Maternal Nutrition and Perinatal Survival

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# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>220</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>220</td>
</tr>
<tr>
<td>EFFECTS OF FAMINE AND DIETARY RESTRICTION</td>
<td>221</td>
</tr>
<tr>
<td>Studies of the Effects of Acute Famine Imposed on Previously Well-nourished Populations</td>
<td>221</td>
</tr>
<tr>
<td>Introduction</td>
<td>221</td>
</tr>
<tr>
<td>Leningrad</td>
<td>221</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>222</td>
</tr>
<tr>
<td>Wuppertal, Germany</td>
<td>222</td>
</tr>
<tr>
<td>Conclusion</td>
<td>222</td>
</tr>
<tr>
<td>Intermittent Severe Deprivation</td>
<td>222</td>
</tr>
<tr>
<td>Keneba, the Gambia</td>
<td>222</td>
</tr>
<tr>
<td>Matlab, Bangladesh</td>
<td>223</td>
</tr>
<tr>
<td>Studies of iatrogenic Dietary Limitation</td>
<td>223</td>
</tr>
<tr>
<td>A US autopsy study</td>
<td>223</td>
</tr>
<tr>
<td>Motherwell, Scotland</td>
<td>223</td>
</tr>
<tr>
<td>Studies in Aberdeen, Scotland</td>
<td>224</td>
</tr>
<tr>
<td>An analysis of the US collaborative perinatal study</td>
<td>225</td>
</tr>
<tr>
<td>Conclusion</td>
<td>225</td>
</tr>
<tr>
<td>STUDIES OF MATERNAL WEIGHT AND WEIGHT GAIN DURING PREGNANCY NOT</td>
<td>225</td>
</tr>
<tr>
<td>EMPHASIZING RESTRICTION OF DIET</td>
<td>225</td>
</tr>
<tr>
<td>Introduction</td>
<td>225</td>
</tr>
<tr>
<td>To What Extent Can Dietary Advice or Supplementation Affect Maternal Weight Gain?</td>
<td>226</td>
</tr>
<tr>
<td>Dietary advice</td>
<td>226</td>
</tr>
<tr>
<td>Intervention studies of dietary advice</td>
<td>227</td>
</tr>
<tr>
<td>Dietary supplementation and weight gain</td>
<td>228</td>
</tr>
<tr>
<td>Conclusion</td>
<td>229</td>
</tr>
<tr>
<td>Birth-weight and Maternal Weight, Weight Gain and Body Composition</td>
<td>229</td>
</tr>
<tr>
<td>Studies depending on skinfold thickness</td>
<td>229</td>
</tr>
<tr>
<td>More complex measurements of body composition</td>
<td>230</td>
</tr>
<tr>
<td>Dietary Improvement Leading to Reduction in Maternal Fat Stores: The National WIC (Special Supplemental Food Program for Women, Infants, and Children) Evaluation</td>
<td>230</td>
</tr>
<tr>
<td>Multivariate Analysis of Diet, Weight Gain, and Birth-weight</td>
<td>230</td>
</tr>
<tr>
<td>Summary</td>
<td>231</td>
</tr>
<tr>
<td>Maternal Weight (and Weight Gain) and Perinatal Death</td>
<td>231</td>
</tr>
<tr>
<td>Maternal BMI and congenital malformation</td>
<td>234</td>
</tr>
<tr>
<td>LESSONS FROM DIABETES LITERATURE</td>
<td>234</td>
</tr>
<tr>
<td>Weight Gain in Women with GDM</td>
<td>234</td>
</tr>
<tr>
<td>Birth-weight</td>
<td>234</td>
</tr>
<tr>
<td>Weight gain, insulin sensitivity, leptin, and birth-weight</td>
<td>234</td>
</tr>
<tr>
<td>DIET, FOETAL GROWTH, AND PERINATAL SURVIVAL</td>
<td>235</td>
</tr>
<tr>
<td>Introduction</td>
<td>235</td>
</tr>
<tr>
<td>Intervention Studies of Dietary Advice</td>
<td>235</td>
</tr>
<tr>
<td>Dietary Supplementation Studies during Pregnancy Aimed at Accelerating Foetal Growth</td>
<td>236</td>
</tr>
</tbody>
</table>
A study in which the level of supplementation was controlled by the participants:  
the Guatemalan INCAP four-village study ................................................................. 236

Studies in which decision to supplement and level of supplementation offered  
were not under control of subjects ........................................................................... 237

Studies in developed countries ............................................................................... 237

Studies in developing countries ............................................................................. 243

Conclusion .................................................................................................................. 248

PUBLIC-HEALTH NUTRITION PROGRAMMES IN DEVELOPING COUNTRIES AIMED AT  
LOWERING INFANT MORTALITY BY INCREASING MATERNAL DIET, WEIGHT GAIN, AND  
BIRTH-WEIGHT: EXAMPLES FROM TAMIL NADU (INDIA) AND BANGLADESH ............. 248

Introduction ................................................................................................................ 248

The First Tamil Nadu Integrated Nutrition Project (TINP I) ........................................... 249

The Second Tamil Nadu Integrated Nutrition Project (TINP II) .................................... 250

Bangladesh Integrated Nutrition Project (BINP) .......................................................... 252

Conclusion .................................................................................................................. 252

GENERAL CONCLUSIONS ......................................................................................... 253

ACKNOWLEDGEMENTS ............................................................................................. 254

REFERENCES ........................................................................................................... 254

ANNEXURE A ............................................................................................................ 261

ANNEXURE B ............................................................................................................ 263
Maternal Nutrition and Perinatal Survival

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Abstract
This review addresses the relationship between maternal nutrition and the survival of the foetus and infant. This survey was undertaken because wide-scale programmes on maternal feeding are in process, based, not on a critical synthesis of currently-available empirical research, but on a series of nested and, at times, weakly supported, assumptions. It is concluded that: (i) maternal weight and weight gain are remarkably resistant to either dietary advice or supplementation; (ii) nutritionally-induced increased birth-weight does not universally increase the chance of survival of the offspring, since pre-pregnancy weight, at least in affluent, industrialized societies–while associated with increased birth-weight–is also associated with higher perinatal mortality; (iii) while dietary supplements during pregnancy do have a modest effect on birth-weight, in contrast to a large effect in famine or near-famine conditions, this is not mediated by maternal energy deposition; and (iv) declining peripheral fat stores in late pregnancy are associated with accelerated foetal growth, and improved nutrition can lead to lower fat stores. Rather, the component of maternal weight gain associated with accelerated foetal growth is water, and, presumably, plasma volume. In the few studies, large and thorough enough to adequately address the issues, maternal feeding—both in famine and non-famine conditions—has led to lower perinatal, primarily foetal, mortality; the mechanisms are not likely to have been due only to the acceleration of foetal growth. It is concluded that there is currently an inadequate base of secure knowledge to foster improvement in the health and nutrition of poor mothers and children. The public and policy-makers alike must be informed that greater knowledge relating maternal nutrition to perinatal outcome is urgently needed to create sound health advice and to mount effective programmes.

Key words: Maternal nutrition; Body weight; Child survival; Nutrition status; Pregnancy; Nutritional support; Nutritional requirements; Birth-weight; Perinatal mortality; Infant mortality; Famine; Poverty; Literature review

INTRODUCTION
This review is written in a time when clarity about the role of nutrition during pregnancy on the foetus and young child is only apparent. Wide-scale programmes of nutritional intervention during pregnancy are being promoted and implemented as if their values were obvious and clear-cut. This review aims at identifying contradictions and gaps in knowledge that may be hindering their effectiveness. It follows an earlier summary of the effects of nutrition on maternal mortality (1).

Our appreciation of the importance of mother’s nutrition to the well-being of the offspring follows from observations just before and during the World War II. On one hand, there were unexpected benefits from the social provision of food in Great Britain during a time of scarcity, and on the other, there was devastation caused by wartime or post-war starvation. There followed intense scientific scrutiny of the impact of the mother’s nutrition status on her and her child’s well-being. The intervening six decades have been remarkable for their
volume of scientific inquiry, but also for the persistent uncertainties in our knowledge. Despite these uncertainties, many large public-health nutrition programmes for poor pregnant women have been implemented.

There is little information on the direct effects of maternal nutrition on foetal and infant survival. This led to the use of surrogate outcomes, both for mother and infant. The most common surrogate infant outcome is birth-weight, and it is the focus of much of this review.

Several lines of inquiry are now beginning to converge, while others, such as the effect of the intrauterine environment on adult chronic disease, are just opening. The former include research on normal maternal and foetal physiology, especially anthropometric change; on the effects of famine and severe chronic and cyclical nutritional deprivation; on diet during pregnancy; and on the care of gestational diabetes. It seems timely to attempt to integrate and summarize these works.

Research on, and policy formulation relating to, maternal nutrition were once scientific and policy backwaters. This is no longer the case. At present, millions of dollars are being spent on programmes aimed at benefiting maternal nutrition among large populations of poor women, especially in developing countries. Most of these distribute food and micronutrient supplements. Bright initial promises are now being questioned (2-6), but defended with equal vigor (7-11). Not only the effectiveness, but also the safety of such programmes, is under scrutiny (1,4,12). This review aims at making a contribution to this debate.

We will update and broaden the goals of a review published a decade ago (13). Subsequently, several reviews on the effects of nutritional supplementation on birth-weight have been published. Two excellent ones, which both depend primarily on the results of randomized clinical trials, are by Kramer (14) and de Onis et al. (15).

The sequence of this review will be to consider first the negative effects on maternal weight gain, birth-weight, and perinatal mortality of dietary deprivation during famine, then the effects of iatrogenic energy restriction, and finally, the effects of improving maternal diet (stressing additional macronutrient intake), whether through advice or supplementation, or both. The impacts reviewed will be on maternal anthropometric indices, on foetal growth and birth-weight, and on perinatal mortality. This review does not address the relationship between foetal growth and later chronic disease, a literature too large to encompass as a subsection. The review closes with a few examples of how this body of knowledge has been applied in several very large public-health nutrition programmes in developing countries. The review is not limited to controlled clinical trials, since there are many important, and some unique, studies that predate sophisticated trial techniques. It rather points out limitations in methodology and analysis that affect conclusions.

EFFECTS OF FAMINE AND DIETARY RESTRICTION

In most socially- and economically-deprived populations, birth-weights are low, although there are notable exceptions, e.g. among Native Americans. During acute famine, just as among people living in poverty, dietary restriction is accompanied with other insults. In both the cases, it is difficult to isolate the effects of restricted food intake from other forms of deprivation, although the quasi-experiment of Grieve (16-18) comes close (see below).

Studies of the Effects of Acute Famine Imposed on Previously Well-nourished Populations

Introduction

Three studies on the effects of famine on reproductive health of mothers during and immediately after the World War II have been reviewed. Antonov (19) described the effects of the siege of Leningrad from 1941 to 1943. Stein et al. (20), following the original report of Smith (21), studied the acute starvation in the winter of 1944-1945 in Holland. Dean studied the residents of Wuppertal, Germany in 1945-1946 (22). In both Leningrad and the Netherlands, famine was associated with a marked decrease in fertility.

Leningrad

The famine in Leningrad was extremely severe and of long duration. The siege lasted from August 1941 to January 1943, while the worst period was from September 1941 to February 1942. That winter was long and bitter; fuel was rarely available; and grinding physical labour was inescapable for those who were even moderately fit. Bread rations fell to 250 g per day among manual and 125 g per day among non-manual workers.
Antonov reported on the births in one clinic (19). Perinatal death rates were appalling and fertility plummeted; over a quarter of babies died during January-June 1942. Mean birth-weight of live newborns at that time was 2,789 g, a depression of almost 550 g.

The Netherlands

The Dutch famine lasted six months during the winter of 1944-1945 (20). Official rations fell as low as 590 calories a day; maternal postpartum weight fell, during the severest famine, about two and a half kg from pre-famine levels, and maternal weight rose, on an average, over 5 kg after relief of famine. Mean birth-weight fell by about 300 g at the depths of the famine. Due to the sudden onset of the famine, the effects on foetal growth could be distinguished from those on fertility. The greatest effects on birth-weight were among infants conceived before the onset of, but delivered during, the famine.

Third-trimester exposure to famine was associated with lowest birth-weights. There was little difference in impact between those exposed to the famine only during the third trimester and those exposed during both second and third trimesters. There was no birth-weight depression among infants conceived during, and exposed to, famine through the second trimester but whose mothers received adequate rations during the third trimester. At the height of the famine, perinatal death rates rose about six-fold, from about 4/1,000 births to as high as 24/1,000. Postpartum weight was restored very soon after the relief of famine, and birth-weights followed within weeks.

Wuppertal, Germany

After the end of the World War II, there was a shortage of food in many areas of Germany. The effects of the shortage of food were studied in the town of Wuppertal (22). Official rations fell as low as 1,052 kcal a day. The only statement about maternal weight in Dean’s report was that pre-pregnancy weight was depressed by about 9%. Weight gain from the eighth month of pregnancy to delivery, and to eight or nine days postpartum, was said to be similar to that in a control group drawn from the literature, but no quantitative data were presented. During the worst deprivation, mean birth-weight was depressed by 170 g among private patients and by 227 g among public patients. Later, when official rations were as high as 1,550 kcal per day, birth-weight depression was 81 g among private patients and 117 g among public patients.

Conclusion

Maternal weights were probably lower than normal by about 5 or 6 kg in Holland and Wuppertal. The 550-g decline in birth-weight in Leningrad is the largest reported in a population that was previously well-nourished. The Dutch experienced severe famine, with about a 300-g depression in birth-weight. In Wuppertal, the shortage of food was acute, and there were long periods during which rations were down to half the usual intake, but birth-weight was depressed at most by about 227 g, and considerably less among private patients, or when the shortage of food was less severe, but with official rations still low (under 1,550 kcal per day). The decline in birth-weight in the Netherlands was apparently far greater than the estimate of a 20-g reduction in birth-weight per one-kg reduction of maternal weight gain made by the Institute of Medicine (23). Perinatal mortality in Leningrad was about 10 times higher (25%) than in the Netherlands at the peak of the famine, although the peak rate in the Netherlands was six times what it was immediately before and after the famine.

Intermittent Severe Deprivation

Prentice and Cole have reviewed the general issue of seasonal changes in growth and energy intake (24).

Keneba, the Gambia

During the wet season, when heavy work was at its peak, Roberts et al. observed depressed energy intake in August and September, but not in June and July (25). Before the wet season (in May), average birth-weight of male newborns was 3,310 g, but was 480 g lower in June and July. There were striking changes in activity associated with both pregnancy (a 25% decrease) and seasonal demands of agricultural work. Among pregnant women, the percentage of the waking 15 hours spent working during the wet season was 83% compared to 55% in the dry season. Prentice et al. (26,27) concluded from maternal anthropometric measurements that women underwent a predictable yearly period of famine during this wet or hunger season (this was not supported by their dietary data; see below). It is of interest that Lamb et al. (28), in their studies of infant mortality in the same village, did not mention seasonal variation, but did state, “The long-term improvements in infant growth and morbidity patterns associated with this maternal nutritional intervention do not seem to be directly related to patterns of mortality (to be published elsewhere).” No such publication has yet appeared. Billewicz and
McGregor reported seasonal variation in infant death rates in the Gambia (29), as did Simondon et al. in Senegal (30).

### Matlab, Bangladesh

Pebley et al. observed that the risk of foetal death was two and a half times as high for conceptions in May and June as during the rest of the year (31). Women who conceived in those months continued to have lower maternal weight at all stages of gestation—about 1 to 2 kg (only 2.7 kg weight gain for the entire pregnancy compared to an average of 5 kg for women conceiving during the rest of the year) (32). The proportion of all conceptions ending in stillbirth, foetal or neonatal death was 16.4% for conceptions from August to October, 18.8% from November to February, and 22.4% from March to July. July-October is the period of greatest food scarcity, so the highest rates of perinatal loss were associated with the third-trimester food deprivation.

### Studies of Iatrogenic Dietary Limitation

There are surprisingly few systematic studies on the formerly widespread medical practice of advising women to limit diet and weight gain during pregnancy.

#### A US autopsy study

Naeye et al. studied total body and organ weights of 1,044 consecutive autopsied perinatal deaths in one hospital (33). Adjusted for duration of gestation, there was a difference in body weight of 2% between infants whose mothers had been put on 1,200-1,500-calorie diets compared to other infants. At term, this would translate to a deficit in birth-weight in the range of 60-70 g. However, it is difficult to generalize from these results. No data were presented on over half the cases (n=577) that were excluded from analysis, because they “had any fetal or maternal disorder known to influence fetal or placental growth, amniotic fluid volume, or mothers’ extracellular fluid volume.” Whether dietary advice preceded aberrant weight gain was not reported, nor was the duration for which dietary restriction was prescribed. Thus, it is difficult to judge whether diet affected growth patterns or vice versa, or if the pathway was via depression of maternal weight gain. In addition, data derived from perinatal deaths surely are only partially applicable to survivors.

### Motherwell, Scotland

J.F.K. Grieve, the obstetric consultant (specialist) in the town of Motherwell, Scotland from 1938 until at least the late seventies, developed a unique, idiosyncratic programme of prenatal care. The programme included avoiding smoking, strictly limiting weight gain, not restricting salt, using no diuretics, eating at least one pound (454 g) of red meat daily throughout gestation, eating no bread or potatoes, limiting milk intake to no more than 10 ounces per day, and eating no prunes, plums, bananas, tinned fruits, nuts, or dates (16-18). By 1959, his management system was in place, and he compiled statistics about the outcome of this intervention, mostly for the period from 1960 to 1976. A book was to be published on this remarkable experience, but was not. Some unpublished material was shared by the authors (M Campbell-Brown, F Johnstone, D Shanklin. Personal communication).

Most births were surgically induced (67.4%), but the rate of caesarean section was low—less than one per two hundred inductions. Weight gain and birth-weight were markedly depressed compared to a population of similar stature and social status from Aberdeen. For instance, the median weight gain among primigravid women of Motherwell during 1965-1966 was 0.25 kg/w compared to 0.46 kg/w in Aberdeen. The mean birth-weight of infants in Motherwell was more than 400 g lower than in Aberdeen—a remarkable difference (18). In the three famine studies during the World War II, this depression in mean birth-weight was exceeded only in Leningrad. High protein content of the diet, in conjunction with the restriction of calories, might have accounted for some of this dramatic depression in birth-weight (see below).

Among key lingering questions are whether this extreme regimen, with marked depression of both maternal weight gain and birth-weight, was otherwise disadvantageous. Grieve stratified outcomes by whether, at 38 weeks gestation, women had met his criteria of ‘success’ (16,17). Those whom he considered most successful had very low weight gain (<250 g/w) and high haemoglobin concentration (12+ g%). He combined these with women who had similar low weight gain but had intermediate haemoglobin levels (10-12 g%), or high haemoglobin and intermediate weight gain (250-500 g/w), and categorized such women as ‘highly successful’: 48.2% of 15,755 pregnant women under study achieved this level of ‘success’ (Table 1).

While the internal analyses that related success in adherence to the regimen to toxemia of pregnancy were logically circular (the analysis relating low weight gain to any form of toxemia is confounded: high weight gain...
could follow onset of disease and accompanying oedema and cannot, at 38 weeks, be considered to have precipitated toxaemia), there are, even in these flawed analyses, some possibly important findings (Table 2).

| Table 1. Grieve’s definitions of ‘success’ (assessed at 38 weeks gestation) |
|-----------------------------|-----------------------------|-----------------------------|
| Haemoglobin g/dL            | Average weight gain per week (g) | Haemoglobin g/dL |
|                             | <250 | 250-500 | >500 |
| >12                         | High | High    | Low  |
| 10-12                       | High | Medium  | Low  |
| <10                         | Low  | Low     | Very low |

Unfortunately, mean birth-weights were not presented, and other outcomes were not stratified separately by levels of weight gain and haemoglobin concentration. The differences observed were very high and do not conform to expectations, given the low maternal weight gains and birth-weights that were produced by Grieve’s regimen. Overall levels of perinatal morbidity and mortality were reported to be low relative to surrounding communities. Pregnant women who were ‘successful’ in following the regimen, had, by definition, low weight gains and surely had infants with relatively low birth-weights; yet the mortality rates of their infants were reported to be the lowest of all infants born to women under his care.

The central lesson may be that famine and conditions of poverty comprise not only deprivation of food, but also other factors that may be contributing to perinatal outcome. Thus, in a stable, peacetime Scottish working-class community in which women were induced to eat very high protein, micronutrient-rich but energy-restricted diets, weight gains and birth-weights were depressed to a remarkable degree, but without any evidence of increased mortality or pregnancy-related morbidity. Whether the children later suffered growth deficit, other developmental abnormality, or increased rates of diabetes or cardiovascular disease is unknown (given some current theories, children born in Motherwell during this era should now be experiencing an epidemic of diabetes and cardiovascular disease). It would be a wastage of a remarkable opportunity not to follow the later health and well-being of children born to mothers who were his patients.

The experience of Grieve challenges us to reconsider the theory underlying nutritional interventions to raise birth-weight. We will argue, below, from other evidence as well, that there is an ethical and scientific need to demonstrate that there is benefit to nutritionally-induced increased birth-weight outside conditions of famine.

### Studies in Aberdeen, Scotland

Campbell and MacGillivray prescribed a 1,200-calorie low-carbohydrate diet for 51 primigravidae who had an average weight gain of over 570 g per week between the 20th and 30th weeks gestation (34). Fifty-one matched controls received no intervention, and an additional 51 matched women received two tablets of cyclopenthiazide (a diuretic) a day with potassium. The incidence of pre-eclampsia was similar in the three groups, but depressed maternal weight gain and reduced skinfold thickness were associated with the restricted diet. Infants of women who dieted or received diuretics were considerably smaller at birth than those of controls. Only 3.4% of infants of control normotensive mothers were under the 25th centile in weight compared to 34.4% on the restricted diet and 27.3% who received diuretics (mean birth-weights were not reported). When the children were examined between four and six years of age, 43.2% of those whose mothers had been put on restricted diet were at or below the 50th centile in weight compared to only 17.6% of infants whose mothers have been given diuretics and 18.2% of controls (35). This finding is provocative: one form of intrauterine growth retardation (IUGR), induced by dietary restriction, was followed by growth deficits in early childhood; another form of IUGR, induced by diuretics, was not.

The same group re-studied this issue, but with somewhat different results (36). Ninety-one primigravidae over the 75th centile in weight-for-height, and with normal glucose tolerance tests at 28 weeks gestation, were matched on height, weight gain from 20 to 30 weeks gestation, and smoking, with 91 controls, and placed on 1,250-kcal diets from 30 weeks gestation to term. Toward the end of pregnancy, women who were prescribed restricted diets reported taking 1,479 calories a day, almost 500 fewer calories than controls. Mean birth-weights were identical in the two groups, but 25.3%
of diet-restricted women had infants with birth-weights under the 25th centile vs 17.6% of controls (NS). Twice as many subjects had gestations of over 40 weeks compared to controls (31.9% vs 15.4%). Whether this difference in duration of gestation was a treatment effect is uncertain, but it certainly influenced birth-weight.

**An analysis of the US collaborative perinatal study**

Barsa Gregory and Rush used a case referent design to study the relationship of low-calorie diet with weight gain and birth-weight among women who participated in the Collaborative Perinatal Project from 1959 to 1963 (37). Singleton term infants, who were below the 31st centile in birth-weight, were identified within strata defined by ethnic group and duration of gestation. These 255 births were matched to higher-weight infants for ethnicity, duration of gestation, smoking, parity, and pre-pregnancy weight. There was no significant difference in the frequency of prescription of low-calorie diet among groups—37.3% in the low-birth-weight group vs 40.4% among matched controls. Late pregnancy weight gain was not significantly related to whether a low-calorie diet had been previously prescribed, after adjusting for prior weight gain. Thus, there was no strong or significant relationship between medical advice to limit calorie intake during pregnancy and either later weight gain or foetal growth retardation. On the other hand, since women who had been asked to limit calorie intake continued to gain as much or more weight than others, the results are most consistent with poor compliance with the dietary regimen.

**Conclusion**

Effects of famine on reproductive health are dramatic: fertility plummets, maternal weight gain is depressed, and birth-weights can fall by 10-15%. While diet obviously plays a major role in these events, other accompanyingprivations make it difficult to generalize from famine to non-famine conditions. Other factors are also at play during periods of economic and social disruption. Brenner has shown how foetal, infant and maternal mortality rates are strongly related to economic conditions, particularly unemployment (38). Fisher et al. found that a brief economic recession was associated with worse prenatal care and higher rates of low birth-weight, the latter confined to low-income areas (39). These adverse economic conditions surely could have affected diet, but also many other aspects of life. All the available evidence suggests that if women limit energy intake during pregnancy, they will have low weight gain, and their children will experience IUGR. Under the stressful conditions of either acute or seasonal famine, foetal, and possibly infant, death rates also rise. The seasonal fluctuations in diet and anthropometric status among poor women in many developing countries are probably akin to short-term famine, which might not be compatible with reproduction, or even life, if sustained year round. There is little or no evidence of increased mortality associated with low maternal weight gain and birth-weight following the formerly common practice of iatrogenic dietary limitation during healthy pregnancy, but this has not been well or systematically studied.

**STUDIES OF MATERNAL WEIGHT AND WEIGHT GAIN DURING PREGNANCY NOT EMPHASIZING RESTRICTION OF DIET**

**Introduction**

Weight and weight gain during pregnancy have often been studied; the review done by the Institute of Medicine (IOM) is a detailed recent example (23). The reason for interest in these topics is straightforward: high weight gain (secondary to fluid retention) accompanies the toxaemias of pregnancy, and maternal weight gain is also strongly associated with infant size, which, in turn, is strongly associated with survival. Given that pre-pregnancy weight, weight gain, level of blood pressure, proteinuria, presence of oedema, and birth-weight are relatively easily measured, there have been many studies inter-relating two or more of these issues. In the 1930s and 1940s, it was posited (with essentially no direct empirical evidence) that, since toxaemia was associated with accelerated weight gain, weight gain was causing toxaemia, and that weight restriction should, therefore,
prevent toxaemia. Hytten, along with many others, dismissed this assumption (42). The second phase of research on the relationship of weight and weight gain with size at birth has led to another paradigm based on the unproven assumption that a series of disparate observations are causally linked. The observations are that: one reason for increased weight gain may be increased energy intake, weight gain is associated with foetal growth, and birth-weight (at least up to about 4,000 g) is exponentially associated with perinatal survival. In the earlier US literature, birth-weights of over 4,000 g were associated with somewhat increased risk of perinatal death (43), while in a more recent national US study, this was no longer true for the whites (44). The assumption that these relationships are causally linked leads to the conclusion that increased energy intake will result in lower perinatal mortality, mediated by increased maternal weight gain and higher birth-weight.

It is now clear that these linked assumptions are, in important instances, not correct. Only a few studies have sequentially examined all these assumptions in the same population. Rather, most studies have assumed and not tested one or more of the steps in this causal sequence. Based on some results, in combination with a critical re-appraisal of past research, we will re-assess whether increased protein/energy intake before or during pregnancy, either by dietary counselling or by supplementation, or by both, leads to energy deposition (reflected as increased peripheral or central fat stores, weight and/or weight gain), which, in turn, leads to accelerated foetal growth, and hence to lower perinatal mortality.

Among the key studies in this re-evaluation are attempts to induce increased weight gain, whether by advice or by dietary supplementation, and the studies of the components of weight gain that relate to foetal growth. Of the latter, the studies of Lederman and colleagues (45,46) are pivotal. They used sophisticated techniques to measure maternal body composition during pregnancy and showed that the component of maternal weight gain that related most strongly to foetal growth was water and that variation in maternal body fat is at best only weakly related to birth-weight. Another landmark was the multivariate analysis by Susser (47), which demonstrated that a statistical pathway between increased dietary intake and birth-weight via maternal weight gain is limited to famine conditions. This conclusion is strongly supported by the few controlled studies of dietary advice or supplementation that have reported on weight gain. Thus, it appears less and less tenable to prescribe to women that they increase energy intake to accelerate weight gain, since, more often than not, they are unable to respond. Indeed, the evidence is that birth-weights are higher with lower maternal fat pad thickness in the third trimester. Two studies, carried out in Scandinavia, on weight, weight gain in pregnancy, and perinatal survival, go farther. These are the largest among many which have demonstrated that high maternal weight at conception is associated with both higher birth-weight and concomitant higher risk of perinatal death. In this instance, higher birth-weight associated with maternal nutrition status is not at all beneficial.

To What Extent Can Dietary Advice or Supplementation Affect Maternal Weight Gain?

Dietary advice

Introduction

The prescriptive policy to manipulate weight gain, implicit in weight-gain charts and explicit in the recommendations of the Institute of Medicine (23) and the American College of Obstetricians and Gynecologists (ACOG) committees (48), assumes that dietary and nutritional advice can induce women to increase (or restrict) dietary intake, thereby increasing (or decreasing) weight gain during pregnancy. The Institute of Medicine report states, “Everyday experience and carefully-controlled experimental studies have demonstrated that people who consume excess energy gain weight.” However, such studies have not been done among pregnant women, and this assumption begs the question of whether pregnant women living under the conditions of ordinary life, with relatively unrestricted access to diets of choice, can and will increase dietary intake if advised to eat more to gain more weight. The evidence is weak and mixed.

Secular change

The strongest evidence (weak as it is) is probably from secular trends in weight gain. Gormican et al. compared total weight gains in one clinic before 1971, when a policy of weight gain limitation was in place, with subsequent pregnancies, after this policy was liberalized (49). They found a remarkable increase in mean weight gain, from 15.9 lbs to 24.2 lbs (p<0.01). However, the clinic policy was not the only change: there was also a
concurrent secular increase in the weight of the adult population, and their later subjects were entering pregnancy 4.7 lbs heavier (p<0.01). It is unknown whether the changes during pregnancy reflected secular change, changing expert advice, or some combination of the two.

Flegal et al. (50) reported that among non-pregnant US women aged 18-34 years, between 1960 and 1980, BMIs increased from 22.9 to 23.8 in the whites and 25.1 to 26.2 in the blacks (one BMI unit is equivalent to 2.56 kg for a woman of 1.6 m tall.)

Observational study of diet and weight change

A study of prenatal care in Camden, New Jersey

Scholl et al. (51) concluded that the rate of low pregnancy weight gain was reduced by a factor of two among adolescents who received ‘adequate’ prenatal care, defined by trimester of entry into care, and number of prenatal visits (adjusted for estimated duration of gestation). In addition to the problems of reverse causality (longer duration of gestation, even after adjustment, can lead to both more prenatal visits and higher weight gain), there is a problem of circularity (number of prenatal visits may reflect the response of care-givers to the presence of prenatal complications, such as ‘excess’ weight gain). Although valiant efforts were made to contend with confounding, in the end, these results may well reflect the extreme inaccuracy of estimates of duration of gestation†.

A study of diet history and weight gain

Aaronson and MacNee found no relationship between diet and weight gain (52). On the other hand, their index of diet was not energy content, but whether the diet was adequate on six indices of nutrient content. There is not much reason to expect that this index should relate to weight gain.

† Misclassification due to imprecise estimation of duration of gestation could confound results in the following ways: If duration of gestation at registration is misreported low, duration of gestation at term will also be speciously low, and weight gain and birth-weight adjusted for duration of gestation will appear speciously high, and vice versa. At the same time, misreportedly low duration of gestation at registration can cause misclassification of prenatal care scores: for those apparently registering in the first trimester, but actually in the second, the same number of visits for care might be classified as inadequate care; if duration of gestation is misreportedly high, this same number of visits might be classified as better than warranted.

Other studies

There are many more observational studies relating estimated diet to weight gain. Some are positive (53), and some are negative (54). Getting definitive answers from observational studies may be futile.

Intervention studies of dietary advice

Introduction

The most important evidence to convince us that weights could and would be raised following advice to do so would be from trials of dietary counselling, and this evidence is not encouraging; there has been a recent review (55). As examples, we will review a few studies.

Orstead et al.

Orstead et al. used medical records to compare the outcomes of 86 clinic patients from 1975 to 1977 with 114 patients from 1979 to 1981 (56). The former patients received a 20-minute nutrition class, and the latter 10 additional class-minutes and counselling from a clinic dietician at every visit. The results were dramatic. The later, counselled, group had 2.5 kg more weight gain and a low birth-weight rate of 4% vs 13% among the earlier cohort. However, the groups were not otherwise comparable: “Almost three-fourths of the clients in the test group came during the first two trimesters, compared with less than one-half of the women in the control group.” On an average, the counselled group registered for care almost four weeks earlier than controls. Only 12% of counselled women had fewer than six prenatal visits compared to 44% of controls. Pre-pregnancy weight, smoking, and race were not presented and, presumably, not controlled. These differences in outcome cannot be easily attributed to nutritional counselling.

Sweeney et al.

Sweeney et al. compared 22 women to whom the Higgins method (see below) was recommended with 21 highly-matched controls (57). No quantitative results were presented, but the authors stated, “there was no significant difference in maternal weight gain during the study period.”

Sun et al.

Sun et al. gave nutrition counselling to 80 women and compared them with 63 randomly-allocated controls (58). The intervention group gained 9.37 kg–1.85 kg less than controls (calculated from the authors’ data, t=2.97,
While we do not know explicitly if higher energy intake was counselled, we must presume it was, since the intervention group increased their reported energy intake by 357 kcal/day more than controls.

Bruce and Tchabo

Bruce and Tchabo observed significantly higher total weight gain in a nutritionally-counselled clinic population compared to a subsequently-recruited reference group (59). However, they neither adjusted for the two-week longer duration of gestation among the counselled nor for the ethnic and other differences between the groups.

Tharp et al.

Unfortunately, one of the best of these studies was never fully published, but only alluded to in a letter-to-the-editor (60). Results of the research were presented at a conference, and the full manuscript was shared for this review (61). The investigators compared 84 women in two prenatal clinics, who received intensive counselling aimed at increasing weight gain, with 147 women in another clinic receiving no counselling. Weight gains were nearly identical. Unfortunately, this result was not adjusted for other characteristics of the women. For example, the intervention group was, on an average, four pounds heavier at conception, and women in the intervention group were significantly more often married.

Conclusion

Although nutritional and prenatal care specialists have confidently prescribed policies promoting advice to gain weight, it has not been shown that this can be done, even in highly-controlled experimental conditions, let alone in routine practice. The best evidence that increased weight gain during pregnancy might possibly follow professional advice (and it is weak) is the secular increase in weight gain.

Dietary supplementation and weight gain

Deprivation of energy intake in pregnant women leads to reduced weight gain, and relief from starvation leads to increased weight gain. On the other hand, the impact of nutritional supplements on weight gain in other-than-famine conditions appears to be minimal. In the six supplementation studies reviewed by Susser (47), the differences in weight gain among the supplemented, compared to controls, were very small; the means of differences in total weight gain were 0.23, 0.14, 0.8, and 0.98 kg; one study found 0.08 kg per week, and in another study, -0.8 to 0.24 kg per week in six different (very small) treatment groups. Kramer (14), in a review of balanced protein-calorie supplementation during pregnancy, included the results of 10 trials: in three, the supplemented groups gained less than controls; in another six, the range of increased weight gain among the supplemented group was 10 to 76 g per week (only one of which was significant); and in the tenth—an outlier (which Kramer tended to dismiss for methodological reasons), the difference was 174 g per week (significant). The mean weight gain per week without the outlier was 23.2 g, and with it, 38.4 g. This translates into a total of 302 g, or 499 g, for one trimester of supplementation, which is very small indeed. Further, the increase in birth-weight from supplementation was less in the offspring of supplemented women who were judged malnourished and, in theory, more appropriate candidates for supplementation. Thus, the evidence from these supplementation trials is that there is no basis to justify the common prescription of increasing weight gain during pregnancy by manipulating diet.

The two trials conducted in the Gambia warrant special attention (the results for foetal growth are addressed below) (26,27,62). The conditions under which these trials were done appear to be similar to recurrent famine, and should be the most convincing tests of the premise that maternal weight gain might mediate the effects of maternal diet on birth-weight. There were marked seasonal patterns in maternal weight gain, mid-upper arm circumference, and triceps skinfold thickness, with peaks at the ends of the year, during the dry, or harvest season, and troughs in the middle of the year, during the wet, or hunger season. In the first trial, the effects of supplementation were not significant, but quantitative data were not presented. In the second trial, while the rate of weight change was calculated, it was not presented or discussed. Rather, they presented results for total weight gain, which was less specific to the trial, since it also reflected experience during the two trimesters before supplementation. The results do not conform to the hypothesis that supplementation had a far stronger effect during the hunger months: while there was an overall increase of 0.58 kg on total weight gain from supplementation, it was confined to women who delivered in the dry season, a time of relative abundance (Table 3).

Thus, in these conditions analogous to famine, hefty energy and protein supplements led only to small, non-significant effects on weight gain in the first trial and
small, albeit significant, effects in the second trial that were inconsistent with the authors’ hypothesis of season-specific vulnerability. Clearly, dietary supplementation had, at best, small and unpredictable effects on maternal weight gain. This is probably as close as we will ever come to a direct test of whether weight gain during pregnancy can be accelerated much by a strategy of dietary supplementation, and, even among women under great nutritional stress, there was little or mixed impact.

**Conclusion**

Despite the proliferation of weight gain grids to identify women gaining what expert opinion deems to be suboptimal weight during pregnancy, there is no consistent or convincing evidence that weight gain, other than during overt starvation, is open to much upward shift by dietary advice or supplementation. There has been a secular upward trend in women’s weight and weight gain during pregnancy in the USA. It is by no means clear that the latter is connected to professional advice or opinion—the former certainly is not.

The creators of these grids and the IOM (23) and ACOG (48) committees that have pronounced on how much weight women should gain have felt confident in prescribing dietary change to manipulate weight gain upward (there is ample evidence that weight gain can be reduced by dietary restriction). In the wake of these recommendations, statements are being made in the literature such as “an advantage in deferring a larger portion of required weight gain to late pregnancy” (63) or that “black women (should) strive for prenatal weights at the upper end of the recommended range for pregravid BMI” (64). These prescriptions are questionable on several counts. First, it has not been demonstrated that weight can be increased much, if at all, by dietary advice or supplementation, at least after the first trimester. Second, since weight gain grids cannot easily identify those not gaining ‘adequate’ amounts until weight gain begins to accelerate after the first trimester, by the time adverse patterns were recognized, it is unlikely that intervention would have much impact. In our supplementation studies among poor, black US women, we found that dietary supplements initiated in the first trimester could affect weight gain, but they had no impact on weight gain if initiated after that (65,66).

Third, without better clarified goals, it seems unconscionable to prescribe an upward shift in weight gain, which could have many costs, including the burden of excess postpartum weight, especially among women who do not breastfeed. Fourth, we need evidence that nutritionally-induced increased weight gain leads not only to increased birth-weight, but, more importantly, to lower perinatal morbidity and mortality. Thus, the minimum criteria for a policy of prescribing increases in weight gain do not exist. Were this a policy for prescription of a drug, vaccine, or medical device or procedure, it would undergo close scrutiny and regulation. Apparently, prescriptions for the benefit of mothers and infants by nutritional means are not required to meet the same standard.

**Birth-weight and Maternal Weight, Weight Gain and Body Composition**

**Studies depending on skinfold thickness**

Taggart *et al.* (67) demonstrated that maternal triceps, biceps, and costal skinfolds fall in late pregnancy. What has since become apparent is that the extent of this fall is strongly and positively associated with accelerated foetal growth. Naeye and Tafari studied longitudinal changes in skinfold thickness and birth-weight in Ethiopia; in the absence of declining third-trimester skinfolds, foetal growth was impaired (68). Briend found that, at a given maternal weight, birth-weight was inversely proportional to skinfold thickness in a large under-privileged population in Senegal (69). In a prospective study of 56 healthy Swedish primiparous, Langhoff-Roos *et al.* found, “lean body mass, and not fat mass, were strongly correlated with infant birthweight” (70,71). Lawrence *et al.*, in 115 parous Scottish women, found that fat gain from 10 weeks gestation to 2-3 weeks postpartum was not related to birth-weight (72). Hediger *et al.* found that change in the upper arm fat area among teenage pregnant women in the last trimester was inversely associated with birth-weight (73). This effect was blunted or obliterated among under-weight women. The studies of Viegas *et al.* (12,74,75) are discussed later in this review.
More complex measurements of body composition

Duffus et al. serially estimated plasma volume after 30 weeks gestation by the Evan’s blue technique, and total body water using deuterium oxide, in Scottish primagravidae (76). Twenty women had high weight gain (>0.64 kg/w) from 20 to 30 weeks gestation, 13 had average weight gain (0.36-0.54 kg/w), and 20 had low weight gain (<0.27 kg/w). The high-weight-gain group more often had oedema and had bigger babies. High plasma volume and total body water were associated with greater birth-weight, but this study did not include any multivariate analyses that might tease out which factors were most strongly associated with infant size.

Campbell-Brown and McFayden (77) re-analyzed the earlier study of Pipe et al. (78) and, among 27 women, related birth-weight to body composition at 10-14 weeks gestation determined by skinfold measurements and total body potassium (from which lean body mass was calculated). They found correlations of 0.44, 0.24, 0.22, and 0.07 between birth-weight and lean body mass, height, weight, and skinfold thickness respectively. Thus, lean body mass was far more strongly related to birth-weight than were fat stores. In multivariate analysis, maternal lean body mass accounted for more variance in birth-weight than height and weight together.

In one of the few reports that found fat accretion positively associated with birth-weight, Villar et al. followed 105 healthy pregnant Guatemalan women measuring bioimpedance (BIA) and skinfolds (79). They found early pregnancy skinfold thickness associated with higher birth-weight, but fat-free mass gain only associated in the last trimester (p=0.08). On the other hand, Jackson et al., using hydrostatic weighing as a standard, found that BIA was considerably less valid as a measure of body fat than an estimate based on the sum of seven skinfold thicknesses (80).

Mardones-Santander et al. studied 224 women near term with deuterium dilution to assess fat mass (81). They concluded, “Maternal fat-free mass was the most important variable influencing birth weight.” Fat mass was also significant, but in their analyses, they did not control for height or other indices of maternal size. It is, therefore, unclear how much these relationships are accounted for by the mother’s size as opposed to her body composition.

Using the sophisticated body composition techniques (under-water weighing with nitrogen washout, estimation of deuterium space, and dual energy absorbiometry), Lederman et al. found that the increase in net body fat from 14 to 37 weeks gestation was only slightly (and not significantly) related to birth-weight, while net increase in total body water was strongly (and significantly) related (46). Thus, the component of maternal weight gain that was correlated with birth-weight was not maternal energy stores, but rather body water, most likely increased plasma volume, which may have led to increased uterine blood flow and nutrient transfer.

Dietary Improvement Leading to Reduction in Maternal Fat Stores: The National WIC (Special Supplemental Food Program for Women, Infants, and Children) Evaluation

Third-trimester reduction in maternal fat stores is associated with acceleration of foetal growth. Does this have anything to do with diet? In the longitudinal study of the National WIC (Special Supplemental Food Program for Women, Infants, and Children) Evaluation (82-86), we were at first confused by the very significantly smaller skinfold thicknesses in late pregnancy among WIC participants compared to similar women not receiving benefits. Women who received WIC benefits from registration had triceps skinfolds at about 36 weeks gestation, adjusted for entry levels, 0.87 mm smaller than controls, and subscapular skinfolds, 0.80 mm smaller (both p<0.001). Thus, WIC participation, which led to an increased energy and micronutrient intake and only marginal change in weight gain, resulted in the pattern of maternal fat storage, i.e. lower stores, associated with foetal growth acceleration. In this substudy, while birth-weight was not affected, newborn’s head-circumference was significantly increased by WIC participation. Detailed discussion follows.

Multivariate Analysis of Diet, Weight Gain, and Birth-weight

Susser, using path analysis, reviewed seven sets of studies of nutrition during pregnancy, five of which were controlled supplementation trials, two of which were quasi-experimental studies, and all of which presented comprehensive data on diet, weight gain, and birth-weight (47). He summarized, “The causal sequence maternal nutrition > maternal weight gain > infant birth-weight is not sustained by available evidence except under extreme nutritional deprivation,” that is, only in the face of starvation, but not of social deprivation and
chronic milder under-nutrition. He surmised that the pathway that is typical of famine conditions operates when energy intake falls below about 1,750 kcal (7.326 MJ) per day. In the Dutch famine study, there were direct relationships between diet intake and both weight gain and birth-weight throughout, but the relationship: diet > weight gain > birth-weight operated only under famine conditions. In non-famine conditions, diet affected maternal weight gain, and weight gain affected birth-weight independently, consistent with Thomson’s interpretation (87) that “maternal weight was dictating both dietary intake and birth-weight.” In the other six studies, the pathway, diet > weight gain > birth-weight was present in only one, for male offspring only (88). Susser concluded, “where dietary change has produced a birth-weight change under ordinary conditions of life, i.e. not during starvation, maternal weight during pregnancy is not an apparent intermediary. Maternal weight change relates strongly and consistently with birth-weight, but it is still to be shown that these associations followed from diet. Hence, it is fair to infer that, in terms of birth-weight, maternal diet and nutrition deserve more attention than does maternal weight gain.” If anything, this conclusion can now be more strongly asserted, given subsequent research.

Summary

It is clear that weight gain during pregnancy is suppressed during famine, and by medical advice leading to energy restriction and/or increased protein intake. If weight gain is suppressed, birth-weight will also be lowered. In famine, perinatal mortality is increased. We do not know if perinatal mortality is increased after iatrogenic advice to decrease weight gain, although birth-weight can be lowered.

While there has been a recent secular trend of higher weight gain during pregnancy, controlled trials of dietary advice to raise weight gain have shown minimal or mixed effects. Some supplementation studies have reported increased weight gain, but of small magnitude, and just as many trials have had no, or hardly any, impact. If, under non-famine conditions, there is an effect of dietary supplementation on weight gain, it seems to be confined to supplementation begun in the first trimester of pregnancy.

The component of weight gain during the latter two trimesters of pregnancy that is directly associated with birth-weight is body water and not fat (stored energy). In fact, decreasing third-trimester fat stores are associated with increased birth-weight. What seems to be important is not so much maternal storage or accretion of energy (as fat), rather mobilization of nutrient stores or intake. Not only is increased birth-weight associated with accelerated loss of maternal fat stores in late pregnancy, but at least one very large nutrition intervention has shown that increased and improved diet led to lower late-pregnancy fat stores. We are, thus, challenged to develop strategies to test whether lean body mass, especially plasma volume, can be increased, but not to increase fat deposition.

Maternal Weight (and Weight Gain) and Perinatal Death

During the last 25 years, several papers have explored the relationship of maternal weight and weight gain with perinatal survival. Seen in toto, these have radical implications for how we conceive of the impact of maternal nutrition on the survival of the offspring. In brief, the risk of perinatal death falls with increasing weight gain during pregnancy, but tends to rise with increasing pre-pregnancy weight, at least outside famine conditions. We will explore this apparent contradiction (at least in terms of some strongly-held current assumptions about the unequivocal benefit of increasing birth-weight or decreasing IUGR), how these observations relate to maternal glucose intolerance and insulin insensitivity, and what these findings imply both for needs for subsequent research and formulation of nutrition policy during pregnancy.

The US collaborative perinatal study

A series of analyses were done using this very large (~50,000 births) US national data set.

<table>
<thead>
<tr>
<th>Weight gain (lbs)</th>
<th>Whites (risk ratio)</th>
<th>Blacks (risk ratio)</th>
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<tbody>
<tr>
<td>Loss</td>
<td>36.6 (4.0)</td>
<td>34.4 (2.5)</td>
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<tr>
<td>0-9</td>
<td>20.6 (2.2)</td>
<td>23.0 (1.7)</td>
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<tr>
<td>10-19</td>
<td>14.1 (1.5)</td>
<td>14.6 (1.1)</td>
</tr>
<tr>
<td>20-29</td>
<td>9.2 (1.0)</td>
<td>13.7 (1.0)</td>
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<tr>
<td>30+</td>
<td>11.4 (1.2)</td>
<td>13.6 (1.0)</td>
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<tr>
<td>Total</td>
<td>12.4</td>
<td>15.4</td>
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</table>

There was a clear downward trend in perinatal death with increasing total weight gain. Despite limiting the
analysis to term births, there is still strong likelihood of confounding by duration of gestation, given imprecision in its measurement.

b. Naeye (90) re-studied the same data set, including pre-term births. Assuming that 27 lbs was the optimal total weight gain at term, he extrapolated optimal weight gain for pre-term births, and then expressed weight gain as a percentage of the optimum value at each stage of gestation. The relationship of optimal weight gain to perinatal mortality is given in Table 5.

<table>
<thead>
<tr>
<th>Table 5. Perinatal deaths/1,000 births (risk ratio) by percentage of optimal weight gain</th>
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<tr>
<td>Optimal weight gain (%)</td>
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<td>&lt;25</td>
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<tr>
<td>25-54</td>
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<td>55-79</td>
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<tr>
<td>80-120</td>
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<tr>
<td>&gt;120</td>
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<tr>
<td>Total</td>
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Increased risk was only marginally related to weight gain except below 55% of optimum weight gain. In the same paper, Naeye related percentage of optimal weight at conception (based on the Metropolitan Life Tables) to perinatal mortality (Table 6).

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<tr>
<th>Table 6. Perinatal deaths/1,000 births (risk ratio) by percentage of optimal weight at conception</th>
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<tr>
<td>Optimal weight at conception (%)</td>
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<tr>
<td>&lt;90</td>
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<tr>
<td>90-109</td>
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<tr>
<td>110-135</td>
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<tr>
<td>&gt;135</td>
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<tr>
<td>Total</td>
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</table>

The perinatal death rate was 42% higher among offspring of women 35% or heavier than those of optimum weight.

c. Eleven years later, Naeye (91) again related perinatal mortality to maternal weight, this time expressed as Body Mass Index (BMI; wt/ht$^2$). The results are presented in Table 7.

<table>
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<tr>
<th>Table 7. Perinatal deaths/1,000 births (risk ratio) by pre-pregnancy BMI (kg/m$^2$)</th>
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<tbody>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>&lt;20 (low)</td>
</tr>
<tr>
<td>20-24 (normal)</td>
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<tr>
<td>25-30 (mild over-weight)</td>
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<tr>
<td>&gt;30 (obese)</td>
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Optimal weights at the three heights of 60, 64, and 69 inches were equivalent to BMIs of 20.9, 20.6, and 20.7, each within the normal range, and increases by 35% in optimal weight at these three heights would yield BMIs of 28.3, 27.9, and 28.0. Thus, the extreme weight categories were not very different and should have yielded comparable results.

For the moment, no firm conclusions from these conflicting analyses seem justified, except possibly that perinatal mortality was higher among offspring of women who were very heavy at conception, but by how much, and to what level, is uncertain. In the later paper (91), Naeye reports, “The correlation of low socioeconomic status with high perinatal mortality completely disappeared when relative maternal body weight and other risk factors for perinatal mortality were taken into consideration.” However, the reverse is also logically possible: the relationship with relative body weight might possibly be explained by differences in social class.

Study of pre-term births at several English hospitals

A social class differential in body weight might explain some of the results of Lucas et al., who observed increased mortality between two days and 18 months of age among prematurely-born infants of heavier mothers (92). A biological explanation for increased maternal weight leading to perinatal mortality, while still not obvious, seems at least plausible; why, however, should older infants and young children of heavier mothers have increased risk of death? The authors reported that they controlled for social class (no details are given), but it is almost inevitable that social class was under-controlled. What is meant by social class is not easily quantified, and there would surely have been a residual relationship of obesity with social status, even after adjusting for the father’s occupational status. Another potential pitfall in this study is that it is limited to pre-term births. There is inevitable measurement error in duration of gestation, and it is likely that the babies of big women will also be bigger, and thus, more likely to be categorized as
‘mature.’ The ‘premature’ babies of heavier women will tend to be less mature, on an average, than those of lighter women at constant birth-weight (this is the cigarette smoking paradox in reverse: low birth-weight infants of smokers have lower death rates than those of non-smokers; one needs to take into account that the frequency of low birth-weight among smokers is much increased).

**US National 1980 Natality and Fetal Mortality Surveys**

Little and Weinberg calculated that the odds ratio for rate of foetal death for an increase in 10 points in BMI units was 1.70 (CI 1.47-1.96) for all foetal deaths and 1.57 (CI 1.32-1.86) for antepartum death only (93). The rate was somewhat higher for intrapartum deaths, but this is not surprising, given the greater likelihood of traumatic delivery for heavier babies and among heavier women. Extrapolated from a figure in their publication, the odds ratio for stillbirth was approximately 1.00, 1.16, 1.48, 1.63, and 2.17 for women with BMIs from below 18.2, 18.2-22.1, 22.2-26.1, 26.2-30.1 and over 30.1 respectively. The latter three were statistically significant.

There was an approximately 50% excess of stillbirths among women with total weight gain below 20 lbs. However, this could well have been an artifact, because low weight gain is associated with shortened gestation, and the increased death rate could have been due to shorter duration of gestation.

**Two Finnish cohorts**

Rantakallio et al. (94) studied about 20,000 births—half in 1966 and half in 1985-1986. The more recent mothers were 2.9 cm taller, and there were almost twice as many women with BMIs below 20 in the later cohort. The authors related pre-pregnancy weight and BMI to perinatal outcome. The index of survival was the combined total of stillbirths and deaths of children up to four years of age. The results are dominated by, but not exclusive to, the period around delivery: 84.3% of the deaths in the first cohort occurred during the perinatal period, as did 78.5% in the second one. The key results (unadjusted for social class; the adjusted results were only presented as figures) are presented in Table 8.

The dramatic fall in death rates over two decades is not our central concern here. Rather, it is that in both the cohorts, rates of IUGR were consistently lower with higher BMI (except among very obese women), but the trend for death rates was in the opposite direction. These results are similar to those of the Swedish study that follows: a nutritional index, mother’s pregravid BMI, is strongly related to lower rates of IUGR and is equally strongly related to higher risk of perinatal and early childhood death.

**A Swedish national study and a Swedish multi-hospital study**

Cnattingius et al. studied 167,759 births in Sweden in 1992-1993 (95). They demonstrated, not surprisingly, that increasing maternal pre-pregnancy BMI was very strongly associated with decreased likelihood of IUGR. This was not confined to the obese; rather, compared to women with BMI below 20, the odds ratio for women with BMI 20-24.9 was 0.7, and above this level was 0.6 (the two higher BMI categories were 25-29.9 and >29.9). However, the odds ratios of late foetal death rose with maternal BMI from 1.0 to 1.2, to 1.6, and to 2.6 in the four BMI categories. Odds ratios for early neonatal death also rose, but less steeply (1.0, 1.1, 1.3, and 1.2). While no statistical tests for trend were performed, the two higher odds ratios for late foetal death were significant, as were all those for IUGR. In this generally healthy and well-cared-for population, pre-pregnancy BMI was strongly and positively associated with accelerated foetal growth and was also associated with decreased perinatal survival. For the approximately one-third of subjects for whom mothers’ weight gain was known, weight gain was strongly and inversely related to the chances of IUGR, unrelated to late foetal death, and inversely related to early neonatal death.

**Conclusion**

Higher maternal relative weight or BMI at conception is strongly associated with higher birth-weight and lower rates of IUGR, but is also strongly and monotonically associated with increased foetal death rates (and obese

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<th>Table 8. Occurrence per 1,000 births</th>
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<tr>
<td><strong>BMI</strong></td>
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<td>&lt;20.0</td>
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<td>30.0-</td>
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<tr>
<td>&gt;35.0</td>
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<tr>
<td>Total</td>
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women more frequently give birth to infants with neural tube defect—see below). It is, thus, not true that all nutritional factors that raise birth-weight increase perinatal survival. Thus, increased birth-weight associated with maternal nutrition is not a surrogate for better infant health and survival. We are obliged to test further which interventions that raise birth-weight also increase survival and improve function. Cnattingius et al. found that foetal death rates associated with IUGR were much lower among shorter women (96). In other words, IUGR of different aetiologies confers different risks, and prevention strategies cannot be tested without reference to this differential risk. Frisancho et al. found that survival rates of children were considerably higher among shorter poor Peruvian mothers (97). They attributed this to ‘adaptation’, without further specifying a mechanism. Greater stature, as with higher birth-weight, cannot be assumed to be beneficial. All mechanisms promoting foetal growth cannot be presumed to lead to lower perinatal morbidity and mortality. As we identify one or another intervention that accelerates foetal growth, it still must be demonstrated that the intervention also confers advantageous functional consequences, such as survival, or improved later health and development, of mother or child.

Maternal BMI and congenital malformation

Prentice and Goldberg (98) reviewed the relationship of maternal obesity and neural tube defect following simultaneous publication of two studies (99,100) that found strong relationships of maternal obesity with rates of neural tube defect. Risks did not rise gradually, but seemed to be confined to very high weights [over 100 kg in women studied by Shaw et al. (99) and over 80 kg in Werler et al. (100)]. The same pattern was also probably true in an earlier study (101). The reasons may have to do with defects in folate metabolism. The pattern of maternal BMI with risk of neural tube defect is dissimilar with that for perinatal mortality, and presumably, has different basic pathophysiology.

LESSONS FROM DIABETES LITERATURE

There is a rich body of research on the physiology, management, and outcome of gestational diabetes mellitus (GDM). There seem to be important lessons to be learnt from this research on the processes of maternal weight and weight gain and also on foetal growth in normal pregnancies.

Weight Gain in Women with GDM

In women with GDM, weight gain during pregnancy is lower than in other women and appears to be only very weakly related to birth-weight (102-104). It is likely that, with the lowered insulin sensitivity of GDM, a pathway of energy mobilization via lipolysis becomes more active. Since normal pregnancy is a state of decreased insulin sensitivity (but less so than in GDM), the physiologic adaptations of GDM may also open insights into the processes of normal pregnancy.

Birth-weight

Birth-weight in both normal pregnancy and with GDM is strongly correlated with blood glucose levels (105-113). Further, birth-weight of infants of women with GDM depends intensely on level of diabetic control. In the study of Langer et al. among women under tightest control (whose average glucose was <87 mg/dL), the rate of IUGR was 20%, two and half times as great as for other infants of women with GDM, and double that of controls (114). Among those with low average blood glucose, the rate of large-for-gestational-age births was 1.4%, 21 times lower than among those with high blood glucose levels. In other words, foetal growth is probably not a direct function of GDM, but rather of the level of circulating glucose to which the foetus is exposed.

Sermer et al. did glucose challenge and tolerance tests on 3,637 non-diabetic pregnant women of Toronto at 26 and 28 weeks gestation respectively (115). Fasting blood sugar was very strongly and significantly associated with risk for birth-weights over both 4,000 g and 4,500 g (1 mmol/L increase in glucose level was associated with an odds ratio of 2.0 for birth-weight over 4,000 g, and 2.4 for birth-weight over 4,500 g). Pre-eclampsia and caesarean section rates were also significantly increased with higher blood glucose levels.

Weight gain, insulin sensitivity, leptin, and birth-weight

Insulin sensitivity appears to be strongly related to weight gain: the greater the decrease in insulin sensitivity, the greater the accretion of adipose tissue, and the higher the birth-weight (104). Blood glucose is also higher with decreased insulin sensitivity. Given that levels of leptin are also related to the amount of weight gained and retained after pregnancy (116), the relationships of these
various metabolic factors and pregnancy outcome are under active scrutiny.

**DIET, FOETAL GROWTH, AND PERINATAL SURVIVAL**

**Introduction**

This section reviews efforts to improve or increase the diet of the mother and the effect on the growth of her foetus. Birth-weight is exponentially related to perinatal survival (43,44), and given the difficulty of directly studying the effect of nutrition on perinatal survival, birth-weight has been almost universally used (by now, almost mechanically) as a surrogate for viability. In the few intervention studies large enough to test the issue, maternal feeding has often been associated with lower foetal death rates.

Observational studies on the relationship of estimated maternal diet (whether by historical or prospective methods) with foetal growth, morbidity, and mortality, in which there has been no intervention to change diet, have generated uncertain and, as often as not, contradictory results. Some, for example, the studies of Burke et al. (117), have led to great optimism, while others have been depressingly negative (118). Because of the inconclusiveness of observational study, this review will be limited to interventional studies.

**Intervention Studies of Dietary Advice**

**World War II, Scotland**

Cameron and Graham gave dietary advice during the last trimester of pregnancy to approximately 400 women at the Glasgow Royal Maternity and Women’s Hospital (119). They also encouraged these women to apply for priority allowances of food. Among those who received dietary attention, the rates of stillbirth (4.2% vs 7.2%), low birth-weight (6.2% vs 10.0%), and neonatal death (1.6% vs 2.0%) were lower than among 500 comparison women who did not receive advice. This was not a controlled trial, and the characteristics of subjects and controls were neither compared nor taken into account in analysis. No mention was made of weight gain or whether diet was monitored; levels of dietary intake were not presented.

**New York City in the forties**

Berry and Wiehl assigned alternate pregnant women registering in a New York City public-hospital clinic to nutritional counselling or to a control group (120). Suggestions about specific ways to improve on her reported diet were given to each woman in the instructed group. One hundred sixteen women receiving instruction had a rate of low birth-weight of 6.2% and perinatal death of 5.2% compared to 9.9% and 6.4% respectively, among 110 women who did not receive counselling.

**Intervention scheme of Thomas Brewer**

The clinical programme of Thomas Brewer at the prenatal clinic of the Contra Costa County Hospital, Richmond, California, was evaluated by Frank Lundin and Charles Stark, then of the National Institutes of Child Health and Human Development, but the results were never published (Personal communication, 1980). Brewer stressed the advisability of eating high-quality protein, vegetables, and fruits, whilst discouraging high-carbohydrate and high-fat ‘junk’ foods and beverages. Weight control was not imposed, nor was salt restriction. No saluretic diuretics were prescribed. Compared to 2,441 women from the same or other clinics who were not enrolled in Brewer’s programme, 1,222 women had indistinguishable mean birth-weights, and rates of preterm delivery, of birth-weight below 2,500 g, and of neonatal death.

**Agnes Higgins and the Montreal Diet Dispensary**

Sweeney et al. (57) randomly assigned 22 women to counselling by the ‘Higgins method’ (see below). The study women took, on an average, 2,563 kcal and 92 g of protein a day vs 2,373 kcal and 81 g each by 21 controls (not statistically significant, but of appreciable magnitude). Maternal weight gain, birth-weight, and duration of gestation were said not to differ.

**Another trial of dietary advice**

Bruce and Tchabo observed higher total weight gain and birth-weight in 57 nutritionally-counselled under-weight pregnant women compared to 52 controls who were recruited after those who were counselled (59). However, their results are probably confounded by the two-week longer duration of gestation of the counselled women. This large difference is inconsistent with an effect of counselling, but rather suggests that late registrants with shorter durations of gestation might have been systematically excluded from the treatment group.
Comparison among three prenatal clinics
Tharp et al. recruited 84 women in two prenatal clinics (61), who were given intense nutritional advice aimed at raising weight gain. Controls (n=147) were recruited from a third, uninvolved clinic. There was no overall impact on weight gain; birth-length was 0.8 cm shorter (p<0.05), and birth-weight was 79 g lower in the counselled group (NS). The rate of breast-feeding was three times higher 4-6 weeks postpartum in subjects (29.8%) vs controls (10.9%; p<0.05).

Dietary Supplementation Studies during Pregnancy Aimed at Accelerating Foetal Growth
A study in which the level of supplementation was controlled by the participants: the INCAP Guatemalan four-village study
This study (121) began as a controlled trial with random allocation of four villages to two different supplements—one was energy-dense and contained protein (Atole), and the other was a sweetened clear liquid without protein (Fresco). In initial analysis, comparisons were not across treatments (Atole villages compared to Fresco villages), but of 178 women who chose to consume >20,000 kcal during the entire pregnancy from either supplementary food compared to 240 who did not. While data on total dietary intake were collected, they appear never to have opportunity to pass this threshold, and an unknown amount of the observed difference in birth-weight was probably due to artifactually longer gestation in the more highly-supplemented group.

The authors support their conclusion that increased energy supplementation caused increased birth-weight on the grounds that those who ingested larger amounts of supplements were socially more disadvantaged than those who ingested less, and further, that the results were not a function of high compliance (Since the energy density of the two forms of supplement was different, volume of supplementation could be distinguished from energy intake. The investigators used ingested volume as a measure of compliance and concluded that it was the amount of energy, not the volume ingested, that was related to birth-weight).

An important paper from the INCAP studies related supplementation during two pregnancies and the interpartum period to birth-weight in the second pregnancy (122). The investigator’s hypothesis was that feeding during an index pregnancy may not be enough to appreciably affect foetal growth, which also was the basis of the feeding experiment led by Chow in Taiwan (123,124). These are the mean birth-weights related to levels of supplementation over time (Table 9).

These results are not consistent with the authors’ hypotheses. The authors concluded that extended supplementation was highly beneficial because of the

<table>
<thead>
<tr>
<th>Supplementation level (1st pregnancy, lactation, 2nd pregnancy) (n)</th>
<th>Birth-weight</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>First pregnancy</td>
<td>Second pregnancy</td>
<td></td>
</tr>
<tr>
<td>High, High, High (n=21)</td>
<td>3,379</td>
<td>3,290</td>
</tr>
<tr>
<td>Low, High, High (n=55)</td>
<td>2,856</td>
<td>3,105</td>
</tr>
<tr>
<td>Low, Low, High (n=27)</td>
<td>3,073</td>
<td>3,056</td>
</tr>
<tr>
<td>Low, Low, Low (n=50)</td>
<td>2,969</td>
<td>2,944</td>
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been published. There was about an 110-g difference in birth-weight, favouring those with higher levels of supplementation. The problems in interpreting the results of this studies are: (a) 38% of infants were excluded from analysis, because they were not weighed immediately after birth; (b) relationship of supplementation with duration of gestation was not presented; (c) the total diets remain unknown; (d) duration of gestation was unknown for many women (see below); and (e) most seriously, there was a confounding bias in favour of those taking over >20,000 kcal. Given longer duration of pregnancy, there is greater higher birth-weights in the second pregnancies of the ‘Low, High, High’ group. Their logic (that only with a duration of feeding beyond one pregnancy would there be much of an effect) dictates that the ‘High, High, High’ group should also have done much better during the second pregnancy, as did the ‘Low, Low, High’ group. In fact, it did not. (As an aside, this publication throws some light on analytic problems with the INCAP birth cohort. To judge whether the results on birth-weight are confounded by duration of gestation, it is important to relate birth-weight to rate of supplementation (not confounded) rather than total amount of supplementation...
(very likely confounded). The authors of this paper could not do so, because 42% of their subjects with low total intake during the first pregnancy had unknown duration of gestation: “this analysis required information about gestational age.” Thus, an analysis of the relationship of supplementation with birth-weight not confounded by duration of gestation is probably impossible in the INCAP cohort).

**Studies in which decision to supplement and level of supplementation offered were not under control of subjects**

**Studies in developed countries (Annexure A)**

**Ebbs et al. in Toronto**

Ebbs et al., at a Toronto public prenatal clinic, gave high protein and calorie supplements for at least one trimester to pregnant women who were assessed, by history, as having a poor diet (125). Controls were alternate cases with poor diet. Mean birth-weight of infants of supplemented mothers was 85 g lower than among controls, although prematurity (not defined) rates and perinatal death rates were lower among the supplemented group.

**World War II, England**

Balfour reported the results of supplementing diets to over 11,000 women in the poorer areas of England and Wales with dried milk, ‘Ovaltine’, and iron-rich food (126). Although the more deprived areas probably were chosen for supplementation, they had a lower perinatal death rate than control areas (5.9% vs 7.1%).

**Chicago in the forties**

Dieckmann et al., in Chicago, studied the effects of supplementation with 100 g of cereal daily (127). Reported intakes of cereal ranged from 30 to 50 g. Those receiving cereal had infants who, on an average, 45 g heavier than those who did not, as well as slightly less frequent pre-term delivery, and slightly higher foetal death rates. Mothers with cereal supplementation gained 0.9 kg more than controls.

**Philadelphia in the fifties**

Tompkins et al. gave a 50-g protein supplement daily to women in Philadelphia (128). Rates of low birth-weight were slightly lower with protein supplementation (5.2% vs 7.0%), but women who did not cooperate with dietary supplementation were reallocated to the control group, which undermines comparability.

**Philadelphia in the sixties**

Osofsky, after studying 118 controls, supplemented 122 women with ‘Meritene’, a dietary supplement containing 26% calories as protein (129). He found significantly depressed birth-weight, infant-length and head-circumference, and lower Apgar scores among those given dietary supplementation. However, these results were not controlled for differences in the supplemented and the control groups, which were not fully described in the paper.

**Harlem, New York City, in the seventies**

We performed a randomized, partially double-blinded, controlled trial of nutritional supplementation in a black public-clinic population in New York City (65,66). The high-protein supplement was associated with 32 g lower birth-weight than among controls (NS), with significantly depressed birth-weight among those born pre-term, and with increased very early pre-term delivery and neonatal death rates at the margins of statistical significance. The balanced protein/calorie complement was associated with a 41-g increase in birth-weight compared to controls (NS) and with slightly longer duration of gestation and lower proportion of births under 2,500 g compared to the other two groups combined, both at the margins of statistical significance.

**A small study using the nutritional supplements developed for the Harlem Study**

The small study of Adams et al. (130) used the same supplements developed for the Harlem study (65,66). Mean birth-weight in the high-protein supplemented group was 45 g lower than among controls, while in the group who received the balanced protein/calorie supplement, birth-weight was 92 g greater than among controls.

**Milk supplements in South Wales**

Elwood et al., in South Wales, randomly offered tokens which allowed the daily purchase of 20 ounces of whole milk at half-price, beginning in mid-pregnancy and continuing until the child was aged five years (131). Of those for whom birth-weight was reported, after correcting for the disproportionately high number of smokers in the study group, there was about a 55-g increase in birth-weight associated with supplementation.

**The Montreal Diet Dispensary**

A large retrospective study using matched controls

The impact of the dietary programme of the Montreal Diet Dispensary (MDD) at the Royal Victoria Hospital
in Montreal, under the direction of the late Agnes Higgins, was evaluated in a large, retrospective matched-pair cohort study; matching included trimester at entry to prenatal care (132). This intensive programme consisted of dietary education and (for three-quarters of those served) provision of milk, eggs, and oranges. There was a statistically significant difference in birth-weight of 40 g favouring women served by the MDD. Effects were higher in first births and declined with rising parity. Differences in duration of gestation and perinatal mortality were small and not statistically significant. Weight-gain patterns of women were consistent with the effect on birth-weight, but were also small and not statistically significant. Referral bias associated with poor past pregnancy outcome (see below) could not have been operative among primiparae, and the largest effects were among them. The smaller effects among multiparae could have been, because they might have been less responsive, or, in part, because those at higher risk might have been preferentially referred to the MDD.

A sibling control study

Higgins et al. compared the outcome of pregnancy among 552 multiparous women enrolled in the MDD with that of one of their prior pregnancies without MDD services (133). The investigators reported large effects, but doubts remain. The overall impact on birth-weight (adjusted for parity and sex) in the ‘effectiveness’ (i.e. including all subjects) analysis was estimated as 107 g ($p \leq 0.01$). The ‘efficacy’ analysis, in which only high compliers were included, is confounded by duration of gestation. Women were only included if they had a minimum of four sessions with the MDD dietician, and women delivering prematurely were, thus, systematically under-represented because of this criterion, as were their low-birth-weight infants. This bias was obvious for MDD impact on birth-weight among women with ‘stress conditions’: 107 g in the effectiveness analysis but almost three times higher (319 g) in the efficacy analysis. Stress conditions included ‘poor outcome of prior pregnancy’ which also introduced bias, since some improvement in women delivering prematurely were, thus, systematically under-represented because of this criterion, as were their low-birth-weight infants. This bias was obvious for MDD impact on birth-weight among women with ‘stress conditions’: 107 g in the effectiveness analysis but almost three times higher (319 g) in the efficacy analysis. Stress conditions included ‘poor outcome of prior pregnancy’ which also introduced bias, since some improvement of women delivering prematurely were, thus, systematically under-represented because of this criterion, as were their low-birth-weight infants. This bias was obvious for MDD impact on birth-weight among women with ‘stress conditions’: 107 g in the effectiveness analysis but almost three times higher (319 g) in the efficacy analysis. Stress conditions included ‘poor outcome of prior pregnancy’ which also introduced bias, since some improvement in poor past pregnancy outcome (see below) could not have been operative among primiparae, and the largest effects were among them. The smaller effects among multiparae could have been, because they might have been less responsive, or, in part, because those at higher risk might have been preferentially referred to the MDD.

A twin study

Dubois et al. reported on the MDD experience with twin pregnancies; we will not review this paper here, given that all other reports are for singletons (134).

A study of adolescents

Dubois et al. did a retrospective matched pair analysis of 1,203 adolescent pregnant women served by the MDD between 1981 and 1991 (135). Participants were matched to controls for age, year of service, and hospital of delivery. The (adjusted) odds ratios for rates of low birth-weight, very low birth-weight, pre-term delivery and very pre-term delivery (2.3% vs 5.1%) were all significantly in favour of the intervention group. The impact on mean birth-weight was 46 g (NS); this rose to 55 g ($p < 0.05$) with adjustment for several factors, including smoking. This increase with adjustment is counter-intuitive, given that the intervention group had significantly fewer smokers (it is unclear what effect was of adjustment of birth-weight for ‘involvement of a social worker’). While the results for mean birth-weight were congruent with the prior matched-control study (132), the difference in very pre-term delivery, while dramatic, actually casts serious doubt on these results. There is little biologic basis for it, and there is a likely explanation...
due to biased matching of subjects and controls. Kramer, in his systematic review of controlled trials of balanced energy and protein supplementation during pregnancy, concluded, “no significant effects were detected on preterm birth” (136). The methodologic problem exists because women receiving MDD care had to be registered early enough to receive such care, and controls did not. Thus, there is a strong likelihood of bias, such that women registering late for care, or even coming to the hospital in labour could be included in the control group, but were excluded from MDD services. Until these results are re-analyzed holding duration of gestation at registration for prenatal care constant, they should be considered preliminary. Terris and Glasser reported, “...the relationship of prematurity to initiation of prenatal care...was found due largely to the fact that early birth prevents the initiation of prenatal care instead of vice versa” (137). The intervention group was also significantly more likely to be on social assistance (20% vs 10%), suggestive evidence of referral bias (the units of variability presented in the results were said to be standard errors of the mean; their magnitude suggests that they were more likely to have been standard deviations).

Studies in Birmingham, England, and Their Replication

Viegas et al.’s first trial

Viegas et al. performed two supplementation trials among women of South Asian origin in Birmingham, England (74,75). In the first trial, women were randomly allocated to one of three treatment groups—47 to a daily regimen of 26 g of protein and 273 kcal, 50 to a comparable level of energy supplementation, but without protein, and 45 were controls (74). All received iron and vitamin C. Results of the trial were confusingly presented. It is unclear whether they were for the total treatment groups, or excluded women with vaginal bleeding, hypertension, or ‘low compliance.’ In the first trial, the control group had higher mean birth-weight than those who received energy supplementation alone (30 g) or those receiving protein and energy supplements (40 g). However, the controls differed from those supplemented in potentially important ways, and these differences were not adjusted in analysis. For example, there were fewer Hindus among controls (5% vs 20% in the supplemented groups); controls were considerably less likely to have been vegetarians or to have had past low-birth-weight infants or foetal or perinatal losses; their body weights were higher, as were their initial triceps skinfolds. These problems, along with very small numbers of subjects, obscuring the meaning of the results.

Viegas et al.’s second trial

In a second trial, a group of pregnant women of South Asian origin was stratified by amount of change in triceps skinfold between 20 and 28 weeks gestation (75). Women with low and high skinfold change were then randomly allocated to a supplement containing either 425 kcal and 40 g of protein a day, one containing 425 kcal a day without protein, or to a control group. All women received vitamin-mineral tablets. The treatment groups were extremely small: for example, they varied between 14 and 17 among those with low triceps gains. The authors found only one significant difference in outcome: 14 women who had low prior triceps skinfold gain and received the high protein-energy supplement had infants with mean birth-weight of 3,340 g compared to 3,010 g for controls and 2,950 g among those supplemented with energy alone. Contrary to their hypothesis, birth-weights in the high prior triceps-gain groups were low (2,980, 3,160, and 3,110 g respectively). Thus, the 14 women with low triceps gain and with protein and energy supplementation had infants with birth-weights that were 180 g greater than the high triceps gain controls, 130 g heavier than high triceps gain energy-supplemented women, and 360 g heavier than the high triceps gain group who received protein-energy supplementation.

This pattern is more consistent with random variation than with a coherent treatment effect. There is no logical reason to expect treatment among those at high risk to do more than to bring them to parity with those at low risk. In fact, these women did considerably better than those at presumably lower risk. Further, it is not possible to judge whether the supplemented and control women were comparable, since comparability was judged on the combined low and high triceps gain groups, while the treatment results were presented separately. Applying the standard conventions of power analysis, given cell sizes of 14, with a power of 0.80, and with an alpha error of 0.05, we could hope to detect a treatment effect between 1 and 1.2 standard units, or somewhere between 600 and 800 g, outside any past experience. Thus, the differences observed in this study were most likely due to chance.

Replication of Viegas et al.’s second trial by Atton and Watney

Atton and Watney (138) replicated the design of Viegas et al. (75) and randomly assigned 62 women with low
mean triceps skinfold gain from 18 to 28 weeks pregnancy to a moderately protein-dense (14% of energy as protein) liquid supplement, supplying approximately 406 kcal a day, from 28 weeks to term. There were 61 unsupplemented controls and 265 women with high skinfold gain. Babies of supplemented women were 90 g lighter than those of unsupplemented control women. Among Asian women, the largest ethnic group studied, those with high skinfold gain had babies 100 g lighter than supplemented women and 150 g lighter than the unsupplemented. Thus, low mid-trimester triceps gain was associated with higher birth-weight (consistent with most other studies), and supplementation did not raise and might have lowered birth-weight in this supposedly high-risk group. It seems fair to dismiss low mid-trimester triceps skinfold gain as a risk characteristic for low birth-weight and criterion for supplementation.

A study in Aberdeen

Campbell-Brown, in Aberdeen, matched primigravidae at 30 weeks gestation for height and weight, as well as height-to-weight ratio at 20 weeks gestation, and weight gain from 20 to 30 weeks gestation (139). The first member of 90 matched pairs was assigned to dietary supplementation with dairy products, which contained between 15 and 20 g of protein and between 293 and 387 kcal per day. The supplemented group gained more weight (at the margins of statistical significance). Mean birth-weight of infants of supplemented women was 37 g higher than that of controls (NS), and head-circumference was 0.2 cm larger (NS).

The US Special Supplemental Food Program for Women, Infants, and Children (WIC Program)

Introduction

WIC, begun in 1973, is available to women with low income and at least one of a variety of criteria of nutritional risk. The programme, which also supplements postpartum women and pre-school children aged up to five years, served about 7.2 million clients and was funded at four billion dollars in fiscal year 2001. Approximately, one-third of American pregnant women meet the income-eligibility criterion, and we estimated that, in 1980, 40% of income-eligible women were enrolled in the programme; this has now risen to around 60%. The benefits are substantial: for pregnant women, they come to about 800 kcal per day of supplemental dairy products, cereals, vitamin C-rich juices, and several miscellaneous items, such as eggs, peanut butter, and lentils. The programme, carried out by health professionals, usually nutritionists or dieticians, aims not only at improving diet, but also at coordination of health and nutritional services, thereby improving health care.

The National WIC evaluation

In 1978, when the US Congress re-authorized the WIC programme, it mandated that a thorough evaluation of its health effects be carried out. Results of the evaluation were reported in a journal supplement (40,82-86,139,140). As part of the evaluation, we reviewed some 85 past studies of effects of the WIC programme, both published and unpublished. Those relevant to this review and published before 1987 have been presented in detail (139) and later summarized (13). We will focus here on several studies published since these reviews. Studies of WIC are best aggregated into two groups—those whose controls (a) had their health care funded by Medicaid, the US Government-funded health-care scheme for the low-income and indigent, or whose children were recruited postpartum into the WIC programme, or (b) health services were found in other ways. The reason for this distinction is that Medicaid has more stringent economic criteria for benefits than does the WIC programme, and controls drawn from that roster would be, on an average, financially worse-off than WIC participants, and the programme effects would tend to be over-estimated. The bias toward over-estimating programme effects by using postpartum WIC recruits as controls is more severe: one of the most frequent criteria used for enrolling infants into the programme is that they were of low birth-weight. On the other hand, there is probably a bias against the programme with controls selected from other sources, such as by matching for items available on birth certificates. The birth certificate contains a very limited description of the social status of the mother. It rarely includes social descriptors beyond race, parity, education, and, occasionally, marital status and does not include any physiologic data, such as weight or weight gain. Data on smoking (in Missouri, for instance) are only rarely available. This paucity of social or physiologic descriptors means that matching will be incomplete, with consequent under-estimation of programme effects. The choice of control group profoundly influences the estimation of programme effects.

The national WIC evaluation followed the 1978 mandate of the US Congress to perform a comprehensive
evaluation of the health effects of participation in the WIC programme. Four large studies were conducted between 1982 and 1984. Two of the four are germane to this review. One was a retrospective study which related WIC benefits to perinatal outcome in over 13 million births in 1,322 counties in 19 states over the first decade of the WIC programme (40); the other one was a prospective controlled study of over 7,000 births to income-eligible women done in 58 randomly-selected areas (82-86). All contemporary studies of a widespread public programme, such as WIC, are biased toward under-estimating programme effects for two reasons. First, income-eligible women not formally participating in the programme, who might serve as controls, cannot be assumed to be unaffected by the existence of the programme. The WIC programme is the largest employer of nutrition professionals in the USA, and it must be presumed that these nutritionists, and former participants, are likely to have affected the dietary knowledge, beliefs, and habits of women not formally enrolled in the programme. In addition, this is an eligibility, as distinct from an entitlement, programme. The number of beneficiaries is limited, and in general, the staff will tend to allocate the limited numbers of places in the programme to those who appear to be at greatest need. The tendency will be that the residuum of unserved women and children would be at lower nutritional risk, and likely to have better outcome, all other things being equal, than those in the programme. Comparison of those enrolled with the residuum of income-eligible women would, thus, also tend to under-estimate programme effects. Therefore, we predicted that results would be least biased if we were able to estimate programme effects at the time when the programme was not yet widespread. Since there was no way to identify individual women who had received WIC benefits early in the life of the programme, we performed a study at what is technically called the ecological level, relating rates of receipt of WIC benefits within geographical areas (in this case, counties) with countywide rates of change in perinatal outcome, specified from linked birth and death certificates.

Nineteen states and the District of Columbia had all three necessary data sets in reasonably convenient and accessible form (the US census; birth certificates linked with foetal and infant death certificates; WIC service data), with a total of approximately 13,000,000 births between 1972 and 1981. Each county served as its own control, and results were stratified by race and education. With some algebraic manipulation, we were able to estimate the effect of WIC service to an average beneficiary.

While there are weaknesses in ecological studies (among them both a tendency to under-estimate effects, secondary to measurement error, and possible confounding by unknown factors), there are also special strengths. First, the estimates of effect apply to the total population and are not confined to some limited subset of participants recruited into a trial. Typically, it takes a leap of faith to generalize results among trial participants to a larger population without further empirical testing, since trial participants can rarely be presumed to be representative of the population from which they were drawn; this limitation does not exist in an ecological study. Second, trial results are observed in the special circumstances of an expensive, small-scale study, not in a widespread programme implemented with all its inherent practical and resource restraints. Thus, the generalizability of the results of an ecological study, such as the one done in the WIC evaluation, is far more secure than for the typical small-scale trial.

In this study, we found significant relationships between rates of WIC service and the following outcomes: early registration for prenatal care (an increase of 4.1%), higher rates of adequate number of prenatal visits (5.0%), increased duration of gestation (0.2 week), reduction in rates of pre-term delivery (0.9%), higher mean birth-weight (22.7 g), and possibly, most importantly, reduction in late foetal death rate (2.1%). The magnitude of reduction in neonatal death rate (2.3%) was comparable to that of foetal death rate, but was not statistically significant. The pattern of results strongly suggests that this was an effect on maternal physiology, and not mediated predominantly by better prenatal or obstetrical care. First, there were also effects consistent with physiologic change in our contemporary longitudinal study on the woman’s diet, weight gain, and skinfold thickness. Second, although there were marked changes during the decade under study in the general population in some perinatal outcomes (neonatal and foetal death rates went down, and birth-weight went up by about 60 g), there was no increase in duration of gestation or frequency of pre-term delivery. Since WIC did significantly affect the duration of gestation and the rate of pre-term delivery, it seems more likely that WIC was primarily affecting maternal physiologic status and
was not just a vehicle for entry into better health care. Third, the results of the ecological study, when stratified by race and education, suggest that programme effects were more pronounced among subsets of women most likely to have been enrolled in the programme (and at greatest obstetrical risk): black participants and those with less formal education.

The effect of WIC participation on foetal death rate is particularly important. Most studies on the effect of nutritional supplementation during pregnancy have focused almost exclusively on birth-weight. Studies of effects on mortality have been rare, since much larger numbers of subjects are needed. This is, thus, one of the few secure demonstrations of a direct effect of a feeding programme during pregnancy with lowered mortality rates in the offspring.

While, for those outcomes specified in the birth certificate, the retrospective, ecological study probably gave a less-biased estimate of programme effects, the range of outcome measures was severely limited. To study outcomes other than those included on birth certificates, we executed a prospective study on a large nationwide representative sample of low-income pregnant women (84,85). We found that (a) diets of women enrolled in WIC were increased in energy and in nutrient density, (b) small deficits in weight gain were made up, and (c) late-pregnancy fat deposition was markedly lowered. Further, while we detected no effects on birth-weight and duration of gestation, the head-circumferences of infants of mothers who participated in WIC were significantly larger than those of controls. As with mortality, this has been a relatively infrequently-studied outcome, and the credibility that this was a real, rather than a chance, finding is strengthened, because we found a similar (although not statistically significant) relationship among pre-school children whose mothers had been enrolled in the WIC programme during pregnancy that was not present among children enrolled after birth. This association with accelerated head, and presumably, brain, growth is potentially of great importance and would have required follow-up in early childhood to test whether it was still present in later infancy and childhood, and whether it was accompanied with changes in cognition and behaviour. Such follow-up had been agreed to by the funding agency, the US Department of Agriculture, which later reversed itself. We also found significant relationships between the quality of the individual WIC programme, as judged by the administrators responsible for all WIC programmes within a state, and perinatal outcome.

Some important and recent studies of the impact of the WIC programme

State of Missouri

Probably, the best of the statewide studies for all births are from Missouri (141-143) and the subset of the same births receiving health care from Medicaid (144-147). Stockbauer and Blount (141-142), drawing controls from all birth certificates, found a significant effect on birth-weight (a 16-g increase) from WIC participation, almost entirely contributed by non-whites, for whom the difference was 48 g. Although the Missouri birth certificates allow better matching than most others in the USA, since they include history of cigarette smoking, the white control group is still probably considerably more privileged than white WIC service recipients; this is probably less true among black recipients. The two most recent analyses estimate the impact of WIC in the same year (1982) but with appreciably different results. One, using Medicaid as a sampling frame, found an overall impact of WIC on birth-weight of 31 g and lower rates of low birth-weight (10.1% vs 13.1%) (143). The second, drawing matched controls from vital statistics records, found no difference in mean birth-weight, and somewhat lower rates of low birth-weight (7.8% vs 9.2%) (145). The results in both studies are far more positive among blacks than whites. Conclusions in both the papers about the need for long duration of benefits are probably unjustified. Longer duration of gestation may be the cause of longer benefits (and higher birth-weight) and not vice versa.

In summary, the array of results is reasonably consistent with other studies of nutritional supplementation on birth-weight, with an effect somewhere between 15 and 50 g, and a reduction in rates of low birth-weight of about 1-2%, with the greatest impact among blacks, who are more economically deprived.

Michigan in 1992

Ahuwalia et al. linked WIC records and birth certificates for term births in Michigan in 1992 and concluded that longer duration of benefits reduces IUGR (148). However, their study, while limited to term births, could have produced its results for at least three reasons other than the impact of the WIC programme: (a) their comparison group was recruited from births where mothers were enrolled in Medicaid (the results, when WIC births were also limited only to Medicaid recipients, were far less dramatic), and (b) those enrolled earliest
for benefits (high exposure) included a much higher proportion of white subjects and women with more years of education. When these issues were controlled, ‘effects’ were markedly reduced, and controls almost surely had fewer weeks of prenatal care. It was important to have matched or controlled in analysis when women entered prenatal care (as well as duration of gestation). In the absence of this methodologic necessity, the results cannot be securely attributed to the WIC programme.

A US national study in 1998

In an elegant study, Moss and Carver (149) used linked birth and death records from the 1988 National Maternal and Infant Health Survey. They found that WIC benefits were associated with a reduction of 40-50% in what they called endogenous (i.e. prenatal) causes of infant death and nearly as great reductions in exogenous (i.e. postnatal) causes of infant death. The analysis was sophisticated, but there were real problems with the data set they used. The non-response rate was 38% for the follow-back portion of the infant death cohort (in which the key data were collected), and there were other potential sources of bias. For example, women responding to a questionnaire about an infant who died may have been less motivated or able to specify what services they received during pregnancy than those with a live-born infant.

Caan et al. (150) compared perinatal outcome for the second WIC birth among non-breastfeeding WIC service recipients in California, some from clinics offering 0-2 month(s) postpartum benefits (n=307) and some offering 5-7 months benefits (n=335). The ethnic composition of the two groups was very different, and women with extended benefits were about 3 kg lighter at the beginning of their second pregnancy compared to those with limited benefits. This opens the possibility that the major impact was not from food, but possibly from the professional counselling that is an obligatory part of the WIC Program. One of the inexplicable findings was that the impact of extended benefits on birth-weight (383 g) was essentially limited to women who had inadequate (<20 lbs) weight gains compared to those with higher weight gains (41 g). This issue badly needs further study.

Studies in developing countries (Annexure B)

A hospital study in Hyderabad

Iyengar hospitalized two small groups of women in Hyderabad, India, four weeks before their expected date of delivery (151). They received identical rations of energy, with one group receiving more protein. There was no difference in either weight gain or birth-weight associated with this differing protein intake. She then compared the newborns of the combined groups with 26 infants whose mothers were first seen in labour. The difference in mean birth-weight between infants of those hospitalized and of women presenting in labour cannot be attributed to nutritional intervention. Fed mothers had to go to full term, while women arriving in labour were at differing stages of gestation, including an unknown number who were delivering before term. Also, the medical care of controls clearly differed from subjects, as they presented during labour with no prior prenatal care, whether by choice or because of limited access to care. Further, they may well have been referred to the hospital due to intrapartum complications of pregnancy. For all these reasons, they cannot be assumed to be an unbiased control group.

A community study in Hyderabad

Qureshi et al., in Hyderabad, gave women protein-energy supplementation, plus iron and folate; alternately assigned controls received iron and folate alone (152). Supplementation began at 20 weeks gestation and was associated with a one-kg greater maternal weight gain than controls and 540 g higher mean birth-weight, a birth-weight difference far exceeding that in any other reported trial. There are several problems in accepting these results. The study was small; pre-term infants were excluded from analysis; duration of gestation was not reported; and outcome was not controlled for duration of gestation. A prior survey had indicated that the usual diet of each pregnant woman was about 1,800 calories and 42 g of protein a day, and given that dietary intake is usually under-estimated, these are not levels usually associated with nutritional deprivation. The standard deviation of birth-weight was much larger for the treated group than for controls (470 g vs 270 g). The standard deviation for controls is remarkably low, and it is biologically implausible to have such differences in variance in subgroups drawn from the same population. Nevertheless, this study stands out: the effect of supplementation on birth-weight is very much higher than in any other.

A community study in Taiwan, with feeding during the inter-pregnancy interval

The study of Chow and colleagues in Taiwan, initially analyzed by Herriott et al. (123) and later by McDonald et al. (124), was double-blinded, and supplementation
was observed. The analysis of Herriott et al. was limited to those taking over 50% of the prescribed supplements, thus vitiating the utility of random allocation. Supplementation began at the end of the previous pregnancy, which was unusual in these studies. After taking into account birth-weights from the prior (unsupplemented) pregnancy, the results presented by Herriott et al. suggested a 51-g difference favouring the supplemented group (79 g for male and 34 g for female infants), while in the analysis of McDonald et al., there was a 16-g difference (90 g for males; -61 g for females).

A community study in Bogotá

Mora et al. conducted a well-designed randomized, controlled trial of third-trimester supplementation among poor women in Bogotá, Colombia (88). They found a 51-g advantage in birth-weight with supplementation (significant on a one but not a two-tailed test). The effect was confined to males.

A hospital clinic study in Bombay

Merchant and Sheth (Personal communication, 1980) conducted a large randomized trial in Bombay among a group of working-class mothers registered for prenatal care. Unfortunately, the results of this large and apparently meticulous study were never published, but were shared by the investigators. There were four different protein-calorie supplementation groups—two offering different amounts of a low-protein-dense supplement and two offering different amounts of a high-protein-dense supplement. Both the groups receiving the low-protein supplement showed positive increments in birth-weight (36 g for the smaller amount and 83 g for the larger amount) compared to controls. In contrast, those who received the high-protein supplement experienced birth-weight decrements of 17 g and 23 g. The only statistically significant difference was the 83-g increment with larger amounts of the low-protein-dense supplement. Information on maternal weight gain and perinatal survival are not available.

A small Indian village study

Devadas et al. recruited 25 pregnant women early in the second trimester in each of three Indian villages (153). In one village, subjects received a daily rice-based supplement; in the second, a supplement based on an indigenous carbohydrate source—ragi; and in the third, no supplements. Neither the nutrient composition of the supplements nor the quantity offered was described. Both the supplemented groups had higher total weight gain (7.96 kg and 7.92 kg) than controls (5.98 kg, both, p<0.01), and greater increase in maternal haemoglobin (0.63 g/dL and 0.62 g/dL vs 0.09 g/dL, p<0.01 for both). Birth-weights were also higher by an identical 320 g in both the supplemented groups (p<0.01). It was inconsistent with the results for birth-weight that birth-lengths, and the arm-, chest-, and head-circumferences were unaffected. Given these remarkable results, it would be re-assuring to have somewhat more detail from this trial.

Two studies in the Gambia

The studies of Prentice and colleagues in the Gambia are important for several reasons (26,27,62). These are studies of nutritional supplementation implemented after initiating basic health services, which should allow a fair test of the impact of nutritional supplementation alone. Lamb et al. found that, after basic health services had been introduced, but before women received dietary supplements, “almost all the described improvements in mortality” had already occurred, and could be attributed to health care alone (28). Conditions during the wet, or hunger season, approximated those of the World War II famines.

A village study in which controls were studied before supplementation

There were two different nutritional supplementation studies in the Gambia. The first study was a comparison of outcomes before and after the initiation of supplementation in one village—initially reported in 1983 (26), but later extended and re-analyzed (27), and a subsequent controlled trial (62) was conducted with randomization of 28 villages (not individuals). Seasonality was central to these studies. The authors concluded that supplements were powerfully effective during the wet season, under conditions of heavy physical labour and shortage of food, but had far less impact during the dry season, when local food supplies were not constrained. Interpretation of these studies is clouded by the changing and possibly circular definitions of season. In the first paper (26), the definition was “...the dry season (February-June)...the wet season (July-January)...” In the next (1987) publication (27), the authors reported “...a long, hot, dry season (November-June) and a discrete wet season (July-October).” In the 1997 publication (62), the definition of the wet season was changed again, this time ‘June to October,’ and the dry season ‘November to May.’ The authors stated in this last paper “...the hungry season was defined as June
to October on the basis of environmental and nutritional events and because post hoc analysis yielded the greatest discrimination between hungry and harvest season events (emphasis added).” In fact, births during the month of June, previously in the dry season, contributed approximately 40% of the total effect on birth-weight during the five-month wet season. Thus, the definition of season is not only different in each of the three published analyses, but it appears to have been adjusted to fit the trial’s results.

In the first study (26), baseline birth-weights were collected for four years among all births in one village—95 during the wet season and 86 during the dry season. Supplementation was then instituted in the subsequent four years (1,100 kcal were offered for six days a week for 51 births during the wet season, and 950 kcal a day for six days a week during the dry season for 42 births). In the 1983 analysis of the first two years of supplementation, supplemented women had infants of higher birth-weights compared to the prior, control, years, but only during the wet season. The investigators interpreted this result to mean that only with the additional stress of the wet season (greater field work, and presumably lower food supplies) could the effect of supplementation be detected. The dietary data (and, to an extent, the birth-weight results) they presented are not fully consistent with this interpretation. During the control years (before supplementation), daily dietary intake (calculated from their paper) during the wet season was not lower than in the dry season (1,464 vs 1,468 kcal per day), and the incremental intake in the years of supplementation was also identical across season (430 kcal/d during the wet season and 433 kcal/d during the dry season). Thus, estimated base and supplementary diets were identical in the two seasons. The only factor that could then have varied was physical labour.

Understanding the results for birth-weight is impeded by some analytic decisions taken. The authors presented raw birth-weights and then adjusted for parity, sex of infant, but also for month of birth. This last adjustment makes it impossible to easily understand the seasonal effects. Therefore, what follows can only be an approximate understanding of the outcome of their first trial. The logic of their interpretation demands that, prior to supplementation, wet-season birth-weights should have been markedly lower than those in the dry season, and the unadjusted birth-weights were lower by 151 g in the 1983 publication, and 136 g in that of 1987. However, with adjustment, this fell to only 44 g in the first publication, but remained large (149 g) in the later analysis. In the first analysis, during the control, dry, season, adjusted mean birth-weight was 2,889 g, and in the wet season, 2,844 g—a difference of only 45 g, although the authors’ hypotheses would suggest a larger difference. Further, their logic dictates that supplementation during the wet season would bring birth-weights up to levels already prevailing during the dry season. In fact, what was observed was that supplemented women in the wet season had infants with adjusted birth-weights considerably higher than supplemented (+138 g) or control women (+141 g) during the dry season, and unadjusted differences, although smaller (+72 g and +74 g respectively), were still of considerable magnitude. In the second analysis (27), the unadjusted differences rose to 87 g and 89 g respectively. This pattern of results for birth-weight is somewhat inconsistent with the author’s interpretations, and the reported dietary intakes do not support the conclusion that dietary intake was lower during the wet season.

A trial in which randomization was by village

The second trial in the Gambia had very positive and apparently clear-cut results (62). In this large trial (2,047 singleton live-births and 35 stillbirths), pregnant women received a supplement containing around 1,000 kcal per day, or nothing. There were substantial effects on all outcomes, not only on birth-weight, but also on maternal weight gain, length of infant, head-circumference, and perinatal and infant survival. However, some of these observations were not congruent with an effect specific to the ‘hungry’ or wet season (see the weight gain results above). The shifting definitions of seasons remain troubling, since June was a month originally classified as in the dry season. In June, birth-weights were the highest of the year in supplemented villages and lowest in control villages. By far the largest impact of the trial on birth-weight was confined to births during June and July: June contributed approximately 40% of the entire five-month (wet season) impact on birth-weight (calculated from Fig. 2 in the publication). The birth-weight effects of supplementation (after controlling for several possible confounding variables, but, this time, not month) were 94 g (p<0.01) during the dry season and 201 g (p<0.001) during the wet season. Head-
circumference increased by 0.25 cm (p<0.05) in the dry season and 0.39 cm (p<0.01) in the wet season. Birth-length was affected only in the wet season (0.41 cm; NS). Supplementation lowered the odds ratios for low birth-weight significantly, but not differently by season (both 0.61; p<0.001). The effect on the odds ratio for risk of stillbirth was dramatic (OR=0.47, p<0.05); that for neonatal death, while of considerable magnitude (0.64), was not significant. The only obvious caveats about the impact on survival are that it is unclear if they had any relationship with season, and whether, somehow, the presence of more research staff in test villages had some effect on obstetric services at the time of labour due to greater availability of staff, transport, etc.

Unsatisfying aspects of this paper include that few unadjusted or raw results were presented and that several key outcomes were presented only as coefficients in regression equations. We are also not told how many test and control villages were there. While it would be helpful to have more detailed results, this large and apparently well-executed trial appears to be the most positive of any of the large trials so far available. The relationship with season strongly suggests that the conditions of privation during the wet season were nearly comparable to those during several of the famines studied during the World War II. The study begs for replication, preferably in South Asia. It is essential to remember that these investigators had preceded their nutrition intervention by instituting good basic health services, at least at their initial research site, which led to steep reductions in mortality before any attempts at nutritional supplementation. It may be instructive to compare the results on mortality presented by this study and those of Lamb et al. (28) in the Gambia 13 years earlier, which were due to health care instituted from 1974 and independent of nutritional intervention (Table 10).

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>From earlier report (Lamb et al., 1984) (28)</th>
<th>From later trial (Ceesay et al., 1997) (62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>57.5</td>
<td>47.1</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>83.7</td>
<td>60.4</td>
</tr>
</tbody>
</table>

This comparison suggests that the effect on mortality was most likely limited to reduction in stillbirth rate. Neonatal mortality rates in test villages were not lower than those achieved more than a decade earlier by health care alone. Further, it is very unlikely that such good results could have been achieved from the nutritional intervention in the absence of adequate health services (154).

A tiny study in Hyderabad

Girija et al. supplemented 10 low-income pregnant women in their third trimester in Hyderabad, India, and studied 10 controls (155). The very large difference in birth-weight (263 g) between the supplemented and control women was not statistically significant.

A small study in Southern Africa contrasting high-and low-bulk diets

Ross et al. performed a small study in which pregnant women were randomly allocated at 20 weeks gestation to one of four treatments (156). The size of treatment groups ranged from 31 to 33. The only group with increased birth-weight (205 g more than controls; p<0.05) was the one in which mothers received a high-energy supplement of ‘low bulk’; those who received a high-energy ‘high bulk’ supplement or a zinc supplement (30 to 90 mL of zinc gluconate a day) had lower mean birth-weight than had controls. There was no effect either on duration of gestation or on maternal weight gain. Women who received the low-bulk supplement gained 0.7 kg (NS) less than the control group.

A small study in rural Thailand

In a small study in rural Thailand, Tontisirin et al. assigned by rotation 43 rural Thai women who were around 28 weeks gestation to one of two dietary supplements or to a control group (157). Each of the supplements was said to supply 400 to 560 kcal and 16.6-20.1 g of protein a day. Weight gain and arm-circumference were significantly accelerated by both the supplements; only one supplemented group also had significantly increased triceps skinfold thickness. Birth-weight was significantly greater in both the treatment groups than in controls (236 g and 251 g). However, mean birth-weight in the control group was suspiciously low for healthy non-smokers (2,853 g), especially since mean maternal heights (152.1 cm) and weights (53.9 kg) at the onset of the experiment were not strikingly low. This study was too small to generalize from its results.
A trial on two forms of supplement among poor women in Santiago

Mardones-Santander et al. conducted a trial that was, in effect, a strong confirmation of the toxicity of high-density protein supplements during pregnancy (81). They alternately assigned 1,135 poor low-weight Chilean women registering for prenatal care before the twentieth week of gestation to either a powdered milk formula that supplied 498 kcal a day, 22.4% of which were derived from protein, or to a commercial formulation that supplied 470 kcal a day, 12.3% as protein calories (final n=391 in both the groups). Both maternal weight gains (0.98 kg; p<0.05) and birth-weights (73 g; p<0.05) were significantly lower in the high-protein group. Perinatal survival was not mentioned.

A trial in two villages in East Java

Kusin et al. conducted an initially randomized trial of dietary supplementation in rural East Java (158). This appears to be a meticulously-executed study, but there were problems in research design, data analysis, and in presentation and interpretation of results. The randomized trial took place in three, then two, villages in East Java. The final analysis included 272 third-trimester pregnant women who received a high-energy supplement (HE), which contained 465 kcal and 7.1 g protein per day; 265 (or 266) women who received a low-energy (LE) supplement, which contained 52 kcal and 6.2 g protein per day; and 205 (or 204) women judged to be non-compliers, drawn from both the treatment groups. Because non-compliers were analyzed as a separate group, the results no longer had the analytic strengths derived from randomization. Total dietary intakes that included intake from the supplements were not presented. The LE supplement supplied 48% of its energy content as protein; this is the highest protein density of any reported supplement.4

The project had no effect on weight gain and had no overall beneficial impact on birth-weight. The HE group had infants with the mean birth-weight of 2,908 g–40 g less than both the LE group and of non-compliers. No results by ‘intention-to-treat’ were presented. The authors based their central analyses on relationships with the number of days of supplementation. These analyses are strongly confounded by duration of gestation and cannot yield a true estimate of the impact of supplementation on birth-weight. A woman with longer duration of pregnancy, independent of any treatment effect, also had greater opportunity to ingest supplement for more days and would also have had a bigger baby, totally independent of nutrition. Thus, while the association may have been real, it is unlikely to have been causal. The HE group gained 0.12 kg more than the LE group in the third (supplemented) trimester (NS). The weight gain patterns are interesting, nevertheless, since the long-duration users of the LE supplement have depressed third-trimester weight gain (-0.6 kg) compared to the shorter duration users, despite a systematic bias that would tend to produce results in the opposite direction.

This trial had many indications that suggest protein toxicity. For instance, the highest compliers in the LE group had the lowest maternal weight gains and birth-weights in the study, opposite the trend in the HE group. Given that the results were likely confounded by duration of gestation (high compliers, those who ingested supplementary foods on 90 or more days, almost surely had longer durations of gestation that led to, rather than were caused by, high compliance), the actual extent of protein toxicity from the LE supplement may have been greater than it appears. Although the birth-weight results may be biased toward a spurious ‘effect’ of apparently higher birth-weight with more days of supplementation, in the LE group, the users of longer duration (90+ daily packets) had infants with lower birth-weight than the users of short duration (<45 packets) (-45 g) and the intermediate (45-89 packets) users (-56 g). Further, in the authors’ multiple regression analyses, protein intake, holding energy constant, was associated with significantly lower birth-weight. While the units of regression coefficients were not given, assuming that the unit for protein was g per day, and for energy, kcal per day, the relationships were +0.24 g birth-weight for an increase of one kcal per day, but -0.87 g birth-weight for every kcal per day derived from protein.

The authors attributed the upward secular trend of birth-weight in their villages to supplementation, but this is inconsistent with their results, since it occurred not only in the two treatment groups, but also among non-compliers. No data on effect of supplementation on

4In 1980, we reported that the high-density protein supplements in pregnancy that we used were toxic (65,66), and in a review published two years later (13,159) that this had also been true in all other past trials. The threshold for toxicity is about 20% of calories as protein (as in powdered skim milk). While only 52 kcal per day were offered in Kusin et al.’s LE supplement, in most supplementation trials the mean observed energy increment (not what was offered, but what was taken) was usually only around 100 kcal per day; therefore, an increment of 52 kcal per day was probably not trivial.
perinatal mortality were presented. The authors did not test whether women with low pre-pregnancy BMI responded to the nutritional supplements more vigorously than others, despite their advice that supplements should be targeted to women with low BMIs.

**Conclusion**

We can make several fairly secure conclusions about the effects of dietary advice and supplementation during pregnancy on perinatal outcome:

1. Among poor women not experiencing famine, in both industrialized and developing countries, there is reasonably consistent evidence that food supplements during pregnancy that are of low and moderate protein density can raise birth-weights to a modest degree. It is likely that, unlike during famine, supplementation needs to be started before the beginning of the third trimester. The major studies with negative results (in East Java, for example) did not start supplementing until the beginning of the third trimester (158).

2. In the larger and more sophisticated trials, the observed increments in birth-weight have been considerably smaller than had been hoped. The typical increments are in the range of 20 to 50 g, except in conditions that approximate famine, such as the seasonal deprivation in the Gambia, during which birth-weights may have been raised by supplements by as much as ~200 g (26,27,62). Even that experience is clouded by the meaning of the reported dietary intakes during the first trial (26,27): there were no differences in intake across season, and the only factor that could, therefore, have varied across season were intensity and duration of physical work. Dietary data were not reported from the second, larger trial (62).

3. There is repeated and consistent evidence that high-density protein supplements (those in which protein supplies over 20% of energy) are toxic: birth-weights are consistently lower than those among unsupplemented women. This may be mediated by the anorectic effect of high-density protein, since, typically, maternal weight gains are also lowered. As this review goes to press, another confirmation of this finding by Sloan *et al.* has been published in *Nutrition Research* 2001;129-39.

4. While few studies have been large enough to address the impact of dietary supplementation on foetal survival, there does seem to be benefit. There is some reason to be skeptical, however, that the effects of dietary supplementation on foetal mortality are mediated entirely by increased birth-weight. This conclusion follows the consistent relationship of higher maternal weight at conception being associated with higher birth-weight, but also higher perinatal mortality. Thus, it is no longer enough to show that birth-weight is increased by a nutritional intervention without demonstrating additional benefits. The relationship between maternal weight at conception and higher perinatal mortality also suggests caution in pursuing a strategy of feeding before pregnancy: the studies of inter-pregnancy feeding are, as of yet, fragmentary and unconvincing.

5. The standard of research in this field needs to improve. Further observational studies relating diet to foetal growth should only be undertaken if they have something new to offer: most do not. There is recurrent confounding of the effect of feeding by not dealing correctly with duration of gestation, either in design or analysis, leading to false claims of impact when none has been proven.

**PUBLIC-HEALTH NUTRITION PROGRAMMES IN DEVELOPING COUNTRIES AIMED AT LOWERING INFANT MORTALITY BY INCREASING MATERNAL DIET, WEIGHT GAIN, AND BIRTH-WEIGHT: EXAMPLES FROM TAMIL NADU (INDIA) AND BANGLADESH**

**Introduction**

Up to this point, this review has primarily addressed research conducted by the scientific community aimed at benefiting the health and well-being of women and children through the advancement of knowledge. The section that follows will explore, from the perspective of interested non-participants, some public-health nutrition projects funded by the World Bank, one of the central international agencies that deal with the consequences of poverty in the developing nations. There is a substantial overlap in the work of the scientific community and national and international organizations aiming at promoting public health, such as the World Bank. Does there exist, or could there exist, the kind of inter-communication which, it seems clear, would be of immeasurable benefit to both? To what extent do Bank programmes follow procedures and practices, which have evolved within, and are expected by, the scientific community? Do Bank programmes give evidence that
they are benefiting as much as they might from new knowledge that is generated? How accessible are findings concerning programme outcomes to scientists and the public?

While the primary goal of World Bank–funded nutrition programmes is service rather than research, its projects always include evaluation of both fiscal management and operational effectiveness. These evaluations are of crucial importance in understanding the potential benefits of Bank-funded interventions to improve maternal nutrition. Without searching evaluation, it is impossible to judge whether project goals have been accomplished, and, far more importantly, whether a project should be extended to other populations, and if so, how to best refine and improve such an extension.

These projects are carried out in the real world and are, thus, inevitably more likely to be generalizable to other wide-scale public-health programmes than are small (and relatively expensive) intervention trials. Also, only these public-health nutrition programmes, like the WIC programme in the USA, are large enough to study some infrequent outcomes, such as infant, and even maternal, survival, which cannot be adequately addressed in small trials. These programmes, especially when testing new interventions or ways to deliver more established ones, are actually huge human experiments, and the ethical imperatives developed for human experimentation are applicable to them. At minimum, there must be very little likelihood that participation will entail harm, and participants should be honestly and fully informed of potential risks and benefits; if they choose not to participate, their health care should not be prejudiced. Innovative projects must be meticulously designed and evaluated. Effective evaluation requires an appropriate intervention design and the allocation of sufficient human and fiscal resources.

Large-scale nutrition projects in developing countries are typically funded by such international donors as the World Bank, UNICEF, WHO and/or bilateral development aid agencies, such as USAID, and are carried out by local government and non-government organizations, with varying levels of ongoing support and oversight by the funders and/or their contracted representatives. The larger the project, the more complex the administrative and fiscal arrangements, and the greater danger that, under field conditions, the best laid plans for both project management and evaluation may go awry.

What follows is an attempt to look closely at one set of World Bank-funded nutrition interventions aimed primarily at benefiting malnourished pre-school children, but also pregnant women: the First and Second Tamil Nadu Integrated Nutrition Projects (TINP I and II), and the Bangladesh Integrated Nutrition Project (BINP), and its follow-on, the Bangladesh National Nutrition Programme (NNP). These projects address both child and maternal malnutrition; we will focus primarily, but not exclusively, on maternal nutrition.

This review is done from the perspective of an ‘outsider’; while this may impose some limits on access to information, it also tests whether anyone who might need to learn from these projects can, in fact, do so. Are the requisite data available, in ways that do not impose an undue burden on those who seek them? For this reviewer, they were not: many documents are stored only at the project site, or at Bank headquarters, rather than in the indexed literature, and for those at the Bank headquarters, there were several administrative hurdles before they could be obtained. This made it difficult to judge how successful the projects have been, or whether alternative interventions might not have been more effective in terms either of cost or health outcome. The few journal articles about TINP I found in a literature search are not relevant to the goals of this review, nor is a glossy public relations brochure of the World Bank (161). The Bank reports of TINP I provide internal evidence of these difficulties. The 1990 Project Completion Report of TINP I (162) listed twelve references; ten were internal mimeos, another an unpublished Bank document, and the last an internal report of the Tamil Nadu government. None of these is easily available.

The first Tamil Nadu Integrated Nutrition Project (TINP I)

The “Staff Appraisal of a Nutrition Project in Tamil Nadu” (163) was the basic document approving TINP I. It describes an innovative project, aimed primarily at preventing childhood malnutrition rather than only treating children after they become malnourished. The goals for improving the nutrition of pregnant women were relatively modest, especially compared to later projects. The report states that pregnant and nursing women constitute the highest priority group after weaning children because of their influence on the health and growth of infants (not because the health and well-being of women). Further, the report states, “the main
objective of the project would be to improve the nutrition and health conditions of pre-school children, pregnant and nursing women. Additionally, the project would contribute to the Government’s goal of around a 25% reduction in the infant mortality rate (from 125/1000 to 94/1000).” To this end, there would be “distribution of food supplements for on-site consumption by eligible young children and selected pregnant and nursing women.” The overall cost over the five years of TINP I was estimated to be US$40,000,000, 80% to be financed by the World Bank. In fact, while the Bank credit (in World Bank terminology, a credit is a loan at much lower than market rates; with inflation, it would become even less expensive to the recipient government) remained as originally estimated, the local contribution rose to US$49,000,000 (162). The 1980 Staff Appraisal Report gives detailed descriptions of various project activities: 2.1% of the total budget is allocated to monitoring and evaluation (163). However, while the five pages used for describing monitoring and evaluation go into great detail on staffing and administrative issues, they do not mention pregnant or lactating women, and never say what health indices will be measured, nor how. Thus, there was to be a massive infusion of resources aimed, as a major goal, at improving the nutrition of pregnant and lactating women, but nothing describing how these goals were to be met, or which outcomes to be measured.

The ‘Project Completion Report’ (162) and ‘Impact Evaluation Report’ (164) are directly relevant to judging the impact of TINP I, as is an economic analysis that includes some early evaluative data for TINP I (165). None of these reports provides any secure information on the effect of the project on maternal nutrition or on birth-weight, perinatal mortality, or other pregnancy outcomes. The Project Completion Report states (p.12), “The project’s health goals were not satisfactorily met. Infant mortality went down by 12%-26% in different areas of the project; but it is not clear how far these declines were caused by the project.” The Impact Evaluation Report is far harsher: “Data on infant mortality are based on far too small sample sizes, and varying methodologies across the different survey rounds. Nonetheless, these reports suggest tentative reductions in IMR of 12 to 30 percent in different project areas over the life of the project.” However, none of these evaluations takes account of changes going on at the same time in areas not served by the project. For instance, there was a concurrent statewide decrease in infant mortality of 34% between 1976 and 1989, while TINP I was active in only 122 of Tamil Nadu’s 385 rural blocks (administrative areas of approximately equal population size) (160). TINP I, therefore, cannot be credited with contributing to the statewide decline, which was greater, on an average, in areas not being served by the project. Infant mortality and birth-weight change were not directly measured as part of the evaluation of TINP I, and there were no project-collected data on the basis of which one can conclude that the project had any impact via improvement in maternal nutrition, one way or the other. The Impact Evaluation Report (166) stated, “All the above data on changes in health indicators (e.g., infant mortality rate, anemia, vitamin A status, maternal mortality: ed) are “guesstimates” rather than empirical data. ... Process evaluation does not present a plausible case for an impact on these indicators.” Even this report did not take into account the effect on these estimates of the secular trend in childhood malnutrition throughout India: between 1979 and 1990, the average rate of severe malnutrition for one-to five-year olds, judged by weight-for-age, in the eight states covered by the National Nutrition Monitoring Bureau, was 41%, compared to 67% in Tamil Nadu (160). Ho’s economic analysis (165) depends centrally on a reduction 17.3% to 13.4% in the prevalence of severe malnutrition among 7-60-month old children early after initiation of the project. However, by application of the chi-square statistic, this reduction was not significant, and it is not legitimate to generalize from it.

The Second Tamil Nadu Integrated Nutrition Project (TINP II)

The failure of TINP I to assess project impact on maternal nutrition was evidently understood by the evaluators (166); yet it is not clear how this was taken into account in formulating the succeeding Bank- and UNICEF-funded public-health nutrition programmes/projects in South Asia, based on TINP I: TINP-II, and BINP (Bangladesh Integrated Nutrition Project). The Staff Appraisal Report for TINP II (166) recommends substantial changes in the project as a whole (e.g. a redrawing of service provision areas to include previously excluded population groups, increased use of mothers’ groups, upgrading referral facilities, and a more explicit division of responsibilities between health and nutrition field workers), but it fails to rectify past errors in assessment of project impact on pregnant women, and especially on perinatal or child mortality.
The document says that during TINP I, “Infant mortality went down by 12-26% in different project areas, as against the project goal of 25%” (p.3). This statement in the new project implementation document is not qualified by any caution about the security of this estimate, nor any mention of the downward secular trend in infant mortality in India as a whole, including the parts of Tamil Nadu not served by TINP I. The goals for maternal nutrition in TINP II were extended beyond those of TINP I: to “contribute to a reduction in infant mortality rate from around 84 to 55 per 1000 live births and to a 50% reduction in the incidence of low birth weight from present levels.” This extension was justified on the grounds that “Recent Indian research indicates that regular therapeutic supplementation for about 180 days during the pregnancy of at-risk women can increase infants’ birth weights by an average of 230 g, thereby reducing the risk of low birth weight (less than 2.5 kg) by at least a third.” No reference is given for this remarkably optimistic projection, one at marked variance with the world experience of the impact of feeding during pregnancy on birth-weight (13).

The total costs of TINP II for 1991 to 1998 were initially estimated to be US$139 million, of which $95.8 million would be drawn as a credit from the Bank. (The final expenditures were almost identical to these estimates.) Of this, US$1,352,000 (0.97%) was allocated to monitoring and evaluation. In the three-page annex on monitoring and evaluation, women, pregnancy, and birth-weight go unmentioned. The only explicit reference to goals for maternal nutrition is a statement that morbidity and mortality information (with no further amplification or qualification) would be collected. The results of TINP II are presented for the public in a popular pamphlet (161), in a book chapter (167), and in the Implementation Completion Report (168), which, in its summary, states, “The project was successful in achieving its...infant mortality rate reduction objectives,” and “Limited data render it difficult to come to a conclusion with regard to the low birth weight incidence objective although there is some evidence to suggest a significant improvement.” On the contrary, there is ample evidence in the report to suggest that any conclusions are, at best, weakly justified by the available data. For instance, the report concludes that “service delivery was patchy,” “evaluation has been weak throughout the project,” and “the timeliness, quality, and utility of operational research was unsatisfactory.”

This raises two important issues. First, why did the writers of the report judge that these crucial outcome goals were met, or might have been met? For infant mortality, they depended on the nationwide Sample Registration System, which reported that, in 1996 the rate for Tamil Nadu was 54 per 1,000 live-births. However, they did not use a comparison population: nothing is said about the rate of decline in mortality in any populations not served by TINP II. Regarding rates of low birth-weight, the report stated, “The situation regarding the ambitious objective of halving low birth weight incidence is unclear owing to a lack of reliable data.” Despite this conclusion, it goes on to say that the “1992-93 NFHS (National Family Health Survey) data provide a figure of 23% low birth weight incidence in Tamil Nadu, almost identical to the 23.5% figure arrived at in the 1996 MTS (Mid-Term Survey of TINP II) from a limited sample of institutional data. Antenatal care indicators suggest such an improvement is plausible... it is clear that low birth-weight incidence has declined from its baseline level of about 30%.” It is unclear to this reviewer whence such clarity arose. Within the report, other results of the MTS are described as invalid, and as for routine monitoring data, a quarter of centre scales did not work, and birth-weight recording was described as ‘poor.’ The report estimated that only 10% of women had 12 weeks of iron folate supplementation, against a goal of 60%. What does seem clear is that a few, if any, conclusions can be drawn on the project’s impact on the incidence of low birth-weight and infant mortality. Even around the core issues of the project, uncertainties abound. The sequential results on severe childhood malnutrition are abstracted from the report (Table 11).

<table>
<thead>
<tr>
<th>Data source (date)</th>
<th>Prevalence of Grade III and IV malnutrition (%)</th>
<th>0-36-month old children, TINP II (168)</th>
</tr>
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<tbody>
<tr>
<td>Baseline survey, phases I-III (1992-1993)</td>
<td>4.9*</td>
<td></td>
</tr>
<tr>
<td>National Family Health Survey (1992-1993)</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Baseline survey, phase IV-V (1995)</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Monitoring data (1995)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Mid-term survey (1996)</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Monitoring data (April 1996)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Monitoring data (December 1996)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Terminal evaluation (1997)</td>
<td>3.1*</td>
<td></td>
</tr>
</tbody>
</table>

* Refers to 6-36-month olds, rates should be slightly higher than for 0-36-month olds

These data at best only partially support the optimism of the report about reduction in severe malnutrition. First,
rates varied to an extent that suggests that measurement techniques were not adequately standardized. Second, the survey rates are consistently higher than were rates derived from monitoring; monitoring rates are biased, because these are the children who were active participants, while survey results should be less biased estimates of population impact. Third, the reduction in survey rates was from about 4-5% in the initial surveys, to about 3% in the terminal evaluation, a change that could easily be accounted for by secular change or random variation.

The Bank’s internal documents, while very positive about the benefits derived from TINP II, are candid about its failures in operations; the public document is silent about these shortcomings (160). It is difficult not to conclude that the potential beneficiaries of subsequent programmes have been deprived of important help, because insufficient attention was paid to assessing whether this project’s goals, especially those relating to maternal nutrition, were actually achieved.

What were the barriers to effective mid-course corrective action? Once funds are approved and transferred, the Bank removes itself to an intermittent and advisory role, and, while it retains ongoing working contact with the project, its ability to modify project performance is severely constrained. The recipient government becomes almost totally responsible for project implementation, including the evaluation design and execution. A searching re-examination of current Bank administrative and oversight procedures seems in order: some better provision needs to be made for mid-course correction. Since Bank staff and consultants are intimately involved with the initiation of these projects, withdrawal to a more passive role probably ought to be modified. Further, the Bank’s frequent site-reviews are often performed by outside contractors who may be unfamiliar with the project and may find it difficult to learn a great deal in a very short time.

Measham and Chatterjee (160) reported that the Indian state of Tamil Nadu spent almost 3% of its state budget on nutrition in 1994-1995; the average Indian state spent 0.63%, and only two other states spent more than 1%. Thus, Tamil Nadu spent almost five times the national average. Given the state of the evaluations of TINP I and II, other states could not increase their nutrition funding to a level similar to Tamil Nadu’s in an informed way based on the data generated in those projects.

The Bangladesh Integrated Nutrition Project (BINP)

The Staff Appraisal Report for BINP (169) describes a serious attempt to improve overall project design, particularly in addressing the nutritional needs of pregnant women. Nevertheless, the goals for maternal nutrition in BINP were markedly inflated from those of its predecessor projects, without new supporting information to justify them: for all project areas, the goals included “reduction of iron-deficiency anemia among children and lactating women by a third, and contribution towards the national goals of reducing infant mortality from 110 to 55 per 1,000 live births and reducing maternal mortality from 600 to 300 per 100,000 live births by the year 2000”, and in those geographic areas “where malnourished pregnant women will also be included in the supplementary feeding program... reduction of low birth-weight by half the baseline level” and “improvement in maternal weight gain by at least 50% in at least 50% of the pregnant women.” The five-year budget for BINP was US$67,289,600, of which $793,900 (1.2%) was allocated to operational research, $3,078,800 (4.6%) to surveys and evaluative studies, and $2,127,400 (3.2%) to monitoring and review activities, a marked increase from TINP I and II. There is a nine-page annex on monitoring and evaluation; low birth-weight and low weight gain during pregnancy are defined, but there is no other mention of what is to be measured, or how to assess maternal nutrition.

While the mid-term evaluation of BINP reported substantial reductions of severe malnutrition among young children, and major improvements in pregnancy services (e.g. a 10-fold increase in women reporting the receipt of antenatal services and iron/folate supplements), there were no data to assess whether pregnancy outcomes and mortality had been affected.

Conclusion

Past experience made it predictable that the objectives relating to perinatal outcome set for these projects could not be met; given the low priority placed on evaluation, it is impossible to know whether they were met, at least in TINP I and II. Ideally, in complex, multicentric research or service projects, there is continuing and functional oversight by an independent, technically competent, review and supervisory group, a group with a commitment to remain in place for the life of the project, with a mandate to investigate, and authority to correct, problems of project execution and evaluation.
Continuing and effective oversight appears not to have been in place in these projects. An evaluation design was not included in the initial project documents; evaluation came late, was conceptually and methodologically weak and led to results that raise as many questions as they answer.

Although much may have been learnt from these projects in terms of operational management, and possibly, the reduction of malnutrition among young children, these programmes were unique, but lost, opportunities to understand whether large-scale nutrition interventions among poor, pregnant women in developing countries could affect maternal health and perinatal outcome.

It is encouraging that the new Bank-financed Bangladesh National Nutrition Programme (NNP) (170), designed to take BINP-type services nationwide, has somewhat more modest, if still unrealistic, goals, but it includes a far more sophisticated system of monitoring and evaluation for pregnant women — and for unmarried adolescent girls and newly-married couples — than in previous Bank-financed South Asian nutrition projects. The goals associated with maternal nutrition include achieving “sustainable improvements in birth-weights.” The specific objectives are to “increase weight gain during pregnancy to more than or equal to 9 kg in 50% of pregnant women” and “to reduce the incidence of low birth weight (<2,500 g) to <30%.” The NNP baseline survey includes data collection, in both participating and control areas, on pregnancy weight gains and birth-weights, in addition to maternal weights, heights, age, parity, and other essential social and demographic information. Thus, the NNP aims at assuring consistency of subsequently collected data by using the same data collection team and methods in initial, mid-term and final evaluations. In a major advance over TINP and BINP procedures, the NNP will systematically monitor behavioural practices of pregnant women to assess the effects of the project communication efforts on behavioural change and to assess the extent to which such change might itself improve pregnancy outcomes.

GENERAL CONCLUSIONS

Results of this review suggest that a series of assumptions that undergird current understanding and practice of maternal feeding in pregnancy are not supported by scientific evidence.

Despite considerable expert opinion to the contrary, dietary advice or supplementation among pregnant women (other than in famine or near-famine conditions) has minimal impact on weight gain. However, dietary supplements do have a modest effect on birth-weight (in contrast to a large effect in famine or near-famine conditions), but it is not mediated via maternal energy deposition, since the component of maternal weight gain associated with accelerated foetal growth is water (presumably, plasma) volume. Accelerated foetal growth is associated with lower peripheral maternal fat stores in late pregnancy. Pre-pregnancy weight (at least in affluent, industrialized societies), while associated with increased birth-weight, is also associated with higher perinatal mortality. While it has been demonstrated that increased maternal feeding, notably in the WIC programme and the second Gambian trial, leads to lower foetal mortality, such studies, though expensive and tedious, need replication and extension.

Costly nutritional programmes for pregnant women worldwide are enthusiastically promoted and implemented, although the underlying research is inconsistent, and certainly fragmentary. These large-scale programmes are rarely evaluated in ways that would fill in these gaps in knowledge. One temptation has been to substitute nutritional programmes for more expensive and complex health-care programmes rather than to have them serve as adjuncts.

It often seems very difficult, when questions arise about a potential large-scale nutrition intervention, to simply say, “We don’t know.” Rather, what is often on offer when there are few empirical data is projection or modelling. This delivers a conclusion in the form: If birth-weight could be increased, and if birth-weight-specific mortality rates still applied, so many deaths might be prevented. We have not educated our clients, the public and policy-makers, that our recommendations are often no more than hypotheses (sometimes very shaky ones) and are imperatives to do necessary empirical research. For example, Pelletier et al., in an exercise in modelling, ‘attribute’ a proportion of childhood mortality to nutrition status (170). The authors observed that death rates rise as weight-for-age declines. They then calculated what death rates would have been if all children were at the same risk of dying as those at optimal weight, and they attribute to nutritional deprivation the difference between the observed and the theoretically-optimal death rates. There can be no reasonable objection to their calculations: they represent the limits of benefit that a nutrition intervention might achieve. However, the authors go on to use the language
of causality ("42-57% of all child deaths are due to [emphasis added] potentiating effects of malnutrition on infectious disease..."). These estimates are guesses, which can only be confirmed in carefully evaluated field nutritional interventions aimed at discovering whether preventing or correcting growth failure leads to lower mortality.

There are similar examples for maternal nutritional supplementation. Prentice (7), in discussing nutritional supplementation during pregnancy, concluded, “Statistical projections would predict that...increase(s) in birth-weight should be accompanied with a significant decrease in neonatal mortality (emphasis added).” He does add an essential caveat: “large-scale effectiveness and cost-benefit trials are required with neonatal mortality as the primary outcome.” This caveat has often been observed more in the breach than in practice. Other attempts at modelling suggest that, where perinatal mortality rates are high, even if birth-weight were to be raised by nutritional intervention, and even if these gains were translated into reductions in perinatal mortality to the level projected by current birth-weight-specific mortality rates, the reductions in mortality would be trivial, and the programmes are likely to be futile (151). The argument is simple: where death rates are high, additional birth-weight would lower birth-weight-specific risk of death very little.

Garner et al. (4), who concluded that maternal feeding programmes had not yet been shown to be justified, stated that “it seems important to examine the effects of nutritional...interventions on outcomes that are more important than birth-weight” and that, in their estimation, “interventions to augment foetal growth [have given] no convincing evidence of benefits to duration of gestation or infant morbidity or mortality.” They call for more highly-focused research, since “there is a dearth of relevant, experimentally-derived evidence.” While these authors and Prentice (7) have markedly different interpretations of our current body of knowledge, their final positions are, in effect, identical: the need to know much more to justify extension of wide-scale programmes of maternal feeding. Each such programme should be considered a human experiment, and it is unethical and unconscionable not to so inform participants and their governments. As in any other human experiment, meticulous assessment of the impact on outcomes of real significance (of which birth-weight is only a relatively weak proxy) is obligatory.

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REFERENCES


92. Lucas A, Morley R, Cole TJ, Bamford MF, Boon


## Annexure A

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Population studied</th>
<th>Assignment method/ research design</th>
<th>Study group no.</th>
<th>Treatment/intervention</th>
<th>Control group no.</th>
<th>Treatment</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balfour</td>
<td>28 areas, S Wales, N of England, 1937-1939, poor women</td>
<td>Discretion of doctors; controls had lower parity, higher social status</td>
<td>11.618</td>
<td>1/2 lb dried milk, 1/2 lb ovaltine/w, + Marmite or Minadex</td>
<td>8095 or 9912</td>
<td>None; local authorities gave preference for their milk supplies</td>
<td>Preterm death (%)</td>
<td>( \chi^2 = 12.48 )</td>
</tr>
<tr>
<td>Ebbs et al.</td>
<td>Toronto General Hospital, c. 1940, &lt; 7m gest., no disease</td>
<td>Alternate if poor diet (A and B), third group with good diet (C)</td>
<td>90 (A)</td>
<td>45 g protein, 840 kcal/d</td>
<td>120 (B)</td>
<td>Cereal diet</td>
<td>Birth-weight (g)</td>
<td>( A = \bar{B} = \bar{C} )</td>
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<td></td>
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<td>170 (C)</td>
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<tr>
<td>Beckman et al.</td>
<td>Chicago, c. 1942; low income</td>
<td>Random</td>
<td>179 (B)</td>
<td>100 g cereal/d, + vitamin A and D</td>
<td>175 (I)</td>
<td>None</td>
<td>Birth-weight, (g)</td>
<td>3377</td>
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<td></td>
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<td>181 (D)</td>
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<td>Tompkins et al.</td>
<td>Philadelphia General Hospital, 1948-1952; &lt; 15 w gest, 74% white</td>
<td>Seriatim</td>
<td>312 (A)</td>
<td>50 g protein, 1.5 g cal/d, + vitamins</td>
<td>467 (C)</td>
<td>None</td>
<td>Birth-weight (g)</td>
<td>3397</td>
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<td>354 (B)</td>
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<td>447 (D)</td>
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<tr>
<td>Ooshsy</td>
<td>Low income, Temple University clinics</td>
<td>Supplemented studied after controls</td>
<td>122</td>
<td>Meritene, unk amount</td>
<td>118</td>
<td>Routine care</td>
<td>Birth-weight (g)</td>
<td>3045</td>
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<tr>
<td>Rush et al.</td>
<td>Black women, N.Y. public hospital clinic, 1970-1974, &lt; 30 w gestation</td>
<td>Matched on wt, w gain, prior low birth weight, diet and then randomized</td>
<td>265</td>
<td>Supplement (40 g protein, 470 kcal/d)</td>
<td>272</td>
<td>Control (multivitamins/milk tablets)</td>
<td>Birth-weight (g)</td>
<td>3995</td>
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<td>Adams et al.</td>
<td>Kaiser Clinic, San Francisco</td>
<td>Not stated</td>
<td>36</td>
<td>Supplement (as above)</td>
<td>43</td>
<td>Regular care</td>
<td>Birth-weight (g)</td>
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<tr>
<td>Montreal diet dispensary studies</td>
<td>Public patients at Royal Victoria Hospital, Montreal</td>
<td>Controls matched retrospectively on parity and wt</td>
<td>1213</td>
<td>Higgins method (dietary advice; 1/2 also received milk, eggs, and oranges)</td>
<td>1213</td>
<td>Regular care</td>
<td>Birth-weight (g)</td>
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<td>Name of author Population Assignment method/ research design Study group no. Treatment/intervention Treatment/Dispensary Control group no. Treatment Results Comments</td>
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<tr>
<td>Montreal diet dispensary studies</td>
<td>Higgins et al. (133) Sib pairs; comparison with past (untreated) pregnancy 552 (A) Higgins method; index birth 552 (B) Prior birth, not enrolled in Montreal Diet Dispensary</td>
<td>Birth-weight (g)</td>
<td>Prior (control) treated</td>
<td>3233 + 107 (p&lt;0.01)</td>
<td>Total population: &quot;Efficacy&quot; analysis confounded by length of gestation (see text). Suspicion of referral bias from results: largest effects among those with prior preg- nancy problems (see text).</td>
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<td>Dubois et al. (135) Adolescents at 15 Montreal area hospitals Retrospective matching on age, year, and hospital 1203 Enrolled at MDD 1203 Regular care</td>
<td>Birth-weight (g)</td>
<td>MDD Controls</td>
<td></td>
<td>Results confounded by failure to match on stage of gestation of enrollment. Magnitude of difference for rate of very preterm birth strong confirmation (see text).</td>
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<td>Elwood et al. (131) S. Wales Random, from booking 276 Males (A) 20 oz. milk/d half price 237 Males (C) Unequal distribution of smoking; adjusting birth-weight for smoking (approx). A-C=56 g, B-D=54 g</td>
<td>Birth-weight (g)</td>
<td></td>
<td></td>
<td>Unequal distribution of smoking; adjusting birth-weight for smoking (approx). A-C=56 g, B-D=54 g</td>
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<td>Birmingham studies and replication</td>
<td>Viegas et al. (74) S. Asian women, Birmingham, UK 1979 Random; Treatment from 18-20 to 38 w gestation 47 (or 33) (A) + Fe + vitamin C 45 (or 34) (Q) Fe + vitamin C</td>
<td>Birth-weight (g)</td>
<td></td>
<td></td>
<td>Not clear whether women excluded from analysis with vaginal bleeding, hypertension, and low compliance</td>
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<td>Viegas et al. (75) S. Asians Birmingham, UK 1979-1980 Stratified by change in triceps skinfold, 20-30 w, Random, Treated 28-38 w 12 or 14 (A) Low SF gain; 425 kcal + 40 g prot/d 12 or 14 (E) Low SF gain: orovite 7</td>
<td>Birth-weight (g)</td>
<td></td>
<td></td>
<td>Exclusions as above. Results stratified by SF gain, but across treatment comparability judged on combined group (Low SF + High SF). Numbers too small to test hypotheses. Interpretations inconsistent with results (see text).</td>
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<td>Atton and Watney (138) S. Asians + others randomized; high gain if at high risk from 28 w gestation 62 (A) 407 kcal + 14.6 g prot 64 (B) Low sf,controls</td>
<td>Birth-weight (g)</td>
<td>Low sf, obese Low sf, non-compliers without supplementation</td>
<td></td>
<td>Skinfold gain from 18 to 28 w not associated with birth-weight or response to supplementation</td>
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<td>Campbell Brown (139) Matching, with alternation 90 293 kcal + 15 g prot or 367 kcal+20 g prot or 319 kcal+18 g prot/d</td>
<td>Birth-weight (g)</td>
<td></td>
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<tr>
<td>Name of author</td>
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<tr>
<td>Iyengar</td>
<td>Indian manual</td>
<td>Controls recruited in labour</td>
<td>12 (A)</td>
<td>Hospitalized 36 w gest + (A) 2450 kcal &amp; 95 g prot/d (B) 2450 kcal &amp; 60 g prot/d</td>
<td>26 (C)</td>
<td>Recruited in labour 4 week wt gain (kg)</td>
<td>A  1.25  1.27  1</td>
<td>Outcome not controlled for during gestation. Birth-weight difference most likely artifactual</td>
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<td></td>
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<td>15 (B)</td>
<td></td>
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<tr>
<td>Quereshi et al (152)</td>
<td>Indian rural</td>
<td>Alternate, ABR, 12 (C)</td>
<td>39 (A)</td>
<td>500 kcal, 20 g prot/d, +Fe, folate</td>
<td>37 (B)</td>
<td>Fe, folate</td>
<td>A  3.9  2.9  2</td>
<td>During gestation not reported; prem by dates excluded from analysis. How group C recruited, not stated</td>
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<td></td>
<td></td>
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<td>13 (B)</td>
<td></td>
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<tr>
<td>Herriot et al. 123</td>
<td>Taiwan, rural</td>
<td>Randomized, supplemented from end of prior pregnancy</td>
<td>128 (A)</td>
<td>800 kcal, 40 g prot/d</td>
<td>128 (B)</td>
<td>80 kcal/d</td>
<td>A  2.9  2.9  2</td>
<td>Ingestion observed. Herriot et al. limited analysis to those ingesting ≥50% of supplements. Almost all positive effects among male infants only</td>
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<td></td>
<td>128 (C)</td>
<td>80 kcal/d</td>
<td>128 (D)</td>
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<tr>
<td>Mora et al. 88</td>
<td>Bogotá, 25 yrs, children &lt;5 yrs, malnourished</td>
<td>Randomized trial, third trimester only</td>
<td>200 (A)</td>
<td>856 kcal, 38.4 g prot/d</td>
<td>207 (B)</td>
<td>Healthcare only</td>
<td>A  3.9  2.9  2</td>
<td>Birth-weight difference NS on two-tailed test; oneailed test probably not legitimate</td>
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<td></td>
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<td></td>
<td>136 (B)</td>
<td>300 kcal, 30 g prot</td>
<td>122 (C)</td>
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<td></td>
<td></td>
<td></td>
<td>136 (D)</td>
<td>450 kcal, 7.5 g prot</td>
<td>134 (C)</td>
<td>Regular care</td>
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<tr>
<td>Mercorea et al. 158</td>
<td>Bombay, wives’ wives</td>
<td>Randomized trial</td>
<td>97 (A)</td>
<td>450 kcal, 45 g prot</td>
<td>501 (E)</td>
<td>Lysine+ Methionine</td>
<td>A  2.9  2.9  2</td>
<td>Never published. All (except F) received Fe, folate. B12: Half received lysine and methionine, which was unrelated to outcome. Dose of supplements raised 50% during study, i.e. B and D preceded A and C</td>
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<td></td>
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<td></td>
<td>136 (B)</td>
<td>300 kcal, 30 g prot</td>
<td>122 (C)</td>
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<td></td>
<td></td>
<td></td>
<td>136 (D)</td>
<td>450 kcal, 7.5 g prot</td>
<td>134 (C)</td>
<td>Regular care</td>
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<tr>
<td>Devadas et al. 153</td>
<td>Indian women in 3 villages</td>
<td>Each village assigned one treatment</td>
<td>25 (A)</td>
<td>Rag-based supplement, 2.5 g prot</td>
<td>25 (B)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>25 (B)</td>
<td></td>
<td></td>
<td>No feeding</td>
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<tr>
<td>MRC Gambia 26, 27</td>
<td>All births in one village during 4 yrs prior to pregnancy</td>
<td>Supplementation 6 d/w, observed, (Ex: initial report of first 2 years)</td>
<td>116 (A)</td>
<td>Wet (hunger) season; 1100 kcal/d</td>
<td>1100 kcal/d</td>
<td>Rice-based supplement, 950 kcal/d</td>
<td>A  2.9  2.9  2</td>
<td>Definition of seasons changed between publications. Meaning of adjustment for month unclear</td>
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<td></td>
<td>51 (A)</td>
<td>Wet season</td>
<td>95 (B)</td>
<td>Wet season</td>
<td>A  2.9  2.9  2</td>
<td>Mean basal diets and amts of supplementation identical across season. Why supplemented birth-weights in wet season higher than in dry season confusing. All changes in mortality preceded supplementation</td>
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<td></td>
<td>82 (C)</td>
<td>Dry season</td>
<td>86 (D)</td>
<td>Dry season</td>
<td>A  2.9  2.9  2</td>
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<tr>
<td>Name of author (Reference no.)</td>
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<td>Ceesay et al. (62)</td>
<td>Low SES Indian multipara, 3rd trimester</td>
<td>Randomized</td>
<td>10</td>
<td>417 kcal, 30 g prot/d</td>
<td>10</td>
<td>Not specified</td>
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<tr>
<td>Girija et al. (155)</td>
<td>Low SES Indian multipara, 3rd trimester</td>
<td>Randomized</td>
<td>10</td>
<td>417 kcal, 30 g prot/d</td>
<td>10</td>
<td>Not specified</td>
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<td>Ross et al. (156)</td>
<td>Rural Thai women &quot;same socio-economic class&quot;</td>
<td>Randomized, by rotation</td>
<td>14 (I)</td>
<td>400-466 kcal, 16.6 g prot/d</td>
<td>14 (II)</td>
<td>515-560 kcal, 20.1 g prot/d</td>
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<tr>
<td>Tontisirin et al. (157)</td>
<td>Rural Thai women &quot;same socio-economic class&quot;</td>
<td>Randomized, by rotation</td>
<td>14 (I)</td>
<td>400-466 kcal, 16.6 g prot/d</td>
<td>14 (II)</td>
<td>515-560 kcal, 20.1 g prot/d</td>
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<tr>
<td>Mardones-Santander et al. (81)</td>
<td>Low income, Santiago, Chile, 1983-4, from 20 w gestation</td>
<td>Alternate</td>
<td>298 PUR</td>
<td>498 kcal, 27 g prot/d</td>
<td>None</td>
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<tr>
<td>Kusin and Kardjati (158)</td>
<td>Rural Thai women &quot;same socio-economic class&quot;</td>
<td>Randomized to 2 supplements, non-compliers (NC) post-hoc controls</td>
<td>276 (HE)</td>
<td>465 kcal, 7.1 g prot/d</td>
<td>205 (NC)</td>
<td>Non-compliers from both treatment groups</td>
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