Effects of Exposure to Organic Solvents on Menstrual Cycle Length

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To investigate the association between organic solvent exposure and menstrual disturbance, we conducted a cross-sectional study among 1408 petrochemical workers in China. Based on an industrial hygiene evaluation, we classified the workshops according to the presence or absence of organic solvents (benzene, styrene, toluene, or xylene). We used logistic regression to estimate odds ratios and 95% confidence intervals for prolonged menstrual cycle length (oligomenorrhea: average cycle length >35 days during the previous year) associated with the exposure. After adjustment for confounders, each additional year of work in an exposed workshop was associated with a 7% increase in oligomenorrhea (odds ratio, 1.07; 95% confidence interval, 1.00 to 1.14). Compared with no exposure, 3 or more years of exposure was associated with a 53% increase in oligomenorrhea (odds ratio, 1.53; 95% confidence interval, 1.00 to 2.34). We concluded that exposure to organic solvents is associated with a trend toward increased frequency of oligomenorrhea. (J Occup Environ Med. *2001;43:567–575*)

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A woman's menstrual pattern is an important indicator of her reproductive health.[1] Characteristics of the menstrual cycle reflect an internal endocrine environment that may be associated with various chronic diseases. For example, increased risks of breast cancer[2] and pre- and postmenopausal fractures[3] have been observed in women with a prolonged menstrual cycle.

Some environmental exposures have been reported to influence menstrual patterns.[4,5] Exposure to volatile organic chemicals, such as benzene, is common in both industrial and non-industrial countries.[6] Several studies have shown adverse reproductive outcomes (eg, spontaneous abortions,[7,8] subfertility,[9] and small-for-gestational-age babies[10]) to be associated with exposure to various organic solvents. Fewer studies have investigated the effects of organic solvents, especially at a low level, on menstrual patterns, despite findings in some early studies that suggested such an association.[11] In one study of married women working in the petrochemical industry in Beijing, China, self-reported benzene exposure was associated with both prolonged (>35 days) and shortened (<21 days) menstrual cycle.[12]

The purpose of this study was to examine whether an association exists between low-level exposure to organic solvents and menstrual patterns in women employed in a large petrochemical industry in Beijing, China. By using the industrial hygiene method of exposure assessment, which is more objective than the self-report method used by Thurston et al,[12] we sought to improve the estimates of the effects of organic solvent exposure on menstrual patterns.

Methods

Study Design

The Chinese health care system mandates that every couple planning to marry visit a designated district health center to receive a marriage health examination (MHE) and to participate in family planning counseling. Married couples are required to obtain childbirth permission (CBP) from the local family planning office before having a baby. We exploited these requirements of the health care system to identify newlywed women (from MHEs) and nonparous married women (from CBP records) 20 to 40 years of age who work in the Beijing Yanshan Petrochemical Corporation (BYPC). They were invited to participate in a prospective study of the effects of exposure to organic solvents on reproductive health outcomes. On enrollment, a baseline questionnaire was administered to each participant by a trained interviewer. The CBP enrollment group was prepared for a follow-up study by keeping a daily menstrual diary and providing daily urine samples. The current study is a cross-sectional analysis of the data obtained at the time of enrollment. This study was approved by the institutional review boards of Harvard School of Public Health and Beijing Medical University.

Study Population

From 1994 to 1998, we recruited employees from BYPC, a large governmental industrial park of petroleum and chemical processing plants. BYPC is made up of 17 different, but well-integrated, production plants and administrative units. As of 1998, BYPC employed approximately 39,500 production workers, of whom nearly 40% were women. The major occupational exposures include aromatic solvents such as benzene, toluene, styrene, and xylene. Because BYPC is a modern industry, the level of exposure is very low. For example, the time-weighted average for benzene during the shift for exposed workers ranged from 0.017 ppm (Rubber Plant) to 0.191 ppm (Chemical Plant #1), a level well below the limit recommended by the National Institute for Occupational Safety and Health. Average levels of toluene, styrene, and xylene were all below 1 ppm.[13]

All women who visited for a marriage health examination or childbirth permit were contacted and screened for eligibility. The eligibility criteria were (1) female workers in BYPC who were 20 to 40 years of age, (2) no previous marriage, (3) no previous clinical pregnancy, and (4) no medically diagnosed gynecologic or endocrine disease. In the MHE group, all eligible workers from the 17 facilities of BYPC were enrolled. In contrast, in the CBP group that had daily urine collection, there was a fifth eligibility criterion to make the data collection more efficient: working in one of the nine selected production facilities. These facilities included the refinery, chemical #1 to #3, synthetic rubber, polyester, chemical fiber and carpet, water treatment, and power plants. These plants were selected on the basis of feasibility of subsequent follow-up in terms of the workers' schedule as assessed in the pilot study. This selection was independent of any reproductive outcomes. The facilities excluded from this selection were the machinery manufacture and repair plant, architectural engineering unit, transportation unit, supply unit, business administration offices, food service unit, affiliated hospital, and affiliated technical school.

Among the MHE group, 150 women were ineligible and excluded from the study because of prior marriage, pregnancy, or a gynecologic/endocrine disease. In the CBP group, approximately 470 women who obtained a childbirth permit were not eligible because they were not working in the selected plants. Among women from the selected plants, 55 were ineligible and excluded from the study because of prior marriage, pregnancy, or a disease. Of 1510 enrolled women, 1134 (75%) were identified by MHEs. Those who were identified by both MHE and CBP were classified as CBP enrollees. The participation rate was greater than 95% among the eligible women. Seven subjects were excluded because of smoking; three were active smokers and the information on smoking status for four others was incomplete. An additional 95 subjects were excluded from the analysis because of incomplete menstrual or current employment information. Data from the remaining 1408 subjects were used in our analyses.

Assessment of Exposures

Each woman's exposure to organic solvents was determined by an evaluation of the production process in her workshop(s). The petrochemical industry involves a complex integrated system of well-defined unit processes.[14,15] Each unit process reflects a set of chemical conversions that starts with raw materials and ends with product materials. These unit processes require specialized equipment that is located in the appropriate sections of the plant. Each plant is divided into a number of sections, or workshops, that reflect the unit processes of chemical reaction or other type of production. BYPC comprises 17 different facilities, each with various workshops. Overall, there are 218 workshops, each representing a single unit process.

We previously conducted methodologic research on exposure assessment and developed a database for workshop evaluation.[13] An industrial hygienist in the research team familiar with the petrochemical process visited each of the nine production plants selected for the CBP group and obtained detailed information on the production process of each workshop. For the other facilities, information on work processes in each workshop was obtained by reviewing documents provided from the company and by contacting engineers working in the plants. For example, a chemical workshop database includes a process map; a brief description of the unit process; a list of job tasks; and a list of chemicals in the workshop, such as raw material, product material, impurities, and background exposure.

Based on the workshop evaluation database, an industrial hygienist qualitatively classified each workshop as either exposed or unexposed to benzene, toluene, styrene, and/or xylene. An exposed workshop was one in which one or more of these organic solvents was routinely used. The method of exposure assessment based on the process information will be described in a separate report.[15a] The steps are as follows: (1) Draw a production-process flowchart for each workshop, indicating each step of the chemical reaction. (2) Identify whether benzene, toluene, xylene, or styrene is involved in the workshop as raw material, end product, intermediate chemical, or an element of mixture products. (3) If a particular aromatic solvent is present in the workshop as any of these components, classify the workshop as exposed to the solvent; otherwise, classify it as unexposed. For example, women working in the electric control room, packing workshop, workers' union, administration office, information center, or library were designated as unexposed. (4) Because the facilities other than the nine production plants do not involve a routine process involving aromatic solvents, treat the women from these workplaces as being unexposed to aromatic solvents. Evaluation of all workshops in which a subject worked yields each subject's exposure status to each solvent.

The measurement "years of exposure," defined as the number of years worked in an exposed workshop, was used as a surrogate variable to investigate potential exposure-response trend. Thirty-two subjects reported having worked in more than one workshop. All workshops were evaluated for organic solvent exposure as outlined above and were included in each subject's years of exposure.

In the baseline questionnaire, a checklist was provided for 26 potential reproductive toxicants other than aromatic organic solvents that were identified in the petrochemical process. Women who reported routine handling of, or contact with, any of these chemicals were considered "exposed to other chemicals."

Assessment of Menstrual Patterns

Assessment of menstrual patterns was based on a questionnaire administered by an interviewer at the time of enrollment. Information on each subject's menstrual pattern in the year before enrollment included average cycle length, longest and shortest cycle length, average duration of bleeding, perceived irregularity, intermenstrual spotting, and perimenstrual symptoms. We defined *oligomenorrhea* as an average cycle length greater than 35 days, according to accepted definitions of menstrual cycle length disorder.[1,16,17] Our definition of oligomenorrhea also includes amenorrhea, usually defined as a menstrual cycle lasting longer than 90 days. *Polymenorrhea* was defined as an average cycle length of less than 21 days. *Prolonged bleeding duration, or menorrhagia*, was defined as an average menstrual bleeding period of greater than 7 days.

Potential Confounders

In addition to information on reproductive history and menstrual patterns, detailed information was collected on several potential confounders: age, body weight and height, date of marriage, current and past contraceptive use, parity, history of active and passive smoking, presence of indoor coal combustion and cooking oil fumes, alcohol consumption, diet, use of herbal medicines, heavy lifting, body position during work, rotating shift work, perceived work stress based on a four-point scale (0 to 3), and physical activities outside the workplace.

Statistical Analysis

Menstrual pattern variables were coded as indicator variables, where 1 indicated the presence and 0 the absence of each outcome variable. Exposure to solvents was similarly coded as binary. For unexposed subjects, years of exposure was given as 0. Years of exposure was treated as a continuous variable. Passive smoking was defined as having exposure to at least one active smoker either at home or in the workplace on a regular basis. Rotating shift work was coded as 1 if three or more different shifts were worked within 1 month and as 0 otherwise. College education, perceived work stress, physical exertion, and heavy lifting during regular work shifts were also coded as indicator variables. We analyzed the data for nonlinear relationships between the outcome variables and all continuous covariates by generalized additive models.[18] Results lacked evidence for departures from linearity for both age and body mass index (BMI). Therefore both covariates were included as linear predictors for all models. Data on years of exposure to solvents suggested that the risk of oligomenorrhea starts to increase after 3 years, although the overall linearity assumption could not be rejected. Therefore, the effect of "years of exposure to any solvents" is presented as both interval-scaled and ordinal-scaled in the multivariate analysis.

Multiple logistic regression was used to estimate the effect of exposure variables, with adjustment for covariates.[19] Model selection was carried out by first examining the full model, including all the variables of interest. Covariates that did not change the association between the exposure and outcome and were not

TABLE 1
Characteristics of the Study Population

Variable	MHE Enrollment Group (n = 1070)*	CBP Enrollment Group (n = 338)†
Age (yrs)		
Mean ± SD	24.4 ± 1.7	25.4 ± 1.9
Range	20.0–34.5	21.2–34.4
Body mass index (kg/m^2)		
Mean ± SD	20.6 ± 2.6	21.0 ± 2.7
Range	14.8–36.7	15.8–33.5
Employment (yrs)		
Mean ± SD	4.1 ± 2.1	5.7 ± 2.6
Range	0.1–19.0	1.0–15.7
Education (*n*/%)		
College	316/29.6	70/20.7
High school or lower	753/70.4	268/79.3
Passive smoking (*n*/%)	532/49.7	176/52.1
Rotating shiftwork (*n*/%)	285/26.9	167/49.6
Aromatic solvent exposure (*n*/%)‡	247/23.1	193/57.1
Other chemical exposure (*n*/%)§	76/7.1	88/26.0
Perceived work stress (*n*/%)	77/7.3	23/6.9
Heavy lifting (*n*/%)	114/10.8	58/17.2
Physical exertion (*n*/%)	97/9.1	37/11.0
Noise at work (*n*/%)	194/18.4	179/53.0

* Enrolled at marriage health examination.
† Enrolled at child birth permission.
‡ Exposure to benzene, toluene, styrene, or xylene, based on qualitative industrial hygiene assessment of workshops.
§ Exposure to other chemicals, based on self-report.

significant independent predictors were excluded from the final model. As one exception, the variable "exposure to other chemicals" was included to ensure the adjustment for potential confounding, although the variable did not show significant association with the outcome in a univariate analysis. Because the low prevalence of polymenorrhea (9 of 1408) and menorrhagia (20 of 1408) might lead to unreliable estimates of the effect of exposure status in the presence of other covariates, these outcomes were not included in our analyses. All analyses were performed with either SAS[20] or S-PLUS.[21]

Results

The characteristics of the study population are described by enrollment group in Table 1. The CBP enrollment group was slightly older, with a longer work history (an expected finding, because a Chinese couple must have a marriage health examination before obtaining a childbirth permit). BMI and passive smoking were comparable between the two groups. Women in the CBP group had a higher frequency of shift work, exposure to solvents and other chemicals, heavy lifting, and noise at work than those in the MHE group, but the level of physical exertion was similar. These differences reflect the selection scheme for the CBP group, which undersampled unexposed subjects by restricting enrollment to nine production plants.

The prevalence of oligomenorrhea stratified by exposure status is presented in Table 2. Of the 138 subjects (9.8% of 1408) who had oligomenorrhea, 6 were amenorrheic. Because a small number of subjects were exposed to only one of the four aromatic organic solvents studied (benzene, toluene, xylene, and styrene), mutually exclusive categories were formed from all possible combinations. Of the 15 possible combinations, only seven contained at least one subject (Table 2). A higher prevalence of oligomenorrhea was found among subjects exposed to any aromatic solvent than among unexposed subjects.

Table 3 compares the prevalence of oligomenorrhea between the exposed and the unexposed groups for each stratum of potential confounders. Higher rates were observed in the exposed group consistently across the strata of nearly all confounders examined. Women with

TABLE 2
Prevalence of Oligomenorrhea* by Solvent Exposure Category Among Newlywed Female Employees

Solvent Exposure	Oligomenorrhea (%)	Total
None	8.5	968
Any aromatic solvent	12.7	440
Benzene†	12.8	437
Toluene†	12.9	356
Styrene†	14.5	276
Xylene†	14.1	284
Mutually exclusive categories‡		
Benzene only	12.1	33
Styrene only	0	3
Benzene and toluene	9.3	43
Benzene and styrene	12.5	48
Benzene, toluene, and styrene	6.9	29
Benzene, toluene, and xylene	9.1	88
Benzene, toluene, styrene, and xylene	16.3	196
Total	9.8	1408

* Defined as average cycle length >35 days.[16]
† Exposure to each solvent, with or without exposure to the other aromatic solvents.
‡ Categories such as "toluene only" and "xylene only" are not presented because they applied to none of the subjects.

TABLE 3

Prevalence of Oligomenorrhea* Among Newlywed Female Subjects Within the Categories of Solvent Exposure and Potential Risk Factors

	Prevalence of Oligomenorrhea					
	Unexposed		Exposed†		Total	
Variables	%	*n*	%	*n*	%	*n*
Age (tertiles)						
20.0–23.6	6.5	355	9.1	121	7.1	476
23.7–25.0	8.3	315	11.5	156	9.3	471
25.0–34.5	11.1	298	16.6	163	13.0	461
BMI (tertiles)						
14.8–20.3	6.4	326	5.6	144	6.2	470
20.3–22.0	8.7	321	10.1	148	9.2	469
22.0–36.7	10.3	319	22.3	148	14.1	467
Education						
High school or lower	9.3	674	13.0	347	10.6	1021
College	6.5	295	11.8	93	7.8	386
Passive smoking						
No	6.6	469	10.4	231	7.9	700
Yes	10.2	499	15.3	209	11.7	708
Enrollment group‡						
MHE	7.7	823	9.3	247	8.0	1070
CBP	13.1	145	17.1	193	15.4	338
Other chemicals§						
No	8.7	907	13.4	337	10.0	1244
Yes	4.9	61	10.7	103	8.5	164
Rotating shift						
No	8.3	749	15.5	194	9.8	943
Yes	9.2	207	10.2	245	9.7	452
Perceived work stress						
No	8.3	884	13.7	410	10.0	1294
Yes	11.3	71	0	29	8.0	100
Heavy lifting						
No	7.6	830	12.3	391	9.1	1221
Yes	13.8	123	16.3	49	14.5	172
Total	8.5	968	12.7	440	9.8	1408

* Defined as average cycle length >35 days.[16] BMI, body mass index.
† Exposure to any aromatic solvents, ie, benzene, toluene, xylene, or styrene.
‡ MHE, enrolled at marriage health examination; CBP, enrolled at childbirth permission.
§ Exposure to chemicals other than aromatic solvents.

older age, higher BMI, passive smoking, perceived work stress, and lifting work had a higher percentage of long menstrual cycles. Women in the CBP group had a higher frequency of long cycles. In addition, the CBP group included more women from the chemical processing plant and women who were, on average, 2 years older than women in the MHE group.

Results from the multivariate logistic regression analysis of oligomenorrhea are displayed in Table 4. Odds ratios (ORs) are adjusted for age, BMI, enrollment group, smoking status, and exposure to other solvents. The tested covariates of noise, heavy lifting, exertion, perceived work stress, rotating shift work, and education were not statistically significant, nor did they modify the association between exposure and oligomenorrhea. Therefore, they were not included in the final models. "Any aromatic solvent" exposure was associated with a 34% increase in the odds of oligomenorrhea. Individually, exposure to each of the four solvents indicated a trend of increased frequency of oligomenorrhea; styrene exposure showed the greatest increase.

As shown in Table 4, exposure to "any aromatic solvent" resulted in a smaller OR compared with the exposure to each of the aromatic solvents examined separately. This is an interesting finding arising from the fact that the greatest effect resulted from the combined exposure to all four aromatic solvents. The exposure to "all aromatic solvents" was associated with an adjusted OR of 1.76 (95% CI, 1.08 to 2.82), compared with the "no exposure" group. In the group exposed to "any aromatic," the effect of exposure to "all aromatic solvents" was diluted by the inclusion of more subjects who were exposed to fewer aromatic solvents.

The increased frequency of oligomenorrhea associated with any aromatic solvent exposure was indicated

TABLE 4

Adjusted OR and 95% CI for Oligomenorrhea* Associated With Exposure, Estimated by Different Models for Newlywed Female Employees

Exposure	$n^{\dagger}$	Oligomenorrhea (%)	OR‡	95% CI
Any aromatic solvent	440	12.7	1.34§	0.90–1.99
Benzene	437	12.8	1.35§	0.90–2.00
Toluene	356	12.9	1.43§	0.93–2.17
Styrene	276	14.5	1.65§	1.05–2.55
Xylene	284	14.1	1.63§	1.04–2.53
All aromatic solvents	196	16.3	1.76§	1.08–2.82
Any aromatic solvent (yr)	1387	9.9	1.07‖	1.00–1.14
Any aromatic solvent (yr)				
None	949	8.5	(Referent)	
>0, ≤3	103	5.8	0.73	0.27–1.63
>3	335	14.9	1.53	1.00–2.34

* Defined as average cycle length >35 days.[16] OR, odds ratio; CI, confidence interval.
† Number of subjects in the exposure category (total $n = 1408$).
‡ Adjusted for age, body mass index, enrollment cohort, passive smoking, and exposure to chemicals other than aromatic solvents.
§ Separate models with the same unexposed group as the reference ($n = 968$).
‖ OR for 1 additional year of exposure. Some observations were deleted from the calculation because of a missing value in the years of employment.

in both the MHE and the CBP groups, although the effect appeared to be higher in the CBP group. Stratified analysis by enrollment groups showed an 18% increase in the odds due to the exposure (OR, 1.18; 95% confidence interval [CI], 0.71 to 1.96) in the MHE group, compared with a 52% increase (OR, 1.52; 95% CI 0.81 to 2.86) in the CPB group.

Duration of employment was longer in the exposed group (mean, 4.9; range, 0.4 to 14.8 years) compared with the unexposed group (mean, 4.2; range, 0.1 to 19 years). A potential exposure-response relationship between oligomenorrhea and years of exposure was investigated by using the years of employment at an exposed workshop as a continuous variable. The unexposed group was assigned 0 years of exposure. A 7% increase in the odds of oligomenorrhea was associated with 1 additional year of exposure, assuming a linear association. The “years-of-exposure” measurement was examined in categories of 0 to 3 years, 4 to 6 years, and greater than 6 years of exposure and was compared with the risk of oligomenorrhea in unexposed subjects. The results in Fig. 1 suggest an increased risk in the groups with 3 or more years of exposure. When the two groups with exposure for more than 3 years were combined, the OR for the group was 1.53 (Table 4), compared with the unexposed group.

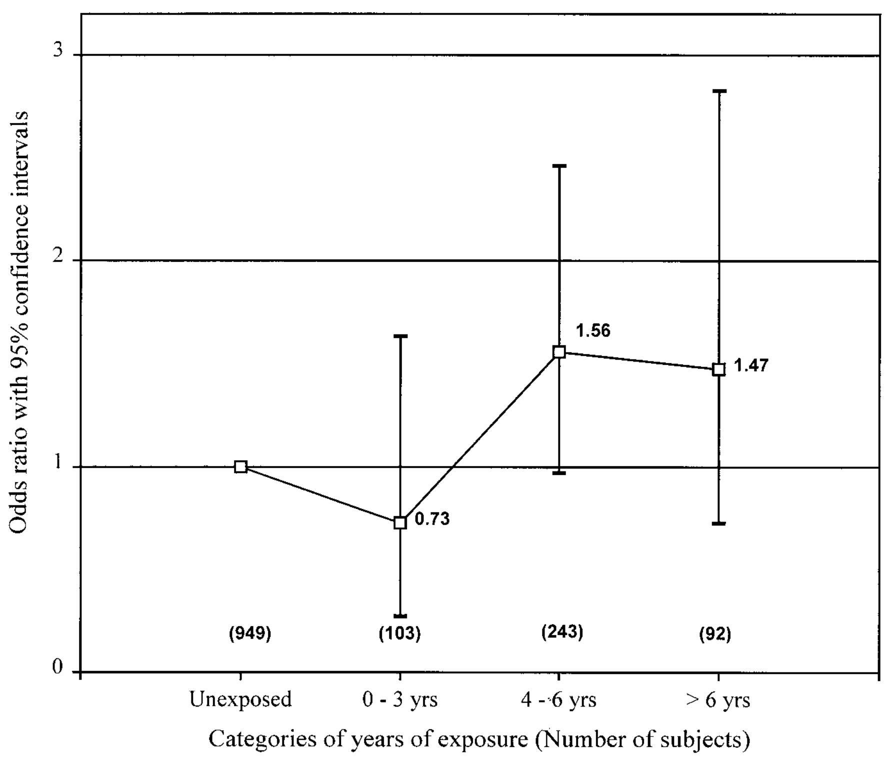

Fig. 1. Adjusted ORs and 95% CIs for oligomenorrhea (average cycle length >35 days) associated with 3 levels of years of exposure. Newlywed female employees of the BYPC, 1994 to 1998.

The correlation coefficient between age and duration of employment is 0.53 ($P < 0.01$). To assess for collinearity, we examined the results by treating age as dichotomous, above or below the median. The estimates for the effect of exposure duration remained the same

(OR, 1.07; 95% CI, 1.00 to 1.14). We also tried age categories in tertiles and centered the age by subtracting the population mean. Neither approach changed the results. The correlation coefficients were smaller between BMI and age (0.086, $P < 0.01$) and between BMI and exposure duration (0.093, $P < 0.01$). We similarly examined the results treating BMI as a dichotomous variable and in tertiles. Both approaches gave the same results (OR, 1.08; 95% CI, 1.01 to 1.15), which was consistent with the results when treating BMI as a continuous variable. Therefore, we did not consider the correlation between age, BMI, and exposure duration to be a concern in our analyses.

Discussion

Menstrual cycle length greater than 35 days is defined as oligomenorrhea (36 to 90 days) or amenorrhea (>90 days).[16] The difference between oligomenorrhea and amenorrhea lies only in the degree of the abnormality.[22] Both can be described as menstrual cycle length disorder.[1]

Oligomenorrhea and amenorrhea reflect depressed ovarian function that can be either primarily of ovarian origin or secondary to a disturbance at the hypothalamic or pituitary level. In a study of 101 women with oligomenorrhea, the dysfunction was associated with anovulation in 89% of the women, and among those, in 31%, it was due to hypothalamic dysfunction.[23] Siegberg et al investigated the endocrinologic features of oligomenorrheic adolescent girls.[24] Compared with control subjects who had cycles of 26 to 32 days, oligomenorrheic girls had elevated levels of androgen and luteinizing hormone and depressed levels of estradiol and progesterone.

In this study, we found an increased frequency of oligomenorrhea among women exposed to aromatic solvents. The association remained after adjustment for confounders such as age, BMI, passive smoking, and enrollment group. There was a suggestion of an exposure-response trend with years of exposure to aromatic solvents. A 7% increase in the odds of oligomenorrhea for each additional year of exposure seems to be a small magnitude. Nevertheless, for female workers with oligomenorrhea, chronic exposure to solvents should be considered as a potential risk factor along with other factors, especially if the levels of exposure are higher than those observed in the current study population.

The study population was selected from woman attending government-mandated premarital health examinations or those being screened for a childbirth permit. Because the eligible women were newlyweds or nonparous women planning to conceive, our results were unlikely to be influenced by a selection bias such as "reproductively unhealthy worker effect."[25] As part of a prospective cohort study, the CBP enrollment group selection was restricted to 9 of 17 facilities in the BYPC. The participants from the nine production plants were similar those from the other facilities in age (24.6 and 24.7, respectively) and BMI (20.6 and 20.8, respectively). We collected detailed information by interview questionnaire from all participants and adjusted for major potential confounders for all analyses. To examine whether the selection of the study plants in the CBP group was likely to result in a bias, we performed additional analyses restricted to these nine plants, both in MHE and CBP groups. Exposure to "any aromatic solvents" was associated with an OR of 1.62 (95% CI, 1.01 to 2.62), and "years of exposure" with an OR of 1.08 (95% CI, 1.01 to 1.17). Other analyses restricted to the nine plants also showed results consistent with those without the restriction. These findings suggest that the selection of the study plants in the CBP group was unlikely to have led to a bias in our results.

Menstrual function was assessed retrospectively. We assumed that each subject's report of her menstrual cycle history was independent of her exposure status. Recall of menstrual cycle characteristics has been reported to have reasonable reliability in an occupational setting.[5]

Assessment of exposure to organic solvents poses a major challenge, especially in the petrochemical industry, where the exposure levels are low. Exposure to volatile solvents is usually highly variable, and biomarkers often are not useful in the lower exposure range. We conducted a qualitative industrial hygiene assessment of each workshop, independently of the study participants, using the information on production steps in the processing of petrochemicals. However, individuals perform different tasks within the same workshop, so a certain degree of misclassification of exposure among subjects who work in the same workshop is inevitable. We expected such misclassification to be nondifferential with respect to menstrual function and to lead to an underestimation of the true association. This misclassification may explain some of the observed difference in the effects of exposure between the MHE and CBP groups. The CBP group was undersampled for unexposed individuals because of the restriction to the nine production plants, excluding some non-chemical and administrative units. The misclassification bias may have been smaller in the CBP group because of the higher prevalence of exposure. The effect of misclassification may also explain the fact that the unexposed group showed a slightly higher risk of oligomenorrhea than the group with exposure for 3 years or less. Considering that the unexposed group had been employed for an average of 4.2 years, the risk estimate may have been attenuated because of misclassification.

Employees may have been exposed to other chemicals in addition to the reported aromatic solvents. We prepared a list of chemicals that have been implicated in the literature as possible reproductive toxins. During the baseline interview, subjects were asked whether they handled one or more of the chemicals. Exposure to these chemicals was adjusted for in multivariate analyses. Although underreporting is expected, a substantial confounding effect would have been adjusted for. Furthermore, the prevalence of the exposure to most of the chemicals was low compared with that of exposure to the volatile organic solvents. Thus the observed oligomenorrhea was more likely due to organic solvents than to other chemical(s). Because of limitations in exposure assessment, we could not separate the effects of individual solvents. Further studies using more sensitive methods of exposure assessment are needed to compare the effects of individual solvents and to examine effect modification. In the current study, we had insufficient power to determine whether a certain duration of exposure is required until the effect is observed. There was an indication that the effect became apparent after 3 years. However, this may be because of the low levels of exposure and misclassification in the assessment, and the question of threshold remains for further studies.

Solvents have been associated with various adverse reproductive outcomes, including spontaneous abortion,[7,8] birth outcomes,[10] and reduced fertility.[9] Toluene was shown to interfere with luteinizing hormone and follicle-stimulating hormone secretion,[26] and styrene with menstrual cycle.[27] In animals, xylene was shown to lower serum progesterone and estrogen levels and to compromise ovulation.[28]

Determining the exact mechanism of the effect of aromatic solvents on menstrual cycle would require further detailed investigations. However, the direction of further study may be focused by certain facts. It is well known that the luteal phase of the menstrual cycle is highly consistent among women. To a large extent, cycle variability is determined by the length of the follicular phase. Harlow and Zeger[29] developed a model for predicting menstrual cycles by using the lag time between the end of one ovarian cycle and the start of the next. This lag time would reflect any delay in the follicular phase that might be due to an environmental insult. Such an insult may act as an acute and a chronic effect, particularly among employees with both short- and long-term exposures. Additional data are required to determine whether such a delay in the follicular phase occurs at the ovarian level or at a higher level such as the pituitary gland or hypothalamus. A prospective study with serial measurements of gonadotropins (follicle-stimulating hormone, luteinizing hormone) and ovarian hormones (estrogen, progesterone) would help to answer some of these questions. Another approach to strengthen the current observation is to study time to conception, because oligomenorrhea is likely to be associated with anovulation. We will report separately our assessment of time to conception from the prospective study.

Early studies of the effect of aromatic solvents on menstrual function reported an increased risk of heavy uterine bleeding.[30] The prevalence of these menstrual outcomes was extremely low in the current study, possibly because exposures in the current study were substantially lower than those reported in early studies. The increased uterine blood loss previously reported may indicate a tendency to bleed caused by exposure to high levels of benzene that is not observable at lower levels of exposure. Exposure-induced oligomenorrhea likely derives from a mechanism involving endocrine disturbance, and the relatively subtle outcome we describe may have been difficult to observe in the earlier studies.

Acknowledgments

This study was supported in part by grants 1R01 HD32505-01 from the National Institute of Child Health and Human Development, 1R01 ES08337-01 from the Institute of Environmental Health Science, 1R01 OH03027 from the National Institute of Occupational Safety and Health, and G73B1382 from the Environmental Protection Agency. We thank Dr Richard Monson of the Occupational Health Program, Harvard School of Public Health for his comments on our manuscript.

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The Buzz On Buzz

Buzz is the stuff of marketing legends. Dark and witty Harry Potter, the traffic-stopping retro Beetle, the addictive Pokemon, cuddly Beanie Babies, the hair-raising "Blair Witch Project"—all are recent examples of blockbuster commercial successes driven by customer hype. People like to share their experiences with one another. . . . and when those experiences are favorable the recommendations can snowball, resulting in runaway success. But ask marketing managers about buzz, and many will simply shrug their shoulders. It's just serendipity, they say, or sheer luck.

The 5 Myths of Buzz

	The Myth	The Reality
1	Only outrageous products are buzz-worthy.	The most unlikely products can generate buzz.
2	Buzz just happens.	Buzz is increasingly the result of shrewd marketing tactics.
3	The best buzz-starters are the best customers.	Often a counterculture has more ability to start buzz.
4	To profit from buzz, one must act first and fast.	Copycats can reap substantial profits if they know when to jump in, and when not.
5	The media and advertising are needed to create buzz.	When used too early or too much, they can squelch buzz.

—From Dye R. The Buzz on Buzz. *Harvard Business Review* 2000;78(6):139–146.