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Prospective Monitoring of Early Fetal Loss and Clinical Spontaneous Abortion Among Female Semiconductor Workers

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Women who work in silicon wafer fabrication rooms (fabs) have been reported to have an increased risk of spontaneous abortion (SAB). Although previous studies have included only clinically recognized SABs, more than two-thirds of SABs may be clinically unrecognized. To determine whether fab work is associated with SAB, we recruited 152 fab and 251 nonfab workers, who collected urine samples for a 6-month period. Samples were analyzed by immunoradiometric assay for the presence of human chorionic gonadotropin to detect early fetal losses. Approximately 63% of fab and 46% of nonfab pregnancies ended in SAB [adjusted relative risk (RR) = 1.25; 95% confidence interval (CI) = 0.63–1.76]. Similar RR were seen for women who worked in dopant and thin-film processes (adjusted RR = 1.30; 95% CI = 0.51–1.96) or in masking (adjusted RR = 1.30; 95% CI = 0.59–1.84). The four pregnancies among women who worked with ethylene-based glycol ethers ended in SAB.

Key words: miscarriage, occult pregnancy, subclinical pregnancy, wafer fabrication, glycol ethers, semiconductor manufacturing

INTRODUCTION

Pastides et al. [1988] reported that women semiconductor workers in silicon wafer fabrication rooms (fabs) had a higher risk of spontaneous abortion (SAB) than nonfab workers. Among women working in the processes of diffusion (etching, ion implantation, thin film, and epitaxy) and photolithography, the SAB risk was more than double that for nonfab workers. Diffusion workers worked with acids and metals, whereas photolithography workers were primarily exposed to positive photore-

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sists containing glycol ethers, which are known reproductive toxicants [NIOSH, 1991]. Although the diffusion group was initially enlisted as a control group because these women were not exposed to glycol ethers, diffusion workers were found to have higher SAB rates than photolithography workers.

The Pastides et al. [1988] study was limited in several ways, including small numbers of pregnancies and retrospective determinations of recognized SAB. A study by Wilcox et al. [1988] suggested that reliance on recognized SABs could lead to incomplete and perhaps biased SAB assessment. They enrolled 221 women who were attempting pregnancy. These women collected daily urine samples, which were measured for concentrations of human chorionic gonadotropin (hCG) using an immunoradiometric assay (IRMA). These assays identified 198 pregnancies, 22% of which ended before they were recognized (subclinical or early fetal loss) and 9% of which ended in clinically recognized SAB. Thus, more than two-thirds of SABs may be missed if only recognized pregnancies are studied.

The goal of the present study was to examine whether silicon wafer fab workers have an increased risk of SAB compared with nonfab workers and to determine whether specific work processes were associated with increased risk. To avoid the potential for incomplete or biased reporting of SAB, we collected pregnancy information prospectively by measuring hCG in urine samples collected from a cohort of women employed in the semiconductor industry.

METHODS AND MATERIALS

Selection of Participants

Participants included all women aged 18–44 who worked in silicon wafer fab clean rooms at seven sites in five U.S. companies. The comparison group comprised a sample of nonfab women employed at the same sites. The two groups were frequency matched on age (5-year age groups) and ethnicity (non-Hispanic white, black, Hispanic, Asian, other).

Women were eligible to participate in the followup study if they could potentially become pregnant, even if they were not actively trying. Women were considered ineligible if they: were sterilized or had a hysterectomy, were currently pregnant, used oral contraceptives or steroid hormones that interfere with urinary hormone measurements, used an intrauterine device, had a sterilized partner, did not have sexual intercourse within the previous 2 months, or had not menstruated within the previous 2 months. Women also had to have a working freezer (for specimen storage), no plans to leave the company within the upcoming 3 months, and speaking ability in English, Spanish, Vietnamese, or Tagalog.

Recruitment and Data Collection Procedures

Two study investigators (B.E., E.B.G.) conducted informational group meetings scheduled to accommodate the varied work and shifts of participants. The primary purpose of these meetings was to answer questions about the study and to determine each woman's preferred language for interview. To determine eligibility for the prospective study, 3,915 fab and nonfab women were selected to complete self-administered screening questionnaires. This group included 3,480 still employed at the company. Among women still employed, 2,639 (75.9%) completed questionnaires, and 739 (28%) were eligible for the followup study.

Eligible women were advised of the study procedures, the methods for maintaining confidentiality, and the voluntary nature of the study. Two-hour in-person interviews were scheduled with the women who agreed to participate. Interviews included questions about sociodemographic characteristics; current use of medications; medical and reproductive history; consumption of caffeinated or artificially sweetened beverages or alcohol; use of cigarettes; exposure to passive smoke; physical activity at and away from work; current job activities and duration; current work shift; tasks involving potential exposures to selected chemical and physical agents such as solvents, metals, acids, and extremely low-frequency magnetic fields; job-related stress; sources of social support; and sources of medical care and medical insurance. Of the 739 eligible women, 481 (65%) completed baseline interviews. Eligible and interviewed women were similar in gravidity, parity, and history of SAB, although interviewed fab and nonfab women were more likely to be trying to become pregnant at the time of the screening than uninterviewed women.

Participants were asked to collect 5 ml of urine and to complete daily diaries for 6 months, starting the day after the baseline interview. They were instructed to void upon awakening each day and to keep the urine samples frozen until the scheduled monthly kit exchange. Kits were stored in a freezer at a field office and then shipped (about once a month) with dry ice to the endocrinology laboratory at University of California, Davis. Specimens were logged using a bar-code reader and stored in a walk-in freezer at −20°C. A total of 403 women contributed at least one complete cycle of urine samples.

Diaries took the women about 5 minutes to complete each day. In the diaries, women indicated whether menstrual bleeding had begun, whether they had had intercourse, and whether they had used contraception. They also answered questions about daily activities in and out of the workplace. Women were telephoned monthly and at the end of the 6 months to determine any changes in work activities, study eligibility, or pregnancy status. Women who became ineligible during the course of the study were terminated at the end of the following month. Women who became pregnant were interviewed by telephone about pregnancy outcomes soon after the estimated date of confinement.

All data collection instruments were translated into Tagalog and Spanish. Screening questionnaires, diaries, and urine collection instructions were also translated into Vietnamese. The study protocol and all data collection instruments were approved by human subjects institutional review boards at University of California (UC), Berkeley and UC Davis. Participants in the follow up study received paid time off to complete baseline questionnaires and $35 for each completed month of participation. All women in the followup study were eligible for a prize drawing for a trip to Hawaii or a local resort. Other details of methods appear elsewhere [Gold et al., 1995; Eskenazi et al., 1995].

Definition of Spontaneous Abortion

SAB was defined as clinical SAB (recognized by the woman and/or her clinician prior to 20 weeks of gestation) or early fetal loss (EFL, detected by elevated urinary hCG and unrecognized by the woman and/or her clinician). Clinical pregnancies were reported at the monthly interviews. Pregnancy outcomes were reported at monthly interviews or at a pregnancy interview conducted after the estimated date of confinement. All clinical SABs were confirmed by IRMA for hCG.

Laboratory methods for detecting early pregnancy loss appear elsewhere [Lasley et al., 1995]. EFL was determined from timing and elevation of urinary hCG. All samples were screened for hCG by a sensitive but nonspecific immunoenzymetric assay (IEMA). Samples were hCG positive by IEMA if hCG rose above baseline to ≥0.15 ng hCG/mg creatinine (Cr) for two of three consecutive days. The hCG-positive samples were analyzed in duplicate by IRMA, a less sensitive but more specific assay. The discriminator used to detect a rise in hCG was based on the study of Taylor et al. [1992], in which a relative rise from baseline of 0.25 ng hCG/mg Cr was required for three of four consecutive days. Negative hCG values (below −0.1 ng hCG/mg Cr) were obtained in the present study because some sample values fell below the standard control values obtained from urine of prepubescent boys. Therefore, the discriminator was changed to an absolute rise of 0.15 ng hCG/mg Cr for two of three consecutive days for either IRMA or for the arithmetic mean of the duplicate assays. This criterion set the discriminator to more than three times the sensitivity of the assay. Assays were restricted to the 16-day window from 10 days prior through 5 days after onset of menstrual bleeding.

To confirm EFL, the elevated hCG must have occurred during an ovulatory cycle. Any sample with a creatinine level <0.15 mg/ml was ignored. Ovulation criteria were based on a study of 10 ovulatory cycles analyzed for serum progesterone and urinary pregnanediol-3-glucuronide (PdG), a progesterone metabolite [Munro et al., 1991]. In all ovulatory cycles, PdG concentrations were >4 μg PdG/mg Cr for >4 days and corresponded to circulating progesterone levels >5 ng/ml. Our ovulation criteria included a peak of luteinizing hormone (LH) or of estrone conjugate (E_1C, an estrogen metabolite) followed by a rise in PdG of ≥3 μg PdG/mg for ≥4 days. The luteal phase (time from LH peak to next menses) must have been ≥8 days.

To avoid detection of hCG-like material associated with the midcycle LH surge, the acceptable time for appearance of hCG was 8 days after the LH peak (or after the E_1C peak, if there was no LH peak). This criterion was based on data showing the first appearance of hCG in paired blood and urine samples from 20 normal and failing pregnancies [B.L. Lasley, unpublished data].

A computer algorithm was constructed to identify cycles containing a possible EFL based on the above criteria. These cycles were reviewed by the study endocrinologist (B.L.L.), who was blind to exposure status. Among the 21 EFLs identified, a subset of eight were less certain than others because only one of the duplicate IRMAs was elevated and/or the rise in hCG was not seen for ≥3 consecutive days. These uncertain EFLs were omitted from some analyses when indicated.

Exposure Assessment

Exposure assessments were based on women's answers to baseline questionnaires and on industrial hygiene site visits to fabs where participants worked. A three-tiered exposure assessment was employed [Hammond et al., 1995].

At the first tier, women who worked ≥5 hours in fabs were classified as fab workers; they were compared with women who did no fab work (nonfab). Women who worked >0 but <5 hours in fabs were excluded from fab–nonfab analyses.

At the second tier, women were divided into work groups based on tasks they performed. Nonfab workers were divided into office and nonoffice groups. Fab operators were divided into two supergroups: masking (MASK) and dopants and thin film (DOPEFILM). The MASK supergroup included two work groups, photolithography

(PHOTO) and etching (ETCH), and the dopefilm supergroup included two work groups, furnace (FURN) and thin-film and ion implantation (TFII). Because of the small numbers of women in the individual work groups, the unit of analysis was the supergroup. Supervisors/engineers (SUPV/ENGR), which included women working in fab and nonfab areas, were excluded from the nonfab group. For comparisons, women classified into more than one supergroup (n = 4) were counted in both supergroups as relevant. Workers in fab supergroups were compared with all nonfab workers and to office workers alone. Because comparisons of fab with all nonfab and with office workers alone were similar, we present only comparisons with all nonfab workers.

At the third tier, women were grouped based on exposures to specific agents. Each work group had a different set of exposures, but some exposures overlapped work groups. Estimates of each woman's exposures to specific agents (categorized 0–3, none to high) were based on her reported tasks performed, on specific agents used for each task in each fab, and on evaluation of emission factors specific to each fab. Two agents—ethylene-based glycol ethers (EGE) and fluoride—were identified as related to elevated SAB risk in the historical component of the Semiconductor Health Study (SHS) [Swan et al., 1995] and were examined in this study. We compared women exposed to EGE or fluoride with those exposed to neither.

Statistical Analysis

To account for issues of nonindependence of the outcome, all study pregnancies and the first study pregnancy were subjected to separate analyses. Tables present results for first study pregnancies only, with any differences resulting from analysis of all pregnancies noted. Crude relative risks (RRs) (fab vs. nonfab) and 95% confidence intervals (CI) were calculated for clinical SABs, EFLs, and all SABs (clinical SABs plus EFLs) using the Epi Info program [Dean et al., 1990].

Logistic regression was used to control for potential confounders. Because of the small number of SABs, only a limited number of covariates could be included in the logistic model. Therefore, we estimated each woman's prior risk (probability of *clinical* SAB prior to entering the prospective study) by constructing two variables summarizing potential risk factors for clinical SAB. Results from the historical cohort [Beaumont et al., 1995; Swan et al., 1995] provided a relevant source of risk information, because analogous data were collected from women with similar sociodemographic characteristics. Two logistic regression models for risk of clinical SAB were run on historical cohort data with the final set of covariates selected for that cohort (age, smoking, ethnicity, gravidity, education, income) but excluding stress (no comparable data were available in the prospective component) and fab status. The two regression models differed only in their inclusion or exclusion of a variable for history of SAB. Prior clinical SAB increased the risk for a later SAB in previous studies [Kline et al., 1989] and in the historical component of the SHS. However, if the prior SAB occurred while the woman was working a fab, then there was potential for overcontrol if history of SAB was included as a covariate.

Two risk scores were derived from the two logistic models. The risk scores consisted of the prior log odds of clinical SAB and were calculated by applying to prospective cohort data the intercept and coefficients for covariates from historical component logistic models. Each woman's values for the variables were entered into the equation to obtain her risk scores. Each risk score was entered as a single covariate into the logistic regression models developed for the prospective study and served to

adjust the model's intercept for prior risk of clinical SAB. The risk score was entered as a continuous variable, and fab status (0 nonfab, 1 fab) was entered as an indicator variable. State of residence (Utah or California) was included in some models to adjust for possible regional differences. Shift worked (day or other) was included in some models to control for differences in shift among fab and nonfab workers. The risk score effect was reported as the effect of the doubling of the prior odds.

For analysis by supergroup, indicator variables for supergroups replaced fab status in the model. The small numbers of exposed women precluded the use of logistic regression to examine any relationship of EGE or fluoride to SAB.

Logistic regression models produced an adjusted odds ratio (OR) for pregnancy loss. However, because the nonfab SAB rate exceeded 40%, OR did not provide a good estimate of relative risk [Fletcher et al., 1988]. To avoid this distortion, we converted the estimated OR to RR by choosing as a "reference risk" (R_{NF}) the crude rate for SAB in the nonfab group, 0.47. The reference odds (D_0) corresponding to the reference risk were calculated, that is, $D_0 = R_{NF}/1 - R_{NF}$. We then calculated the adjusted odds in the fab group (D_1) by multiplying the reference odds (D_0) by the adjusted OR from the logistic regression ($D_1 = OR\ H\ D_0$). The resulting fab odds were converted to an adjusted fab risk (R_F), that is, $R_F = D_1/(1 + D_1)$. Last, we calculated the adjusted RR as $RR = R_F/R_{NF}$.

Eighteen clinical pregnancies were reported during baseline interviews but had not been reported on the screening questionnaires. Presumably, these pregnancies occurred during the approximately 40 days (M± SD = 42± 28 days) which elapsed between screening and interview. (This time period did not differ for fab and nonfab women.) Thus, no urine specimens were collected during this interval and thus, if an EFL occurred we would not have detected it at the time that the EFL was likely to have occurred. We used a modified Kaplan–Meier fetal life-table analysis to include these pregnancies [Samuels, 1984]. The life-table analysis allowed for adjustment of gestational age at entry and at termination of each pregnancy. Cumulative SAB rate curves were based on computation of cumulative loss rates at each gestational age (measured in days, up to 140, from the last menstrual period). A pregnancy was first included as at risk on the first day it was observed and was removed from the at-risk sample when the pregnancy terminated through SAB or therapeutic abortion. Pregnancies viable at 20 completed weeks were considered censored. Because ectopic pregnancies were not at risk for SAB, they were excluded from these analyses.

Cumulative loss rates, adjusted for the risk scores, were constructed from the SAS proportional hazards regression procedure PROC PHREG (Version 6.07, SAS Institute).

RESULTS

During the prospective followup, 52 women (19 fab, 33 nonfab) became pregnant (Table I). Four of these women (one fab, three nonfab) had two pregnancies, the first an SAB and the second a live birth (n = 3) or an induced abortion (n = 1), yielding a total of 56 pregnancies. One other woman became pregnant, but this pregnancy was excluded from fab–nonfab analyses because she worked <5 hours in a fab. Fewer fab than nonfab pregnancies ended in live births. Considering only the first study pregnancy and clinical pregnancies (excluding EFL, therapeutic abortion,

TABLE I. Crude Relative Risks (RR) and 95% Confidence Intervals (CI) for Pregnancy Outcomes in Fabrication (Fab) and Nonfabrication (Nonfab) Workers (First Study Pregnancy)

	Fab (n = 19)[a]		Nonfab (n = 33)[a]		Crude RR
Outcome	n	%	n	%	(95% CI)
Live births	5	26.3	18	54.5	
Ectopic	1	5.3	0	0	
Therapeutic abortion	1	5.3	0	0	
Spontaneous abortion	12	63.2	15	45.5	1.39 (0.84–2.31)
Clinical abortions (% of pregnancies)	3	(15.8)	3	(9.1)	1.74 (0.39–7.76)[b]
Early fetal losses (% of pregnancies)	9[c]	(47.4)	12[c]	(36.4)	1.30 (0.68–2.51)

[a]Four women (one fab, three nonfab) had one other pregnancy; three ended in live births, and the fourth ended in a therapeutic abortion.

[b]Considering clinical pregnancies only, RR = 2.10 (95% CI = 0.51–8.62).

[c]Three of the fab early fetal losses (EFLs) and five of the nonfab EFLs were considered less certain. Excluding these EFLs would change the overall proportion of spontaneous abortions (SABs) to 56% for fab and 36% for nonfab women and the RR for SAB to 1.58 (95% CI = 0.82–3.04). The proportion of EFL would change to 38% for fab and 25% for nonfab women with an RR of 1.50 (95% CI = 0.61–3.69).

and ectopic pregnancy), 63% of fab pregnancies and 86% of nonfab pregnancies ended in live births (crude RR = 0.73; 95% CI = 0.41–1.28).

Among the 27 SABs, 21 were EFLs identified by laboratory assays for hCG in urine (Table I). Overall SAB rates for first study pregnancies were slightly higher for fab than nonfab pregnancies (63% vs. 46%, crude RR = 1.39). Although numbers were very small, fab pregnancies resulted in proportionally more clinical SABs than nonfab pregnancies (30% vs. 14%, crude RR for clinical pregnancies only = 2.10) and slightly more EFLs (47% vs. 36%, crude RR = 1.30). Including all study pregnancies did not appreciably alter results for SAB (60% fab vs. 50% nonfab), for clinical SAB alone (27% fab vs. 13% nonfab), or for EFL (45% fab vs. 33% nonfab). No differences were statistically significant.

Evaluation of Potential Confounders

Risk score I (including the variable for history of SAB) predicted a median clinical SAB risk of 12.6% for nonfab workers and 19.4% for fab workers. This suggested that fab workers had a higher prior risk for clinical SAB. Indeed, women with risk score I values above the median were 1.5 times as likely to have had an SAB during the prospective followup than those below the median (95% CI = 0.74–3.16).

Most individual variables in the risk score were related to higher SAB rates in the prospective study. SAB rates were higher in women who were older, less educated, and from Utah (Table II). Nonfab SAB rates were lowest in white, non-Hispanic women. Fab SAB rates were higher among smokers; however, only three nonfab smokers became pregnant, and they had no SABs. Fab women with high household income had higher SAB rates than low-income women, whereas nonfab women with high household income had lower SAB rates than lower-income women. SAB rates were also higher in multigravid and multiparous women (not shown) and in women with a history of SAB.

Relationship of Fabrication Work and SAB

The multivariate logistic models for fab work and SAB, controlling for risk score I or II, gave results similar to those in the unadjusted analyses (Table III).

TABLE II. Crude Spontaneous Abortion (SAB) Rates Among Fabrication and Nonfabrication Employees, by Stratum of Demographic Variables (First Study Pregnancy)

	Fabrication (n = 19)			Nonfabrication (n = 33)		
Covariate	Pregnancies (n)	SAB (n)	SAB rate (%)[a]	Pregnancies (n)	SAB (n)	SAB rate (%)[a]
Age (years)						
<35	13	7	53.9	26	10	38.5
≥35	6	5	83.3	7	5	71.4
Ethnicity						
White, non-Hispanic	12	8	66.7	17	6	35.3
Filipino, other Asian	4	2	50.0	11	6	54.5
Other	3	2	66.7	5	3	60.0
Location						
California	9	5	55.6	28	12	42.9
Utah	10	7	70.0	5	3	60.0
Education (grade completed)						
≤12	8	6	75.0	7	5	71.4
13–15	8	4	50.0	16	8	50.0
≥16	3	2	66.7	10	2	20.0
Annual household income						
<$40,000	13	7	53.9	7	5	71.4
≥$40,000	6	5	83.3	26	10	38.5
Cigarettes/day						
0	13	7	53.9	30	15	50.0
≥1	5	4	80.0	3	0	0
Gravidity						
0	1	0	0.0	6	1	16.7
≥1	18	12	66.7	27	14	51.9
Prior SAB						
0	12	7	58.3	27	11	40.7
≥1	4	3	75.0	2	2	100.0

[a]SAB rate = SAB/pregnancies in stratum.

Models controlling for employment state (California vs. Utah) or shift worked did not appreciably change results and are not presented. Depending on the model and on whether the first study pregnancy or all pregnancies (not shown) were included, the adjusted RR for SAB ranged between 1.16 (95% CI = 0.51–1.74) and 1.33 (95% CI = 0.73–1.79). No adjusted RR was statistically significant. When we excluded the eight less certain occult pregnancies, RR for fab status remained unchanged (RR = 1.32, 95% CI = 0.65–1.83, controlling for risk score I, and RR = 1.36, 95% CI = 0.70–1.84, controlling for risk score II).

Supergroups and SAB

SAB rates for fab supergroups were based on very small numbers of pregnancies, especially in the SUPV/ENGR group (n = 3) (Table IV). Compared with nonfab workers, the crude RR for MASK workers was 1.47 for first study pregnancies, whereas the crude RR for DOPEFILM workers was slightly higher at 1.57. No RR was significant. When all pregnancies were included, results did not change markedly. Crude SAB rates were similar among nonfab nonoffice and office workers (50.0% vs. 42.9% for first study pregnancies and 42.9% vs. 40.9% for all study pregnancies).

TABLE III. Multiple Logistic Regression Models [Adjusted Relative Risks (RR) and 95% Confidence Intervals (CI)] for Spontaneous Abortion (SAB) Among Fabrication and Nonfabrication Workers (First Study Pregnancy) (n = 52)

	Adjusted RR	(95% CI)	p value
Model I			
Fabrication vs. nonfabrication	1.25	(0.63–1.76)	0.46
Risk score I[a]	1.46	(1.01–1.79)	0.05
Model II			
Fabrication vs. nonfabrication	1.30	(0.69–1.79)	0.35
Risk score II*	1.48	(0.97–1.81)	0.07

[a]Risk scores combine the intercept and coefficients from the logistic model derived from the historical cohort component as follows:

Risk score I = −2.5508 + (0.8984 × Age) + (0.3515 × Smoking) + (−0.3263 × Ethnicity 1) + (0.1665 × Ethnicity 2) + (−0.3485 × Gravidity) + (0.8137 × History of SAB) + (0.4623 × Education 1) + (−0.2244 × Education 2) + (0.1544 × Household Income).

Risk score II = −2.2243 + (0.9018 × Age) + (0.3125 × Smoking) + (−0.4344 × Ethnicity 1) + (0.1146 × Ethnicity 2) + (−0.6268 × Gravidity) + (0.4226 × Education 1) + (−0.2546 × Education 2) + (0.1299 × Household Income).

Age = 0 if <35 years, = 1 if ≥35 years; Smoking = 1 if yes, = 0 if no. Ethnicity: "white" is the comparison group: ethnicity 1 = 1 for Filipino and other Asians, = 0 if otherwise, Ethnicity 2 = 1 for black, Hispanic and other, = 0 if otherwise; Gravidity = 0 if gravidity = 0, = 1 if gravidity ≥1; SAB History = 0 if no prior SAB, = 1 if any prior SAB; Education: ≥12 years is the comparison group: Education 1 = 1 if 13–15 years, = 0 if otherwise, Education 2 = 1 if ≥16 years, = 0 if otherwise; Household Income = 0 if <$40,000, = 1 if ≥$40,000 per year.

Risk score II includes all variables in risk score I except SAB history. RR and CI are those associated with a doubling of "prior" odds of SAB.

Thus, results were similar when fab workers were compared with all nonfab workers or with office workers alone.

Multivariate logistic regression models were constructed to examine SAB risk in fab supergroups. (The SUPV/ENGR group was not considered because of the small number of pregnancies). Supergroup vs. nonfab RRs were adjusted for risk score I (Table IV). For the first study pregnancy, the adjusted RR of SAB was 1.30 for MASK and 1.39 for DOPEFILM workers, while the adjusted RR for all pregnancies was 1.31 for MASK and 1.52 for DOPEFILM (not shown). No RR achieved significance. Results of the models were similar when we controlled for risk score II or employment state and when we used office workers instead of all nonfab workers as the comparison group.

Specific Exposures and Spontaneous Abortion

Of the 52 women who became pregnant, only three were exposed to EGE (Table V), but all three had SABs after working in the group with the lowest EGE exposures. Two of the three were also exposed to fluoride. Of the 14 pregnant women exposed to fluoride, eight had SABs (57%), and five worked in the group with the lowest category of fluoride exposure. Small sample size precluded multivariate analyses.

Fetal Life-Table Analyses

Another 18 pregnancies (five fab, 13 nonfab) began before the baseline interview and were not included in the prospective followup. Four of these (three nonfab,

TABLE IV. Crude and Adjusted Spontaneous Abortion (SAB) Rates and Relative Risks (RR) and 95% Confidence Intervals (CI) for Fabrication (Fab) Groups* Compared With Nonfabrication (Nonfab) Workers (First Study Pregnancy)

Group	Pregnancies (n)	SAB (n)	Crude SAB rate (%)	Crude RR (95% CI)	Adjusted[a] RR (95% CI)	p value
Fab[b]						
MASK	12	8	66.7	1.47 (0.85–2.54)	1.30 (0.59–1.84)	0.35
DOPEFILM	7	5	71.4	1.57 (0.86–2.86)	1.39 (0.51–1.96)	0.35
SUPV/ENGR	3	2	66.7	1.47 (0.61–3.55)	N/A	—
Nonfab[c]	33	15	45.5	1.0	1.0	—

*MASK, masking; DOPEFILM, dopants and thin film; SUPV/ENGR, supervisors/engineers.
[a]Multivariate logistic regression models controlling for risk score I (including age, ethnicity, education, smoking, gravidity, income, SAB history).
[b]Two women who worked in both MASK and DOPEFILM supergroups were counted in both.
[c]Excludes SUPV/ENGR working in nonfab areas.

TABLE V. Spontaneous Abortion (SAB) Rates and Crude Relative Risks (RR) for Exposures to Specific Agents (First Pregnancies Only)

Agent[a]	Pregnancies (n)	SAB (n)	Crude SAB Rate (%)	Crude RR
Ethylene glycol ethers	3	3	100.0	2.00 (1.46–2.75)
Fluoride	14	8	57.1	1.14 (0.66–1.99)
Neither	38	19	50.0	1.00

[a]The two women exposed to both ethylene glycol ethers and fluoride are included in both groups.

one fab) ended in SAB, and one ended in an ectopic pregnancy (nonfab). Only one of these 18 women was exposed to EGE, and she also had an SAB. Thus, including all study pregnancies all four pregnant women exposed to EGE had SABs. Fetal life-table analyses allowed us to include these 18 pregnancies with those in the prospective followup study [Samuels, 1984]. The estimated cumulative loss rate was 46% in nonfab pregnancies and 66% in fab pregnancies (Fig. 1). The greatest difference in the cumulative fetal loss rate between fab and nonfab pregnancies occurred between 30 and 40 days of gestation. After this period, there was no apparent difference in the fetal loss rate. Using a Cox proportional hazards model, we compared gestational age-specific SAB rates of fab and nonfab women. The adjusted risk was 1.57 (95% CI = 0.76–3.24) controlling for risk score I, with similar results controlling for risk score II.

DISCUSSION

Results of this prospective cohort study suggest that SAB risk is slightly elevated in fab workers (adjusted RR = 1.25) but does not differ significantly from SAB risk for nonfab workers. Small numbers of observed pregnancies led to low power to detect significant differences in SAB rates. The lack of a significant result does not contradict the difference in clinical SAB rates observed by Pastides et al. [1988] or in the historical component of the SHS [Beaumont et al., 1995; Swan et al., 1995]. In fact, the magnitude of the nonsignificant elevation in SAB rate among fab workers in this study is consistent with previously reported risk ratios. Unlike the historical component, in which MASK workers had higher SAB rates than other fab workers [Beaumont et al., 1995; Swan et al., 1995], we observed little difference in adjusted

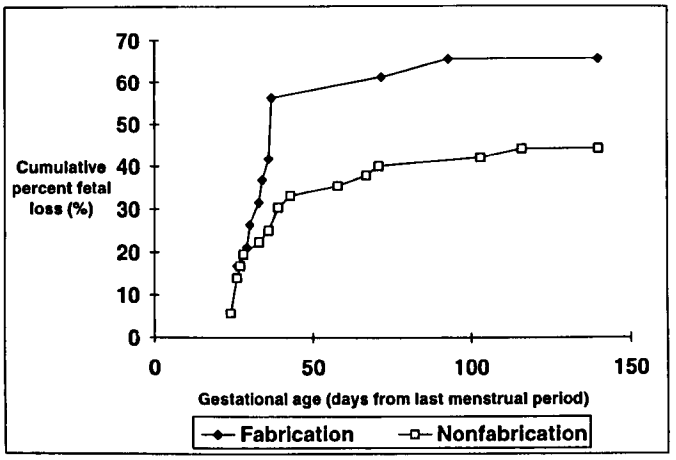

Fig. 1. Unadjusted cumulative fetal loss curves for fabrication (♦) and nonfabrication (□) workers. These curves include the 18 women already pregnant at the baseline interviews for whom an early fetal loss would not have been detected. The curves use fetal life-table methods to account for gestational age of the fetus at the time the women entered the study.

RR for MASK (adjusted RR = 1.30) and DOPEFILM workers (adjusted RR = 1.39) when compared with nonfab workers.

Most previous reports included only clinically recognized pregnancies. Despite the small number of clinical pregnancies in the present study, the crude RR for clinical SAB exceeded 2.0, a finding consistent with previous reports. Furthermore, the 14% rate of clinical SAB among nonfab workers in the prospective study was in the expected range of 10–15% [Kline et al., 1989] and was similar to the 10% crude clinical SAB rates reported for nonfab workers in the historical component. EFLs, which made up the bulk of our SABs, may differ biologically from clinical SABs, and thus results including all SABs may not be comparable to those of other studies.

Only one other current investigation [Gray et al., 1993] included EFL in the evaluation of SAB among semiconductor workers. Its results are noteworthy in their similarity to the present study. Preliminary findings in this IBM study revealed crude RR of 1.2 for all SABs and 2.1 for clinical SABs. As in the present study, these results were not significant. The SAB rate in fab workers was 57%, compared with 48% among women in nonfab jobs. Among pregnant woman exposed to EGE, four of the six in the IBM study had miscarriages, compared with four of the four in the present study.

One strength of our study was the use of endocrine assays to gather complete, objective information about EFL and clinical SAB. Use of endocrine data avoided the potential problems of reporting inaccuracies and bias inherent in historical studies. Another strength was exposure assessment based on data gathered before and during the pregnancy rather than on historical data or subjects' recall. The industrial hygienists who classified exposures were blind to outcomes, and pregnancy determinations were also made without knowledge of exposures. Another strength of the study was our control for confounding using a risk score despite the small sample size.

SAB is not a homogeneous outcome—about 60% of clinical abortions are chromosomally normal, and the remaining 40% are comprised of chromosomal anomalies [Kline et al., 1989]. The etiologies of chromosomally normal and abnormal SAB may be quite different. Chromosomally abnormal SAB may result from a heritable genetic mutation in the gamete or from exposure to a mutagen, whereas chromosomally normal SAB may be caused by maternal factors—factors that affect the viability of the fetus or the uterine environment [Kline et al., 1989].

The present study did not determine whether SABs were chromosomally normal or abnormal. However, fetal life-table analysis indicated that SABs occurred earlier in fab than nonfab women. The maximum difference in SAB rates of fab vs. nonfab women occurred between 30 and 40 days of gestation. This result is similar to that reported by Pastides et al. [1988], who found that fetal losses among diffusion workers occurred on average at 6.8 weeks, compared with an average of 11.5 weeks in unexposed workers and 11.0 weeks in the photolithography group. However, SABs in the present study included both clinical events and EFLs; had we not identified EFLs, these early differences probably would not have been seen. Kline et al. [1989] reported that approximately 75% of SABs occurring prior to 40 days of gestation in the New York City study were chromosomally normal.

The EFL rate of 36% for nonfab workers in the present study was somewhat higher than the 22% rate reported by Wilcox et al. [1988] for a population of primarily white, educated volunteers attempting to become pregnant, and much higher than the 8% rate reported by Whittaker et al. [1983] for a clinical population of English women. It is possible that the rate of EFL observed in this study is higher than in Wilcox et al.'s [1988] study due to differences in the age of the population (approximately 90% of Wilcox et al.'s sample was younger than 35 years vs. approximately 60% of ours) and sociodemographic characteristics, However, when we eliminate the eight less certain pregnancies, the EFL rate falls to 26% in nonfab women, and thus this rate is very similar to the rate reported by Wilcox et al. [1988]. The nonfab EFL rate was lower than the >50% rate in a sample of patient volunteers [Edmonds et al., 1982]. However, nonfab rates for clinical SAB and EFL were quite similar to those reported by Miller et al. [1980]. These studies by Edmonds et al. [1982] and Miller et al. [1980] used an assay which may have been more likely to identify false positives [Baker et al., 1987].

The small number of pregnancies made it impossible to control for more than a limited number of covariates in the regression models. Hence, risk scores (prior log odds of clinical SAB) were constructed by applying the coefficients of the logistic models of the historical component to covariates of women in the prospective component. These variables were selected for the historical component based on previous literature relating them to clinical SAB. Therefore, it is reassuring that risk scores were at or near statistical significance ($p = 0.05–0.17$). However, these analyses did not control for risk factors for EFL, which may differ from those for clinical SAB. Thus, uncontrolled confounding could explain our findings.

A major limitation of this study is its small sample size and the consequent low power. For example, the power to detect a significant increase in SAB rate from 40% to 70% (an RR of 1.75) at $\alpha = 0.05$ was <50% for a two-sided test and 60% for a one-sided test. The power to detect a significant difference was even lower for subcategories of fab workers. A harmonic mean of 39 pregnancies per group would have been required to detect a shift from 40% to 70% with an α of 0.05 and 80%

power in a crude two-sample test [Fleiss, 1981]. A larger number would have been required to offset risk score differences. The life-table analyses increased the power to detect a significant difference by permitting inclusion of 18 clinical pregnancies conceived prior to the baseline interviews. However, counting all pregnancies including the 18 prior conceptions yielded 25 fab and 49 nonfab pregnancies, for a harmonic mean of 33 per group. The lower conception rates in fab workers accounted in part for the low numbers [Eskenazi et al., 1995].

CONCLUSION

This prospective investigation of SAB found a slight but not significantly higher risk for SAB in fab than in nonfab workers. This higher risk was not specific to a work group, although it is noteworthy that the four pregnant women who used positive photoresists containing ethylene-based glycol ethers had SABs. These results are consistent with the larger historical study of clinical SAB [Beaumont et al., 1995; Swan et al., 1995].

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