Association of maternal fat and alcohol intake with maternal and umbilical hormone levels and birth weight

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High levels of estrogen during pregnancy have been hypothesized to increase the risk of breast cancer in offspring. Some studies have reported a positive association of estrogen level during pregnancy with fetal size, which has been linked to the subsequent risk of breast cancer in offspring. We examined whether maternal diet, including fat and alcohol intake, was associated with hormone levels during pregnancy, as well as with birth weight. The concentrations of estradiol, estriol, and testosterone were measured in the maternal serum and umbilical cord blood of 189 women during pregnancy and at delivery. Intakes of fat, alcohol, and other nutrients were assessed by 5-day diet records at approximately the 29th week of pregnancy before blood sampling. Intake of polyunsaturated fatty acids was moderately but significantly positively correlated with the umbilical cord estriol level ($r = 0.17$, $P = 0.03$) after controlling for covariates. The positive association between intake of polyunsaturated fatty acids and birth weight was of borderline significance ($r = 0.14$, $P = 0.06$). Intake of long-chain n-3 fatty acids was significantly inversely correlated with the umbilical cord estradiol and testosterone levels ($r = -0.18$, $P = 0.02$ and $r = -0.24$, $P = 0.002$, respectively). Alcohol intake was significantly positively correlated with the maternal estradiol level in the 29th week of pregnancy ($r = 0.19$, $P = 0.01$), but was unrelated to birth weight. Estrogen level during pregnancy may be regulated by dietary polyunsaturated fatty acids and mediate their effects on fetal growth. (*Cancer Sci* 2007; 98: 869–873)

Intrauterine and perinatal exposure to high levels of estrogen is hypothesized to increase the risk of breast cancer in offspring.[1] Several studies,[2–4] have reported positive associations of estrogen levels during pregnancy with fetal size, which has been linked to the subsequent risk of breast cancer in offspring.[5–7] Certain dietary components during pregnancy may affect estrogen levels during pregnancy. Hilakivi-Clarke *et al*. proposed that maternal intake of a high-fat diet is a source for high estrogen levels during pregnancy and increases breast cancer risk among the female offspring.[8] Their animal studies showed that a high maternal consumption of corn oil, consisting mainly of linoleic acid (n-6 polyunsaturated fatty acid), increases both circulating estradiol levels during pregnancy and the risk of developing carcinogen-induced mammary tumors among the female rat offspring.[8] This risk may also occur in humans. Dietary fat has been implicated in the etiology of breast cancer.[9] However, data are inconsistent. The majority of prospective cohort studies among postmenopausal women have failed to find a significant positive association between intake of total fat or specific types of fat and breast cancer risk,[10] but some recent studies have supported a positive association of animal fat or saturated fat with breast cancer risk.[11,12] There is speculation that a high-fat diet increases breast cancer risk if consumed during the periods in which the mammary gland is sensitive to endogenous estrogens, such as during the fetal period.[13]

In the present study, we examined the association between maternal fat intake and maternal and umbilical cord hormone levels during pregnancy and at birth. We also assessed the direct association between fat intake and birth weight, which has been associated with the risk of breast cancer in offspring. In addition to estradiol and estriol, testosterone and insulin-like growth factor (IGF)-1 were measured because they are also of interest in the context of the prenatal origin of breast cancer. We included another dietary component, alcohol, which has been linked to both circulating estrogen levels and breast cancer risk in adult women.[13–15] The associations of maternal dietary soy and serum and urinary isoflavone metabolites with pregnancy hormones have been described elsewhere.[16]

Materials and Methods

The present investigation was undertaken using data from a longitudinal study on the relationships between maternal lifestyle, pregnancy hormones, and gestational and neonatal factors.[17] We recruited women who visited a maternal clinic in Gifu, Japan, and were identified as pregnant between May 2000 and October 2001. A total of 600 pregnant women agreed to participate in the study. We did not obtain the precise number of women who were recruited on their first visit. However, we obtained information showing that from among women who gave birth in the clinic during the study period, 52.2% participated in the study. The actual participation rate should be higher because women who may have visited the clinic for the first time during middle or late pregnancy were included in the denominator to calculate the response rate. Informed consent was obtained from each woman. The study was approved by the institutional review board.

Of 600 women, eight had a spontaneous or induced abortion, 34 moved or changed the clinics, and 23 chose to end their participation. Each woman responded to a health questionnaire designed to obtain demographic characteristics, smoking status, and past medical and reproductive histories at the time of enrollment or first blood drawing. For the collection of dietary information before the pregnancy, we used a validated 169-item semiquantitative food-frequency questionnaire.[18]

The clinic provided a health check-up for all pregnant women at approximately the 10th and 29th weeks of gestation. Clinical and auxological data for the mother and fetus or newborns were recorded at these visits and at delivery. Blood samples for hormone measurements were obtained from each woman at each visit. Diet was assessed by diet records for 5 days prior to the visit at the 29th week of pregnancy. All the supplements used during the 5 days were also recorded. Intakes of fat and other nutrients were estimated based on the diet records using Japanese Standard

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Table 1. Diet and serum hormone levels in maternal and umbilical cord blood samples of 189 pregnant women

Variables	Mean (SD)	Range
Diet at 29th week (per day)		
Total energy (kcal)	1 863 (270)	1059–2560
Total protein (g)	66.1 (11.4)	40.6–98.2
Carbohydrate (g)	256 (38.8)	153–363
Total fat (g)	61.3 (13.7)	27.3–105.2
Saturated fatty acids (g)	18.9 (4.5)	9.4–33.3
Monounsaturated fatty acids (g)	22.1 (4.5)	9.1–41.0
Polyunsaturated fatty acids (g)	12.8 (3.4)	5.3–24.1
n-3 polyunsaturated fatty acids (g)	2.1 (0.7)	0.6–6.4
n-6 polyunsaturated fatty acids (g)	10.7 (2.9)	3.9–20.8
Long-chain n-3 polyunsaturated fatty acids (mg)	527 (387)	30.5–2450
Alcohol (mL)	1.3 (2.6)	0–33.4
Hormone levels		
10th week		
Estradiol (pg/mL)	2 665 (1586)	632–9090
Estriol (ng/mL)	5.7 (1.9)	5.0–18.5
Testosterone (ng/dL)	55.7 (26.6)	8–207
29th week		
Estradiol (pg/mL)	21 632 (7020)	7390–38 000
Estriol (ng/mL)	89.7 (35.3)	31.4–280
Testosterone (ng/dL)	54.3 (25.8)	18–166
Delivery		
Estradiol (pg/mL)	31 471 (9282)	3960–67 300
Estriol (ng/mL)	239.6 (113.2)	35.4–707
Testosterone (ng/dL)	90.0 (39.4)	35–237
Umbilical cord		
Estradiol (pg/mL)	5 926 (5164)	554–41 300
Estriol (ng/mL)	2 129 (565)	725–3860
Testosterone (ng/dL)	137.9 (31.2)	70–250
IGF-1 (ng/mL)	71.9 (25.5)	19–150

IGF-1, insulin-like growth factor-1.

Tables of Food Composition, 5th edition, published by the Science and Technology Agency of Japan. Fatty acid composition was evaluated using data published by Sasaki *et al*.[19] Intake of long-chain n-3 polyunsaturated fatty acid was calculated as the sum of eicosapentanoic and docosahexiaenoic acids. Umbilical cord artery blood was immediately drawn after birth. The blood samples were centrifuged and the sera were stored at –80°C until assay.

We restricted the subjects for the present study to those who had no or one parity previously and gave birth to a singleton female baby ($n = 250$). Out of them, we excluded 14 women who had taken hormonal medications during the index pregnancy or those who had been diagnosed with hypertension, diabetes mellitus or thyroid disease before or during the index pregnancy. In addition, women who had not responded to the health questionnaire or diet records ($n = 17$), or those who provided no umbilical blood samples were excluded ($n = 30$). Thus, 189 pregnant women and their newborn girls were included in the present study.

Serum estradiol and testosterone were measured by radioimmunoassay kits purchased from Roche Diagnostics, (Tokyo, Japan). Serum estriol was measured by radioimmunoassay using kits purchased from Abbott (Tokyo, Japan). Serum IGF-1 was measured by immunoradiometric assay using kits purchased from TFB (Tokyo, Japan). The interassay coefficients of variation (CV) were ≤2.6% for estradiol, ≤10.9% for estriol, ≤9.1% for testosterone, and ≤5.6% for IGF-1.

Because blood volume was insufficient, serum estriol was not measured in three umbilical cord samples. Serum testosterone was not measured in five umbilical cord samples. Serum hormone data were missing for 11 women at delivery because no blood samples had been obtained. Serum estriol was undetectable (<6 ng/mL) for most of the women ($n = 152$, 80.4%) in the 10th week of gestation; the value of assay sensitivity minus one unit (=5 ng/mL) was assigned for them.

For statistical analyses, serum hormone concentrations and dietary intake were log-transformed. Dietary intake was adjusted for total energy according to the residual methods proposed by Willett.[20] Spearman rank correlation was used to assess the associations of dietary factors with serum hormone levels and birth weight. Several non-dietary factors covering the spectrum of the likely measured confounders were used for adjustment. These variables included age, parity, smoking status, years of education, pre-pregnancy height and weight, weight gain, and weeks of gestation at the time of measurement. Adjustment for these potential confounders was accomplished by regressing dietary variable and log-transformed hormone or birth weight separately on the confounders. The correlations (Spearman) between the residuals were then calculated. We also calculated the mean hormone levels and birth weight according to quartiles of each dietary factor using the analysis of covariance method. All statistical analyses were carried out using SAS (SAS Institute, Cary, NC, USA).

Results

Table 1 presents the dietary intake and serum hormone levels of the 189 study subjects. Most of the women abstained from alcohol. Only nine women (4.8%) consumed more than 5 mL of alcohol.

Total fat intake was not significantly correlated with any hormone during any pregnancy week after controlling for covariates (Table 2). Intake of polyunsaturated fatty acids was significantly positively correlated with umbilical cord estriol level. Intake of n-6 but not n-3 and long-chain n-3 polyunsaturated fatty acids

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Table 2. Partial correlation coefficients of fat and alcohol intake with hormone levels in maternal and umbilical cord blood and with birth weight†

	Maternal blood									Cord blood				Birth weight
	10th week			29th week			Delivery			E2	E3	T	IGF-1	
	E2	E3	T	E2	E3	T	E2	E3	T					
Total fat	0.05	0.003	–0.02	–0.003	0.09	–0.03	0.11	0.12	0.02	0.10	0.14	0.12	0.05	0.04
	(0.53)	(0.97)	(0.84)	(0.96)	(0.25)	(0.66)	(0.16)	(0.14)	(0.80)	(0.19)	(0.08)	(0.13)	(0.55)	(0.57)
SFA	–0.03	–0.02	–0.02	–0.02	0.04	–0.04	0.03	0.05	–0.001	0.10	0.05	0.05	–0.09	–0.10
	(0.71)	(0.82)	(0.81)	(0.74)	(0.64)	(0.56)	(0.73)	(0.56)	(0.99)	(0.18)	(0.56)	(0.54)	(0.26)	(0.20)
MUFA	0.09	0.01	0.04	–0.01	0.05	–0.01	0.12	0.12	0.06	0.05	0.14	0.16	0.06	0.10
	(0.23)	(0.94)	(0.63)	(0.88)	(0.47)	(0.90)	(0.12)	(0.12)	(0.44)	(0.48)	(0.06)	(0.045)	(0.42)	(0.19)
PUFA	0.03	–0.02	–0.12	–0.01	0.10	–0.05	0.13	0.08	–0.05	0.05	0.17	0.13	0.16	0.14
	(0.68)	(0.84)	(0.13)	(0.94)	(0.19)	(0.51)	(0.11)	(0.34)	(0.51)	(0.48)	(0.03)	(0.10)	(0.049)	(0.06)
n-3 PUFA	–0.04	0.08	–0.04	–0.01	–0.01	0.02	0.04	0.01	–0.001	–0.12	0.04	–0.10	0.18	0.14
	(0.62)	(0.29)	(0.60)	(0.91)	(0.94)	(0.82)	(0.64)	(0.91)	(0.99)	(0.13)	(0.61)	(0.19)	(0.02)	(0.07)
n-6 PUFA	0.03	–0.03	–0.12	–0.002	0.13	–0.06	0.12	0.09	–0.06	0.10	0.19	0.19	0.12	0.11
	(0.70)	(0.69)	(0.10)	(0.98)	(0.08)	(0.41)	(0.13)	(0.24)	(0.47)	(0.20)	(0.02)	(0.01)	(0.12)	(0.16)
Long n-3 PUFA	–0.11	0.12	0.01	–0.01	–0.14	0.07	–0.05	–0.08	0.04	–0.18	–0.07	–0.24	0.14	0.05
	(0.53)	(0.13)	(0.87)	(0.85)	(0.07)	(0.37)	(0.97)	(0.30)	(0.58)	(0.02)	(0.37)	(0.002)	(0.08)	(0.55)
Alcohol	–0.05	0.04	–0.06	0.19	0.07	0.07	0.15	–0.07	0.01	–0.04	0.04	–0.11	–0.09	0.05
	(0.52)	(0.65)	(0.42)	(0.01)	(0.39)	(0.38)	(0.06)	(0.39)	(0.86)	(0.62)	(0.65)	(0.17)	(0.26)	(0.55)

†Adjusted for age, parity, smoking status, years of education, pre-pregnancy height and weight, weight gain and weeks of gestation at measurements. Dietary intake is adjusted for total energy. *P*-values in parenthesis. IGF-1, insulin-like growth factor-1; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

was significantly positively correlated with umbilical cord estriol and testosterone levels. Intake of long-chain n-3 fatty acids was significantly inversely correlated with umbilical cord estradiol and testosterone levels. Intake of monounsaturated fatty acids was non-significantly positively correlated with umbilical cord estriol levels and was significantly positively correlated with umbilical cord testosterone level.

Alcohol intake was significantly positively correlated with maternal estradiol levels in the 29th week of pregnancy and was non-significantly positively correlated with maternal estradiol levels at delivery. Neither coffee nor tea intake were confounders of the observed association between alcohol and estradiol levels (data not shown). Alcohol intake was unrelated to birth weight.

The mean level of umbilical cord estriol in the lowest quartile of polyunsaturated fat intake was 1977 ng/mL, while that in the highest quartile was 11.5% higher, at 2205 ng/mL. Umbilical cord testosterone levels decreased from 149 ng/dL in the lowest quartile of long-chain n-3 fatty acid intake to 127 ng/dL in the highest quartile, a decrease of 15.7%. The mean umbilical cord estradiol levels were 6047 and 4440 pg/mL in the lowest and highest quartile of long-chain n-3 fatty acid intake, respectively, a decrease of 26.6%. The increase in the means of estradiol levels in the 29th week of pregnancy in the lowest and highest quartiles of alcohol intake was 17.0%, with means of 18 772 and 21 964 pg/mL, respectively.

Umbilical cord IGF-1 levels were significantly positively correlated with intakes of polyunsaturated fatty acids and n-3 polyunsaturated fatty acids. The positive correlation between umbilical cord IGF-1 and intake of long-chain n-3 fatty acid was of borderline significance.

Birth weight was non-significantly positively correlated with intake of polyunsaturated fatty acids. The overall mean (SD) of birth weight was 3003.3 (362.3) g. The mean birth weight in the highest quartile of polyunsaturated fatty acids was 4.7% higher than in the lowest quartile of the intake (the means were 3054 and 2917 g, respectively).

Pre-pregnancy dietary factors, including fat and alcohol intake, were estimated by using a food frequency questionnaire and were unrelated to maternal and umbilical hormone levels and birth weight.

Discussion

We found a modest but significant positive association between intake of polyunsaturated fatty acids and umbilical cord estriol level. The type of fatty acid seems to be important. Umbilical cord estriol levels were significantly positively associated with intake of n-6 polyunsaturated fatty acids, but not with n-3 or long-chain n-3 polyunsaturated fatty acids. Intake of long-chain n-3 polyunsaturated fatty acids was significantly inversely associated with umbilical cord estradiol and testosterone levels. Previous studies among non-pregnant women have suggested that the association between fat intake and blood estrogen may differ according to the type of fatty acid. Although the results of studies concerning the type of fatty acid and estrogen level have been inconsistent, long-chain n-3 polyunsaturated fatty acid does not appear to raise estrogen levels.[21,22]

Intake of polyunsaturated fat was significantly positively associated with IGF-1 levels. Polyunsaturated fat intake may also affect the IGF-1 system. However, a similar magnitude of associations was observed between IGF-1 and n-3 or long-chain n-3 polyunsaturated fatty acids and between IGF-1 and n-6 polyunsaturated fatty acids. N-3 and n-6 polyunsaturated fatty acids compete for the same elongase and desaturase metabolizing enzyme system in the biosynthesis of eicosanoids, which may lead to alternation of estrogen metabolism.[23,24] However, n-3 and n-6 polyunsaturated fatty acids may have similar effects on the IGF-1 system.

Previously, we observed a significant positive association between umbilical cord estriol and birth weight ($r = 0.41$).[17] Although the direct association between intake of polyunsaturated fatty acids and birth weight was of borderline significance, similar patterns of associations of type of dietary fat with umbilical cord estriol and with birth weight may indicate that fat intake affects birth weight, a surrogate marker of future breast cancer risk, by modifying the pregnancy estriol. Umbilical cord IGF-1 is known as one of the major determinants of birth weight,[25]

and we observed a significantly positively association between umbilical cord IGF-1 and birth weight in the subjects of the present study ($r = 0.57$).[17] However, in spite of a positive association between intake of long-chain n-3 polyunsaturated fatty and umbilical cord IGF-1, intake of long-chain n-3 polyunsaturated fatty acids was unrelated to birth weight, which may decrease the possibility of an involvement of IGF-1 in the relationship between the type of fat and birth weight. Nonetheless, any observed association between fat intake and hormones, IGF-1, or birth weight was modest. An apparent difference according to the type of fat may not be significant.

So far, to our knowledge, two studies have examined the associations between maternal diet and pregnancy hormone levels.[26,27] In a study of 141 pregnant Greek women, there were no significant associations between intake of any nutrients and foods, as estimated using a food-frequency questionnaire in the 26th week of pregnancy, and plasma levels of estradiol and estriol in the 26th and 31st weeks of pregnancy.[26] In a study of 270 US women who completed a food-frequency questionnaire during the 27th week of pregnancy, estradiol and estriol levels in the 16th and 27th weeks of pregnancy were not significantly associated with any diet-related variables.[27] Neither study included measurements of androgens in the umbilical cord blood. We used diet records to assess diet during pregnancy. The diet records may present an advantage over the food-frequency questionnaire in measurement of fat intake during pregnancy. The differences in characteristics of study population in terms of ethnicity, body size, overall diet, and hormone levels may also explain, in parts, the inconsistent results among the studies. The relationship between diet during pregnancy and birth weight was also examined in these studies. Monounsaturated fat intake was positively significantly associated with the birth weight of the offspring of the Greek women.[28] Intake of animal fat and vegetable fat was not associated with the birth weight of the offspring of the US women.[29]

Three studies have reported a relationship between alcohol and pregnancy hormones.[30,31] In the Greek study,[30] alcohol intake was significantly positively associated with the total estrogen level in the 26th week of pregnancy and was unrelated to birth weight. Significantly increased estradiol levels in the 16th and 27th weeks of pregnancy were observed in the US women who drank alcoholic beverages during pregnancy.[31] These findings were similar to the results of our study. However, in another study, alcohol intake was unrelated to the maternal estradiol level and was significantly inversely associated with maternal testosterone levels.[32] Alcohol consumption was generally low in our study subjects, which may have obscured the associations between alcohol and pregnancy hormones, as well as birth weight.

The strengths of the present study include its prospective nature, repeated measurements of maternal pregnancy hormones, and the inclusion of hormone measurements of umbilical cord blood. However, diet was assessed only once, in the 27th week of pregnancy. The effect of diet on pregnancy hormones or birth size may differ between early and late pregnancy. As with all other dietary assessment methods, the estimation of nutrient intake is subject to measurement error. However, it is unlikely that the measurement errors are dependent on hormone levels or birth weight. Therefore, the observed associations between dietary fats and pregnancy hormones, as well as birth weight are likely to be underestimated. Nonetheless, because of multiple testing, some of the significant findings may be due to chance.

In conclusion, we have found evidence that maternal intake of polyunsaturated fatty acids may be associated with pregnancy hormones and birth weight. Pregnancy estriol may be regulated by dietary polyunsaturated fatty acids and mediate their effect on fetal growth. The present results raise the possibility that breast cancer risk could be reduced by dietary manipulation of pregnancy estrogen. The observed positive association of alcohol intake with maternal estradiol levels and the inverse association of intake of long-chain n-3 polyunsaturated fat with umbilical estradiol and testosterone levels are of interest, although these dietary factors were unrelated to birth weight.

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