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Prospective Assessment of Fecundability of Female Semiconductor Workers

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To investigate a possible effect of reduced fecundability (probability of conception per menstrual cycle) among women who fabricate silicon wafers, 152 fabrication-room (fab) and 251 nonfab workers were followed for an average of five menstrual cycles. Daily urine samples were analyzed to confirm clinical spontaneous abortions (SABs) and early fetal losses (EFLs). Adjusted fecundability odds ratios (FRs) for fab workers ranged from 0.59 to 0.72 ($p = 0.09–0.28$ vs. nonfab). For clinical pregnancies only, the adjusted FR ranged from 0.43–0.50 ($p = 0.04–0.09$ vs. nonfab). This lower fecundability was most pronounced among dopants and thin-film workers [adjusted FR = 0.61, 95% confidence interval (CI) = 0.27–1.40 for all pregnancies; adjusted FR = 0.22, 95% CI = 0.05–0.96 for clinical pregnancies] and in workers exposed to ethylene-based glycol ethers (adjusted FR = 0.37, 95% CI = 0.11–1.19).

Key words: fertility, infertility, reproduction, glycol ethers, fluoride, semiconductor manufacturing

INTRODUCTION

Several investigators have suggested that women working in silicon wafer fabrication-room (fab) jobs are at a higher risk of spontaneous abortion (SAB) than other semiconductor workers [Pastides et al., 1988; Gray et al., 1993; Beaumont et al., 1995; Swan et al., 1995; Eskenazi et al., 1995]. This finding is biologically plausible because several chemicals used in wafer fabrication are suspected reproductive toxicants. For example, ethylene-based glycol ethers (EGE), used for positive photore-

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sist in the masking process, have been related to embryolethality and teratogenicity in several animal species [NIOSH, 1991]. Arsenic and its compounds, some commonly used as dopants, were teratogenic in rodents [Hood et al., 1977]. These compounds were also related to higher rates of SAB and low infant birthweights among exposed women [Hemminki et al., 1980; Nordstrom et al., 1979].

Although chemicals used in fabs may have a broad array of reproductive effects, most studies have focused on the effects of fab work on SAB. Chemicals associated with SAB may also reduce fertility or fecundability [Baird et al., 1986]. Some investigators have suggested that fecundability (average probability of pregnancy in each menstrual cycle) may be a sensitive indicator of the effects of environmental and occupational exposures [Baird et al., 1986; Baird, 1992]. Reduced fecundability in an exposed population may reflect reproductive failure in gametogenesis, fertilization, and implantation or in early development [Schaumburg and Boldsen, 1992]. Reduced fecundability has been associated with increased maternal age [Baird et al., 1986], recent oral contraceptive (OC) use [Harlap and Baras, 1984], recent breastfeeding [Baird and Wilcox, 1985], maternal smoking [Baird and Wilcox, 1985], and caffeine consumption [Wilcox et al., 1988].

The present study examined the relationship between fab work and fecundability. Because this study included a prospective evaluation of early fetal loss (EFL), we detected pregnancies that might otherwise have appeared as reduced fecundability.

METHODS AND MATERIALS

Selection of Participants

All women 18–44 years of age who worked in silicon wafer fabs at seven sites in five U.S. companies were selected to participate in the prospective component. The comparison group consisted of a sample of nonfab women at the same sites, frequency matched to fab women in 5-year age groups and ethnicity. Nonfab women were oversampled by 25% in anticipation of potentially different participation rates.

Women were considered eligible for participation if they were 18–44 years of age, were not currently pregnant, had menstruated within the past 2 months, had had sexual intercourse within the previous 2 months, were not sterilized, were not using OCs, were not using an intrauterine device (IUD), had a partner who was not sterilized, and were not using steroid hormones that interfere with urinary hormone assays. Women also had to have a working freezer (for storing urine specimens), no plans to leave the company within the next 3 months, and speaking ability in English, Spanish, Vietnamese, or Tagalog.

Recruitment and Data Collection Procedures

Women were screened for eligibility by a self-administered questionnaire completed on company time. Of the 3,480 women selected and still employed at participating companies, 2,639 completed the questionnaire (75.9%), and 739 (28.0%) were eligible for the follow-up study. The procedures, the methods for maintaining confidentiality, and the voluntary nature of the study were explained to the eligible women. Of the 739 eligible women, 481 (65%) completed baseline interviews. In these 2-hour, in-person interviews, participants provided information on sociodemographic characteristics; medical and reproductive history; habits, including consumption of alcohol, caffeine, and tobacco; job activities and exposures; work shift; occupational stress; and current job duration.

Starting the day after the baseline interview and continuing for 6 months, women collected 5 ml of urine each day upon awakening and completed a daily diary. Diaries took about 5 minutes to complete and included information on whether the woman had had menstrual bleeding, contraceptive use, or intercourse. Diaries also included questions about activities at work and elsewhere. A total of 403 women (152 fab and 251 nonfab, 84% of those interviewed) completed at least one menstrual cycle of diary entries and urine collection.

Women were telephoned once monthly and at the end of the 6 months to determine any changes in work activities, eligibility, or pregnancy status. Women who became ineligible (by use of OCs, IUDs, etc.) during the course of the study were terminated at the end of the following month.

All data collection instruments were translated into Tagalog and Spanish. The screening questionnaire, diary, and urine collection instructions were also translated into Vietnamese. The study protocol and data collection instruments were approved by human subjects institutional review boards at University of California (UC), Berkeley and at UC Davis. Further details on methods appear elsewhere [Eskenazi et al., 1995; Gold et al., 1995a].

Definition of Outcomes and Exposures

A cycle was defined as starting the first day of menses and ending the day before the first day of the next menses. Pregnancy included EFLs, clinically recognized SABs, therapeutic abortions, ectopic pregnancies, live births, and stillbirths. For analyses, clinical pregnancies included all but EFLs.

SAB was defined as fetal loss occurring prior to 20 weeks of gestation. Clinically recognized SAB was identified by the woman and/or her clinician; EFL was detected by elevation and subsequent drop in urinary human chorionic gonadotropin (hCG) before the woman or her clinician became aware of the pregnancy. To identify cycles in which conception may have occurred, cycles with complete data (at least 11 of the 16 daily urine samples collected in the window from 10 days before until 5 days after the onset of menstrual bleeding) were screened for hCG using a highly sensitive immunoenzymometric assay (IEMA). Cycles identified as hCG positive by IEMA were analyzed by a more specific immunoradiometric assay (IRMA). EFL was defined as an absolute rise of at least 0.15 ng hCG/mg creatinine (Cr) (measured by the arithmetic average of two replicate IRMA) during two of three consecutive days in the 16-day window. This rise must have occurred ≥8 days after the midcycle luteinizing hormone (LH) peak or after the estrone conjugate peak (E_1C), and must have occurred with a rise of at least 3 μg/mg in pregnanediol-3-glucuronide (PdG), a progesterone metabolite, for at least 4 days. Any sample with a creatinine value of <0.15 mg/ml was ignored. All clinically recognized SABs were confirmed by IRMA assay [Eskenazi et al., 1995; Lasley et al., 1995].

Only cycles with sufficient samples for laboratory analyses were included in data analyses of conception rates. Cycles of undeterminable length were excluded. To remove statistical difficulties in dealing with multiple nonindependent events, all cycles following a woman's first conception during the study were excluded.

Because participants could have used birth control, it was necessary to determine their relative opportunities for pregnancy, based on occurrence and timing of intercourse and on use and type of contraception. Because potentially conceptive cycles indentified by IEMA were the only cycles analyzed for LH and E_1C, the time of increased fertility was estimated from cycle length rather than from hormonal indicators of ovulation. For each cycle, the days of greatest opportunity for pregnancy were selected. This period of relative fertility included days 9–19 prior to the predicted first day of the next menstrual period. This interval was based on reported rates of conception on days before and after the presumed day of ovulation [Barrett and Marshall, 1969] and on days of confirmed intercourse for all clinically recognized pregnancies. In cycles in which a clinically recognized pregnancy occurred, the interval of opportunity was determined by estimating the date menses would have begun had no pregnancy occurred. Estimates were based on usual cycle length reported in the baseline interview for women with regular cycles, on mean cycle length of nonconceptive cycles during the study for women with irregular cycles, and on a 28-day cycle when neither of the preceding values was reported. Two conceptive cycles (one fab EFL, one nonfab EFL) had no confirmed intercourse during the interval of opportunity; one had no reported intercourse for the entire cycle, and the other reported intercourse only on days 4 and 27 of a 29-day cycle.

Based on the 11-day opportunity intervals, each cycle was assigned to one of six categories of opportunity for pregnancy: high risk, medium risk, low risk, unknown birth control, unknown intercourse, and no intercourse. The highest risk activity reported in the interval determined the category of opportunity for the cycle. For example, high-risk cycles had at least one reported day of intercourse without contraception; medium-risk cycles had no high-risk days and at least one day of intercourse with sponge, diaphragm, cap, condom, foam or jelly, withdrawal alone, or diaphragm combined with foam or jelly; low-risk cycles had no high- or medium-risk days and at least one reported day of intercourse with OC, IUD (N.B. women may have begun to use these methods of contraception during the study; if so, they were excluded from the study in the subsequent cycle), or condom in combination with diaphragm or foam or jelly; no-risk cycles were those when the women reported not to have had intercourse and there was no missing data on intercourse or contraceptive use [Hatcher et al., 1990]. Cycles were assigned as unknown birth control if intercourse occurred in the interval, but birth control information was missing; cycles were assigned as unknown intercourse if no intercourse was reported in the interval, but intercourse data were missing for part or all of the interval. Conception rates for each category of opportunity were calculated by dividing number of conceptions by the number of cycles in that category.

Exposure Assessment

Exposure assessment was based on women's responses on baseline questionnaires and on industrial hygiene site visits to fabs. A three-tiered exposure assessment was used [Hammond et al., 1995]. At the first level, women who worked ≥5 hours/week in fabs were classified as fab workers; those who did no fab work were nonfab. Women who worked >0 but <5 hours/week in fabs were not classified and were excluded from fab–nonfab analyses.

In the second tier, women were placed into work groups based on tasks they performed. Nonfab women were divided into office and nonoffice workers. Operators who spent any time in fabs were divided into two super groups: masking (MASK), which included workers in photolithography (PHOTO) and etching (ETCH), and dopants and thin film (DOPEFILM), which included workers in furnace (FURN) and thin-film and ion implantation (TFII). Supervisors and engineers (SUPV/ENGR) included fab and non-fab workers. Each work group had a different set of exposures, but some exposures overlapped work groups.

In the third tier, two specific exposures identified in the historical component of the study [Swan et al., 1995] as significantly related to higher SAB rates—ethylene-based glycol ethers (EGE) and fluoride—were examined in relation to fecundability. Exposure estimates were based on industrial hygiene assessments of actual tasks performed by each woman, on use of targeted chemicals in each task in each fab, and on evaluation of emission factors specific to each fab. Exposures to these agents were classified without regard to fab–nonfab status using a dichotomous variable (none vs. any) and also four exposure levels (none to high, 0–3) [Hammond et al., 1995].

Statistical Analysis

Crude conception rates were calculated for fab and nonfab groups by dividing the number of women who became pregnant at least once during the study by the number of cycles in that group. Crude relative risks (RRs) for conception were calculated using the Epi Info program [Dean et al., 1990]. Logistic regression models were constructed to examine the probability of conception ("fecundability") at each cycle [Weinberg and Gladen, 1986]. For example, if at the jth cycle under study, a woman had covariate values $Z = (Z_{1j}, Z_{2j}, \ldots, Z_{pj})$, the risk of conception at cycle j was $P_j(Z)$, where $\log (P_j[Z]/1 - P_j[Z]) = a_j + b_1Z_{1j} + b_2Z_{2j} + \ldots + b_pZ_{pj}$. Because women contributed more than one cycle, a conditional logistic regression procedure SAS PROC PHREG [SAS, 1989] was used with cycle as the stratifying variable. Because conception was rare, the odds ratio approximated the relative probability of conception per cycle or the fecundability ratio (FR). Women were at risk until their first conception, if any, or until the last cycle observed. A dichotomous indicator of fab status was formed, and a number of covariates were considered. For each woman, the only variables that could change from cycle to cycle were indicator variables for pregnancy opportunity and cycle number.

The small number of pregnancies limited the number of covariates that could be included in each multivariate model. Therefore, alternative subsets of confounders were selected with an "all subsets" search using the SAS PROC PHREG and with fab status forced into the procedure. Potential covariates were ethnicity (white vs. Filipino and other Asians *and* vs. black, Hispanic, and other ethnicity), body mass index (1.89–2.57 kg/m^2 vs. <1.89 kg/m^2 *and* vs. >2.57 kg/m^2); smoking (none vs. any); alcohol consumption (<1/week vs. ≥1/week); parity (none vs. 1 *and* vs. ≥2); education (college graduate or more vs. high school or less *and* vs. some college); recent pregnancy or lactation (never or >6 months ago vs. ≤6 months ago); adverse reproductive history, including endometriosis, uterine fibroids, ovarian growths, pelvic inflammatory disease, or fallopian tube infection (none vs. any); recent OC use (never or >6 months ago vs. ≤6 months ago); household income (<$40,000 vs. ≥$40,000); caffeine consumption (≤150 mg/day vs. >150 mg/day); age at menarche (12–13 years vs. <12 years *and* vs. >13 years); paternal smoking (none vs. any); paternal alcohol consumption (none vs. any); and mother of participant smoking while participant in utero (none vs. any).

Exposure was also categorized by supergroup and by agent-specific exposure (none vs. any). The multivariate models for both analyses included the three most important covariates identified in the fab–nonfab analysis: opportunity for pregnancy, maternal age, and recent OC use. For supergroup analyses, fab supergroups were classified as exposed, with nonfab workers as the comparison group. Women classified in more than one supergroup (n = 14) were counted in both. For agent analyses, indicator variables representing any exposure to the agent were included in the model, and those with neither exposure of interest were the comparison group. Women with both exposures were counted in both groups.

The same models were used to examine the relationship of exposure and fecundability for all pregnancies and for clinical pregnancies only. We undertook the clinical pregnancy fecundability analysis because clinical pregnancy is the outcome of interest to the women themselves and because clinically detected conceptions were much less likely than EFLs to be false events. In addition, clinical pregnancy fecundability analysis provided for comparisons with studies in which fecundability analyses did not include EFLs.

Some models included an additional covariate for the number of months prior to enrolling in the study that a woman had not used contraception. If the last contraceptive method was used sporadically, the number of months of sporadic use was halved and added to the number of noncontraceptive months. Crude life-table estimates of the cumulative percentage of women becoming pregnant were obtained for all pregnancies and for clinical pregnancies only using a modified Kaplan–Meier method [Samuels, 1984]. This method allowed us to include menstrual cycle data for women with one or more ineligible study cycles (e.g., >5 days of missing urine samples in the 16-day window, not followed for full six cycles).

RESULTS

Crude Conception Rates

Enrollees in the prospective component included 152 fab women who contributed 736 cycles and 251 nonfab women who contributed 1,179 cycles. During the study, 19 fab women (12.5%) and 33 nonfab women (13.1%) became pregnant; these pregnancies included clinically recognized pregnancies and EFLs. Four women (one fab, three nonfab) had two pregnancies each. The overall crude conception rate (first pregnancy/woman only) for fab workers was similar to that for nonfab workers (crude RR = 0.95, 95% CI = 0.56–1.61). Pregnancy occurred in 2.6% of menstrual cycles of fab workers and 2.8% of cycles of nonfab workers (crude RR = 0.92, 95% CI = 0.53–1.61).

Evaluation of Potential Confounders

We examined the characteristics of fab and nonfab groups by comparing the percentages of women (rather than cycles) between the two groups (not shown). Compared with nonfab workers, fab workers were less likely to be >34 years old (39% vs. 44%), more likely to be white (54% vs. 41%), and less likely to have graduated from college (15% vs. 38%). More fab than nonfab women smoked (25% vs. 16%). Similar proportions of fab and nonfab women had histories of reproductive disease (24% vs. 23%). Compared with nonfab women, fab workers were more likely to have had a previous live birth (74% vs. 62%) but less likely to have had a recent pregnancy or to have breastfed (25% vs. 38%). Fab women were more likely than nonfab women (61% vs. 47%) to report a history of infertility (trying to get pregnant

TABLE I. Conception Rates/100 Cycles for Fabrication (Fab) and Nonfabrication (Nonfab) Workers, by Selected Covariates

	Fab cycles (n = 736)				Nonfab cycles (n = 1,179)				Total cycles (n = 1,915)
	Cycles		Pregnancies		Cycles		Pregnancies		Pregnancies
Covariate	n	%	n	n/100 cycles	n	%	n	n/100 cycles	/100 cycles
Age (years)									
<35	447	60.7	13	2.9	604	51.2	26	4.3	3.7
≥35	289	39.3	6	2.1	575	48.8	7	1.2	1.5
Ethnicity									
White, non-Hispanic	406	55.2	12	2.9	471	40.0	17	3.6	3.3
Filipino, other Asian	165	22.4	4	2.4	394	33.4	11	2.8	2.7
Other	165	22.4	3	1.8	314	26.6	5	1.6	1.7
Education									
High school or less	352	47.8	8	2.3	257	21.8	7	2.7	2.5
Some college or vocational school	270	36.7	8	3.0	446	37.8	16	3.6	3.4
College graduate	114	15.5	3	2.6	476	40.4	10	2.1	2.2
Smoking									
Yes	192	27.8	5	2.6	166	14.1	3	1.8	2.2
No	542	72.2	13	2.4	1,012	85.9	30	3.0	2.8
Prenatal smoke exposure									
Yes	154	21.9	2	1.3	248	21.5	8	3.2	2.5
No	550	78.1	16	2.9	906	78.5	25	2.8	2.8
History of reproductive disease									
Yes	169	23.0	6	3.6	293	24.9	7	2.4	2.8
No	567	77.0	13	2.3	886	75.2	26	2.9	2.7
Recent pregnancy or lactation									
Yes	556	75.5	15	2.7	724	61.4	20	2.8	2.7
No	180	24.5	4	2.2	455	38.6	13	2.9	2.7
Recent oral contraceptive use									
Yes	10	1.4	0	0.0	6	0.5	3	50.0	18.8
No	726	98.6	19	2.6	1,173	99.5	30	2.6	2.6

for more than a year). Approximately 54% of nonfab women and 44% of fab women were still contracepting at the time of enrollment.

We compared conception rates (pregnancies/100 cycles) of fab and nonfab workers for selected potential confounders identified from the "all subsets" procedures (Table I). Comparisons by age and ethnicity showed lower conception rates among fab and nonfab women of ages >34 years and ethnicity other than white non-Hispanic or Filipino or other Asian (17% black, 58% Hispanic, 25% other) (Table I). Although crude conception rates among nonfab workers were slightly lower

TABLE II. Number and Percent of Menstrual Cycles of High, Medium, Low, and No Risk for Pregnancy, Based on Frequency of Intercourse and Type of Contraceptive Used, With Conception Rates (Clinically Recognized Pregnancies + Early Fetal Losses) per 100 Cycles for Fabrication (Fab) and Nonfabrication (Nonfab) Workers

	Fab cycles (n = 736)				Nonfab cycles (n = 1,179)			
	Cycles		Pregnancies		Cycles		Pregnancies	
Risk of cycles	n	%	n	n/100 cycles	n	%	n	n/100 cycles
High risk	293	39.8	13[a]	4.4	379	32.2	24[a]	6.3
Medium risk	221	30.0	3[b]	1.4	437	37.1	5[b]	1.1
Low risk	6	0.8	0	0.0	5	0.4	0	0.0
No risk	99	13.5	1	1.0	175	14.8	1	0.6
Unknown birth control	19	2.6	1	5.3	30	2.5	1	3.3
Unknown intercourse	98	13.3	1[c]	1.0	153	13.0	2[c]	1.3
Total	736	100.0	19[d]	2.6	1,179	100.0	33[d]	2.8

[a]Among high-risk cycles, fab women had eight clinical pregnancies (2.7/100 cycles) and nonfab women had 21 clinical pregnancies (5.5/100 cycles).
[b]Among medium-risk cycles, fab women had one clinical pregnancy (0.5/100 cycles), as did nonfab women (0.2/100 cycles).
[c]Among unknown intercourse risk cycles, fab women had one clinical pregnancy (1.0/100 cycles), as did nonfab women (0.7/100 cycles).
[d]Fab workers had 10 clinical pregnancies or 1.4/100 cycles, while nonfab workers had 1.8/100 cycles (see Table III).

TABLE III. Crude Conception Rates (Pregnancies/100 Cycles) for all Pregnancies (Clinically Recognized + Early Fetal Losses) and for Clinical Pregnancies Only, by Work Group vs. Nonfabrication Workers

		All pregnancies		Clinical pregnancies	
Group	Cycles	n	n/100 cycles	n	n/100 cycles
Fabrication[a]					
Masking	376	12	3.2	6	1.6
Dopants and thin film	301	7	2.3	2	0.7
Supervisors/engineers	108	3	2.8	2	1.9
Nonfabrication	1,169	33	2.8	21	1.8

[a]The 14 women who worked in more than one job category are counted in all relevant groups.

for college graduates than nongraduates, educational level did not affect rates among fab workers. Smoking lowered conception rates among nonfab women but not among fab women. Fab women whose mothers smoked during pregnancy had lower conception rates than those whose mothers did not; this relationship was reversed for nonfab workers. Among recent OC users (four nonfab, two fab), three nonfab women became pregnant. Fab women with a history of reproductive disease had unexpectedly higher rates of conception than those with no such history; this pattern was reversed in nonfab women. Recent pregnancy or lactation did not appear to be related to conception rates.

Opportunity for pregnancy during each cycle was determined from diary reports of intercourse and contraception. Among fab and nonfab women, conception rates including all pregnancies were higher in high-risk (noncontraceptive) cycles than in medium-risk cycles, and no pregnancies occurred in low-risk cycles (Table II). Two pregnancies resulting in EFL (one fab, one nonfab) occurred in cycles in which women did not report having sexual intercourse. High-risk cycles comprised 32.2% of the total

TABLE IV. Logistic Regression Models for Comparison of Fabrication/Nonfabrication Fecundability Ratio (FR) for All Pregnancies (Clinically Recognized + Early Fetal Losses) and for Clinical Pregnancies Only

Model	Variables	All Pregnancies Adjusted FR (95% CI)	p Value	Clinical only Adjusted FR (95% CI)	p Value
I	Opportunity (none/low, medium/unknown intercourse, high), age, recent oral contraceptive use	0.72 (0.40–1.30)	0.28	0.49 (0.23–1.08)	0.08
II	Model I + recent pregnancy or lactation	0.69 (0.38–1.25)	0.22	0.50 (0.23–1.11)	0.09
III	Model I + ethnicity	0.65 (0.36–1.19)	0.16	0.43 (0.20–0.96)	0.04
IV	Model I + recent pregnancy or lactation + ethnicity	0.59 (0.32–1.09)	0.09	0.43 (0.19–0.97)	0.04

The range of FR for other variables in models including all pregnancies were low/no risk vs. high risk/unknown birth control (FR = 0.11–0.12) and medium risk/unknown intercourse vs. high risk/unknown birth control (FR = 0.20–0.22); maternal age ≥35 vs. <35 years (FR = 0.39–0.42); oral contraceptive use ≤6 months ago vs. >6 months ago or never (FR = 3.76–4.11); pregnancy or lactation ≤6 months ago vs. >6 months ago or never (FR = 0.64–0.75); and other ethnicity vs. white non-Hispanic, Filipino, or other Asian ethnicity (FR = 0.44–0.49).

cycles for nonfab workers but 39.8% of the total for fab workers. The conception rate during high-risk cycles was somewhat lower among fab than nonfab workers (4.4% vs. 6.3%, crude RR = 0.70, 95% CI = 0.36–1.35). Proportion of cycles with unknown birth control or unknown intercourse were similar for fab and nonfab women.

Crude conception rates were determined separately for all pregnancies and for clinically recognized pregnancies among all fab workers, fab supergroups, and nonfab workers (Table III). These rates were only slightly lower among fab than nonfab workers. However, DOPEFILM workers had relatively fewer pregnancies (particularly clinical pregnancies) per 100 cycles than nonfab workers.

Logistic regression models were constructed to compare the fecundability of fab and nonfab workers, while controlling for covariates. Using the "all subsets" procedure, we selected the best models (Table IV). Because we could control for only a limited number of variables at a time, we combined opportunity categories (high risk with unknown birth control risk; medium risk with unknown intercourse; and no risk with low risk) based on similarities in observed and hypothesized risk. The adjusted FR for fab versus nonfab workers ranged from 0.59 to 0.72 for all pregnancies, but fab workers had about half the fecundability of nonfab workers for clinical pregnancies, with adjusted FR ranging from 0.43 to 0.50 (Table IV). In each menstrual cycle, the estimated cumulative crude probability of conception for all pregnancies was somewhat lower, and for clinical pregnancies alone was markedly lower for fab than nonfab women (Figs. 1,2). These estimated probabilities are slightly higher than the crude per-100-cycles conception rates because the estimates took into account the women not observed for the entire study period (six full menstrual cycles).

Crude RR and adjusted FR for women employed in fab supergroups were compared with those for nonfab workers (Table V). When all pregnancies were included, DOPEFILM workers had somewhat lower adjusted FR than nonfab workers

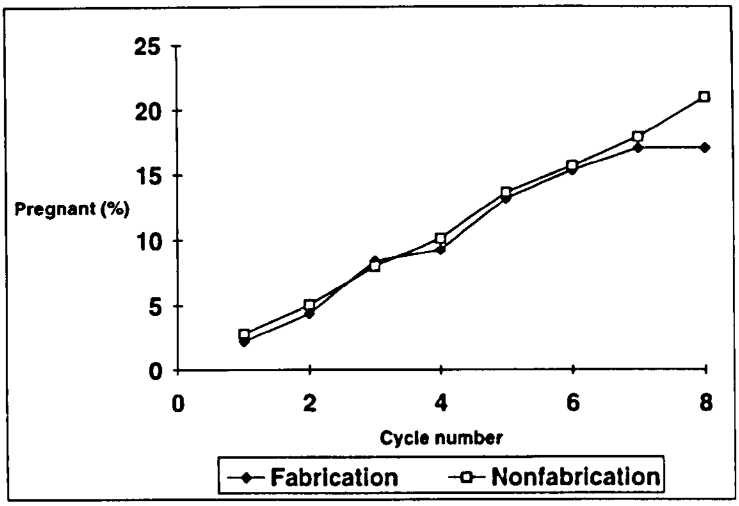

Fig. 1. Modified Kaplan–Meier life-table estimate of cumulative percentage of fabrication (♦) and nonfabrication (□) workers becoming pregnant (including all pregnancies). This method allows for inclusion of menstrual cycle data for women with one or more ineligible study menstrual cycles (e.g., women with >5 days of missing urine samples in a 16-day window surrounding the menstrual period, women not followed for the full six cycles, etc.).

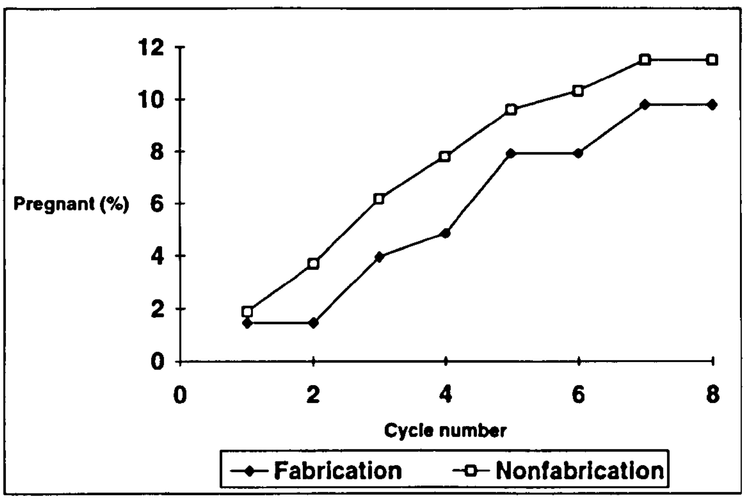

Fig. 2. Modified Kaplan–Meier life-table estimate of cumulative percentage of fabrication (♦) and nonfabrication (□) workers becoming pregnant (including clinical pregnancies only). This method allows for inclusion of menstrual cycle data for women with one or more ineligible study menstrual cycles (e.g., women with >5 days of missing urine samples in a 16-day window surrounding the menstrual period, women not followed for the full six cycles, etc.).

(adjusted FR = 0.61), but results were not significant. However, the adjusted FR for clinical pregnancies was significantly lower among DOPEFILM workers (adjusted FR = 0.22) than among nonfab workers.

Exposure to EGE and fluoride was examined in relationship to conception rates

TABLE V. Crude Relative Risks (RR) for Conception Rates and Adjusted Fecundability Ratios (FR) for All Pregnancies (Clinically Recognized + Early Fetal Losses) and for Clinical Pregnancies Only, by Work Groups, Compared With Nonfabrication Workers

	All pregnancies		Clinical pregnancies only	
Group	Crude RR (95% CI)	Adjusted[a] FR (95% CI)	Crude RR (95% CI)	Adjusted[a] FR (95% CI)
Fabrication				
Masking	1.13 (0.59–2.17)	1.02 (0.52–2.02)	0.89 (0.36–2.18)	0.67 (0.25–1.70)
Dopants and thin film	0.82 (0.37–1.84)	0.61 (0.27–1.40)	0.37 (0.09–1.57)	0.22 (0.05–0.96)
Supervisors and engineers	0.98 (0.31–3.16)	0.86 (0.26–2.87)	1.03 (0.24–4.34)	0.84 (0.19–3.67)
Nonfabrication	1.0	1.0	1.0	1.0

[a]Variables included in model are opportunity for pregnancy (none/low, medium/unknown intercourse, and high/unknown contraception), recent use of oral contraceptives, and maternal age.

TABLE VI. Crude Relative Risks (RR) for Conception Rates and Adjusted Fecundability Ratios (FR) for All Pregnancies (Clinically Recognized + Early Fetal Losses) for Women Exposed to Ethylene Glycol Ethers (EGE) and Fluoride

		Pregnancies			
Agent[a]	Cycles (n)	(n)	(n/100 cycles)	Crude RR (95% CI)	Adjusted FR (95% CI)
EGE	259	3[b]	1.2	0.39 (0.12–1.26)	0.37 (0.11–1.19)
Fluoride	480	14[c]	2.9	0.99 (0.54–1.81)	0.93 (0.49–1.76)
Neither exposure	1,287	38	3.0	1.0	1.0

[a]The two women exposed to both EGE and fluoride are included in both groups.
[b]Includes one clinical pregnancy.
[c]Includes eight clinical pregnancies.

for all pregnancies (Table VI). No analysis was performed for clinical conceptions only because only one clinical pregnancy occurred among women exposed to EGE. Compared with women not exposed to EGE or fluoride, the crude RR of conception was 0.39 for workers exposed to EGE and 0.99 for workers exposed to fluoride. After adjustment for opportunity, age, and recent OC use, somewhat lower fecundability was observed for workers exposed to EGE (adjusted FR = 0.37). Within high-risk cycles, the proportion of nonconceptive cycles increased with increasing exposure to EGE (χ^2 test for trend = 3.25, p = 0.07). In the lowest EGE exposure group, three conceptions were observed—compared with an expected value of 5.2. Although the number of exposed women was small, no conceptions occurred in the medium- and high-exposure groups (expected values 0.6 and 1.4, respectively). For workers exposed to fluoride, the FR was not significantly lower than that for workers exposed to neither fluoride nor EGE (adjusted FR = 0.93).

DISCUSSION

Results of this prospective study suggest that fab workers, and particularly DOPEFILM workers, have a lower probability than nonfab workers of becoming pregnant in each menstrual cycle. These findings are in addition to adverse reproductive effects observed by others, including the higher SAB rates associated with fab work exposures [Beaumont et al., 1995; Swan et al., 1995; Eskenazi et al., 1995; Gold et al., 1995b; Gray et al., 1993; Pastides et al., 1988]. A prospective investigation by Gray et al. [1993] also found reduced fecundity among clean room (fab) workers. The nonsignificant reduced fecundability among EGE-exposed women in our study is independent of the reduced fecundability seen in the DOPEFILM supergroup, because EGE is not used by DOPEFILM workers. These findings are consistent with those of Gray et al. [1993], whose retrospective study showed increased odds of "subfertility" associated with work in processes using EGE at the time of conception. The reduced fecundability in the present study cannot be readily explained by confounding, since we controlled for or examined potentially confounding effects of many variables considered to be related to subfecundability, such as maternal age [Baird et al., 1986] and recent pregnancy or nursing [Baird and Wilcox, 1985].

Women did not enter the study when they started trying to conceive or when they stopped contraception. Thus, their fecundability during the study could have been related to their fertility history. Childless women are more likely to remain in the workforce than women who have had children. Childlessness may be due to subfertility. Therefore, our sample of fab and nonfab women might be less fertile than a sample of all women who have ever worked in the industry. Also, because of "length-biased sampling" [Fletcher et al., 1988], women with short times to conception are most likely to be missed. The question remains as to whether these factors would differ for fab and nonfab women, and thus bias our results. Fab women may have been less likely than nonfab women to become pregnant during the study because they considered their families already complete. In fact, fab women were more likely than nonfab women to have had children (74% vs. 62%) and to have had ≥2 children (45% vs. 37%). Nevertheless, fab women were less likely to use birth control. When we controlled for opportunity for pregnancy, the fecundability of fab women remained lower.

Despite their averaging more children, fab women were more likely to have reported a history of infertility. They also reported not using contraception for longer periods before entering the study than did nonfab women. The number of months without contraception or pregnancy prior to study enrollment should predict lower conception rates during the study, because it indicates lower overall fertility. However, adjustment for this covariate could constitute overcontrol, because prior infertility might also be related to fab work. Among fab women not using contraception at the time of enrollment, 95% had been employed in fab work the entire time they had not used contraception, and all but one had worked in a fab part of the time they did not use contraception. Nevertheless, when we included in the logistic models a variable for the number of months not using contraception prior to enrollment, the adjusted FR for clinical pregnancies rose only slightly for fab workers (0.48 to 0.54) and for DOPEFILM workers (0.24).

Reduced fecundability can reflect perturbations anywhere in the early stages of reproduction, including failures in ovulation, fertilization, or implantation or inadequate development of the conceptus [Hendrickx, 1984]. Higher rates of unrecognized EFL may appear as lowered fecundability [Bloch, 1978; Sharp et al., 1986]. A major strength of this study was the use of endocrine assays to gather complete, objective evidence of both EFL and clinical SAB. The use of endocrine data to determine SAB avoided the potential for reporting inaccuracy and bias inherent in historical studies. In this study, the slightly higher EFL rates among fab workers did contribute to the reduced fecundability for clinical pregnancies [Eskenazi et al., 1995]. Nevertheless, when we examined fecundability for all pregnancies, fab women still had about two-thirds the fecundability of nonfab women. This suggests a direct effect of fab work on conception rates, independent of the higher EFL rates appearing as reduced clinical fecundability.

The etiology of the lower conception rates for fab women in general and for DOPEFILM workers in particular is unknown. However, these lower rates could relate to workplace exposures to specific agents, such as arsenic or EGE, and could be associated with SAB risk. Schaumburg and Boldsen [1992] reported that the mean time to conception was longer for textile workers whose pregnancies ended in clinical SAB than for those whose pregnancies ended in live birth. They suggested that an environmental factor could increase time to conception and SAB risk. One study found reduced fertility in dental hygienists exposed to high levels of nitrous oxide [Rowland et al., 1992], and others reported higher SAB risk among women exposed to anesthetic gases including nitrous oxide [Cohen et al., 1971]. Neither Rowland et al. [1992] nor Schaumburg and Boldsen [1992] included endocrine assays to detect EFLs, and therefore neither could determine whether higher EFL rates contributed to the longer times to pregnancy.

Gold et al. [1995b] found evidence of longer menstrual cycles among women working exclusively in TFII than among women in nonfab jobs ($p = 0.02$ for mean cycle length) and greater variability in cycle lengths of fab than nonfab women ($p = 0.10$ for standard deviation in cycle length/woman). Variable cycle length could make it more difficult for couples to predict ovulation, resulting in lower conception rates. This greater cycle variability also suggests that fab women were more likely to have a combination of long and short cycles, perhaps related to delayed ovulation or to anovulation, respectively [Aksel, 1981; Matsumoto et al., 1979]. Because hormonal assessment of ovulation was not available for nonconceptive cycles, opportunity for pregnancy was crudely determined based on women's reports of intercourse and type of contraceptives used during the wide time interval around the estimated time of ovulation. This method of classifying opportunity for pregnancy, along with possibly inaccurate reporting of information about intercourse or contraceptive use, may have resulted in misclassification of opportunity for pregnancy. Future assessment of hormonal profiles could determine when intercourse occurred relative to ovulation and any abnormalities in ovulatory function.

Although we did have adequate power (about 74%) to detect a relative risk of 0.5 among women with a high risk of pregnancy, the total number of pregnancies in this study was considerably smaller than expected. We predicted that in six cycles about 60% of high-risk women (women not using contraception) [Wilcox et al., 1988] and about 13% of medium-risk women (based on data about employed and unemployed women using condoms or diaphragms) would become pregnant [National Center for Health Statistics, 1980]. Given the number of high- and medium-risk cycles in the study, we expected about 100 *clinical* pregnancies, but only 31 were identified. A number of factors could explain the unexpectedly low number of pregnancies. Reduced fecundability of fab workers is part of the explanation. In addition, the estimates did not take into account the likelihood of reduced fertility among women who had been at risk of conceiving but had not conceived before they entered the study. Selection bias could also have been a factor, because we could not include the clinical pregnancies of eligible women who did not participate in the study.

CONCLUSION

Results of this study suggest that women employed in fabs and in dopant and thin-film processes in particular have fewer pregnancies. Women exposed to EGE also have somewhat lower fecundability than women unexposed to EGE. Baird [1992] suggests that studies examining fecundability are crucial to understanding the reproductive effects of chemical exposures. As she suggests, "the length of time to conception may in fact be a more sensitive indicator of adverse outcomes than other variables that have been more commonly measured, serving in effect as a 'distant early warning' of danger."

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