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Prospectively Assessed Menstrual Cycle Characteristics in Female Wafer-Fabrication and Nonfabrication Semiconductor Employees

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Women aged 18–44 years in silicon-wafer fabrication-room (fab) jobs and frequency-matched women in nonfab jobs were screened for a prospective study of reproductive health (n = 2,639). Among the 739 (28%) eligible women, 481 (65%) completed a baseline interview; 402 completed at least one menstrual cycle of follow-up with daily diaries and urinary assays to exclude conceptive cycles. Adjusted mean cycle lengths (MCL) did not differ between fab and nonfab women (p = 0.97). Women working in thin film and ion implantation (TFII) had the highest adjusted MCL (34.8 ± 1.7 days) compared with nonfab workers (32.5 ± 1.4 days, p = 0.07). Among women working exclusively in one group, TFII women had significantly higher MCL (36.1 ± 2.04 days) than nonfab women (32.0 ± 1.38 days, p = 0.017). TFII women were also more likely to have *all* cycles >35 days (adjusted relative risk [RR] = 2.45; 95% CI = 0.85–6.06). Variability was assessed by logarithmic transformation of the mean standard deviation (MLSD) in cycle length per woman and adjusted for age and ethnicity (4.5 days for fab vs. 4.0 days for nonfab, p = 0.16). Women working exclusively in TFII or photolithography (PHOTO) had significantly higher adjusted MLSD in cycle length (6.68 ± 1.28 and 5.72 ± 1.24 days, respectively) than women in nonfab (4.1 ± 1.16 days, p = 0.013 and 0.019, respectively). Fab and nonfab women did not differ significantly in mean days of bleeding or risk of having cycles >35 or <24 days. However, elevated risks of having cycles <24 days were seen in supervisor engineers (adjusted RR = 2.46, 95% CI = 1.19–3.63) and PHOTO women (adjusted RR = 1.83, 95% CI = 0.94–2.88).

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INTRODUCTION

Increased risks of spontaneous abortion (SAB) have been reported among women fabrication-room (fab) workers [Pastides et al., 1988]. The present study was part of the larger Semiconductor Health Study (SHS) [Schenker et al., 1995], initiated to investigate this initial finding. The prospective component of the SHS was designed to determine whether occupational exposures and activities involved in silicon-wafer fabrication affect menstrual cycle characteristics, which are potential indicators of effects on ovarian function. For the prospective component, women were recruited into a follow-up study of menstrual cycle characteristics, conceptions, and SAB rates. The reproductive health of workers engaged in different fab activities or work groups was compared with that of nonfab workers. Although few investigations exist of the effects of occupational exposures on menstrual function, menstrual dysfunction has important implications for women's general and reproductive health, and can cause serious concern among working women.

METHODS

The sample selection, recruitment, and data collection methods are described in detail elsewhere [Gold et al., 1995] but are described briefly here.

Sample Selection and Recruitment

All noncontract women employees aged 18–44 years and working in fab jobs at seven sites in five companies were selected to be screened for eligibility for a prospective study of reproductive health. Fab status was determined by work location, job title, or both. A sample of nonfab women employees aged 18–44 years was also selected by frequency matching to fab women by 5-year age group and ethnicity (non-Hispanic, white, black, Hispanic, Asian, other).

All selected women were invited to 30-min group meetings consisting of a slide presentation about the study and a question-and-answer period conducted by study investigators on company time to accommodate work shifts. Women completed a one-page language survey to determine their preferred speaking and reading language, so that a bilingual interviewer (Spanish or Tagalog) could be provided, if necessary. To determine eligibility for the follow-up study, women completed a four-page, self-administered screening questionnaire on company time in a private room. Of the 3,840 women selected and still employed at the participating companies, 2,639 (75.9%) completed the screening questionnaire.

The following eligibility criteria were established to identify women at risk of pregnancy: age 18–44 years; not currently pregnant; menstruated within the previous 2 months; had sexual intercourse within previous 2 months; self and partner not sterilized; not using oral contraceptives, intrauterine device, or steroid hormones that interfere with assessment of urinary reproductive hormones; had a working freezer; not leaving the company within the next 3 months; and ability to speak English, Tagalog, Spanish, or Vietnamese. Of the 2,639 women who completed the screening questionnaire, 739 (28.0%) were eligible for follow-up, and 481 (65%) of them were enrolled.

Data Collection

After informed consent was obtained, detailed, in-person, baseline interviews were conducted to determine sociodemographic and lifestyle characteristics, medical and reproductive history, and job activities. For the next 6 months, participants collected daily urine samples and completed daily diaries in which they recorded menstrual bleeding, premenstrual symptoms, medication use, illnesses, sexual intercourse, contraceptive use, daily habits, and workplace hours and activities. Women were paid $35 for each month of follow-up completed, and drawings for prizes of weekend or weeklong trips were awarded at the end of the study. Of the 481 enrolled women, 402 completed at least one menstrual cycle of daily urine collection and diaries while not using exogenous reproductive steroids. More than half the enrolled women completed five or more menstrual cycles; fab and nonfab women did not differ in number of cycles completed. Women were telephoned monthly and at the end of follow-up to determine any changes in work activities, eligibility, or pregnancy status.

Data Analyses

Outcome variables. Menstrual cycle characteristics were obtained from baseline interviews and daily diaries. Urine samples were analyzed for human chorionic gonadotropin to determine cycles in which conceptions occurred [Lasley et al., 1995]; these cycles were excluded from analyses of menstrual characteristics. The following measures were computed from diary data: mean cycle length (MCL) per woman, standard deviation (SD) of MCL per woman, mean days of bleeding (MDB) per woman, percentages of women with any short (<24 days) cycles, and percentages of women with any long (>35 days) cycles.

Means of the MCL observed, the SD in cycle length, and the MDB per woman were computed for each group. Because the observed values for the means of the MCL and MDB were normally distributed, and the means are more amenable to statistical manipulations, the means were used instead of medians. Each day of bleeding was noted in the daily diary, permitting calculation of cycle lengths (days from the beginning of one bleeding episode to the beginning of the next). Each woman's MCL was computed, and the means of the MCLs were compared for fab and nonfab workers to measure central tendency.

Standard deviations in cycle length were computed for each woman who contributed ≥2 cycles. Crude means of these values for fab and nonfab workers were compared to measure variability in cycle lengths. Because the distribution of the means of the SD in cycle length per woman was skewed to the right, per-woman SDs were transformed with natural logarithms (ln) for all computations. For women with SD of zero, 0.25 day was used to take the ln, since the lowest non-zero value for SD was 0.56. The 0.25 day was subtracted following exponentiation of the mean of the ln SD (MLSD).

Per-woman analyses of MDB were based on 408 women. This group included 402 women who had completed at least one menstrual cycle and six additional women who had diary data on bleeding days but missing data on the length of the first or last cycle.

To measure the probability of extreme cycle lengths, the percentages of women who had any short (<24 days) or long (>35 days) cycles were computed. Cutoffs of 24 and 35 days were selected based on prospective studies [Vollman, 1956; Treloar et al., 1967; Chiazze et al., 1968] showing that 10% of all cycles in women in this age group are <24 days, and 10% are >35 days.

The mean of the MCL, the MLSD per woman, the percentages of women with any cycles <24 days or >35 days, and the mean of the MDB per menstrual period per woman were examined in relation to fab-nonfab and work group [Hammond et al., 1995] and in relation to potentially confounding factors. Cycles with missing data on menstrual bleeding were excluded from these analyses.

Two separate sets of analyses were performed to determine the probability of long or short cycles. The first analysis was restricted to women who completed at least four cycles, because the number of completed cycles might have been related to having had long or short cycles. The second approach involved analyzing a number of cycles until a long or short cycle occurred by fitting a logistic model to the risk of such a cycle for all women whose prior cycles were not of extreme length. In this approach, all women were at risk in the first cycle, with decreasing numbers at risk in each succeeding cycle; the probability of having a cycle >35 or <24 days was computed, adjusting for covariates.

Confounding variables. The influence of potential confounding variables (data ascertained from screening questionnaires or baseline interviews) on MCL, MLSD, and MDB per woman was evaluated and controlled with two-factor analyses of variance (ANOVA), using the SAS General Linear Models program, version 6 (SAS Institute, Cary, NC), with fab status as one factor and each potentially important confounder as the other. The influence of potential confounders on the proportion of women with any cycle <24 or >35 days was determined by computing Mantel-Haenszel odds ratios (ORs) and 95% confidence intervals (CI), with stratification on each potential confounder.

A limited subset of important confounders was selected from a broad set of potential confounders, based on (1) a priori variables in the literature (e.g., age), (2) evidence of a trend in outcome over the strata of a confounder with ordinal data (such as smoking) in the nonfab group, or (3) a difference in the outcome among strata of a confounder with nominal data (such as ethnicity) in the nonfab group larger than the crude difference in the outcome between the fab and nonfab groups. This subset of confounding variables was included in multivariate models as described later.

Exposure variables. Exposure assessment was based on information reported on baseline interviews and industrial hygiene site visits to fabs. Exposure assessments and outcome measurements were performed independently. A three-tiered exposure assessment was employed [Hammond et al., 1995]. At the first level, women who worked ≥5 hr/week in a fab were classified as fab workers; those who did no fab work were classified as nonfab (including both office workers and non-office nonfab workers). More specific categories were defined at the second tier—women were placed into work groups based on tasks performed. Fab workers were divided into supervisor-engineers or operators. Fab operators were further divided into four work groups: photolithography (PHOTO), etching (ETCH), furnace (FURN), and thin film and ion implantation (TFII). Each work group had a different set of exposures, although some exposures occurred in multiple work groups, and women could be placed in more than one work group. Finally, exposures to selected chemical, physical, and ergonomic agents were estimated by industrial hygiene assessment of actual tasks each woman performed, by use of targeted chemicals in each task in each fab, and by evaluation of fab-specific emission factors. Exposures to ethylene-based glycol ethers (EGE) and fluoride were identified in the historical component as related to significantly increased SAB rates [Swan et al., 1995] and were examined for their relationship to the five menstrual cycle outcomes. Industrial hygienists independently assessed exposures to these agents and categorized exposures on an ordinal scale (0–3), with 0 indicating no exposure and 3 the highest exposure [Woskie et al., 1995]. Because 22 women were exposed to both agents (6 of them with level-2 or -3 exposures to both), the potential effect of each agent on menstrual cycle outcomes was analyzed separately, adjusting for exposure to the other. Women with level-2 and -3 exposures to each agent were combined because of the small numbers in each group (18 with EGE exposures at level 2 or 3, and 38 with fluoride exposures at levels 2 or 3).

Multivariate analyses. The selected subset of potential confounders was included for simultaneous adjustment in multiple regression analyses of MCL, MLSD, and MDB per woman (using the PROC REG program in SAS) and in logistic regression for probability of any short or long cycles. Levels of all confounders except ethnicity were treated as scores in these regressions; values for dependent variables were compared with the mean of the score. For ethnicity, adjustment was to the white, non-Hispanic group. Robust regressions of MCL and MLSD were performed, first to identify any large influence of outliers that would have changed multiple regression results. Three outliers that influenced MCL (means = 85, 105, or 143 days) were excluded from further multiple regression analyses of this outcome but were included in other analyses. (None had evidence of pregnancy, but two had urinary hormone evidence of anovulation.)

Odds ratios are good predictors of RR only when an outcome is rare, but the probability of long or short cycles was not rare. Thus, ORs were converted to RRs and 95% CI by

1. choosing a "reference risk" (R_{NF}) based on the crude rate in the nonfab group,
2. calculating the reference odds, (p_0) from the reference risk, that is, $p_0 = R_{NF}/(1 - R_{NF})$,
3. calculating the odds in the fab group (p_1) by multiplying the reference odds (p_0) by the odds ratio,
4. converting the resulting fab odds to a fab risk (R_F): $R_F = p_1/(1 + p_1)$, and
5. calculating the adjusted RR as $RR = R_F/R_{NF}$.

A "reference risk" of 21.9% (seen in nonfab women) was used to convert OR to RR for the percentage of women with any cycle <24 days. Similarly, a "reference risk" of 30.8% was used to convert OR to RR for the percentage of women with any cycle >35 days.

RESULTS

Potential Confounding Factors at Baseline

Baseline demographic factors that might affect menstrual cycle characteristics were compared for 152 fab and 250 nonfab workers (Table I).

TABLE I. Demographic and Lifestyle Characteristics in an Eligible Sample of Fabrication and Nonfabrication Employees Who Contributed at Least One Menstrual Cycle of Follow-Up

	Fabrication (n = 152)		Nonfabrication (n = 250)	
Covariates	n	%	n	%
Age (yr)				
<25	12	7.9	5	2.0
25–29	24	15.8	46	18.4
30–34	55	36.2	89	35.6
35–39	40	26 3	73	29.2
≥40	21	13.8	37	14.8
Ethnicity				
White, non-Hispanic	82	53.9	103	41.2
Filipino	23	15.1	46	18.4
Other Asian	13	8.6	36	14.4
Hispanic	23	15.1	35	14.0
Black	3	2.0	14	5.6
Other	8	5.3	16	6.4
Location				
California	79	52.0	213	85.2
Utah	73	48.0	37	14.8
Education (yr)				
≤12	72	47.4	53	21.2
13–15	57	37.5	101	40.4
≥16	23	15.1	96	38.4
Annual household income ($)				
<20,000	27	17.8	13	5.2
20–39,000	52	34.2	69	27.6
40–59,000	50	32.9	67	26.8
≥60,000	21	13.8	101	40.4
Body mass index (gm/cm^2)				
<1.89	10	6.7	21	8.4
1.9–2.57	87	58.4	156	62.7
>2.57	52	34.9	72	28.9
Cigarettes/day				
0	113	74.8	210	84.3
1–10	15	9 9	29	11.6
≥11	23	15.2	10	4.0
Alcoholic drinks/week				
<1	76	50.7	109	44.0
1–3	47	31.3	102	41.1
4–6	18	12.0	20	8.1
>6	9	6.0	17	6.9
Marijuana use in month before baseline				
No	143	94.1	239	95.6
Yes	9	5.9	11	4.4
Caffeine intake (mg/day)				
≤150	79	54.9	147	61.0
151–300	34	23.6	56	23.2
>300	31	21 5	38	15.8
Physical activity (hr/wk)				
0	25	16.4	49	19.6
1–3	71	46.7	130	52.0
4–7	34	22.4	51	20.4
>7	22	14.5	20	8.0
Passive smoke at home or work				
None	63	55.8	154	73.3
Any	50	44.2	56	26.7
Age at menarche[a]				
<12	27	17.8	50	20.0
12–13	75	49.3	131	52.4
14–15	40	26.3	49	19.6
>15	7	4.5	16	6.4
Gravidity				
0	24	15.9	58	23.2
1	33	21.9	56	22.4
2	36	23.8	66	26.4
≥3	58	38.4	70	28.0
Parity				
0	40	26.3	94	37.6
1	44	28.9	61	24.4
2	41	27.0	64	25.6
≥3	27	17.8	31	12.4
History of infertility				
No	59	38.8	130	52.0
Yes	93	61.2	120	48.0

[a]Excludes three fab and four nonfab workers in "Don't know" category.

TABLE II. Baseline Menstrual Cycle Characteristics in Women Working in Fabrication and Nonfabrication Jobs: "Eligible" Participants in Semiconductor Health Study

Characteristic	Fabrication (n = 152)	Nonfabrication (n = 250)	t or χ^2 (p value)
Usual cycle length (days)			
Median	28.0	28.0	2.27
Mean (SD)	28.0 (3.7)	28.9 (3.7)	(0.02)
Irregular cycles	25.0%	18.4%	2.49 (0.11)
Usual cycle length <24 days	17.1%	12.4%	1.72 (0.19)
Usual cycle length >35 days	1.3%	5.2%	3.97 (0.05)
Mean (SD) of usual number of days of bleeding	5.0 (1.4)	5.3 (2.0)	1.70 (0.09)

SD = standard deviation.

Menstrual Cycle Characteristics at Baseline

Fab and nonfab women did not differ significantly in the *median* self-reported usual cycle length or in the percentage with usual cycles <24 days (Table II). The *mean* self-reported usual cycle length was significantly shorter in fab than nonfab workers ($p = 0.02$). More fab than nonfab workers reported irregular cycles or cycles that varied by >4 days ($p = 0.11$). Fewer fab than nonfab workers reported usual cycle lengths >35 days ($p = 0.05$). Mean days of menstrual bleeding were slightly lower in fab than in nonfab workers ($p = 0.09$). Because prospective menstrual cycle data from daily diaries were likely to be more accurate than recall at baseline interviews, detailed analyses of menstrual cycle characteristics were based solely on diary data.

Menstrual Cycle Outcomes From Diaries, by Fabrication Status

Mean cycle length per woman. The unadjusted mean of the MCL per woman from daily diaries was 0.6 days longer in fab than nonfab workers ($p = 0.53$) (Table III). No clear relationships of crude MCL to years since first hire or hours worked per week were observed. Fab and nonfab women who worked only days tended to have slightly, but insignificantly longer crude MCLs, as did fab (but not nonfab) workers who reported standing >7 hr/day. When MCL was simultaneously adjusted for age, education, smoking, body mass index (ratio of weight in grams to the square of height in centimeters), passive smoke exposure at home or work, gravidity, physical activity, caffeine consumption, and ethnicity, the difference in MCL between fab and nonfab workers was 0.03 days ($p = 0.97$) (Table III).

Standard deviation in cycle length per woman. The crude mean of SD in cycle length per woman was higher in fab than nonfab workers (4.8 vs. 3.9 days, $p = 0.10$) (Table III). Because of the skewed distributions of SD per woman, the value for each woman's SD in cycle length was transformed for all future analyses, using the natural logarithm for computations. The unadjusted exponentiated mean of the MLSD per woman was 0.9 days longer in fab than nonfab workers. Nonfab women working >40 hr/week had higher crude MLSDs per woman than those working ≤40 hr/week, and women who worked only nights or evenings had higher crude MLSDs

TABLE III. Prospective Menstrual Cycle Characteristics Among "Eligible" Women Who Worked in Fabrication (Fab) and Nonfabrication (Nonfab) Jobs and Contributed at Least One Menstrual Cycle of Follow-Up in Semiconductor Health Study

Characteristic	Fab (752 cycles) (n = 152)	Nonfab (1,210 cycles) (n = 250)	t or χ^2 (p value)
Cycles per woman			
Median	6.0	5.0	NA
Mean (SD)	5.0 (2.2)	4.8 (2.2)	
Mean cycle length (MCL) per woman			
Median	28	29	
Mean[a] (SD)	31.2 (9.9)	30.6 (8.8)	−0.63 (0.53)
SD[b] in cycle length per woman			
Median	2.6	2.6	
Mean[c] (SD)	4.8 (5.4)	3.9 (4.0)	−1.94 (0.10)
Percentage of women with any cycle >35 days[d]	32.9%	30.4%	0.27 (0.60)
Percentage of women with any cycle <24 days[e]	27.0%	21.6%	1.51 (0.22)
Mean[f] (SD) days of bleeding per woman	5.15 (1.1)	5.19 (0.9)	0.27 (0.79)

SD = standard deviation.
[a]Difference in MCL = 0.03 days (p = 0.97), adjusting for age, education, body mass index, cigarette smoking, gravidity, ethnicity, caffeine consumption, physical activity, and passive smoke exposure at home or work (as scores).
[b]Only includes women with more than one complete cycle.
[c]Difference in MLSD = 0.60 (p = 0.12), adjusted for age and ethnicity (as scores).
[d]RR = 1.00 (95% CI = 0.64–1.45) for at least one long cycle among women who contributed at least four cycles, adjusting for age, education, cigarette smoking, gravidity, ethnicity, body mass index, caffeine consumption, and physical activity (as scores).
[e]RR = 1.41 (95% CI = 0.85–2.12) for having at least one short cycle among women who contributed at least four cycles, adjusting for age, education, ethnicity, cigarette smoking, caffeine consumption, gravidity, passive smoke exposure at home or at work, and physical activity (as scores).
[f]Difference in mean days of bleeding = 0.13 (p = 0.45), adjusting for age, ethnicity, income, education, body mass index, caffeine consumption, and physical activity (as scores).

per woman than women who worked only days. These relationships were not observed among fab women. The age- and ethnicity-adjusted exponentiated MLSD was not significantly greater in fab than nonfab workers (difference = 0.60 days, p = 0.12) (Table III).

Percentage of women with any long cycles. Compared with nonfab workers, the unadjusted RR was 1.08 for fab workers' having any cycles >35 days (95% CI = 0.80–1.42). Approximately one third of *all* women had at least one long cycle, and about 10% of *all* cycles and of *all* MCLs exceeded 35 days. In the nonfab group, percentages of women with any long cycles rose with hours worked per week, with working only nights or evenings, and with work that did not involve standing; these statistically insignificant relationships were not seen among fab workers.

Women who contributed fewer completed cycles could have done so because they had longer cycles [Burch et al., 1967]. However, the distributions of total number of cycles observed were similar in fab and nonfab women (Table IV). Further adjusted analyses of the probability of having a long cycle among women who contributed at least four cycles (to provide adequate follow-up to observe any long cycles) resulted in an RR of having any long cycles of 1.00 (95% CI = 0.64–1.45) for fab compared with nonfab workers, adjusting for age, education, cigarette smok-

TABLE IV. Prospective Comparison of Number and Percentage of Total Cycles >35 Days, by Total Completed Cycles, Among Eligible Fabrication (Fab) and Nonfabrication (Nonfab) Employees in Semiconductor Health Study

Total cycles completed	Numbers and percentages of total cycles >35 days									
	0		1		2		3		≥4	
	n	%	n	%	n	%	n	%	n	%
Fab										
1 (n = 15, 9.9%)	11	73.3%	4	26.7%	—	—	—	—	—	—
2 (n = 14, 9.2%)	9	64.3%	3	21.4%	2	14.3%	—	—	—	—
3 (n = 11, 7.2%)	8	72.7%	1	9.1%	1	9.1%	1	9.1%	—	—
≥4 (n = 112, 73.7%)	67	59.8%	26	23.2%	9	8.0%	6	5.4%	4	3.6%
Nonfab										
1 (n = 25, 10%)	15	60.0%	10	40.0%	—	—	—	—	—	—
2 (n = 27, 10.8%)	18	66.7%	7	25.9%	2	7.4%	—	—	—	—
3 (n = 19, 7.6%)	11	57.9%	2	10.5%	4	21.0%	2	10.5%	—	—
≥4 (n = 179, 71.6%)	116	64.8%	31	17.3%	17	9.5%	8	4.5%	7	3.9%

ing, gravidity, ethnicity, caffeine consumption, body mass index, and physical activity (Table III). The adjusted RR of having a long cycle by the fourth cycle among *all* women who contributed at least one cycle was 1.17 (95% CI = 0.76–1.81).

Percentage of women with any short cycles. Compared with nonfab workers, the unadjusted RR for fab workers was 1.25 (95% CI = 0.87–1.72) for having any cycles <24 days. Approximately 25% of *all* women had a short cycle. Moreover, 8% of *all* cycles and 4% of *all* MCLs were <24 days. Among nonfab workers, short cycles were more common among women working >48 hr/week and women working nights and evenings; these associations were not seen among fab workers.

Among women completing at least four cycles, the RR of having any short cycles was 1.41 (95% CI = 0.85–2.12) for fab compared with nonfab workers, adjusting for age, education, ethnicity, cigarette smoking, caffeine intake, gravidity, physical activity, and passive smoke exposure at home or work (Table III). When the multiple logistic model was fitted for the probability of having a short cycle by the fourth cycle, the adjusted RR for all women completing at least one cycle was 1.06 (95% CI = 0.64–1.76).

Mean days of bleeding per woman. The crude mean of the MDB per woman was 0.04 day shorter in fab than nonfab workers (p = 0.79) (Table III). Adjusting for age, ethnicity, body mass index, education, income, physical activity and caffeine intake, the mean of the MDB was 0.13 day shorter in fab than nonfab workers (p = 0.45) (Table III).

Menstrual Cycle Outcomes, by Work Group

Although the five menstrual cycle outcomes did not differ significantly between fab and nonfab workers, this relatively crude comparison might have obscured potential effects of specific workplace exposures or tasks on menstrual cycle characteristics. Therefore, analyses were also performed by work groups defined during industrial hygiene exposure assessments [Hammond et al., 1995]. Women could be placed in more than one work group (which is why the sum of women in each work group is greater than the total number of fab workers in Tables V and VI), although most women (77% fab, 99% nonfab) worked exclusively in one group. Thus, analyses of menstrual cycle outcomes were first performed to compare each work group

TABLE V. Adjusted[a] Mean Cycle Length (MCL) and Geometric Mean of the Natural Logarithm (ln) of Standard Deviation (SD) in Cycle Length per Woman, by All Work Groups to Which Women Were Assigned and by Exclusive Work Groups: Sample of Eligible Women in Semiconductor Health Study

			Adjusted[b] mean of MCL[c] (days)		Adjusted[d] mean of ln SD[e] (days)	
Work group assignment	All groups (n)	Exclusive groups (n)	All groups	Exclusive groups	All groups	Exclusive groups
Fab	152	117	32.5	32.5	4.5	4.5
FURN	40	26	31.5	31.5	3.6	3.9
TFII	31	16	34.8[f]	36.1[g]	4.6	6.7[g]
PHOTO	56	34	30.3	30.8	4.1	5.7[g]
ETCH	42	20	30.6	30.8	2.6	5.1
SUPV/ENGR	23	21	33.4	33.8	4.2	4.5
Nonfab	250	247	32.5	32.0	4.0	4.1

Fab, fabrication; nonfab, nonfabrication; FURN, furnace; TFII, thin film and ion implantation; PHOTO, photolithography; ETCH, etching; SUPV/ENGR, supervisors and engineers.
[a]Adjusted values for fab work groups are comparisons with all nonfab employees.
[b]Adjusted for age, education, body mass index, cigarette smoking, caffeine consumption, gravidity, ethnicity, physical activity, and passive smoke exposure at home or work (as scores).
[c]Includes women with at least one cycle.
[d]Adjusted for age and ethnicity (as scores).
[e]Includes women with at least two cycles.
[f]$p = 0.07$ compared with nonfab group.
[g]$p \leq 0.02$ compared with nonfab group.

to the nonfab group for all work groups to which fab women were assigned. Later analyses were restricted to women assigned exclusively to one work group, to more clearly distinguish any differences. Because only four women worked in fab equipment maintenance, this group was not analyzed separately; however, these four women were also assigned to and included in analyses for the other work groups. Women in each work group were compared with all nonfab women.

Mean of mean cycle lengths per woman. Crude MCLs of fab workers ranged from 30.0 days in the PHOTO group to 34.1 days in the TFII group; the crude MCL of nonfab workers was 30.6 days. After adjustment for confounders, TFII workers had a longer MCL than nonfab workers (34.8 ± 1.7 days vs. 32.0 ± 1.4 days, $p = 0.07$) (Table V). In analyses of women assigned exclusively to one work group, the adjusted MCL was significantly higher among TFII workers (36.1 ± 2.04 days) than nonfab workers (32.0 ± 1.38 days, $p = 0.017$).

Mean of logarithm of standard deviations in cycle length per woman. Crude MLSD ranged from 2.6 days in ETCH to 3.7 days in PHOTO workers, whereas the crude MLSD was 3.1 days among nonfab workers. After statistical adjustment for confounders, no significant differences in MLSD were found. In comparison with nonfab workers (4.0 days), the MLSD was highest in TFII (4.6 ± 1.2 days, $p = 0.43$) (Table V). Analyses limited to women working exclusively in one group showed that TFII and PHOTO workers had significantly higher MLSD (6.7 ± 1.3 days and 5.7 ± 1.2 days, respectively) than nonfab women (4.1 ± 1.2 days, $p = 0.013$ and 0.019, respectively).

Women with any long cycles. Among women providing data on at least four

TABLE VI. Crude and Adjusted Relative Risks (RR)[a] and 95% Confidence Intervals (CI) for Women With any Long (>35 Days) Cycle, by Work Group in Sample of Eligible Women in Semiconductor Health Study

Work group assignment	All groups (n)	% with any cycles >35 days	Crude RR	95% CI	Adjusted[b] RR	95% CI
Fab	152	31.4	1.08	0.80–1.42	1.00	0.64–1.45
FURN	40	22.5	0.73	0.32–1.26	0.90	0.40–1.66
TFII	32	41.9	1.36	0.82–1.97	1.07	0.48–1.90
PHOTO	56	33.9	1.10	0.71–1.58	0.95	0.46–1.65
ETCH	42	31.0	1.01	0.59–1.55	1.15	0.54–1.96
SUPV/ENGR	23	34.8	1.13	0.58–1.84	0.87	0.31–1.80
Nonfab	250	30.8	1.00	—	1.00	—

Fab, fabrication; nonfab, nonfabrication; FURN, furnace; TFII, thin film and ion implantation; PHOTO, photolithography; ETCH, etching; SUPV/ENGR, supervisors and engineers.
[a]Referent is all nonfab employees.
[b]Adjusted for age, ethnicity, education, body mass index, cigarette smoking, caffeine consumption, gravidity, and physical activity (as scores) among women with at least four completed cycles.

cycles, the RR of any cycles >35 days was slightly higher among certain fab groups than among all nonfab workers, but these differences were not significant, particularly after multivariate adjustment for confounders (Table VI). When the multiple logistic model was fitted for the probability of any long cycles among *all* women (not just those contributing four or more cycles), no adjusted RR was significantly elevated; the highest RR was 1.75 (95% CI = 0.82–3.76) in TFII. However, when the risk for having *all* long cycles was examined, the RR was 1.56 (95% CI = 0.38–5.85) for SUPV/ENGR and 2.45 (95% CI = 0.85–6.06) for TFII compared with all nonfab women. When the multiple logistic model was fitted for the probability of any long cycle among all women contributing at least one cycle, the RR was elevated among women working exclusively in TFII (RR = 1.70, 95% CI = 0.63–4.54) or PHOTO (RR = 1.99, 95% CI = 0.96–4.12); among women contributing at least four cycles, women working exclusively in ETCH had the highest RR (RR = 1.96, 95% CI = 0.91–2.78).

Women with any short cycles. The crude RR for any short (<24 days) cycles was significantly higher among women in the PHOTO group than among all nonfab workers (RR = 1.63, 95% CI = 1.05–2.32) (Table VII). Among women completing at least four cycles, the adjusted RR for SUPV/ENGR was significantly higher than that for all nonfab women (RR = 2.46, 95% CI = 1.19–3.63). In analyses of women assigned to only one work group, SUPV/ENGR also had the only significantly elevated RR (RR = 2.61, 95% CI = 1.28–3.75), but the risk for PHOTO women was also elevated (RR = 1.93, 95% CI = 0.82–3.25). When the multiple logistic model was fitted for the probability of a short cycle by the fourth cycle in all women contributing at least one cycle, the RR for PHOTO women was significantly higher than for all nonfab women (RR = 1.99, 95% CI = 1.03–3.83). This relationship held in analyses of women assigned exclusively to one work group; the RR for PHOTO women was 1.97 (95% CI = 0.92–4.23).

Mean of mean days of bleeding per woman. The crude mean of MDB per woman ranged from 5.07 ± 14 days in the FURN group to 5.25 ± 1.3 days in the ETCH group (Table VIII). The crude mean of MDB per woman did not differ

TABLE VII. Crude and Adjusted Relative Risks (RR)[a] and 95% Confidence Intervals (CI) for Percentage of Women With any Short (<24 Days) Cycle, by Work Group of Sample of Eligible Women in Semiconductor Health Study

Work group assignment	All groups (n)	% with any cycles <24 days	Crude RR	95% CI	Adjusted RR[b]	95% CI
Fab	152	25.5	1.25	0.87–1.72	1.41	0.85–2.12
FURN	40	20.0	0.92	0.45–1.67	1.06	0.39–2.29
TFII	31	16.1	0.74	0.30–1.57	0.79	0.25–1.96
PHOTO	56	35.7	1.63	1.05–2.32	1.83	0.94–2.88
ETCH	42	21.4	0.98	0.50–1.72	1.48	0.65–2.66
SUPV/ENGR	23	30.4	1.39	0.46–2.41	2.46	1.19–3.63
Nonfab	250	21.9	1.00	—	1.00	—

Fab, fabrication; nonfab, nonfabrication, FURN, furnace; TFII, thin film and ion implantation; PHOTO, photolithography; ETCH, etching; SUPV/ENGR, supervisors and engineers.
[a]Relative to all nonfab workers.
[b]Adjusted for age, education, ethnicity, cigarette smoking, caffeine consumption, gravidity, physical activity, and passive smoke exposure at home or at work (as scores) among women with at least four completed cycles.

significantly between any fab work group compared with all nonfab workers (5.19 ± 0.9 days). After adjustment for covariates, no differences in MDB by work group were statistically significant. Analyses of women assigned exclusively to one work group showed similar results.

Menstrual Cycle Outcomes in Relation to Agents

After controlling for confounders, analyses for effects of high EGE or fluoride exposures showed no trends in relation to MCL, MLSD, MDB, or percentages of women with any cycles >35 days or <24 days.

DISCUSSION

Present Findings

Measures of central tendency, variability, and probability of extremes in cycle lengths are most objectively ascertained from the daily diaries, which do not depend on recall but do require conscientious record-keeping [Snowden, 1977]. Diaries showed a slightly higher MCL per woman in fab than nonfab workers (31.1 vs. 30.4 days), but this difference was not statistically significant, even after adjustment for confounding variables ($p = 0.97$). Although the crude mean of the SD in cycle length per woman was significantly longer in fab than nonfab workers (5.2 vs. 4.0 days) workers, the difference was not statistically significant after data were normalized by logarithmic transformation and confounding variables of age and ethnicity were controlled ($p = 0.16$). Although there were few significant differences among work groups in adjusted MCL and MLSD per woman, the adjusted MCL was 3.2 days longer in the TFII group than in the nonfab group ($p = 0.07$), an elevation that became significant ($p = 0.017$) when analyses were restricted to women working exclusively in one group. These analyses also showed that TFII and PHOTO groups had significantly higher MLSD (6.7 ± 1.3 and 5.7 ± 1.2 days, respectively) than nonfab workers (4.1 ± 1.2 days) ($p = 0.013$ and 0.019, respectively). The significantly higher MCL and MLSD in TFII workers are consistent with the reduced

TABLE VIII. Crude and Adjusted Mean Days of Bleeding (MDB) per Woman Among Women With at Least One Menstrual Period During Follow-Up, by Work Group vs. all Nonfabrication Workers in "Eligible" Sample in Semiconductor Health Study

Work group assigment	All groups (n)	Crude mean MDB (SD)	p	Adjusted[a] mean MDB (SD)	p
Fab	152	5.15 (1.1)	0.79	5.18 (0.36)	0.45
FURN	41	5.07 (1.4)	0.61	5.40 (0.49)	0.49
TFII	32	5.09 (1.3)	0.70	4.98 (0.45)	0.83
PHOTO	58	5.12 (1.4)	0.70	5.34 (0.49)	0.53
ETCH	42	5.25 (1.3)	0.83	5.24 (0.42)	0.53
SUPV/ENGR	23	5.10 (1.6)	0.76	4.96 (0.46)	0.76
Nonfab	250	5.19 (0.9)	—	5.05 (0.35)	—

Fab, fabrication; nonfab, nonfabrication; FURN, furnace; TFII, thin film and ion implantation; PHOTO, photolithography; ETCH, etching; SUPV/ENGR, supervisors and engineers.
[a]Adjusted for age, ethnicity, education, income, body mass index, and caffeine consumption.

probability of conception (fecundability) seen in the dopants and thin film (DOPE-FILM) super group [Eskenazi et al., 1995], comprised of the FURN and TFII work groups.

The proportion of women with any short (<24 days) or long (>35 days) cycles was slightly higher in fab than nonfab workers. Among women providing data on at least four cycles, these differences were insignificant after adjustment for confounding variables. Women exclusively assigned to the ETCH group were the only fab workers whose risk of any long cycles was higher than that among all nonfab women (RR = 1.96, 95% CI = 0.91–2.78). The risk of *all* cycles being long was highest among TFII workers (RR = 2.45, 95% CI = 0.85–6.06). The adjusted RR for having any short cycles by the fourth cycle was highest among SUPV/ENGR (RR = 2.46, 95% CI = 1.19–3.63); the adjusted RR for PHOTO workers was almost double that of nonfab workers.

The mean MDB per woman did not differ significantly between fab and nonfab workers or among work groups. Levels of EGE or fluoride exposure did not appear to affect any of the five menstrual cycle outcomes.

Comparisons With Previous Studies

The present findings relating menstrual cycle characteristics, particularly MCL and SD in cycle length, to age and other factors showed consistencies with previous work. The MCL (28–29 days) and SD (3–4 days) reported in previous studies [Vollman, 1956; Treloar et al., 1967; Chiazze et al., 1968] were slightly lower than those found among women in the same age groups as were studied here. However, subjects in the previous studies were almost exclusively white, middle-class women, whereas our study followed a more ethnically and socioeconomically diverse group. We did find that MCL and SD in cycle length decreased with age (data not shown), consistent with landmark prospective diary studies of menstrual cycle characteristics. However, other investigators have found that MCL increased in younger cohorts over time [Chern, 1981].

In the present study, MCL was longer in women who smoked >10 cigarettes/day and in women with a high body mass index (data not shown). These findings are consistent with studies showing more physician-attended menstrual disorders among smokers [Sloss and Frerichs, 1983]. Our findings also support previous reports of more menstrual abnormalities and longer cycle lengths among obese women [Hartz et al., 1979] and of greater probability for long (>43 days) cycles among overweight college women [Harlow and Matanoski, 1991]. In the latter study, Harlow and Matanoski found that 5% of cycles lasted >43 days. In the present study, analyses of all cycles and MCL showed that 5% of nonfab workers' cycles lasted >39 days and 5% of fab workers' cycles lasted >44 days. Although these findings might appear to be consistent with those of Harlow and Matanoski [1991], that study was limited to college freshmen aged 18–19 years, ages when cycles are usually longer and more variable. Our older population (median age, 34 years) should have been more likely to have shorter and less variable MCLs, further highlighting the cycle variability in this working population and particularly in fab workers. Previous studies [Treloar et al., 1967] showed longer cycles during the teen years and decreases with age, consistent with the age-related decline in the length of the follicular phase [Lenton et al., 1984]. Thus, the cycle lengths observed in fab workers were somewhat unexpected.

Previous studies suggested that long cycles may indicate delayed ovulation [Aksel, 1981], and short cycles may reflect a shortened follicular phase [Lenton et al., 1984] or anovulation [Matsumoto et al., 1979], but a one-to-one relationship does not exist. Although few have investigated the relationship of occupational exposures to menstrual cycle changes, an early Russian study noted a strong dose-response association between irregular menses and manufacturing exposure to superphosphate dust containing fluoride [Kuznetsova, 1969]. In one recent study, irregular cycles and long cycles were related to work-schedule variability and cold stress but not to time spent standing [Messing et al., 1992]. No relationship was found between toluene exposure and menstrual cycle changes [Ng et al., 1992]. A recent Johns Hopkins report found that semiconductor fab work did not affect menstrual cycle length, but the investigators did not attempt to determine cycle variability or possible differences in cycle length among women in different work groups [Gray et al., 1993].

Limitations of Findings

The findings on menstrual cycle characteristics indicate possible disturbances in menstrual function in some work groups, but the limitations of these analyses must be noted. First, the primary objective in the prospective component was to compare the SAB risk in fab vs. nonfab workers. Therefore, the eligibility criteria for follow-up were designed to exclude women at low risk of pregnancy. Because women were excluded if they had not menstruated within the past 2 months, women likely to have had infrequent or irregular cycles were likely to have been excluded. Thus, variability in menstrual cycle characteristics was less likely to have been observed among women in the follow-up study. However, 2–3% of both fab and nonfab women reported no menstrual periods during the previous 2 months, suggesting that the frequency of exclusion for menstrual cycle abnormalities did not differ between these groups.

Selection bias was a second possible limitation—women with menstrual cycle disturbances might have been more likely to participate. The 65% participation rate might have produced an artifactual increase in cycle abnormalities if fab women were more concerned about the relationship of such disturbances to their work. The general lack of significant differences in cycle characteristics in fab vs. nonfab comparisons suggests that selection bias was unlikely. Moreover, women reporting no menstrual periods in the prior 2 months were excluded, and the frequency of such responses was similar in fab and nonfab groups. Nonetheless, in future studies it would also be desirable to expand the study population to include women with no recent menstrual periods.

Another limitation is that menstrual cycle data may not be a sensitive indicator of changes or disturbances in hormonal function resulting from occupational and environmental exposures [Kesner et al., 1992]. Aberrations in ovarian physiology, such as short luteal phase, luteal-phase insufficiency, or anovulation, cannot be accurately detected without daily measurements of reproductive hormones or their metabolites during each cycle; such problems are likely to be missed in analyses focused only on data on vaginal bleeding [Keizer and Rogol, 1990]. Data on menses alone cannot rule out the possibility that fab work affected ovarian function, because abnormalities can exist even with regular vaginal bleeding. Daily hormonal assays could establish whether adverse effects of fab work on pregnancy or conception were associated with preconceptional changes in endocrine function. Such investigations could also determine whether occupational exposures were associated with anovulation, mistimed ovulation, or other endocrine abnormalities that might have long-term health implications. Unfortunately, such daily hormone measurements for all women in the follow-up study were beyond the scope of this study. With additional time and resources, these possibilities could be evaluated by assaying gonadotropins and steroid hormone metabolites in the stored frozen urine samples obtained in the present study.

A few menstrual cycle findings were statistically significant. However, many crude and adjusted comparisons were made for the five outcomes and different categories of exposures (fab-nonfab, work groups, and agents). Thus, the few observed differences could have resulted by chance and must be regarded cautiously.

CONCLUSIONS

This large multidisciplinary, prospective study of menstrual cycle characteristics of women semiconductor workers revealed that the mean of the MCL and SD in cycle length were significantly greater among women in the TFII group than among nonfab workers. It also revealed a significantly higher variability in cycle length in women working exclusively in PHOTO and a higher risk of short cycles among SUPV/ENGR and PHOTO workers than among nonfab workers. These findings require further investigation. Although most thin-film processes are fully enclosed and automated with minimal opportunities for exposure, ion-implantation processes do provide opportunities for exposures to dopants, such as arsenic compounds, for which data on reproductive toxicology are limited. Women working in the PHOTO group are potentially exposed to organic solvents, which have been associated with adverse reproductive outcomes [Swan et al., 1995]. These findings must be carefully considered in light of the restricted population studied, the lack of hormonal measurements of ovarian function, and the multiple comparisons made. Nonetheless, the longer cycle lengths and greater cycle variability in TFII workers are consistent with other results indicating reduced fecundability in DOPEFILM workers [Eskenazi et al., 1995].

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