidance in computerizing the bibliography, and Ms Susan Ashwell and Ms Rosemary Bourne helped prepare the manuscript.

RÉSUMÉ

FACTEURS DÉTERMINANTS DE L'INSUFFISANCE PONDÉRALE À LA NAISSANCE: ÉVALUATION MÉTHODOLOGIQUE ET MÉTA-ANALYSE

On admet généralement que l'insuffisance pondérale à la naissance peut avoir de nombreuses causes. Néanmoins, les recherches dans ce domaine ont souvent donné des résultats contradictoires, de sorte que l'identification des facteurs susceptibles d'exercer des effets indépendants et l'importance quantitative de ces effets soulèvent des controverses et qu'une certaine confusion entoure la question. Ces résultats contradictoires s'expliquent par l'absence de distinction entre le retard de croissance intra-utérine (IUGR) et la prématurité, par l'importance plus ou moins grande accordée à certains critères (poids moyen à la naissance ou âge gestationnel dans certains cas, taux de croissance intra-utérine ou prématurité dans d'autres), par l'emploi de méthodes statistiques mal conçues et, ce qui est peut-être le plus grave, par une prise en compte insuffisante des facteurs confondants potentiels.

Devant la confusion et les désaccords qui subsistent en dépit de la profusion des études, le présent article propose une évaluation critique et une méta-analyse de la littérature médicale publiée en anglais et en français sur cette question de 1970 à 1984. L'évaluation est limitée aux grossesses uniques survenues chez des femmes vivant au niveau de la

mer et ne souffrant d'aucune maladie chronique. On n'a pas tenu compte des facteurs dont la prévalence est extrêmement faible. De même, on a exclu les complications médicales de la grossesse car ces conditions devraient probablement être considérées comme des conséquences intermédiaires, plutôt que des facteurs déterminants, de la croissance intra-utérine et de la durée de la gestation. Compte tenu de ces restrictions et exclusions, il restait 43 facteurs ou groupes de facteurs à évaluer.

Des normes méthodologiques ont été établies à priori pour l'étude de chaque facteur retenu. Certaines de ces normes concernent des aspects généraux de l'organisation de l'étude, comme la définition de la population cible et l'échantillonnage, les taux de participation à l'étude et de suivi, la mise en évidence de la succession chronologique des facteurs et de leurs conséquences, et l'utilisation d'un modèle de recherche expérimentale (lorsque cela était possible). Les autres normes, différentes selon le facteur à évaluer, portaient sur des paramètres susceptibles de constituer des variables confondantes qu'il fallait contrôler,

Des études répondant à toutes les normes (SM) ou à une partie d'entre elles (PM) ont été choisies en vue d'une analyse plus poussée. Les études SM devaient satisfaire à la majorité des critères préétablis, contrairement aux études PM, qui devraient néanmoins remplir des conditions rigoureuses de conception et d'analyse. Pour plusieurs facteurs, on a accordé une importance particulière à certaines normes avant de classer une étude dans la catégorie SM ou PM.

A partir des résultats des études SM et/ou PM, on a évalué chaque facteur afin de déterminer s'il avait un effet indépendant sur le poids à la naissance, l'âge gestationnel, la prématurité et l'IUGR. Si un lien de cause à effet était démontré pour un facteur particulier, la différence attribuée à ce facteur était calculée pour chaque étude. L'importance de chaque effet ainsi calculé était ensuite pondérée en fonction de la taille de l'échantillon ayant fait l'objet de l'étude, de façon à obtenir une estimation globale pour chaque facteur. Enfin, on a calculé des fractions étiologiques (risques attribuables à une population) pour la prématurité et l'IUGR à partir des données concernant la prévalence de chaque facteur dont l'influence a été démontrée dans différents groupes de population.

Une recherche bibliographique a permis de dénombrer 921 publications pertinentes, dont 895 (97,2%) ont pu être retrouvées et examinées. La majorité d'entre elles provenaient des pays développés d'Amérique du Nord et d'Europe occidentale, mais un grand nombre provenait également des pays en développement d'Afrique, d'Amérique latine, d'Asie du Sud-Est et de l'Inde. Au total, 1566 évaluations de facteurs ont été effectuées.

Les facteurs dont l'incidence directe sur la croissance intra-utérine est bien établie comprennent: le sexe de l'enfant, l'origine raciale ou ethnique, la taille de la mère, son poids avant la grossesse, la taille et le poids du père, le poids de la mère à sa naissance, la parité, une insuffisance pondérale à la naissance chez les enfants précédents, le gain de poids et l'apport calorique pendant la grossesse, la morbidité générale et les antécédents de maladies épisodiques, le paludisme, le tabagisme, la consommation d'alcool et l'habitude de chiquer le tabac. Parmi les facteurs n'ayant que des effets indirects, c'est-à-dire ceux dont l'incidence s'exprime par l'intermédiaire d'un ou plusieurs facteurs directs, on peut citer l'âge de la mère et son niveau socio-économique.

L'importance *relative* des facteurs ayant une incidence directe sur l'IUGR a été estimée à partir des fractions étiologiques correspondantes dans deux environnements "typiques" différents: un pays en développement à caractère rural où le paludisme est modérément endémique, mais où les femmes enceintes ne fument pas, et un pays développé où 40% des femmes fument pendant la grossesse. Des différences raciales/ethniques semblent être responsables d'une forte proportion des IUGR dans les pays en développement qui comptent une importante population noire ou indienne. Les autres facteurs importants dans les pays en développement sont une mauvaise alimentation pendant la grossesse, un faible poids avant la grossesse, la petite taille de la mère et le paludisme. Sur ces cinq facteurs, trois peuvent être modifiés à court terme: l'alimentation pendant la grossesse, le poids avant la grossesse et le paludisme.

Dans les pays développés, le facteur le plus important est de loin le tabagisme. Il est suivi par la mauvaise alimentation pendant la grossesse, le faible poids avant la grossesse, la primiparité, le sexe de l'enfant (fille) et la petite taille de la mère.

En ce qui concerne la durée de la grossesse, les seuls facteurs dont l'effet direct est bien établi sont le poids avant la grossesse, les antécédents de prématurité ou d'avortement spontané, l'exposition *in utero* au diéthylstilbestrol et le tabagisme. L'âge et le niveau socio-économique de la mère semblent influer indirectement sur la durée de la grossesse en modifiant un ou plusieurs des facteurs déterminants directs. Il est difficile de déterminer l'importance relative de ces facteurs, la majorité des naissances avant terme qui se produisent tant dans les pays en développement que dans les pays développés restant inexpliquées.

Cette importante lacune dans nos connaissances découle en partie du fait que la recherche est beaucoup moins active dans le domaine de la durée de la grossesse que dans celui de la croissance intra-utérine.

A l'avenir, la recherche devrait porter en priorité sur les facteurs qui ont une importance quantitative potentielle et pour lesquels les données sont inexistantes ou non concluantes. Dans les pays en développement, le plus important de ces facteurs pour la croissance intra-utérine est peut-être la dépense calorique due à l'obligation pour la mère de se livrer à un travail fatigant pendant la grossesse. Parmi les autres facteurs qui méritent d'être étudiés plus avant, on peut citer les soins pré-nataux, les carences en certaines vitamines et oligo-éléments, l'hémodynamique maternelle et l'exposition à la fumée à l'intérieur des habitations. Dans les pays développés, les futures recherches étiologiques sur la croissance intra-utérine devraient être axées sur l'hémodynamique maternelle, l'influence du bruit et des toxines présentes dans l'environnement et les soins pré-nataux.

La recherche sur l'insuffisance pondérale à la naissance dans les pays développés devrait porter principalement sur la prématurité, compte tenu de son importance relative et de l'ignorance entourant ses causes. A cet égard, il semble que plusieurs facteurs pourraient être étudiés avec profit, notamment les infections de l'appareil génital, la profession et l'activité physique de la mère, le stress et l'anxiété, la morbidité générale et les soins pré-nataux.

Les futurs programmes de recherche et les politiques de santé publique devraient être établis sans perdre de vue l'importance de la mortalité, de la morbidité et du développement fonctionnel des nouveau-nés et des enfants, car le poids à la naissance et l'âge gestationnel n'ont d'intérêt que dans la mesure où ils ont un effet dans ces domaines. La plupart des chercheurs et des décideurs prennent pour acquis qu'une modification des facteurs de l'insuffisance pondérale à la naissance aura automatiquement des conséquences plus lointaines en matière de santé, mais des liens directs devraient être établis chaque fois que cela est possible. La santé pour tous, que ce soit en l'an 2000 ou dans un avenir plus lointain, et un objectif louable. Visons à obtenir que tous les nourrissons aient un bon poids de naissance, non pas comme solution de rechange, mais comme un premier pas dans cette direction.

REFERENCES

1. McCormick, M. C. The contribution of low birth weight to infant mortality and childhood morbidity. *New England journal of medicine*, **312**: 82–90 (1985).
2. Chase, H. C. *International comparison of perinatal and infant mortality: the United States and six west European countries*. Washington, DC, U.S. Government Printing Office, 1967 (Public Health Service Series 3(6), Publication No. 1000).
3. Chase, H. C. Infant mortality and weight at birth: 1960 United States birth cohort. *American journal of public health*, **59**: 1618–1628 (1969).
4. Puffer, P. R. & Serrano, C. V. *Patterns of mortality in childhood: report of the Inter-American investigation of mortality in childhood*. Washington, DC, 1973 (Pan American Health Organization Scientific Publication No. 262).
5. Saugstad, L. F. Weight of all births and infant mortality. *Journal of epidemiology and community health*, **35**: 185–191 (1981).
6. Pethybridge, R. J. et al. Some features of the distribution of birthweight of human infants. *British journal of preventive and social medicine*, **28**: 10–18 (1974).
7. Yerushalmy, J. et al. Birth weight and gestation as indices of "immaturity": neonatal mortality and congenital anomalies of the "immature". *American journal of diseases of children*, **109**: 43–57 (1965).
8. Lubchenco, L. O. et al. Neonatal mortality rate: relationship to birth weight and gestational age. *Journal of pediatrics*, **81**: 814–822 (1972).
9. Hoffman, H. J. et al. Classification of births by weight and gestational age for future studies of prematurity. In: Reed, D. M. & Stanley, F. J., ed. *The epidemiology of prematurity*. Baltimore, Urban & Schwarzenberg, 1977, pp. 297–333.
10. Ellenberg, J. H. & Nelson, K. B. Birth weight and gestational age in children with cerebral palsy or seizure disorders. *American journal of diseases of children*, **133**: 1044–1048 (1979).
11. Ounsted, M. & Taylor, M. E. The postnatal growth of children who were small-for-dates or large-for-dates at birth. *Developmental medicine and child neurology*, **13**: 421–434 (1971).
12. Fitzhardinge, P. M. & Steven, E. M. The small-for-date infant. I. Late growth patterns. *Pediatrics*, **49**: 671–681 (1972).
13. Hofvander, Y. International comparisons of postnatal growth of low birthweight infants with special reference to differences between developing and affluent countries. *Acta Paediatrica Scandinavica, Supplementa*, **296**: 14–18 (1982).
14. Westwood, M. et al. Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: follow-up through adolescence. *Pediatrics*, **71**: 376–382 (1983).
15. Fitzhardinge, P. M. & Steven, E. M. The small-for-date infant. II. Neurologic and intellectual sequelae. *Pediatrics*, **50**: 50–57 (1972).
16. Miller, H. C. & Merritt, T.A. *Fetal growth in humans*. Chicago, Year Book Medical Publishers, 1979.
17. Villar, J. & Belizan, J. M. The timing factor in the pathophysiology of the intrauterine growth retardation syndrome. *Obstetrical and gynecological surveys*, **37**: 499–506 (1982).
18. Villar, J. et al. Heterogeneous growth and mental development of intrauterine growth-retarded infants during the first 3 years of life. *Pediatrics*, **74**: 783–791 (1984).
19. Habicht, J.-P. et al. Maternal nutrition, birth weight, and infant mortality. In: *Size at birth*. (Ciba Foundation Symposium 27), Amsterdam, Elsevier, 1974, pp. 353–377.
20. World Health Organization. The incidence of low birth weight: a critical review of available information. *World health statistics quarterly*, **33**: 197–224 (1980).
21. World Health Organization. The incidence of low birth weight: an update. *Weekly epidemiological record*, **59**: 205–211 (1984).
22. Spiers, P. S. & Wacholder, S. Association between rates of premature delivery and intra-uterine growth retardation. *Developmental medicine and child neurology*, **24**: 808–816 (1982).
23. Stein, Z. et al. *Famine and human development: the Dutch hunger winter of 1944–1945*. New York, Oxford University Press, 1975.
24. Niswander, K. R. Obstetric factors related to prematurity. In: Reed, D. M. & Stanley, F. J., ed. *The epidemiology of prematurity*. Baltimore, Urban & Schwarzenberg, 1977, pp. 249–268.

25. BLAIR, R. G. Pregnancy associated with congenital malformations of the reproductive tract. *Journal of obstetrics and gynaecology of the British Empire*, **67**: 36–42 (1960).
26. ZABRISKIE, E. Pregnancy and the malformed uterus—report of 92 cases. *West journal of surgery, obstetrics and gynecology*, **26**: 293–296 (1962).
27. SUSSER, M. *Causal thinking in the health sciences*. New York, Oxford University Press, 1973.
28. HUNTER, J. E. ET AL. *Meta-analysis: cumulating research findings across studies*. Beverly Hills, Sage, 1982.
29. LEVIN, M. L. The occurrence of lung cancer in man. *Acta Unio Internationalis Contra Cancrum*, **19**: 531–541 (1953).
30. MEYER, M. B. ET AL. Perinatal events associated with maternal smoking during pregnancy. *American journal of epidemiology*, **103**: 464–476 (1976).
31. HINGSON, R. ET AL. Effects of maternal drinking and marijuana use on fetal growth and development. *Pediatrics*, **70**: 539–546 (1982).
32. ZUCKERMAN, B. ET AL. Neonatal outcome: is adolescent pregnancy a risk factor? *Pediatrics*, **71**: 489–493 (1983).
33. TAFFEL, S. *Factors associated with low birth weight. United States, 1976*. Washington, DC, U.S. Government Printing Office, 1980 (Vital Health Statistics Series 21(37), DHEW Publication No. (PHS) 80–1915).
34. ARMSTRONG, R. J. *A study of infant mortality from linked records. By birth weight, period of gestation, and other variables. United States, 1960 live-birth cohort*. Washington, DC, U.S. Government Printing Office, 1972 (Vital Health Statistics Series 20(12), DHEW Publication No. (HSM) 72–1055).
35. CHASE, H. C. A study of risks, medical care, and infant mortality. *American journal of public health*, **63**(Suppl.): 1–56 (1973).
36. HOFFMAN, H. J. ET AL. Analysis of birth weight, gestational age, and fetal viability, U.S. births, 1968. *Obstetrics and gynecology survey*, **29**: 651–681 (1974).
37. NISWANDER, K. R. & GORDON, M. *The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke: the women and their pregnancies*. Washington, DC, U.S. Government Printing Office, 1972 (DHEW Publication No. 73–379).
38. BERKOWITZ, G. S. An epidemiologic study of preterm delivery. *American journal of epidemiology*, **113**: 81–92 (1981).
39. WIENER, G. & MILTON T. Demographic correlates of low birth weight. *American journal of epidemiology*, **91**: 260–272 (1970).
40. GARN, S. M. ET AL. Effects of socioeconomic status and race on weight-defined and gestational prematurity in the United States. In: Reed, D. M. & Stanley, E. J., ed. *The epidemiology of prematurity*. Baltimore, Urban & Schwarzenberg, 1977, pp. 127–143.
41. GARN, S. M. & BAILEY, S. M. Genetics of maturational processes. In: Falkner, F. & Tanner, J. M., ed. *Human growth, vol. 1: principles and prenatal growth*. New York, Plenum Press, 1978, pp. 307–330.
42. KAMINSKI, M. ET AL. La grossesse des femmes migrantes à Paris. *Revue française de gynécologie et d'obstétrique*, **70**: 483–491 (1975).
43. MAMELLE, N. ET AL. Prematurity and occupational activity during pregnancy. *American journal of epidemiology*, **119**: 309–322 (1984).
44. HUGHES, K. ET AL. Low birthweight of live singletons in Singapore, 1967–1974. *International journal of epidemiology*, **13**: 465–471 (1984).
45. DAVIES, D. P. ET AL. Size at birth of Asian and White Caucasian babies born in Leicester: implications for obstetric and paediatric practices. *Early human development*, **6**: 257–263 (1982).
46. HORON, I. L. ET AL. Birth weight among infants born to adolescent and young adult women. *American journal of obstetrics and gynecology*, **146**: 444–449 (1983).
47. SHOWSTACK, J. A. ET AL. Factors associated with birthweight: an exploration of the roles of prenatal care and length of gestation. *American journal of public health*, **74**: 1003–1008 (1984).
48. YUDKIN, P. L. ET AL. High birthweight in an ethnic group of low socioeconomic status. *British journal of obstetrics and gynaecology*, **90**: 291–296 (1983).
49. PALTI, H. & ADLER, B. Body size of Israeli newborn infants in relation to regional origin of their mothers. *Human biology*, **49**: 41–50 (1977).
50. MUNROE, M. ET AL. Birth weight, length, head circumference and bilirubin level in Indian newborns in the Sioux Lookout Zone, northwestern Ontario. *Canadian Medical Association journal*, **131**: 453–456 (1984).
51. LINN, S. ET AL. The association of marijuana use with outcome of pregnancy. *American journal of public health*, **73**: 1161–1164 (1983).
52. NATIONAL CENTER FOR HEALTH STATISTICS. *Vital statistics of the United States, 1978, vol. I. Natality*. Washington, DC, U.S. Government Printing Office, 1982 (DHSS Publication No. (PHS) 82–1100).
53. NISWANDER, K. & JACKSON, E. C. Physical characteristics of the gravida and their association with birth weight and perinatal death. *American journal of obstetrics and gynecology*, **119**: 306–313 (1974).
54. THOMSON, A. M. Physiological determinants of birth weight. *Proceedings of the Second European Congress on Perinatal Medicine, London, 1970*. Basel, Karger, 1971, pp. 174–180.
55. SCOTT, A. ET AL. The relative contributions of different maternal factors in small-for-gestational-age pregnancies. *European journal of obstetrics, gynecology and reproductive biology*, **12**: 157–165 (1981).
56. FEDRICK, J. & ADELSTEIN. P. Factors associated with low birth weight infants delivered at term. *British journal of obstetrics and gynaecology*, **85**: 1–7 (1978).
57. KAMINSKI, M. ET AL. Prediction of low birthweight and prematurity by a multiple regression analysis with maternal characteristics known since the beginning of the pregnancy. *International journal of epidemiology*, **2**: 195–204 (1973).
58. EDWARDS, L. E. ET AL. Pregnancy in the underweight

woman: course outcome and growth patterns of the infant. *American journal of obstetrics and gynecology*, **135**: 297–302 (1979).
59. MOODIE, A. D. ET AL. Low-weight Cape coloured mothers and their infants. *South African medical journal*, **44**: 1400–1408 (1970).
60. EDWARDS, L. E. ET AL. Pregnancy in the massively obese: course, outcome, and obesity prognosis of the infant. *American journal of obstetrics and gynecology*, **131**: 479–484 (1973).
61. GIBSON, H. M. Plasma volume and glomerular filtration rate in pregnancy and their relation to differences in fetal growth. *Journal of obstetrics and gynaecology of the British Commonwealth*, **80**: 1067–1074 (1973).
62. CROALL, J. ET AL. Non-pregnant maternal plasma volume and fetal growth retardation. *British journal of obstetrics and gynaecology*, **85**: 90–95 (1978).
63. BILLEWICZ, W. Z. & THOMSON, A. M. Birthweights in consecutive pregnancies. *Journal of obstetrics and gynaecology of the British Commonwealth*, **80**: 491–498 (1973).
64. NAEYE, R. L. Maternal blood pressure and fetal growth. *American journal of obstetrics and gynecology*, **141**: 780–787 (1981).
65. NAEYE, R. L. Maternal nutrition and pregnancy outcome. In: Dobbing, J., ed. *Maternal nutrition in pregnancy—eating for two?* London, Academic Press, 1981, pp. 89–102.
66. PRITCHARD, C. W. ET AL. Birthweight and paternal height. *British journal of obstetrics and gynaecology*, **90**: 156–161 (1983).
67. MAGNUS, P. ET AL. Parental determinants of birth weight. *Clinical genetics*, **26**: 397–405 (1984).
68. LAZAR, P. ET AL. Individual correction of birth weight for parental stature with special reference to small-for-date and large-for-date infants. *Journal of perinatal medicine*, **3**: 242–247 (1975).
69. WINIKOFF, B. & DEBROVNER, C. H. Anthropometric determinants of birth weight. *Obstetrics and gynecology*, **58**: 678–684 (1981).
70. JOHNSTONE, F. & INGLIS, L. Familial trends in low birth weight. *British medical journal*, **3**: 659–661 (1974).
71. HACKMAN, E. ET AL. Maternal birth weight and subsequent pregnancy outcome. *Journal of the American Medical Association*, **250**: 2016–2019 (1983).
72. KLEBANOFF, M. A. ET AL. Low birth weight across generations. *Journal of the American Medical Association*, **252**: 2423–2427 (1984).
73. SUSSER, M. & STEIN, Z. Third variable analysis: application to causal sequences among nutrient intake, maternal weight, birthweight, placental weight, and gestation. *Statistical medicine*, **1**: 105–120 (1982).
74. POLEDNAK, A. P. ET AL. Birth weight and birth defects in relation to maternal spermicide use. *Teratology*, **26**: 27–38 (1982).
75. MILLS, J. L. ET AL. Maternal alcohol consumption and birth weight. How much drinking during pregnancy is safe? *Journal of the American Medical Association*, **252**: 1875–1879 (1984).
76. PACHAURI, S. & MARWAH, S. M. A study of the effect of certain maternal factors on birth weight. *Indian journal of medical sciences*, **24**: 650–659 (1970).
77. MATA, L. J. *The children of Santa Maria Cauqué: a prospective field study of health and growth*. Cambridge, MIT Press, 1978.
78. COETZEE, L. F. Pregnancy in the South African non-White teenager. *South African medical journal*, **44**: 1373–1376 (1970).
79. DUENHOELTER, J. H. ET AL. Pregnancy performance of patients under fifteen years of age. *Obstetrics and gynecology*, **46**: 49–52 (1975).
80. CORREY, J. F. ET AL. Adolescent pregnancy in Tasmania. *Medical journal of Australia*, **141**: 150–154 (1984).
81. SCHOLL, T. O. ET AL. Early adolescent pregnancy: a comparative study of pregnancy outcome in young adolescents and mature women. *Journal of adolescent health care*, **5**: 167–171 (1984).
82. LEGG, S. ET AL. Patterns of low birthweight in West Jerusalem with special reference to maternal origin. *British journal of preventive and social medicine*, **24**: 89–96 (1970).
83. EISNER, V. ET AL. The risk of low birthweight. *American journal of public health*, **69**: 887–893 (1979).
84. DAVANZO, J. ET AL. Assessing socioeconomic correlates of birthweight in peninsular Malaysia: ethnic differences and changes over time. *Social science and medicine*, **18**: 387–404 (1984).
85. QUICK, J. D. ET AL. Prenatal care and pregnancy outcome in an HMO and general population: a multivariate cohort analysis. *American journal of public health*, **71**: 381–390 (1981).
86. LINN, S. ET AL. No association between coffee consumption and adverse outcomes of pregnancy. *New England journal of medicine*, **306**: 141–145 (1982).
87. LECHTIG, A. ET AL. Maternal nutrition and fetal growth in developing societies: socioeconomic factors. *American journal of diseases of childhood*, **129**: 434–437 (1975).
88. DONALDSON, P. J. & BILLY, J. O. G. The impact of prenatal care on birth weight: evidence from an international data set. *Medical care*, **22**: 177–188 (1984).
89. KENNEDY, E. T. ET AL. Evaluation of the effect of WIC supplemental feeding on birth weight. *Journal of the American Dietetic Association*, **80**: 220–227 (1982).
90. PAPIERNIK, E. & KAMINSKI, M. Multifactorial study of the risk of prematurity at 32 weeks of gestation. I. A study of the frequency of 30 predictive characteristics. *Journal of perinatal medicine*, **2**: 30–36 (1974).
91. KAMINSKI, M. & PAPIERNIK, E. Multifactorial study of the risk of prematurity at 32 weeks of gestation. II. A comparison between an empirical prediction and a discriminant analysis. *Journal of perinatal medicine*, **2**: 37–44 (1974).
92. TENNES, K. & BLACKARD, C. Maternal alcohol consumption, birth weight, and minor physical anomalies. *American journal of obstetrics and gynecology*, **138**: 774–780 (1980).
93. NEWTON, R. W. & HUNT, L. P. Psychosocial stress in pregnancy and its relation to low birth weight. *British medical journal*, **288**: 1191–1194 (1984).
94. MCNEIL, T. F. & KAIJ, L. Obstetric complications and physical size of offspring of schizophrenic,

schizophrenic-like, and control mothers. *British journal of psychiatry*, **123**: 341–348 (1973).
95. McNeil, T. F. & Kaij, L. Reproduction among female mental patients: obstetric complications and physical size of offspring. *Acta Psychiatrica Scandinavica*, **50**: 3–15 (1974).
96. Berkowitz, G. S. & Kasl, S. V. The role of psychosocial factors in spontaneous preterm delivery. *Journal of psychosomatic research*, **27**: 283–290 (1983).
97. Meirik, O. et al. Outcome of delivery subsequent to induced vacuum aspiration abortion in parous women. *American journal of epidemiology*, **116**: 415–429 (1982).
98. Soysa, P. E. & Jayasuriya, D. S. Birth weight in Ceylonese. *Human biology*, **47**: 1–15 (1975).
99. Newton, R. W. et al. Psychosocial stress in pregnancy and its relation to the onset of premature labour. *British medical journal*, **2**: 411–413 (1979).
100. Olsen, J. et al. Alcohol use, conception time, and birth weight. *Journal of epidemiology and community health*, **37**: 63–65 (1983).
101. Gortmaker, S. L. The effects of prenatal care upon the health of the newborn. *American journal of public health*, **69**: 653–660 (1979).
102. Peters, T. J. et al. Plus ça change: predictors of birthweight in two national studies. *British journal of obstetrics and gynaecology*, **90**: 1040–1045 (1983).
103. Fabia, J. Régression multiple du poids de naissance utilisant dix variables "prédictives". *Canadian journal of public health*, **64**: 548–551 (1973).
104. Philipps, C. & Johnson, N. E. The impact of quality of diet and other factors on birth weight of infants. *American journal of clinical nutrition*, **30**: 215–225 (1977).
105. Selvin, S. & Janerich, D. T. Four factors influencing birth weight. *British journal of preventive and social medicine*, **25**: 12–16 (1971).
106. Naeye, R. L. Teenaged and pre-teenaged pregnancies: consequences of the fetal–maternal competition for nutrients. *Pediatrics*, **67**: 146–150 (1981).
107. Carr-Hill, R. & Samphier, M. Birthweight and reproductive careers. *Journal of biosocial science*, **15**: 453–464 (1983).
108. Erickson, J. D. & Bjerkedal, T. Interpregnancy interval: association with birth weight, stillbirth, and neonatal death. *Journal of epidemiology and community health*, **32**: 124–130 (1978).
109. Elster, A. B. The effect of maternal age, parity, and prenatal care on perinatal outcome in adolescent mothers. *American journal of obstetrics and gynecology*, **149**: 845–847 (1984).
110. Speroff, L. & Ramwell, P. W. Prostaglandins in reproductive physiology. *American journal of obstetrics and gynecology*, **107**: 1111–1130 (1970).
111. Naeye, R. L. Coitus and associated amniotic-fluid infections. *New England journal of medicine*, **301**: 1190–1200 (1979).
112. Viegas, O. A. C. et al. Nipple stimulation in late pregnancy causing uterine hyperstimulation and profound fetal bradycardia. *British journal of obstetrics and gynaecology*, **91**: 364–366 (1984).
113. Solberg, D. A. et al. Sexual behaviour in pregnancy. *New England journal of medicine*, **288**: 1098–1103 (1973).
114. Grudzinskas, J. G. et al. Does sexual intercourse cause fetal distress? *Lancet*, **2**: 692–693 (1979).
115. Mills, J. L. et al. Should coitus late in pregnancy be discouraged? *Lancet*, **2**: 136–138 (1981).
116. Rayburn, W. F. & Wilson, E. A. Coital activity and premature delivery. *American journal of obstetrics and gynecology*, **137**: 972–974 (1980).
117. Guzick, D. S. et al. Predictability of pregnancy outcome in preterm delivery. *Obstetrics and gynecology*, **63**: 645–650 (1984).
118. Rush, D. et al. Antecedents of low birthweight in Harlem, New York City. *International journal of epidemiology*, **1**: 375–387 (1972).
119. Kaminski, M. et al. Consommation d'alcool chez les femmes enceintes et issue de la grossesse. *Revue d'épidémiologie et de santé publique*, **24**: 27–40 (1976).
120. Pantelakis, S. N. et al. Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies. *American journal of obstetrics and gynecology*, **116**: 799–805 (1973).
121. WHO Task Force on Sequelae of Abortion. Gestation, birth-weight, and spontaneous abortion in pregnancy after induced abortion: report of collaborative study. *Lancet*, **1**: 142–145 (1979).
122. Schoenbaum, S. C. et al. Outcome of the delivery following an induced or spontaneous abortion. *American journal of obstetrics and gynecology*, **136**: 19–24 (1980).
123. Ganguly, M. et al. Factors associated with "low" and "high" birth weight. *American journal of epidemiology*, **96**: 161–167 (1972).
124. Daling, J. R. & Emanuel, I. Induced abortion and subsequent outcome of pregnancy. *Lancet*, **2**: 170–173 (1975).
125. Daling, J. R. & Emanuel, I. Induced abortion and subsequent outcome of pregnancy in a series of American women. *New England journal of medicine*, **297**: 1241–1245 (1977).
126. Obel, E. Pregnancy complications following legally induced abortion with special reference to abortion technique. *Acta obstetrica et gynecologica Scandinavica*, **58**: 147–152 (1979).
127. Slater, P. E. et al. The effect of abortion method on the outcome of subsequent pregnancy. *Journal of reproductive medicine*, **26**: 123–128 (1981).
128. Peoples, M. D. & Siegel, E. Measuring the impact of programs for mothers and infants on prenatal care and low birth weight: the value of refined analyses. *Medical care*, **21**: 586–608 (1983).
129. Bibbo, M. et al. Follow-up study of male and female offspring of DES-exposed mothers. *Obstetrics and gynecology*, **49**: 1–8 (1977).
130. Kaufman, R. H. et al. Upper genital tract changes and pregnancy outcome in offspring exposed *in utero* to diethylstilbestrol. *American journal of obstetrics and gynecology*, **137**: 299–308 (1980).
131. Herbst, A. L. & Scully, R. E. Adenocarcinoma of the vagina in adolescence: a report of seven cases including six clear-cell carcinomas (so-called mesonephromas). *Cancer*, **25**: 745–757 (1970).

132. HERBST, A. L. ET AL. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *New England journal of medicine*, **284**: 878–881 (1971).
133. DIECKMANN, W. J. ET AL. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? *American journal of obstetrics and gynecology*, **66**: 1062–1081 (1953).
134. HERBST, A. L. ET AL. A comparison of pregnancy experience in DES-exposed and DES-unexposed daughters. *Journal of reproductive medicine*, **24**: 62–69 (1980).
135. HERBST, A. L. ET AL. Reproductive and gynecologic surgical experience in diethylstilbestrol-exposed daughters. *American journal of obstetrics and gynecology*, **141**: 1019–1028 (1981).
136. BARNES, A. B. ET AL. Fertility and outcome of pregnancy in women exposed *in utero* to diethylstilbestrol. *New England journal of medicine*, **302**: 609–613 (1980).
137. COUSINS, L. ET AL. Reproductive outcome of women exposed to diethylstilbestrol *in utero*. *Obstetrics and gynecology*, **56**: 70–76 (1980).
138. HYTTEN, F. & CHAMBERLAIN, G. *Clinical physiology in obstetrics*. Oxford, Blackwell Scientific Publications, 1980.
139. PICONE, T.A. ET AL. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress, and weight gain on placentas, and on neonatal physical and behavioral characteristics. *American journal of clinical nutrition*, **36**: 1214–1224 (1982).
140. FRISANCHO, A. R. ET AL. Influence of growth status and placental function on birth weight of infants born to young still-growing teenagers. *American journal of clinical nutrition*, **40**: 801–807 (1984).
141. NAEYE, R. L. Nutritional/non-nutritional interactions that affect the outcome of pregnancy. *American journal of clinical nutrition*, **34**: 727–731 (1981).
142. DELGADO, H. ET AL. Nutrition and length of gestation. *Nutrition research*, **2**: 117–126 (1982).
143. HABICHT, J.-P. ET AL. Relation of maternal supplementary feeding during pregnancy to birth weight and other sociobiological factors. In: Winick, M., ed. *Current concepts in nutrition, vol. 1. Nutrition and fetal development*. New York, John Wiley & Sons, 1974, pp. 127–145.
144. LECHTIG, A. ET AL. Effect of food supplementation during pregnancy on birthweight. *Pediatrics*, **56**: 508–520 (1975).
145. MCDONALD, E. C. ET AL. The Bacon Chow study: maternal nutrition supplementation and birth weight of offspring. *American journal of clinical nutrition*, **34**: 2133–2144 (1981).
146. RUSH, D. ET AL. A randomized controlled trial of prenatal nutritional supplementation in New York City. *Pediatrics*, **65**: 683–697 (1980).
147. RUSH, D. Nutritional services during pregnancy and birthweight: a retrospective matched-pair analysis. *Canadian Medical Association journal*, **125**: 567–575 (1981).
148. PAIGE, D. M. ET AL. Nutritional supplementation of pregnant adolescents. *Journal of adolescent health care*, **1**: 261–267 (1981).
149. PAPOZ, L. ET AL. Maternal smoking and birth weight in relation to dietary habits. *American journal of obstetrics and gynecology*, **142**: 870–786 (1982).
150. BLACKWELL, R. Q. ET AL. Prospective maternal nutrition study in Taiwan: rationale, study design, feasibility, and preliminary findings. *Nutrition reports international*, **7**: 517–532 (1973).
151. MORA, J. O. ET AL. Nutritional supplementation and the outcome of pregnancy. I. Birth weight. *American journal of clinical nutrition*, **32**: 455–462 (1979).
152. HERRERA, M. G. ET AL. Maternal weight/height and the effect of food supplementation during pregnancy and lactation. In: Aebi, H. & Whitehead, R., ed. *Maternal nutrition during pregnancy and lactation*. Bern, Hans Huber, 1980, pp. 252–263.
153. PRENTICE, A. M. ET AL. Prenatal dietary supplementation of African women and birthweight. *Lancet*, **1**: 489–492 (1983).
154. VIEGAS, O. A. C. ET AL. Dietary protein-energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. II. Selective during third trimester only. *British medical journal*, **285**: 592–595 (1982).
155. BRIEND, A. Fetal malnutrition: the price of upright posture? *British medical journal*, **2**: 317–319 (1979).
156. BRIEND, A. Feeding the fetus in the tropics: rest is best. *Journal of tropical medicine*, **30**: 126–128 (1984).
157. EMMANOUILIDES, G. C. ET AL. Fetal responses to maternal exercise in the sheep. *American journal of obstetrics and gynecology*, **112**: 130–137 (1972).
158. SUONIO, S. ET AL. Effect of the left lateral recumbent position compared with the supine and upright positions on placental blood flow in normal late pregnancy. *Annals of clinical research*, **8**: 22–26 (1976).
159. ORR, J. ET AL. Effect of exercise stress on carotid, uterine, and iliac blood flow in pregnant and nonpregnant ewes. *American journal of obstetrics and gynecology*, **114**: 231–217 (1972).
160. PRENTICE, A. M. Variations in maternal dietary intake, birthweight and breast-milk output in the Gambia. In: Aebi, H. & Whitehead, R., ed. *Maternal nutrition during pregnancy and lactation*. Bern, Hans Huber, 1980, pp. 167–182.
161. PRENTICE, A. M. ET AL. Long-term energy balance in child-bearing Gambian women. *American journal of clinical nutrition*, **34**: 2790–2799 (1981).
162. BERKOWITZ, G. S. ET AL. Physical activity and the risk of spontaneous pre-term delivery. *Journal of reproductive medicine*, **28**: 581–588 (1983).
163. MURPHY, J. F. ET AL. Employment in pregnancy: prevalence, maternal characteristics, perinatal outcome. *Lancet*, **1**: 1163–1166 (1984).
164. WILLIAMS, J. H. Employment in pregnancy. *Lancet*, **2**: 103–104 (1984).
165. SAUREL-CUBIZOLLES, M. J. ET AL. Activité professionnelle des femmes enceintes, surveillance prénatale et issue de la grossesse. *Journal de gynécologie, obstetrique et biologie de la réproduction*, **11**: 959–967 (1982).
166. SAUREL, M. J. & KAMINSKI, M. Pregnant women at work. *Lancet*, **1**: 475 (1983).
167. WHITEHEAD, R. G. ET AL. Factors influencing lac-

tation performance in rural Gambian mothers. *Lancet*, **2**: 178–181 (1978).
168. PAUL, A. A. ET AL. The quantitative effects of maternal dietary energy intake on pregnancy and lactation in rural Gambian women. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **73**: 686–692 (1979).
169. TAFARI, N. ET AL. Effects of maternal undernutrition and heavy physical work during pregnancy on birth weight. *British journal of obstetrics and gynaecology*, **87**: 222–226 (1980).
170. NAEYE, R. L. & PETERS, E. C. Working during pregnancy: effects on the fetus. *Pediatrics*, **69**: 724–727 (1982).
171. PITKIN, R. M. Nutritional support in obstetrics and gynecology. *Clinical obstetrics and gynecology*, **19**: 489–513 (1976).
172. OSOFSKY, H. J. Relationships between prenatal medical and nutritional measures, pregnancy outcome, and early infant development in an urban poverty setting. I. The role of nutritional intake. *American journal of obstetrics and gynecology*, **123**: 682–690 (1975).
173. ADAMS, S. O. ET AL. Effect of nutritional supplementation in pregnancy. *Journal of the American Dietetic Association*, **72**: 144–147 (1978).
174. VIEGAS, O. A. C. ET AL. Dietary protein-energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I. Unselective during second and third trimesters. *British medical journal*, **285**: 589–592 (1982).
175. METCOFF, J. ET AL. Maternal nutrition and fetal outcome. *American journal of clinical nutrition*, **34**: 708–721 (1981).
176. BHARGAVA, V. ET AL. Fetal growth variations. I. Influence of maternal size and nutrition on identification of fetal growth retardation. *Indian pediatrics*, **20**: 549–559 (1983).
177. KITAY, D. Z. & HARBORT, R. A. Iron and folic acid deficiency in pregnancy. *Clinics in perinatology*, **2**: 255–273 (1975).
178. FLEMING, A. F. ET AL. Effects of iron and folic acid antenatal supplements on maternal haematology and fetal wellbeing. *Medical journal of Australia*, **2**: 429–436 (1974).
179. MCLAUGHLIN, B. & KEVANY, J. Haemoglobin concentration in pregnancy: relationships with maternal age and birth weight. *Irish journal of medical science*, **151**: 71–74 (1982).
180. BAUMSLAG, N. ET AL. Reduction of incidence of prematurity by folic acid supplementation in pregnancy. *British medical journal*, **1**: 16–17 (1970).
181. ROBERTS, P. D. ET AL. Vitamin B_{12} status in pregnancy among immigrants to Britain. *British medical journal*, **3**: 67–72 (1973).
182. GILES, P. F. ET AL. 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 (1971).
183. FLETCHER, J. ET AL. The value of folic acid supplements in pregnancy. *Journal of obstetrics and gynaecology of the British Commonwealth*, **78**: 781–785 (1971).
184. ROLSCHAU, J. ET AL. Folic acid supplement and intrauterine growth. *Acta obstetricia et gynecologica Scandinavica*, **58**: 343–346 (1979).
185. BLOT, L. ET AL. Influence of routine administration of folic acid and iron during pregnancy. *Gynecologic and obstetric investigation*, **12**: 294–304 (1981).
186. TRIGG, K. H. ET AL. Folate supplements during pregnancy. *Journal of the Royal College of General Practitioners*, **26**: 228–230 (1976).
187. IVENGAR, L. Folic acid requirements of Indian pregnant women. *American journal of obstetrics and gynecology*, **111**: 13–16 (1971).
188. SACHS, B. P. & STERN, C. M. Activity and characterization of a low molecular fraction present in human amniotic fluid with broad spectrum antibacterial activity. *British journal of obstetrics and gynaecology*, **86**: 81–86 (1979).
189. TAFARI, N. ET AL. Failure of bacterial growth inhibition by amniotic fluid. *American journal of obstetrics and gynecology*, **128**: 187–189 (1977).
190. APPELBAUM, P. C. ET AL. The effect of diet supplementation and addition of zinc *in vitro* on the growth-supporting property of amniotic fluid in African women. *American journal of obstetrics and gynecology*, **135**: 82–84 (1979).
191. WIDDOWSON, E. M. ET AL. Trace elements in foetal and early postnatal development. *Proceedings of the Nutrition Society*, **33**: 275–284 (1974).
192. HUNT, I. F. ET AL. Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *American journal of clinical nutrition*, **40**: 508–521 (1984).
193. CROSBY, W. M. ET AL. Fetal malnutrition: an appraisal of correlated factors. *American journal of obstetrics and gynecology*, **128**: 22–31 (1977).
194. GIBSON, R. S. & DE WOLFE, M. S. Copper, zinc, manganese, vanadium, and iodine concentrations in the hair of Canadian low-birth-weight neonates. *American journal of clinical nutrition*, **32**: 1728–1733 (1979).
195. PITKIN, R. M. Calcium metabolism in pregnancy: a review. *American journal of obstetrics and gynecology*, **121**: 724–737 (1975).
196. RAMAN, L. ET AL. Effect of calcium supplementation to undernourished mothers during pregnancy on the bone density of the neonates. *American journal of clinical nutrition*, **31**: 466–469 (1978).
197. BROOKE, O. G. ET AL. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British medical journal*, **1**: 751–754 (1980).
198. MAXWELL, J. D. ET AL. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *British journal of obstetrics and gynaecology*, **88**: 987–991 (1981).
199. WACHSTEIN, M. & GRAFFEO, L. W. Influence of vitamin B_6 on the incidence of pre-eclampsia. *Obstetrics and gynecology*, **8**: 177–180 (1956).
200. KLIEGER, J. A. ET AL. Abnormal pyridoxine metabolism in toxemia of pregnancy. *American journal of obstetrics and gynecology*, **94**: 316–321 (1966).
201. KAMINETZKY, H. A. ET AL. The effect of nutrition in teen-age gravidas on pregnancy and the status of the

neonate. I. A nutritional profile. *American journal of obstetrics and gynecology*, **115**: 639–646 (1973).
202. SCHUSTER, K. ET AL. Vitamin B_6 status of low-income adolescent and adult pregnant women and the condition of their infants at birth. *American journal of clinical nutrition*, **34**: 1731–1735 (1981).
203. LUMENG, L. ET AL. Adequacy of vitamin B_6 supplementation during pregnancy: a prospective study. *American journal of clinical nutrition*, **29**: 1376–1383 (1976).
204. BAKER, H. ET AL. Vitamin levels in low-birth-weight newborn infants and their mothers. *American journal of obstetrics and gynecology*, **129**: 521–524 (1977).
205. THILLY, C. ET AL. Impaired fetal and postnatal development and high perinatal death-rate in a severe iodine deficient area. In: *Proceedings of the Eighth International Thyroid Congress, Sydney, 3–8 February 1980*. Canberra, Australian Academy of Science, 1980, pp. 20–23.
206. MAENPAA, J. Congenital hypothyroidism: aetiological and clinical aspects. *Archives of disease in childhood*, **47**: 914–923 (1972).
207. LECHTIG, A. ET AL. Effect of morbidity during pregnancy on birth weight in a rural Guatemalan population. *Ecology of food and nutrition*, **5**: 225–233 (1976).
208. REINHARDT, M. C. ET AL. Malaria at delivery in Abidjan. *Helvetica paediatrica acta*, **41** (Suppl.): 65–84 (1978).
209. BRAY, R. S. & ANDERSON, M. J. Falciparum malaria and pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **73**: 427–431 (1979).
210. BRABIN, B.J. An analysis of malaria in pregnancy in Africa. *Bulletin of the World Health Organization*, **61**: 1005–1016 (1983).
211. TAUFA, T. Malaria and pregnancy. *Papua New Guinea medical journal*, **21**: 197–206 (1978).
212. MACGREGOR, J. D. & AVERY, J. G. Malaria transmission and fetal growth. *British medical journal*, **3**: 433–436 (1974).
213. MCGREGOR, I. A. ET AL. Malaria infection of the placenta in The Gambia, West Africa; its incidence and relationship to stillbirth, birthweight and placental weight. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **77**: 232–244 (1983).
214. NAEYE, R. L. Causes of the excessive rates of perinatal mortality and prematurity in pregnancies complicated by maternal urinary-tract infections. *New England journal of medicine*, **300**: 819–823 (1979).
215. POLK, B. F. Urinary tract infection in pregnancy. *Clinical obstetrics and gynecology*, **22**: 285–292 (1979).
216. ELDER, H. A. ET AL. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. *American journal of obstetrics and gynecology*, **111**: 441–462 (1971).
217. BRUMFITT, W. The effects of bacteriuria in pregnancy on maternal and fetal health. *Kidney international*, **8**: 113–119 (1975).
218. SEVER, J. L. ET AL. Urinary tract infections during pregnancy: maternal and pediatric findings. In: Kass, E. H. & Brumfitt, W., ed. *Infections of the urinary tract*. Chicago, University of Chicago Press, 1979, pp. 19–21.
219. ROSS, J. M. ET AL. The effect of genital mycoplasmas on human fetal growth. *British journal of obstetrics and gynaecology*, **88**: 749–755 (1981).
220. HARRISON, H. R. ET AL. Cervical *Chlamydia trachomatis* and mycoplasmal infections in pregnancy. *Journal of the American Medical Association*, **250**: 1721–1727 (1983).
221. BRAUN, P. ET AL. Birth weight and genital mycoplasmas in pregnancy. *New England journal of medicine*, **284**: 167–171 (1971).
222. HARRISON, R. F. ET AL. Genital mycoplasmas and birth weight in offspring of primigravid women. *American journal of obstetrics and gynecology*, **133**: 201–203 (1979).
223. KASS, E. H. ET AL. Genital mycoplasmas as a cause of excess premature delivery. *Transactions of the Association of American Physicians*, **94**: 261–266 (1981).
224. MINKOFF, H. ET AL. Risk factors for prematurity and premature rupture of membranes: a prospective study of the vaginal flora in pregnancy. *American journal of obstetrics and gynecology*, **150**: 965–972 (1984).
225. KUNDSIN, R. B. ET AL. Association of *Ureaplasma urealyticum* in the placenta with perinatal morbidity and mortality. *New England journal of medicine*, **310**: 941–945 (1984).
226. MARTIN, D. H. ET AL. Prematurity and perinatal mortality in pregnancies complicated by maternal *Chlamydia trachomatis* infections. *Journal of the American Medical Association*, **247**: 1585–1588 (1982).
227. EDWARDS, L. E. ET AL. Gonorrhea in pregnancy. *American journal of obstetrics and gynecology*, **132**: 637–641 (1978).
228. WOODS, D. L. ET AL. Amniotic fluid infection at term. *South African medical journal*, **53**: 137–139 (1978).
229. PIRANI, B. B. K. Smoking during pregnancy. *Obstetrical and gynecological survey*, **33**: 1–13 (1978).
230. LONGO, L. D. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *American journal of obstetrics and gynecology*, **129**: 69–103 (1977).
231. QUIGLEY, M. E. ET AL. Effects of maternal smoking on circulating catecholamine levels and fetal heart rates. *American journal of obstetrics and gynecology*, **133**: 685–690 (1979).
232. ANDREWS, J. Thiocyanate and smoking in pregnancy. *Journal of obstetrics and gynaecology of the British Commonwealth*, **80**: 810–814 (1973).
233. BERKOWITZ, G. S. ET AL. Effects of cigarette smoking, alcohol, coffee and tea consumption on preterm delivery. *Early human development*, **7**: 239–250 (1982).
234. Tobacco-hazards to health and human reproduction. *Population reports (Series L (1))*, 1–37 (1979).
235. BUTLER, N. R. ET AL. Cigarette smoking in pregnancy: its influence on birth weight and perinatal mortality. *British medical journal*, **2**: 127–130 (1972).
236. NAEYE, R. L. Influence of maternal cigarette smoking during pregnancy on fetal and childhood growth. *Obstetrics and gynecology*, **57**: 18–21 (1981).
237. RUSH, D. & CASSANO, P. Relationship of cigarette

smoking and social class to birth weight and perinatal mortality among all births in Britain, 5–11 April 1970. *Journal of epidemiology and community health*, **37**: 249–255 (1983).
238. SEXTON, M. & HEBEL, J. R. A clinical trial of change in maternal smoking and its effect on birth weight. *Journal of the American Medical Association*, **251**: 911–915 (1984).
239. RUSH, D. Cigarette smoking during pregnancy: the relationship with depressed weight gain and birthweight. An updated report. In: Kelly, S. et al., ed. *Birth defects: risks and consequences*. New York, Academic Press, 1976, pp. 161–172.
240. MEYER, M. B. How does maternal smoking affect birth weight and maternal weight gain? Evidence from the Ontario Perinatal Mortality Study. *American journal of obstetrics and gynecology*, **131**: 888–893 (1978).
241. DARY, O. ET AL. Carbon monoxide contamination in dwellings in poor rural areas of Guatemala. *Bulletin of environmental contamination and toxicology*, **26**: 24–30 (1981).
242. LEMOINE, P. ET AL. Les enfants de parents alcooliques: anomalies observées à-propos de 127 cas. *Ouest médical*, **25**: 476–482 (1968).
243. JONES, K. L. & SMITH, D. W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet*, **1**: 1076–1078 (1974).
244. MUKHERJEE, A. B. & HODGEN, G. D. Maternal ethanol exposure induces transient impairment of umbilical circulation and fetal hypoxia in monkeys. *Science*, **218**: 700–702 (1982).
245. ABEL, E. L. Consumption of alcohol during pregnancy: a review of effects on growth and development of offspring. *Human biology*, **54**: 421–453 (1982).
246. SILVA, V.A. ET AL. Alcohol consumption during pregnancy and newborn outcome: a study in Brazil. *Neurobehavioural toxicology and teratology*, **3**: 169–172 (1981).
247. ROSETT, H. L. ET AL. Patterns of alcohol consumption and fetal development. *Obstetrics and gynecology*, **61**: 539–546 (1983).
248. MARBURY, M. C. ET AL. The association of alcohol consumption with outcome of pregnancy. *American journal of public health*, **73**: 1165–1168 (1983).
249. STREISSGUTH, A. P. ET AL. Teratogenic effects of alcohol in humans and laboratory animals. *Science*, **209**: 353–361 (1980).
250. VAN DEN BERG, B. J. Epidemiologic observations of prematurity: effects of tobacco, coffee and alcohol. In: Reed, D. M. & Stanley, F. J., ed. *The epidemiology of prematurity*. Baltimore, Urban & Schwarzenberg, 1977, pp. 157–176.
251. RUSSELL, M. Intrauterine growth in infants born to women with alcohol-related psychiatric diagnoses. *Alcoholism*, **1**: 225–231 (1977).
252. LITTLE, R. E. Moderate alcohol use during pregnancy and decreased infant birth weight. *American journal of public health*, **67**: 1154–1156 (1977).
253. WRIGHT, J. T. ET AL. Alcohol consumption, pregnancy, and low birthweight. *Lancet*, **1**: 663–665 (1983).
254. STREISSGUTH, A. P. ET AL. Comparison of drinking and smoking patterns during pregnancy over a six-year interval. *American journal of obstetrics and gynecology*, **145**: 716–724 (1983).
255. WALSH, B. & GRANT, M. Public health implications of alcohol production and trade. Geneva, 1985 (WHO Offset Publication No. 88), pp. 35–55.
256. ALDRIDGE, A. ET AL. The disposition of caffeine during and after pregnancy. *Seminars in perinatology*, **5**: 310–314 (1981).
257. HAWORTH, J. C. ET AL. Fetal growth retardation in cigarette-smoking mothers is not due to decreased maternal food intake. *American journal of obstetrics and gynecology*, **137**: 719–723 (1980).
258. ABEL, E. L. Prenatal exposure to cannabis: a critical review of effects on growth, development, and behaviour. *Behavioural and neural biology*, **29**: 137–156 (1980).
259. FRIED, P.A. Marihuana use by pregnant women: neurobehavioral effects in neonates. *Drug and alcohol dependence*, **6**: 415–424 (1980).
260. GOODLIN, R. C. ET AL. Orgasm during late pregnancy: possible deleterious effects. *Obstetrics and gynecology*, **38**: 916–920 (1971).
261. NAEYE, R. L. ET AL. Fetal complications of maternal heroin addiction: abnormal growth, infections, and episodes of stress. *Journal of pediatrics*, **83**: 1055–1061 (1973).
262. LIFSCHITZ, M. H. ET AL. Fetal and postnatal growth of children born to narcotic-dependent women. *Journal of pediatrics*, **102**: 686–691 (1983).
263. ZELSON, C. ET AL. Neonatal narcotic addiction: 10-year observation. *Pediatrics*, **48**: 178–189 (1971).
264. HARPER, R. G. ET AL. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. *Pediatrics*, **54**: 300–305 (1974).
265. KRISHNA, K. Tobacco chewing in pregnancy. *British journal of obstetrics and gynaecology*, **85**: 726–728 (1978).
266. VERMA, R. C. ET AL. Effect of tobacco chewing by mothers on fetal outcome. *Indian journal of pediatrics*, **20**: 105–111 (1983).
267. VIANNA, N. J. & POLAN, A. K. Incidence of low birth weight among Love Canal residents. *Science*, **226**: 1217–1219 (1984).
268. ANDO, Y. & HATTORI, H. Statistical studies on the effects of intense noise during human fetal life. *Journal of sound and vibration*, **27**: 101–110 (1973).
269. KNIPSCHILD, P. ET AL. Aircraft noise and birth weight. *International archives of occupational and environmental health*, **48**: 131–136 (1981).
270. KESSNER, D. M. ET AL. *Infant death: an analysis by maternal risk and health care*. Washington, DC, Institute of Medicine, National Academy of Sciences, 1973.
271. BOUTALEB, Y. ET AL. Le poids de naissance dans un pays africain. *Journal de gynécologie, obstétrique et biologie de la reproduction*, **11**: 68–72 (1982).
272. RAMANKUTTY, P. ET AL. A study on birth weight of Iraqi children. *Journal of tropical pediatrics*, **29**: 5–10 (1983).
273. JINADU, M. K. ET AL. Effects of antenatal care and parity on birthweights of Nigerian children. *Journal of*

the Royal Society of Health, **103**: 194–195 (1983).
274. TERRIS, M. & GLASSER, M. A life table analysis of the relation of prenatal care to prematurity. *American journal of public health*, **64**: 869–875 (1974).
275. TAFFEL, S. *Prenatal care in the United States, 1969–1975*. Washington, DC, 1978, U.S. Government Printing Office, (Vital health statistics series 21(33), DHEW Publication No. (PHS) 78–1911).
276. REHAN, N. Effect of ante-natal care on birth weight. *Journal of the Pakistan Medical Association*, **32**: 93–99 (1982).
277. GOUJON, H. ET AL. The prevention of preterm delivery through prenatal care: an intervention study in Martinique. *International journal of gynaecology and obstetrics*, **22**: 339–343 (1984).
278. SOKOL, R. J. ET AL. Risk, antepartum care, and outcome: impact of a maternity and infant care project. *Obstetrics and gynecology*, **56**: 150–156 (1980).
279. WILNER, S. ET AL. A comparison of the quality of maternity care between a health maintenance organization and fee-for-service practices. *New England journal of medicine*, **304**: 784–787 (1981).
280. ERSHOFF, D. H. ET AL. Behavioral, health, and cost outcomes of an HMO-based prenatal health education program. *Public health reports*, **98**: 536–547 (1983).
281. PEOPLES, M. D. ET AL. Evaluation of the effects of the North Carolina Improved Pregnancy Outcome Project: implications for state-level decision-making. *American journal of public health*, **74**: 549–554 (1984).
282. FELICE, M. E. ET AL. The young pregnant teenager: impact of comprehensive prenatal care. *Journal of adolescent health care*, **1**: 193–197 (1981).
283. JEKEL, J. F. ET AL. An analysis of statistical methods for comparing obstetric outcomes: infant health in three samples of school-age pregnancies. *American journal of obstetrics and gynecology*, **112**: 9–19 (1972).
284. BRUZZI, P. ET AL. Estimating the population attributable risk for multiple risk factors using case-control data. *American journal of epidemiology*, **122**: 904–914 (1985).
285. EDOZIEN, J. C. ET AL. Medical evaluation of the special supplemental food programme for women, infants, and children. *American journal of clinical nutrition*, **32**: 677–692 (1979).
286. KOTELCHUCK, M. ET AL. WIC participation and pregnancy outcomes. Massachusetts Statewide Evaluation Project. *American journal of public health*, **74**: 1086–1092 (1984).