Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine Study[1–3]

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See corresponding editorial on page 857.

ABSTRACT

Background: Total homocysteine (tHcy) measured in serum or plasma is a marker of folate status and a risk factor for cardiovascular disease.

Objective: Our objective was to investigate associations between tHcy and complications and adverse outcomes of pregnancy.

Design: Plasma tHcy values measured in 1992–1993 in 5883 women aged 40–42 y were compared with outcomes and complications of 14 492 pregnancies in the same women that were reported to the Medical Birth Registry of Norway from 1967 to 1996.

Results: When we compared the upper with the lower quartile of plasma tHcy, the adjusted risk for preeclampsia was 32% higher [odds ratio (OR): 1.32; 95% CI: 0.98, 1.77; *P* for trend = 0.02], that for prematurity was 38% higher (OR: 1.38; 95% CI: 1.09, 1.75; *P* for trend = 0.005), and that for very low birth weight was 101% higher (OR: 2.01; 95% CI: 1.23, 3.27; *P* for trend = 0.003). These associations were stronger during the years closest to the tHcy determination (1980–1996), when there was also a significant relation between tHcy concentration and stillbirth (OR: 2.03; 95% CI: 0.98, 4.21; *P* for trend = 0.02). Neural tube defects and clubfoot had significant associations with plasma tHcy. Placental abruption had no relation with tHcy quartile, but the adjusted OR when tHcy concentrations >15 μmol/L were compared with lower values was 3.13 (95% CI: 1.63, 6.03; *P* = 0.001).

Conclusion: Elevated tHcy concentration is associated with common pregnancy complications and adverse pregnancy outcomes. *Am J Clin Nutr* 2000;71:962–8.

KEY WORDS Total homocysteine, folate, pregnancy complications, congenital malformations, observational study, preeclampsia, abruptio placentae, placental abruption, neural tube defects, the Hordaland Homocysteine Study, Norway, whites, tHcy

INTRODUCTION

Randomized trials have shown that folic acid supplementation before pregnancy can reduce the risk of having a baby with a neural tube defect (1, 2). Further follow-up of the Hungarian randomized trial (3) and reports from observational studies also suggested a role of vitamin supplementation in preventing other congenital malformations (4–8). Additionally, prenatal vitamin supplementation was linked to decreased risks of preterm delivery, low birth weight (9, 10), and fetal death (10).

Elevated total homocysteine (tHcy) concentration measured in serum or plasma is a strong and independent risk factor for vascular disease (11). In addition, it is a sensitive marker of impaired folate status (12, 13). Deranged homocysteine metabolism has been found both in patients with neural tube defects and in their mothers (14, 15). Moreover, several studies have shown relations between plasma tHcy and pregnancy complications or adverse neonatal outcomes that also are associated with impaired folate status (16–20). Whether an elevated Hcy concentration is only a reflection of folate status or is harmful by itself, for example, through its vascular effects, is being debated (21).

The Hordaland Homocysteine Study (22) included measurement of plasma tHcy in >6000 women aged 40–42 y in 1992 or 1993. Linkage with data kept by the Medical Birth Registry of Norway provided an opportunity to study associations between tHcy concentration and previous complications and outcomes of 14 492 pregnancies registered for these women during the period from 1967 to 1996.

SUBJECTS AND METHODS

Baseline data for the population-based Hordaland Homocysteine Study were collected in 1992–1993 by the National Health Screening Service in Oslo in cooperation with the University of Bergen, Norway. Men and women aged 40–67 y were invited to a cardiovascular health screening. The screening included measurements of height, weight, blood pressure, heart rate, serum

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TABLE 1
Characteristics of the 5883 women in 1992–1993 and their 14 492 pregnancies during the period from 1967 to 1996 according to quartile of plasma total homocysteine (tHcy)[1]

Characteristic	All	tHcy quartile (μmol/L)			
		3.6–7.5	7.6–8.8	8.9–10.6	10.7–78
Age at first birth (y)[2]	23.3 ± 4.3[3]	23.9 ± 4.5	23.6 ± 4.4	23.1 ± 4.2	22.7 ± 3.9
Number of children	2.5 ± 0.9	2.5 ± 0.9	2.4 ± 0.9	2.5 ± 0.9	2.5 ± 0.9
Pregnancies in 1980 or later (%)[2]	33	38	34	30	29
Ever smokers (%)[2]	62	51	59	65	71
Coffee > 5 cups/d (%)[2]	39	26	35	42	51
University or college education (%)[2]	26	33	28	24	21
No use of vitamins (%)[2]	23	17	22	24	27
Cholesterol > 6.5 mmol/L (%)[2]	12	9	11	12	14
Diastolic blood pressure > 90 mm Hg (%)	9	9	8	10	10

[1] Blood pressure, smoking status, educational level, and vitamin use are based on 5881, 5877, 4960, and 4311 women, respectively, with available data on these characteristics.
[2] Significant linear trend across tHcy quartiles, $P < 0.001$.
[3] $\bar{x}$ ± SD.

total cholesterol, serum triacylglycerol, and plasma tHcy (nonfasting). Self-administered questionnaires provided information about cardiovascular disease risk factors, lifestyle, diet, and reproductive history. Details of the data collection were published previously (22). Information on educational level and vitamin intake was available in a subset of women (86%) who returned a second questionnaire after the initial visit. Plasma tHcy, which includes both the free and protein-bound fraction of Hcy, was determined by using a modification of a fully automated assay based on precolumn derivatization with monobromobimane followed by reversed-phase HPLC (23, 24).

By using the national identification number, data from all women who participated in the Hordaland Homocysteine Study were linked with data on the same women registered by the Medical Birth Registry of Norway from 1967 to 1996. Thus, women with no pregnancies registered were not included in this study. Since 1967, the Medical Birth Registry has received notification of all births of >16 wk gestation. The notification, which covers the first 8 d of life, includes birth weight, length of gestation, medical conditions, complications during pregnancy and birth, congenital malformations, and obstetric interventions. A Norwegian adaptation of the eighth revision of the International Classification of Diseases (ICD-8) was used as the basis for classification of congenital malformations (25). The definition of a congenital malformation used by the Medical Birth Registry of Norway (26) is wider than the ICD-8 group of congenital malformations (ICD-8 codes 740–759). In addition to 189 cases falling into the ICD-8 malformation group, 4 cases of omphalocele, 2 of other abdominal hernia, and 1 unspecified neoplasm were classified as malformations. Three clubfoot cases with a coexistent neural tube defect were excluded from the clubfoot group.

The number of events used for the analyses do not generally represent the number of women experiencing a pregnancy with a given outcome or complication. All placental abruptions, however, occurred in different women, and only 3 women had more than one pregnancy with a malformation. For the other outcomes the number of women experiencing a specific event was 7–22% lower than the number of events given. With use of PROC GENMOD of SAS (release 6.12 for WINDOWS, subversion T055 in which an error in the GEE part of PROC GENMOD concerning clusters of size one has been corrected; SAS Institute, Inc, Cary, NC), dependency among pregnancy outcomes in the same woman was taken into account by performing the analyses with logistic regression for clustered binary data using generalized estimating equations methodology (27). All pregnancies in the same woman defined the cluster, and we used an exchangeable working correlation structure. Covariates were grouped and represented in the model as indicator variables to avoid assumptions of linearity. Plasma tHcy was represented by quartile groups with the lowest quartile as the reference category, or by binary groups with tHcy <15 μmol/L as the reference level. Growth retardation (small for gestational age) was defined as a birth weight under the sex-specific 10th percentile for the corresponding gestational age (28). All statistical analyses were carried out separately for the years from 1980 to 1996, which were closer to the tHcy measurement and thus more likely to reveal associations between tHcy and pregnancy complications and outcomes. The odds ratios (ORs) are presented with adjustment for parity, year of birth, age of mother at birth, and smoking habit reported in 1992–1993 (coded as never smoker, former smoker, or 1–9, 10–19, or ≥20 cigarettes smoked/d). Essentially, all results were upheld in models with further adjustment for educational level and coffee-drinking habit but are not presented because they reduced the number of cases of adverse events and the precision of the point estimates.

Dose-response relations were also studied with generalized additive logistic regression as implemented in S-PLUS (version 4.0 for WINDOWS; MathSoft, Inc, Seattle). The method generates a graph of the relation between plasma tHcy and the outcome in question on a logit scale and allows adjustment for other variables. Point-wise 95% confidence curves are also given and show that the dose-response estimation is most accurate in the central part of the tHcy distribution. A two-sided significance level of 0.05 was used throughout.

RESULTS

Characteristics of the 5883 women aged 40–42y who had their plasma tHcy measured in 1992–1993 and who were registered in the Medical Birth Registry during 1967–1996 are shown in **Table 1**. Compared with women with lower tHcy concentrations, women in the upper quartile of plasma tHcy smoked

more, drank more coffee, had university or college education less often, and used vitamin supplements less often. Also, women in the upper tHcy quartile tended to have their children at an earlier age than did women with lower tHcy concentrations. From 1967 to 1996, the women had a total of 14 492 pregnancies that were reported to the Medical Birth Registry. About 80% of these pregnancies took place >10 y before the blood sample used for tHcy measurement was collected.

Associations between plasma tHcy in 1992–1993 and previous pregnancy complications and adverse pregnancy outcomes are shown in **Table 2**. Preeclampsia was reported in 451 of the pregnancies. Among these, 60 pregnancies were of <37 wk duration. We observed a weak but highly significant positive association between preeclampsia and tHcy concentration. This association was stronger in the subgroup that delivered prematurely (<37 wk), and was further strengthened when only births from 1980–1996 were considered (OR comparing the upper with the lower tHcy quartile: 4.74; 95% CI: 1.34, 16.83; *P* for trend = 0.006). Preeclampsia was negatively associated with smoking and strongly positively associated with both systolic and diastolic blood pressure in 1992–1993. Adjustment for blood pressure weakened the tHcy-preeclampsia relation moderately, but more so with all preeclampsia cases as the outcome than with the subgroup of preeclampsia pregnancies of <37 wk. In this subgroup, the OR when comparing the upper with the lower quartile of plasma tHcy in the latter time period was 4.42 (*P* for trend = 0.01).

Placental abruption was reported in 0.5% of the pregnancies and showed no association over tHcy quartiles. A strongly elevated risk of placental abruption, however, was seen in women with high tHcy concentrations. The adjusted OR was 3.13 (95% CI: 1.63, 6.03) when comparing tHcy concentrations >15 μmol/L with lower concentrations (*P* = 0.001). The tHcy-abruption association was of similar strength in the time periods before and after 1980.

There was a significant association of plasma tHcy with premature delivery both of <37 wk and <32 wk gestation. The association was slightly stronger in the latter group, and was stronger for the time period closest to the tHcy determination (1980–1996). In the latter period, the OR when comparing the upper with the lower tHcy quartile for premature delivery (<32 wk gestation) was 1.93 (95% CI: 0.96, 3.93; *P* for trend = 0.03).

We found a strong association between low birth weight (<2500 g) and tHcy concentrations. The relation was strengthened with very low birth weight (<1500 g) as the outcome, and was particularly strong for the group weighing 500–1000 g. The relation of plasma tHcy to low or very low birth weight was strengthened when the analyses were confined to those births closest to the tHcy measurement. In pregnancies occurring in 1980 or later, the OR for very low birth weight when comparing the upper with the lower tHcy quartile was 2.07 (95% CI: 1.02, 4.22; *P* for trend = 0.02).

We also found a strong association between smoking and low birth weight but this association was strongest for infants weighing between 1500 and 2500 g; smoking had no association with very low birth weight. Plasma tHcy was significantly related to growth retardation, but the strength of the association was weaker than the associations between tHcy and low birth weight. In contrast, smoking showed a much stronger association with growth retardation than with low birth weight.

The prevalence of stillbirth was 1.2% (>16 wk gestation) and the mortality during the first week of life was 0.4%. There was no association of plasma tHcy with neonatal mortality, but there was a weak and nonsignificant overall association between plasma tHcy and stillbirth. This association was significant for the period 1980–1996 when the adjusted OR comparing the upper with the lower tHcy quartile was 2.03. The association of plasma tHcy with stillbirth was strongest for pregnancies with a reported gestational length between 24 and 32 wk. The tHcy-stillbirth association was strong for birth weights <1500 g, for the time period 1980–1996 in particular; there was no such association for birth weights >1500 g. In contrast, we found a strong relation between smoking and stillbirths with reported weights ≥2500 g. This latter relation was also stronger in the time period closer to the collection of tHcy and lifestyle data.

Among the 14 492 pregnancies analyzed, one or more malformations were reported for 196 pregnancies (1.4%). We observed a weak, nonsignificant association between all malformations combined and plasma tHcy. Several malformation types were present in sufficient numbers to provide meaningful analyses and are shown in **Table 3**. The strongest association was found for 16 cases of neural tube defects with an OR of 3.57 when comparing the highest tHcy quartile with the lowest. Congenital clubfoot also showed a highly significant association with tHcy, which was of similar strength for talipes equinovarus and valgus deformities. Orofacial clefts were not related to tHcy concentration, but showed a significant positive association with cigarette smoking (OR when comparing smokers of ≥10 cigarettes/d with never smokers: 3.27; 95% CI: 1.2, 9.3). The associations of tHcy with malformations were not strengthened when analyses were restricted to the period 1980–1996.

Except for placental abruption, all tHcy associations were confined to the central part of the tHcy distribution (5–15 μmol/L). For placental abruption, a different pattern was observed with a threshold at ≈15 μmol/L (**Figure 1**). Neither coffee-drinking habit nor educational level reported in 1992–1993 was an important predictor of risk in this study and additional adjustment for these factors did not change the results significantly.

DISCUSSION

By linking a population-based cardiovascular survey of 40–42-y-old women to the Medical Birth Registry of Norway, we showed a strong association between plasma tHcy and previous pregnancy complications and adverse pregnancy outcomes. Eighty percent of these pregnancies took place >10 y before the tHcy measurement. It is unlikely that the observed associations are artifacts of the design. On the contrary, we would expect that any true association between plasma tHcy and pregnancy outcome would be weakened by the long time interval between the pregnancy and the blood sampling used for the tHcy measurement. The finding of stronger associations with plasma tHcy in those pregnancies closest to the time of the cardiovascular survey supports this assumption. Our findings are consistent with a series of investigations showing similar relations between plasma tHcy and low birth weight, premature delivery, recurrent abortions, preeclampsia, placental abruption, and neural tube defects (14, 16–20). However, there was no relation of plasma tHcy to orofacial clefts, which could be anticipated in view of the suggested etiologic role of folate deficiency in these congenital anomalies (21). Unexpectedly, we found a strong association with clubfoot in the malformation group, a finding that has not been reported previously.

TABLE 2
Relative risks of pregnancy complications and adverse outcomes by quartile of plasma total homocysteine (tHcy)[1]

	Number of outcomes (%)		Odds ratio (95% CI) for adverse outcome	
Outcomes by tHcy quartile (μmol/L)	1967–1996	1980–1996[2]	1967–1996	1980–1996[2]
Preeclampsia	451 (3.1)	168 (3.6)		
3.6–7.5	111 (3.1)	43 (3.2)	1	1
7.6–8.8	89 (2.5)	35 (2.9)	0.82 (0.60, 1.13))	0.92 (0.56, 1.52)
8.9–10.6	121 (3.3)	44 (4.0)	1.18 (0.88, 1.58)	1.36 (0.85, 2.16)
10.7–78	130 (3.5)	46 (4.3)	1.32 (0.98, 1.77) [0.02][3]	1.50 (0.92, 2.44) [0.05]
Preeclampsia <37 wk	60 (0.4)	32 (0.7)		
3.6–7.5	15 (0.4)	4 (0.3)	1	1
7.6–8.8	7 (0.2)	5 (0.4)	0.57 (0.21, 1.52)	1.50 (0.40, 5.68)
8.9–10.6	15 (0.4)	10 (0.9)	1.16 (0.49, 2.74)	3.34 (0.98, 11.42)
10.7–78	23 (0.6)	13 (1.2)	1.87 (0.78, 4.46) [0.10]	4.74 (1.34, 16.83) [0.006]
Placental abruption	73 (0.5)	29 (0.6)		
3.8–14.9	63 (0.5)	26 (0.6)	1	1
15.0–78	10 (1.5)	3 (1.8)	3.13 (1.63, 6.03) [0.001]	3.12 (0.91, 10.75) [0.07]
Premature delivery <32 wk	188 (1.4)	71 (1.6)		
3.6–7.5	39 (1.1)	15 (1.2)	1	1
7.6–8.8	39 (1.1)	12 (1.1)	1.03 (0.64, 1.67)	0.91 (0.42, 1.99)
8.9–10.6	56 (1.6)	22 (2.1)	1.44 (0.92, 2.26)	1.68 (0.81, 3.52)
10.7–78	54 (1.5)	22 (2.2)	1.48 (0.93, 2.36) [0.04]	1.94 (0.96, 3.93) [0.03]
Premature delivery <37 wk	770 (5.6)	279 (6.3)		
3.6–7.5	168 (4.9)	69 (5.4)	1	1
7.6– 8.8	172 (5.0)	61 (5.4)	1.04 (0.81, 1.33)	1.03 (0.70, 1.52)
8.9–10.6	196 (5.6)	69 (6.6)	1.16 (0.91, 1.48)	1.19 (0.80, 1.76)
10.7–78	234 (6.7)	80 (8.1)	1.38 (1.09, 1.75) [0.005]	1.45 (0.99, 2.14) [0.05]
Low birth weight (<2500 g)	708 (4.9)	250 (5.3)		
3.6–7.5	141 (4.0)	55 (4.1)	1	1
7.6–8.8	166 (4.7)	53 (4.5)	1.19 (0.92, 1.55)	1.11 (0.73, 1.69)
8.9–10.6	177 (4.9)	57 (5.2)	1.20 (0.93, 1.56)	1.11 (0.72, 1.71)
10.7–78	224 (6.1)	85 (8.0)	1.48 (1.15, 1.91) [0.003]	1.69 (1.12, 2.55) [0.02]
Very low birth weight (<1500 g)	172 (1.2)	68 (1.5)		
3.6–7.5	28 (0.8)	13 (1.0)	1	1
7.6–8.8	40 (1.1)	11 (0.9)	1.47 (0.89, 2.45)	0.92 (0.40, 2.15)
8.9–10.6	51 (1.4)	20 (1.8)	1.84 (1.14, 2.96)	1.62 (0.78, 3.36)
10.7–78	53 (1.4)	24 (2.3)	2.01 (1.23, 3.27) [0.003]	2.07 (1.02, 4.22) [0.02]
Growth retardation	1727 (12.5)	451 (10.1)		
3.6–7.5	373 (10.8)	103 (8.0)	1	1
7.6–8.8	382 (11.2)	106 (9.4)	0.95 (0.79, 1.13)	1.10 (0.81, 1.51)
8.9–10.6	433 (12.4)	101 (9.7)	1.03 (0.87, 1.22)	1.07 (0.78, 1.46)
10.7–78	539 (15.3)	141 (14.3)	1.21 (1.02, 1.43) [0.01]	1.54 (1.14, 2.08) [0.009]
Stillbirth	177 (1.2)	60 (1.3)		
3.6– 7.5	39 (1.1)	14 (1.0)	1	1
7.6–8.8	40 (1.1)	7 (0.6)	1.07 (0.67, 1.71)	0.58 (0.23, 1.41)
8.9–10.6	47 (1.3)	18 (1.7)	1.21 (0.75, 1.95)	1.60 (0.77, 3.30)
10.7–78	51 (1.4)	21 (2.0)	1.34 (0.82, 2.19) [0.21]	2.03 (0.98, 4.21) [0.02]
Stillbirth <1500 g	112 (0.8)	39 (0.8)		
3.6–7.5	18 (0.5)	6 (0.4)	1	1
7.6–8.8	22 (0.6)	2 (0.2)	1.26 (0.67, 2.38)	0.36 (0.07, 1.82)
8.9–10.6	35 (1.0)	14 (1.3)	2.00 (1.12, 3.58)	2.73 (1.03, 7.27)
10.7–78	37 (1.0)	17 (1.6)	2.20 (1.20, 4.01) [0.003]	3.68 (1.38, 9.82) [0.001]
Neonatal mortality (first week)	58 (0.4)	17 (0.4)		
3.6–7.5	16 (0.5)	7 (0.5)	1	
7.6–8.8	14 (0.4)	4 (0.3)	0.86 (0.42, 1.76)	0.63 (0.19, 2.10)
8.9–10.6	14 (0.4)	3 (0.3)	0.83 (0.39, 1.74)	0.50 (0.13, 1.93)
10.7–78	14 (0.4)	3 (0.3)	0.82 (0.40, 1.65) [0.57]	0.49 (0.14, 1.76) [0.24]

[1] Multiple logistic regression analysis of 14 415 (4698 for 1980–1996) pregnancies with complete data; odds ratios were adjusted for age of mother at birth, parity, and smoking habits in 1992–1993.
[2] The data in the 1980–1986 column are a subset of the data in the 1967–1996 column.
[3] *P* value for linear trend over tHcy concentration in brackets.

In the women of the Hordaland Homocysteine Study, the major lifestyle determinants of tHcy concentration were low folate intake, cigarette smoking, and coffee drinking (29). A role for folate in relation to both pregnancy complications and adverse outcomes has been suggested, but often not confirmed (30–34). Hence, the results of several previous studies and our data are consistent with a role of

TABLE 3
Congenital malformations according to plasma total homocysteine (tHcy) concentration[1]

Congenital malformation by tHcy quartile (μmol/L)	Number of outcomes 1967–1996 (%)	Odds ratio (95% CI) for malformation
All congenital anomalies	196 (1.36)	
3.6–7.5	43 (1.20)	1
7.6–8.8	48 (1.36)	1.16 (0.77, 1.75)
8.9–10.6	46 (1.27)	1.11 (0.73, 1.69)
10.7–78	59 (1.60)	1.45 (0.97, 2.17) [0.09][2]
Neural tube defects	16 (0.11)	
3.6–7.5	2 (0.06)	1
7.6–8.8	2 (0.06)	1.02 (0.14, 7.17)
8.9–10.6	5 (0.14)	2.49 (0.50, 12.30)
10.7–78	7 (0.19)	3.57 (0.78, 16.29) [0.04]
Orofacial clefts	22 (0.15)	
3.6–7.5	4 (0.11)	1
7.6–8.8	6 (0.17)	1.42 (0.39, 5.17)
8.9–10.6	6 (0.17)	1.29 (0.35, 4.76)
10.7–78	6 (0.16)	1.12 (0.27, 4.66) [0.96]
Clubfoot[3]	62 (0.43)	
3.6–7.5	10 (0.28)	1
7.6–8.8	11 (0.31)	1.12 (0.48, 2.65)
8.9–10.6	17 (0.47)	1.74 (0.80, 3.77)
10.7–78	24 (0.65)	2.53 (1.19, 5.37) [0.007]

[1] Multiple logistic regression analysis of 14 415 pregnancies with complete data; odds ratios were adjusted for age of mother at birth, parity, and smoking habits in 1992–1993.
[2] *P* value for linear trend over tHcy concentration in brackets.
[3] Three cases of neural tube defect with clubfoot were excluded.

folate, Hcy, or both in pregnancy beyond the prevention of neural tube defects. Furthermore, we showed previously that elevated tHcy concentrations are associated with a C-to-T substitution (C677T polymorphism) of the methylenetetrahydrofolate reductase (MTHFR) gene combined with impaired folate status (35). The reported associations between MTHFR status and neural tube defects (36–38), preeclampsia (39, 40), and spontaneous abortions (41) support a role for folate and Hcy metabolism in pregnancy. Associations between plasma tHcy and pregnancy complications and outcomes, however, cannot confirm a specific role for folate. A diet associated with elevated Hcy concentrations is likely to be low in other important nutrients in addition to folate, and our results may reflect more general nutritional inadequacies. Furthermore, although elevated plasma tHcy concentration is a sensitive marker of folate status (12, 13), other nutrients and many nonnutritional factors are also associated with plasma tHcy (11). Lack of exercise and other characteristics of the cardiovascular disease risk profile, including blood pressure and total cholesterol, were important determinants of the tHcy concentration in the Hordaland population (22, 29, 42). In the women considered in this report, educational level was also strongly related to tHcy concentration. Several of these factors, most notably the C677T polymorphism, smoking, and coffee drinking, are known or suspected to play a role in the etiology of pregnancy complications and adverse pregnancy outcomes.

We considered the possibility that coffee drinking, educational level, smoking, and blood pressure were confounders in the present study. We found that coffee intake as reported at age 40–42 y was not associated with previous pregnancy complications or outcomes, and adjustment for coffee intake did not influence the tHcy associations. Additional adjustment for educational level did not change the reported results. On the other hand, a strong association was seen between blood pressure and previous preeclampsia, and adjustment for blood pressure weakened the tHcy-preeclampsia association to some extent, more for all preeclampsia cases combined than for the subgroup of women with combined preeclampsia and premature delivery. In contrast with plasma tHcy, smoking was associated with orofacial clefts, and had an inverse relation with preeclampsia. Both smoking and plasma tHcy were associated with low birth weight and growth retardation. However, there were certain differences in these associations. Compared with tHcy, smoking had a stronger association with growth retardation. Smoking was most strongly associated with low birth weights in the range of 1500–2500 g, whereas plasma tHcy had a strong relation with birth weights < 1500 g.

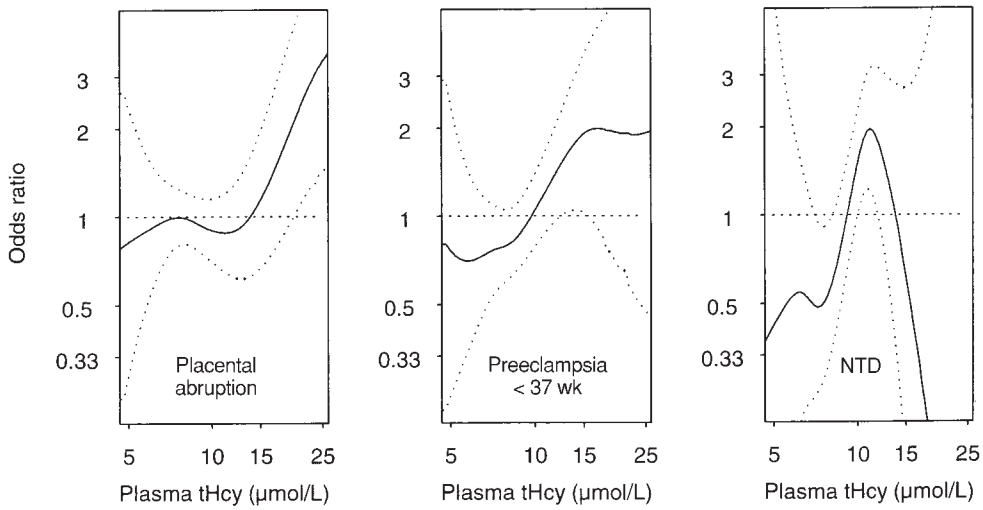

FIGURE 1. Dose-response relation between log plasma total homocysteine (tHcy) and the risk of placental abruption, preeclampsia in pregnancies < 37 wk gestation, and neural tube defects (NTD). The smooth dose-response curves were estimated by using generalized additive logistic regression with adjustment for the age of mother at birth, parity, and smoking habits in 1992–1993. The dotted lines represent 95% point-wise confidence curves.

Likewise, the associations with stillbirth were strongest in different weight groups for the 2 factors. These observations make it unlikely that smoking confounds the tHcy findings. In fact, the relations between tHcy and various outcomes were only moderately affected by adjustment for smoking.

Interestingly, we observed different dose-response relations between plasma tHcy and various outcomes. For placental abruption, the excess risk was confined to women with tHcy concentrations >15 μmol/L. In contrast, malformations and the other outcomes studied were related to the central distribution of tHcy (5–15 μmol/L), with no excess risk associated with high tHcy concentrations. This may indicate different underlying mechanisms. A moderately elevated tHcy concentration may be due to impaired vitamin B status, which in turn may affect tHcy remethylation, biological methylation, and DNA synthesis, and thereby cell proliferation and normal fetal growth (43). High Hcy, on the other hand, may cause vascular dysfunction (44), which predisposes to placental abruption. Accurate estimation of the form of the dose-response curve, however, requires large numbers of observations, and these findings should be regarded as preliminary.

The fact that the majority of the outcomes preceded the tHcy measurement by >10 y is certainly a weakness of this observational study, but makes the strong relations to plasma tHcy even more remarkable. The results also add indirect evidence of the long-term stability of individual Hcy concentrations (45). Because of the timing of the data collection, however, we cannot rule out the possibility that elevated tHcy concentrations are a consequence of the study outcomes. Therefore, our results need to be confirmed in a design in which the tHcy measurement is done before or early in pregnancy. Because a substantial and folate-independent reduction in tHcy occurs during pregnancy (46, 47), tHcy may be a better biomarker of future pregnancy outcomes when measured in the nonpregnant state.

In conclusion, our data suggest an important role of tHcy as a marker of pregnancy complications and adverse pregnancy outcomes. A strength of our study relative to previous studies is the large number of pregnancies studied and the cohort sampling approach that allowed us to investigate all outcomes that were reported to the Medical Birth Registry. Our results underline the need for large prospective studies on the role of homocysteine and B vitamins in all types of complications and adverse outcomes of pregnancy.

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