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Maternal Nutrition and Adverse Pregnancy Outcomes: Lessons from Epidemiology

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Introduction

Until recently adverse pregnancy outcomes such as stillbirth, infant mortality, and low birth weight (including its components, preterm birth and intrauterine growth restriction (IUGR)) provided a coherent 'package' of adverse pregnancy outcomes with consistent geographic and temporal trends. The poorest developing countries were generally those with the highest rates of all of these adverse outcomes, whereas northern Europe, Japan, and other highly developed industrialized countries had the lowest rates. In terms of temporal trends, most of these adverse pregnancy outcomes were decreasing over time in both developed and developing countries.

Over the past 10 or 15 years, however, increasing obstetric intervention, new treatments for infertility, and changing sociodemographic patterns among childbearing women have had differential effects on various outcomes within the 'package'. In particular, although stillbirth, infant mortality, and IUGR rates have continued to fall, preterm rates have risen sharply. Moreover, there is heightened concern about the increasing prevalence of high birth weight, i.e., infants who are large for their gestational age, and the potential adverse consequences of this trend for child and adult health over the long term.

In this chapter, I will attempt to highlight what we have learned from epidemiologic studies about the role of maternal nutrition in the etiology of adverse pregnancy outcomes and its contribution to the changing pattern of these outcomes in both developed and developing countries.

Descriptive Epidemiology: Patterns of Occurrence

Low birth weight (LBW) is defined by the World Health Organization (WHO) as a birth weight of <2,500 g. Birth weight, however, is determined by two processes: the duration of gestation and the rate of fetal growth [1]. Thus infants can have a birth weight of <2,500 g either because they are born early (preterm birth) or because they are born small for their gestational age (SGA), a proxy for IUGR. The WHO defines preterm birth as delivery before 37 completed weeks of gestation, and SGA as a birth weight below the 10th percentile for gestational age based on the sex-specific reference by Williams et al. [2]. It is important to point out, however, that newborn infants may be growth-restricted or preterm without having LBW, since the majority of term infants who fall below the 10th percentile of the Williams et al. [2] reference have birth weights exceeding 2,500 g, and many infants born at 35 and 36 weeks (who comprise the majority of preterm infants) also weigh over 2,500 g. It is also worth noting that fetal growth restriction can occur without reducing birth weight to the SGA cutoff and that, conversely, some constitutionally small infants (e.g., those born to short mothers) may have birth weights below the SGA cutoff without true (pathological) growth restriction.

Many perinatal researchers and public health policy makers have questioned whether the universal cutoff of 2,500 g for LBW or a Western industrialized country reference for defining SGA should be applied worldwide. For example, it has long been recognized that newborn girls are somewhat smaller than newborn boys and yet have lower gestational age- and birth weight-specific infant mortality than their male counterparts [3]. In many areas of Asia, and particularly on the Indian subcontinent, up to 30–40% of infants are born weighing <2,500 g [4]. In fact, recent evidence suggests that one size may not fit all, and that the use of ethnic-specific standards of birth weight for gestational age may provide stronger associations with perinatal mortality than use of a single Western standard [5].

Figure 1 shows the increasing disparity between temporal trends in LBW and preterm birth in Canada. Until the mid 1980s, both LBW and preterm birth were falling in parallel. Since that time, however, while low birth weight has continued to fall, preterm birth has been steadily increasing [6]. A rising incidence of preterm birth has also been reported from other developed and developing countries [7–9]. Evidence strongly suggests that the rise in preterm birth is due to more frequent obstetric intervention (to prevent stillbirth and/or reduce maternal health risks), particularly in documented cases of poor fetal growth diagnosed in utero, severe preeclampsia, decreased fetal movements, or other signs of a suboptimal intrauterine environment [10, 11]. Although no randomized trials have rigorously assessed the benefits and risks of this more aggressive obstetric approach, stillbirth and infant mortality rates have continued to fall concomitantly.

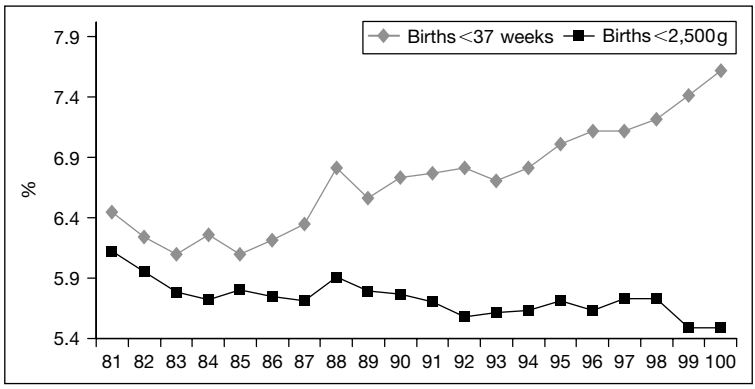

Fig. 1. Trends in preterm birth and LBW: Canada, 1981–2000.

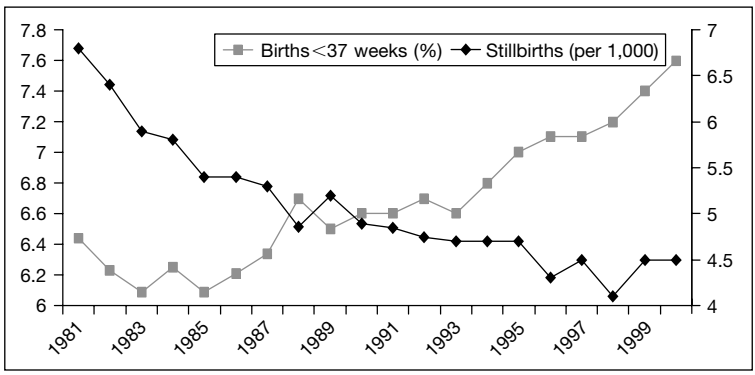

Fig. 2. Trends in preterm birth and stillbirth: Canada, 1981–2000. The y axis on the left shows preterm birth rates in percent, while the y axis on the right shows stillbirth rates per 1,000.

Figure 2 shows temporal trends in preterm birth and stillbirth for Canada over a 20-year period.

The other major contributor to the rise in preterm birth is treatment for infertility, including hormonal therapy to stimulate ovulation and in vitro fertilization. Such treatment has led to a large increase in twins and higher-order multiple births, which are associated with a greatly increased risk of preterm birth [12, 13]. Sociodemographic changes have also had an impact. These include an increasing trend toward delayed childbearing and pregnancy outside of (legal) marriage; women ≥35 years of age and women who are legally unmarried are at increased risk of delivering preterm [10, 14].

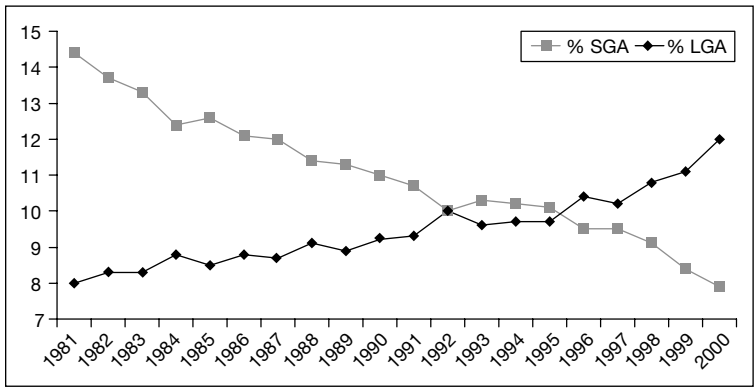

Fig. 3. Trends in SGA and LGA: Canada, 1981–2000.

The Canadian trend of falling LBW rates combined with rising preterm birth rates strongly suggests that fetal growth, i.e., birth weight for gestational age, has been increasing. Indeed, evidence from several countries indicates that newborn infants, particularly those born at term, have been increasing in size [15–17]. Figure 3 shows the 20-year trends in SGA and LGA for Canada, where the criteria for SGA and LGA are defined using a published reference based on 1994–1996 Canadian births [18]. The trend toward larger babies is largely attributable to increases in prepregnancy body mass index (BMI) and gestational weight gain, and to a reduction in maternal smoking during pregnancy [19]. Although a reduction in SGA (IUGR) may indeed be associated with both short- and long-term health benefits to the offspring, the temporal increase in fetal growth at term has also led to a very appreciable rise in large-for-gestational age (LGA) infants. LGA has been shown to be associated with later child obesity [20, 21], which is a known risk factor for persistent obesity in adulthood, type-2 diabetes, hypertension, and other chronic adult diseases. Although high birth weight may not be as important as reduced physical activity and increased energy intake in explaining the current obesity epidemic, more epidemiologic research and public health attention should be paid to the causes and consequences of the trend toward larger babies.

Analytic Epidemiology: Maternal Nutritional Effects on Pregnancy Outcome

Two broad research strategies are available to epidemiologists wishing to study the (causal) effects of maternal nutrition on pregnancy outcome: human experiments (controlled clinical trials) and observational (nonexperimental)

cohort and case-control studies. Observational approaches are unavoidable in investigating associations between maternal anthropometry (height, BMI, and gestational weight gain) and pregnancy outcome, but most macro- and micronutrients lend themselves to controlled (and preferably randomized) supplementation trials. Randomized trials minimize bias due to confounding (bias due to third variables that can affect the pregnancy outcome and are associated with the intake or status of the nutrient under study) and are often conducive to blinding, and thus unbiased reporting and measurement of study outcomes. The Cochrane Database of Systematic Reviews is an invaluable resource for locating such trials and synthesizing their results.

Maternal Anthropometry

Low prepregnancy BMI, short maternal stature, and low gestational weight gain during pregnancy are important determinants of IUGR and account for a large proportion of IUGR occurring in developing country settings [1, 22]. In developed countries, however, cigarette smoking is associated with the highest etiologic fraction (population attributable risk) [1, 22]. Based on data from the WHO Collaborative Study of maternal anthropometry and pregnancy outcomes, women in the lowest quartile of height have an odds ratio (OR) of 1.9 (95% confidence interval 1.8–2.0) of delivering an IUGR infant compared with those in the upper quartile, even after adjusting for prepregnancy BMI and weight gain during pregnancy [23]. Similarly elevated risks are seen in those in the lowest quartile of prepregnancy BMI (OR = 1.8 (1.7–2.0)) or of weight gain (OR = 1.8 (1.5–2.2)).

The only one of these maternal anthropometric factors that has been consistently associated with preterm birth, however, is low prepregnancy BMI [1, 22]. Even that association, however, has not been a universal finding. In fact, the above-cited WHO Collaborative Study found no increased risk of preterm birth associated with low prepregnancy BMI [3].

More is not always better. Not only is a high prepregnancy BMI associated with gestational diabetes, preeclampsia, hypertension, and increased risk of cesarean delivery, i.e., with adverse maternal health consequences, but the outcome for the offspring is not always favorable either. For example, a robust association has been found between higher maternal BMI and antepartum stillbirth [24, 25]. In Sweden, the increased risks associated with high maternal BMI are not restricted to obese women. Those risks are observed across the entire range of maternal prepregnancy BMI; the thinner the woman, the lower her risk of delivering a stillborn fetus [24]. Recent data from Uruguay and Brazil support the increased risk of antepartum stillbirth with maternal obesity, although reduced risks were not observed among thin women [26].

The high risk of LGA associated with high maternal prepregnancy BMI and high weight gain is also of concern, given the increased risks of child and adult obesity associated with LGA at birth. Because obesity is such an important risk factor for adult chronic disease, the temporal trend towards

higher prepregnancy BMI and gestational weight gain should be a cause of public health concern, even in developing country settings [19, 27]. As developing countries proceed rapidly through epidemiologic transition [28], the traditional focus on maternal undernutrition should be balanced by appropriate attention to the short- and long-term health consequences of maternal obesity and high weight gain.

Maternal Energy and Protein Intake

The best epidemiologic evidence bearing on the effects of energy and protein intakes on the outcome of pregnancy comes from the 'unnatural experiments' associated with acute famine and from controlled clinical trials of energy and protein supplementation or restriction. The evidence from these sources is reasonably consistent in demonstrating significant effects of energy intake, particularly on fetal growth. The strongest nonexperimental (observational) evidence comes from the careful epidemiologic analysis of the Dutch Famine Study [29]. Women who were exposed to the severely limited food rations (below 1,000 cal/day during the 'hunger winter' of 1944–1945) imposed by the Germans in the western part of the Netherlands experienced an approximately 300-gram reduction in mean birth weight, which paralleled reductions in placental weight and maternal weight. Similar, albeit relatively smaller, effects were observed on newborn length and head circumference. No impact was observed on mean gestational age or risk of preterm birth. Of note, unlike of a recent experimental study in sheep [30], no adverse effects on fetal growth or gestational duration were observed when exposure to the famine occurred either preconceptionally or in the first trimester. The contrast with the results in sheep may be due to the far more severe dietary restriction imposed in the sheep study. That restriction led to a 15% reduction in maternal weight, as compared with the 5–6% reduction in maternal weight that occurred in women exposed to the Dutch famine.

Controlled clinical trials of balanced energy/protein intake (where 'balanced' refers to a supplement in which protein constituted <25% of the energy content of the supplement) are consistent with those of the Dutch Famine Study [31]. Most of the supplementation trials reported modest increases in mean birth weight (weighted mean difference = 38 g; 95% CI 0–75 g), with a substantial reduction in risk of SGA (RR = 0.68 (0.56–0.84)) and significantly reduced risks of stillbirth (RR = 0.55 (0.31–0.97)) and neonatal death (RR = 0.62 (0.37–1.05)). The largest effects were seen in the Gambia, where the net increase in energy intake averaged approximately 900 kcal/day during the 'hungry' season in that country [32]. This is approximately 4-fold higher than the net energy increase achieved in most of the other trials. Somewhat surprisingly, the evidence from the supplementation trials does not suggest an increased effect of supplementation, independent of the quantity of energy supplemented, in women who are undernourished prior to pregnancy. Although inconclusive, the evidence from trials of isocaloric protein

supplementation or high-protein supplementation not only demonstrates no beneficial impact on pregnancy outcome but even suggests a possible increased risk of SGA [31]. Energy restriction among women with high prepregnancy BMI or early pregnancy weight gain does not reduce such women's risk of preeclampsia (RR = 1.13 (0.59–2.18)) but may adversely affect the fetal growth of her offspring (weighted mean difference in birth weight = −218 (−665 to +229) g) [31].

The evidence from both experimental and observational studies of energy/protein supplementation or restriction does not suggest that the timing of the supplementation or restriction differentially affects fetal body proportions. Previous suggestions that maternal undernutrition in early pregnancy (before 20 weeks) differentially affects fetal length were based on highly schematic growth curves published by Tanner [33]. Evidence from both prostaglandin and hysterotomy pregnancy terminations, however, indicates no reduction in fetal length velocity prior to 35 or 36 weeks [34, 35]. As mentioned above, evidence from both famine and supplementation studies points to late pregnancy as the period in which supplementation or restriction has its greatest effects. Fetal body proportions appear to be largely a function of the severity of IUGR [36]. Once severity has been controlled, the timing of maternal nutritional insult or supplement does not appear to have a major differential impact on weight, length, or head circumference or on proportionality ratios based on these measurements.

Micronutrient Intake

A low periconceptional maternal intake of folic acid is associated with a substantially increased risk of neural tube defects [37–39], and a low maternal iodine intake can lead to congenital hypothyroidism and cretinism [40]. Apart from these widely acknowledged effects, the impact of maternal status is not well established for most micronutrients. Because the intakes of most micronutrients are strongly associated among themselves and with the intake of macronutrients (energy and protein), the most rigorous evidence about the etiologic role of micronutrients in pregnancy outcome comes from controlled clinical trials and systematic reviews of those trials contained in the Cochrane Database of Systematic Reviews (CDSR). There is little evidence that supplementation with specific micronutrients improves fetal growth or lowers the risk of IUGR or preterm birth. A systematic review in the CDSR associates magnesium supplementation with reduced risks of both preterm birth (RR = 0.73 (95% CI = 0.57–0.94)) and IUGR (RR = 0.70 (0.53–0.93)), but the quality of the trials included in the review is poor [41]. No significant effect on reducing preterm birth or IUGR has been found in a systematic review of trials of supplementation with iron [42] or folate [43], even in combination [44]. In the case of zinc, although the most recent Cochrane review [45] reports a significant effect of supplementation in reducing preterm birth (but not SGA), the encouraging results for preterm birth have not been confirmed in two

recent trials from Peru [46] and Bangladesh [47] that are not included in the Cochrane review. The Cochrane review of maternal iodine supplementation in iodine-deficient areas reports a significant increase in mean birth weight (147 (51–244) g), but no data are reported on preterm birth or SGA [48]. Calcium supplementation is associated with a nearly significant reduced risk of preterm birth (RR = 0.66 (0.43–1.01)) overall in the Cochrane review, and a larger, significant effect (RR = 0.45 (0.24–0.83)) in four small trials in women at high risk for hypertension [49].

Diets rich in fish oil contain high concentrations of n-3 long-chain polyunsaturated fatty acids, which are known to inhibit prostaglandin synthesis and to exhibit antioxidant properties [50]. The evidence from observational studies and randomized trials is mixed, although 6 recent multicenter trials suggest that fish oil supplementation prolongs gestational duration and augments fetal growth, at least in singleton pregnancies [51]. Finally, a high-dose multivitamin and mineral preparation has been shown to reduce preterm birth among poorly nourished, HIV-positive women in Tanzania who were not receiving anti-retroviral therapy [52]. A trial of lower-dose multivitamin supplements in HIV-negative women in Mexico found no benefit of such supplements [53]. Additional trials of multivitamin supplements in HIV-negative women are under way, and their results are eagerly awaited.

Conclusions

Maternal energy intake is an important determinant of fetal growth. Energy restriction increases the risk of IUGR, while energy supplementation reduces that risk. No clear associations have been found between most micronutrients and pregnancy outcome. Rigorous randomized trials in populations with low or borderline intakes of these micronutrients should help resolve residual uncertainty about the etiologic roles of n-3 long-chain polyunsaturated fatty acids, calcium (in high-risk populations), and multivitamin supplements. Finally, the current trend toward reduced energy expenditure (and perhaps increased intake) in both developed and developing countries should lead to greater attention to the potential adverse effects of maternal prepregnancy obesity and high weight gain on fetal mortality, cesarean section, and excessive fetal growth and long-term obesity, with important adverse consequences for adult chronic disease.

References

1 Kramer MS: Determinants of low birth weight: Methodological assessment and meta-analysis. Bull WHO 1987;65:663–737.
2 Williams R, Creasy R, Cunningham G, et al: Fetal growth and perinatal viability in California. Obstet Gynecol 1982;59:624–632.

3 WHO Expert Committee on the Use and Interpretation of Anthropometry: Physical Status: The Use and Interpretation of Anthropometry. Geneva, World Health Organization, 1995.
4 de Onis M, Blossner M, Villar J: Levels and patterns of intrauterine growth restriction in developing countries. Eur J Clin Nutr 1998;52:S5–S15.
5 Kierans WJ, Joseph KS, Luo Z, et al: Does one size fit all? The case for ethnic-specific standards of fetal growth. Unpublished work.
6 Joseph KS, Kramer MS, Marcoux S, et al: Determinants of secular trends in preterm birth in Canada. N Engl J Med 1998;339:1434–1439.
7 Demissie K, Rhoads GG, Ananth CV, et al: Trends in preterm birth and neonatal mortality among Blacks and Whites in the United States from 1989 to 1997. Am J Epidemiol 2001;154: 307–315.
8 Silva AAM, Barbieri MA, Gomes UA, Bettiol H: Trends in low birth weight: A comparison of two birth cohorts separated by a 15-year interval in Ribeirao Preto, Brazil. Bull WHO 1998; 76:73–84.
9 Barros FC, Victora CG, Vaughan JP, et al: The epidemiological transition in maternal and child health in a Brazilian city, 1982–93: A comparison of two population-based cohorts. Pediatr Perinat Epidemiol 2001;15:4–11.
10 Kramer MS, Platt R, Yang H, et al: Secular trends in preterm birth: A hospital-based cohort study. JAMA 1998;280:1849–1854.
11 Joseph KS, Demissie K, Kramer MS: Obstetric intervention, stillbirth, and preterm birth. Semin Perinatol 2002;26:250–259.
12 Blondel B, Kogan MD, Alexander GR, et al: The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: An international study. Am J Public Health 2002;92:1323–1330.
13 Blondel B, Kaminski M: Trends in the occurrence, determinants, and consequences of multiple births. Semin Perinatol 2002;26:239–249.
14 Luo Z, Wilkins R, Kramer MS, for the Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System: Disparities in pregnancy outcomes according to marital and cohabitation status. Obstet Gynecol 2004;103:1300–1307.
15 Skjaerven R, Gjessing HK, Bakketeig LS: Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand 2000;79:440–449.
16 Ananth CV, Wen SW: Trends in fetal growth among singleton gestations in the United States and Canada, 1985 through 1998. Semin Perinatol 2002;26:260–267.
17 Wen SW, Kramer MS, Platt R, et al: Secular trends of fetal growth in Canada, 1981 to 1997. Paediatr Perinat Epidemiol 2003;17:347–354.
18 Kramer MS, Platt RW, Wen SW, et al, for the Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System: A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001;108:e35.
19 Kramer MS, Morin I, Yang H, et al: Why are babies getting bigger? Temporal trends in fetal growth and its determinants. J Pediatr 2002;141:538–542.
20 Hediger ML, Overpeck MD, McGlynn A, et al: Growth and fatness at three to six years of age of children born small- or large-for-gestational age. Pediatrics 1999;104:1–6.
21 He Q, Karlberg J: Prediction of adult overweight during the pediatric years. Pediatr Res 1999; 46:697–703.
22 Kramer MS, Séguin L, Lydon J, Goulet L: Socio-economic disparities in pregnancy outcome: Why do the poor fare so poorly? Paediatr Perinat Epidemiol 2000;14:194–210.
23 Maternal anthropometry and pregnancy outcomes: A WHO collaborative study. Bull World Health Organ 1995;73(suppl):1–98.
24 Cnattingius S, Bergstrom R, Lipworth L, Kramer MS: Prepregnancy weight and risk of adverse pregnancy outcome. N Engl J Med 1998;338:147–152.
25 Galtier-Dereure F, Boegner C, Bringer J: Obesity and pregnancy: Complications and cost. Am J Clin Nutr 2000;71:1242S–1248S.
26 Matijasevich A, Barros F, Kramer MS, for PAHO: Late fetal death and maternal anthropometric characteristics (height, pre-pregnancy body mass index and pregnancy weight gain). Unpublished, 2004.
27 Martorell R, Khan LK, Hughes ML, Grummer-Strawn LM: Obesity in women from developing countries. Eur J Clin Nutr 2000;54:247–252.

28 Popkin BM: The nutrition transition and obesity in the developing world. J Nutr 2001;131: 871S–873S.
29 Stein Z, Susser M, Saenger G, Marolla F: Famine and Human Development: The Dutch Hunger Winter of 1944–1945. New York, Oxford University Press, 1975.
30 Bloomfield FH, Oliver MH, Hawkins P, et al: A periconceptional nutritional origin for non-infectious preterm birth. Science 2003;300:606.
31 Kramer MS, Kakuma R: Energy and protein intake in pregnancy (Cochrane Review). Cochrane Library, Issue 2, 2004.
32 Ceesay SM, Prentice AM, Cole TJ, et al: Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. BMJ 1997;315:786–790.
33 Tanner JM: Foetus into Man: Physical Growth from Conception to Maturity. Cambridge, Harvard University Press, 1979.
34 Birkbeck JA, Billewicz WZ, Thomson AM: Fetal growth from 50 to 150 days gestation. Ann Hum Biol 1975;2:319–326.
35 Kaul SS, Bahn A, Chopra SRK: Fetal growth from 12 to 26 weeks of gestation. Ann Hum Biol 1986;13:563–570.
36 Kramer MS, McLean F, Olivier M, et al: Body proportionality and head and length 'sparing' in growth-retarded neonates: A critical reappraisal. Pediatrics 1989;84:717–723.
37 Czeizel AE, Dudas I: Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832–1835.
38 MRC Vitamin Study Research Group: Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. Lancet 1991;338:131–137.
39 Berry RJ, Li Z, Erickson JD, et al: Prevention of neural-tube defects with folic acid in China. N Engl J Med 1999;341:1485–1490.
40 International Task Force for Disease Eradication: Recommendations. MMWR 1992;42: 1–25.
41 Makrides M, Crowther CA: Magnesium supplementation in pregnancy (Cochrane Review). Cochrane Library, Issue 1, 2004.
42 Mahomed K: Iron supplementation in pregnancy (Cochrane Review). Cochrane Library, Issue 1, 2004.
43 Mahomed K: Folate supplementation in pregnancy (Cochrane Review). Cochrane Library, Issue 1, 2004.
44 Mahomed K: Iron and folate supplementation in pregnancy (Cochrane Review). Cochrane Library, Issue 1, 2004.
45 Mahomed K: Zinc supplementation in pregnancy (Cochrane Review). Cochrane Library, Issue 1, 2004.
46 Caulfield LE, Zavaleta N, Figueroa A, Leon Z: Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. J Nutr 1999;129:1563–1568.
47 Osendarp SJ, van Raaij JMA, Ariffeen SE, et al: A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. Am J Clin Nutr 2000;71:114–119.
48 Mahomed K, Gülmezoglu AM: Maternal iodine supplements in areas of deficiency (Cochrane Review). Cochrane Library, Issue 1, 2004.
49 Atallah AN, Hofmeyer GJ, Duley L: Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Cochrane Review). Cochrane Library, Issue 1, 2004.
50 Olsén SF: Consumption of marine n-3 fatty acids during pregnancy as a possible determinant of birth weight. Epidemiol Rev 1993;15:399–413.
51 Olsen S, Secher N, Tabor A, et al: Randomised clinical trials of fish oil supplementation in high risk pregnancies. Br J Obstet Gynaecol 2000;107:382–395.
52 Fawzi W, Msamanga G, Spiegelman D, et al: Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. Lancet 1998;351:1477–1482.
53 Ramakrishnan U, Gonzalez-Cossio T, Neufeld LM, et al: Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: A randomized controlled trial in a semirural community in Mexico. Am J Clin Nutr 2003;77:720–725.

Discussion

Dr. Uauy: Before we get on to the discussion, could you give us some idea about the efforts that are actually ongoing, WHO, UNICEF, in which you have been involved, in terms of addressing some of the issues that you raised? What is going on at the international level, especially considering the panorama in Asia where most of the low birth weight babies occur?

Dr. Kramer: I think that we should postpone some of that discussion until Dr. Yajnik's talk, because there are a lot of things going on internationally and I am not sure all of them are good. There is a large calcium supplementation trial in the field that I think is going to help us learn more. The large NIH trial [1] found no evidence of benefit for calcium supplementation, but some trials in other parts of the world have reported such a benefit [2]. This may be explained by the relatively good calcium intake and low risk among the women participating in the NIH trial, but we will have to await the results of additional trials in progress to resolve this controversy. Several large multivitamin studies are also currently in the progress. The major controversy right now is whether it is a good idea or not to mount massive supplementation programs, particularly in places in the world that have the lowest birth weights, for example the Indian subcontinent. Besides the fact that such programs are logistically difficult to mount and very expensive, legitimate concerns remain about whether they would actually do more good than harm. My colleagues and I have evidence suggesting that South Asian and Chinese babies shouldn't be the same weight as Caucasian babies. In fact, South Asian immigrants to Canada have lower weights and yet lower perinatal mortality at a given gestational age than Caucasians. Dr. Yajnik is going to present some data suggesting that efforts to increase birth weight in that part of the world can increase infants' fat content and put them at increased risk for long-term chronic disease. So I think the issue of what to do about low birth weight, which in the developing world is primarily a problem of intrauterine growth restriction (IUGR), is rather controversial. We need to understand more about all the public health programs to date that have not been very successful. None of these programs have changed birth weights anywhere that I am familiar with, and I have some concern whether it is a good idea even to try. Dr. Yajnik may want to comment on that now or we can postpone some of the discussion until after he has talked.

Dr. Yajnik: Taking your point further, the definitions of low birth weight at 2.5 kg and IUGR, which is based on a reference curve developed from some countries predominantly influenced by the Western statistics, may be inappropriate for developing countries. You pointed out that for a given gestation a smaller migrant Indian baby might do better than a Western baby. There is a database in London showing that Indians have a gestation which is 5–7 days smaller, black women have a gestation about 10 days smaller, and these Indian babies do much better than the white babies. The second point is to relate this to maternal pre-pregnant size because, as I will show you in our study, if the mothers started their pregnancies at 42 kg and a height of 1.52 m with a body mass index of 18 kg/m^2, a birth weight of 2.8 kg is perhaps proportional to maternal size, and if we superimpose a sort of standard based on the mother being 62 kg and 1.65 m, it may be inappropriate. This point was strongly brought to me when people from the Pacific Islands asked me to collaborate with them. In the Pacific Islands the migrant Indians contribute to more than 90% of the low birth weight and IUGR babies, while the babies of Pacific Island mothers, who are big, are also quite big. It was still found that even though Indians contributed to the IUGR and the small for gestational age (SGA) side, the outcomes were not bad. So maternal size needs to be considered in this definition. My third point is about the body composition of these babies at birth which might have important relationships with the short-term as well

as the long-term outcomes. I will discuss the long-term outcomes because that is where my interest in diabetes comes in.

Dr. Kramer: This raises the larger issue of 'customization', if you will, of fetal growth, i.e., of birth weight for gestational age. Gardosi et al. [3] and others in the UK have argued that we should adjust the definition of SGA as a function of maternal factors like height, pre-pregnancy body mass index, parity, ethnicity, etc. Although it is true that mothers who are short, thin, or primiparous have, on average, smaller babies for their gestational age, that doesn't necessarily mean that those reductions are physiologic rather than pathologic. We need to relate the observed differences in fetal growth to differences in some meaningful health outcomes, like mortality and morbidity. We are trying to compare patterns of birth weight for gestational age to patterns in perinatal mortality. As I alluded to before, we have seen that babies born to Chinese and South Asian immigrants to British Columbia (which has a substantial number of both these ethnic groups) have lower mean birth weights and larger SGA rates when using a single standard for defining SGA; yet they have lower perinatal mortality at all gestational ages. We are using the Swedish Birth Registry to see if the same pattern is observed for maternal height. I suspect that babies who are small because their mothers are short may not be at increased risk of perinatal death. Interestingly we have just completed an analogous analysis related to parity. It is well known that babies of primiparous women, i.e. women having their first pregnancy, weigh about 100 g less on average than babies of women having their second or subsequent pregnancies. But we find that using a single reference for birth weight for gestational age yields SGA rates that closely parallel those for perinatal mortality, suggesting that the reduced birth weight for gestational age seen in primiparous women is in fact pathologic rather than physiologic. Even though the reduced fetal growth is 'normal' and 'expected', it does have implications for perinatal mortality. So all these relationships are more complicated than we thought in the past; why a baby is small is probably as important, if not more important, than whether he or she is small.

Dr. Waller: While we are on the subject of the definition of SGA, I was wondering what you think about the use of percentiles to define that, because as the distribution of birth weight changes across different populations the use of percentiles means that you always have to have the same percent SGA, and that may not be the case. Is there any movement to develop an absolute measure?

Dr. Kramer: That is a really good question. Of course it is artificial to say that the risk below the 10th percentile is elevated, and at the 11th percentile it is not. Most of you are probably aware of the fact that the lowest risk for mortality is not the 11th percentile, nor even the 50th percentile, but closer to the 90th percentile. Whatever percentile you use, even if you use a birth weight below the optimal birth weight for gestational age, the risk will not remain constant across all gestational ages or across populations. So some of us are actually trying to use not a fixed percentile or z score for birth weight for gestational age, but rather the birth weight at each gestational age that increases the risk of perinatal mortality by 50 or 100%, and that percentile or that z score is likely to vary by gestational age. That makes things more complicated, but at least we can relate fetal growth to some health outcome that we think is important. It may be that the threshold percentile for perinatal mortality is not the same as the threshold percentile for serious neonatal morbidity, but we should try to relate different cutoffs for defining SGA at different gestational ages to important health outcomes rather than just size alone. We often assume that there is something magic about the 10th percentile. You are right; that assumption is rather naïve.

Dr. Quillamor: Since we are talking about energy supplementation, are we referring to only carbohydrate or carbohydrate and fat supplementation? My second question is, is there any role for diet modification among underweight or overweight and

obese women before they get pregnant so as to prevent these adverse pregnancy outcomes of low birth weight babies or growth-restricted fetuses, stillbirth and neonatal death?

Dr. Kramer: Two very good questions. I invite any of you who know more about this subject than I do to comment, but the only epidemiologic studies of which I am aware that have assessed different macronutrient compositions of the diet are those bearing on the relative contributions of energy and protein [4]. There is some suggestion that high protein, in which the energy content due to protein in the diet is more than 25%, can actually inhibit fetal growth, so most people are against using high-protein diets during pregnancy. But with carbohydrate vs. fat or with the type of carbohydrate, there has been very little investigation, except for carbohydrates of different glycemic indices in women with gestational diabetes. I haven't seen any trials or even observational studies that have looked into this for other population groups. I don't know if anybody else is aware of such data, even from animal studies. In terms of preventing the adverse effects of obesity on pregnancy outcome, I think all of us would agree that pregnancy is not the time to diet. I have some problems with the sheep study [5] suggesting that pre-conceptional and early pregnancy maternal undernutrition increases the risk of preterm birth, because experimental starvation resulted in a 15% loss of maternal body weight. There was no evidence of adverse effects of pre-conceptional or early exposure to the Dutch famine, in which the famine was severe and yet maternal weight loss was only around 6% [6], Nonetheless, a woman planning to get pregnant should probably not choose that time to start dieting. The prevention of obesity should perhaps even start in utero, but certainly in early childhood. When women are of childbearing age it is almost too late. If a women in adolescence or her early 20s is able to lose weight and follow a diet, she should do that before she plans to get pregnant rather than while trying to conceive. I think that is probably a safe recommendation, but it is one based on pretty flimsy information.

Dr. Sun: I would like to ask about fish oil supplementation during pregnancy.

Dr. Kramer: Most of the evidence comes from a very convinced and very convincing perinatal epidemiologist from Denmark, Dr. Olsén, who has carried out several observational studies and randomized trials [7–10]. The observational studies examined fish intake, while the randomized trials randomized women to receive a fish oil supplement. The studies aren't completely consistent, and some of the observational data came from the Faroe Islands, where fish intake is large, the duration of gestation is several days longer, and babies born at term are heavier on average than in other populations, even those elsewhere in Scandinavia. Other investigators have not had quite the same success Dr. Olsén has, but the evidence suggests small increases in birth weight for gestational age and a few days in duration of gestation with fish oil supplementation. The mechanism is unclear. People are interested in n-3 long-chain polyunsaturated fatty acids with respect to their antioxidant actions, but how they work to prolong gestation or increase fetal growth is not known.

Dr. Butte: I would like to return to the Cochrane review on energy and protein supplementation [4]. One of the conclusions of that study is that we need to target at-risk women and that the supplement has to be of sufficient quantity to have an effect. But I would also like to consider the effect of the amount of protein, not just in the supplement as a percent of energy, but the amount of protein in the total diet and the other micronutrients because if you don't have the whole gamete you won't promote proper growth. The second thing, there is no study in these randomized trials that considered the effect of infection, and so I still think we don't have the ideal design to answer that question. Across all the studies that were done, there was a very modest effect on birth weight, but we still have not addressed the major effect of intrauterine infections or the completeness of the diet.

Dr. Kramer: Unless the infections are confounded with the treatment intervention, the high incidence of infection in developing countries should be distributed randomly among those who were supplemented and those who weren't. I don't think that the prevalence of infection would in any way bias the results of those studies.

Dr. Butte: It could possibly minimize the effect.

Dr. Kramer: It could, but then perhaps the energy protein supplementation by itself is not sufficient and you have to combine it with anti-malarial, anti-helminthic, antibiotic, or antiviral treatment. Much of the morbidity that occurs in developing countries is due to rotavirus infection, for which there is no effective treatment. Combined nutrition-infection trials have not been done, and it is speculative to say whether such treatment would result in greater effects. Many people assume that the effects of energy-protein supplementation are greater in undernourished women. In fact, there is no evidence of such differential effects from the available trials; the average effect is about the same as in well-nourished women. In fact before the Gambian trial [11], the pooled estimate on mean birth weight was actually higher in well-nourished women than it was in undernourished women. The magnitude of the effect is determined by the amount of supplement consumed, and unless women are in a starving situation, as they are in certain seasons of the year in the Gambia, it is very hard to get a net increase in energy intake of more than 100 or 200 kcal/day above the normal intake. You can give women larger supplements, but then they tend to eat less when they go home after consuming their supplements. If they are given the supplements to take at home, they often distribute them to other family members because they are simply not hungry. If they are used to taking X calories per day, there is a limit to the increased number of calories per day you can get into them. I suspect that is true even if you treat infections as well. At certain times of the year, perhaps because the women were hungry and because of the way that the supplements were given (i.e., the supplemental biscuits had to be eaten before they left), the Gambian study was able to increase the net energy supplement to 4 or 5 times higher than in any other supplementation trial. The reason they got a larger effect was the higher energy intake increase, not because the women were at greater risk.

Dr. Vandenplas: We know that 20–30% of the population is atopic or allergic. Do you know if there are any epidemiological data on fetal growth, birth weight in this group of atopic mothers?

Dr. Kramer: All I can tell you is that I have also reviewed the trials on maternal antigen avoidance during pregnancy and lactation, and the antigen avoidance trials during pregnancy (which are not very good trials, by the way) did not succeed in reducing the risk of atopic disease in the offspring [4]. One of the things they did do was to reduce the size of the babies, probably because the foods the mothers were avoiding weren't replaced with equivalent energy intakes. So there may be some harm (reduction in fetal growth) in trying to change maternal diets in an attempt to prevent allergy in the offspring. There has been some suggestion that large birth weights for gestational age are associated with higher risks of atopy later on. That has nothing to do with maternal supplementation or avoidance diets during pregnancy.

References

1 Levine RJ, Hauth JC, Curet LB, et al: Trial of calcium to prevent preeclampsia. N Engl J Med 1997;337:69–76.

2 Atallah AN, Hofmeyer GJ, Duley L: Calcium supplementation during pregnancy for preventive hypertensive disorders and related problems. Cochrane Review. The Cochrane Library. Chichester, Wiley, 2004, Issue 2.

3 Gardosi J, Mul T, Mongelli M, Fagan D: Analysis of birthweight and gestational age in antepartum stillbirths. Br J Obstet Gynaecol 1998;105:524–530.
4 Kramer MS, Kakuma R: Energy and protein intake in pregnancy (Cochrane Review). The Cochrane Library. Chichester, Wiley, 2004, Issue 1.
5 Bloomfield FH, Oliver MH, Hawkins P, et al: A periconceptional nutritional origin for non-infectious preterm birth. Science 2003;300:606.
6 Stein Z, Susser M, Saenger G, Marolla F: Famine and Human Development: The Dutch Hunger Winter of 1944–1945. New York, Oxford University Press, 1975.
7 Olsen SF: Consumption of marine n-3 fatty acids during pregnancy as a possible determinant of birth weight. A review of the current epidemiologic evidence. Epidemiol Rev 1993;15: 399–413.
8 Olsen SF, Hansen HS, Sommer S, et al: Gestational age in relation to marine n-3 fatty acids in maternal erythrocytes: A study of women in the Faroe Islands and Denmark. Am J Obstet Gynecol 1991;164:1203–1209.
9 Olsen SF, Sorensen JD, Secher NJ, et al: Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet 1992;339:1003–1007.
10 Olsen SF, Secher NJ, Tabor A, et al: Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. BJOG 2000;107:382–395.
11 Ceesay SM, Prentice AM, Cole TJ, et al: Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. BMJ 1997; 315:786–790.