Papers

Influence of maternal nutrition on outcome of pregnancy: prospective cohort study

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Abstract

Objective To investigate the relations of maternal diet and smoking during pregnancy to placental and birth weights at term.
Design Prospective cohort study.
Setting District general hospital in the south of England.
Participants 693 pregnant nulliparous white women with singleton pregnancies who were selected from antenatal booking clinics with stratified random sampling.
Main outcome measures Birth and placental weights at term.
Results Placental and birth weights were unrelated to the intake of any macronutrient. Early in pregnancy, vitamin C was the only micronutrient independently associated with birth weight after adjustment for maternal height and smoking. Each ln mg increase in vitamin C was associated with a 50.8 g (95% confidence interval 4.6 g to 97.0 g) increase in birth weight. Vitamin C, vitamin E, and folate were each associated with placental weight after adjustment for maternal characteristics. In simultaneous regression, however, vitamin C was the only nutrient predictive of placental weight: each ln mg increase in vitamin C was associated with a 3.2% (0.4 to 6.1) rise in placental weight. No nutrient late in pregnancy was associated with either placental or birth weight.
Conclusions Concern over the impact of maternal nutrition on the health of the infant has been premature. Maternal nutrition, at least in industrialised populations, seems to have only a small effect on placental and birth weights. Other possible determinants of fetal and placental growth should be investigated.

Introduction

Barker and colleagues have shown strong associations between infant and placental size and the risk of later chronic disease, such as cardiovascular disease and diabetes.[1 2] On the basis of data from animal studies and cross country comparisons, poor maternal nutrition has been implicated as one of the key "adverse environmental influences in utero," which could lead to compromised fetal and placental growth and adverse long term consequences.[1] Their observational studies of British women also suggest that maternal diet is an important determinant of infant and placental size.[3–5] The "Barker hypothesis" has led to calls for improvements in maternal diet, which have generated some concern among obstetricians.[6]

Although there is widespread recognition of the importance of adequate maternal nutrition during pregnancy in developing countries, there is considerable uncertainty about its role in industrialised countries, where profound malnutrition is uncommon. Even near starvation, such as occurred during the "Dutch hunger winter," reduced mean birth weight by only 300 g.[7] The evidence from adequately nourished populations is conflicting. Observational studies have found only weak and inconsistent associations between intake of macronutrients and infant size,[3 5 8 9] and few data are available for micronutrients.[9–11] In supplementation trials, micronutrients have not been shown to have important impact on mean birth or placental weights.[10–13] Protein and energy supplementation have produced both increases and decreases in birth weight, with high density protein supplements seeming to reduce birth weight.[14 15] The results of such trials are difficult to generalise, however, as intakes are often increased well beyond normal levels. In addition, trials are usually designed to detect changes in adverse outcomes of pregnancy rather than in birth weights within the normal range. We therefore conducted a large scale observational study in an attempt to elucidate the role of maternal nutrition in pregnancy. We set out to detect differences in birth weight between women with high and low intakes of nutrients early in pregnancy.[2]

Participants and methods

Full details of the survey methods are reported elsewhere.[16] Briefly, healthy white nulliparous women attending antenatal clinics in Portsmouth between May 1994 and February 1996 were stratified by smoking status, and simple random selection was carried out within each stratum (details on request). Of the 1002 women invited to participate, 963 were recruited. The sampling procedure resulted in the prevalence of smoking among respondents being similar to nationally representative samples of pregnant women.[17 18]

Sample size
To detect a 150 g difference in mean birth weight (SD 500 g) between the two extreme thirds of nutrient intake (two sided $\alpha = 0.05$, power = 90%) required a

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sample of 750 women. The expected difference was based on the results of a pilot study. To allow for non-completion of the food diary we aimed to recruit 1000 women.

Data collection

Structured interviews were conducted by trained researchers during visits to antenatal clinics. Social class was based on the woman's most recent occupation.[19] Height, weight, blood pressure, and blood count were as measured routinely. Women were classified as smokers if they reported smoking or if their serum cotinine concentration was greater than 14 ng/ml.[20 21]

The main method of dietary assessment was a 7 day semiquantitative food diary completed the week after booking.[16] Usual diet since booking was reported in a food frequency questionnaire mailed at 28 weeks' gestation. The questionnaire was based closely on that used by the European prospective investigation of cancer (EPIC).[22] Reliability tests indicate that diary data correspond better to weighed records than do estimates based on a food frequency questionnaire [23]; indeed, the relatively low accuracy and reproducibility of food frequency questionnaires has been widely reported.[24 25] This method was nevertheless used in late pregnancy as a second food diary would have compromised participation rates.

Babies were weighed at delivery to the nearest 5 g. Placentas were weighed to the nearest 1 g after the amnion was stripped to the cord, the chorion cut at the edge of the placenta, and the cord removed flush with the placenta.

Statistical analysis

Over the ranges studied, placental and birth weights showed linear relations with gestational age and were also associated with sex. For clarity, and for comparison with other studies,[3–5] individual measurements were adjusted to the mean gestational age and sex of the cohort. All subsequent analyses used these adjusted values.

The relations of placental and birth weights to maternal factors, sex of the baby, and gestational age were examined with analyses prespecified in the protocol. Means were compared by using z tests and proportions by using χ^2 tests. Tests of significance were two tailed. The sociodemographic variables considered were smoking status; cigarettes smoked in day before interview (0 and approximately equal groups: 1-8; 9-16; ≥17); maternal age at booking (days); reported weight before conception (kg); maternal weight (kg) at booking; maternal height (m); body mass index (kg/m^2) before conception; body mass index at booking; diastolic blood pressure at booking; haemoglobin concentration at booking (g/dl); social class in three groups (I and II; III non-manual and III manual; IV and V); and education in three groups (higher than O level (>GCSE); O level (GCSE grades A-C); and less than O level (GCSE grades D and E)).

The fit of multiple linear regression models was ascertained by examination of residuals. Placental weights were ln transformed to satisfy the assumptions of normality; total intakes of all micronutrients were ln transformed to reduce the leverage of outlying values. Transformation did not materially affect the results. Maternal variables were considered for inclusion if they were significantly ($P<0.05$) associated with nutrient intake or pregnancy outcome in univariate analysis or if this association had been reported elsewhere. Each model was built by using a combination of forced entry and forward stepwise procedures (criterion for entry was $P<0.05$ and for removal $P>0.10$).

Results

Of the 963 women recruited, 917 had live singleton deliveries in Portsmouth. Food diaries were completed by 739 (80.6%) of these women ("respondents"). To permit comparisons with the results of Godfrey et al[4 5] the 46 respondents who delivered before 259 days' gestation were excluded. The results obtained from the entire cohort did not differ from those presented for term deliveries, and no nutrient was associated with preterm delivery.[21]

Table 1 shows the characteristics of the 693 mothers and babies. The nulliparous women in our cohort were sociodemographically similar to those studied by Godfrey et al[4 5] and their social class distribution was comparable with a nationally representative sample of mothers.[26]

Dietary intakes—Table 2 shows nutrient intakes (from food and supplements) in early and later pregnancy. Nutrient intakes from food alone as well as totals including supplements are shown for iron and folate as supplements made a substantial contribution to intakes for these nutrients.

Maternal characteristics and placental and birth weights—In univariate analyses maternal height, weight before conception, weight at booking, self reported smoking status, and smoking status validated by cotinine measurements were all predictive of birth weight ($P<0.001$). In multiple regression, however, the only independent predictors of birth weight were smoking status validated by cotinine measurement

Table 1 Characteristics of 693 mothers and babies. Figures are number (percentage) of participants unless stated otherwise

Detail	No (%) or mean (SD)
Mothers	
Smokers by self report	209 (30.2)
Validated smokers	282 (40.7)
Social class by maternal occupation*:	
I and II	153 (22.9)
IIIM and IIINM	357 (53.5)
IV and V	157 (23.5)
Education:	
>O level (>GCSE)	191 (27.6)
O level (GCSE grades A-C)	355 (51.2)
<O level (GCSE grades D-E)	147 (21.2)
Mean (SD) height (cm)	164.4 (6.6)
Mean (SD) body mass index (kg/m^2) before pregnancy†	23.2 (3.9)
Mean (SD) age (years)	25.8 (4.9)
Babies (boys; girls) (mean (SD))	
Birth weight (g)	3425 (480); 3281 (433)
Trimmed placental weight (g)‡	545 (141); 524 (120)
Placental weight:birth weight (%)	15.9 (3.5); 16.0 (3.1)
Gestational age (days)	280.4 (9.9); 281.4 (9.1)

*26 mothers had no current or previous occupation.
†28 mothers could not recall their weight before pregnancy so body mass index could not calculated.
‡Trimmed placental weight unavailable for 53 women.

Table 2 Daily intakes of mothers as assessed in early pregnancy (7 day food diary) and later pregnancy (food frequency questionnaire)

Intake	Median	Lower quartile	Upper quartile
Early pregnancy (n=693)			
Energy (kcal)	2044	1755	2305
Carbohydrate (g)	256.0	218.0	292.5
Fat (g)	84.7	70.6	99.2
Protein (g)	72.9	62.1	85.1
% energy from carbohydrate	47.3	44.1	50.4
% energy from fat	37.8	34.7	40.9
% energy from protein	14.5	13.1	16.0
Total vitamin C (mg)	77.0	47.0	117.0
Total vitamin E (mg)	8.5	6.1	12.0
Folate from food only (μg)	238	190	283
Total folate (μg)	261	201	358
Iron from food only (mg)	10.2	8.6	12.1
Total iron (mg)	10.8	8.7	13.4
Total zinc (mg)	8.2	6.7	9.7
Total β carotene (μg)	895	476	1418
Total selenium (mg)	50.7	40.6	64.4
Late pregnancy* (n=624)			
Energy (kcal)	2197	1824	2660
Carbohydrate (g)	290.1	242.5	350.5
Protein (g)	86.7	70.5	104.5
Fat (g)	81.7	64.1	103.1
% energy from carbohydrate	50.1	46.1	53.7
% energy from fat	33.7	30.0	38.0
% energy from protein	15.7	14.0	17.3
Total vitamin C (mg)	110.8	74.3	159.8
Total vitamin E (mg)	5.8	4.4	7.6
Folate from food only (μg)	338.0	278.5	420.9
Total folate (μg)	668.8	377.5	830.2
Iron from food only (mg)	12.4	10.1	15.1
Total iron (mg)	15.7	11.3	81.3
Total zinc (mg)	11.1	8.8	14.0
Total β carotene (μg)	1617	968	2527

*624 respondents completed food frequency questionnaire. Selenium intakes not estimated from food frequency questionnaire. Complete data on use of supplements unavailable for four women.

(P < 0.001) and maternal height (P < 0.001). Smoking predicted a 104 g (95% confidence interval 47 g to 161 g) decrease in birth weight, and each 10 cm of additional height predicted a 172 g (129 g to 215 g) increase in birth weight. In univariate analyses placental weight was associated with maternal height (P = 0.033), weight before pregnancy (P = 0.002) and weight at booking (P = 0.001) but with no other maternal characteristics. In multiple regression maternal height was the only independent predictor of placental weight (P < 0.001), with each 10 cm of additional height predicting a 5% (2% to 8%) increase in placental weight.

Nutrient intakes in early pregnancy and birth weights—Birth weight was positively associated with intakes of vitamin C, vitamin E, and total folate but with no other nutrient (table 3). After adjustment for maternal smoking and height, birth weight remained associated only with vitamin C (P = 0.031). There was no interaction between smoking and vitamin C intake. These findings were unaltered by simultaneous adjustment for energy intake.

Nutrient intakes in early pregnancy and placental weights—Placental weight was positively associated with vitamin C, vitamin E, and total folate (table 4) and remained so after adjustment for maternal height. Simultaneous adjustment for energy intake did not alter these relations. As intakes of vitamin C, vitamin E, and folate were correlated, the independent effect of each nutrient was investigated. After adjustment for vitamin C intake no other nutrient independently predicted placental weight.

Nutrient intakes later in pregnancy, birth weight, and placental weight—The 624 respondents to the food frequency questionnaire were similar to the whole cohort in their nutritional intakes early in pregnancy, placental and infant weights, and associations between early pregnancy nutrition and outcome. No nutrient in late pregnancy was significantly associated with any outcome, and this remained true after adjustment for other maternal factors.

Discussion

In this large and detailed study we found no clinically important effects of maternal nutrition on the placental or birth weight of infants born at term. Dietary intake and smoking status were measured as accurately as possible, and account was taken of maternal charac-

Table 3 Birth weights, individually adjusted for sex and gestational age, by nutrient intake in early pregnancy (n=693)

	Results before adjustment for maternal characteristics		Results after adjustment for maternal height and smoking		
Daily intake approximate thirds	Mean birth weight (g)*	P value for nutrient effect on birth weight*	Adjusted mean expected birth weight (g)†	Expected change in birth weight (g) for unit change in nutrient (95% CI)†	P value for nutrient effect on birth weight†
Energy (kcal):		0.51		−0.01	0.72
<1855	3315		3342	(−0.08 to 0.06)	
1855-2204	3384		3373		
≥2205	3360		3344		
Carbohydrate (g):		0.33		0.03	0.90
<233	3334		3355	(−0.47 to 0.53)	
233-276	3344		3337		
≥277	3380		3366		
Fat (g):		0.54		−0.08	0.91
<75	3323		3340	(−1.35 to 1.20)	
75-93	3385		3386		
≥94	3352		3334		
Protein (g):		0.97		−1.24	0.14
<66	3372		3397	(−2.90 to 0.42)	
66-79	3323		3318		
≥80	3361		3341		
Total vitamin C (mg)‡:		0.002		50.8	0.031
<55	3310		3322	(4.6 to 97.0)	
55-97	3336		3341		
≥98	3410		3393		
Total vitamin E (mg)‡:		0.049		36.2	0.21
<7	3297		3315	(−20.7 to 93.0)	
7-10.5	3386		3384		
≥10.5	3378		3362		
Total folate (μg)‡§:		0.029		47.0	0.11
<222	3309		3328	(−9.1 to 103.2)	
222-299	3334		3320		
≥300	3415		3410		

*Mean values derived after individual adjustment for sex and gestational age. P values based on univariate regression of birth weights, individually adjusted for sex and gestational age, on nutrient intake (entered as continuous variables).
†Mean values derived after individual adjustment for sex, gestational age, height, and smoking. Regression coefficients and P values based on multiple linear regression of birth weight, individually adjusted for sex and gestational age, on maternal height, smoking, and nutrient intake.
‡Nutrients ln transformed for regression analysis.
§One outlier excluded.

Table 4 Placental weights, individually adjusted for sex and gestational age, by nutrient intakes in early pregnancy (n=640)

	Results before adjustment for maternal characteristics		Results after adjustment for maternal height		
Daily intake approximate thirds	Geometric mean placental weight (g)*	P value for nutrient effect on placental weight*	Adjusted geometric mean expected placental weight (g)†	Expected % change in placental weight for unit change in nutrient (95% CI)†	P value for nutrient effect on placental weight†
Energy (kcal):		0.21		0.002	0.37
<1855	511		513	(−0.002 to 0.006)	
1855-2204	518		518		
≥2205	530		527		
Carbohydrate (g):		0.16		0.02	0.26
<233	507		509	(−0.01 to 0.05)	
233-276	524		523		
≥277	527		526		
Fat (g):		0.37		0.02	0.54
<75	518		520	(−0.06 to 0.11)	
75-93	513		514		
≥94	526		524		
Protein (g):		0.50		0.01	0.87
<66	517		520	(−0.09 to 0.11)	
66-79	516		516		
≥80	525		522		
Total vitamin C (mg)‡:		0.016		3.2	0.027
<55	510		510	(0.4 to 6.1)	
55-97	510		511		
≥98	538		537		
Total vitamin E (mg)‡:		0.022		3.8	0.038
<7	502		504	(0.2 to 7.4)	
7-10.4	528		527		
≥10.5	529		528		
Total folate (μg)‡§:		0.025		4.0	0.036
<222	506		508	(0.3 to 7.7)	
222-299	515		513		
≥300	537		537		

*Mean values derived after individual adjustment for sex and gestational age. P values based on univariate regression of ln placental weights (individually adjusted for sex and gestational age) on nutrient intake.
†Mean values derived after individual adjustment for sex, gestational age, and maternal height. Regression coefficients and P values based on multiple linear regression of ln placental weights, individually adjusted for sex and gestational age, on maternal height and nutrient intake.
‡Nutrients ln transformed for regression analysis.
§One outlier excluded.

teristics that might confound associations between dietary intake and infant size. The inclusion of only nulliparous women also removed the possible confounding effect of parity.

Vitamin C, but no other nutrient, was positively related to birth weight, with about a 100 g difference between the lowest and highest thirds of intake. The significance of this relation, however, was considerably reduced after adjustment for smoking and maternal height. Vitamin C showed some association with placental weight, but again this relation was weaker after adjustment for maternal height. As in previous research, there was no association between any nutrient in later pregnancy and placental or birth weights.[3 4 9]

Comparison with Barker's data

Our findings differ from those of Barker and colleagues, who studied a cohort with similar social class and age distributions. In early pregnancy, Godfrey et al found significant negative relations between energy intake and placental and birth weights.[4] These relations were largely due to strong associations between the outcomes and carbohydrate intakes. It is notable that the median values and the variability of all nutrient intakes, particularly carbohydrate and energy, were much higher than in our study. For example, the median intakes of energy and carbohydrate were 9.8 MJ (2346 kcals) and 303 g, respectively[4] compared with 8.5 MJ (2044 kcals) and 256 g in our cohort. The interquartile ranges for carbohydrate and energy consumption were about two thirds greater (125 g *v* 74.5 g and 3.8 MJ *v* 2.3 MJ, respectively). This increased variability resulted mainly from an extended right hand tail in the distribution of intakes.

It would be surprising if these differences reflected a greater intrinsic variability in the diets of women from Southampton compared with those in Portsmouth. Not only are the two coastal cities extremely close geographically but they are of similar size and sociodemographic structure. Indeed, there is considerable population exchange between the two conurbations. We are also confident that our lack of positive findings was not the result of greater error in measurement. There is considerable evidence that our main method of dietary assessment—a 7 day food diary—suffers less measurement error than food frequency methods.[23–25] It is notable that both the median values and variability in nutrient intakes in our study with food diaries were similar to those obtained by Barker's group when their subjects completed a 4 day food diary; their data, however, were not analysed in relation to outcome measures.[27] Further, the variability in our data was almost the same as that for women in the national dietary and nutritional survey of British adults (7 day weighed diary).[28]

In later pregnancy we, like Godfrey et al, used a food frequency questionnaire. In neither study was any individual nutrient found to predict pregnancy outcome. Godfrey et al, however, found that low intake of meat protein later in pregnancy, in conjunction with high carbohydrate early in pregnancy, was associated with reduced birth and placental weights.[4] This observation contrasts with their earlier report that diets with a high proportion of energy from animal protein were associated with reduced birth weight.[3] In our study, combinations of nutrients were not investigated,

Key messages

- Placental and infant birth weights were not associated with the intake of any macronutrient early or later in pregnancy
- After adjustment for the effects of maternal height and smoking, only vitamin C independently predicted birth weight. The expected mean difference in birth weight for infants with mothers in the upper and lower thirds of intake was about 70 g
- Vitamin C was the only nutrient that independently predicted placental weight, but again this relation was of doubtful clinical significance
- Among relatively well nourished women in industrialised countries, maternal nutrition seems to have only a marginal impact on infant and placental size. Other causes of variation in the size of clinically normal infants should now be investigated

given the lack of main effects for carbohydrate, protein, and total energy; the high correlation between carbohydrate and protein intakes (0.62 in diary and 0.72 in food frequency questionnaire); and the likelihood of "positive" findings due to multiple significance testing.

Maternal malnutrition may be an important determinant of fetal growth in developing countries. Our work suggests that among the reasonably well nourished women of industrialised countries, however, maternal diet in pregnancy has, at most, a small impact on placental and birth weights. We are currently analysing stored serum samples from our cohort to help to clarify the relation of maternal nutrition to the outcome of pregnancy.

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Contributors: FM was the principal investigator. She designed the study, obtained funding, supervised research staff, collected data from pregnant women, measured infants, coded and entered food diaries, performed statistical analyses, and prepared the paper for publication. PY was involved in design of the study and had a major input to the statistical analysis, interpretation of results, and writing of the paper. AN participated in designing the study, obtaining funding, and supervision of the project and contributed to interpretation of the results and preparation of the paper. FM is the guarantor.

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A memorable patient

Our duty lasts until the end of life

I am covering the coronary care unit. My bleep goes off. It's the accident and emergency department. "We've got a 93 year old gentleman, two hours of chest pain, looks like an anterior, but he's also sustained a right fracture neck of femur." I hurry down. My patient, a previously active, independent man is in pain. Though I cannot thrombolyse him, I take him to the coronary care unit for analgesia, supportive treatment, and observation.

Over the next 12 hours my crash bleep goes off three times. Three times I successfully defibrillate my patient. He is increasingly distressed with pulmonary oedema, chest pain, and hip pain despite our best efforts. The outlook does not look great. There are no relatives with whom to discuss prognosis and management. Left with no choice I tentatively decide to broach the subject with my patient. As I begin, uncomfortably, he turns and looks me in the eyes. "Listen, son, I have had a good long life. My wife died last year and I am no good in this condition. Please let me go so I can join her in heaven," he requests. One hour later he dies.

The above incident, some years ago, made me reflect on my discomfiture in discussing death with a patient. Advances in medicine and technology in the Western world have led to a perception of death in hospital as a failure on our part. Whereas historically (and in many parts of the developing world today) death for doctors, patients, and families alike was very visible and accepted, it now seems to have retreated into the closet. Though we are better at talking to relatives, I suspect that many of us find ourselves uneasy and ill equipped to discuss end of life issues directly with patients outside the sphere of oncology or palliative care.

I have since found that frank discussion with patients is usually appreciated, resolves management dilemmas, and that our preconceptions as to what patients might wish for, even after discussions with relatives, are often wrong. Our duty and obligation to care and communicate with our patients lies not only at the beginning and middle of their lives but also to their very end.

Khalid Khan, *clinical research fellow, Leice*