Balance between fetal growth and maternal weight retention: Effects of maternal diet, weight and smoking behaviour

by

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PREFACE

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judgement to be made of the importance and originality of the research reported in the thesis.

In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defence. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers. Under no circumstances can a co-author of any component of such a thesis serve as an examiner for that thesis."

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ABSTRACT

The interrelation among maternal dietary intake, pregravid weight, amount and pattern of gestational weight gain and cigarette smoking in influencing the balance between fetal growth and maternal postpartum weight retention was investigated in 1,330 healthy participants in the PEI Nutritional Counselling Program. Among nonsmokers, gestational weight gain was the main predictor of postpartum weight retention and explained 65.3% of its variability, while explaining only 4.7% of infant birth weight variability. Women with higher postpartum weight retention gained more weight during pregnancy and most of the difference between higher and lower weight retention groups occurred in the first 20 weeks. When comparing infant size between smoking and nonsmoking mothers, birth weight increased linearly with maternal weight gain in all weight status groups except in overweight nonsmokers where birth weight reached a plateau at weight gains >17 kg. Among smokers, infant length increased at a higher rate with weight gain than nonsmokers. Although higher weight gains seemed to partially mitigate the effect of smoking on the risk of small-for-gestational-age (SGA) infants, such risk remained $>10\%$ at elevated weight gains among underweight smokers. The effects of smoking in reducing maternal and infant weights were not mediated by lower energy intake, as smokers consumed more energy than nonsmokers after controlling for physical activity and pregravid weight. The independent relative risks of SGA infants due to maternal smoking, pregravid underweight and low weight gain, were 3.23, 1.80 and 1.72 respectively, implying that smoking has the greatest effect on SGA. Based on current smoking prevalence in Canada, the population etiologic fraction of SGA due to the direct effect of smoking is 30.8%; approximately twice that for maternal underweight or low weight gain. Efforts to increase

infant birth weight through higher maternal weight gain would require impractically high energy intake and could lead to postpartum obesity. To attain a properly balanced pregnancy outcome among well-nourished women, deferring a larger portion of required weight gain to later part of pregnancy, particularly in the overweight, may help reduce postpartum obesity, while smoking cessation and adequate weight gain in normal and underweight women are most important for promoting fetal growth.

ABRÉGÉ

Chez 1330 participantes en santé au programme nutritionnel de l'Ile du Prince Edouard, les relations entre, d'une part, le régime alimentaire, le quantité et le patron du gain maternel ainsi que le tabagisme durant la grossesse, le poids maternel avant la grossesse, et d'autre part, l'équilibre entre la croissance foetale et la rétention de poids post-partum ont été étudiées. Parmi les non-fumeurs, le gain de poids maternel était le principal facteur de prédiction de la rétention de poids post-partum. En effet, le gain de poids maternel a expliqué 65.3% de la variabilité de la rétention du poids post-partum, mais seulement 4.7% de la variabilité du poids à la naissance. Les femmes ayant une rétention de poids post-partum plus élevée que la moyenne ont gagné plus de poids que les autres femmes durant leur grossesse, particuliérement avant la vingtième semaine de gestation. Cette étude a démontré que le poids du bébé était relié de façon linéaire au gain maternel indépendamment du tabagisme ou du poids maternel avant la grossesse. Cependant, le poids des bébés des femmes non-fumeurs obèses a atteint un plateau à partir d'un gain total de 17 kg. La taille des bébés était plus affectée par le gain de poids maternel parmi les fumeurs que parmi les non-fumeurs. Même si un gain de poids maternel plus élevé diminue le risque d'un enfant petit pour l'âge gestationnel, le risque demeurerait élevé (> 10%) chez les fumeurs de poids insuffisant. Les effets du tabagisme sur le poids du bébé à la naissance et sur le poids maternel

n'étaient pas dus a un apport réduit en énergie. En effet, en tenant compte de l'activité physique et du poids maternel avant la grossesse, l'apport énergétique des fumeurs était plus élevé que celui des non-fumeurs. Les risques relatifs d'avoir un bébé de petit poids à la naissance étaient plus importants chez les fumeurs (RR 3.23) que chez les mères de poids insuffisant avant la grossesse (RR 1.80) ou chez celles qui ne gagnaient pas suffisamment de poids durant la grossesse (RR 1.72). Basé sur la prédominance du tabagisme au Canada, 30.8% de l'incidence des bébés de petit poids à la naissance est attribuable directement aux effets de la cigarette. Cet effet est deux fois plus important que celui du poids insuffisant de la mère avant la grossesse ou de gain de poids insuffisant durant la grossesse. Les tentatives de réduire le nombre de bébés de petit poids à la naissance parmi les fumeurs par une augmentation substantielle de l'apport énergétique risqueraient d'augmenter le nombre de mères obèses post-partum. Afin d'équilibrer la croissance foetale et d'éviter un surplus de poids important post-partum parmi les mères bien nourries, il est important de favoriser une plus grande portion du gain de poids exigé à la dernière partie de la gestation. Pour les femmes d'un poids normal ou sous leur poids idéal, il est important de ne pas fumer et de gagner suffisamment de poids durant la grossesse afin de promouvoir la croissance foetale.

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As the Ph.D. research supervisor, Dr. Katherine Gray-Donald provided continuous comments on the research work described in this thesis, in addition to her support and encouragement throughout the entire challenging period of the Ph.D. study. Her patience in reviewing the text of numerous drafts of this thesis is greatly appreciated. Dr. Koski provided invaluable help in reviewing the manuscripts and pointing to relevant literature citations. Her continued critical input helped to bring this research work into a better focus.
Ms. Newson's contribution in transferring the data used in this research from the PEI Department of Health and Social Services to the School of Dietetics and Human Nutrition of McGill University is gratefully acknowledged.

STATEMENT OF ORIGINALITY

The author of this thesis initiated all original concepts and new ideas, developed the study design, carried out all statistical analyses for the research work and prepared the three manuscripts in Sections 4.4-4.6. These manuscripts were co-authored by Dr. K. Gray-Donald, Dr. K. Koski, and Ms. E. Newson who assisted in reviewing and proof-reading the manuscripts and in pointing to literature citations.

A comprehensive data set of infant and maternal variables was obtained from the Prenatal Nutrition Counselling Program of the PEI Department of Health & Social Services. This data set was for exclusive use by McGill University and had not been fully analyzed before. The diversity of variables included in the data set offered a unique opportunity to explore the balance of fetal growth and maternal weight retention, while controlling for a large number of measured confounders. The relatively high percentage of smokers in the study population allowed a more thorough exploration of the role of smoking in pregnancy than what has been reported in the literature.

The methodology presented in Section 4.2 contains novel approaches to enhance precision and accuracy of the analysis beyond what is reported in the literature. The new methodological approaches are as follows:

1. Infant birth weight was classified into small (SGA), adequate (AGA) and large (LGA) by considering both gestational age of the infant and its gender. This is to take into account the lower average birth weight among female infants, and thus avoid misclassification of infant birth weight commonly found in the literature.

2. Maternal size was analyzed as two uncorrelated components: (a) standard weight for height and frame size, and (b) actual difference from standard weight. The former served to reflect maternal height and frame size, while the latter was used to reflect over- or underweight status. This new approach was to avoid multicollinearity between maternal pregravid weight and height that are often used in the literature as independent predictors of pregnancy outcome.

3. Throughout this research, smokers and nonsmokers were treated as two distinct groups to compare their pregnancy performance relative to a multiplicity of determinants and to explore possible interrelations between smoking status and other predicting variables (Section 4.4).

This is the first rigorously controlled study to investigate the relationship between maternal dietary energy intake and the level of cigarette smoking during pregnancy after controlling for measured variables influencing energy balance. The new findings in Section 4.5 that higher smoking levels were associated with increased energy intake and decreased weight gain during pregnancy refute previous hypotheses that smoking reduces weight gain through appetite suppression.

This study added important new information to the controversy concerning dietary compensation for the negative effect of maternal cigarette smoking on infant birth weight. The results of Sections 4.4 and 4.5 show that impractically high amounts of dietary intake and weight gain would be required to compensate for the smoking effect.

This research was the first to explore the combined effect of the main modifiable risk factors (pregravid underweight, low gestational weight gain, and

smoking) and to evaluate their relative importance in terms of their respective etiologic fractions concerning a study population in Canada (Section 4.5). The proportion of SGA infants independently attributable to maternal smoking was found to be approximately twice that attributable to each of pregravid underweight and low gestational weight gain. This provides a new emphasis on the primary importance of smoking cessation in prenatal programs.

This is the first study to investigate both fetal growth and maternal postpartum weight retention concurrently, as opposed to previous studies which investigated either maternal or fetal outcome separately. The author conceived the original hypothesis that the timing of weight gain during pregnancy affects fetal growth and maternal weight retention differently (Chapter 3). No previous studies have explored the contribution of partial weight gains during different stages of pregnancy (as opposed to the total amount) to pregnancy outcome. By exploring this novel hypothesis, this research has led to unprecedented findings on the contribution of weight gain pattern to maternal postpartum weight retention and infant birth weight (Section 4.6). A controversy exists in the literature on the merits of increasing maternal weight gain that may enhance fetal growth but may at the same time adversely affect the mother. This research explored, for the first time, possible means for achieving a balance in pregnancy outcome that would decrease both risks of SGA infants and maternal postpartum obesity. The new findings revealed the importance of the appropriate timing of weight gain during pregnancy (Section 4.6) to achieve such a balance.

The results of this thesis are intended to set a direction for defining recommendations for both the total amount and pattern of weight gain among healthy mothers who do not smoke during pregnancy (Section 4.6). Existing weight gain recommendations address only the total amount of weight gain and are based on studies using mixed populations of smokers and nonsmokers. The novel research

concepts presented in this thesis can be implemented in further research on other study populations in order to establish recommendations for the total amount and pattern of weight gain in different conditions.

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1. INTRODUCTION

Pregnancy is a growth process, and its optimum outcome represents a proper balance between fetal growth and maternal tissue accretion. In this process, different genetic and environmental factors interrelate with each other to influence pregnancy outcome. Although the effects of various factors on fetal growth have been reported extensively, the effect of each factor has been studied in isolation [Kramer 1987], and there is limited knowledge on the inter-relationship among them in their influence on fetal growth. Moreover, the influence of such factors on the balance between both maternal and neonatal outcomes, has received little attention. Maternal nutrition is a main environmental factor that plays an important role in supporting the required growth for both the mother and her fetus. While a nutritional deficiency may undermine fetal growth, an excess in dietary energy intake may expose the mother to pregnancy complications and subsequent obesity.

The following two sections briefly review determinants of the two outcomes of pregnancy; fetal growth and maternal postpartum weight retention. More detailed literature review specific to each of the modifiable determinants primarily addressed in this thesis will follow in Chapter 2.

1.1 Summary of fetal growth determinants

This section reviews the effect of maternal nutrition and other factors on fetal growth. Factors such as maternal age, height, parity, medical risk conditions, past obstetric history, ethnic origin, socioeconomic status, gestational length and infant gender are **non-modifiable** but are useful to consider in the assessment of pregnancy risks. Other factors such as maternal nutrition, weight gain, cigarette smoking, alcohol intake and physical exercise during pregnancy are **modifiable** and can be targeted in prenatal intervention programs. Pregravid weight status can be changed prior to pregnancy, and because of its interaction with weight gain, it will be treated as potentially modifiable.

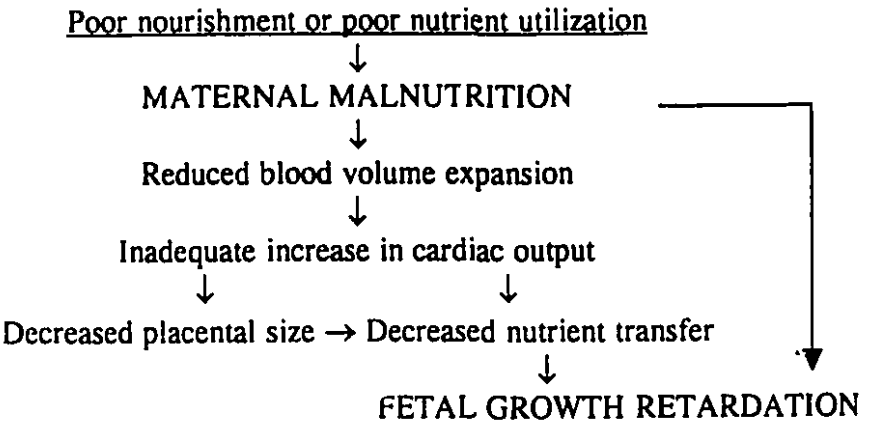
In studying the impact of modifiable and non-modifiable factors on pregnancy outcome, **infant size at birth** is used as proxy for fetal growth. Infant birth weight is considered as the primary indicator of infant health and survival [Saugstad *et al* 1981, McCormick *et al* 1985, Buehler *et al* 1987, Sappenfield *et al* 1987, Rona *et al* 1993], and subsequent neurological development [Seidman *et al* 1992, Geerdink & Hopkins 1993, Forfar *et al* 1994]. The lowest mortality and morbidity rates are reported for birth weights between 3 and 4 kg [Hogue *et al* 1987, Wilcox 1993, DHHS 1994]. Infant morbidity linked to low birth weight may be in the form of either cerebral palsy, epilepsy, hypoglycaemia, hypocalcemia, polycythemia, or birth asphyxia [Usher 1970, Ellenberg *et al* 1979, Shapiro 1980, Ounsted *et al* 1984, Arora 1987, Ounsted *et al* 1988, Kramer 1989]. The higher side of birth weight is also implicated with various maternal and fetal risks. Maternal complications include lacerations requiring repair and cesarian section delivery [Lipscomb *et al* 1995]. Macrosomic neonates (>4 kg) are at higher risks of bronchial and facial paralysis, clavicular

and cranial fractures, birth trauma [Modanlou *et al* 1980, Boyd *et al* 1983, Bromwick 1986], and of being overweight in late adolescence [Seidman *et al* 1991].

Infant birth weight by itself reflects not only fetal growth, but also the length of gestation. Although low birth weight (LBW), defined as <2.5 kg, is considered in itself as an undesirable outcome of pregnancy, this definition reflects both preterm infants (<37 weeks gestation), and those born at term but too small for their gestational age as a result of fetal growth retardation. When comparing infants of wide range of gestational ages, the degree of maturity is a stronger index of survival than weight [IOM 1990]. However, in full term infants, weight for gestational age becomes the main indicator of infant health [Arnold *et al* 1988]. This thesis focuses on full term infants and uses infant birth weight for gestational age to characterize fetal growth. Each determinant of fetal growth is reviewed below, starting with **maternal nutrition** and other **modifiable factors**, followed by a short summary of **non-modifiable factors**.

1.1.1 Maternal nutrition

Maternal nutritional deficiency during pregnancy, due either to poor nourishment or poor nutrient utilization interferes with normal fetal growth by impeding placental growth and function, and by limiting availability of nutrients to the fetus [Rosso 1981]. Rosso (1990) suggested that reduced flow of maternal blood or nutrients to the placenta reduces the efficiency of fetal access to nutrients when maternal stores fall below a certain threshold, as illustrated below.



The direct effect of restricted intake during pregnancy on fetal growth retardation may depend on what stage of pregnancy it occurs. This effect has been established by the natural experiment of the Dutch Famine from October 1944 to May 1945 [Stein *et al* 1975]. There, sharp time-limited changes in food supply within well demarcated areas allowed both place and time comparisons. The study by Stein *et al* (1975) included a total of 2,411 pregnancies from a region exposed to famine and 2,439 from unexposed regions. Those affected by the famine had had their intake reduced to an individual daily ration of ≤1,500 kcal/d (6,270 kJ/d) including ≤50 g/d of protein. Comparison of pregnancies from exposed and unexposed regions during the famine period provided control for seasonal variations. In these regional comparisons, pregnancies most affected by the famine were those exposed during both second and third trimesters, where infant birth weight fell 327 g from a level of 3,338 g in the unexposed controls. The other two dimensions of fetal growth, *i.e.* body length and head circumference were also reduced by this exposure to the famine. Comparison of pregnancies from the same region during and after the famine, provided control for regional differences. Third trimester intakes of approximately 3,200 kcal/d (13,380 kJ/d) in mothers exposed to the famine in

earlier months restored infant birth weight by 297 g above those exposed throughout their entire pregnancy.

Since this historical establishment of a clear impact of dietary deficiency on reduced infant size, different approaches have been adopted for improving maternal nutrition and enhancing fetal growth; The two principal approaches are

(a) to provide prenatal dietary intervention and **supplementation** to nutritionally disadvantaged women, with either balanced protein-energy, high energy, or high protein supplements [Susser 1991, Kramer 1993, IOM 1990]; and

(b) to define additional dietary **requirements** in pregnancy for the general healthy populations [ACOG 1983, FAO/WHO/UNU 1985, NRC 1989, HWC 1990].

Studies of dietary **supplementation** during pregnancy have produced inconsistent results with respect to changes in mean birth weight [Susser 1991, Kramer 1993, IOM 1990]; Several studies showed no significant improvement in infant birth weight with prenatal dietary supplementation, while others showed relatively small but significant improvements primarily among under-nourished and underweight mothers. There are several possible explanations to this inconsistency. Fundamental problems with research design may have prevented the detection of significant effects of energy supplementation. For example, randomization was sometimes ruled out for ethical reasons related to the population nutritional needs [Higgins 1989], or the sample size was too small to randomize [Adams *et al* 1978]. In other studies, the amount of supplements consumed may have been insufficient: (1) because the supplement was shared with other family members [Mora *et al* 1979], (2) due to non-compliance [Blackwell *et al* 1973], or (3) because subjects replaced their customary diet with the supplement

[Rush *et al* 1980, Kardjati *et al* 1988]. Even when supplementation was more rigorously administered, the study subjects who did not benefit from it may have not been under-nourished and fetal growth retardation may have resulted from factors other than under-nutrition [Viegas *et al* 1982a, Rush *et al* 1988a]. In general, it seems that supplementation can only benefit those women who have poor nutritional status. It is therefore important to assess maternal nutritional status when determining the necessity of dietary supplementation during pregnancy by considering maternal characteristics which are related to nutritional status, such as pregravid weight, height, physical activity, health conditions and age.

With respect to the general healthy population, estimated dietary energy **requirements** for pregnancy are found to be substantially higher than observed intakes. The factorial method estimates a total energy cost of pregnancy as 80,000-85,000 kcal (334-355 MJ) [FAO 1973, Hytten & Chamberlain 1980, 1991]. In contrast to these estimated requirements, the increase in energy intake over the entire pregnancy was estimated to be no more than 22,000 kcal (92 MJ) among well-nourished Scottish and Dutch women by using the weighed inventory technique for 3 or 5 consecutive days every 2, 4 or 6 weeks throughout the pregnancy [Durnin *et al* 1985, 1991]. In the absence of data on actual dietary intake or energy expenditure by Canadian pregnant women, Health and Welfare Canada [HWC 1990] recommended 65,000 kcal (270 MJ) for a cumulative pregnancy increment as an intermediate value between estimated requirements and observed intakes. This value falls between the two levels of FAO/WHO/UNU recommendations; 56,000 kcal (234 MJ) for reduced physical activity and 80,000 kcal (334 MJ) for normal activity [FAO 1985].

Part of the large discrepancy between observed increase in energy intake and estimated energy cost of pregnancy can be attributed to some **energy**

conservation mechanisms that may reduce energy expenditure per kg of body weight. Energy conservation can occur from decreases in basal metabolism [Tauzon *et al* 1986, Durnin 1987, 1991, Lawrence *et al* 1987], physical activity and/or thermogenesis [Thongpraser & Valyaseri 1986, Tauzon *et al* 1986, van Raaij *et al* 1986]. Measured actual changes in total energy expenditure during pregnancy (basal metabolism, thermogenesis and activity) have been found to vary widely among individuals depending largely on maternal weight status [Poppitt *et al* 1994, King *et al*], dietary intake [Durnin 1987], and the pace and intensity of physical activity [Banerjee *et al* 1971, Blackburn & Colloway 1976, Langhoff-Roos *et al* 1987b]. This wide variability makes it difficult to establish standard requirements for energy intake during pregnancy for all women. Energy intake and expenditure during pregnancy are further reviewed in Chapter 2.

1.1.2 Other modifiable determinants

Maternal weight gain during pregnancy, in contrast to energy intake, reflects the net balance between energy intake and expenditure, provided that no excess fluid is retained. Weight gain also can be measured more accurately and objectively than dietary intake. Despite its wide variation among women having infants of normal birth weight (3-4 kg at term) [Taffel 1986, Dawes & Grudzinskas 1991b, Johnston & Kandell 1992], weight gain is well established as an important determinant of infant birth weight [Abrams & Laros 1986, Hediger *et al* 1989, Wen *et al* 1990a,b, Hickey *et al* 1993]. Weight gain is also reported to be associated with infant length and head circumference [Miller & Merritt 1979]. The rate of weight gain changes at different stages of pregnancy [Dawes & Grudzinskas 1991b], and the timing of such rate is also important to fetal growth in addition to the total amount of weight gain. The rate of weight gain later in pregnancy is reported to be more important to fetal growth than earlier [Stein *et al* 1975, Picone *et al* (1982b), Lawton *et al* 1988]. Trends of

increased emphasis on liberal maternal weight gain were accompanied by increased birth weight [Arbuckle & Sherman 1989, IOM 1990], although other factors may have also contributed to fetal growth during this period such as increased pregravid weight, increased height, decreased smoking during pregnancy, and increased participation in prenatal care programs [Kim *et al* 1992].

More recently, however, there has been a growing concern about pregnancy complications associated with excessive weight gain. Such complications include hypertension, gestational diabetes, and operative delivery [Varma 1984, Shepard *et al* 1986, Dawes & Grudzinskas 1991a, Hytten & Chamberlain 1991], preterm delivery [Wen *et al* 1990a], fetal macrosomia [Boyd 1983, Hogue *et al* 1987], as well as postpartum obesity [Parker 1994, Wolfe & Gross 1994]. The risks of fetal and neonatal deaths may also increase at higher weight gains. In the 1959-65 Collaborative Perinatal Project, Naeye (1979) analyzed 53,518 pregnancies across the US and showed that such risks increased at both lower and higher extremes of weight gain depending on maternal weight status. The lowest mortality rates occurred at weight gains of 7, 9 and 13.5 kg among overweight, normal weight, and underweight mothers respectively. Similar results were obtained by Taffel (1986) using data from the 1980 US National Natality Survey. The effect of pregnancy weight gain on maternal postpartum weight retention will be reviewed further in Chapter 2.

In addition to gestational weight gain and dietary intake, **maternal size** is an important indicator of maternal reserves at conception and serves as a basis for additional growth in maternal tissues. Pregravid maternal size is reflected by two components: (a) height and frame size, and (b) weight status for a given height and frame size [Hunt & Groff 1990]. **Weight status**, has been traditionally expressed as the ratio of observed weight over standard weight for height and

frame size as derived from the tables of the Metropolitan Life Insurance Company (MLI) [MLI 1959, 1983]. The two extremes of pregravid weight status are implicated in higher pregnancy risks. Whereas underweight women (<90% of standard weight) are more likely to have smaller infants, overweight women (>120% of standard weight) have higher risks of fetal macrosomia than normal-weight women (90-120% of standard weight) [Mitchell & Lerner 1989a, Naeye 1990, Larsen *et al* 1990, Wen *et al* 1990a]. **Maternal height** is positively associated with infant birth weight independent of other maternal characteristics [Thomson 1971, Niswander & Jackson 1974, Wen *et al* 1990a], but this factor cannot be modified except possibly over a generation.

Other **modifiable factors** reported to influence fetal growth are those related to maternal life style. They include maternal cigarette smoking, alcohol consumption, and physical exercise. These are briefly reviewed below.

Cigarette smoking is the risk factor reported to have by far the strongest effect in developed countries on retarding fetal growth [Johnston 1981, Brooke *et al* 1989, Secher *et al* 1990, Wen *et al* 1990a]. The independent effect of smoking on reducing birth weight has been estimated to range from 142 g [Abell *et al* 1991] to 224 g [Ash *et al* 1989]. Cigarette smoking is of particular concern in developed countries due to its high prevalence as 25% of Canadian and US women of reproductive age report regular smoking [DHHS 1989a, HWC 1988 & 1989]. Although some of these women stop smoking during pregnancy, approximately 20% of all pregnant women continue to smoke after the first trimester [DHHS 1993, Stewart *et al* 1995, Health Canada 1995]. Smoking is also reported to increase perinatal mortality independent of its effect on reducing birth weight [Wilcox 1993]. This determinant is reviewed in more detail in Chapter 2.

Alcohol is recognized as a potent teratogen in humans [Streissguth 1986]. Moderate alcohol consumption is reported to be associated with reduced infant birth weight [Wright *et al* 1983, Marbury *et al* 1983, Streissguth 1986, Walpole *et al* 1990, Shu *et al* 1995, Hannigan *et al* 1995]. Alcohol abuse leads to fetal alcohol syndrome which is characterised by fetal growth retardation, distinct facial anomalies, and mental deficiency [Rosett 1980, Abel 1984]. The effect of alcohol consumption may be confounded since alcohol drinkers are also more likely to smoke [Van Den Burg 1977, Streissguth 1983, DiFranza & Guerrera 1990], and have a higher tendency for drug abuse [Hingson *et al* 1982]. Peacock *et al* (1990b), and Shu *et al* (1995) reported additive effects of smoking and alcohol consumption in reducing infant birth weight. Based on three controlled studies, Kramer (1987) estimated a sample-size weighted reduction of 155 g in infant birth weight due to maternal consumption of ≥2 drinks per day. This effect could be due in part to caloric replacement of alcohol with reduced overall dietary intake [Sokol *et al* 1980, 1981], or to impairment of placental transport of certain amino acids and other micronutrients to the fetus [Henderson *et al* 1981, Lin 1981].

Physical exercise during pregnancy is reported to have either a negative, a positive or no impact at all on pregnancy outcome, depending on frequency, duration and intensity. On one hand, strenuous physical activity has been linked to increased risks of premature labour and LBW [Clapp & Capeless 1990, Homer *et al* 1990, Bell et 1995]. On the other hand, moderate exercise and/or walking has been credited for fewer labour complications and prevention of excess weight gain [Clapp & Dickstein 1984, Wolfe *et al* 1989, Jarski & Trippet 1990, Clapp *et al* 1992, Artal 1992, Henriksen *et al* 1995]. Mothers who remained physically active during pregnancy were reported in two studies to have a higher birth weight than those with low activity levels [Erkkola 1976, Hall & Kaufman 1987]. Other studies report no impact of physical activity on infant birth weight. A randomized experimental study of

141 women by Kulpa *et al* (1987) reported that the number of sessions of aerobic exercise per week was not related to birth weight or gestational length. Klebanoff *et al* (1990) studied a much larger cohort of 7,101 women, and found that physical activity, either in the form of work or aerobic exercise, was not independently associated with birth weight or gestational age. In a meta-analysis of 18 studies (total n=2,341), Lokey *et al* (1991) showed that although more frequently exercising mothers were thinner by 5.1 kg, they had similar gestational length, pregnancy weight gain and infant birth weight to sedentary mothers after controlling for height and age. In general, available evidence suggests that moderate exercise during pregnancy would have either a favourable effect or no effect on pregnancy outcome [Clapp 1994].

1.1.3 Non-modifiable determinants

In addition to the modifiable factors reviewed above, the main non-modifiable determinants of birth outcome include maternal medical risk conditions, age, parity, ethnic origin, socioeconomic status, infant gender, and gestational length [Kramer 1987, IOM 1990]. These are briefly reviewed below.

Medical risk conditions and health status may influence fetal growth in different ways. Severe chronic hypertension and renal disease may limit fetal growth by interfering with the supply of nutrients and their clearance from the fetus and placenta [Hytten & Thomson 1970, Willis & Sharp 1982, Callan & Witter 1990]. Goldenberg *et al* (1992) reported increased rates of LBW with both low and high maternal blood pressure. In contrast, diabetic mothers tend to have larger babies [Jovanovic-Peterson & Peterson 1988, 1990, Catalano *et al* 1993]. Past obstetric history often predicts present obstetric performance, *e.g.* a woman who previously

experienced a fetal loss or LBW infant is more likely to encounter similar risks in subsequent pregnancies [Lekea-Karanika & Tzoumaka-Bakoula 1994, Wen *et al* 1990a].

Maternal age has a curvilinear relationship with infant birth weight [Lee *et al* 1988, Wen *et al* 1990a, DHHS 1994]. Very young mothers who are still growing have a higher risk of LBW infants than adults independent of socio-demographic factors, even if maternal weight at term is appropriate for height [Haick & Lederman 1988, Muscati *et al* 1988, Scholl *et al* 1994, Unfer *et al* 1995, Fraser *et al* 1995]. The shorter the time interval between menarche and conception, the higher is the risk of LBW [Elster 1984, Fraser *et al* 1995]. It has been suggested that part of the effect of young age is due to the over-representation of risk factors among adolescents, such as poor eating habits and inadequate prenatal care [Johnston *et al* 1991, Gutierrez & King 1993]. Older mothers ≥40 y are also reported to have an increased incidence of LBW [Spellacy *et al* 1986, Milner *et al* 1992, Aldous & Edmonson 1993], but after accounting for age-related medical conditions, advanced maternal age is found to have no association with LBW [Lee *et al* 1988].

Parity is strongly correlated with maternal age and this makes it difficult to distinguish between the independent effects of these two factors on infant birth weight. However, primiparous mothers have consistently smaller infants than multiparous mothers, independent of maternal age and pregravid weight status [Murphy 1971, DaVanzo *et al* 1989, Wen *et al* 1990a, Cnattinigius 1993], despite having higher gestational weight gain [Dawes & Grudzinskas 1991b]. Furthermore, the risk of LBW is reported to increase with five pregnancies or more, regardless of maternal age [Kirz *et al* 1985, Ales *et al* 1990].

Ethnic origin is speculated to exert a direct genetic influence on infant birth weight in addition to its indirect influence through maternal size and nutritional and health status [Wilcox *et al* 1993, Wen *et al* 1990a, 1995a]. The mean values for birth weight are highest in American Indians (3.6 kg), and smallest in Asian Indians (2.9 kg) [Hytten & Chamberlain 1991]. Women of Asian Indian origin, whether living in India or in Europe tend to have smaller babies than European women of the same weight and height [Viegas *et al* 1987].

Socioeconomic status is usually defined in terms of income, education, occupation and marital status. In general, the lower the socioeconomic status, the higher is the risk of LBW [Brooke *et al* 1989, de Sanjose & Roman 1991, Jonas *et al* 1992], although at least part of this effect may be explained by differences in other determinants of fetal growth [Wen *et al* 1990a, Hemminki *et al* 1992]. In a representative sample of US births from the 1988 National Maternal and Infant Health Survey, Parker *et al* (1994) found a statistically significant positive association between infant birth weight and socioeconomic indicators (particularly education) independent of race, parity, maternal height and age. The reduction in maternal weight gain and infant birth weight among mothers of low socioeconomic status have been attributed in part to the mediation of maternal psycho-social stress in terms of high trait anxiety, poor self attitude or inadequate social support network [Edwards *et al* 1994, Hickey *et al* 1995] .

Infant gender is one expression of the genetic contribution to fetal growth pattern. On average, male infants are 140-150 g heavier than females at birth, although there is wide overlap in birth weight distribution [Thomson *et al* 1968, Arbuckle *et al* 1993, Amini *et al* 1994]. Gender differences in fetal size are negligible until about 33 weeks gestation, after which the weight increase of males exceeds that of females, presumably under the influence of the infant sex hormones [Nacye

1979]. The first known study of diet and pregnancy by Prochownick (1901) reported that restricted food intake throughout pregnancy reduced birth weight more in females (~500 g) than in males (~400 g). More recently, controlled dietary supplementation trials among under-nourished women in Columbia [Herrera *et al* 1980] and Taiwan [Adair & Pollit 1985] resulted in increased maternal weight gain and infant birth weight only with male infants. The relationship of infant gender to maternal dietary intake and weight gain during pregnancy seems to warrant further examination.

Gestational length (or gestational age) is the length of time from conception to delivery, and is the most significant biological determinant of birth weight [Amini *et al* 1994]. It has a special role in being both an outcome of pregnancy with regards to neonatal maturity, as well as a strong determinant of both maternal weight gain and infant birth weight [Hytten & Leitch 1971, Ash *et al* 1989]. For this reason, gestational length can confound the relationship between maternal weight gain and infant birth weight by making association appear stronger than what it actually is; *i.e.* longer gestation involves higher weight gain and higher birth weight.

1.2 Summary of postpartum weight retention determinants

The contribution of modifiable or non-modifiable factors to pregnancy outcome has been studied mainly with respect to fetal growth, and very little emphasis has been given to the maternal outcome in terms of postpartum weight retention. Weight gain during pregnancy is the major contributor to postpartum weight retention [Forsum *et al* 1988, Öhlin & Rössner 1990], and excessive total weight gain during pregnancy is reported to increase the risk of postpartum obesity [Parker & Abrams 1993, Keppel & Taffel 1993]. Total weight gain, however, conceals differences in the rate of weight gain at different stages of pregnancy and these differences can have an impact on fetal growth [Lawton *et al* 1988], and possibly postpartum weight retention. However, the effect of the timing of weight gain on postpartum weight retention has not been researched so far.

Other factors known to increase postpartum weight retention are lower socioeconomic status [Parker & Abrams 1993], and single parity as more weight is retained with the first pregnancy than after subsequent pregnancies [Smith *et al* 1994]. Chapter 2 will review the determinants of postpartum weight retention in more detail.

1.3 Rationale and objectives

The above review summarized literature findings on individual determinants of pregnancy outcome. Most reviewed studies have examined the independent effect of each determinant either on neonatal or maternal outcome of pregnancy and emphasized infant birth weight as the outcome of main concern. No studies have yet explored the interrelation among different determinants in affecting both the mother and her infant at the same time.

The main objective of this thesis is to address the need for promoting fetal growth without incurring unnecessary maternal fat accretion. Measures to promote fetal growth by increasing dietary energy intake would inadvertently increase maternal fat accretion. In this context, an optimum pregnancy outcome represents a balance between reducing the two risks of small-for-gestational-age infant, and maternal postpartum obesity. Achieving such a balance could also be conducive to a reduction in other risks associated with excessive weight gain, such as fetal macrosomia (large-for-gestational-age infant), gestational diabetes, pregnancy induced hypertension, cesarean section or preterm delivery. Attaining such a balance may require a proper management of pertinent modifiable factors, the most important of which are dietary intake, pregravid weight status, amount and timing of weight gain, and cigarette smoking [Kramer 1987, Wen *et al* 1990a]. Therefore, the combined impact of these interrelated factors on both neonatal and maternal pregnancy outcomes needs to be studied with a proper control of other confounding variables.

The major hypothesis central to this thesis is as follows. The modifiable maternal factors (dietary intake, pregravid weight status, amount and timing of

weight gain, and cigarette smoking) interrelate with each other in influencing the balance between fetal growth and maternal fat accretion, for similar values of non-modifiable factors. This thesis will give a special emphasis to the effect of maternal cigarette smoking in view of (a) its strong negative impact on fetal growth, (b) its high prevalence among Canadian pregnant women, and (c) its suspected interrelation with maternal nutrition and weight parameters in influencing pregnancy outcome.

2. MODIFIABLE DETERMINANTS OF NEONATAL AND MATERNAL OUTCOMES

Chapter 1 summarized the effect of modifiable and non-modifiable determinants of maternal and neonatal outcomes of pregnancy. The key modifiable determinants identified in Chapter 1 included maternal diet, maternal size at conception, amount and timing of gestational weight gain, and cigarette smoking, which will be the primary focus of the research work of this thesis. The following is a critical review of the literature with respect to the effect of these four determinants on pregnancy outcome. Included in this review are only studies that adequately controlled for potential confounders in exploring the effect of any individual determinant. In experimental studies this requires random assignment of subjects into treatment and control groups. In observational studies, such control is achieved through statistical methods by including the confounders in multivariate analyses. Reported effects are considered to be statistically significant when $p < 0.05$.

As the main research question is concerned with the balance between fetal growth and maternal fat accretion, pregnancy outcomes of interest are as follows:

(a) neonatal outcomes in terms of infant birth weight, length and head circumference, or the risks of small-for-gestational-age (SGA) or large-for-gestational-age (LGA) infants; and

(b) maternal outcomes in terms of fat accretion, postpartum weight retention or the risk of postpartum obesity.

The risks of preterm delivery, maternal and neonatal mortality or morbidity will not be discussed. This review is restricted to adult pregnancies, because in young growing adolescents it is difficult to distinguish between postpartum weight retention due to linear growth and due to fat accretion. The focus will be on studies of term singleton pregnancies with no underlying chronic illnesses, or substance abuse except for cigarette smoking.

2.1 Maternal energy intake and fetal growth

The relationship of dietary energy intake during pregnancy to gestational weight gain and fetal growth has been the subject of considerable controversy over the last several decades. This section reviews the relative importance of dietary energy intake to gestational weight gain and fetal growth.

Evidence from secular trends suggests that increased dietary energy intake contributes to a higher maternal weight gain and infant birth weight [Abrams 1994]. In the 1960's, clinicians used to advise for dietary or weight gain restriction to prevent pregnancy complications and related maternal mortality. With an increasing concern for preventing low birth weight, clinicians began to encourage liberal food intake during the 1970's and 1980's. Such a shift in clinical advice was paralleled by noticeable increases in maternal weight gain and infant birth weight [Arbuckle & Sherman 1989, Amini *et al* 1994].

Evidence from prenatal intervention or supplementation trials, however, shows that increasing energy intake during pregnancy does not increase infant birth weight among all groups of women. A large number of studies in either

developed or developing countries showed no clear effect of increased energy intake during pregnancy on increasing birth weight in comparison to control groups with low-energy supplements [Adams *et al* 1978, Rush *et al* 1980, Kardjati *et al* 1988, Rush *et al* 1988]. Kafatos *et al* (1989) found that pregnant Greek women receiving nutritional advice had significantly higher energy intake by ~150 kcal/d (630 kJ/d) in comparison to controls, but the increases in total maternal weight gain, and in infant birth weight were not significant.

In developing countries, supplementation was beneficial mostly when mothers came from poor families and chronically lacked sufficient nutritional reserves. Examples of successful supplementation trials in developing countries are those done in urban Columbia [Herrera *et al* 1980], rural Guatemala [Delgado *et al* 1982], Indian women from a New Delhi slum area [Bhatnagar *et al* 1983], rural Taiwan [McDonald *et al* 1981, Adair *et al* 1983], black Zulu women in South Africa [Ross 1985], rural Bangkok [Tontisirin *et al* 1986], rural Gambia (during wet season only) [Prentice 1987], and urban Chile [Mardones-Santander *et al* 1988]. In these trials, customary intakes averaged approximately 1,500 kcal/d (13,376 kJ/d), net supplements ranged from 118 to 511 kcal/d (493 to 2,136 kJ/d), and mean increments in birth weight in supplemented groups ranged between 50 and 321 g.

In developed countries, infant birth weight increased with dietary supplementation mostly among underweight women and those identified at risk for delivering LBW infants. For example in the Montreal Diet Dispensary program where food and advice are given, infant birth weight was higher than that of matched controls from the US, only among underweight mothers [Rush *et al* 1981]. In the randomized clinical trial in Birmingham by Viegas *et al* (1982b), crude birth weight increased by 230 g with protein-energy dietary

supplementation only among the subgroup of 12 Asian mothers identified to be nutritionally at risk by showing triceps increments ≤20 µm/week between 18 and 20 weeks of gestation. In the New York trial by Rush *et al* (1980) and the Oklahoma trial by Metcoff *et al* (1985), birth weight of infants born to heavily smoking mothers increased with supplementation, but infants born to nonsmokers showed no improvement. Another successful randomized clinical trial in Aberdeen by Campbell-Brown (1983a) showed that balanced protein-energy supplementation among 90 primigravid women diagnosed for the risk of delivering LBW infants marginally increased infant birth weight by 37 g.

A major prenatal program in the US, the Special Supplemental Food Program for Women, Infants and Children (WIC) offered a combination of food supplementation, nutrition education and health care services. An analysis of 54 evaluations of WIC by the US Government Accounting Office (1984) showed only a modest birth weight increase of <50 g as compared to control groups who did not receive program-related services within the same region. Only one region (Massachusetts) reported more substantial increase in birth weight by 107 g among 418 WIC participants compared to 418 non-participants [Kennedy & Kotelchuk 1984]. In a subsequent evaluation of the WIC Program, Rush *et al* (1988) conducted a longitudinal study of 2,708 WIC participants and found a statistically significant increase in maternal weight gain but an insignificant increase (of 7 g) in birth weight of their infants in comparison to 497 controls receiving prenatal care outside the WIC program. This evaluation, however, may have suffered from major differences between the socioeconomic characteristics of WIC participants and the control groups. The control groups were more often white, married with higher income and occupational status. Higher birth weight is known to be associated with both white race [Taffel 1986, DHHS 1990] and high socioeconomic status [Brooke *et al* 1989]. Although cigarette

smoking is the strongest known determinant of low infant birth weight due to both shortened gestational age and retarded fetal growth, differences in smoking behaviour between the two groups have not been reported, whereas such differences could strongly confound the evaluation.

The inconsistent findings of supplementation studies between populations with widely different characteristics may be explained in part by the lack of adequate control in such studies. Kramer (1993) identified only 12 properly controlled supplementation studies in the UK, US and five developing countries for his meta-analysis. He estimated the sample-size weighted difference in birth weight due to balanced protein and energy supplementation as +30 g with 95% confidence interval of +1 to +58 g.

Not all of the supplementation studies examined the effect of diet on gestational weight gain, but of those which did, some indicated possible direct effect of dietary intake on birth weight bypassing maternal weight gain. For example, Prentice *et al* (1987) found that balanced protein-energy supplementation in Gambian women led to bigger infants by 225 g in comparison to non-supplemented controls, but the observed increase in maternal weight gain was not statistically significant. Similar effects were found in Taiwanese women, but with smaller increase in birth weight [McDonald *et al* 1981]. In a randomized supplementation trial among Zulu women in South Africa, Ross *et al* (1985) found that those women offered low bulk (milk and maize flour) supplements (n=31) consumed more food at home and gave birth to heavier infants by 294 g than those offered isocaloric high bulk (beans and maize) supplements (n=31), but maternal weight gain was not significantly different between the two groups. The direct effect of supplementation on birth weight bypassing maternal weight gain may be explained in part by the small amount of

extra weight of the infant in a relation to a larger maternal weight gain that in turn is highly variable. Another explanation is the beneficial effect of supplementation on improving overall dietary quality (both micro- and macro-nutrients) which is apparently crucial in underfed populations for enhancing fetal growth.

The importance of **micro-nutrients** was demonstrated by Mardones-Santander *et al* (1988) who showed that Chilean underweight pregnant women given a supplement fortified with vitamins and minerals, gave birth to heavier infants by 63 g, as compared to those given an unfortified supplement with similar energy content (~500 kcal/d, or 2,090 kJ/d). The importance of a proper balance of **macro-nutrients** was evident from the study by Rush *et al* (1980) who found that high protein supplementation (34% of energy) in poor black women from New York, did not enhance infant birth weight and even had a slight but statistically non-significant negative effect (−41 g). Picone & Allen (1984) also observed in a retrospective analysis that women who consumed ad libitum diets with high protein content (17.5-25% of energy, n=30) had shorter gestation and smaller neonatal head circumference than those consuming diets with normal protein content (11.7%-17.4% of energy, n=30). In the latter study, a multiple regression analysis which controlled for energy intake showed a negative relationship between protein-to-energy ratio and the two pregnancy outcomes.

Observational studies of non-supplemented women were also not consistent in showing an association between increased food intake and higher maternal weight gains. For example, the two studies by Langhoff-Roos *et al* (1987b) and by Papoz *et al* (1982) reported that energy intake was not related to total maternal weight gain during pregnancy. In contrast, Haworth *et al* (1980) reported a

correlation coefficient of 0.16 between these two variables. Picone *et al* (1982a) found a relatively stronger correlation coefficient of 0.44 between dietary energy intake and weight gain, but this occurred only in nonsmoking women. Siega-Riz & Adair (1993) found that Philippine women in the highest tertile of energy intake gained 0.5 kg more than those consuming less energy.

Two major conclusions may be derived from the above evidence on the relationship among dietary supplementation, maternal weight gain, and fetal growth. First, in developing countries, dietary supplementation increases birth weight of only those infants born to chronically under-nourished women. Second, in developed countries, the benefit of supplementation is limited to underweight women, and results in only a marginal increase in infant birth weight. Third, the increase in birth weight with dietary supplementation can occur with or without a change in weight gain. There may also be a greater effect of supplementation on gestational weight gained by smokers than nonsmokers.

In addition to the concern about the needs of under-nourished women to receive dietary supplementation during pregnancy, the health profession is also concerned about establishing standard dietary requirements for pregnancy in healthy well-nourished populations. Two approaches for establishing such requirements have been considered: (a) estimating the additional energy and protein requirements of pregnancy using the factorial method, and (b) observing ad libitum dietary intake during pregnancy of normal healthy mothers giving birth to normal weight infants.

The factorial method estimates energy requirement as a total of 80,000-85,000 kcal (334-355 MJ) or an average of ~300 kcal/d (1,250 kJ/d)

throughout pregnancy [FAO 1973, Hytten & Chamberlain 1980,1991]. These estimates are obtained by calculating the average cumulative cost of fetal and maternal tissue accretion, plus the additional basal metabolic cost of supporting such tissue accretion. The calculations are based on the assumption that the metabolic cost per kg of body weight during pregnancy is similar to that prior to pregnancy, and did not take into account maternal pregravid weight status which may affect the metabolic rate.

Observed increases in dietary energy intake during pregnancy among well-nourished women were consistently smaller than the above estimates of energy requirements. Longitudinal studies of normal populations in developed countries with healthy pregnancy outcome, showed a very wide variation in dietary changes during pregnancy. The observed pattern of dietary changes during pregnancy show an increase during the first half, followed by a decline during the second half of gestation [Papiernik *et al* 1981, Papoz *et al* 1981 & 1982]. Only slight average increases of 50-100 kcal/d (210-420 kJ/d) in energy intake throughout pregnancy were reported [Durnin *et al* 1985 & 1991, Fidanza & Fidanza 1986, Schofield *et al* 1987, van Raaij *et al* 1986 & 1987, Truswell & Allen 1988]. In these studies, intake prior to pregnancy was estimated from dietary history recalled by the mother, while intake during pregnancy was estimated from 24-hour dietary recall or records. More recently, Murphy & Abrams (1993) reported a higher average increase in energy intake of 260 kcal/d (1,090 kJ/d) in 528 US women, but their average pre-pregnancy intake of ~1,770 kcal/d (7,400 kJ/d) was lower than the RDA standard [NRC 1989]. The authors measured energy intake from 24-hour dietary recall every two months before and during pregnancy. All of the above cited dietary studies reported very high variability in the change in energy intake from the non-pregnant state to pregnancy.

It is difficult to evaluate the role of diet in supporting fetal growth without considering possible changes in energy expenditure which will also contribute to the energy balance. The observed high variability in energy intake during pregnancy may imply a similarly high variability in energy expenditure. The issue of energy intake versus energy expenditure is reviewed in the following section.

2.2 Energy balance during pregnancy

Energy balance during pregnancy determines the amount of energy available for fetal growth. The findings that measured energy intake [Durnin *et al* 1985] are substantially lower than estimated requirements for pregnancy [Hytten & Chamberlain 1991] point to the possibility of some energy conservation mechanisms, such as possible decreases in basal metabolic rate (BMR), physical activity or thermogenesis. Because both BMR and energy cost of physical activity are expected to increase with the weight gain of pregnancy, energy conservation can result only from a possible reduction in physical activity, thermogenesis and/or BMR per kg of body weight as may be induced by hormonal changes during pregnancy.

Changes in total energy expenditure (BMR, thermogenesis and activity) during pregnancy appear to vary widely among individuals within the same population. Goldberg *et al* (1993) measured total energy expenditure using the doubly labelled water method among 12 UK women before pregnancy and at 6-week intervals from 6 to 36 weeks of gestation. They found that the total energy expenditure in pregnancy relative to pre-pregnancy baseline ranged from negative −14,600 kcal (−61 MJ) to +207,900 kcal (+869 MJ) with an average

of 58,100±66,700 kcal (243±279 MJ). In other words, the actual energy expenditure in pregnancy can either exceed the theoretical estimates or even be negative among different individuals. The question is which component of energy expenditure contributes to such wide variability.

A change in the energy cost of physical activity during pregnancy is not well established. Although a decrease in physical activity as pregnancy advances is observed [McNeil & Payne 1985, Durnin *et al* 1986, Schofield *et al* 1987, van Raaij *et al* 1986, Tauzon *et al* 1987, Forsum *et al* 1992], the overall cost of activity is not necessarily reduced when maternal body weight increases [Blackburn & Galloway 1976, Durnin 1987 & 1991]. A change in thermogenic effect of food during pregnancy has not been consistently observed among well-nourished women. A longitudinal study by Illingworth *et al* (1987b) reported a significant reduction by 28% in the metabolic response to food during the second trimester compared to postpartum values among 7 UK women, but a non-significant reduction by 15% in the third trimester. In contrast, studies by Nagy & King (1984) and by Bronstein *et al* (1995) found no cross-sectional difference in the thermogenic response to food between US pregnant women and non-pregnant controls. Two recent longitudinal studies reported no substantial reduction in the thermic effect of food during pregnancy in well-nourished women from Holland (n=27) [Spaaij *et al* 1994] and from India (n=18) [Piers *et al* 1995]. De Groot *et al* (1994) used a respiration chamber to determine complete energy balance in 12 healthy Dutch women before conception and in weeks 12, 23 and 34 of pregnancy. They calculated body composition and estimated metabolizable energy of food intake by analysis of energy in all food items, feces and urine. The authors reported that neither digestion nor metabolism of dietary intake changed significantly during pregnancy from before pregnancy.

The major change in energy expenditure during pregnancy has been attributed to changes in BMR. Poppitt *et al* (1994) performed a meta-analysis of data on BMR and on fat deposition in 360 pregnancies from 10 longitudinal studies in 6 countries; the Netherlands [van Raaij *et al* 1987, Spaaij 1993], Sweden [Forsum *et al* 1988], Scotland [Durnin 1987], England [Goldberg *et al* 1993], the Philippines [Tauzon *et al* 1987], Thailand [Thongprasert *et al* 1986] and the Gambia [Lawrence *et al* 1987, Poppitt *et al* 1993]. In these studies, BMR was assessed throughout pregnancy by measuring O_2 consumption and CO_2 production using either the Douglas bag method or ventilated hood system, except for the English study which used whole body indirect calorimetry. In Dutch, Swedish, English and Scottish pregnant women, BMR started to increase from conception. In contrast, Philippine and Thai women began to increase their BMR only after 12 weeks into pregnancy. Chronically under-nourished Gambian women, on the other hand, decreased their BMR immediately after conception followed by gradual rise to reach pre-pregnancy baseline levels by 30 weeks of gestation. In this meta-analysis the authors calculated the total basal metabolic cost of pregnancy as the net cumulative change in BMR throughout pregnancy (ΔBMR) relative to a pre-pregnancy baseline. In the under-nourished Gambian women who did not receive dietary supplementation, ΔBMR was negative −10,800 kcal (−45 MJ), implying a degree of energy conservation with under-nutrition. In the same population, however, those women who were supplemented had a positive ΔBMR of +1,000 kcal (4 MJ). In contrast, the highest ΔBMR of +50,200 kcal (210 MJ) was observed among the well-nourished Swedish women. In another study, King *et al* (1994) reported that ΔBMR among a group of 15 US women was highly variable ranging from 3,100 to 78,500 kcal (13 to 328 MJ), and averaged 29,700±19,900 kcal (124±83 MJ) giving a 67% coefficient of variation.

In the above cited reports of Poppitt *et al* (1994) and King *et al* (1994), metabolic pregnancy cost (ΔBMR) was positively correlated with maternal pregravid percent fatness. Despite the use of different techniques in assessing maternal body fat content (such as skin-fold thickness, densitometry, total body potassium or deuterium dilution) in the two reports, this correlation was consistent. Such correlation implies that BMR changes during pregnancy respond to maternal fat reserves which reflect maternal energy status at conception. Another possible explanation of the high variability in ΔBMR is the fact that well-fed mothers have relatively higher weight gain and larger infants, both of which increase ΔBMR. It seems that when maternal reserves are limited, energy conservation early in pregnancy would dominate, to allow building up reserves for possible later mobilization, as demands for both BMR and fetal growth are at a peak. However, when maternal reserves are adequate at conception and a woman is well nourished during pregnancy, she will not need to increase her fat reserves early in pregnancy to the same extent as an under-nourished woman and no energy conservation may take place.

Maternal weight status at conception plays an important role in energy balance by its influence not only on energy expenditure, but also on dietary energy intake. Papiernik *et al* (1981) studied 202 French women and observed that energy intake at gestational week 30 (as determined by one-day records) was higher than that at conception (determined by dietary history) among underweight and normal weight women having AGA infants, but there was no change for overweight women. Papoz *et al* (1981) assessed dietary behaviour in 537 French women, using 24-hour dietary recall at conception, three, six, and nine months into pregnancy. They observed increased intakes from conception until 6 months among underweight and normal-weight women, with higher dietary increase among the underweight who gained 12.2 kg. In contrast,

overweight women continued to decrease their intake from conception until term, but they still gained 11.2 kg. The considerable weight gain by overweight women cannot be reconciled with the reported decrease in energy intake and the expected higher BMR expenditure. The data used in the above two studies were from the 1970's when advice for food restriction during pregnancy was not uncommon, especially for overweight women who may choose to restrict (or perhaps under-report) their intake after experiencing a rapid weight gain in pregnancy.

In general, obtaining accurate measurement of ad libitum dietary intake has its inherent methodological problems, especially when assessing energy intake in mothers of different maternal weight status. Goldberg *et al* (1993) showed that overweight pregnant women had a greater tendency than normal-weight women to under-report their food intake relative to their measured energy expenditure (used as a proxy for actual intake). They determined total energy expenditure by adding energy expenditure measured under controlled conditions (*e.g.* by indirect calorimetry), to theoretically estimated energy cost of tissue accretion. Other studies suggested that the degree of under-estimation were more pronounced with higher actual intake or after more than one assessment repeated for the same subject [Schoeller 1990, Forsum *et al* 1992], thus leading to an under-estimation of the increases in dietary intake during pregnancy. Another source of error in measuring dietary intake, is the increased variability during pregnancy due to concerns about weight gain and feelings of nausea and other non-specific changes in patterns of intake [Murphy & Abrams 1993]. Large differences in reported intakes may also result from the different methods to measure intake, including dietary record, recall or history [Garn *et al* 1976, Beaton *et al* 1983, Sampson 1985]. Furthermore, measuring dietary intake precisely is

problematic and tedious over the nine months of pregnancy during which actual intake changes rapidly [Durnin 1987, 1991].

The inherent complexity in dietary measurement techniques and other problems in dietary assessment during pregnancy, together with the very wide variation in energy expenditure (BMR and physical activity), make it difficult to accurately determine energy balance during pregnancy. The true variable of interest is how much energy is available for fetal growth, which is a very small proportion of maternal dietary intake [Durnin 1985]. Because of these concerns, gestational weight gain may provide a more reliable indicator of the energy available for fetal growth, than energy intake during pregnancy.

2.3 Maternal weight gain and infant birth weight

Maternal weight gain reflects not only energy balance during pregnancy, but also other factors, such as expanded maternal plasma volume, which influence fetal growth. Thus weight gain has a closer relationship than energy intake with birth weight, and it is simpler to set weight gain guidelines according to weight status where the effect of energy balance is already reflected in weight gain, provided no excess fluid retention (edema) occurs. Weight gain is also easier to monitor than dietary intake for clinical evaluation of pregnancy performance. This section reviews the reported effects of gestational weight gain on infant birth weight from its three aspects of total amount, timing and composition throughout gestation.

2.3.1 Total amount of weight gain

The simplest way of describing weight gain and studying its impact on birth weight is by its total amount from conception to term. The relationship between the amount of maternal weight gain and infant birth weight is well indicated by secular trends of increasing average gestational weight gain from ~10 kg in the 1960's to ~15 kg in the 1980's, accompanied by ~120 g increase in birth weight from 3,300 to 3,420 g [Abrams 1994, IOM 1990]. This reflects approximately 24 g increase in birth weight for every 1 kg increase in weight gain. Consistent with these secular trends, longitudinal studies reported that higher gestational weight gains were associated with higher birth weights [Gormican *et al* 1980, Luke *et al* 1981, Johnson *et al* 1992, Lawrence *et al* 1991, Johnston *et al* 1991, Cogswell *et al* 1995] and lower risk of low birth weight [Parker & Abrams 1992, Hickey *et al* 1993]. Vobecky *et al* (1983) found that infants of Canadian women with total gestational weight gain >9 kg had a higher mean birth weight by 185 g than those with weight gain <9 kg. However, in this comparison no distinction was made between different pregravid weight or smoking status categories. In well-controlled studies of US pregnant women, the average magnitude of the independent effect of weight gain on birth weight ranged from 19 to 21 g/kg [Niswander & Jackson 1974, Abrams & Laros 1986, Kramer 1987]. A larger effect of 31.3 g/kg was observed by Villar *et al* (1992) in thin Guatemalan women. These different effects may indicate an interaction between pregravid weight status and gestational weight gain, as will be discussed further in Section 2.4.

The strength of the reported associations is due in part to the fact that the total amount of weight gain includes birth weight. Kleinman *et al* (1990) used data from the 1980 US National Natality Survey to study the effect of net weight gain (total weight gain minus birth weight). They found a statistically

significant association, but at a reduced magnitude of 13 g increment in birth weight per kg of net weight gain as compared to 20 g per kg of total weight gain. The net weight gain includes maternal tissue accretion during pregnancy, which contributes to the large variability in total weight gain observed among well-nourished women giving birth to AGA infants (3-4 kg at term) [Hytten & Chamberlain 1991]. Coefficients of variation around 33-35% for weight gain are typical among mothers of AGA infants in Western countries [Abrams & Laros 1986, Hytten & Chamberlain 1991]. Part of this variability can be explained by differences in maternal weight status at conception [Siega-Riz *et al* 1994, Copper *et al* 1995].

The most recent recommendations by the US Institute of Medicine [IOM 1990] for the total amount of weight gain take into account such large variability and specify a relatively wide range of weight gain for each maternal pregravid weight for height category, as given in the table below.

Pregravid weight status category	Total weight gain	Mid-point
Underweight (BMI < 19.8)	12.5 to 18.0 kg	15.3 kg
Normal weight (BMI = 19.8 to 26)	11.5 to 16.0 kg	13.8 kg
Overweight (BMI > 26 to 29)	7.0 to 11.5 kg	9.3 kg
Obese (BMI > 29)	at least 6.0 kg	

In this table, however, no upper weight gain limit for obese women is specified. In the absence of definitive data regarding optimal weight gains, these recommendations were based on results of observational studies on weight gain distribution among mothers from different weight status categories of adequate birth weight infants (3-4 kg) with gestational age of 39-41 weeks [Ounsted & Scott 1981, Taffel 1986, Abrams & Laros 1986, Brown *et al* 1981 & 1986, Scholl *et al* 1988, Mitchell & Lerner 1989b, Kleinman 1990].

Subsequent to these recommendations, US surveys show that the weight gain of more than half of all pregnant women do not fall within the IOM recommended ranges, relative to their pregravid weight status. For example, 32% of low income women in Birmingham, Alabama gained less than the recommended amount for their weight status and 30% gained more [Hickey *et al* 1993]. In contrast, 23% of middle class women in San Francisco gained less than the recommended amounts and 34% gained more [Parker & Abrams 1992]. A larger proportion of overweight women (>50%) are reported to gain more than the IOM recommendations [Siega-Riz *et al* 1994]. These findings suggest that in order not to exceed the IOM recommendations, >30% of all pregnant women would have to reduce their weight gain. In this respect, it would be important to know at which stage of gestation, women of a given weight status should apply such a restriction to optimize maternal and neonatal outcomes of pregnancy. It is known that the division of gestational weight gain between maternal and fetal tissues, occurs at a varying degree throughout pregnancy [Hytten & Chamberlain 1991]. The question is whether such a division could be optimized by paying a closer attention to the timing and composition of weight gain. These two aspects of weight gain may impact upon maternal and fetal access to required amounts of nutrients at the right time. This subject is reviewed further in the following section.

2.3.2 Timing and composition of weight gain

Trends in maternal weight gain from conception until delivery are not linear [Dawes & Grudzinskas 1991b]. The rate of weight gain is lower before 16 weeks and after 36 weeks and peaks between 28 and 32 weeks of gestation [Dawes & Grudzinskas 1991a]. The earliest study to recognize the importance of the timing of weight gain to fetal growth, is that of Dutch Famine during the Winter of 1944-45. There, low weight gain due to dietary deprivation in the second and third trimesters had the greatest impact on reducing birth weight, length and head circumference [Stein *et al* 1975]. In a later observational study, Picone *et al* (1982b) found that birth weight was significantly associated with weight gain during the second and third trimesters but not the first. Lawton *et al* (1988) observed that among 158 healthy British women, those with SGA infants had a lower rate of weight gain (0.25 kg/wk compared to 0.49 kg/wk) between the 28^{th} and the 32^{nd} weeks, than those with AGA infants (10^{th}-90^{th} percentile). This difference was statistically significant despite no differences in pregravid weight or total weight gain. Recently, Abrams & Selvin (1995) found a higher contribution of weight gain to infant birth weight during the second trimester (33 g/kg) than the first or third trimesters (18 or 17 g/kg).

Further to its 1990 recommendations for the total amount of weight gain [IOM 1990], the IOM recommended provisional patterns of weight gain specific to maternal pregravid weight status as given in the following table.

Weight status	Trimester 1	Trimesters 2 & 3	Total weight gain
Underweight	0.17 kg/wk	0.49 kg/wk	15.3 kg
Normal weight	0.12 kg/wk	0.44 kg/wk	13.4 kg
Overweight	0.07 kg/wk	0.30 kg/wk	8.9 kg

These patterns lead to approximately the middle points of the recommendations for total weight gain. These provisional recommendations were based on old data from the UK, in the absence of data representative of the US population. In this respect, the IOM made an assumption that a representative US sample would have rates similar to those represented by most other population groups. In particular, the IOM report cites two UK studies. One study used 1950-55 data from the Aberdeen Maternity Hospital for a relatively small sample of 486 healthy women aged 20-29 and at least 160 cm tall who had no dietary restriction and delivered term infants (39-41 wk) [Hytten & Leitch 1971]. The Aberdeen data showed that the lowest incidence of preeclampsia, low birth weight and perinatal death was associated with gaining an average of 0.45 kg/wk during the second half of gestation. The other study by Thomson & Billewicz (1957) used 1949-54 data from a larger sample of 2,868 Scottish primigravid women, and reported favourable average weight gain rates as 0.42, 0.47, and 0.40 kg/wk during gestational weeks 13-20, 20-30 and 30-36 respectively.

Data on desirable patterns of weight gain in North American pregnant women are limited. Brown *et al* (1986) reported the rate of weight gain among 459 low income women who delivered infants weighing 3-4.5 kg, as 0.22, 0.52 and 0.40 kg/wk during the first, second and third trimesters respectively. Petitti *et al* (1991) reported the rates of weight gain among 162 white and black women from California with infant birth weight >3 kg, as 0.30 kg/wk and 0.48 kg/wk

during the first and second halves of pregnancy respectively. Abrams *et al* (1995) used a larger data set (n=10,418) from California and reported a weight gain pattern of 0.17, 0.56 and 0.52 kg/week during the three consecutive trimesters. These three studies made no distinction among women from different weight status groups, and the reported rates are somewhat higher than the IOM provisional recommendations given above. More research is needed before recommendations for the pattern of weight gain can be defined for US and Canadian pregnant women of different weight status categories.

Besides the pattern of maternal weight gain, its composition at different stages of pregnancy is important for supporting the changing maternal and fetal needs. Although the amount of weight gain is clinically useful in identifying some cases of abnormal progress during pregnancy, it provides only limited information on changes in body composition of an individual woman even when the amount of weight gain is close to the average. Weight gain consists of fluid, fat and fat-free mass (mainly protein and minerals), which are deposited in different rates at different gestational stages. Most of the maternal fat accretion is known to occur in the first two trimesters of pregnancy, whereas most of the fat-free mass accretion occurs during the second half of gestation [Hurley 1980]. Through measurements of body weight, total body potassium (^{40}K) or body water, and skinfold thickness, Pipe *et al* (1979) showed that maternal body fat accretion reached a plateau towards the end of the second trimester, whereas growth in lean body mass accelerated during the third trimester. Hytten & Chamberlain (1980, 1991) estimated that normal healthy pregnant women who gain an average of 12.5 kg without edema, acquire about 3.5 kg of fat, 90% of which is deposited as maternal stores. Clapp *et al* (1988) estimated fat proportion of weight gain during pregnancy, using skinfold measurements, and found that

by the fifteenth week of gestation, fat accretion accounted for most of the observed weight gain.

Fetal growth may be influenced differently by different maternal tissue changes, *i.e.* accretion of lean tissue, fat or body water. Among well-nourished women, fat accretion during pregnancy seems not to influence birth weight. Langhoff-Roos *et al* (1987a) estimated maternal fat stores and fat accretion during pregnancy from body weight and skinfold thickness, and found that infant birth weight was not correlated with maternal fat accretion among 56 Swedish mothers. Lawrence *et al* (1991) estimated the total maternal fat gain during pregnancy as the difference between maternal weight at 10 weeks gestation and that at 2-3 weeks postpartum. They found no correlation with infant birth weight among 115 Scottish mothers.

In contrast, under-nourished mothers seem to use early fat gain in building up maternal stores to support fetal growth later in pregnancy. Villar *et al* (1992) found that among 105 Guatemalan women with smaller weight gain during pregnancy than in developed countries, the fat component of their weight gain (based on skinfold thickness and bioimpedance) before the 30^{th} week of gestation was significantly correlated with infant birth weight, after controlling for pregravid weight. Mothers with low fat gains ($<25^{th}$ percentile) before the 30^{th} gestational week gave birth to lighter infants by 204 g than those with higher fat gains. In the same study, the rate of fat-free mass accretion (estimated from weight and bioimpedance) after 20 weeks of gestation was positively associated with infant birth weight. The authors suggested that the contribution of weight gain to birth weight was explained mainly by the fat components of weight gain in the first half and fat-free component in the second half of pregnancy. Along a similar line, Thompson & Halliday (1992) reported progressive increases in the

rate of protein turnover throughout pregnancy among 6 healthy UK women in comparison with 17 healthy non-pregnant controls.

In the case that under-nourished women had little chance to gain fat early in pregnancy, a later fat gain may still contribute to fetal growth. Viegas *et al* (1987) observed this effect among 81 Asian mothers of low socioeconomic status in Birmingham, England. They studied women who failed to accumulate adequate fat early in pregnancy (as measured by triceps skinfold thickness), and found that dietary supplementation for these women increased fat gain during the second trimester, which was associated with an increased infant birth weight.

The above review suggests that the contribution of weight gain during pregnancy to fetal growth depends not only on the total amount but more importantly on what component (*i.e.* fat versus fat-free mass) is gained at which stage of gestation. Available evidence indicates that earlier in pregnancy, a greater proportion of what is laid down is fat than later in pregnancy [Hytten & Chamberlain 1980, 1991]. There is possibly a critical range for maternal fat gain early in pregnancy which depends on maternal weight status at conception. Below such critical range, fetal growth is reduced whereas above this range fluctuation in energy balance may have little effect on fetal growth. In other words, an earlier requirement for fat deposition and its use later in pregnancy is more important among under-nourished than well-nourished women, whereas the need for later fat free mass accretion is important for both groups of women. In this respect, the contribution of gestational weight gain to fetal growth cannot be studied in isolation of maternal weight status at conception.

2.4 Maternal size at conception and infant birth weight

The evidence reviewed in the preceding section suggests that the requirements for weight gain and energy balance during pregnancy largely depend on the level of maternal reserves which can be represented by pregravid weight-for-height status. The lower the weight status at conception, the higher is the tendency to gain more weight during pregnancy [Mitchell & Lerner 1986b, Abrams & Laros 1986, Allen *et al* 1994, Siega-Riz *et al* 1994]. For this reason, the individual effects of the two variables on pregnancy outcome cannot be examined in isolation. Not only the two factors are interrelated in many aspects, but aiso the effect of weight gain may be modified by maternal size [Taffel 1986, Abrams & Laros 1986, Frentzen *et al* 1988, Allen *et al* 1994].

The size of the mother at conception has two dimensions; weight and height. They both reflect her genetic make-up as well as her nutritional status before pregnancy, since not all women reach their genetic potential for height if they are not well nourished. In Aberdeen women, the tallest and heaviest mothers (180 cm and 80 kg) had bigger babies by ~1 kg than those of shortest and lightest mothers (145 cm and 35 kg) [Thomson *et al* 1968]. This early study, however, did not control for gestational weight gain to isolate the birth weight difference due to solely maternal size neither did it separate between the effects of pregravid weight and height.

More recent studies on the influence of maternal size on pregnancy outcome have treated weight and height as independent predictors and reported positive partial association of each with birth weight independent of weight gain [Dougherty & Jones 1982, Langhoff-Roos *et al* 1987a, Wen *et al* 1990a]. A meta-analysis of 8 controlled studies by Kramer (1987) estimated sample-size weighted effects of

height and pregravid weight on birth weight as 7.5 g/cm and 9.5 g/kg respectively, independent of gestational weight gain. Although these two aspects of maternal size clearly have independent effects on fetal growth, they are correlated as taller women are normally heavier [MLI 1983]. It is, therefore, difficult to accurately estimate the individual effects of height and weight unless they are expressed in different terms to remove their correlation with each other, such as the use of weight status for a given height instead of simple weight.

Maternal pregravid weight for height status in terms of body mass index (BMI) is found to be related to the risk of low birth weight (SGA birth) in underweight women, and fetal macrosomia (LGA birth) in overweight women [Wolfe *et al* 1991]. In a longitudinal study of 3,191 healthy term pregnancies in Florida, Johnson *et al* (1992) reported an odds ratio of 2.1 for low birth weight (<2.5 kg) among underweight women (BMI<20), and an odds ratio of 1.5 for fetal macrosomia (>4 kg) among obese women (BMI>29) as compared to normal-weight women (BMI of 20-26). These odds ratios were not adjusted and the effect of pregravid weight status on birth weight independent of weight gain, could actually be higher as heavier women are reported to gain lower weight during pregnancy [Siega-Riz & Adair 1995, Siega-Riz *et al* 1994, Copper *et al* 1995]. Another study by Larsen *et al* (1990) reported odds ratio for fetal macrosomia of 1.3, 1.6 and 2.2 among women of different degrees of overweight whose percentiles for BMI were 75^{th}-84^{th}, 85^{th}-94^{th} and $\geq 95^{th}$ respectively in comparison with normal-weight women (25^{th}-75^{th} percentile).

In addition to its independent effect on birth weight, maternal weight status is known to modify the effect of gestational weight gain on birth weight indicating an interaction between the two determinants. Analysis of the data from the 1980 National Natality Survey in the US [Taffel 1986] has demonstrated

that the effect of a given weight gain is greatest in underweight women (<90% of standard weight for height), and least in overweight and obese women (>120% of standard weight). Similar interaction between pregravid weight status and gestational weight gain in influencing birth weight was observed by Mitcheli & Lerner (1989b) in middle class US women, and by Brown *et al* (1986) in low-income US women. Two other US studies by Abrams & Laros (1986) and by Frentzen *et al* (1988) found a significant interaction after controlling for other determinants of infant birth weight within a linear regression model. The regression slope of birth weight versus gestational weight gain decreased in strata of increasing maternal pregravid weight status, and the slope was not significant for obese mothers (>135% of standard weight). Abrams & Laros (1986) reported a regression coefficient for birth weight of 17.8 g/kg of weight gain among moderately overweight women (120-135% of standard weight), as compared to 28.3 g/kg among normal-weight women. Both studies found that infant birth weight increased with maternal weight gain among moderately overweight women, but this relationship was not significant among obese women.

Subsequent to the 1986 publication by Abrams & Laros, another study by Parker & Abrams (1992) used a larger sample from the same population base and reported that low weight gain among obese women significantly increased the incidence of SGA infants (<10^{th} percentile). Obese women gaining less than the IOM recommendation (≤6.0 kg) had 3.8 times higher risk of SGA than those with higher weight gains. Unfortunately, the authors did not indicate whether obese women with negative weight gain were excluded from the lower weight gain group, neither did they report the average weight gain of this group. Although the 1986 and 1992 studies used the same population base, they did not give consistent results with respect to the degree of interaction. Whereas weight

gain in the earlier study seems to lose its effect on mean birth weight among obese mothers in a linear regression model, weight gain still has an effect on the risk of SGA infants in the later study. In contrast, a recent study of 53,541 singleton pregnancies in 8 states by Cogswell *et al* (1995) found that weight gains beyond 14 kg among overweight women did not reduce SGA risk but increased the risk of LGA.

Using logistic regression, Kleinman (1990) analyzed data from the 1980 US National Natality Survey and found that increasing gestational weight gain above 13 kg decreased the risk of SGA in mothers of BMI ≤26, but increased the risk of SGA in mothers of BMI>26. Furthermore, Haiek & Lederman (1988) found that among overweight women, birth weight increased with weight gain below 7 kg, but birth weight decreased after weight gain exceeded 7 kg. These findings may suggest a threshold effect of weight gain on SGA for overweight women, above which the birth weight distribution may widen, such that both SGA and LGA rates increase while the mean value is unchanged. It is therefore important to study neonatal outcome not only in terms of mean values of infant birth weight, but also in terms of its variability which may be reflected in the rates of SGA and LGA infants. Furthermore, the inconsistent findings on the relationship between maternal weight gain and birth outcome among obese women make it difficult to set weight gain recommendations for this group of women.

The above review suggests that the impact of maternal weight status and gestational weight gain on pregnancy outcome cannot be studied independently without considering their interaction with each other, and neither can their effects be assumed to be linear. One major factor that could confound the interaction between weight status and weight gain is maternal smoking which has

not been controlled adequately in relation to pregravid weight and gestational weight gain.

2.5 Maternal smoking and infant birth weight

Cigarette smoking is a major modifiable risk factor for both low birth weight and premature delivery. Average reported birth weight differences between smoking and nonsmoking mothers are in the 70-356 g range [Johnston 1981, Papoz *et al* 1982, Kramer 1987, Muscati *et al* 1988, Brooke *et al* 1989, Secher *et al* 1990, Frank *et al* 1994, Cliver *et al* 1995, Shu *et al* 1995]. However, the reported effect of smoking on birth weight is likely to be somewhat over-estimated as smoking is positively associated with other risk factors such as alcohol consumption [Istvan & Matarazzo 1984, HWC 1989], lower pregravid weight [Fehily *et al* 1984, Albanes *et al* 1987, Klesges *et al* 1989], lower socioeconomic status [Rush & Cassano 1983, Fehily *et al* 1984, DHHS 1989b, Stewart *et al* 1995], higher psychological stress [Picone *et al* 1982a, Perkins *et al* 1987, Brooke *et al* 1989], and poorer health status [Stewart & Dunkley 1985]. Thus the reported birth weight reduction due to smoking may vary widely depending on which confounders are controlled in the analysis. More compelling evidence on the causal link between maternal smoking and infant birth weight is available from studies of smoking cessation during pregnancy. Complete smoking cessation early in pregnancy is found to improve birth weight by 90-217 g and bring it to values similar to those of nonsmokers [Sexton & Hebel 1984, Windsor *et al* 1985, MacArthur & Knox 1988, Olsen 1992, Mainous & Hueston 1994, Frank *et al* 1995].

The effect of cigarette smoking also depends on the level of smoking where a dose-dependent relationship between exposure to tobacco and birth weight is well established [Meyer *et al* 1976, Abell *et al* 1991, McDonald 1992, Walsh 1994,

Cliver *et al* 1995], with a possible threshold effect [Peacock *et al* 1991]. Based on results from 26 controlled studies, Kramer (1987) estimated the sample-size weighted independent effect of smoking on reducing mean birth weight as 150 g or 11.1 g/cigarette/day, and the relative risk for low birth weight (<2.5 kg at term) for smokers as 2.42.

Smoking is known to suppress fetal growth directly by depressing tissue uptake and placental transfer of oxygen and nutrients to the fetus [Picone *et al* 1982b, Bakketeig *et al* 1993, Sastry *et al* 1993, Wilcox 1993], and/or through a reduction in maternal blood glucose values in late pregnancy [Langhoff-Roos *et al* 1993]. Some studies report lower maternal weight before and during pregnancy among smoking women [Garn *et al* 1979, Picone *et al* 1982a, Rush *et al* 1990], implying an indirect effect of smoking on reducing fetal growth. The latter effect may possibly result from either lower energy intake due to depressed appetite or increased energy expenditure in the form of physical activity or basal metabolic rate (BMR). It has not been established, however, that smokers in general consume lower energy during pregnancy than nonsmokers, since reported findings in this area are not consistent; some report higher intake among pregnant smokers [Haworth *et al* 1980, Picone *et al* 1982a, Papoz *et al* 1982, McDonald & Newson 1986], while others report lower intake [Haste *et al* 1990] in comparison to pregnant nonsmokers. Furthermore, cross-sectional evidence suggests that non-pregnant smokers may in fact consume more energy, although they stay leaner than nonsmokers [Jacobs & Gottennborg 1981, Stamford *et al* 1986, Cade & Margetts 1989].

With respect to energy expenditure, physical activity patterns of smokers have tended to show similar or lower activity levels than nonsmokers [Blair *et al* 1985, Marks *et al* 1991] and may therefore not explain the lower weight among smokers. Longitudinal measurements of basal metabolic expenditure (by O_2

consumption and CO_2 production) among non-pregnant women before and after smoking cessation followed by resumption of smoking, showed little or no chronic change in BMR due to cessation of smoking [Moffat 1991, Perkins 1992, Warwick *et al* 1995]. However, short term studies in controlled environments showed an acute effect of smoking on increasing metabolic expenditure by up to 10% during 30-60 minutes after exposure to nicotine [Perkins *et al* 1989, Audrain *et al* 1991, Collins *et al* 1994]. It remains to be determined whether the reduced weight gain among smokers is mediated by differences in dietary intake and/or energy expenditure.

In order to compensate for the weight reducing effect of smoking, it has been suggested that pregnant smokers might benefit from increased food intake before and during pregnancy [Davies *et al* 1976, Garn *et al* 1979, Rush *et al* 1980, Papoz *et al* 1982, Metcoff *et al* 1985]. Nevertheless, some data show that infants of obese smokers are still significantly smaller than infants of obese nonsmokers [Haworth *et al* 1980], indicating that extra weight before pregnancy may not have a compensatory effect. The question remains as to what extent increased food intake during pregnancy can compensate for the negative effect of smoking on fetal growth.

Maternal smoking is not only associated with other determinants of infant birth weight, but may also interact with them in influencing birth outcome. For this reason, the effect of maternal smoking on birth weight cannot be studied in isolation of those other interrelated predictors.

Smoking is found to interact with maternal age and parity, both of which increase its deleterious effect on fetal growth. Wen *et al* (1990b) studied 15,539 births in Alabama during 1983-84 using multiple linear regression stratified by

age groupings with adjustment for race, parity, marital status, maternal pregravid weight, gestational weight gain and alcohol use within each age group. They found that smoking reduced the mean birth weight by 301 g in older mothers (>35 y), and by 134 g in younger mothers (<17 y). Similarly, Fox *et al* (1994) studied all 347,650 singleton births in Washington State during 1984-88 to investigate the effect of smoking (yes/no) and maternal age on birth weight, using multiple linear regression with adjustment for race, parity, and socioeconomic factors. The authors found that the decrement in mean birth weight associated with smoking, grew steadily from 117 g for the youngest mothers (<16 y) to 376 g for the oldest (>40 y). Another population based study of 538,829 Swedish women by Cnattingius *et al* (1993) also reported that the smoking-related effect on SGA risk increased with advancing maternal age and was greater among multiparous than nulliparous women. These studies did not indicate whether the number of cigarettes smoked or the intensity of smoke inhalation changed with age, thus possibly explaining part of this interaction between age and smoking. It is unlikely that a stronger effect of smoking on the infants of older mothers is due to a cumulative effect of smoking on maternal physiology or health status, because smoking cessation at the beginning of pregnancy is shown to restore infant birth weight to similar levels as nonsmoking mothers [Sexton & Hebel 1984, Windsor *et al* 1985, MacArthur & Knox 1988, Olsen 1992, Mainous & Hueston 1994, Frank *et al* 1995]. It is conceivable, however, that some of the other risk factors of low birth weight may be more strongly associated with smoking in older women, thus explaining part of the reported larger impact of smoking on reducing birth weight.

There is also some evidence on the interaction between smoking and dietary supplementation in affecting birth weight. In the New York supplementation trial among poor black women, Rush *et al* (1980) observed that

the only significant favourable effect of dietary supplementation was the prevention of depressed birth weight in the offspring of 19 heavily smoking mothers (≥15 cigarette/day) as compared to 27 heavily smoking unsupplemented controls. No effect of supplementation on birth weight was found among nonsmokers. The authors did not adjust infant birth weight for other determinants that could confound the results. In another supplementation trial in Oklahoma under the WIC program, Metcoff *et al* (1985) reported a significant increase in mean adjusted values of infant birth weight by 176 g due to supplementation only among 68 heavily smoking mothers (≥10 cigarette/day) as compared to 53 unsupplemented heavily smoking mothers. Unlike the results reported by Rush *et al* (1980), the study by Metcoff *et al* (1985) reported that dietary supplementation of smoking mothers did not fully restore infant birth weight to levels similar to those of nonsmokers.

In both the New York and Oklahoma studies, heavily smoking mothers may have been more severely under-nourished with considerably lower infant birth weight (≤3 kg) than other groups, thus leaving more room for potential improvement due to supplementation. Part of the birth weight enhancement among the heavy smokers in these two studies might be further explained by a possible reduction in smoking behaviour during pregnancy among the supplemented groups. A large portion of smoking women are known to stop or reduce their smoking behaviour during pregnancy [Stewart & Dunkley 1985], which may increase the likelihood of confounding the relationship between supplementation and birth weight. Both studies had a relatively small sample size, so that despite initial randomization, the groups were later selected on the basis of their smoking behaviour which may have become unbalanced in confounding factors such as maternal race, age, socioeconomic status, *etc.*

No studies have identified a possible interaction between smoking and gestational weight gain in affecting fetal growth. Information on such interaction would be useful for the definition of gestational weight gain requirements since about one quarter of reproductive age women smoke in Canada and the US during early 1990's [DHHS 1993, Health Canada 1993 & 1995, Stewart *et al* 1995].

2.6 Determinants of maternal postpartum weight retention

The previous sections reviewed major determinants of birth outcome. This section reviews the evidence related to the maternal side of pregnancy outcome. Pregnancy outcome not only involves infant survival and well-being, but also has serious implications for the mother. Following the significant improvement in infant birth weight through increased gestational weight gain, over the last two decades, there is now a growing concern about increased risks of excessive maternal postpartum weight retention [Öhlin & Rössner 1990, Keppel & Taffel 1993, Smith *et al* 1994]. Aside from maternal pregnancy complications associated with excessive weight gain, such as hypertension, gestational diabetes and cesarean section [Naeye 1979, Ruge & Anderson 1985, Johnson *et al* 1992], postpartum weight retention may have long-term adverse consequences for the mother [Ruge & Anderson 1985].

Gestational weight gain is reported to be the strongest determinant of maternal fat gain [Forsum *et al* 1988] and subsequent weight retention persisting at 10 to 18 months postpartum [Öhlin & Rössner 1990, Keppel & Taffel 1993]. This suggests that large weight gains during pregnancy increase the risk for excess fat deposition and for obesity after delivery. Another factor reported to be associated with higher postpartum weight retention is smoking cessation during

pregnancy by habitual smokers [Öhlin & Rössner 1990]. Similarly, nonsmokers are reported to retain more weight postpartum than smokers [McCabe 1978]. However, these effects seem to be largely mediated by differences in weight gain during pregnancy which is known to be lower among smokers.

Even when the mean weight gain in a population falls within the IOM recommendations, >30% of all pregnant women will have weight gain exceeding the recommended ranges [Parker & Abrams 1992, Hickey *et al* 1993]. Parham *et al* (1990) reported that of normal-weight women gaining an average of 12.6 kg during pregnancy, 28% gained above the IOM recommended range (> 16 kg). Siega-Riz *et al* (1994) found that less than half of Los Angeles women receiving prenatal care, had weight gains compatible with the recommendations. At the same time, more than half of the overweight portion of these women gained excess weight above their IOM recommendation [Siega-Riz *et al* 1994]. These findings suggest that a large proportion of the population may be exposed to the risk of postpartum obesity, unless they find means of reducing their excess weight after delivery.

When maternal weight gain falls within or exceeds an IOM recommended range, a portion of this weight is likely to stay with the mother postpartum. The average weight loss from labour to two weeks postpartum is around 9 kg [Lawrence *et al* 1988, Hytten & Chamberlain 1991], which is similar to the estimated combined weight of products of conception and surplus fluid [Hytten & Chamberlain 1991]. The remaining weight retained by the mother is predominantly adipose tissue. Sohlstrom & Forsum (1995) used magnetic resonance imaging to assess adipose tissue volume in 15 healthy Swedish women and found an increase of 2.9 L in adipose tissue 12 months after delivery as compared with before pregnancy. The more weight a normal-weight woman gains above 9 kg during

pregnancy, the more she is likely to retain by the start of her next pregnancy [Greene *et al* 1988]. As an example, Parham *et al* (1990) reported that a weight gain of 12.9 kg during pregnancy was associated with 4.2 kg extra weight one year after conception versus 0.5 kg gained by non-pregnant controls over the same period.

Part of the retained weight could be mobilized gradually after delivery by negative energy balance, through such measures as lower energy intake than required [Murphy & Abrams 1993, Öhlin & Rössner 1994], lactation [Illingworth 1987a, Öhlin & Rössner 1990], return to work outside the home [Schaberger *et al* 1992], or becoming more physically active [Öhlin & Rössner 1994]. Nevertheless, each pregnancy is seen to leave the mother with additional weight that is not completely lost between successive pregnancies. Öhlin & Rössner (1990) reported that Swedish women gaining 12.5 kg during the first pregnancy were 2.5 kg heavier at the start of the next pregnancy, after correcting for changes due to aging. Cross-sectional studies demonstrate a greater central adiposity associated with higher number of pregnancies even after adjustment for body weight [Tonkelaar *et al* 1990, Kaye *et al* 1990]. In a retrospective study of a cohort of 41,184 post-menopausal women, Brown *et al* (1992) found that each live birth increased maternal body weight by 0.55 kg from age 18 to 50 years. Parker & Abrams (1993) defined high parity for age as the third or higher birth among women under 25 and the fourth or higher birth among women over 25. They found that high parity under this definition was associated significantly with weight retention of 10 kg or more, measured between 10 and 24 months postpartum among black mothers, after controlling for other maternal characteristics.

The problem of weight retention is found to be more pronounced after the first pregnancy than subsequent pregnancies, as primiparous women are seen to

gain more weight during their pregnancy but give birth to smaller infants [DaVanzo *et al* 1994, Cnattinigius *et al* 1993]. In a recent longitudinal study of 2,788 US women, Smith *et al* (1994) reported that primiparas gained 2-3 kg more weight and had greater increases in adiposity (waist-to-hip ratio) during 5-year follow-up period than both nulliparas and multiparas after adjusting for age, education, smoking, physical activity, and pregravid weight status.

The amount of weight gain increments between pregnancies is found to depend also on maternal smoking status. A national US collaborative study by Garn & Shaw (1978) using longitudinal data reported average weight gain increments of 1.5-2 kg from one pregnancy to the next, and >3 kg from the first to the third pregnancy among nonsmoking mothers, but lower weight increments were gained by smoking mothers. This study controlled for the expected increase in weight over the same age period in women who did not have children. Such findings, however, can be attributed directly to the lower weight gained by smokers during pregnancy. Similarly, Öhlin & Rössner (1990) reported lower weight retention among mothers who resumed smoking behaviour after delivery.

The wide disparity in reported amounts of weight retention per pregnancy in various studies points to the wide variability in postpartum weight retention across populations and among individuals within a population. Not only the weight gained during pregnancy is highly variable, but also the amount lost between pregnancies depends primarily on energy balance which is determined by several life style factors. Due to such high variability in postpartum weight retention within a given population, focusing only on its mean value can obscure the fact that some women retain far more weight than the mean, while others lose weight. For example, a survey of 1,592 US women showed a median

weight retention at 10-18 months postpartum of only 1.5 kg, but in the same population 28% of the women retained >4 kg [Keppel & Taffel 1993]. Öhlin & Rössner (1990) reported that 56% of the 1,423 surveyed Swedish women, retained 0-5 kg one year postpartum from the pregravid level, while 14% retained >5 kg. Ironically, those who were heavier before pregnancy had a higher risk of retaining extra weight postpartum. Obese women had the widest distribution of postpartum weight retention with both low and high values being more likely to occur than among lower-weight women. In a retrospective study of 128 Swedish obese women, Rössner (1992) found that 73% of these women reported >10 kg net weight retention one year postpartum relative to their pregravid level. This is a very large increase in already overweight women and poses a serious health threat.

The above evidence indicates that a substantial portion of women appear to be gaining considerably more weight than necessary during pregnancy, part of which is retained until the following pregnancy. Overweight women are at particularly high risk of developing postpartum obesity, not only because of their higher pre-pregnancy weight, but also because they are at a higher risk of retaining extra weight postpartum than normal weight women. Hence, there is a need to monitor weight gain to minimize the risk of postpartum obesity, especially among normal and over-weight women.

3. RESEARCH QUESTIONS AND ANALYTIC FRAMEWORK

The preceding literature review pointed to several questions concerning the interrelations among dietary energy intake, pregravid weight, gestational weight gain and smoking in influencing pregnancy outcome relevant to the mother and her infant. The review identified a need to investigate pregnancy outcome as a balance between fetal growth and maternal fat accretion. Fetal growth is reflected by infant size at term (weight, length and head circumference), whereas maternal fat accretion is reflected by postpartum weight retention. To explore the two issues of the interrelations among determinants and the balance between pregnancy outcomes, this research specifically addresses the following questions.

1. Can the total amount of gestational weight gain for a given maternal weight status be reduced by following an appropriate pattern (timing) of weight gain to decrease the risk of postpartum obesity, while achieving optimum fetal growth?

2. Can extra weight gain in smokers make up for the effect of cigarette smoking on reducing infant size at birth or increasing the risk of SGA birth? Is the relationship between weight gain and infant size at birth the same in smoking and nonsmoking women of different weight status groups?

3. Are the lower maternal weight gain and infant birth weight found in smokers, mediated by lower dietary energy intake or higher total energy expenditure?

4. What is the relative importance of key modifiable determinants of SGA (pregravid underweight, low weight gain and smoking) in terms of their etiologic fractions within the current Canadian population context?

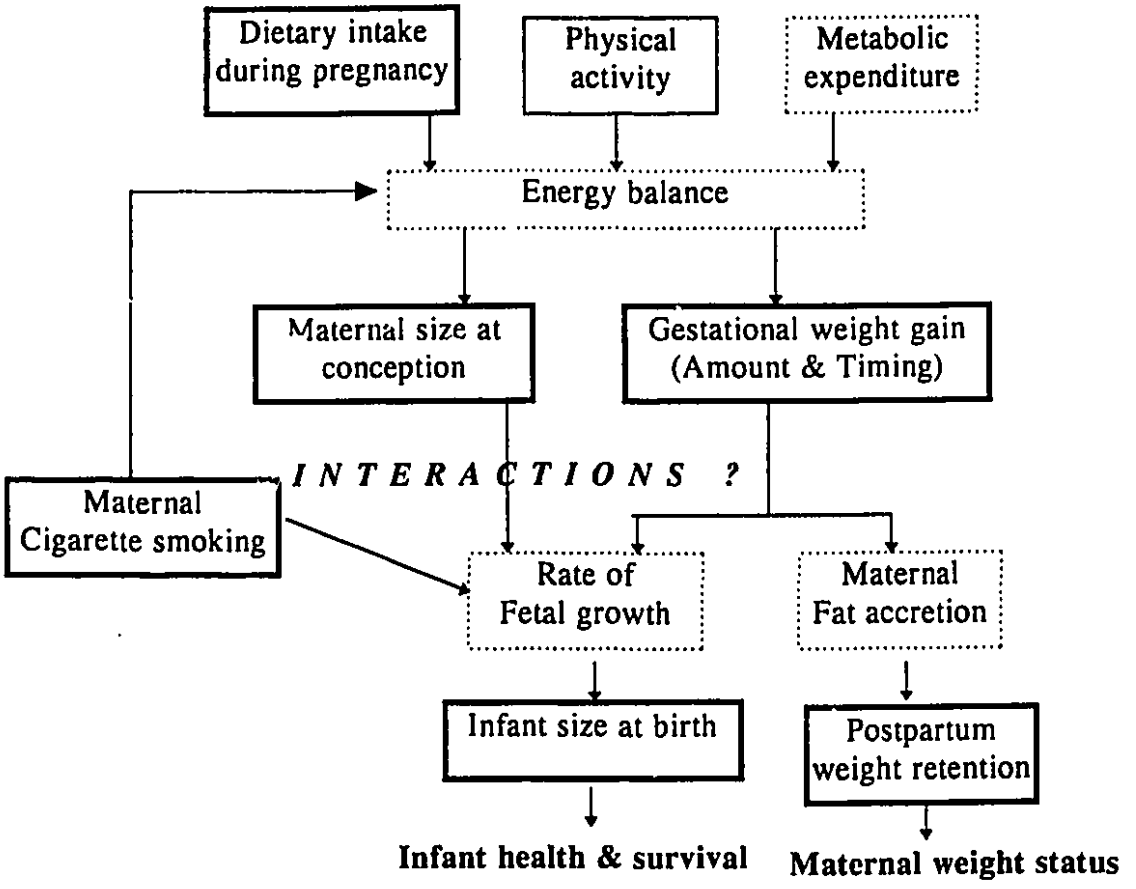
The analytic framework illustrated in Figure 3.1 will be used for addressing these research questions. This framework focuses on the key modifiable determinants; maternal dietary intake, pregravid weight, gestational weight gain, and cigarette smoking. It treats other factors that have significant independent effects on pregnancy outcome as confounders to be controlled in the analysis. These include physical activity, age or parity, socioeconomic status, gestational length and infant gender. Additional confounders such as alcohol intake, young or old maternal age, drug abuse, ethnic origin, and adverse medical condition are controlled by data restriction.

In this framework, three types of interrelations among the determinants are envisaged:

a) **Interaction**, where one determinant modifies (i.e. increases or decreases) the magnitude of the effect of another determinant on pregnancy outcome;

b) **Mediation,** where one determinant affects pregnancy outcome indirectly through another mediating determinant;

c) **Confounding,** where one determinant biases the apparent effect on pregnancy outcome of another determinant by making it appear stronger or weaker than it really is.



Note: Variables in solid boxes were included in the analysis.

Figure 3.1 Analytic framework of interrelations between determinants of pregnancy outcome

4. RESEARCH FINDINGS

4.1 Study population

A comprehensive prenatal and pregnancy outcome data set was collected by the Prenatal Nutrition Counselling Program of the PEI Department of Health & Social Services between 1979 and 1989. This data set was provided exclusively for this research work and had not been fully analyzed before. It offered a unique opportunity to address the research questions raised in the previous chapter. The PEI program provides individual dietary counselling to pregnant women with limited family income who were referred to the counselling program either by a family physician or by the PEI Department of Health & Social Services which administers maternity allowances to pregnant women.

Since this study population was not randomly selected from the general public, it may not represent the Canadian population at large. Nevertheless, it covers a large rural and small-town population in Canada from similar socioeconomic class. The type of counselling provided to participants includes more dietary advice than that typically available from routine visits to a family physician. Despite this dietary advice, there is a broad range of intakes and weight gains. The diverse dietary, obstetric and health related data available on the study population, together with an adequate sample size, allowed an effective control for adverse health conditions using rigorous restriction criteria, while exploring various interrelations among determinants of maternal and neonatal outcomes of pregnancy.

The initial study population consisted of 1,974 white women giving birth to live singleton infants. As this research focused on fetal growth in full term pregnancies, it excluded premature births (<37 weeks gestation). Adolescents <16 years were excluded because of their continuing linear growth which could adversely affect pregnancy outcome [Haick & Lederman 1988]. Older women ≥40 years were excluded because of increased obstetric risk [NRC 1975, Lee *et al* 1988, Aldous & Edmonson 1993] and their small numbers. Women who consumed alcohol (>1 drink/month) were excluded to avoid confounding effects of alcohol on fetal growth. For a similar reason, the study excluded reported users of illegal or narcotic drugs. To remove the confounding effects of maternal health and obstetric risk factors, the study excluded women with pregnancy complications such as proteinuria, hypertension, toxaemia, diabetes, and negative total pregnancy weight gain. Finally the study excluded subjects with extreme values (above or below 3 standard deviations from the mean) for infant birth weight, maternal pregravid weight and gestational weight gain. This exclusion of outliers was intended to preserve normality of the statistical distribution of these variables, minimize potential bias in their means as well as eliminate erroneously recorded values in the data. Some of the analyses were repeated with and without these outliers to verify their impact on study results.

The above exclusions decreased the available study population to 1,330 women consisting of 601 (45%) nonsmokers and 729 (55%) smokers. This was the study sample used in Manuscripts A and B. The sample used in Manuscript C was further restricted to nonsmokers, and to those with complete records of additional maternal weight variables at gestational weeks 20 and 30, and at 6 weeks postpartum, leaving only 329 with non-missing values. The excluded subjects had one or more of the weight variables missing either due to joining the Program after 20 weeks of gestation, leaving the Program before 6 weeks

postpartum, or not paying regular visits to allow the required weight measurements.

4.2 Methodological aspects

The analysis of this thesis addresses several methodological problems identified in the literature review given in Chapter 2. This section describes specific refinements that have been undertaken to add precision to the methodology by addressing problems of misclassification of outcome variables, and multicollinearity among determinants.

Gestational age was restricted to ≥37 weeks, because the analysis was concerned with fetal growth as the birth outcome in full-term pregnancies. A very strong gradient of birth weight with gestational age was found, even after 37 weeks of gestation. This required gestational age to be always included as a covariate in the analysis.

Infant birth weight was categorized into small for gestational age (SGA), adequate for gestational age (AGA) and large for gestational age (LGA). While the confounding effect of gestational age on birth weight has been controlled in the literature by categorizing birth weight in relation to gestational age, the effect of infant gender has not previously been considered in such categorization, and this could lead to some misclassification error, *e.g.* indicating a larger proportion of SGA in female infants. In this thesis, the classification for SGA, AGA and LGA were done using as cut-off values the 10^{th} and 90^{th} percentiles of the 1986 birth weight distribution of Canadian infants [Arbuckle & Sherman 1989] specific for the gestational age as well the gender of each

infant. These percentiles correspond to term birth weights (at 40 weeks gestation) of 2.96 and 4.08 kg, which closely relates to the 3-4 kg birth weight range conventionally used in the literature to characterize AGA infants.

Pregravid weight and height are often reported in the literature as having independent effects on birth weight despite their multicollinearity. Correlation analysis of the present study sample, between pregravid weight and height gave $r=0.40$ ($p<0.0001$). In this research, the separate effects of maternal height and pregravid weight were analyzed by dividing pregravid weight into two uncorrelated components: (a) standard weight for height and frame size, and (b) actual difference from standard weight. The former was based on the 1983 Metropolitan Life Insurance Company (MLI) tables and was used to reflect maternal size in terms of height and frame size. The latter was used to reflect approximately maternal weight status in terms of degree of adiposity or energy reserves. In this respect, pregravid weight status was categorized into three groups; underweight as $<90\%$, normal as 90-120%, and overweight as $>120\%$ of the MLI standard weight. The cut-off values of 90% and 120% of the MLI standard weight correspond to 25^{th} and 85^{th} percentiles of the general population respectively [Kleinman 1990]. They also correspond to body mass index (BMI) values of 19.8 and 26.0 respectively, where BMI is defined as weight (kg) divided by the square of height (m^2). The two extremes of pregravid weight for height are implicated in higher pregnancy risks.

The confounding effect of parity was controlled by the dichotomous variable primiparous versus multiparous, as the relationship of parity to infant birth weight is not linear and the most important difference is between primiparous versus multiparous women [Cnattinigius *et al* 1993].

Graphical relationships between a predictor (*e.g.* weight gain) and pregnancy outcome (*e.g.* birth weight) were studied to observe non-linear trends. Values of the predictor were subdivided over certain intervals and the corresponding mean values of the outcome variable were plotted over each interval. To control for the potential confounding effects of other predictors, the mean value of the outcome over each predictor interval were statistically adjusted, using least-square means procedure of SAS system. To study the different effects of predictors between smoking and nonsmoking mothers, the analysis was stratified for smoking status.

Further details on specific methods of analysis are given in each of the following three manuscripts.

4.3 Outline of research findings

The research findings of this thesis are given in three manuscripts. Each manuscript is presented in the same format as it has been published or submitted for publication in refereed scientific journals. An epilogue follows each manuscript to summarize its results and provide a linkage to the rest of the thesis.

Manuscript A investigates whether the effect of gestational weight gain on infant size at birth is modified by cigarette smoking in different maternal pregravid weight status groups. Infant size is characterized by weight, length and head circumference at birth. This manuscript also investigates the effect of gestational weight gain on the risk of having SGA infants among smoking and nonsmoking mothers of different weight status categories. It explores to what

extent higher weight gain among smokers can compensate for the effect of smoking on reducing infant birth weight and increasing the SGA risk. It also explores the dose-response relationship between the level of cigarette smoking and infant birth weight.

Manuscript B explores whether the lower maternal weight gain during pregnancy and infant birth weight observed among smokers are mediated by lower energy intake, while controlling for maternal weight and height, physical activity, and infant gender. This manuscript further explores the extent to which each of the modifiable risk factors of infant birth weight; namely maternal pregravid underweight, low pregnancy weight gain and cigarette smoking independently contribute to the risk of SGA infants in the current Canadian population context. The etiologic fraction for each of these three risk factors provides a measure of the extent to which each factor is independently responsible for the prevalence of SGA infants. This is to provide a basis for establishing priorities for prenatal intervention programs.

Manuscript C explores the importance of a proper timing of weight gain during pregnancy with respect to the possibility of achieving a balance between promoting fetal growth and minimizing maternal weight retention among healthy nonsmoking pregnant women. It addresses the question whether the total amount of gestational weight gain for a given maternal pregravid weight status can be reduced by following an appropriate weight gain pattern to decrease both risks of maternal postpartum obesity and of SGA infants.

4.4 *MANUSCRIPT A*

Interaction of Smoking and Maternal Weight Status in Influencing Infant Size

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Abstract

The effects of pregravid weight, gestational weight gain and smoking on infant size, and the extent to which weight gain can compensate for smoking behaviour are explored in multivariate analysis of 1330 healthy mothers and their full term infants at the PEI Prenatal Nutritional Counselling Program. Stratified analysis by pregravid weight and smoking status indicated that gestational weight gain was linearly related to birth weight in all groups except among overweight nonsmokers. Gestational weight gain significantly predicted the risk of small-for-gestational-age infants (SGA) only among smokers. Increased weight gain partially mitigated the negative effect of smoking on birth weight but among underweight smokers there was a high risk of SGA (>10%) despite an elevated weight gain. Level of smoking was directly related to infant birth weight, with substantial reduction even for light smoking. Complete smoking cessation is important for preventing low birth weight in Canada, particularly among underweight mothers.

Abrégé

Les effets du poids prégravide, du gain de poids et du tabagisme sur le poids du nouveau-né de même que l'effet du gain de poids maternel pour compenser pour le tabagisme, ont été étudiés par une analyse multivariée. Des données sur 1330 mères et leurs bébés nés à terme obtenues du "Prenatal Nutritional Counselling Program" de l'Ile du Prince Édouard. Des analyses stratifiée pour le poids prégravide et le tabagisme indiquaient que le gain de poids durant le grossesse était associé de façon linéaire avec le poids du bébé. Parmi les fumeuses seulement, le gain de poids durant le grossesse prédisait le risque d'un bébé petit pour l'âge gestationnel. Un gain de poids plus élevé atténuait les effets du tabagisme sur le poids du bébé, sauf que les fumeuses maigres ou minces avant la grossesse continuaient de montrer un risque élevé d'accoucher d'un bébé petit pour l'âge gestationnel (> 10%). Le nombre de cigarettes était directement et négativement associé au poids du bébé, même chez les femmes qui fumaient peu. La cessation complète du tabagisme est importante pour prévenir les bébé de faible poids au Canada, surtout parmi les fumeuses maigres ou minces avant la grossesse.

Introduction

Infant size at birth is a key determinant of health, especially during early infancy,[1-4] and depends on both length of gestation and fetal growth rate. Known independent determinants of infant size are gestational length, gestational weight gain, pregravid weight, height, cigarette smoking during pregnancy, race, parity, infant sex as well as a number of pregnancy disorders.[5-10]

Although the effects of smoking during pregnancy have been intensively studied, the interaction of smoking and maternal weight status in terms of pregravid weight and gestational weight gain has received little attention. In addition to a strong independent effect of smoking on infant size, smoking has an indirect effect on fetal growth, as it is associated with lower maternal weight status.[11] It remains to be seen, however, whether smoking modifies the effect of maternal weight status on infant size at birth, as measured by weight, length and head circumference.

Whereas smoking cessation early in pregnancy may result in an infant comparable in size to that of nonsmoking mothers,[12] it is important to assess whether higher maternal weight status is able to compensate for the negative effect of smoking whenever smoking cessation did not occur.[13]

This study explores how smoking modifies the effects of pregravid weight and gestational weight gain on infant size as indicated by birth weight, length and head circumference, while controlling for potential confounding variables such as gestational age, infant's sex, maternal height and frame size, age and parity. The effect of the number of cigarettes smoked is also explored.

Subjects and methods

Data were abstracted from the Prenatal Nutrition Counselling Program of the Department of Health & Social Services of Prince Edward Island from 1979 to 1989. This program offers individual dietary counselling to pregnant women of primarily low socioeconomic status at nutritional risk.[14,15] Prenatal information is recorded at regular visits throughout pregnancy. A nutritional assessment is made for each woman to determine dietary requirements relative to her weight status and dietary history.

The study was restricted to live singleton mature births (after at least 37 weeks' gestation). Mothers younger than 16 years of age were excluded to remove those less than three years post-menarche who might exhibit different pregnancy performance.[16] Also excluded were those women who drank alcohol more than once a month, used narcotic or illegal drugs, lost weight during pregnancy or had medical risk conditions including toxaemia, diabetes or hypertension. The study sample included 1,330 white mothers from an initial population of 1,974 mothers.

Maternal weight was recorded on admission, at 10, 20, 30 weeks' gestation and just prior to delivery. Pregravid weight was based on recall by the mother followed by verification with family physicians' records. Gestational age was estimated from the date of the last menstrual period obtained from physicians' records. Only subjects with such records were included in the analysis. Infant birth weight, length and head circumference were obtained from hospital records.

Gestational weight gain was used as an indicator of maternal nutritional status, in view of the difficulties inherent in assessing individual dietary intake and pregnancy requirements.[17,18]

To control for the obvious correlation between maternal pregravid weight and height, maternal weight was broken down into two independent continuous variables; (a) standard weight for height and frame size based on the Metropolitan Life Insurance tables,[19] and (b) pregravid weight above standard. The former serves as an indicator for height and frame size, while the latter indicates adiposity. When stratifying for weight status, subjects were divided into three pregravid Body Mass Index (BMI) categories:[20] <20 kg/m^2 for underweight; 20-26 kg/m^2 for normal weight; and >26 kg/m^2 for overweight. They were further divided over seven weight gain intervals at 4 kg spacing.

Infant birth weight was adjusted for gender by subtracting or adding 70 g for males and females respectively, based on an observed mean difference of 140 g in birth weight between the two genders. Statistical adjustments were used for other potential confounders as applicable.

Differences in maternal and infant characteristics between smokers (those who continued to smoke one or more cigarettes per day) and nonsmokers were assessed by t- and chi-square tests. Because these two groups differed in many characteristics and the relationship between weight gain and infant size among smokers was of special interest, the analysis was stratified by smoking status. We evaluated the effects of predictors on infant birth weight, length, and head circumference, using stepwise multiple regression analyses. The effect of predictors on the risk of small-for-gestational-age (SGA) infants ($<10^{th}$

percentile birth weight for gender and gestational age),[21] was evaluated by logistic regression analysis. Graphical results were obtained on infant birth weight and SGA risks vs. maternal weight gain and level of smoking, using general linear model techniques, in order to explore possible non-linear relationships, while controlling for maternal pregravid weight, parity, smoking level among smokers, gestational age and infant sex.

Statistical analyses used SAS software package for Personal Computers Version 6.04, 1990 (SAS Institute Inc., Cary, North Carolina).

Results

Maternal and infant characteristics, stratified by smoking status, are provided in Table I. The sample contained a high proportion of smokers (54%) and single mothers (42%) because of the initial high-risk selection criteria. Unadjusted mean birth weight, length and head circumference were significantly lower among infants born to smoking mothers by 305 g, 1.2 cm and 0.6 cm, respectively. Mean height was not different between smokers and nonsmokers so that the small difference in mean standard weight is likely explained by a higher estimation of frame size for heavier subjects.

Multivariate regression analysis of infant birth weight, length and head circumference, indicated that gestational weight gain, standard weight for height, pregravid weight above standard, gestational age, parity, and smoking level were independent predictors of infant size (Table II). Other maternal variables listed in Table I showed no significant association with infant size in the regression analysis. Although the regression coefficients for weight gain

appeared higher among smokers than nonsmokers, this difference (*i.e.* interaction) was significant only for infant length ($p < 0.05$).

Figure 1 plots adjusted mean birth weight vs. weight gain for different pregravid weight groups of smokers and nonsmokers. Overweight nonsmoking mothers tended to exhibit a plateau in birth weight at higher levels of weight gain, while the other weight groups showed a steady increase in infant birth weight with increasing weight gain. There was no statistical interaction of pregravid weight and weight gain on infant birth weight, among smokers or nonsmokers. Figure 2 shows that mean adjusted birth weight, decreased nonlinearly with smoking level, with the greatest drop being between nonsmoking and low smoking levels.

Results of stepwise logistic regression analyses of the risk of SGA for smokers and nonsmokers are given in Table III. Pregravid weight and gestational weight gain significantly predicted SGA risk among smokers; level of smoking provided no significant contribution to the regression model. Similarly, there was no interaction between maternal weight gain and pregravid weight.

The proportion of SGA infants is plotted against weight gain by smoking and pregravid weight status in Figure 3. Among nonsmoking mothers the overall SGA risk was relatively low (5.4%), and even underweight women had an SGA risk less than 10% if weight gains were greater than 17 kg. In contrast, the proportion of SGA infants was much higher among smokers, and remained above 10% among the underweight smokers even at very high weight gains. Although weight gain among smokers reduced the proportion of SGA infants, underweight smokers remained at elevated risk.

Discussion

Our study population included women followed in a prenatal nutrition counselling program, for whom detailed data throughout pregnancy were available. Although this sample is not representative of the entire Canadian population, it is indicative of a lower socioeconomic population with elevated risk. The mean full-term infant birth weight, however, was comparable to that of the Canadian population.[21] The unusually large proportion of smokers and wide range of gestational weight gain provided an opportunity to assess the interaction among these variables in influencing infant size. Any possible sampling bias due to the high proportion of smokers was controlled through stratified analysis.

Smokers were different from nonsmokers in many respects: they were thinner and gained less weight during pregnancy. These results are consistent with those reported elsewhere,[22] especially among women of lower socioeconomic status.[11] Despite these differences, the effect of smoking on reducing birth weight in our population was independent of maternal weight status, which is also consistent with other studies.[23]

Predictors of mean birth weight, length and head circumference were similar for smokers and nonsmokers. These variables generally agree with determinants of low birth weight cited in previous studies.[24,25] Our results further showed that weight gain had a greater effect on infant length in smokers than nonsmokers: *i.e.* lower weight gains among smokers could involve greater reductions in infant length.

Figure 1 shows that birth weight increased with maternal weight gain at similar rates in different pregravid weight groups except that it reached a plateau among overweight nonsmokers with greater weight gains. Such a non-linear relationship may partly explain the previously reported interaction between weight gain and pregravid weight when using linear regression analysis.[7,26]

Figure 2 shows a dose-response relationship between birth weight and smoking level adjusted for other birth weight predictors. The reduction in birth weight attributed to light smoki ıg (between one and five cigarettes/day) was approximately 160 g, which was comparable to the difference between light and heavy smokers (more than 20 cigarettes/day). Although it is possible that other unmeasured confounders or an under-reporting of the number of cigarettes smoked affected the results, one must consider that the mere habit of smoking, irrespective of its intensity, may create a physiological condition unfavourable to fetal growth. Cigarette smoke components (nicotine, carbon monoxide, hydrogen cyanide, and nitrogen oxides) are shown to depress tissue uptake and placental transfer of amino acids, which are required for fetal growth.[27] Thus an increase in substrate intake as reflected by greater weight gain may partially ameliorate the negative effect of smoking, but with the possible undesirable effect of increasing maternal weight postpartum. Rather, a complete smoking cessation would be much more desirable than a partial reduction or compensation by weight gain

The observed differences in the effects of maternal weight status on birth weight and SGA risk between smokers and nonsmokers point to some important considerations in the nutritional management of pregnancy.

While weight gain significantly predicted mean birth weight in all groups, Table III shows that weight gain was not a significant predictor of the risk of SGA infants among nonsmokers. This may be explained by the lower overall risk of SGA seen in Figure 3A among nonsmokers, particularly the overweight or normal weight women. Even among underweight nonsmokers, the relatively higher SGA risk was effectively reduced at the upper range of currently recommended weight gain levels.[20] In contrast, underweight and normal weight smokers as indicated in Figure 3B have relatively high SGA risks (greater than 10%) even at excessive weight gains, especially among the underweight where the risk remained above 10% throughout the entire weight gain range. Thus, underweight smokers are at a particularly high risk of having an SGA infant, even when exceeding currently recommended weight gain levels.

To estimate average weight gains associated with a mean full-term birth weight of 3,500 g, the regression equations of Table II indicate that while a weight gain of 12 kg is appropriate for nonsmokers, conforming well with published standards,[20] a 20 kg weight gain is required to reach this birth weight among smokers.

These results clearly demonstrate that smoking cessation would be a more desirable alternative than attempting to mitigate the effect of smoking by increasing weight gain to undesirable levels from maternal and fetal perspectives.[28] Smoking during pregnancy is of special concern because of its effect on the proportion of SGA infants, particularly among underweight women. An encouragement of complete smoking cessation through various approaches while weight gain is tailored to individual maternal characteristics should be a prime concern in prenatal health education.

Acknowledgement

The effort and commitment of the PEI Community Nutritionists in the collection of these data are gratefully acknowledged.

TABLE I: Infant and Maternal Characteristics in the PEI Study Population

	All subjects	Nonsmokers	Smokers	p Value
	n = 1330	n = 601	n = 729	
	(mean ± standard deviations, or percentage)			
Infant variables				
Gestational age (wk)	39.6±1.2	39.8±1.2	39.5±1.2	NS
Birth weight (g)	3441±506	3608±481	3303±483	<0.0001
Length (cm)	51.4±3.0	52.0±2.8	50.8±3.0	<0.0001
Head circumference (cm)	34.8±1.5	35.1±1.4	34.5±1.5	<0.0001
%SGA* (<10th percentile)	11.2%	5.4%	16.0%	<0.0001
Maternal variables				
Maternal age (years)	23.2±5.2	24.1±5.7	22.4±4.8	<0.0001
Pregravid weight (kg)	59.4±13.4	61.5±14.5	57.6±12.1	<0.0001
Maternal height (cm)	161±6	161±6	161±6	NS
Standard weight (kg)	54.9±6.1	55.3±6.6	54.6±5.7	<0.05
Weight above standard (kg)	4.4±11.1	6.1±12.2	3.0±9.8	<0.0001
Body mass index (kg/m^2)	22.9±4.9	23.7±5.4	22.3±4.4	<0.0001
Weight gain (kg)	15.3±6.1	16.2±6.0	14.5±6.1	<0.0001
Parity (% primiparous)	50.9%	52.8%	49.2%	NS
Pregnancy interval (yr)	2.7±2.7	2.7±2.8	2.7±2.6	NS
Post-secondary education	13.5%	23.0%	5.6%	<0.0001
Married status	57.6%	65.6%	50.9%	<0.0001
Employment	22.2%	29.4%	16.0%	<0.0001
Cigarettes/day	---	---	13.8±8.7	

* Small for gestational age

NS No significant difference between smokers and nonsmokers

TABLE II: Regression Models of Infant Size Indicators by Smoking Status

	Nonsmokers (n=601)	Smokers (n=729)
	(Regression coefficients estimates)	
A. Infant birth weight (g):	β ± SE	β ± SE
Y-intercept	−2237.4±586.0 ***	−2638.2±515.9 ***
Weight gain (kg)	22.5±3.0 ***	25.7±2.7 ***
Standard weight (kg)	9.8±2.6 ***	11.3±2.7 ***
Weight above standard (kg)	8.7±1.5 ***	8.5±1.6 ***
Gestational age (weeks)	121.6±14.5 ***	124.3±13.0 ***
Parity (primi/multi)	103.3±35.8 **	106.5±31.9 ***
Cigarettes/day	---	−3.4±1.7 *
	R-square = 0.25	R-square = 0.31
B. Infant Length (cm):	β ± SE	β ± SE
Y-Intercept	31.7±3.6 ***	24.4±3.5 ***
Weight gain (kg)	0.046±0.018 **	0.120±0.020 ***
Standard weight (kg)	0.044±0.16 **	0.050±0.019 **
Weight above standard (kg)	0.028±0.009 **	0.019±0.011 *
Gestational age (weeks)	0.43±0.09 ***	0.55±0.09 ***
Parity (primi/multi)	−0.21±0.22 NS	0.47±0.22 *
Cigarettes/day	---	−0.01±0.01 NS
	R-square = 0.08	R-square = 0.16
C. Head Circumference (cm):	β ± SE	β ± SE
Y-intercept	22.9±1.9 ***	19.9±1.8 ***
Weight gain (kg)	0.034±0.010 ***	0.048±0.009 ***
Standard weight (kg)	0.022±0.008 **	0.027±0.009 **
Weight above standard (kg)	0.019±0.005 ***	0.025±0.005 ***
Gestational age (weeks)	0.26±0.05 ***	0.31±0.04 ***
Parity (primi/multi)	−0.03±0.11 NS	0.10±0.11 NS
Cigarettes/day	---	−0.003±0.006 NS
	R-square = 0.11	R-square = 0.17

Significance test of the regression coefficient being different from zero: * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$), NS (not significant). Significance test of the regression coefficient being different between smokers and nonsmokers based on pooled standard error of the estimates yielded $p<0.05$ for weight gain coefficient for infant length, and significance for all other coefficients.

TABLE III:

Logistic Regression Models of Small-for-gestational-age Infants by Smoking Status

	Nonsmokers (n=601)	Smokers (n=729)
Overall proportions	5.4%	18.0%
Variables	Regression coefficient estimates	
	β ± SE	β ± SE
Y-intercept	1.30±1.3 ^{NS}	2.34±0.68 ***
Weight gain (kg)	−0.05±0.04 ^{NS}	−0.10±0.02 ***
Pregravid weight (kg)	−0.06±0.02 **	−0.05±0.01 ***

Significance test of the regression coefficient being different from zero: * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$), NS (not significant). Significance test of the regression coefficient being different between smokers and nonsmokers based on pooled standard error of the estimates, yielded no significance for all coefficients.

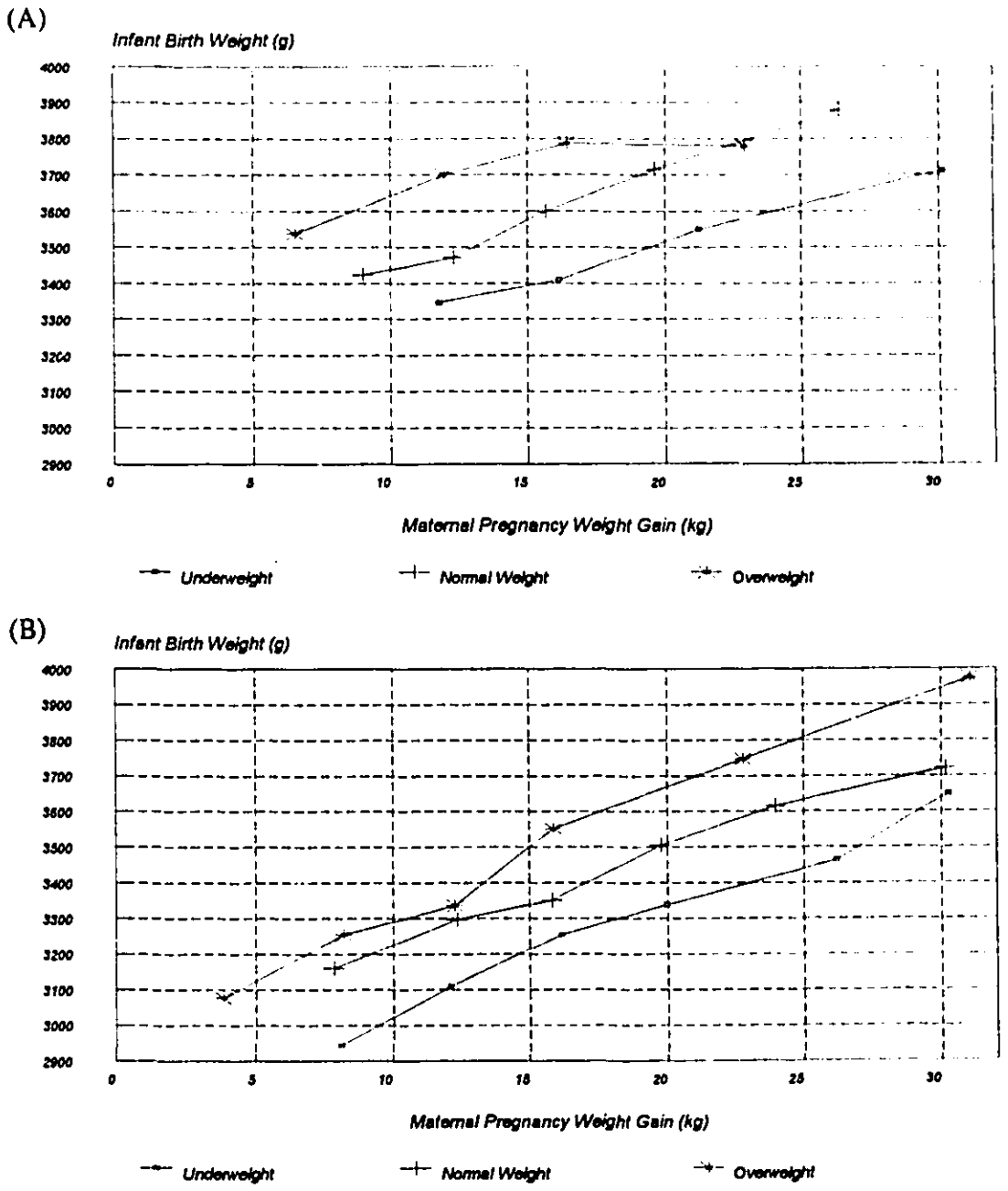

Figure 1. Infant birth weight vs. gestational weight gain stratified by maternal Body Mass Index: (A) in nonsmoking mothers, (B) in smoking mothers.

Mean birth weight was adjusted for parity, gestational age and infant sex, and further adjusted for smoking level among smokers to an avenge of 14 cigarettes per day. Weight gain increments of 4 kg were used giving at least 30 subjects per group.

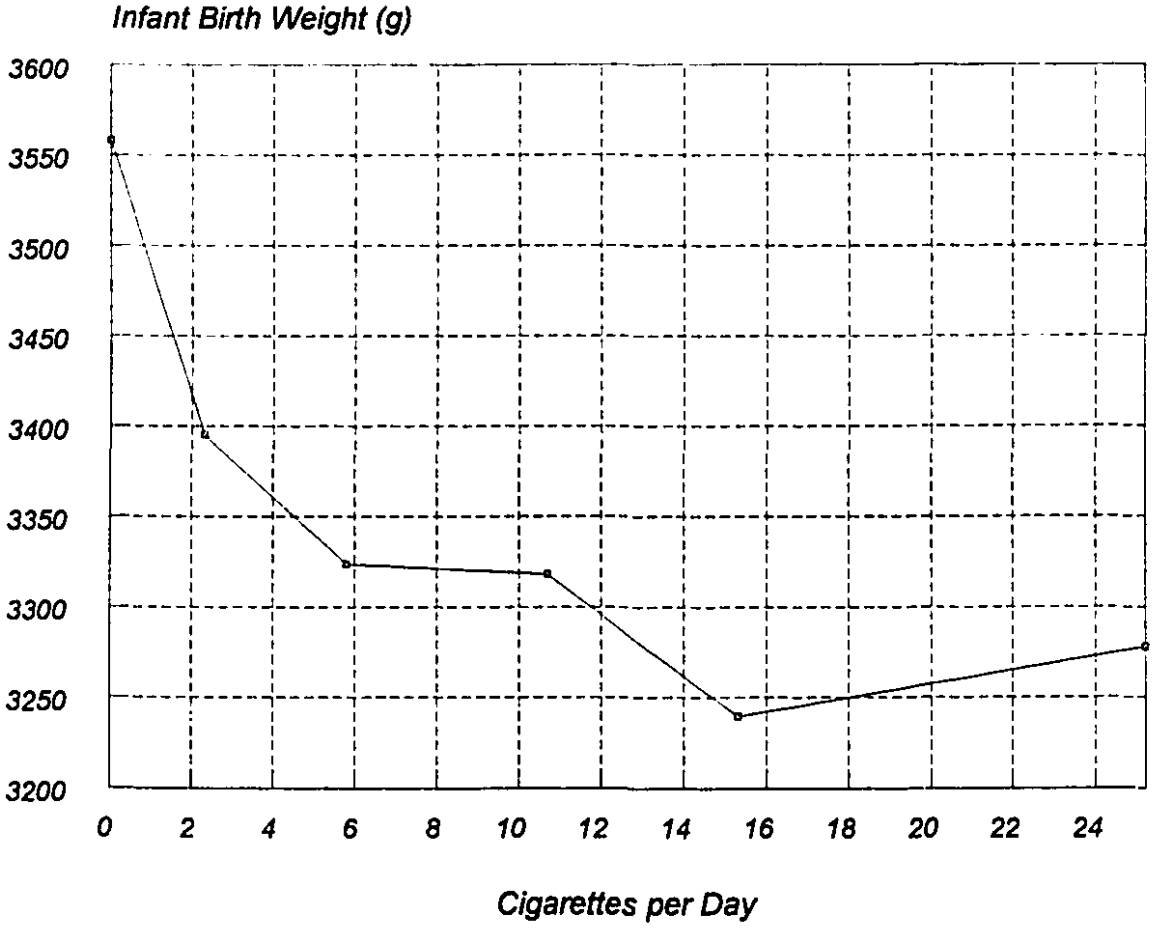

Figure 2. Infant birth weight vs. smoking level.

Mean birth weight was adjusted for gestational age, infant sex, maternal weight gain and parity.

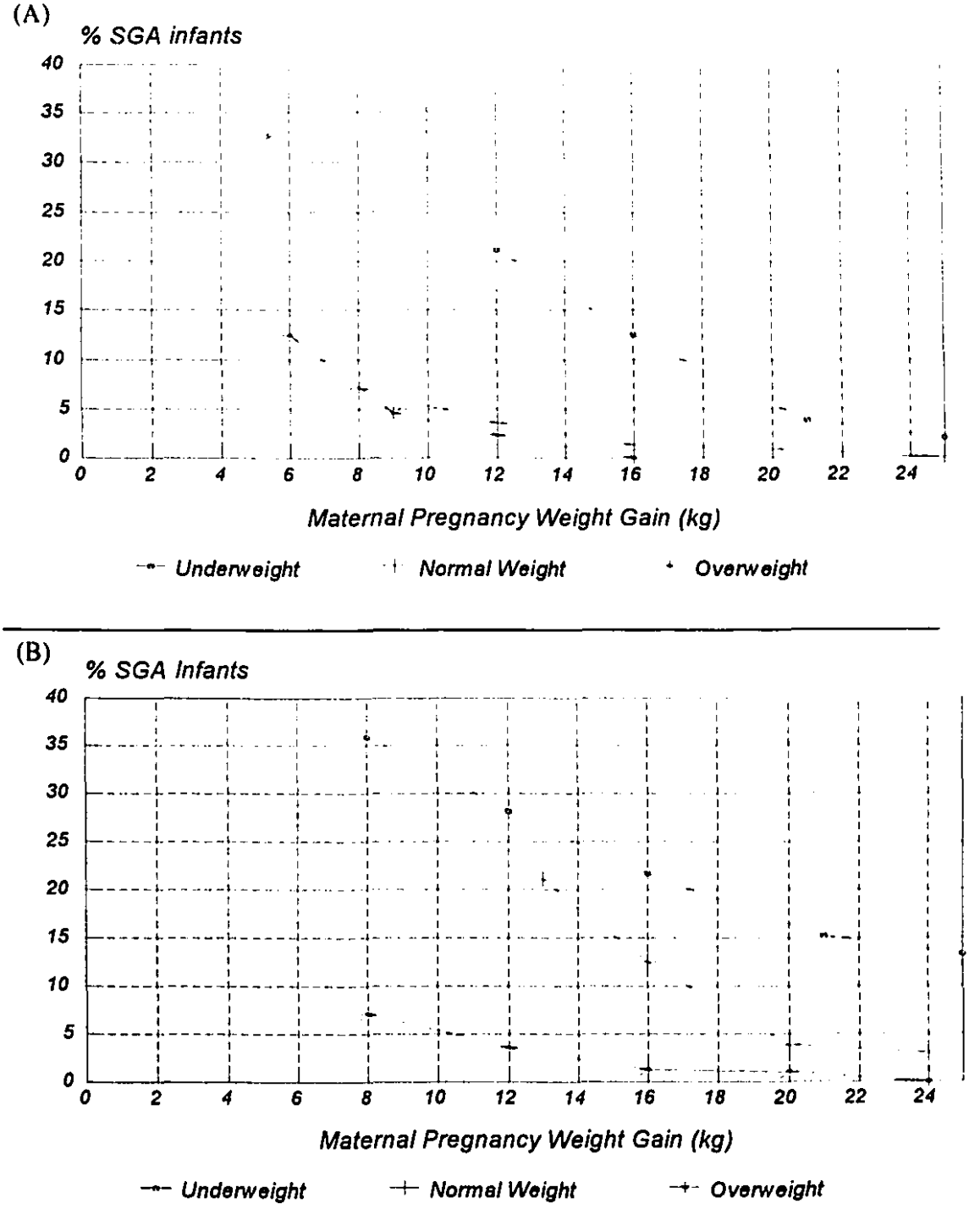

Figure 3. Proportion of SGA infant vs. gestational weight gain stratified by maternal body mass index: (A) in nonsmoking mothers, (B) in smoking mothers

References

1. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;312:82-90.
2. Saugstad LF. Weight of all births and infant mortality. J Epi Commun Health 1981;35:185-93.
3. Sappenfield WM, Buehler JW, Binkin NJ, Hogue CJR, Strauss LT, Smith JC. Differences in neonatal and postneonatal mortality by race, birthweight, and gestational age. Public Health Report 1987;102:182-192.
4. Buehler JW, Kleinmann JC, Hogue CJR, Strauss LT, Smith JC. Birthweight-specific infant mortality, United States, 1960 and 1980. Public Health Report 1987;102:151-61.
5. Ash S, Fisher CC, Truswell AS, Allen JR, Irwig L. Maternal weight gain, smoking and other factors in pregnancy as predictors of infant birth weight in Sydney women. Australian & New Zealand J Obstet & Gynaecol 1989;29(3):212-9.
6. Abell TD, Baker LC, Ramsev CN. The effects of maternal smoking on infant birth weight. Family Medicine 1991;23(2):103-7.
7. Abrams BF, Laros RK. Prepregnancy weight, weight gain, and birth weight. Am J Obstet Gynecol 1986;154:503-9,
8. Secher NJ, Hjortdal J, Hjortdal V. Smoking affects fetal growth selectively. Acta Obstetricia Et Gynecologica Scandinavica 1990;69(6):469-71.
9. MacArthur C, Knox EG. Smoking in pregnancy: effects of stopping at different stages. Brit J Obstet & Gynaecol 1988;95(6):551-5.
10. Souza SW, Black P, Richards B. Smoking in pregnancy: Associations with skinfold thickness, maternal weight gain, and fetal size at birth. Br Med J 1981;282:161.

11. Rush D, Andrews J, Kristal A. Maternal cigarette smoking during pregnancy, adiposity, social class, and perinatal outcome in Cardiff, Wales, 1965-1977. Am J Perinatology 1990;7(4):319-26.
12. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. BMJ 1989;298(6676):795-801.
13. Rush D, Cassano P, Harlap S. Perinatal outcome, maternal weight gain, cigarette smoking and social status in Jerusalem. Revue D Epidemiologie et de Santé Publique 1988;36(3):186-95.
14. McDonald AJ, Newson EE. Dietary changes made by low-income nutritionally high-risk pregnant women. J Can Diet Assoc 1986;47:21-25.
15. PEI Department of Health and Social Services. Manual for an on-going evaluation of the pre-natal nutrition counselling services 1982:4.
16. Haiek L, Lederman SA. The relationship between maternal weight for height and term birth weight in teens and adult women. J Adolesc Health Care 1988;10:16-22.
17. Gibson RS. Principles of Nutritional Assessment. New York, NY: Oxford University Press 1990.
18. Willett W. Nutritional Epidemiology. New York, NY: Oxford University Press 1990.
19. Metropolitan Life Insurance Company. Metropolitan height and weight tables. Stat Bull Metrop Life Found 1983;64:3-9.
20. National Academy of Science: Institute of Medicine (U.S.). Nutrition during pregnancy: Part I, weight gain. Subcommittee on Nutritional Status and Weight Gain During Pregnancy. Washington: National Academy Press, 1990:10-11 or 178-83.
21. Arbuckle TE, Sherman GJ. An analysis of birth weight by gestational age in Canada. Can Med Ass J 1989;140:157-65.

22. Mitchell MC, Lerner E. A comparison of pregnancy outcome in overweight and normal weight women. J Am College of Nutrition 1989;8(6):617-24.
23. Howarth JC, Ellestad-Sayed JJ, King J, Dilling LA. Fetal growth retardation in cigarette smoking mothers is not due to decreased maternal food intake. Am J Obstet Gynecol 1980;137:719-23.
24. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Org 1987;65(5):663-737.
25. Heins HC, Nance NW, McCarthy BJ, Efird CM. A randomized trial of nurse midwifery prenatal care to reduce low birthweight. Obstet Gynecol 1990;75:341-5.
26. Frentzen BH, Dimperio DL, Cruz AC. Maternal weight gain: Effect on infant birth weight among overweight and average-weight low-income women. Am J Obstet Gynecol 1988;159:1114-7.
27. Sastry BVR, Mouton S, Janson VE, Kambam JR. Tobacco Smoking by Pregnant Women: Disturbance in metabolism of branched chain amino acids and fetal growth. Ann NY Acad Sci 1993;566:361-3.
28. Johnson JWC, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. Am J Obstet Gynecol 1992;167:353-72.

Epilogue to Manuscript A

Manuscript A showed that smokers had lower pregravid weight, gestational weight gain and infant birth weight than nonsmokers. However, the effect of cigarette smoking on reducing infant birth weight, remained substantial even after controlling for maternal pregravid weight and gestational weight gain. Smoking, pregravid weight and weight gain acted independently on infant birth weight. The rate of increase in infant birth weight with increasing maternal weight gain was not significantly different between smoking and nonsmoking women of different pregravid weight status categories. However, the birth weight of infants born to overweight nonsmoking mothers reached a plateau at weight gains greater than 17 kg. This implies no significant interactive effects among these three predictors on birth weight, *i.e.* neither smoking nor maternal weight status modified the effect of gestational weight gain on infant birth weight at weight gains < 17 kg. Gestational weight gain, however, had a greater effect on infant length in smokers than in nonsmokers when controlling for maternal pregravid weight.

The risk of SGA decreased with increasing maternal weight gain among nonsmoking women, but among underweight smokers the risk of SGA remained high even at weight gains > 20 kg. Finally a clear dose-response effect of the level of maternal cigarette smoking on reducing infant birth weight was observed.

Manuscript B will investigate whether the lower maternal weight before and during pregnancy, and/or the lower infant birth weight among smokers as observed in Manuscript A are mediated by lower energy intake or higher energy

expenditure. It will explore the relative importance of the three modifiable SGA risk factors (pregravid underweight, low gestational weight gain and smoking), by calculating their independent contributions to the risk of SGA infants at the population level using etiologic fractions.

4.5 *MANUSCRIPT B*

Increased energy intake in pregnant smokers does not reverse fetal growth retardation

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Abstract

A retrospective cohort study of 729 smoking and 610 nonsmoking pregnant women participating in the PEI Prenatal Nutritional Counselling Program (1979-1989) was undertaken to study whether lower energy intake results in lower maternal weight and/or a higher rate of small-for-gestational-age infants (SGA) among smokers. A second objective was to quantify, using etiologic fractions, the independent contributions of cigarette smoking, maternal pregravid underweight and low pregnancy weight gain to the risk of SGA. Measurements of maternal pregravid weight, height, pregnancy weight gain, smoking status, physical activity, energy intake by a series of 3-day food records throughout the duration or pregnancy, and infant birth weight were collected for women with uncomplicated pregnancies resulting in full-term singleton infants. Multiple linear regression analyses to predict the effect of smoking on maternal energy intake, weight gain, and infant birth weight were performed. The independent contributions of smoking, pregravid underweight, and low pregnancy weight gain to the risk of SGA were determined using logistic regression analysis. The results showed that smoking was independently associated with higher energy intake (+168 kcal/d), but with lower maternal weight gain (−2.16 kg) and infant birth weight (−205 g). Dietary energy intake was positively associated with only a small increment in birth weight (5.9 g/100 kcal). The etiologic fraction for SGA attributable to smoking was 30.8%, pregravid underweight 16.7%, and low gestational weight gain 15.3%. We conclude that the important negative effect of smoking on retarding fetal growth cannot be adequately mitigated by simply increasing energy intake.

Introduction

Despite the steady decline in cigarette smoking among the general population in the US and Canada, approximately one quarter of women of reproductive age (18-44 yr) in both countries still report regular smoking (1-3). Although some of these women stop smoking during pregnancy, approximately 20% of all pregnant women continue to smoke after the first trimester (4-6). Smoking is known to suppress fetal growth directly through depressing tissue uptake and placental transfer of oxygen and nutrients to the fetus (7-9). Some studies also report lower maternal pregravid weight and lower weight gain during pregnancy among smoking women, thereby implying an indirect effect of smoking in reducing fetal growth (10-12).

Since the 1970's, it has been suggested that the negative consequences of smoking on fetal growth may be nutritional in origin and that nutritional supplementation of pregnant smokers may prevent reduced maternal weight gain and infant birth weight (11,13-15). Cross-sectional evidence regarding non-pregnant women suggests that smokers consume more energy than nonsmokers and stay leaner (16-18). However, dietary studies comparing energy intake between pregnant smokers and nonsmokers are not as consistent and report higher, lower or similar average daily energy intakes (10,19-21), which are also associated with significant and non-significant increases or decreases in maternal weight gain (10-12,14) and significant decreases in infant birth weight (22-26).

Established determinants of low birth weight in developed countries include in ranked order, cigarette smoking, low energy intake or maternal

weight gain, low prepregnancy weight, primiparity, female infant gender, short stature, non-white race, maternal low birth weight and a prior history of low birth weight, with the first five explaining more than 75% of intrauterine growth retardation (7,22,27). Since smoking can also cause increased rates of prematurity (9,28,29), gestational age must be controlled in all analyses. To date no dietary study has simultaneously controlled for all these variables making it difficult to resolve the independent contribution of increased energy intake during pregnancy to maternal weight gain and infant birth weight in pregnant smokers.

The purpose of the present study is to establish if lower maternal weight gain and/or intrauterine growth retardation in smokers, are mediated by lower energy intake while also controlling for known potential confounders of infant birth weight and including those which may have an impact on energy intake or expenditure (*e.g.* maternal weight, height, physical activity). The study further explores the extent to which each of the potentially modifiable risk factors of infant birth weight, namely maternal pregravid underweight, low pregnancy weight gain and cigarette smoking independently contribute to the risk of small-for-gestational-age (SGA) infants. The etiologic fraction for each of these factors provides a measure of the extent to which each factor is independently responsible for the prevalence of SGA infants.

Subjects and methods

The study population consisted of 601 nonsmoking and 729 smoking white healthy pregnant adult women (16-39 y) who were delivered of singleton infants between 1979 and 1989 with no pregnancy complications. The pregnancies were followed by nutritionists at the Prenatal Nutrition Counselling Program of the

Department of Health & Social Services of Prince Edward Island, Canada. As with the WIC program (30), individual dietary counselling is provided to pregnant women of limited family income.

Gestational length was estimated from the date of the last menstrual period based on family physicians' records. Pregravid weight was also obtained from the family physicians' records. Measurement of maternal weight was done by a dietitian using a balance scale with women wearing light indoor clothing and no shoes. Infant birth weight was obtained from hospital records. The level of physical activity during early pregnancy was assessed upon admission as sedentary, moderate or heavy by using the method described in the 1975 Canadian Dietary Standard (31), which is based on counting the number of hours spent daily on the following activities: resting, sitting, light, moderate or heavy work and exercise both indoors and outdoors.

Upon admission, an assessment of initial daily energy and protein intake was calculated by a dietitian from a diet history (20). Subsequently, average intakes of energy and protein were calculated from the three-day food records completed at regular visits throughout pregnancy. The total number of visits per woman ranged from 4 to 15. The average intake during the entire pregnancy was calculated as the mean of initial intake and subsequent intakes, with each intake weighted for the duration it represented. To ensure their accuracy, all dietary data reported by the mother were cross-checked for consistency with information from her food shopping lists, and size of her household as determined by a home visit to verify her description of food preparation methods. To minimize human errors, all calculations used in the dietary assessment were verified by a second nutritionist.

Statistical analysis

Univariate comparison of maternal and infant weight variables between smokers and nonsmokers was done using Student's t-test for continuous variables, and chi-square test for categorical variables. Pregravid weight was divided into two uncorrelated components; (a) standard weight for height and frame size based on the 1983 Metropolitan Life Insurance company tables (32), and (b) excess pregravid weight expressed as the difference between actual and standard weight at conception. Small-for-gestational-age (SGA) was defined as birth weight falling below the 10^{th} percentile specific for infant gender and gestational age using the 1986 birth weight distribution of Canadian infants (33).

The relationship between cigarette smoking and energy intake was investigated by comparing the intake of smokers and nonsmokers and by correlating the number of cigarettes smoked with energy intake. Multiple regression analysis was performed for energy intake (kcal/d) as the outcome variable in order to estimate its independent association with smoking status, level of physical activity, standard pregravid weight for height and excess pregravid weight. Similar analyses were performed for maternal weight gain and infant birth weight. Parity, infant gender and gestational age were also controlled in these analyses.

In order to calculate the etiologic fractions of SGA attributed to maternal smoking status, low pregravid weight, and low pregnancy weight gain at term, multiple logistic regression analysis was used to obtain the odds ratio (OR) for each factor. Pregravid underweight was defined as $<90\%$ of standard weight for height and frame size in accordance with the 1983 Metropolitan Life Insurance company standards (32). This cut-off coincides with approximately the

25th percentile of the US population (34). Low maternal weight gain was defined as weight gain < 10 kg at term (40 weeks) which coincides with the 25th percentile of the US population described by the 1980 National Natality Survey (34). The prevalence of smoking among pregnant US and Canadian women was taken as 20% (4-6). To estimate the contribution of each risk to the prevalence of SGA infants in the population, the etiologic fraction (EF) was computed as: $EF = P(OR-1)/\{P(OR-1)+1\}$, where P is the prevalence of each risk factor in the general population.

Statistical analyses were done using SAS software for Personal Computers Version 6.04, 1990 (SAS Institute Inc., Cary, NC). The level of statistical significance was chosen as $p<0.05$.

Results

Maternal and infant characteristics of smokers and nonsmokers are provided in **Table I**. On average, smoking mothers consumed 13.8 cigarettes per day. Smokers reported higher energy intake and slightly higher levels of physical activity than nonsmokers. Smokers also entered pregnancy at a lower weight for height status and were twice as likely to have low pregnancy weight gain (< 10 kg at term) and three times more likely to have SGA infants ($p<0.0001$) than nonsmokers.

The multiple regression analysis for energy intake in **Table II** included smoking, physical activity and infant gender which were the only predictors showing independent effects. This analysis indicates that smokers consumed more energy by 168 kcal/d than nonsmokers for similar physical activity. Each successive level of physical activity from sedentary to moderate to heavy was

associated with increased energy consumption by an average of 38.5 kcal/d. Interestingly, pregnant women carrying male infants consumed 145 kcal/d more than those with female infants.

The multivariate model for maternal weight gain from **Table II** indicated that maternal smoking, physical activity, standard weight for height, excess pregravid weight, parity, gestational length and infant gender were all associated with maternal weight gain. Smoking decreased weight gain independently of all other predictors. Maternal standard weight for height was associated with increased maternal weight gain; while excess pregravid weight was associated with decreased maternal weight gain. Multiparous women gained less weight during pregnancy than their nulliparous counterparts. Women pregnant with male infants gained more weight than those with female infants. Average daily energy intake did not significantly predict maternal weight gain. To investigate whether the effect of smoking could have masked this relationship, correlation analysis between energy intake and maternal weight gain was performed separately for smoking and nonsmoking mothers, and a significant correlation was observed among nonsmoking mothers ($r=0.22$, $p<0.0001$). Among smoking mothers, however, energy intake and weight gain were not correlated even after adjusting for the level of cigarette smoking. Further correlation analyses for the daily level of cigarette consumption among smokers indicated that the more cigarettes a mother smoked, the higher her energy intake ($r=0.15$, $p<0.0001$), the lower her weight gain ($r=-0.27$, $p<0.0001$) and the lower her infant birth weight ($r=-0.19$, $p<0.0001$).

The prediction model for infant birth weight from **Table II** showed the expected independent effect of smoking in lowering birth weight. In addition, birth weight was positively associated with maternal standard weight, excess

pregravid weight, dietary energy intake, physical activity, multi-parity, gestational length and male infant gender. Dietary intake predicted a 5.9 g higher birth weight for every 100 kcal/d ingested. Interestingly, physical activity was associated with higher birth weight infants and higher energy intakes but not higher maternal weight gains.

The results of multiple logistic regression analysis given in **Table III** provide the independent effects on SGA for each of the main risk factors. The odds ratio was 3.23 ($p<0.001$) for smoking, 1.80 ($p<0.0001$) for pregravid underweight, 1.72 ($p=0.003$) for low weight gain, 0.87 ($p<0.001$) for 1 kg increment in standard pregravid weight for height (which translates into 0.5 relative risk for every 5 kg increase in weight), and 0.81 ($p=0.04$) for physical activity when it is increased by one level (*e.g.* from sedentary to moderate). Energy intake was not a significant predictor in this analysis and was excluded from the model. The risk of SGA infants decreased with higher standard pregravid weight for height and with increased physical activity.

Based on available prevalence data for smoking, pregravid underweight and low weight gain, we calculated the population etiologic fractions using our estimated odds ratios. The calculations provided an estimate of the percentage of SGA directly attributed to smoking of 30.8%, which represents the percentage of SGA infants that would not occur if all women who smoke during pregnancy (20% of the population) were to stop smoking early in their pregnancy. Similarly, SGA births attributed to pregravid underweight status (<90% of standard weight for height) and low weight gain (< 10 kg) were 16.7% and 15.3% respectively.

Discussion

Recent surveys have reported that smoking during pregnancy has declined in the 1990's in the US and Canada to 20% (4-6). This paper shows that even with such reduced prevalence, the impact of smoking on SGA births remained substantial with an etiologic fraction of approximately 31%. This represents the direct effect of smoking on retarding fetal growth that is not attributable to maternal weight variables. In this study, the etiologic fraction for SGA attributable to smoking alone was approximately double that attributable to either of the two other major risk factors, *i.e.* pregravid underweight and low weight gain. Therefore, a major portion of SGA would still remain because of the direct effect of smoking, even if adequate dietary measures were taken before or during pregnancy to increase maternal weight. Such dietary measures may improve birth weight, but very high maternal weight gains have aslo been associated with increased SGA and maternal postpartum weight retention (34-36).

In our study, smokers reported consuming more energy than nonsmokers, yet they gained less weight during pregnancy for similar physical activity. These findings have two implications. First, the indirect effect of smoking on reducing infant birth weight through lower weight gain was not mediated by appetite suppression as suggested earlier (11,13-15). Second, some aspect of smoking seems to use up energy that is not directed towards maternal weight gain and fetal growth. Our finding that dietary intake during pregnancy was positively correlated with the level of cigarette smoking is consistent with reported findings of an acute effect of increased BMR in non-pregnant smoking women (37-39). Our pregnant smokers seem, therefore, to have elevated energy needs that are possibly related to increased BMR, similar to what has been reported for the non-pregnant state.

It is interesting to find that maternal physical activity had a positive effect on infant birth weight, without a significant effect on maternal weight gain. Reports from the literature indicate either no association (40-42), or a marginal positive association between birth weight and activity (43,44). Strenuous physical work in poor settings, however, has been linked to preterm delivery and therefore lower birth weight (45). The significant positive association between the level of maternal physical activity and birth weight in our study could be due in part to healthier lifestyle among more active women such as higher dietary quality and better health status.

Energy intake, in this study, correlated with maternal weight gain during pregnancy only among nonsmokers but not among smokers, even after controlling the number of cigarettes smoked daily. These findings are similar to those of Picone *et al* (10). It seems that the level and intensity of cigarette smoking mask the relationship between energy intake and maternal weight gain, possibly by introducing large variability not only in metabolic energy expenditure but also in other unmeasured physiological or behavioral factors affecting weight gain. In other words heavier smokers may consume and spend more energy without necessarily gaining more weight. Although in this study dietary energy intake was positively associated with infant birth weight, this effect was relatively small: ~6 g of infant birth weight for every 100 kcal/d. Such a small positive dietary effect of energy intake compared to a smoking effect of −205 g indicates that excessively high dietary intake would be required to compensate for even a small part of the effect of smoking.

In summary, suggestions by clinicians that smokers increase their food intake to prevent SGA are not supported by the findings of this study.

Evaluations of nutritional supplementation in controlled clinical trial have indicated modest increases in birthweight of 30 g (46). In contrast, estimates of the negative effect of smoking on birth weight range from 70 to 356 g (23-25,47). In addition, it has been observed that complete smoking cessation early in pregnancy can improve birth weight by 90-217 g (48-51). Because of the greater birth weight changes precipitated by restricting smoking behavior, healthcare practioners should not ignore this approach and overly promote nutritional supplementation and increased energy intake, except among the underweight and low weight gain pregnant smokers who have a very high risk for SGA and where demonstrable improvement has been observed (7,26).

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Table I: Maternal and infant characteristics in smokers and nonsmokers, means ± SD, or % risk

Variable	Nonsmokers	Smokers	p-value
	n=601	n=729	
Excess weight at conception (kg)	6.1±12.2	3.0±9.8	<0.0001
Pregravid underweight (<90% standard weight for height)	19.1%	28.7%	<0.0001
Energy average intake (kcal/d)	2462±573	2622±605	<0.0001
Maternal weight gain (kg)	16.2±6.0	14.1±6.1	<0.0001
% Low weight gain (< 10 kg at term)	13.6%	26.0%	<0.0001
Smoking level (Cigarettes/day)	----	13.8±8.7	----
Physical Activity (sedentary=0, moderate=1, heavy=2)	0.5±0.8	0.6±0.9	0.002
Infant birth weight (g)	3606±481	3303±483	<0.0001
Risk of SGA infants	5.4%	16.0%	<0.0001

Table II: Predictors of energy intake, maternal weight gain and infant birth weight

	Energy Intake (kcal/d)		Maternal weight gain (kg)		Infant birth weight (g)	
Variable	**β ± SE**	**p-value**	**β ± SE**	**p-value**	**β ± SE**	**p-value**
Y-intercept	2331.9±549.1	<0.0001	−13.36±4.64	0.007	−3472.1±325.1	<0.0001
Smoking (no=0, yes=1)	167.6±74.8	0.025	−2.16±0.33	<0.0001	−204.7±23.3	<0.0001
Physical Activity (sedentary=0, moderate=1, heavy=2)	38.5±12.0	0.014	−0.04±0.20	NS	19.1±9.3	0.040
Infant gender (f=0, m=1)	145.4±44.9	0.012	0.75±0.32	0.019	112.4±22.3	<0.0001
Standard pregravid weight (kg)			0.15±0.04	<0.0001	15.7±2.7	<0.0001
Excess weight at conception (kg)			−0.11±0.02	<0.0001	8.4±1.1	<0.0001
Parity (single=0, multiple=1)			−2.23±0.34	<0.0001	116.1±24.1	0.003
Gestational length (weeks)			0.56±0.10	<0.0001	151.2±7.3	<0.0001
Average energy intake (100 kcal/d)			0.01±0.07	NS	5.9±1.9	0.002
	R^2=0.25		R^2=0.12		R^2=0.42	

Table III: SGA risks attributable to smoking, pregravid underweight and low gestational weight gain

Variable	β ± SE	p-value	Odds ratio	Prevalence (P)	Etiologic fraction
Y-intercept	5.49±1.24	0.003			
Standard pregravid weight (kg)	−0.14±0.02	<0.0001	0.87		
Pregravid underweight (<90% vs. ≥90% of standard weight)	0.59±0.18	<0.0001	1.80	25%	16.7%
Low gestational weight gain at term (<10 vs. ≥10 kg)	0.54±0.19	0.003	1.72	25%	15.3%
Smoking (yes vs. no)	1.17±0.20	<0.0001	3.23	20%	30.8%
Physical Activity (sedentary=0, moderate=1, heavy=2)	−0.21±0.10	0.04	0.81		
Parity (multiple vs. single)	−0.29±0.18	NS			

Note: Etiologic fraction = P(OR−1)/{P(OR−1)+1}

References

1. National Center for Health Statistics (NCHS). Health United States, 1988. DHHS Publ No (PHS) 89-1232, Hyattsville, Md. 1989.
2. Health and Welfare Canada. Health Promotion Survey. Technical Report. Ottawa: Statistics Canada, 1988:17-32.
3. Health and Welfare Canada. The Active Health Report on Alcohol, Tobacco and Marijuana. Ottawa: Statistics Canada, 1989:7-8.
4. Steward PJ, Potter J, Dulberg C, Niday P, Nimrod C, Tawagi G. Change in smoking prevalence among pregnant women 1982-93. Can J Public Health 1995;86(1)37-41.
5. National Center for Health Statistics (NCHS). Health Promotion and Disease Prevention United States, 1990. DHHS Publ No (PHS) 93-1513, Hyattsville, Md. 1993.
6. Health Canada. Fact Sheets: Survey on Smoking in Canada, Cycle 3. February 1995.
7. Bakketeig LS, Jacobson G, Hoffman HJ, Lindmark G, Bergsjo MK, Rodsten J. Pre-pregnancy risk factors of small-for-gestational-age births among parous women in Scandinavia. Act Obstet Gynecol Scand 1993;72:273-9.
8. Sastry BVR, Mouton S, Janson VE, Kambam JR. Tobacco Smoking by Pregnant Women: Disturbance in metabolism of branched chain amino acids and fetal growth. Ann NY Acad Sci 1993;566:361-3.
9. Wilcox AJ. Birth weight and perinatal mortality: the effect of maternal smoking. Am J Epidemiol 1993;137:1098-104.
10. Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. I. Effects of diet, cigarette smoking and psychological stress on maternal weight gain. Am J Clin Nutr 1982;36:1205-13.

11. Garn SM, Hoff K, McCabe KD. Is there nutritional mediation of the "smoking effect" on the fetus. Am J Clin Nutr 1979;32:1181-7.
12. Rush D, Andrews J, Kristal A. Maternal cigarette smoking during pregnancy, adiposity, social class, and perinatal outcome in Cardiff, Wales, 1965-1977. Am J Perinat 1990;7(4):319-26.
13. Davies DP, Gray OP, Ellwood PC, Abernethy M. Cigarette smoking in pregnancy: association with maternal weight gain and fetal growth. Lancet 1976;1:385-9.
14. Papoz L, Eschwege E, Pequignot G, Barrat J, Schwartz D. Maternal smoking and birth weight in relation to dietary habits. Am J Obstet Gynecol 1982;142:870-6.
15. Rush D. Examination of the relationship between birthweight, cigarette smoking during pregnancy and maternal weight gain. J Obstet Gynaecol Br Commonw 1974;81:746-52.
16. Cade J, Margetts B. Cigarette smoking and serum lipid and lipoprotein concentration. Br Med J 1989;298:1312.
17. Jacobs DR, Gottenborg S. Smoking and weight: The Minnesota Lipid Research clinic. Am J Public Health 1981;71:391-6.
18. Stamford BA, Matter S, Fell RD, Papneck P. Effects of smoking cessation on weight gain, metabolic rate, caloric consumption and blood lipids. Am J Clin Nutr 1986;43:486-94.
19. Haworth JC, Ellestad-Sayed JJ, King J, Dilling LA. Fetal growth retardation in cigarette smoking mothers is not due to decreased maternal food intake. Am J Obstet Gynecol 1980;137:719-23.
20. McDonald AJ, Newson EE. Dietary changes made by low-income nutritionally high-risk pregnant women. J Can Diet Assoc 1986;47:21-5.

21. Haste FM, Brooke OG, Anderson HR, Bland JM, Shaw A, Griffin J, Peacock J. Nutrient intakes during pregnancy: observations on the influence of smoking and social class. Am J Clin Nutr 1990;51:29-36.
22. Johnston C. Cigarette smoking and the outcome of human pregnancies: a status report of the consequences. Clin Toxicol **1981**;18:189-209.
23. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization 1987;65(5):663-737.
24. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. Br Med J 1989;298:795-801.
25. Secher NJ, Hjortdal J, Hjortdal V. Smoking affects fetal growth selectively. Acta Obstet Gynecol Scand 1990;69(6):469-71.
26. Muscati SK, Gray-Donald K, Newson EE. Interaction of smoking and maternal weight status in influencing infant size. Can J Public Health **1994**;85(6):407-12.
27. Goldenberg RL, Davis RO, Cliver SP, Cutter GR, Hoffman HJ, Dubard MB, Copper RL. Maternal risk factors and their influence on fetal anthropometric measurements. Am J Obstet Gynecol **1993**;168:1197-205.
28. Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP, Davis RO, DuBard MB. Smoking, maternal age, fetal growth, and gestational age at delivery. Am J Obstet Gynecol 1990;62(1):53-8.
29. Cnattinigius S, Forman MR, Berendes HW, Graubard BI, Isotalo L. Effect of age, parity, and smoking on pregnancy outcome: a population-based study. Am J Obstet Gynecol 1993;168:16-21.
30. US Government Accounting Office. *WIC evaluations provide some favorable but not conclusive evidence on the effects expected for the Special*

Supplemental Program for Women, Infants, and Children. Washington, January 30, 1984.

31. National Health and Welfare Canada, Bureau of Nutritional Sciences. Dietary Standard for Canada, 1975.
32. Metropolitan Life Insurance Company. Metropolitan height and weight tables. Stat Bull Metrop Life Found 1983;64:3-9.
33. Arbuckle TE, Sherman GJ. An analysis of birth weight by gestational age in Canada. Can Med Ass J 1989;140:157-65.
34. Kleinman JC. Maternal weight gain during pregnancy: determinants and consequences. NCHS Working Paper Series No. 33. U.S. Dept of Health and Human Services, National Center for Health Statistics, Hyattsville, Md. 1990.
35. Öhlin A, Rössner S. Maternal body weight development after pregnancy. Int J Obesity **1990**;14:159-73.
36. Muscati SK, Gray-Donald K, Koski KG. Timing of weight gain during pregnancy: promoting fetal growth and minimizing maternal weight retention. Int J Obesity **1996**;(in press).
37. Perkins KA, Epstein LH, Marks BL, Stiller RL, Jacob RG. The effect of nicotine on energy expenditure during light physical activity. N Engl J Med 1989;320:898-903.
38. Audrain JE, Klesges RC, DePue K, Klesges CM. The individual and combined effects of cigarette smoking and food on resting energy expenditure. Int J Obesity 1991;15:813-21.
39. Collins LC, Cornelius MF, Vogel RL, Walker JF, Stamford BA. Effect of caffeine and/or cigarette smoking on resting energy expenditure. Int J Obesity 1994;18:551-6.
40. Kulpa PJ, White BM, Visscher R. Aerobic exercise in pregnancy. Am J Obstet Gynecol 1987;156:1395-403.

41. Klebanoff MA, Shiono H, Carey JC. The effect of physical activity during pregnancy on preterm delivery and birth weight. Am J Obstet Gynecol 1990;163:1450-6.
42. Lokey EA, Tran ZV, Wells CL, Myers BC, Tran AC. Effects of physical exercise on pregnancy outcomes: a meta-analytic review. Med Sci Sports Exerc **1991**;23:1234-9.
43. Erkkola R. The physical work capacity of the expectant mother and its effect on pregnancy, labor, and the newborn. Int J Gynaecol Obstet **1976**;14:153-9.
44. Hall DC, Kaufman DA. Effects of aerobics and strength conditioning on pregnancy outcome. Am J Obstet Gynecol 1987;157:1199-203.
45. Homer CJ, Bereford SA, James SA. Work-related physical exertion and risk of preterm, low birthweight delivery. Paediatr Perinatal Epidemiol 1990;4:161-74.
46. Kramer M. Effects of energy and protein intakes on pregnancy outcome: an overview of the research evidence from controlled clinical trials. Am J Clin Nutr 1993;58:627-35.
47. Muscati SK, Gray-Donald K, Newson EE. Interaction of smoking and maternal weight status in influencing infant size. Can J Public Health 1994;85(6)407-12.
48. Sexton M, Hebel JR. A clinical trial of change in maternal smoking and its effect on birth weight. J Am Med Assoc 1984;251:911-5.
49. MacArthur C, Knox EG. Smoking in pregnancy: effects of stopping at different stages. Brit J Obstet Gynaecol 1988;95(6):551-5.
50. Mainous AG, Hueston WJ. The effect of smoking cessation during pregnancy on preterm delivery and birthweight. J Fam Pract 1994;38:262-6.
51. Frank P, McNamee R, Hannaford PC, Kay CR. Effect of changes in maternal smoking habits in early pregnancy on infant birthweight. Br J Gen Practice 1994;44(379):57-9.

Epilogue to Manuscript B

Manuscript B showed that the effects of maternal smoking on reducing both maternal pregravid weight at conception and gestational weight gain, were not mediated by lower dietary intake among smokers. To the contrary, smokers had a higher energy intake for similar physical activity than nonsmokers. The manuscript indicates that further increasing dietary intake by smokers would not effectively restore infant birth weight to comparable levels to nonsmokers, especially among underweight mothers who are found to be at higher risks of having SGA infants in Manuscript A. Although maternal dietary energy intake was positively associated with infant birth weight both in smokers and nonsmokers, this effect was relatively small compared to the large negative effect of smoking on birth weight.

At the population level, the proportion of SGA births due to the direct effect of smoking would still remain high at ~31%, even if the problem of low pregravid weight and low gestational weight gain could be corrected. The SGA portion due to smoking would be about twice that due to pregravid underweight or lower weight gain. The results of Manuscript B indicate that underweight smoking mothers gaining low weight gain during pregnancy are at an especially high SGA risk.

The combined results of Manuscripts A and B suggest that even if the negative effect of smoking on birth weight were to be partially mitigated by increasing weight gain through excessive dietary intakes, such a measure could expose the mother to the risks of pregnancy complications and/or postpartum obesity known to be associated with high gestational weight gain. This points to

the need for smoking cessation as an important measure for reducing the risk of SGA, in addition to the need for adequate nutrition before or during pregnancy. The improvement of weight status through a positive energy balance is important to counteracting the risk attributed to low weight gain, or possibly to compensate for low pregravid weight, but extra-high weight gain in normal or overweight women to compensate for the effect of smoking is unlikely to be of benefit.

Manuscripts A and B studied the effect of the total amount of weight gain on infant birth weight, without considering the effect of its timing. Manuscript C will explore the importance of the timing of weight gain to both neonatal and maternal outcomes. The literature review in Chapter 2 together with the findings in Manuscripts A and B show that smokers and nonsmokers substantially differ in several characteristics and relationships. Smoking is known to upset the chemical and metabolic balance of the body through various chemicals and toxins found in tobacco smoke, and is therefore expected to distort the normal course and outcome of pregnancy. For these reasons, Manuscript C will be restricted to nonsmokers in exploring the potential for a balance between promoting fetal growth and reducing the risk of postpartum obesity. The results will therefore be more meaningful to a healthy population not affected by substance abuse.

4.6 *MANUSCRIPT C*

Timing of weight gain during pregnancy: promoting fetal growth and minimizing maternal weight retention

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Abstract

Objective: To examine the association of the extent and timing of pregnancy weight gain with infant birth weight (IBW) and maternal postpartum weight retention (PPWR).

Design: Retrospective cohort study of pregnant women followed through 6 weeks postpartum.

Measurements: Birth weight and maternal weight gain before 20 weeks, 21-30 weeks, 31 weeks to term and postpartum weight retention were measured.

Subjects: A total of 371 healthy white nonsmoking pregnant women followed by the Prenatal Nutrition Counselling Program of the Department of Health and Social Services of the province of Prince Edward Island, Canada, between 1979 and 1989 who had uncomplicated pregnancies resulting in full-term singleton infants.

Results: Weight gain during pregnancy (> 12 kg) was associated with PPWR (>2.5 kg) in underweight, normal, and overweight women. Pregnancy weight gain explained 65.3% of the variability in PPWR, but very little of the variability (4.7%) in IBW. Predictors of IBW (gestational age, pregravid weight and infant gender) were not related to PPWR. Early maternal weight gain (≤20 weeks) was a strong predictor of PPWR. Comparisons of mothers with PPWR above and below the median of the group indicated important differences in early weight gain (≤20 weeks) for underweight (3.3 kg), normal weight (3.3 kg), and overweight (6.2 kg) mothers.

Conclusion: The results emphasize the importance of the timing of gestational weight gain and show an advantage in deferring a larger portion of required weight gain to late pregnancy (particularly in well-nourished overweight women) in order to promote fetal growth while reducing the risk of high weight retention and its potential adverse health consequences.

Introduction

Most research on weight gain during pregnancy has focused on the influence of its total amount on fetal growth,[1] with considerably less attention paid to the timing of weight gain or its effect on maternal postpartum weight retention (PPWR). Although adequate weight gain is important to assure optimal fetal growth, the negative health consequences of too high a total weight gain during pregnancy include higher risk of pregnancy induced hypertension, pre-eclampsia, and caesarean section.[2,3] It is also increasingly evident that excessive total weight gain during pregnancy is strongly associated with maternal weight retention at 6 months,[4] one year,[5] or at the start of a new pregnancy.[6] Therefore, the suggestion has arisen that the benefits of enhanced fetal growth, resulting from higher rates of weight gain during pregnancy should be balanced against the risks of pregnancy complications and maternal PPWR,[7] which consists primarily of fat tissue.[8] Such a balance could be facilitated by paying a closer attention to the timing of pregnancy weight gain in addition to its total amount.

Maternal fat accretion,[9] PPWR,[4-6,10] and fetal growth,[1] are influenced by weight gain during pregnancy. The most recent National Academy of Sciences recommendations define a desirable total weight gain range from 7-18 kg, depending on maternal pregravid weight, with a primary objective of promoting adequate fetal growth;[11] but no recommendations are given for the timing of weight gain, nor any mention of the implication for PPWR. However, several researchers have shown that weight gains in excess of 9-13 kg lead to a 3-6 kg residual weight retention 6-9 months later,[6,7,10] and women gaining 12.5 kg or more during the first pregnancy are reported to be at least 2.5 kg heavier at the

start of the next pregnancy after correcting for age and other covariates.[6] National US collaborative studies using longitudinal data reported increases in maternal weight of 1.5-2 kg from one pregnancy to the next, and >3 kg from the first to the third pregnancy among nonsmoking mothers.[12,13] A more recent longitudinal study of 2,547 US women showed that the risk of becoming overweight was increased by 60-110% in women having live births during a 10-year study period.[14] Another recent longitudinal study of 2,788 US women found primiparas gain 2-3 kg more weight during a 5-year follow-up period than nulliparas in both adjusted and unadjusted analyses.[15]

The impact of pregnancy weight gain on maternal weight retention is more pronounced and direct than its impact on infant birth weight (IBW); in normal or overweight women there is no evidence that maternal fat accretion benefits fetal growth.[16,17] In the United States the 15th and 85th percentiles of weight gain for women who delivered normal weight infants (3-4 kg) were 7.3 and 18.2 kg respectively.[18]

The purpose of this study was to examine the timing of weight gain during pregnancy and to establish the relative importance between the requirement for adequate pregnancy weight gain to support fetal growth and the risk of undesirable maternal PPWR. Although a few studies have focused on the effect of temporal pattern of weight gain on fetal growth,[19-21] none has examined its implication for maternal PPWR. Since maternal tissue expansion precedes fetal growth,[22] we hypothesized that a weight gain pattern tracking that of fetal growth would more directly promote fetal growth and would minimize maternal PPWR. It has been observed that towards the end of pregnancy there is a near cessation of maternal fat deposition.[22,23] Since IBW is associated with weight gain during the second and third trimesters,[24,25] we speculated that early

pregnancy weight gain (<20 weeks) is more likely retained by the mother. This paper describes the relationship between the extent and timing of pregnancy weight gain, for nonsmoking mothers of different pregravid weights, with both IBW and maternal PPWR.

Subjects and methods

Data for pregnant women followed by the Prenatal Nutrition Counselling Program of the Department of Health & Social Services of Prince Edward Island, Canada between 1979 and 1989 were abstracted for this study. This program provides individual dietary counselling to pregnant women with limited family income.[26] The study sample (n=371) was a low income population with 31% unmarried women, 71% unemployed, and 77% with no post-secondary education. Additional information about this population has been reported previously.[27]

Subjects were drawn from an initial population consisting of 618 white nonsmoking women giving birth to live singleton infants. Smokers were not included because of previously reported differences in pregravid weight status, weight gain and pregnancy outcome.[27] The following exclusions were made to arrive at a study sample of 371 women: prematurity (<37 weeks) n=37 (6%); adolescents <16 years because of continuing linear growth[28] n=43 (7%); women ≥40 years because of increased obstetric risk[29] n=12 (2%); maternal health problems n=22 (4%); women who consumed alcohol (>1 drink/month) n=24 (5%); reported users of illegal or narcotic drugs n=20 (4%); women with pregnancy complications such as proteinuria, hypertension, diabetes n=52

(11%); negative pregnancy weight gain n=4 (1%); and those with missing values n=33 (8%).

Prenatal information was recorded at regular visits throughout pregnancy and pregravid weight was obtained from the family physicians' records. Maternal pregravid weight was divided into two separate body weight components; (a) standard weight for height and frame size using the Metropolitan Life Insurance tables,[30] and (b) excess pregravid weight which was taken as the difference between actual weight and standard weight. Pregravid weight status was categorized into three groups as a percentage of standard weight; underweight (<90%), normal (90-120%) and overweight (>120%).

Women, wearing light clothing and no shoes, were weighed on a balance scale by a dietitian at admission, at 20 and 30 weeks gestation, <1 week prior to delivery, and at 6 weeks postpartum. We chose 6 weeks postpartum because excess fluids gained during pregnancy are lost by this time.[22,31] After 6 weeks, further weight loss would primarily consist of fat and its rate would be determined by maternal energy balance depending on dietary behaviour and other life style factors. Frame size (small, medium, large) was determined by measuring the wrist circumference and comparing it to established standards.[30] Total pregnancy weight gain was divided into three components: up to week 20, week 21 to 30, and week 31 to term. Maternal weight retention was calculated as the difference between weight at 6 weeks postpartum and pregravid weight.

Length of gestation was estimated from the date of the last menstrual period obtained from physicians' records. Infant birth weight was categorized into small (SGA), adequate (AGA), and large (LGA) for gestational age by using the conventional cut-off points of 10^{th} and 90^{th} percentiles of birth weight

distribution data of Canadian infants,[32] specific for infant gender and gestational age in weeks.

Pearson's correlation coefficients were used to analyze the relationship of weight gain during different time periods to both PPWR and IBW. Multiple regression analysis was used for studying predictors of both maternal PPWR and IBW. Predictor variables were those found to correlate with either IBW or maternal PPWR. They included: pregnancy weight gains up to 20 weeks, 21-30 weeks, 31 weeks to term, pregravid standard weight, pregravid excess weight, gestational length, infant gender (male=1, female=0) and parity (primiparous=0, multiparous=1). Mean values of IBW and PPWR were plotted at weight gain intervals of 4 kg spacing (≤ 6, $>6 \leq 10$, $>10 \leq 14$, $>14 \leq 18$, $>18 \leq 22$, $>22 \leq 26$, and >26 kg) in Figure 1. A cut-off of 12 kg weight gain, the mid-point of the group 10-14 kg was used to divide the slope of each curve into two sections using separate regression analyses.

Logistic regression analysis was performed to predict the risks of SGA and LGA births on the basis of maternal weight variables and parity as described above. Gestational length and infant gender were not included in the analysis since they were already taken into account in categorizing IBW as SGA, AGA, or LGA. A comparison of the weight gain for mothers having PPWR below and above the median weight of the group, stratified by pregravid weight status was done for each of the three time periods during pregnancy using t-tests. Finally, analysis of variance and Sheffe's test were used to compare weight gains among underweight, normal weight and overweight mothers for each of our three designated time periods by postpartum weight retention grouping. Statistical analyses were done using SAS software package for Personal Computers Version 6.04, 1990 (SAS Institute Inc., Cary, North Carolina).

Results

The study sample consisted of 371 healthy nonsmoking white adult women, delivered at term (≥37 weeks). Approximately half (52%) of the mothers were primiparous and 25% were pregnant for the second time. Maternal age (mean ± SD) was 24.5±5.6 years and gestational length was 39.7±1.2 weeks. The average total pregravid weight of 62.8±16.0 kg was composed of a mean standard weight of 57.9±4.3 kg and excess weight of 4.9±14.1 kg. There was a wide range of total pregnancy weight gains with the 15th and 85th percentiles of 10.4 and 22.6 kg respectively, and a mean of 16.1±6.4 kg. PPWR ranged from -8.2 to 27.7 kg with a mean of 5.3±5.7 kg. Approximately 75% of the women retained >2.5 kg postpartum.

In order to explore the effects of pregnancy weight gain, graphs for maternal weight retention at 6 weeks postpartum and infant birth weight adjusted for gestational length and pregravid weight were plotted against total pregnancy weight gain divided into 4 kg intervals (Figure 1). The curve for PPWR indicates that a pregnancy weight gain of 12 kg was associated with a 2.5 kg PPWR and corresponded to values commonly recommended for normal weight women. Separate regression analyses for pregnancy weight gains ≤12 kg and >12 kg gave regression coefficient estimates ± standard errors of 0.58±0.13 and 0.77±0.04 kg/kg for PPWR respectively. This indicates that any additional weight gain above 12 kg was to a large degree retained by the mother. At 12 kg, mean IBW was 3,500 g, and continued to rise to higher values as total pregnancy weight gain increased, reaching an apex between 3,700 g and

3,800 g. At a weight gain of 12 kg the risk of LGA was 5% and this increased to 14% at 20 kg.

Total pregnancy weight gain was much more strongly associated with PPWR than IBW. Data shown in **Table I** indicate that total pregnancy weight gain explained 65.2% of the variability in PPWR, and 4.7% of the variability in IBW. The importance of the timing of pregnancy weight gain is also shown in this table. Weight gain during the first 20 weeks of gestation had the strongest correlation with PPWR ($r=0.68$) compared to weight gain later in pregnancy ($r=0.41$), whereas weight gain at any of these time periods had a weak correlation with IBW ($r=0.11$ to $r=0.16$). Maternal PPWR and IBW were not correlated.

The relative contribution of weight gain during different stages of pregnancy to both PPWR and IBW are quantified in the two multiple regression models (**Table II**). In addition to the weight gain components, pregravid weights, parity, gestational age and infant gender were included in the models. Maternal age was not included as it was correlated with parity and did not show an independent association with either outcome variable. For PPWR, the regression coefficients indicated that 86% of initial weight gain increments (≤20 weeks) was retained by the mother as compared to 68% from weeks 21-30 and 49% after 30 weeks, indicating that the earlier the weight gain the greater the PPWR. None of the other variables (pregravid weight, parity, gestational age or infant gender) had any effect on PPWR. In contrast, weight gain from weeks 21 to 30 had the greatest contribution to IBW with an average 31 g increase in IBW for every additional kg gained in this period. However, the final weight gain from week 31 to term, had the smallest coefficient which is likely due to multicollinearity between the final weight gain and gestational length, a

consistently strong predictor of IBW. Other predictors of IBW included; parity, gestational length, infant gender, standard pregravid weight for height and excess weight at conception. With the addition of these other predictors, 30.2% of the variability in IBW was explained as compared to 4.7% for the pregnancy weight gain alone. Thus in contrast to maternal weight retention, infant birth weight was explained in a very small part by pregnancy weight gain in healthy nonsmoking women.

Results of logistic regression analysis for the risk of SGA and LGA infants are given in **Table III**. These results show the effect of maternal weight gain components at different stages in pregnancy, on the two tails of IBW distribution. According to **Table III**, only weight gain during the second half of pregnancy predicted SGA, while LGA was associated with weight gain up to 30 weeks.

The importance of weight gain pattern in influencing PPWR was further explored by comparing patterns of pregnancy weight gain between mothers retaining weight below and above the median value for the group. The analysis was limited to AGA infants and stratified by maternal pregravid weight status in order to characterize an appropriate weight gain pattern for each subgroup of mothers; overweight, normal weight and underweight (**Table IV**). Among mothers retaining $\geq$ median weight, total pregnancy weight gain was significantly greater than in those retaining $<$ median weight by 9.5 kg in overweight, 7.0 kg in normal weight and 6.3 kg in underweight subjects. The major portion of this difference in weight gain occurred during the first 20 weeks of gestation. On average, higher weight retainers gained more than low weight retainers during this period; the difference was 6.2 kg in overweight and 3.3 kg in normal and underweight subjects. Differences between the groups for

weight gain later in pregnancy were smaller. Of note, comparisons of weight gains among underweight, normal and overweight subjects during the same weeks of pregnancy and for the same PPWR group indicated that the only statistical difference was within the lower PPWR group where overweight women gained 1.4 kg at ≤20 weeks versus weight gains of 3.8 in normal and underweight women during this same period. The total weight gains during pregnancy for those with PPWR < median averaged at 13.3 kg, 13.2 kg and 9.6 kg for underweight, normal weight and overweight women respectively. In contrast, total weight gains during pregnancy in those having PPWR ≥ median averaged at 19.6, 20.2 and 19.1 kg for comparable weight status, respectively.

Discussion

This is the first study to evaluate patterns of weight gain during pregnancy in order to assess whether the timing of weight gain could present an effective means of balancing the needs for promoting fetal growth while minimizing maternal PPWR. Other studies have shown that total weight gain during pregnancy is the main predictor of PPWR.[4-6,10] High weight gains in heavy mothers have also been shown to increase the risk of preterm low birth weight.[33] Our results extend previous findings by showing the importance of timing of weight gain. We demonstrate that (a) maternal weight gain during the first 20 weeks of pregnancy was strongly associated with maternal PPWR; (b) women with high PPWR (>median) had significantly higher weight gains before week 20 regardless of their weight status; and (c) the risk of SGA was predicted by maternal weight gain only during the second half of pregnancy, whereas the risk of LGA was predicted by weight gain throughout pregnancy, indicating that the effect of early weight gain on increasing mean IBW was primarily through an

increase in the proportion of LGA infants rather than a decrease in the proportion of SGA infants. These findings support our hypothesis that fetal growth requirements before week 20 are minimal, and any weight in surplus of what is needed to support pregnancy will be accumulated as long-term fat reserves.

Overweight mothers experiencing higher weight retention started their pregnancy with higher early rate of weight gain, reducing this rate near term, whereas those with lower weight retention had minimal weight gains during the first 20 weeks. Pregravid weight and excess weight at conception were not associated with PPWR and 75% of normal weight women had PPWR above 2.5 kg. Moreover, since weight gain during pregnancy is strongly associated with weight retention at 6 months,[4] one year,[5] or at the start of a new pregnancy,[6] it is likely that those who gain extra weight, regardless of weight status, will not lose the extra weight after pregnancy.[15] Furthermore, the need for extra weight gain during pregnancy to support lactation is controversial,[5,34-38] as the overall effect of breast feeding on subsequent weight loss is small.[4,39] Therefore the results from the present study indicate that for a given recommended weight gain, it might be advantageous for the well-nourished normal and particularly overweight mothers to attain a larger weight gain portion during the second half of pregnancy. In contrast, the first half of pregnancy of underweight women, would offer an opportunity to increase their weight to a more desirable value.

Since maternal weight gain is a well-known predictor of IBW,[1] there is always a concern that restriction in maternal weight gain to reduce PPWR may increase the risk of fetal growth retardation. In fact the 1990 report of the National Academy of Sciences recommended an additional 5-10 lb (2.3-4.5 kg) weight increase for pregnant women in order to avoid SGA and produce heavier

babies.[11] No mention was made as to the appropriate timing for this weight gain. Data from our multivariate analysis support the observation that the strongest relationship of maternal weight gain to predicting IBW while controlling for other established predictors occurred for weeks 21-30. Others have shown that low maternal weight gain (< 1.4 kg) between 28-32 weeks in normal healthy women is a predictor of SGA.[24] Scholl *et al* found that among pregnant adolescents, 25% of whom were underweight and 33% who were smoking, that low weight gains (< th percentile) as early as 16-20 weeks gestation were associated with an elevated risk of low birth weight.[21] In this same study, however, maternal weight gain (>75th percentile) during this same period predicted macrosomia, even among the same high risk population. Another study has suggested that weight gains before 20 weeks were positively associated with IBW and maternal fat deposition in high risk women from developing countries;[40] however, data for developing countries are not comparable to our data, where weight at conception is much higher. In our study, which was restricted to healthy nonsmoking adult women, pregnancy weight gain before 20 weeks was weakly associated with IBW in a multiple regression analysis, and not associated with SGA risk, but significantly associated with LGA risk indicating that the prediction lay with the higher birth weights. The lack of any association of weight gain in the last period of pregnancy (>30 weeks) with IBW could be explained by the strong association of weight gain to gestational length, which was controlled as a covariate in this analysis. Because our data and others show that maternal weight gain from 21 to 30 weeks promotes increased IBW,[24] and that earlier weight gains (<20 weeks) are potentially important for the fetus mostly in high risk settings, it would seem advantageous to shift more of the required total weight gains towards the second half in pregnancy in order to minimize PPWR and its negative health consequences for the well-nourished mothers. This timing would

be associated with minimal negative consequences for fetal growth and development, where a larger portion of weight gain during the second half would be retained by the developing fetus.

Our results conform with current recommendations by the National Academy of Sciences for a total weight gain during pregnancy of 11.5-16.0 kg for normal weight mothers. Our data indicated that our pregnant women with the PPWR < median had an average weight gain, depending on prenatal weight status, between 9.6 kg and 13.3 kg. For normal weight mothers, the National Academy of Sciences has recommended a minimum weight gain of 11.5 kg, which corresponds in our study to a mean IBW of 3,500 g and PPWR of 2-3 kg, a value some authors suggest may meet lactational requirements.[34,39] Our data on the distribution of the weight gains during pregnancy demonstrate that weight gains of approximately 3-4 kg from weeks 0-20, and 4-5 kg for weeks 21-30, and >30 weeks are reasonable for average healthy nonsmoking adult women, to ensure recommended total pregnancy weight gains, without increasing the risk of undesirably high PPWR. For overweight women giving birth to AGA infants, a mean weight gain of 9-10 kg, with only a small portion gained in the first half, was associated with no maternal PPWR. Weight gains above this amount led to unnecessary PPWR. These values fall in the middle of recommended weight gain range (7-11 kg) for overweight women. In order to minimize PPWR in the overweight, our data show that the rate of weight gain for the first half of pregnancy should be carefully monitored.

In an effort to monitor weight gain, it is important for health professionals not to restrict diet in pregnancy below what is needed for optimal fetal growth. A well balanced diet is important to all women and should never be overlooked to arrive at a specific weight gain. Boberg and colleagues,[41] in the only

be associated with minimal negative consequences for fetal growth and development, where a larger portion of weight gain during the second half would be retained by the developing fetus.

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In an effort to monitor weight gain, it is important for health professionals not to restrict diet in pregnancy below what is needed for optimal fetal growth. A well balanced diet is important to all women and should never be overlooked to arrive at a specific weight gain. Boberg and colleagues,[41] in the only

intervention study of obese pregnant women, instructed them to eat a well balanced 1,800-2,000 kcal diet which resulted in a 6.2 kg average weight gain from 16 weeks to term with no evidence of ketonuria or low birth weight. Similarly, in those with diabetes, intakes below this level have been successfully used.[42,43] Normal weight women should eat a balanced diet to ensure weight gains of approximately 11.5-16 kg.

In summary, our results emphasize the importance of the timing of pregnancy weight gain and indicate that proper weight gain management can promote the long term health of women by reducing maternal weight retention while at the same time promoting fetal growth. Because obesity is a major public health problem,[44] and excessive weight gained earlier in pregnancy may lead to high PPWR and adiposity,[15] preventive measures are required. Our study shows that (a) attention to early weight gains during pregnancy, particularly in the overweight women, is required and (b) that excessive total pregnancy weight gains be avoided in normal and overweight women. We caution that our results apply to healthy mothers and are not applicable to smokers or those with other medical risks.

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The effort and commitment of the Prince Edward Island Community Nutritionists in the collection of these data are gratefully acknowledged.

Table I: Pearson's correlation coefficient (R) and determination coefficient (R-square) of maternal weight gain with postpartum weight retention and infant birth weight (n=371).

Pregnancy Weight gain	Maternal postpartum weight retention [2]			Infant birth weight [2]		
	R	R-square	p [1]	R	R-square	p [1]
Total amount	0.808	65.3%	***	0.216	4.7%	***
- Up to week 20	0.682	46.5%	***	0.114	1.3%	*
- Weeks 21-30	0.411	16.9%	***	0.157	2.5%	**
- Week 31-term	0.414	17.1%	***	0.160	2.6%	**

[1] Correlation significance; * $p<0.05$, ** $p<0.01$, *** $p<0.0001$.

[2] Maternal PPWR and IBW were not correlated, with or without controlling for other predictors.

Table II: Regression model of postpartum weight retention and infant birth weight (g) predicted by partial pregnancy weight gains and other determinants (n=371).[4]

	Maternal postpartum weight retention (kg)		Infant birth weight (g)	
	β ± SE [1]		β ± SE [1]	[2]
Y-intercept	-2.39±7.10	NS	-4207±701	***
WG (kg) up to week 20	0.86±0.05	***	22±6	**
WG (kg) weeks 21-30	0.68±0.07	***	31±7	***
WG (kg) week 31-term	0.49±0.07	***	12±6	*
Standard pregravid weight [3](kg)	-0.03±0.06	NS	15±6	**
Excess weight at conception [3](kg)	-0.01±0.02	NS	8±2	***
Parity (single=0, multiple=1)	0.33±0.47	NS	130±48	**
Gestational age (weeks)	-0.01±0.18	NS	165±16	***
Infant gender (f=0, m=1)	0.14±0.43	NS	106±45	*
R-square	**68.4%**		**30.2%**	

[1] β: Estimated regression coefficient and standard error.

[2] Significance of the regression coefficient, * $p<0.05$, ** $p<0.01$, *** $p<0.0001$, NS not significant.

[3] Standard pregravid weight is estimated from the 1983 Metropolitan Insurance Life Tables for a given height and frame size

[4] When the outliers (>3 standard deviations from the mean for IBW, maternal excess weight at conception, or pregnancy weight gain) were removed from the analysis (n=42), no substantial changes in the results were obtained.

Table III: Logistic regression model of SGA and LGA infants predicted by partial pregnancy weight gains and other determinants (n=371).

	Small for gestational age infants (SGA)		Large for gestational age infants (LGA)	
	β ± SE [1]	[2]	β ± SE [1]	[2]
Y-intercept	6.55±1.82	**	-7.40±1.87	***
WG (kg) up to week 20	-0.07±0.04	NS	0.16±0.03	***
WG (kg) weeks 21-30	-0.16±0.04	**	0.15±0.04	**
WG (kg) week 31-term	-0.12±0.04	**	0.02±0.04	NS
Standard pregravid weight [3](kg)	-0.13±0.03	***	0.06±0.03	*
Excess weight at conception [3](kg)	-0.04±0.02	*	0.03±0.01	**
Parity (single=0, multiple=1)	-0.01±0.25	NS	0.45±0.28	NS

[1] β: Estimated regression coefficient and standard error.

[2] Significance of the regression coefficient: * $p<0.05$, ** $p<0.01$, *** $p<0.0001$, NS not significant.

[3] Standard pregravid weight is estimated from the 1983 Metropolitan Insurance Life Tables for a given height and frame size

Table IV: Pregnancy weight gain patterns (mean ± SD in kg) among mothers of AGA infants stratified by PPWR and pregravid weight category.

	PPWR<median	PPWR≥median	Difference [1]	
Normal weight (90-120% of standard pregravid weight for height)				
	n = 85	**n = 89**		
PPWR (median = 5.7 kg)	2.2±2.3	9.9±4.3	7.7	***
Total weight gain (kg)	13.2±3.4	20.2±4.9	7.0	***
WG (kg) up to week 20	3.8±2.3 [a]	7.1±3.3	3.3	***
WG (kg) weeks 21-30	5.3±2.0	6.8±2.3	1.5	**
WG (kg) week 31-term	4.1±2.3	6.2±2.8	2.1	**
Underweight (<90% of standard pregravid weight for height)				
	n = 24	**n = 25**		
PPWR (median = 6.2kg)	2.7±2.5	9.2±2.7	6.5	***
Total weight gain (kg)	13.3±3.8	19.6±4.6	6.3	***
WG (kg) up to week 20	3.8±1.5 [a]	7.1±2.6	3.3	***
WG (kg) weeks 21-30	5.4±2.0	6.4±1.6	1.0	*
WG (kg) week 31-term	4.1±2.4	6.1±2.1	2.0	**
Overweight (>120% of standard pregravid weight for height)				
	n = 34	**n = 40**		
PPWR (median = 3.1 kg)	-0.9±2.6	9.1±5.2	10.0	***
Total weight gain (kg)	9.6±2.8	19.1±7.0	9.5	***
WG (kg) up to week 20	1.4±2.8 [b]	7.6±5.2	6.2	***
WG (kg) weeks 21-30	4.5±2.6	6.2±3.5	1.7	*
WG (kg) week 31-term	3.7±2.3	5.3±2.7	1.6	*

[1] T-test of significant difference between the means of two PPWR groups; * $p<0.05$, ** $p<0.01$, *** $p<0.0001$. Scheffe's multiple comparison test of significant difference between the means in different weight status groups is indicated by different letter superscripts.

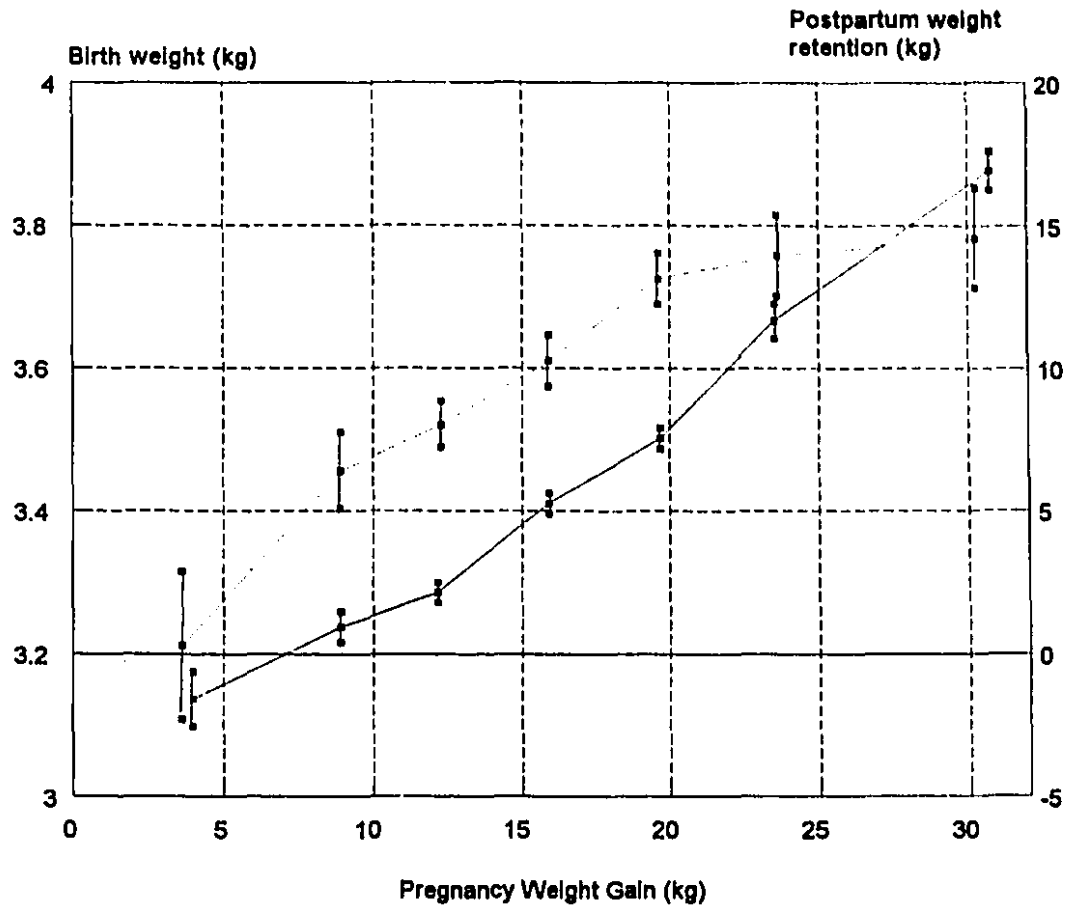

Figure 1. Postpartum weight retention and infant birth weight versus total pregnancy weight gain

..... Infant birth weight _____ Maternal postpartum weight retention

The vertical lines denote mean values ± standard errors.

References

1. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization 1987;65(5):663-737.
2. Shepard MJ, Hellenbrand KG, Bracken MB. Proportional weight gain and complications of pregnancy, labor and delivery in healthy women of normal prepregnancy stature. Am J Obstet Gynecol 1986;155:947-54.
3. Johnson JWC, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. Am J Obstet Gynecol 1992;167:353-72.
4. Schauberger CW, Rooney BL, Brimer LM. Factors that influence weight loss in the puerperium. Obstet Gynecol 1992;79:424-9.
5. Öhlin A, Rössner S. Maternal body weight development after pregnancy. Int J Obesity 1990;14:159-73.
6. Greene WG, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum weight change: How much of the weight gained in pregnancy will be lost after delivery? Obstet Gynecol 1988;71:701-7.
7. McGanity WJ, Dawson EB, Fogelman A. Nutrition in pregnancy In: Shils ME, Olson JA, Shike M, eds. Health and Disease, 8th ed., Philadelphia, Lea and Febiger, 1994;705-727.
8. King JC, Butte NF, Bronstein MN, Kopp LE, Lindquist SA. Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr 1994;59(suppl):4395-455.
9. Forsum E, Sadurskis A, Wager J. Resting metabolic rate and body composition of health Swedish women during pregnancy Am J Clin Nutr 1988:47:942-7.
10. Parham ES, Astrom MF, King SH. The association of pregnancy weight gain with mother's postpartum weight. J Am Diet Assoc 1990;90(4):550-4.

11. National Academy of Sciences: Institute of Medicine (U.S.). Nutrition during pregnancy: Part I, weight gain. Subcommittee on Nutritional Status and Weight Gain During Pregnancy. Washington: National Academy Press, 1990:10-1, 178-83.
12. Weiss W, Jackson EC. Perinatal factors affecting human development. Washington: Pan American Health Organization, 1969:54-69.
13. Garn SM, Shaw HA. Effect of maternal smoking on weight and weight gain between pregnancies. Am J Clin Nutr 1978;13:1302-3.
14. Williamson DF, Madans J, Pamuk, E, Flegal KM, Kendrick JS, Serdula MK. A prospective study of childbearing and 10-year weight gain in US white women 25 to 45 years of age. Int J Obesity 1994;18:561-9.
15. Smith DE, Lewis CE, Caveny JL, Perkins LL, Burke GL, Bild DE. Longitudinal changes in adiposity associated with pregnancy - The CARDIA Study. JAMA 1994;271:1747-51.
16. Lawrence M, Mckillop FM, Durnin JVGA. Women who gain more fat during pregnancy may not have bigger babies: implications for recommended weight gain during pregnancy. Br J Obstet Gynaecol 1991;98:254-9.
17. Langhoff-Roos J, Lindmark G, Gebre-Medhin M. Maternal fat stores and fat accretion during pregnancy in relation to infant birth weight. Br J Obstet Gynaecol 1987;94:1170-7.
18. Taffel SM. Maternal weight gain and the outcome of pregnancy: United States, 1980. Vital and Health Statistics, Series 21, No. 44. DHHS Publ. No. (PHS) 86-1922. National Center for Health Statistics, Public Health Service, U.S. Department Of Health and Human Services, Hyatsville, Md., 1986.
19. Siega-Riz AM, Adair LS. Biological determinants of pregnancy weight gain in a Filipino population. Am J Clin Nutr 1993;57:365-72.

20. Hediger ML, Scholl TO, Belsky DH, Ances IG, Salmon RW. Rate and amount of weight gain during adolescent pregnancy: associations with maternal weight-for-height and birth weight. Am J Clin Nutr 1990;52:793-9.
21. Scholl TO, Hediger ML, Ances IG, Belsky DH, Salmon RW. Weight gain in adolescence: predictive ability of early weight gain. Obstet Gynecol 1990;75:948-53.
22. Hytten F, Chamberlain G. Clinical physiology in obstetrics. Oxford: Blackwell Scientific Publications, 1991.
23. Pipe NG, Smith T, Halliday E, Edmonds CJ, Willliams C, Coltart TM. Changes in fat , fat-free mass, and body water in human normal pregnancy. Br J Obstet Gynaecol 1979:86:929-40.
24. Lawton FG, Mason GC, Kelly KA, Ramsay IN, Morewood GA. Poor maternal weight gain between 28 and 32 weeks gestation may predict small-for-gestational-age infants. Br J Obstet Gyneacol 1988;95:884-7.
25. Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress and weight gain on placentas, and on neonatal physical and behavioral characteristics. Am J Clin Nutr 1982;36:1214-24.
26. McDonald AJ, Newson EE. Dietary changes made by low-income nutritionally high-risk pregnant women. J Can Diet Assoc 1986;47:21-5.
27. Muscati SK, Gray-Donald K, Newson E. Interaction of smoking and maternal weight status in influencing infant size. Can J Public Health 1994;85(6):407-12.
28. Haiek L, Lederman SA. The relationship between maternal weight for height and term birth weight in teens and adult women. J Adol Health Care 1988;10:16-22.

29. Subcommittee on Nutrition and Fertility, Food and Nutrition Board, National Research Council, National Academy of Sciences: Nutrition and fertility interrelationships. Washington, DC: Government Printing Office, 1975.
30. Metropolitan Life Insurance Company. Metropolitan height and weight tables. Stat Bull Metrop Life Found 1983;64:3-9.
31. Schauberger CW, Rooney BL, Brimer LM. Factors that influence weight loss in the puerperium. Obstet Gynecol 1992;79:424-9.
32. Arbuckle TE, Sherman GJ. An analysis of birth weight by gestational age in Canada. Can Med Ass J 1989;140:157-65.
33. Kleinman JC. Maternal Weight Gain During Pregnancy: Determinants and Consequences. NCHS Working Paper Series No. 33. National Center for Health Statistics, Public Health Service, U.S. Dept of Health and Human Services, Hyattsville, Md. 1990.
34. Illingworth PJ, Jung RT, Howie PW. Energy balance in lactation. In Berry EM, Blondheim SH, Eliahow HE, Shafir E, eds: Recent Advances in Obesity Research V. London: John Libbey and Co., 1987.
35. Brewer MM, Bates MR, Vannoy LP. Postpartum changes in maternal weight and body fat depots in lactating vs. nonlactating women. Am J Clin Nutr 1989;49:259-65.
36. Quandt SA. Changes in maternal postpartum adiposity and infant feeding patterns. Am J Phys Anthropol 1983;60:455-61.
37. Rookus MA, Rokebrand P, Burema J, Deurenberg P. The effect of pregnancy on the body mass index 9 months postpartum in 49 women. Int J Obesity 1987;11:609-18.
38. Potter S, Hannum S, McFarlin B, Essex-Sorlie D, Campbell E, Trupin S. Does infant feeding method influence maternal weight loss? Am J Diet Assoc 1991;91:441-6.

39. Dewey KG, Heinig MJ, Nommsen LA. Maternal weight-loss patterns during prolonged lactation. Am J Clin Nutr 1993;58:162-6.
40. Villar J, Cogswell M, Kestler E, Castillo P, Menendez R, Repke J. Effect of fat and fat-free mass deposition during pregnancy on birth weight. Am J Obstet Gynecol 1992;167:1344-52.
41. Boberg C, Gillmen MDG, Brumer EJ, Green PJ, Oakley NW, Beard RW. Obesity in pregnancy: The effect of dietary advice. Diabetes Care 1980;3:476-81.
42. Snyder J, Gray-Donald K, Koski KG. Predictors of infant birth weight in gestational diabetes. Am J Clin Nutr 1994;59:1409-14.
43. Algert S. Shragg P, Hollingworth DR. Moderate caloric restriction in obese women with gestational diabetes. Obstet Gynecol 1985;65:487-91.
44. Kucamarsk RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. J Am Med Assoc 1994;272:205-11.

Epilogue to Manuscript C

The results of Manuscript C support the hypothesis that among healthy nonsmoking women, management of the pattern of weight gain during pregnancy, can contribute to optimizing the requirements for promoting fetal growth and limiting postpartum weight retention. The results show that gestational weight gain was the main predictor of postpartum weight retention explaining a major portion of its variability. This relationship was more pronounced above 12 kg of weight gain, indicating a large portion (77%) of weight gain increment was retained by the mother at the higher range of weight gain among all weight status groups combined. Postpartum weight retention was more strongly associated with weight gained in the first half of pregnancy, than that gained in the second half; the opposite was found for infant birth weight or the risk of SGA. These results indicate the need to shift more of the weight gain to the second half of pregnancy particularly in overweight women, if excessive postpartum weight retention is to be avoided.

5. CONCLUSIONS AND SUMMARY OF FINDINGS

This research was motivated by the need to better understand how maternal factors during pregnancy interrelate in their contribution to both neonatal outcome in terms of infant size at birth, and maternal outcome in terms of postpartum weight retention. The research was guided by an analytical framework that explored the interrelations among major modifiable determinants of pregnancy outcome. These include energy intake, maternal smoking, pregravid weight status and gestational weight gain, all of which have been mostly studied in isolation of each other in the literature. In this thesis, the importance of the timing of weight gain was explored by studying the relative contribution of weight gain at different gestational stages to both infant birth weight and maternal postpartum weight retention, at the same time.

Many prenatal care programs have given a higher priority to dietary intake and total weight gain in pregnant women with less attention to their smoking behaviour. The particular emphasis on increased dietary intake is based on historical evidence linking infant birth weight to maternal energy intake during pregnancy. Such evidence includes the Dutch Famine [Stein *et al* 1975], and trends of increased infant birth weight and maternal weight gain accompanying advice for more liberal dietary intake since the 1970's [IOM 1990, Abrams 1994]. Some studies suggested that the negative effect of smoking on retarding fetal growth, could be compensated by increasing energy intake [Garn *et al* 1979, Rush *et al* 1980, Papoz *et al* 1982, Metcoff *et al* 1985]. Unfortunately, programs focusing primarily on increasing energy intake in developed countries have achieved relatively small increases in infant birth weight, and such increases were observed only among

heavy smokers [Rush 1980a, Metcoff *et al* 1985] and/or under-nourished mothers [Susser 1991].

Although both maternal dietary intake and weight gain were positively associated with infant birth weight in the present study population, the findings of this research did not support the hypothesis that increased dietary intake could sufficiently mitigate smoking effects on fetal growth. Despite receiving similar dietary advice, smoking mothers consumed more dietary energy than their nonsmoking counterparts, yet they were thinner at conception, gained less weight during pregnancy, and had smaller infants at birth (weight, length and head circumference). The more cigarettes a mother smoked daily, the higher was her energy intake, and the lower were her pregnancy weight gain and infant birth weight. These results imply that some aspect of smoking uses up energy that is not directed towards weight gain and fetal growth. Furthermore, cigarette smoking seems to mask the relationship between energy intake and weight gain during pregnancy, as such relationship was found significant in this research only among nonsmokers but not among smokers. This finding remained the same, even after controlling for the level of cigarette smoking. It is likely that smoking introduces a large variability, not only in metabolic energy expenditure, but also in other unmeasured physiological and/or behavioural factors related to fetal growth. However, given the number of variables controlled in this research, potential confounding by other unmeasured variables is expected to be small.

In theory, an excess of dietary energy intake among smokers leading to a higher pregnancy weight gain could increase birth weight and lower the risk of SGA infants. Results of this research indicate that even if smokers increased their intake so as to match nonsmokers in their weight gain, only a marginal but significant increase in birth weight or decrease in SGA risk could be achieved by

removing the indirect effect of smoking. To compensate for the direct effect of smoking on birth weight, however, impractically large increments in dietary intake would be required. Normal-weight smoking mothers who had comparable infant birth weight (3,500 g) to that of nonsmokers, gained an average of ~20 kg during pregnancy as compared to ~12 kg gained by their nonsmoking counterparts. Such a large excess in weight gain would inevitably expose overweight as well as normal-weight mothers to the risk of postpartum obesity. Among underweight smoking mothers, however, the risk of SGA remained high (>10%) even with excessive weight gains (>20 kg). Thus the underweight smoker is of particular concern, because of the very high risk of SGA despite high weight gain. In populations where smoking is still widely prevalent, focusing on diet and weight gain will be a necessary but insufficient measure for promoting fetal growth. The importance of smoking cessation is further emphasized by recent reports that smoking increases neonatal mortality independent of its effect on reducing birth weight [Wilcox 1993].

At the population level, an assessment of the relative contribution of three major modifiable risk factors (smoking, pregravid underweight and low gestational weight gain) to the risk of SGA is essential for establishing prenatal program priorities [Wen & Kramer 1995]. On the basis of current prevalence of these three risk factors in the Canadian and US populations, this research calculated that 31% of SGA births were attributed to smoking; approximately twice that attributed to either pregravid underweight or low gestational weight gain. The 31% etiologic fraction of SGA infants is attributed to the direct effect of smoking on retarding fetal growth not mediated by maternal weight variables which were controlled in the multivariate analysis. This further emphasizes the need for giving a higher priority to smoking cessation in prenatal care, especially in view of previous reports that women quitting smoking before or

early in pregnancy have comparable birth outcome to nonsmokers [MacArthur & Knox 1988, Mainous & Hueston 1994].

The results in this research were obtained from multivariate analysis of data on a single socio-demographically homogeneous Canadian population receiving the same dietary counselling during pregnancy. Therefore, these results can be more meaningful in comparing the relative importance of each risk factor than those previously obtained for individual risk factors from studies of different populations with disparate characteristics by using different methodologies [Kramer 1987].

Smokers and nonsmokers in the studied population differed in certain relationships between predictors and birth outcome. The effect of maternal weight gain on infant length was larger among smokers than nonsmokers for similar maternal weight status. Among overweight nonsmoking mothers, infant birth weight reached a plateau with increasing maternal weight gain, but it continued to increase in overweight smokers. Such differences in pregnancy performance between smokers and nonsmokers are not taken into account by current recommendations for gestational weight gain [IOM 1990], which are based upon studies of mixed populations of smokers and nonsmokers. This research indicated a need for further refinement to tailor the weight gain recommendations to specific pregnancy requirements of healthy nonsmoking groups of mothers, once prenatal smoking cessation programs are effectively implemented.

Unfortunately, cessation of smoking is often accompanied by increased weight in general which may have been a major deterrent to quitting, and a strong motivation for relapse [Gordon *et al* 1975, Moffat & Owens 1991, Williamson *et al* 1991, Perkins 1993]. Smoking cessation during pregnancy has been reported to increase

postpartum weight retention through increased gestational weight gain [Öhlin & Rössner 1990]. This is consistent with the findings of this research that a major portion of the variability in postpartum weight retention was due to gestational weight gain which was higher among nonsmokers. In order to encourage smoking cessation, measures such as the management of the timing of gestational weight gain may be useful for allowing a restriction of the total amount of weight gain without jeopardizing fetal growth. In this respect, it is important to explore the relative contribution of the weight gained during different gestational stages to maternal and neonatal outcomes of pregnancy in nonsmokers, and in those who quit smoking. Thus an opportunity may exist for defining appropriate patterns of weight gain during pregnancy to allow an optimum balance in terms of reducing both risks of SGA births and maternal postpartum overweight. In doing so, however, the need for adequate dietary quality throughout pregnancy should not be ignored. In the population studied, dietary quality was not of a major concern since the women were counselled for a balanced diet and were provided with necessary vitamin and mineral supplements.

In exploring the pattern of gestational weight gain, this research found that weight gain during the first half of pregnancy had a stronger association with maternal postpartum weight retention and weaker association with infant birth weight and the risk of SGA than during the second half of pregnancy. It was also found that among mothers of AGA infants, those with higher postpartum weight retention (> median for specific weight status group) gained a larger portion of their total weight gain in the first half of pregnancy, than those with lower postpartum weight retention. This difference was more pronounced among overweight women. These findings are congruent with previous studies on well-nourished mothers, indicating that most of maternal fat is gained early in pregnancy [Clapp *et al* 1988] and such fat gain does not correlate with birth

weight [Langhoff-Roos *et al* 1987a, Villar *et al* 1992]. In under-nourished mothers, however, fat gained during pregnancy has been reported to correlate with birth weight [Viegas *et al* 1987], indicating a need to accumulate fat throughout the entire gestation, to replenish their reserves. This may also be the case for underweight women in North America since they are at elevated risk of having SGA infants and need to gain more weight than normal women, as confirmed by this research. In contrast to the overweight women, postpartum weight retention for underweight women is not a major concern, and steady rate of weight gain throughout the entire gestation seems desirable. Such women require higher rates of early weight gain than their normal and over-weight counterparts in order to restore their own weight deficit before demands for fetal growth begin to accelerate during the second half of their gestation.

The research results of this thesis, suggest that postpartum weight retention could be minimized, *e.g.* among overweight women, by deferring a larger portion of the required weight gain to later pregnancy. Overweight women who gain weight during non-pregnancy conditions, *e.g.* with overfeeding, are known to accumulate higher proportion of fat than normal-weight women [Forbes *et al* 1986, Webster *et al* 1984], and this situation could be similar to early pregnancy where most of the growth is in maternal tissues. Therefore, limitation of early gestational weight gain in overweight women could avoid unnecessary build up of extra fat. Monitoring the pattern of weight gain during pregnancy is also important for smokers who quit, because they are likely to increase their weight gain after they stop smoking.

Another determinant recently reported to influence postpartum weight retention is parity, as primiparas have been found to retain 2-3 kg more weight postpartum than multiparas during a 5-year follow-up period [Smith *et al* 1994]. This is consistent with the results of this thesis in the sense that primiparas had

higher gestational weight gain (by 2.2 kg) than multiparas, and that such weight gain was the main determinant of postpartum weight retention. This thesis, however, showed that after controlling for gestational weight gain, parity did not have an independent effect on maternal weight retention 6 weeks postpartum. Thus the reported effect of parity on postpartum weight retention seems to be mediated by gestational weight gain. The combination of findings from the literature and from this research, points to the need for giving a special attention to primiparous women who tend to have higher gestational weight gain but smaller infants. More research is needed to study the implications of weight gain and its pattern among primiparous mothers to maternal and neonatal outcomes of pregnancy.

In summary, this thesis presents new results that emphasize the importance of both the timing of weight gain and smoking cessation during pregnancy, to achieve a proper balance between promoting the long-term health of mothers by reducing maternal weight retention, and for their offspring by optimizing fetal growth.

BIBLIOGRAPHY

Abel EL. Fetal alcohol syndrome and fetal alcohol effects. New York: Plenum Press, **1984**.

Abell TD, Baker LC, Ramsev CN. The effects of maternal smoking on infant birth weight. Fam Med **1991**;23(2):103-7.

Abrams BF, Laros RK. Prepregnancy weight, weight gain, and birth weight. Am J Obstet Gynecol **1986**;154:503-9.

Abrams B. Weight gain and energy intake during pregnancy. Clin Obstet Gynecol **1994**;37(3):515-27.

Abrams B, Carmichael S, Selvin S. Factors associated with the pattern of maternal weight gain during pregnancy. Obstet Gynecol **1995**;86(2):170-6.

Abrams B, Selvin S. Maternal weight gain pattern and birth weight. Obstet Gynecol **1995**;86(2):163-9.

ACOG (American Academy of Pediatrics, American College of Obstetricains and Gynecologists). Guidelines for Perinatal Care. American Academy of Pediatrics, Elk Grove, Ill. **1983**.

Adair LS, Pollit E, Mueller WH. Maternal anthropometric changes during pregnancy and lactation in rural Taiwanese population. Hum Biol **1983**;55:771-87.

Adair LS, Pollit E. Seasonal variation in pre- and postpartum maternal body measurements and infant birth weights. Am J Phys Anthropol **1983**;62:325-31.

Adair LS, Pollit E, Mueller WH. The Beacon Chow study: effect of nutritional supplementation on maternal weight and skinfold thickness during pregnancy and lactation. Br J Nutr **1984**;51:537-69.

Adair LS, Pollit E. Outcome of maternal nutritional supplementation: a comprehensive review of the Beacon Cho v study. Am J Clin Nutr **1985**;41:948-78.

Adams SO, Barr GD, Huenemann RL. Effect of nutritional supplementation in pregnancy. I. Outcome of pregnancy. J Am Diet Assoc **1978**;72:144-7.

Albanes DY, Jones MS, Micozzi MS, Mattson ME. Associations between smoking and body weight in the US population. Am J Public Health **1987**;77:439-44.

Aldous MB, Edmonson MB. Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington State. JAMA **1993**;270(21):2574-7.

Ales KL, Druzin ML Santini DL. Impact of advance maternal age on the outcome of pregnancy. Surg Gynecol Obstet **1990**;171:209-16.

Algert S, Shragg P, Hollingworth DR. Moderate caloric restriction in obese women with gestational diabetes. Obstet Gynecol **1985**;65:487-91.

Allen LH, Lung'aho MS, Shaheen M, Harrison GG, Neumann C, Kirksey A. Maternal body mass index and pregnancy outcome in the Nutrition Collaborative Research Support Program. Eur J Clin Nutr **1994**;48 Suppl 3:S68-76; discussion S76-7.

Amini SB, Catalano PM, Hirsch V, Mann LI. An analysis of birth weight by gestational age using a computerized prenatal data base, 1975-1992. Obstet Gynecol **1994**;83:342-52.

Arbuckle TE, Sherman GJ. An analysis of birth weight by gestational age in Canada. Can Med Assoc J **1989**;140:157-65.

Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. Obstet Gynecol **1993**;81:39-48.

Arnold CC, Hobbs CA, Usher RH, Kramer MS. What's wrong with the concept of "very low birth weight" (VLBW)? Pediatr Res **1988**;23:288A.

Arora NK, Paul VK, Singh M. Morbidity and mortality in term infants with intrauterine growth retardation. J Trop Pediatr **1987**; 33:186-9.

Artal R. Exercise and pregnancy. Clin Sports Med **1992**;11:363-77.

Ash S, Fisher CC, Truswell AS, Allen JR, Irwig L. Maternal weight gain, smoking and other factors in pregnancy as predictors of infant birth weight in Sydney women. Austral New Zeal J Obstet Gynaecol **1989**;29(3):212-9.

Audrain JE, Klesges RC, DePue K, Klesges CM. The individual and combined effects of cigarette smoking and food on resting energy expenditure. Int J Obesity **1991**;15:813-21.

Bakketeig LS, Jacobson G, Hoffman HJ, Lindmark G, Bergsjo MK, Rodsten J. Pre-pregnancy risk factors of small-for-gestational-age births among parous women in Scandinavia. Acta Obstet Gynecol Scand **1993**;72:273-9.

Banerjee B, Khew KS, Saha N. A comparative study of energy expenditure in some common daily activities of non-pregnant and pregnant Chinese, Malay and Indian women. J Obstet Gynaecol Br Commonw **1971**;78:113-6.

Beaton GH, Milner J, McGuire V, Feather TE, Little JA. Sources of variance in a 24-hour dietary recall data; implications for nutrition study design and interpretation. Am J Clin Nutr **1983**;37:986-95.

Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. Austral New Zeal J Obstet Gynaecol **1995**;35(1):46-51.

Beazley JM, Swinhoe R. Body weight in parous women: is there any alteration between successive pregnancies? Acta Obstet Gynaecol Scand **1979**;58:45-7.

Bhatnagar S, Dharamshaktu NS, Sundaram KR, Seth V. Effect of food supplementation in the last trimester of pregnancy and early poast-natal period on maternal weight and infant growth. Indian J Med Res **1983**;77:366-72.

Blackburn MW, Calloway DH. Energy expenditure and consumption of mature pregnamt and lactating women. J Am Diet Assoc **1976**;69(1):29-37.

Blackwell RO, Chow BF, Chinn KS, Blackwell BW, Hsu SC. Prospective maternal nutrition study in Taiwan: rationale study design, feasibility and preliminery findings. Nutr Reports Int **1973**;7:517-32.

Blair S, Jacobs D, Powell KE. Relationships between exercise or physical activity and other health behaviors. Public Health Rep **1985**;100:172-80.

Boberg C, Gillmen MDG, Brumer EJ, Green PJ, Oakley NW, Beard RW. Obesity in pregnancy: the effect of dietary advice. Diabetes Care **1980**;3:476-81.

Boyd ME, Usher RH, McLean FH. Fetal macrosomia: prediction, risks, and proposed management. Obstet Gynecol **1983**;61:715-22.

Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. Am J Obstet Gynecol **1976**;126:555-64.

Brewer MM, Bates MR, Vannoy LP. Postpartum changes in maternal weight and body fat depots in lactatin' vs nonlactating women. Am J Clin Nutr **1989**;49:259-65.

Bromwick P. Big babies. Br Med J **1986**;293:293-5.

Bronstein MN, Mak RP, King JC. The thermic effect of food in normal-weight and overweight pregnant women. Br J Nutr **1995**;74(2):261-275.

Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. Br Med J **1989**;298:795-801.

Brown JE, Jacobson HN, Asuke LH, Peick MG. Influence of pregnancy weight gain on the size of infants born to underweight women. Obstet Gynecol **1981**;57(1):13-7.

Brown JE, Berdan KW, Splett P, Robinson M, Harris LJ. Prenatal weight gains related to the birth of healthy sized infants to low-income women. J Am Diet Assoc **1986**;86:1679-83.

Brown JE, Kaye SA, Folsom AR. Parity-related weight change in women. Int J Obesity **1992**;16:627-31

Buehler JW, Kleinmann JC, Hogue CJR, Strauss LT, Smith JC. Birthweight-specific infant mortality, United States, 1960 and 1980. Public Health Rep **1987**;102:151-61.

Butler NR, Alberman ED. Maternal factors affecting duration of pregnancy, birth weight and fetal growth. In: Perinatal Problems. Edinburgh: E&S Livingstone Ltd, **1969**:51.

Cade J, Margetts B. Cigarette smoking and serum lipid and lipoprotein concentration. Br Med J **1989**;298:1312.

Callan NA, Witter FR. Intrauterine growth retardation: characteristics, risk factors and gestational age. Int J Gynaecol Obstet **1990**;33(3):215-20.

Campbell-Brown DM. Protein energy supplements in primigravid women at risk of low birthweight. In: Campbell DM, Gillmer MDG, eds. Nutrition in Pregnancy. Proceedings of the Tenth Study Group of the RCOG, London. **1983**:85-100 (a).

Campbell-Brown DM. Dietary restriction in obesity and its effect on neonatal outcome. In: Campbell DM, Gillmer MDG, eds. Nutrition in Pregnancy. Proceedings of the Tenth Study Group of the RCOG, London **1983**:243-50 (b).

Catalano PM, Roman NM, Tyzbir ED, Merrit AO, Drscoll P, Amini SB. Weight gain in women with gestational diabetes. Obstet Gynecol **1993**;81:523-8.

CDA (The Canadian Dietetic Association). A healthy weight in 1988. Toronto, Ontario, **1987**.

Chase HC. Infant mortality and weight at birth: 1960 United States birth cohort. Am J Public Health **1969**;59:1618-25.

Clapp JF, Dickstein S. Endurance exercise and pregnancy outcome. Med Sci Sports Exerc **1984**;16:556-62.

Clapp JF, Seaward BL, Sleamaker RH, Hise J. Maternal physiologic adaptation to early human pregnancy. Am J Obstet Gynecol **1988**;159:1456-60.

Clapp JF, Capeless EL. Neonatal morphometrics after endurance exercise during pregnancy. Am J Obstet Gynecol **1990**;163:1805-11.

Clapp JF, Rokey R, Treadway JL, Carpenter MW, Artal RM, Warnes C. Exercise in pregnancy. Med Sci Sports Exerc **1992**;24:S294-300.

Clapp JF. A clinical approach to exercise during pregnancy. Clin Sports Med **1994**;13(2):443-58.

Cliver SP, Goldenberg RL, Cutter GR, Hoffman HJ, Davis RO, Nelson KG. The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol **1995**;85(4):625-30.

Cnattinigius S, Forman MR, Berendes HW, Graubard BI, Isotalo L. Effect of age, parity, and smoking on pregnancy outcome: a population-based study. Am J Obstet Gynecol **1993**;168:16-21.

Cogswell ME, Serdula MK, Hungerford DW, Yip R. Gestational weight gain among average-weight and overweight women--what is excessive? Am J Obstet Gynecol **1995**;172(2):705-12.

Collins LC, Cornelius MF, Vogel RL, Walker JF, Starnford BA. Effect of caffeine and/or cigarette smoking on resting energy expenditure. Int J Obesity **1994**;18:551-6.

Copper RL, DuBard MB, Goldenberg RL, Oweis AI. The relationship of maternal attitude toward weight gain to weight gain during pregnancy and low birth weight. Obstet Gynecol **1995**;85(4):590-5.

Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol **1994**;139:1139-52.

D'Souza SW, Black P, Richards B. Smoking in pregnancy: associations with skinfold thickness, maternal weight gain, and fetal size at birth. Br Med J **1981**;282:1661-3.

DaVanzo J, Habicht J-P, Butz WP. Assessing socioeconomic correlates of birthweight in peninsular Malaysia: ethnic differences and changes over time. Social Sci Med **1984**;18:387-404.

Davies DP, Gray OP, Ellwood PC, Abernethy M. Cigarette smoking in pregnancy: association with maternal weight gain and fetal growth. Lancet **1976**;1:385-9.

Dawes MG, Grudzinskas JG. Repeated measurement of maternal weight during pregnancy. Is this a useful practice? Br J Obstet Gynaecol **1991**;98:(189)669-70 (a).

Dawes MG, Grudzinskas JG. Patterns of maternal weight gain in pregnancy. Br J Obstet Gynaecol **1991**;98(2):195-201 (b).

De Groot LCP, Boekholt HA, Spaaij CJK, van Raaij JMA, Drijvers JJM, van der Heijden LJM, van der Heide D, Hauntvast JGA. Energy balance of healthy dutch women before and during pregnancy: limited scope for metabolic adaptations in pregnancy. Am J Clin Nutr **1994**;59(4):827-32

De Sanjose S, Roman E. Low birthweight, preterm, and small for gestational age babies in Scotland, 1981-1984. J Epidemiol Commun Health **1991**;45(3):207-10.

Delgado HL, Valverde VE, Martorell R, Klein RE. Relationship of maternal and infant nutrition to infant growth. Early Hum Dev **1982**;6:278-86.

Dewey KG, Heinig MJ, Nommsen LA. Maternal weight-loss patterns during prolonged lactation. Am J Clin Nutr **1993**;58:162-6.

DHHS (Department of Health and Human Services), National Center for Health Statistics. Health United States 1988. DHHS Publ No. (PHS) 89-1232, Hyattsville, Md, **1989** (a).

DHHS (Department of Health and Human Services). Caring for Our Future: The Content of Prenatal Care. Washington: A Report of the Public Health Service Expert Panel on Human Services, **1989** (b).

DHHS (Department of Health and Human Services), National Institute on Drug Abuse. National household survey on drug abuse: main findings 1990. DHHS Publ No. (PHS) 91-1788, Rockville, Md, **1991**.

DHHS (Department of Health and Human Services), National Center for Health Statistics. Health Promotion and Disease Prevention United States, 1990. DHHS Publ No. (PHS) 93-1513, Hyattsville, Md, **1993**.

DHHS (Department of Health and Human Services), National Center for Health Statistics. Infant Mortality by Birthweight and other Characteristics: United States, 1985 Birth cohort. DHHS Publ No. (PHS) 94-1852, Hyattsville, Md, **1994**.

Dougherty CRS, Jones AD. The determinants of birthweight. Am J Obstet Gynecol **1982**;144:190-200.

Dunn PM. A perinatal growth chart for international reference. Acta Paediatr Scand **1985**;319(Suppl):180-7.

Durnin JVGA, McKillop FM, Grant S, Fitzerald G. Is nutritional status endangered by virtually no extra intake during pregnancy? Lancet **1985**:823-5.

Durnin JVGA. Energy requirement of pregnancy: an integration of the longitudinal data from the five-country study. Lancet **1987**:1131-3.

Durnin JVGA. Energy requirements of pregnancy. Diabetes **1991**;40(Suppl 2):152-6.

Eastman NJ, Hellman LM. Williams' Obstetrics. 13th ed. New York: Appleton-Century -Croft, **1966**:326.

Edwards CH, Cole OJ, Oyemade UJ, Knight EM, Johnson AA, Westney OE, Laryea H, West W, Jones S, Westney LS. Maternal stress and pregnancy outcomes in a prenatal clinic population. J Nutr **1994**;124(6 Suppl):1006S-21S

Ellenberg JH, Nelson KB. Birth weight and gestational age in children with cerebral palsy or seizure disorders. Am J Dis Child **1979**;133:1044-8.

Elster AB. The effect of maternal age, parity, and prenatal care on perinatal outcome in adolescent mothers. Am J Obstet Gynecol **1984**;149:845-7.

Erkkola R. The physical work capacity of the expectant mother and its effect on pregnancy, labor, and the newborn. Int J Gynaecol Obstet **1976**;14:153-9.

FAO Nutrition Meetings Report Series No. 52 and WHO Technical Report Series No. 522: Energy and Protein Requirements. World Health Organization, **1973**.

FAO/WHO/UNU (Food and Agriculture Organization/World Health Organization/United Nations University). Energy and Protein Requirements. Report of a Joint FAO/WHO/UNU Expert Consultations, Tech Rep Ser 724. Geneva: World Health Organization, **1985**.

Fehily A, Phillips K, Yarnell J. Diet, smoking, social class, and body mass index in the Caterphilly Heart Disease Study. Am J Clin Nutr **1984**;40:827-33.

Fidanza AA, Fidanza R. A nutrition study involving a group of pregnant women in Assissi, Italy. Int J Vit Nutr Res **1986**;56:373-80.

Flegal KM. Ratio of actual to predicted weight as an alternative to a power-type weight-height index (Benn index). Am J Clin Nutr **1990**;51:540-7.

Forbes GB, Brown MR, Welle SL, Lipinski BA. Deliberate overfeediong in women and men: energy cost and composition of the weight gain. Brit J Nutr **1986**;56:1-9.

Forfar JO, Hume R, McPhail FM, Maxwell SM, Wilkinson EM, Lin JP, Brown JK. Low birthweight: a 10-year outcome study of the continuum of reproductive casualty. Dev Med Child Neurol **1994**;36(12):1037-48.

Forsum E., Sadurskis A, Wager J. Resting metabolic rate and body composition of healthy Swedish women during pregnancy. Am J Clin Nutr **1988**;47:942-7.

Forsum E, Kabir N, Sadurskis A, Westerterp K. Total energy expenditure of healthy Swedish women during pregnancy and lactation. Am J Clin Nutr **1992**;56(2):334-42.

Fox SH, Koepsell TD, Daling JR. Birth weight and smoking during pregnancy - effect modification by maternal age. Am J Epidemiol **1994**;139:1008-15.

Frank P, McNamee R, Hannaford PC, Kay CR. Effect of changes in maternal smoking habits in early pregnancy on infant birthweight. Br J Gen Pract **1994**;44(379):57-9.

Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. New Engl J Med **1995**;332(17):1113-7.

Frentzen BH, Dimperio DL, Cruz AC. Maternal weight gain: Effect on infant birthweight among overweight and average-weight low-income women. Am J Obstet Gynecol **1988**;159:1114-7.

Fried PA, Watkinson B, Dillon RF, Dulberg CS. Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana, and alcohol. J Dev Behav Pediatr **1987**;8:318-26.

Fried PA. Prenatal exposure to tobacco and marijuana: effects during pregnancy, and early childhood. Clin Obst Gynecol **1993**;36(2):319-37.

Frisancho AR, Matos J, Flegel P. Maternal nutritional status in adolescence and pregnancy outcome. Am J Clin Nutr **1983**;38:739-46.

Garn SM, Larkin FA, Cole PE. The problem with one-day dietary intakes. Ecol Food Nutr **1976**;5:245-7.

Garn SM, Shaw HA. Effect of maternal smoking on weight and weight gain between pregnancies. Am J Clin Nutr **1978**;31:1302-3.

Garn SM, Hoff K, McCabe KD. Is there nutritional mediation of the "smoking effect" on the fetus. Am J Clin Nutr **1979**;32:1181-7.

Geerdink JJ, Hopkins B. Effects of birthweight status and gestational age on the quality of general movements in preterm newborns. Biol Neonate **1993**;63(4):215-24.

Gibson RS. Principles of Nutritional Assessment. New York, NY: Oxford University Press, **1990**.

Goldberg GR, Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Wensing C, Black AE, Hardig M, Sawyer M. Longitudinal assessment of energy expenditure in pregnancy by the doubly labeled water method. Am J Clin Nutr **1993**;57(4):494-505.

Goldenberg RL, Cliver SP, Cutter GR, Davis RO, Hoffman HJ, Wen SW. Blood pressure, growth retardation, and preterm delivery. Int J Technology Assessment Health Care **1992**;8(Suppl 1):82-90.

Goldenberg RL, Davis RO, Cliver SP, Cutter GR, Hoffman HJ, Dubard MB, Copper RL. Maternal risk factors and their influence on fetal anthropometric measurements. Am J Obstet Gynecol **1993**;168:1197-205.

Gordon T, Kannel WB, Dawber TB, McGee D. Changes associated with quitting cigarette smoking: The Farmingham Study. Am Heart J **1975**;90:322-8.

Gormican a, Valentine J, Satter E. Relationships of maternal weight gain, prepregnancy weight and infant birth weight. J Am Diet Assoc **1980**;77:662-7.

Greene WG, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum weight change: How much of the weight gained in pregnancy will be lost after delivery? Obstet Gynecol **1988**;71:701-7.

Gutierrez Y, King JC. Nutrition during teenage pregnancy. Pediatric Annals **1993**;22(2):99-108.

Habicht JP, Yarbrough C, Lechtig A, Klein RE. Relation of maternal supplementary feeding during pregnancy to birthweight and other sociological factors. In: Winick M, ed. Proceedings of the Symposium on Nutrition and Fetal Development. New York: John Wiley & Sons, **1974**:127-46.

Haiek L, Lederman SA. The relationship between maternal weight for height and term birthweight in teens and adult women. J Adol Health Care **1988**;10:16-22.

Hall DC, Kaufman DA. Effects of aerobics and strength conditioning on pregnancy outcome. Am J Obstet Gynecol **1987**;157:1199-203.

Hannigan JH, Martier SS, Naber JM. Independent associations among maternal alcohol consumption and infant thyroxine levels and pregnancy outcome. Alcoholism Clin Exper Res **1995**;19(1):135-41.

Haste FM, Brooke OG, Anderson HR, Bland JM, Shaw A, Griffin J, Peacock J. Nutrient intakes during pregnancy: observations on the influence of smoking and social class. Am J Clin Nutr **1990**;51:29-36.

Haworth JC, Ellestad-Sayed JJ, King J, Dilling LA. Fetal growth retardation in cigarette smoking mothers is not due to decreased maternal food intake. Am J Obstet Gynecol **1980**;137:719-23.

Heald FP. New reference points for defining adolescent nutrient requirements. In: McKigney JI, Munro HN, eds. Nutrient Requirements in Adolescence. Cambridge: The MIT Press, **1973**.

Health Canada. Focus on: Canadians and Tobacco. September **1993**.

Health Canada. Fact Sheets: Survey on Smoking in Canada, Cycle 3. February **1995**.

Hediger ML, Scholl TO, Belsky DH, Ances IG, Salmon RW. Patterns of weight gain in adolescent pregnancy: effects on birth weight and preterm delivery. Obstet Gynecol **1989**;74:6-12.

Hediger ML. Scholl TO. Ances IG. Belsky DH. Salmon RW. Rate and amount of weight gain during adolescent pregnancy: associations with maternal weight-for-height and birth weight. Am J. Clin Nutr. **1990**;52(5):793-9.

Heins HC, Nance NW, McCarthy BJ, Efird CM. A randomized trial of nurse midwifery prenatal care to reduce low birthweight. Obstet Gynecol **1990**;75:341-5.

Hemminki E, Merilainen J, Malin M, Rahkonen O, Teperi J. Mother's education and perinatal problems in Finland. Int J Epidemiol **1992**;21(4):720-4.

Henderson GI, Turner D, Patwardhan RV, Lumeng L, Hoyumpa AM, Schenker S. Inhibition of placental valine uptake after acute and chronic maternal ethanol consumption. J Pharmacol Exp Ther **1981**;216:465-72.

Henriksen TB, Hedegaard M, Secher NJ. Standing and walking at work and birthweight. Acta Obstet Gynecol Scand **1995**;74(7):509-16.

Herrera MG, Mora JO, de Paredes B, Wagner M. Maternal weight/height and the effect of food supplementation during pregnancy and lactation. In: Aebi H, Whitehead RG, eds. Maternal nutrition during pregnancy and lactation. Bern, Switzerland: Hans Huber Publishers, **1980**:252-63.

Hickey C, Cliver S, Goldenber R, Kohatsu J, Hoffman H. Prenatal weight gain, term birth weight, and fetal growth retardation among high risk multiparous black and white women. Obstet Gynecol **1993**;81:529-35.

Hickey CA, Cliver SP, Goldenberg RL, McNeal SF, Hoffman HJ. Relationship of psychosocial status to low prenatal weight gain among nonobese black and white women delivering at term. Obstet Gynecol **1995**;86(2):177-83.

Higgins AC, Moxley JE, Pencgarz PB, Mikolainis D, Dubois S. Impact of the Higgins Nutrition Intervetion Program on birth weight: A within-mother analysis. J Am Diet Assoc **1989**:1097-103.

Hingson R. Alpert JJ, Day N, Dooling E, Kayne H, Morelock S, Oppenheimer, Zuckerman B. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics **1982**;70:539-46.

Hogue CJR, Buehler JW, Strauss LT, Smith JC. Overview of the National Infant Mortality Surveillance (NIMS) Project - design, methods, results. Public Health Rep **1987**;102:126-38.

Homer CJ, Bereford SA, James SA. Work-related physical exertion and risk of preterm, low birthweight delivery. Paediatr Perinat Epidemiol **1990**;4:161-74.

Horwitz L, Ferleger L. Statistics for Social Change, 1st ed. Montreal: Black Rose Books, **1980**.

Hunt SM, Groff JL. Advanced Nutrition and Human Metabolism. Significant. Paul, Mn: West Publishing Company, **1990**:384-401.

Hurley LS. Developmental Nutrition. Englewood Cliffs: Prentice Hall, **1980**

HWC (National Health and Welfare Canada, Bureau of Nutritional Sciences). Dietary Standard for Canada, **1975**.

HWC (Health and Welfare Canada). Recommended Nutrient Intakes for Canadians. Ottawa, **1983**.

HWC (Health and Welfare Canada). Health Promotion Survey. Technical Report. Ottawa: Statistics Canada, **1988**:17-32.

HWC (Health and Welfare Canada). The Active Health Report on Alcohol, Tobacco and Marijuana. Ottawa: Statistics Canada, **1989**.

HWC (Health and Welfare Canada). Nutrition Recommendation: The Report of The Scientific Review Committee. Ottawa: Canadian Government Publishing Centre, Cat No. H49-42/1990E, **1990**.

Hytten F, Chamberlain G. Clinical physiology in obstetrics. Oxford: Blackwell Scientific Publications, **1980 & 1991**.

Hytten FE, Leitch I. The Physiology of Human Pregnancy, 2nd edn. Oxford: Blackwell Scientific Publications, **1971**.

Hytten FE, Thomson AM. Maternal physiological adjustments. In: Committee on Maternal Nutrition, Food and Nutrition Board, National Research Council, National Academy of Sciences: Maternal nutrition and the course of pregnancy. Washington: Government Printing Office, **1970**.

Illingworth PJ, Jung RT, Howie PW. Energy balance in lactation. In: Berry EM, Blondheim SH, Eliahow HE, Shafir E, eds. Recent Advances in Obesity Research. London: John Libbey & Co., **1987** (a).

Illingworth PJ, Jung RT, Howie PW, Isles TE. Reduction in postprandial energy expenditure during pregnancy. Br Med J **1987**;294:1573-6 (b).

IOM (National Academy of Science: Institute of Medicine), Food and Nutrition Board, Subcommittee on Nutritional Status and Weight Gain During Pregnancy. Nutrition during pregnancy: Part I, Weight gain. Part II. Nutrient supplements. Washington: National Academy Press, **1990**.

IOM (National Academy of Science: Institute of Medicine), Food and Nutrition Board, Committee on Nutritional Status during Pregnancy and Lactation, Subcommittee for Clinical Application Guide. Nutrition during pregnancy and Lactation: An Implementation Guide. Washington: National Academy Press, **1992**.

Istvan J. Matarazzo JD. Tobacco, alcohol and caffeine use: a review of their interaction. Psychol Bull **1984**;95:301-26.

Jacobs DR, Gottenborg S. Smoking and weight: The Minnesota Lipid Research Clinic. Am J Public Health **1981**;71:391-6.

Jarski RW, Trippett DL. The risks and benefits of exercise during pregnancy. J Fam Pract **1990**;30:185-9.

Johnson JWC, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. Am J Obstet Gynecol **1992**;167:353-72.

Johnston C. Cigarette smoking and the outcome of human pregnancies: a status report of the consequences. Clin Toxicol **1981**;18:189-209.

Johnston CS, Christopher FS, Kandell LA. Pregnancy weight gain in adolescents and young adults. J Am Coll Nutr **1991**;10(3)185-9.

Johnston CS, Kandell LA. Pregnancy weight and rate of maternal weight gain in adolescents and young adults. J Am Diet Assoc **1992**;92(12)1515-7.

Jonas O, Roder D, Chan A. The association of low socio-economic status in metropolitan Adelaide with maternal demographic and obstetric characteristics and pregnancy outcome. Eur J Epidemiol **1992**;8(5):708-14.

Jovanovic-Peterson L, Peterson CM. Diabetes in pregnancy. Curr Ther Endocrinol Metabol **1988**;3:296-9.

Jovanovic-Peterson L, Peterson CM. Dietary manipulation as a primary treatment strategy for pregnancies complicated by diabetes. J Am Coll Nutr **1990**;9:320-5.

Kafatos AG, Bada A, Christakis S, Doxiadis G, Fordyce M. Nutritional problems in early adolescent pregnancy. In: Scott, Field & Robertson. Teenage parents and their offspring. New York: Grune & Stratton, **1981**.

Kafatos AG, Vlachonikolis IG, Codrington CA. Nutrition during pregnancy: the effects of an educational intervention program in Greece. Am J Clin Nutr **1989**;50:970-9.

Kardjati S, Kusin JA, With CD. Energy supplementation in the last trimester of pregnancy in East Java: I. Effect on birthweight. Brit J Obstet Gynaecol **1988**;95:783-94.

Kaye SA, Folsom AR, Prineas RJ, Potter JD, Gapstur SM. The association of body fat distribution with lifestyle and reproductive factors in a population study of postmenopausal women. Int J Obesity 1990;14:583-91.

Kennedy ET, Kotelchuk M. The effect of WIC supplemental feeding on birth weight: a case-control analysis. Am J Clin Nutr **1984**;40:579-85.

Keppel KG, Taffel SM. Advice about weight during pregnancy and actual weight gain. Am J Public Health **1986**;76:1396-9.

Keppel K, Taffel S. Implications of the 1990 Institute of Medicine guidelines on weight gain during pregnancy for postpartum weight retention. Am J Public Health **1993**;83:1100-3.

Kim I, Hungerford DW, Yip R, Kuester SA, Zyrkowski C, Trowbridge FL. Pregnancy nutrition surveillance system--United States, 1979-1990. MMWR CDC Surveillance Summaries **1992**;41(7):25-41.

King JC, Bronstein MN, Fitch WL, Weininger J. Nutrient utilization during pregnancy. World Rev Nutr Diet **1987**;52:71-142.

King JC, Butte NF, Bronstein MN, Kopp LE, Lindquist SA. Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr **1994**;59(Suppl):439S-55S.

Kirz DS, Dorchester W, Freeman RK. Advanced maternal age, the mature gravida. Am J Obstet Gynecol **1985**;152:7-12.

Klebanoff MA, Shiono H, Carey JC. The effect of physical activity during pregnancy on preterm delivery and birth weight. Am J Obstet Gynecol **1990**;163:1450-6.

Kleinman JC, Kopstein A. Smoking during pregnancy, 1967-80. Am J Public Health **1987**;77:823-5.

Kleinman JC. Maternal weight gain during pregnancy: determinants and consequences. NCHS Working Paper Series No. 33. U.S. Dept of Health and Human Services, National Center for Health Statistics, Hyattsville, Md. **1990**.

Klesges RC, Meyers AW, Klesges LM, Lavasque ME. Smoking, body weight and their effects on smoking behaviour. Psychol Bull **1989**;2:204-30.

Kline J, Stein K, Hutzler M. Cigarettes, alcohol and marijuana, varying association with birthweight. Int J Epidemiol **1987**;16:44-51.

Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Org **1987**;65(5):663-737.

Kramer MS, McLean FH, Boyd ME, Usher RH. The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestaion. JAMA **1988**;260(22):3306-8.

Kramer MS, McLean FH, Olivier M, Willis DM, Usher RH. Body proportionality and head and length 'sparing' in growth retarded neonates: a critical reappraisal. Pediatrics **1989**;84:717-23.

Kramer M. Effects of energy and protein intakes on pregnancy outcome: an overview of the research evidence from controlled clinical trials. Am J Clin Nutr **1993**;58:627-35.

Kraus MV, Mahan LK. Food, Nutrition and Diet Therapy, 7th ed. Toronto: W.H. Saunders, **1984**:964.

Kristjansson EA, Fried PA, Watkinson B. Maternal smoking during pregnancy affects children's vigilance performance. Drug and Alcohol Dependence **1989**;24:11-9.

Kucamarsk RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. JAMA **1994**;272:205-11.

Kulpa PJ, White BM, Visscher R. Aerobic exercise in pregnancy. Am J Obstet Gynecol **1987**;156:1395-403.

Langhoff-Roos J, Lindmark G, Gebre-Medhin M. Maternal fat stores and fat accretion during pregnancy in relation to infant birthweight. Br J Obstet Gynaecol **1987**;94:1170-7 (a).

Langhoff-Roos J, Lindmark G, Kylberg E, Gebre-Medhin M. Energy intake and physical activity during pregnancy in relation to maternal fat accretion and infant birthweight. Br J Obstet Gynaecol **1987**;94:1178-85 (b).

Langhoff-Roos J, Wibell L, Gebre-Medhin M, Lindmark G. Effect of smoking on maternal glucose metabolism. Gynecol Obstet Investigation **1993**;36(1):8-11.

Larsen CE, Serdula MK, Sullivan KM. Macrosomia: influence of maternal overweight among a low-income population. Am J Obstet Gynecol. **1990**;162(2):490-4.

Lawrence M, Lamb WH, Lawrence F, Whitehead RG. Maintenance energy cost of pregnancy in rural Gambian women and influence of dietary status. Lancet **1984**;2:363-5.

Lawrence M, Lawrence F, Coward WA, Cole TJ, Whitehead RG. Energy requirements of pregnancy in the Gambia. Lancet **1987**;2:1072-6.

Lawrence M, McKillop FM, Durnin JVGA. The composition of weight gained during pregnancy and its relationship to birthweight. Lausanne: Nestlé Foundation Report, **1988**:55-73.

Lawrence M, Mckillop FM, Durnin JV. Women who gain more fat during pregnancy may not have bigger babies: implications for recommended weight gain during pregnancy. Br J Obstet Gynaecol **1991**;98(3):254-9.

Lawton FG, Mason GC, Kelly KA, Ramsay IN, Morewood GA. Poor maternal weight gain between 28 and 32 weeks gestation may predict small-for-gestational-age infants. Br J Obstet Gynaecol **1988**;95:884-7.

Lechtig A, Habicht JP, Delgado H, Klein RE, Yarbrough C, Martorell R. Effect of food supplementation during pregnancy on birth weight. Pediatrics **1975**;56(4):508-20.

Lederman SA. The effect of pregnancy weight gain on later obesity. Obstet Gynecol **1993**;82:148-55.

Lee K-S, Ferguson RM, Corpuz M, Gartner LM. Maternal age and incidence of low birth weight at term: a population study. Am J Obstet Gynecol **1988**;158:614-20.

Lekea-Karanika V, Tzoumaka-Bakoula C. Past obstetric history of the mother and its association with low birthweight of a subsequent child: a population based study. Paediatr Perinat Epidemiol **1994**;8(2):173-87.

Lin GWJ. Effect of ethanol feeding during pregnancy on placental transfer of alpha-aminoisobutyric acid in the rat. Life Sci **1981**;28:595-601.

Lipscomb KR, Gregory K, Shaw K. The outcome of macrosomic infants weighing at least 4500 grams: Los Angeles County - University of Southern California experience. Obstet Gynecol **1995**;85(4):558-64.

Lokey EA, Tran ZV, Wells CL, Myers BC, Tran AC. Effects of physical exercise on pregnancy outcomes: a meta-analytic review. Med Sci Sports Exerc **1991**;23:1234-9.

Luke B, Dickenson C, Petrie RR. Intrauterine growth: correlation of maternal nutritional status and rate of gestational weight gain. Eur J Obstet Gynecol Reprod Biol **1981**;12(2):113-21.

Luke B. Nutritional influences on fetal growth. Clin Obstet Gynecol **1994**;37(3):538-49.

MacArthur C, Knox EG. Smoking in pregnancy: effects of stopping at different stages. Brit J Obstet Gynaecol **1988**;95(6):551-5.

Mahan KL, Rees MJ. Nutrition in Adolescence. Toronto: Time Mirror/Mosby College Publishing, **1984**.

Mainous AG, Hueston WJ. The effect of smoking cessation during pregnancy on preterm delivery and birthweight. J Fam Pract **1994**;38:262-6.

Marbury MC, Linn S, Monson R, Schoenbaum S, Stubblefield PG, Ryan KJ. The association of alcohol consumption with outcome of pregnancy. Am J Public Health **1983**;73:1165-8.

Mardones-Santander F, Rosso P, Stekel A, Ahumada E, Llaguno S, Pizarro F, Salinas J, Vial I, Walter T. Effect of a milk-based food supplement on maternal nutritional status and fetal growth in underweight Chilean women. Am J Clin Nutr **1988**;47:413-9.

Marks BL, Perkins KA, Metz KF, Epstein LH, Roberstson RJ, Goss FL, Sexton JE. Effects of smoking status on content of caloric intake and energy expenditure. Int J Eat Dis **1991**;10:441-9.

McCabe KD. Effect of maternal smoking on weight and weight gain between pregnancies. Am J Clin Nutr **1978**;31:1302-3.

McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med **1985**;312:82-90.

McDonald AD, Armstron BC, Sloan M. Cigarette, alcohol and coffee consumption and congenital defects. Am J Public Health **1992**;82:91-3.

McDonald AJ, Newson EE. Dietary changes made by low-income nutritionally high-risk pregnant women. J Can Diet Assoc **1986**;47:21-5.

McDonald EC, Pollit E. Mueller WH, Hsueh AM, Sherwin R. The Bacon Chow study: maternal nutritional supplementation and birth weight of offspring. Am J Clin Nutr **1981**;34:2133-44.

McGanity WJ, Dawson EB, Fogelman A. Nutrition in pregnancy. In: Shils ME, Olson JA, Shike M, eds. Health and Disease, 8th ed. Philadelphia: Lea & Febiger, **1994**:705-27.

McNeill G, Payne PR. Energy expenditure of pregnant and lactating women. Lancet **1985**;2:1237-8.

Mesorole LP, Worthington-Roberts BS, Rees JM. Wright LS. Prenatal weight gain and postpartum weight loss patterns in adolescents. J Adol Health Care **1984**;5:21-7.

Messimer SR, Hickner JM, Henry RC. A comparison of two anti-smoking interventions among pregnant women in eleven private primary care practices. J Fam Pract **1989**;28:283-8.

Metcoff J Castiloe JP, Crosby W, Bentle L, Seshachalom D, Sunstead HH, Bodwell CE, Weaver F, McClain P. Maternal nutrition and fetal outcome. Am J Clin Nutr **1981**;34:708-21.

Metcoff JP, Costiloe WM, Crosby S, Dutta HH, Sanstead D, Milne CE, Majors SH. Effect of food supplementation (WIC) during pregnancy on birth weight. Am J Clin Nutr **1985**;41:933-47.

Meyer MB, Jonas BS, Tonascia JA. Perinatal events associated with maternal smoking during pregnancy. Am J Epidemiol **1976**;103:464-76.

Meyer MB. How does maternal smoking affect birth weight and maternal weight gain? Evidence from the Ontario Perinatal Mortality Study. Am J Obstet Gynecol **1978**;131:888-93.

Miller HC, Merritt TA. Fetal growth in humans. Year Book Medical Publishers, Chicago **1979.**

Milner M, Barry-Kinsella C, Unwin A, Harrison RISK FACTORS. The impact of maternal age on pregnancy and its outcome. Int J Gynaecol Obstet **1992**;38(4):281-6.

Mitchell MC, Lerner E. A comparison of pregnancy outcome in overweight and normal weight women. J Am Coll Nutr **1989**;8(6):617-24 (a).

Mitchell MC, Lerner E. Weight gain and pregnancy outcome in underweight and normal weight women. J Am Diet Assoc **1989**;89:634-8 (b).

MLI (Metropolitan Life Insurance Company). New weight standards for men and women. Stat Bull Metrop Life Insur Co **1959**;40:1-4.

MLI (Metropolitan Life Insurance Company). Metropolitan height and weight tables. Stat Bull Metrop Life Found **1983**;64:3-9.

Modanlou HD, Dorchester WL, Thorosian A, Freeman RK. Macrosomia - maternal, fetal, and neonatal implications. Obstet Gynecol **1980**;55:420-4.

Moffat RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. Metabolism **1991**;40:465-70.

Mora JO, de Paredes B, Wagner M, de Navarro L, Suescun J, Christiansen N. Nutritional supplementation and outcome of pregnancy. I. Birthweight. Am J Clin Nutr **1979**;32(2):455-62.

Morgan BLG. Nutritional needs of the female adolescent. In: Health Care of the Female Adolescent, Women and Health Series, vol. 9 No. 2/3. The Howarth Press Inc., **1984.**

Mueller WH, Pollitt E. The Bacon Chow study: effects of nutrition supplementation on sibling-sibling anthropometric correlation. Hum Biol **1982**;54(3):455-68.

Murphy JF, Mulcahy R. The effect of age, parity and cigarette smoking on baby weight. Am J Obstet Gynecol **1971**;111:20-5.

Murphy SP, Abrams BF. Changes in energy intake during pregnancy and lactation in a national sample of US women. Am J Public Health **1993**;83(8):11161-3.

Muscati SK, Mackey MA, Newson B. The influence of smoking and stress on prenatal weight gain and infant birth weight of teenage mothers. J Nutr Education **1988**;20:299-302.

Muscati SK, Gray-Donald K, Newson EE. Interaction of smoking and maternal weight status in influencing infant size. Can J Public Health **1994**;85(6):407-12.

Muscati SK, Gray-Donald K, Koski KG. Timing of weight gain during pregnancy: promoting fetal growth and minimizing maternal weight retention. Int J Obesity **1996**;(in press).

Naeye RL. Weight gain and the outcome of pregnancy. Am J Obstet Gynecol **1979**;135:3-9.

Naeye RL. Maternal body weight and pregnancy outcome. Am J Clin Nutr **1990**;52:237-9.

Nagy LE, King JC. Postprandial energy expenditure and respiratory quotient during early and late pregnancy. Am J Clin Nutr **1984**;40:1258-63.

Niswander K, Jackson EC. Physical characteristics of the gravida and their association with birthweight and peri-natal death. Am J Obstet Gynecol **1974**;119:306-13.

NRC (National Academy of Sciences - National Research Council). Recommended Dietary Allowances. Report of the Food and Nutrition Board, **1958**.

NRC (National Academy of Sciences - National Research Council), Food and Nutrition Board, Subcommittee on Nutrition and Fertility). Nutrition and fertility interrelationships: implications for policy and action. Washington: Government Printing Office, **1975**.

NRC (National Academy of Sciences - National Research Council), Committee on Nutrition of the Mother and Preschool Child. Laboratory indices of nutritional status in pregnancy. Washington: National Academy Press, **1978**.

NRC (National Research Council). Recommended Dietary Allowances, 10th ed. Report of the Subcommittee on the Tenth Edition of the RDA's, Food and Nutrition Board, Commission on Life Sciences. Washington: National Academy Press, **1989**

Öhlin A, Rössner S. Maternal body weight development after pregnancy. Int J Obesity **1990**;14:159-73.

Öhlin A, Rössner S. Trends in eating patterns, physical activity and socio-demographic factors in relation to postpartum body weight development. Br J Nutr **1994**;71(4):457-70.

Olsen LC, Mundt MH. Postpartum weight loss in a nurse-midwifery practice. J Nurse Midwifery **1986**;31:177-81.

Olsen J. Cigarette smoking in pregnancy and fetal growth: Does the type of tobacco play a role?. Int J Epidemiol **1992**;21(2):279-84.

Osofsky HJ. Relationships between prenatal medical and nutritional measures, pregnancy outcome, and early infant development in an urban poverty setting. I. The role of nutritional intake. Am J Obstet Gynecol **1975**;123:682-90.

Ounsted M, Moar VA, Scott A. Children of deviant birth weight at the age of seven years: health, handicap, size and developmental status. Early Hum Dev **1984**;9:323-40.

Ounsted M, Moar VA, Scott A. Neurological development of small-for-gestational age babies during the first year of life. Early Hum Dev **1988**;13:163-72.

Ounsted M, Scott A. Association between maternal weight, height, weight-for-height, weight gain and birth weight. In: Dobbing J, ed. Maternal Nutrition in Pregnancy: Eating for Two? London: Academic Press, **1981**:113-29.

Paige DM, Cordano A, Mellits ED, Baertl JM, Davis L. Nutritional supplementation of pregnant adolescents. J Adol Health Care **1981**;1:261-7.

Papiernik E, Frydman R, Belaisch J. Nutrition in slim, normal and obese pregnant women. In: Dobbing J, ed. Maternal Nutrition in Pregnancy - Eating for Two? New York: Academic Press, **1981.**

Papoz L, Eschwege E, Pequignot G, Barrat J. Dietary behavior during pregnancy. In: Dobbing J, ed. Maternal Nutrition in Pregnancy - Eating for Two? New York: Academic Press, **1981.**

Papoz L, Eschwege E, Pequignot G, Barrat J, Schwartz D. Maternal smoking and birth weight in relation to dietary habits. Am J Obstet Gynecol **1982**;142:870-6.

Parham ES, Astrom MF, King SH. The association of pregnancy weight gain with mother's postpartum weight. J Am Diet Assoc **1990**;90(4):550-4.

Parker JD, Abrams B. Prenatal weight gain advice: an examination of the recent prenatal weight gain recommendations of the Institute of Medicine. Obstet Gynecol **1992**;79:664-9.

Parker JD, Abrams B. Differences in postpartum weight retention between black and white mothers. Obstet Gynecol **1993**;81:768-74.

Parker JD, Schoendorf KC, Kiely JL. Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. Annals Epidemiol **1994**;4(4):271-8.

Parker JD. Postpartum weight change. Clin Obstet Gynecol **1994**;37(3):528-37.

Peacock JL, Bland JM, Anderson HR, Brooke OG. Cigarette smoking and birthweight: type of cigarette smoked and a possible threshold effect. Int J Epidemiol **1991**;20:405-12 (a).

Peacock JL, Bland JM, Anderson HR. Effects on birthweight of alcohol and caffeine consumption in smoking women. J Epidemiol Commun Med **1991**;45:159-63 (b).

PEI (Prince Edward Island Department of Health and Social Services). Manual for an on-going evaluation of the pre-natal nutrition counselling services **1982.**

PEI (Prince Edward Island Department of Health and Social Services), Nutrition Services. Prenatal Nutrition Intervention Program Evaluation Report, **1983**.

Pencharz, P.B. Adolescent nutrition: pregnancy and diet. Can Med Assoc J **1983**;129:691-2.

Perkins KA, McKenzie SJ, Stoney CM. The relevance of metabolic rate in behavioral medicine research. Behav Mod **1987**;11:286-311.

Perkins KA., Epstein LH, Stiller RL, Marks BL, Jacob RG. Acute effects of nicotine on resting metabolic rate in cigarette smokers. Am J Clin Nutr **1989**;50:545-50.

Perkins KA. Metabolic effects of cigarette smoking. J Appl Physiol **1992**;72:401-9.

Perkins KA. Weight gain following smoking cessation. J Consult Clin Psychol **1993**;61:768-77.

Petitti DB, Croughan-Minihane MS, Hiatt RA. Weight gain by gestational age in both black and white women delivered of normal-birth-weight and low-birth-weight infants. Am J Obstet Gynecol **1991**;164:801-5.

Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. I. Effects of diet, cigarette smoking and psychological stress on maternal weight gain. Am J Clin Nutr **1982**;36:1205-13 (a).

Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress and weight gain on placentas, and on neonatal physical and behavioral characteristics. Am J Clin Nutr **1982**;36:1214-24 (b).

Picone TA, Allen LH. Maternal diet during human pregnancy: effects of the percent of calories as protein on outcome. Federation Proceedings **1984**;43:492, (Abstract 1209).

Piers LS, Diggavi SN, Thangam S, van Raaij JM, Shetty PS, Hautvast JG. Changes in energy expenditure, anthropometry, and energy intake during the course of pregnancy and lactation in well-nourished Indian women. Am J Clin Nutr **1995**;61(3):501-13.

Pipe NG, Smith T, Halliday E, Edmonds CJ, Willliams C, Coltart TM. Changes in fat, fat-free mass, and body water in human normal pregnancy. Br J Obstet Gynaecol **1979**:86:929-40.

Poppitt SD, Prentice AM, Jequier E, Schutz Y, Whitehead RG. Energy sparing during pregnancy in rural Gambian women asessed by whole-body calorimetry. Am J Clin Nutr **1993**;57:353-64.

Poppitt SD, Prentice AM, Goldberg GROUP, Whitehead RG. Energy-sparing strategies to protect human fetal growth. Am J Obstet Gynecol **1994**;171(1):118-25.

Potter S, Hannum S, McFarlin B, Essex-Sorlie D, Campbell E, Trupin S. Does infant feeding method influence maternal weight loss? J Am Diet Assoc **1991**:91:441-6.

Prentice AM, Cole TJ, Foord FA, Lamb WH, Whitehead RG. Increased birth weight after prenatal dietary supplementation of rural African women. Am J Clin Nutr **1987**;46:912-25.

Pritchard JA, McDonald PC, Gant NF. Williams' Obstetrics. 13th ed. New York; Appleton-Century-Croft, **1985**.

Prochownick L. Ueber Ernährungscuren in der Schwangerschaft. Ther Monatsh **1901**;15:446-63.

Quandt SA. Changes in maternal postpartum adiposity and infant feeding patterns. Am J Phys Anthropol **1983**;60:455-61.

Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. Br Med J **1993**;306(6881):817-20.

Rookus MA, Rokebrand P, Burema J, Deurenberg P. The effect of pregnancy on the body mass index 9 months postpartum in 49 women. Int J Obesity **1987**;11:609-18.

Rosett HL. A clinical perspective of the fetal alcohol syndrome. Alcoholism **1980**;4:119-22.

Ross SM, Nel E, Naeye R. Differing effects of low and high bulk maternal dietary supplements during pregnancy. Early Hum Develop **1985**;10:295-302.

Rössner S. Pregnancy, weight cycling and weight gain in obesity. Int J Obesity **1992**;16(2):145-7.

Rosso P, Winick M. Intra-uterine growth retardation: a new systematic approach based on the clinical and biochemical characteristics of this condition. J Perinat Med **1974**;2:147-60.

Rosso P. Nutrition and maternal-fetal exchange. Am J Clin Nutr **1981**;34:744-55.

Rosso P. A new chart to monitor weight gain during pregnancy. Am J Clin Nutr **1984**;41:644-52.

Rosso P. Nutrition and Metabolisn in Pregnancy: Mother and Fetus. New York: Oxford University Press **1990**.

Ruge S, Anderson T. Obstetric risk in obesity: an analysis of the literature. Obstet Gynecol Surv **1985**;40(2):57-60.

Rush D. Examination of the relationship between birthweight, cigarette smoking during pregnancy and maternal weight gain. J Obstet Gynaecol Br Commonw **1974**;81:746-52.

Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York City. Pediatrics **1980**;65(4):683-97.

Rush D. Nutritional services during pregnancy and birth weight: a retrospective matched pair analysis. Can Med Assoc J **1981**;125:567-76.

Rush D, Cassano P. Relationship of cigarette and social class to birth weight and perinatal mortality among all births in Britain. J Epidemiol Commun Health **1983**;37:249-55.

Rush D, Sloan NL, Leighton J, Alvir JM, Horvitz DG, Seaver WB, Garbowski GC, Johnson SS, Kulka RA, Holt M, Devore JW, Lynch JT, Woodside MB, Shanklin DS. The National WIC Evaluation: Evaluation of the Special Supplemental Food Program for Women, Infants and Children.

V. Longitudinal study of pregnant women. Am J Clin Nutr **1988**;48:439-83. (a)

Rush D, Cassano P, Harlap S. Perinatal outcome, maternal weight gain, cigarette smoking and social status in Jerusalem. Revue D Epidemiologie et de Santé Publique 1988;36(3):186-95. (b)

Rush D, Andrews J, Kristal A. Maternal cigarette smoking during pregnancy, adiposity, social class, and perinatal outcome in Cardif, Wales, 1965-1977. Am J Perinat **1990**;7(4):319-26.

Salans LB. Natural history in obesity. In Bray GB, ed: Obesity in America. DHEW Publ No (NIH) 79-359, **1979**.

Sampson L. Food frequency questionnaires as a research instrument. Clin Nutr **1985**;4:171-8.

Sandstead HH. Methods for determining nutrient requirements in pregnancy - I. Am J Clin Nutr **1981**;34:697-704.

Sappenfield WM, Buehler JW, Binkin NJ, Hogue CJR, Strauss LT, Smith JC. Differences in neonatal and postneonatal mortality by race, birthweight, and gestational age. Public Health Rep **1987**;102:182-92.

SAS Institute Inc. SAS Procedures Guide for Personal Computers, Version 6 Edition. Cary, North Carolina, **1985**.

SAS Institute Inc. SAS/STAT Guide for Personal Computers, Version 6 Edition. Cary, North Carolina, **1985**.

Sastry BVR, Mouton S, Janson VE, Kambam JR. Tobacco Smoking by Pregnant Women: Disturbance in metabolism of branched chain amino acids and fetal growth. Ann NY Acad Sci **1993**;566:361-3.

Saugstad LF. Weight of all births and infant mortality. J Epidemiol Commun Health **1981**;35:185-93.

Schauberger CW, Rooney BL, Brimer LM. Factors that influence weight loss in the puerperium. Obstet Gynecol **1992**;79:424-9.

Schoeller DA. How accurate is self-reported dietary energy intake. Nutr Rev **1990**;48:373-9.

Schofield C, Wheeler E, Stewart J. The diets of pregnant and post-pregnant women in different social groups in London and Edingburgh: energy, protein, fat and fibre. Br J Nutr **1987**;58:369-81.

Scholl TO, Salmon RW, Miller LK, Vasilenko P, Furey CH, Christine M. Weight gain during adolescent pregnancy: associated maternal characteristics and effects on birth weight. J Adol Health Care **1988**;9:286-90.

Scholl TO, Hediger ML, Belsky DH, Ances IG, Salmon RW. First and second trimester weight gain and birthweight: importance of diet and early detection. UMDNJ-SOM, Camden, NJ 08103, **1989**.

Scholl TO, Hediger ML, Ances IG, Belsky DH, Salmon RW. Weight gain in adolescence: predictive ability of early weight gain. Obstet Gynecol **1990**;75:948-53.

Secher NJ, Hjortdal J, Hjortdal V. Smoking affects fetal growth selectively. Acta Obstet Gynaecol Scand **1990**;69(6):469-71.

Seidman DS, Laor A, Gale R, Stevenson DK, Danon YL. A longitudinal study of birth weight and being overweight in late adolescence. Am J Dis Child **1991**;145(7):782-5.

Seidman DS, Laor A, Gale R, Stevenson DK, Mashiach S, Danon YL. Birth weight and intellectual performance in late adolescence. Obstet Gynecol **1992**:79(4):543-6.

Sexton M, Hebel JR. A clinical trial of change in maternal smoking and its effect on birth weight. JAMA **1984**;251:911-5.

Shapiro S, McCormick MC, Starfield BH, Krischer JP, Bross D. Relevance of correlates of infant deaths for significant morbidity at 1 year of age. Am J Obstet Gynecol **1980**;136:363-73.

Sheik GN. Observations of maternal weight behaviour during the puerperium. Am J Obstet Gynecol **1971**; 111:244-50.

Shepard MJ, Hellenbrand KG, Bracken MB. Proportional weight gain and complications of pregnancy, labor and delivery in healthy women of normal prepregnancy stature. Am J Obstet Gynecol **1986**;155:947-54.

Shu XO, Hatch MC, Mills J, Clemens J, Susser M. Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: results from a prospective study. Epidemiology **1995**;6(2):115-20.

Siega-Riz AM, Adair LS. Biological determinants of pregnancy weight gain in a Filipino population. Am J Clin Nutr **1993**;57:365-72

Siega-Riz AM, Adair LS, Hobel CJ. Institute of Medicine maternal weight gain recommendations and pregnancy outcome in predominantly Hispanic population. Obstet Gynecol **1994**;84:565-73.

Smith DE, Lewis CE, Caveny JL, Perkins LL, Burke GL, Bild DE. Longitudinal changes in adiposity associated with pregnancy - The CARDIA Study. JAMA **1994**:271:1747-51.

Snyder J, Gray-Donald K, Koski KG. Predictors of infant birth weight in gestational diabetes. Am J Clin Nutr **1994**;59:1409-14.

Sohlstrom A, Forsum E. Changes in adipose tissue volume and distribution during reproduction in Swedish women as assessed by magnetic resonance imaging. Am J Clin Nutr **1995**;61(2):287-95.

Sokol RJ, Miller SI, Reed G. Alcohol abuse during pregnancy: an epidemiologic study. Alcoholism **1980**;4:135-45.

Sokol RJ, Miller SI, Debanne S, Golden N, Collins G, Kaplan J, Martier S. The Cleveland NIAAA prospective alcohol-in-pregnancy study: the first year. Neurobehav Toxicol Teratol **1981**;3:203-9.

Spaaij CJK. The efficiency of energy metabolism during pregnancy and lactation in well-nourished Dutch women [Dissertation]. Wageningen, The Netherlands: University of Wageningen, **1993**.

Spaaij CJ, van Raaij JM, Van der Heijden LJ, Schouten FJ, Drijvers JJ, De Groot LC, Boekholt HA, Hautvast JG. No substantial reduction of the thermic effect of a meal during pregnancy in well-nourished Dutch women. Br J Nutr **1994**;71(3):335-44.

Spellacy WN, Miller SJ, Winegar A. Pregnancy after 40 years of age. Obstet Gynecol **1986**;68:452-4.

Stamford BA, Matter S, Fell RD, Cresanta MK. Cigarette smoking, physical activity, and alcohol consumption: relationship to blood lipids and lipoproteins in premenopausal females. Metabol Clin Exper **1984**;33:585-90.

Stamford BA, Matter S, Fell RD, Papneck P. Effects of smoking cessation on weight gain, metabolic rate, caloric consumption and blood lipids. Am J Clin Nutr **1986**;43:486-94.

Stein Z, Susser M, Saenger G, Marolla F. Famine and Human Development: The Dutch Hunger Winter of 1944/45. New York: Oxford University Press, **1975**.

Stewart PJ, Dunkley GC. Smoking and health care patterns among pregnant women. Can Med Assoc J **1985**;133:989-94.

Stewart PJ, Potter J, Dulberg C, Niday P, Nimrod C, Tawagi G. Change in smoking prevalence among pregnant women 1982-93. Can J Public Health **1995**;86(1)37-41.

Stockbauer JW. Evaluation of the Missouri WIC program: Prenatal components. J Am Diet Assoc **1986**;86(1):61-7.

Streissguth AP, Martin DC, Barr HM. The Seattle longitudinal prospective study on alcohol and pregnancy. Neurobehav Toxicol **1981**;3:323-33.

Streissguth AP, Darby BL, Barr HM, Smith JR, Martin DC. Comparison of drinking and smoking during pregnancy over a six-year interval. Am J Obstet Gynecol **1983**;145:716-24.

Streissguth AP. The behavioral teratology of alcohol: performance, behavioral and intellectual deficits in prenatally exposed children. In: West J, ed. Alcohol and Brain Development. New York: Oxford University Press, **1986**.

Susser M. Maternal weight gain, infant birth weight, and diet: causal consequences. Am J Clin Nutr **1991**;53:1384-96.

Taffel SM. Maternal weight gain and the outcome of pregnancy: United States, 1980. Vital and Health Statistics, Series 21, No. 44. DHHS Publ. No. (PHS) 86-1922, U.S. Department Of Health and Human Services, National Center for Health Statistics, Hyatsville, Md. **1986**.

Tauzon MAG, Barba CVC, van Raaij JMA, Peek MEM, Hautvast JGAJ. Maternal energy requirements during pregnancy of rural Phillipine women. Geneva: Nestlé Foundation Annual Report **1986:**113-46.

Tauzon M, Van Raaij JMA, Hautvast JGAJ, Barba CVC. Energy requirements of pregnancy in the Philippines. Lancet **1987**;2:1129-31.

Thompson GN, Halliday D. Protein turnover in pregnancy. Eur J Clin Nutr **1992**;46(6):411-7.

Thomson AM, Billewicz WZ. Clinical significance of weight trends during pregnancy. Br Med J **1957**;1:243-7.

Thomson AM, Billewicz WZ, Hytten FE. The assessment of fetal growth. J Obstet Gynaecol Br Commonw **1968**;75:903-16.

Thomson AM. Physiological determinants of birth weight. Proceedings of the Second European Congress on Perinatal Medicine, London, 1970. Basel: Karger, **1971**:174-80.

Thongprasert K, Tanphaichitre V, Valyasev A. The energy requirements of pregnant rural Thai women. Geneva: Nestlé Foundation Annual Report **1986**:105-12.

Thongprasert K, Tanphaichitre V, Valyasev A, Kittigool J, Durnin JVGA. Energy requirements of pregnancy in rural Thailand. Lancet **1987**;2:1010-2.

Tonkelaar ID, Seidell JC, van Noord PAH, Baanders-van Halewijn EA, Ouwehand IJ. Fat distribution in relation to age, degree of obesity, smoking habits, parity, and estrogen use: a cross-sectional study in 11 825 Dutch women participating in the Dom-project. Int J Obesity 1990;14:753-61.

Tontisirin K, Booranasukajorn U, Hongsumatn A, Thewtong D. Formulation and evaluation of supplementary foods for Thai pregnant women. Am J Clin Nutr **1986**;43:931-9.

Truswell AS, Allen JR. Energy intake during pregnancy. Lancet **1988**;1:49.

Unfer V, Piazze Garnica J, Di Benedetto MR, Costabile L, Gallo G, Anceschi MM. Pregnancy in adolescents. A case-control study. Clin Exper Obstet Gynecol **1995**;22(2):161-4.

US Government Accounting Office. *WIC evaluations provide some favorable but not conclusive evidence on the effects expected for the Special Supplemental Program for Women, Infants, and Children.* Washington, January 30, **1984**.

Usher RH. Clinical and therapeutic aspects of of fetal malnutrition. Pediatr Clin North Am **1970**;17:169-83.

Van Raaij JMA, Peek MEM, Hautvast JGAJ. Maternal energy requirements in pregnancy in Dutch women. Nestlé Foundation Annual Report **1986**;53-75.

Van Raaij JMA, Vermaat-Miedema SH, Schonk CM, Peek MEM, Hautvast JGAJ. Energy requirements of pregnancy in the Netherlands. Lancet **1987**;2:953-5.

Van Raaij JMA, Schonk CM, Vermaat-Miedema SH, Peek MEM, Hautvast JGAJ. Body fat mass and basal metabolic rate in Dutch women before, during and during pregnancy: a reappraisal of energy cost of pregnancy. Am J Clin Nutr **1989**:49:765-72.

Van Den Burg BJ. Epidemiologic observations of prematurity: effects of tobacco, coffee, and alcohol. In: Reed DM, Stanely FJ, eds. The Epidemiology of Prematurity. Baltimore: Urban & Schwartzenberg, **1977**:157-76.

Varma TR. Maternal weight and weight gain in pregnancy and obstetric outcome. Int J Gynaecol Obstet **1984**;22:161-6.

Viegas OAC, Scott PH, Cole TJ, Mansfield HN, Wharton P, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorento, Birmingham. I: Unselective during second and third trimesters. Br Med J **1982**;285:589-92 (a).

Viegas OAC, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA. Dietary protein-energy supplementation of pregnant Asian mothers at Sorento, Birmingham. II. Selective during third trimester only. Br Med J **1982**;285:592-5 (b).

Viegas OAC, Cole TJ, Wharton BA. Impaired fat deposition in pregnancy: an indicator for nutritional intervention. Am J Clin Nutr **1987**;45:23-8.

Villar J, Belizan JM. The timing factor in the pathophysiology of the intrauterine growth retardation syndrome. Obstet Gynecol Surv **1982**;37:499-506.

Villar J, Dorgan J, Menendez R, Bolanos L, Pareja G, Kestler E. Perinatal data reliability in a large teaching obstetric unit. Br J Obstet Gynaecol **1988**;95:841-8.

Villar J, Kestler E, Pareja G. Measurement errors in clinical perinatal data. Am J Obstet Gynecol **1989**;160:380-2.

Villar J, Cogswell M, Kestler E, Castillo P, Menendez R, Repke J. Effect of fat and fat-free mass deposition during pregnancy on birth weight. Am J Obstet Gynecol **1992**;167:(5)1344-52.

Vobecky JS, Vobecky J, Shapcott D, Cloutier D, Demers PP, Blanchard R, Black R. Relationship of maternal weight gain to maternal and early neonatal nutritional status. Nutr Rep Int **1983**;27:845-55.

Walpole I, Zubrick S, Pontre J. Is there a fetal effect with low to moderate alcohol use before or during pregnancy? J Epidemiol Commun Health - London. **1990**;44(4):297-301.

Walsh RA. Effects of maternal smoking on adverse pregnancy outcomes: examination of the criteria of causation. Hum Biol **1994**;66(6):1059-92.

Warwick PM, Edmundson HM, Thomson ES. No evidence for a chronic effect of smoking on energy expenditure. Int J Obesity **1995**;19:198-201.

Webster JD, Hesp R, Garrow JS. Human Nutrition. Clin Nutr **1984**;38:299-306.

Weiss W, Jackson EC. Perinatal factors affecting human development. Washington: Pan American Health Organization, **1969**;54-69.

Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP, Davis RO, DuBard MB. Smoking, maternal age, fetal growth, and gestational age at delivery. Am J Obstet Gynecol **1990**;162(1):53-8. (a)

Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP. Intrauterine growth retardation and preterm delivery: prenatal risk factors in an indigent population. Am J Obstet Gynecol **1990**;162(1):213-8. (b)

Wen SW, Kramer MS, Usher RH. Comparison of birth weight distributions between Chinese and Caucasian infants. Am J Epidemiol **1995**;141(12):1177-87. (a)

Wen SW, Kramer MS. Etiologic fraction analysis for continuously distributed outcome variables and empirical analogy with dichotomized outcome variables. Int J Epidemiol **1995**;24(2):457-61. (b)

Widdowson EM, Southgate DAT. Fetal growth and body composition. In Lindblad BS, ed: Perinatal Nutrition. San Diego: Academic Press **1988**.

Wilcox AJ. Birth weight and perinatal mortality: the effect of maternal smoking. Am J Epidemiol **1993**;137:1098-104.

Wilcox M, Gardosi J, Mongelli M, Ray C, Johnson I. Birth weight from pregnancies dated by ultrasonography in a multicultural British population. Br Med J **1993**;307(6904):588-91.

Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analysis. Am J Epidemiol **1986**;124:17-27.

Willett W. Nutritional Epidemiology. New York: Oxford University Press; **1990**.

Williamson DF, Serdula MK, Kendrick JS, Binkin NJ. Comparing the prevalence of smoking in pregnant and nonpregnant women, 1985 to 1986. JAMA **1989**;261:70-4.

Williamson DF, Madans J, Anda RG, Kleinman JC, Giovino GA, Byers T. Smoking cessation and severity of weight gain in national cohort. N Engl J Med **1991**;324:739-45.

Williamson DF, Madans J, Pamuk, E, Flegal KM, Kendrick JS, Serdula MK. A prospective study of childbearing and 10-year weight gain in US white women 25 to 45 years of age. Int J Obesity **1994**;18:561-9.