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Epidemiologic Methods for Prospective Assessment of Menstrual Cycle and Reproductive Characteristics in Female Semiconductor Workers

Ellen B. Gold, PhD, Brenda Eskenazi, PhD, Bill L. Lasley, PhD, Steven J. Samuels, PhD, Marianne O'Neill Rasor, MA, James W. Overstreet, MD, PhD, and Marc B. Schenker, MD, MPH

Methods were developed to assess potential adverse effects of semiconductor fabrication work in a prospective study of reproductive health. All women aged 18–44 years who worked in seven silicon-wafer fabrication sites in five companies and a frequency-matched sample of women in nonfabrication jobs were included. Among 3,480 selected for screening, 2,639 (75%) completed a self-administered questionnaire to identify women at risk of pregnancy. Among the 739 (28%) eligible women, 481 (65%) completed baseline interviews and 402 (83.6%) completed at least one menstrual cycle of follow-up by providing daily diaries and daily urine samples. Menstrual cycle characteristics were assessed from questionnaires and diaries. Urine samples were assayed for reproductive hormones to identify conceptions. The usual cycle length recalled at baseline was 28 days. The mean cycle length (MCL) recorded in diaries was 29 days, with greater dispersion than at baseline. The median of the MCL from diary data was 28 days for women reporting regular cycles at baseline but 34 days for women reporting irregular cycles at baseline, and the median standard deviation in cycle length per woman was 2.5 days and 7.5 days, respectively. The prospective method, while expensive and labor intensive, showed good compliance. Nevertheless, recall also provided reasonably accurate estimates and distinguished women with regular and irregular cycles.

Key words: menstrual cycle, reproduction, epidemiology, semiconductor manufacturing, occupational exposure

Division of Occupational/Environmental Medicine and Epidemiology, Department of Internal Medicine, School of Medicine, and Institute of Toxicology and Environmental Health, University of California, Davis (E.B.G., S.J.S., M.O.R., M.B.S.).
Maternal and Child Health and Epidemiology Programs, School of Public Health, University of California, Berkeley (B.E.).
Division of Reproductive Biology, Department of Obstetrics and Gynecology, School of Medicine, and Institute of Toxicology and Environmental Health, University of California, Davis (B.L.L., J.W.O.).
Address reprint requests to Ellen B. Gold, PhD, Division of Occupational/Environmental Medicine and Epidemiology, ITEH, University of California, Davis, CA 95616-8648.
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INTRODUCTION

Increasing numbers of women have entered the workforce over the past 30 years, many in occupations potentially hazardous to their reproductive health in terms of physical, chemical, or psychological stressors or exposures. Standards for workplace exposures are often based on levels associated with acute effects and are rarely based on their reproductive effects. Because the reproductive system may be compromised at lower exposure levels, reproductive health effects may be sensitive indicators of adverse occupational exposures. The emotional impact and prevalence of menstrual dysfunction, infertility, and abnormal pregnancy are sources of concern for a large segment of the working population. For these reasons, occupational epidemiologists have turned their attention to adverse effects of workplace exposures on reproductive health.

An optimal design is needed for these studies. Case-control studies, while generally less labor intensive and expensive than historical cohort or prospective studies, raise legitimate concerns about recall bias and validation of past exposures. These problems are somewhat mitigated in historical cohort designs, which still present difficulties in identifying former workers, tracing subjects, and validating past outcomes and exposures. Prospective designs produce the most accurate exposure assessment and outcome determination but involve the potential problems of subject recruitment, compliance, and dropout. This article describes methods and methodological issues that arose during and some comparisons of observed and self-reported menstrual cycle characteristics from a prospective study of potential adverse effects of semiconductor fabrication work on women's reproductive health.

METHODS

Sample Selection

Site. Seven sites from five companies in three metropolitan areas of two states were selected. These sites were chosen because they offered an adequate number of subjects and geographic proximity to study investigators but were not confined to a single state.

Subjects. Company human resources personnel provided lists of all full-time, noncontract employees at each site. Lists indicated age, ethnicity, job title (or title and department), work location, and work status—fabrication room (fab) or nonfab worker. All women fab workers aged 18–44 years were selected. Initially, if the woman's fab-nonfab status was unknown, she was included in the fab group, since these women were likely to have performed some fab work, and, if they did not, the bias would be conservative. After in-depth interviews of eligible women enrolled in the follow-up portion, unknown status was clarified for these women. Fab women at each plant were then stratified by 5-year age groups and ethnicity (non-Hispanic white, black, Hispanic, Asian, other), and the proportions of the total in each stratum were determined.

By frequency matching to these strata, a sample of nonfab women aged 18–44 years was selected as a comparison group. At two sites, this procedure resulted in selection of all women aged 18–44, with an approximate 1:1 match of fab:nonfab. At the remaining five sites, a frequency-matched sample was randomly selected from among nonfab women within the 5-year age-group and ethnicity strata. At these five

sites, nonfab women were oversampled by 25% in anticipation of potentially different rates of participation and eligibility.

Group meetings. Company managers and direct supervisors assisted in scheduling informational group meetings for women selected for the study (Fig. 1). Held on company time, these meetings were scheduled days, evenings, and nights to accommodate work and shift schedules. In advance of the meetings, study publicity posters were displayed at the plants, and company management sent employees a letter notifying them of the study and encouraging their participation. Women selected for the study sample were then sent a letter from the study investigators informing them of their scheduled group meeting time.

The study investigators (E.G., B.E.) conducted 273 group meetings with workers. Meetings included a 15- to 20-min slide presentation explaining the purpose (to study the health, particularly reproductive health, of women working in the semiconductor industry) and methods of the study and a 10-min question-and-answer period. Women also received pamphlets (in English, Tagalog, Spanish, or Vietnamese) describing the study and providing the telephone number of the study field office that the women could call for information. At group meetings, each woman was asked to complete a one-page survey indicating her preferred language for reading and speaking, and information about her work schedule, supervisor, mail stop, and work telephone number. This information was used to arrange for future contacts and scheduling, and for bilingual interviewers, if necessary.

Data Collection

Screening. Following the group meetings, women were scheduled through their managers and supervisors for 30-min appointments to complete a self-administered *screening questionnaire,* available in English, Spanish, Tagalog, or Vietnamese. Prior to completing the questionnaire, women read and signed an informed consent statement in the language of their choice. Questionnaires were completed on company time, in a private room, without management present. Approximately 25% of the women (those recruited toward the end of the study) completed the screening questionnaire immediately after attending the group meeting. The four-page screening questionnaire was designed primarily to determine eligibility (see later) for the follow-up portion of the study.

If a questionnaire appointment could not be scheduled after three attempts, a screening questionnaire and a prepaid return envelope was mailed to the woman's home. Women who did not return this questionnaire were sent a second, final mailing; women who were to be screened near the end of the study's recruitment period were also sent a $3 check with the questionnaire to encourage completion. Questionnaires returned by mail were reviewed for eligibility, and all eligible women were telephoned to confirm their eligibility and willingness to participate in the follow-up study.

Women whose questionnaire responses made them eligible (see later) for the follow-up were recruited at the screening session. A trained staff member met in private with each eligible woman to explain the follow-up procedures, the methods for maintaining confidentiality, and the voluntary nature of the study. If the woman agreed to participate, she was scheduled through her supervisor for a 2-hr appointment to complete an in-depth, in-person baseline interview on company time.

Eligibility criteria. Criteria for the follow-up study were developed to include

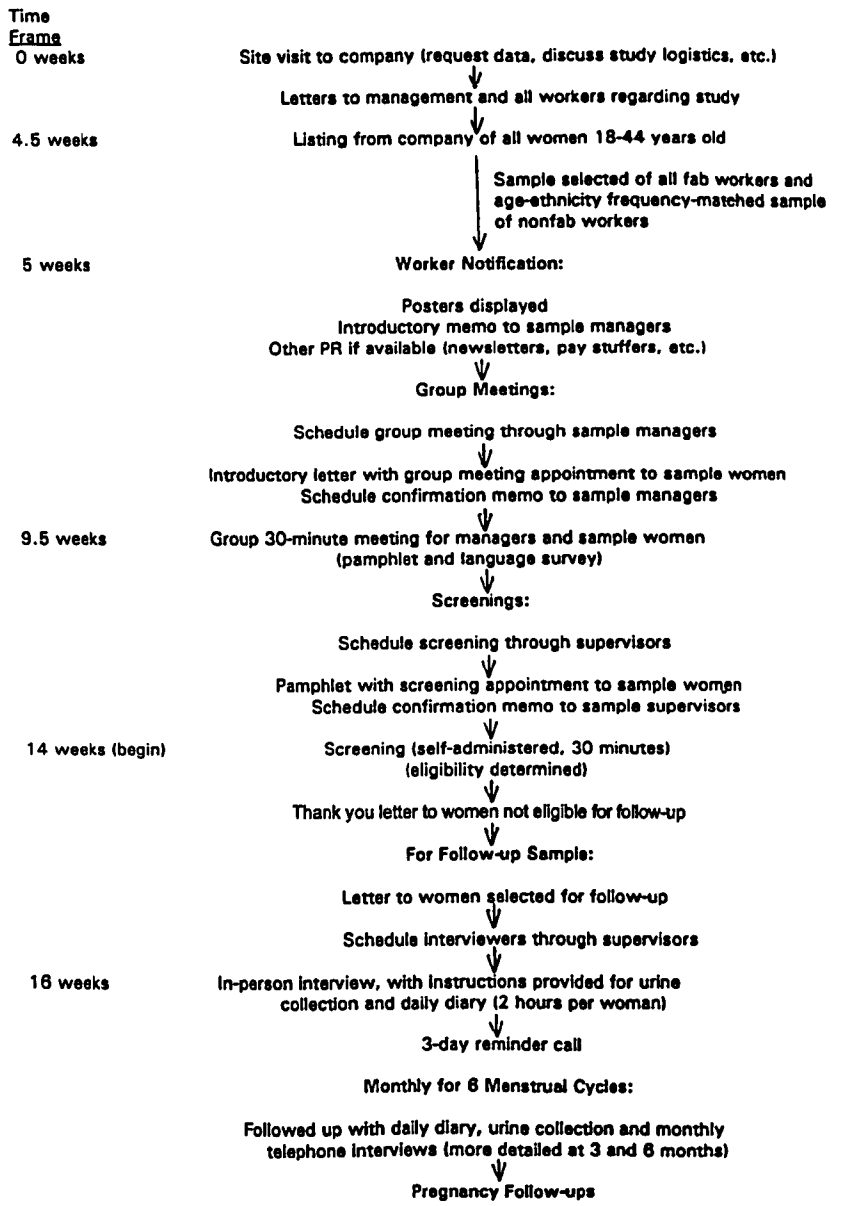

Fig. 1. Flow diagram of contacts in the prospective component of the Semiconductor Health Study (SHS). SIA, Semiconductor Industry Association.

women with a potential to conceive, even if they were not necessarily trying or allowing themselves to become pregnant. Criteria were (1) age 18–44 years; (2) not currently pregnant; (3) menstruated within the previous 2 months; (4) had sexual intercourse within the previous 2 months; (5) not sterilized; (6) not using oral contraceptives; (7) not using an intrauterine device; (8) partner not sterilized; (9) not

using steroid hormones (which interfere with urinary hormone assays); (10) had a working freezer (for storage of urine specimens); (11) not planning to leave the company within the next 3 months; and (12) ability to speak English, Spanish, Vietnamese, or Tagalog. The first eight criteria directly affected the woman's risk of pregnancy; items 9–10 affected reliability of laboratory assays to detect conceptions; and items 11–12 were included for practical reasons. To maintain confidentiality of participant data, eligibility criteria were not divulged to company personnel or to study participants.

Follow-up. After eligible women read and signed the informed consent statement for the follow-up study, *baseline interviews* were administered to them on company time, in private, by a study interviewer (bilingual if necessary) and took 60–90 min. Since few Vietnamese women were eligible and willing to participate, the baseline interviews were administered in English, Tagalog, or Spanish. The interview consisted predominantly of closed-ended questions (but also included a few open-ended questions) about sociodemographic characteristics, current drug use (prescription, nonprescription, illicit), chronic illnesses, smoking history, passive smoke exposure, current average home use of electrical appliances, usual menstrual cycle characteristics, pregnancy history, history of infertility, physical activity, current consumption of caffeinated or artificially sweetened beverages or alcohol, history of gynecologic disorders or surgery, home or office use of video display terminals, current job activities and duration, current work shift, operation of machinery and tools involving exposure to chemicals (including solvents, metals, acids) or extremely low frequency magnetic fields, ergonomic aspects of workplace activities, job-related stress, sources of social support, sources of medical care, and type of medical insurance. The interview also included questions about demographic characteristics of the woman's partner, his smoking or alcohol consumption, and his employment.

One innovative feature of the follow-up was the *daily diary* (Fig. 2), used to obtain critical daily information that might change over time. Although previous investigators [Treloar et al., 1967; Harlow and Matanoski, 1991; Wilcox et al., 1988] used diaries, theirs contained very few questions, usually focusing on menstruation and intercourse. The daily diary for the present study consisted of two parts: the diary envelope with the questions and the diary insert with spaces to write answers each day. The diary envelope was an outer, two-sided 8 × 8-inch envelope on card stock, with a vertical opening at one end for the diary insert.

Each diary insert card had a column of answer boxes for each day of the month. To help the woman fill in information for the correct day, each side of the diary envelope had a vertical cutout large enough to expose one column (one day) of answer boxes. Designed to slide through the diary envelope to expose only the day for which questions were being answered, diary insert cards showed the day and date for each day of the month at the top. Cards had horizontal lines for each question and vertical lines separating days of the month.

One side of the diary envelope had nonworkplace questions; the other had work-related questions to be answered only on work days. Non–work-related questions covered daily urine collection, menstrual bleeding, premenstrual symptoms, prescription or nonprescription drug use, illnesses, sexual intercourse, contraceptive use, cigarettes smoked, consumption of caffeinated or alcoholic beverages, and amount of vigorous physical activity. Workplace questions included hours worked, time spent standing, time spent at inspection equipment with eye pieces, time spent

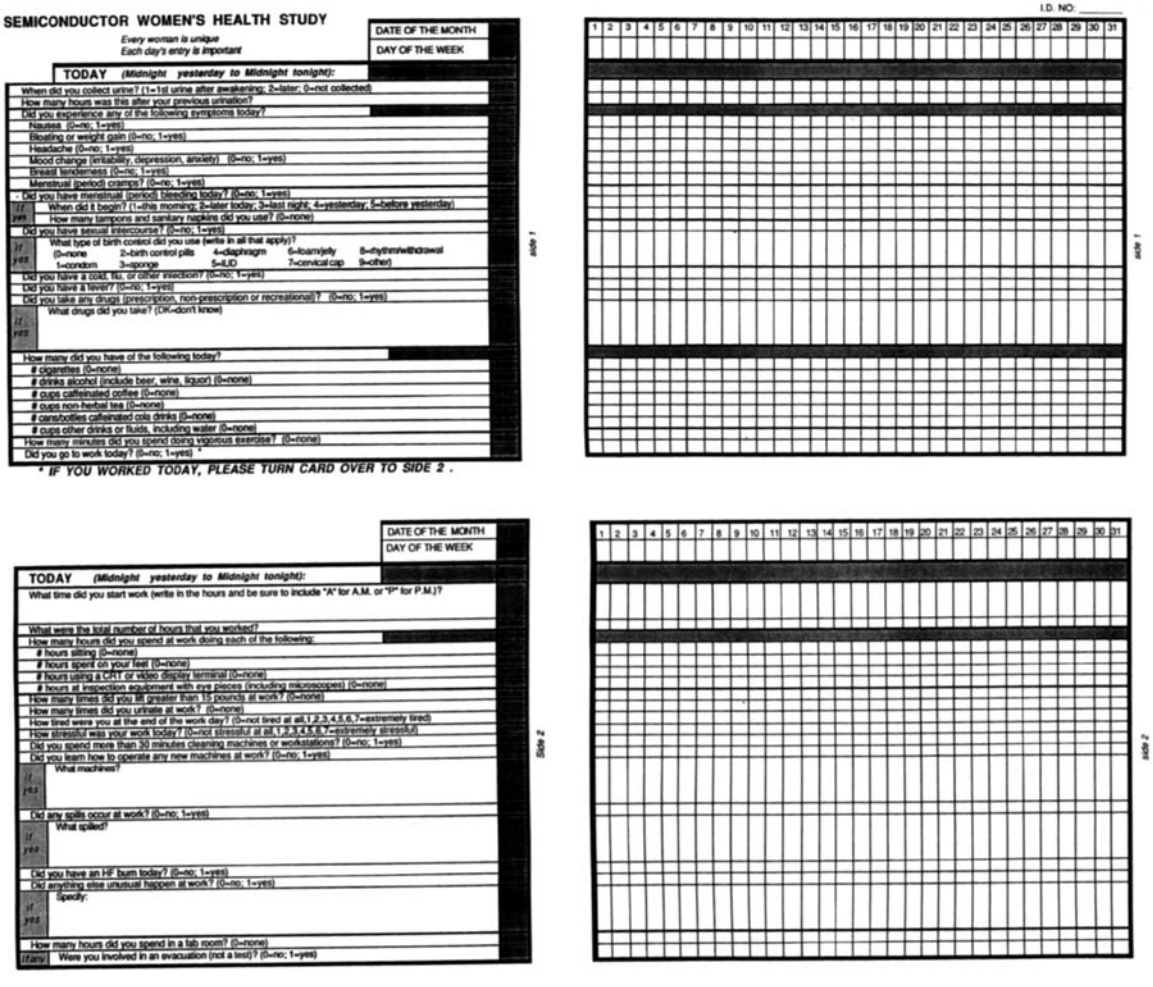

Fig. 2. Daily diary.

lifting >15 lb, hours spent at video display terminals, hours worked in a fab, hours spent learning to use new tools or machinery, emergencies (spills or evacuations), and other unusual occurrences. The diary envelope was available in English, Tagalog, Vietnamese, and Spanish.

Diaries took about 5 min each day to complete. Each month, women turned in diaries and completed urine kits and received new diary inserts and urine kits (see later). The few women unable or unwilling to answer all daily diary questions were asked to provide at least the date of their last menstrual period. To ensure that this item was completed, the field staff checked it each month when urine kits and diaries were returned.

Monthly questionnaires were designed to maintain monthly contact with subjects, to answer questions, to address problems, and to obtain information about changes from the previous month in job status, job activities, work shift, job exposures, smoking, pregnancy, medical conditions, surgery, medications, partner's habits and job, computer use, and selected habits. *Six-month (exit) questionnaires* included all questions from monthly questionnaires, along with more detailed questions about workplace exposures and activities, beverage consumption, physical activity, home appliance use, and work-related stress during the previous 6 months.

Another major innovation in the present study was the *urine collection kit* for daily urine samples (Fig. 3) from the non–clinic-based population of working women. At the beginning of the follow-up period, each woman received a small, soft-sided, insulated foam cooler (which she could keep at the end of the study) and blue ice for transporting the urine kits. She also received a 250-ml beaker to collect urine. Urine kits consisted of a plain, unmarked, brown cardboard box measuring 6¾ × 5¼ × 2½ inches. The bottom of each box was lined with a calendar for the month; a light cardboard insert separated the vials; and one plastic 5-ml vial with screw-on lid was provided for each day of the month. Once vials were filled with urine, they were placed in the box, which was kept in the freezer compartment of their home refrigerators.

Each month, women received mail reminders of the next date to bring in completed kits and diaries. When they brought them in, they were paid $35 and were provided kits and diaries for the next month. At the end of the study, women who had completed the follow-up were entered into a raffle for three first prizes (a weeklong trip to Hawaii) or three second prizes (a weekend trip) or cash equivalent.

Frozen urine samples were stored in a freezer in the study field office until enough kits were accumulated for a shipment. Samples were shipped (about once a month) with dry ice to the U.C. Davis endocrinology laboratory, where they were stored in a walk-in freezer kept at −20°C.

Bar codes on vials in the urine kit encoded the woman's human subject number (HSN) and the day and date of urine collection. A computerized bar-code reader transmitted this information to a computerized database in the laboratory, which logged and tracked samples as they were received, stored, and retrieved for assays [Lasley et al., 1995]. As each sample was logged, information about empty vials and the first day of each menstrual cycle was entered by hand. At the completion of the study, women who participated not only received notification of the overall study results, but also received a personal letter summarizing their own individual results of urinary assays (see Saiki et al. [1995] for more detailed description of notification procedures).

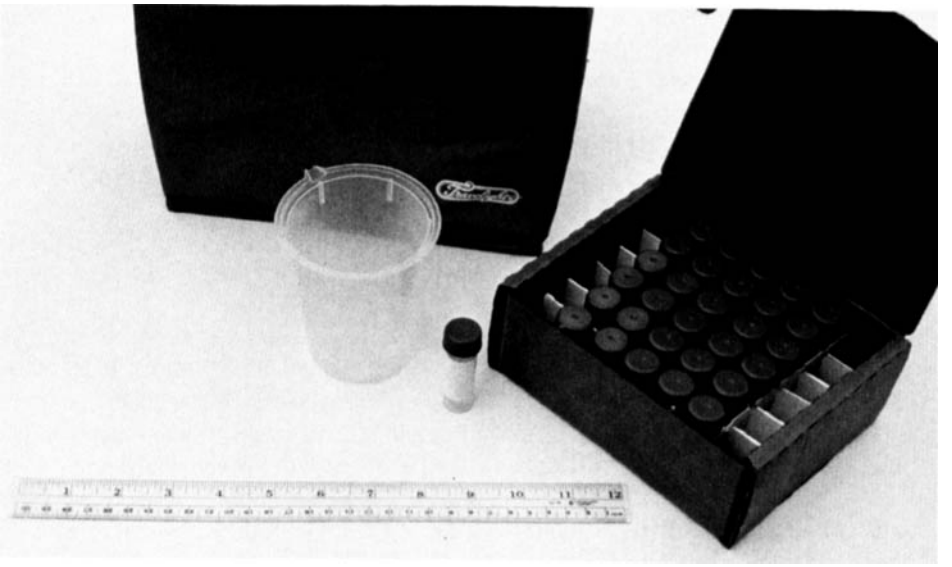

Fig. 3. Urine collection kit.

Pilot Study

Sampling, recruitment, and data-collection procedures and instruments were tested in a pilot study at one site. Of the 354 women selected for the pilot study, 238 (67%) completed a screening questionnaire, 48 (20.2%) were identified as eligible, and 33 (69% of eligibles) participated. Pilot information was used to revise and streamline procedures, to clarify questions, and to shorten questionnaires. Because the fundamental study design and questions did not differ between pilot and full-scale studies, all women included in the pilot study were included in analyses of the full-scale study. Additional women from the pilot-study site were also included in the full-scale study.

Confidentiality

The study protocol and all data-collection instruments were reviewed and approved by human subjects institutional review boards at U.C. Davis and U.C. Berkeley. Every effort was made to protect the confidentiality of each participant's identity and information. Names of participating companies were not divulged to anyone outside the research staff.

Women who did not want their company to know they were in the study had the option of being interviewed outside of work time, so that supervisors would not be aware of their participation; however, no women chose this option. Baseline interviews were scheduled through supervisors. Companies did not receive names of study participants or dropouts. Interview documents and computer data had no name identifiers; only the HSN was used. A password-protected master file with subjects' names and HSN was maintained on a separate Macintosh computer and used only for employee notification. All completed documents were stored in locked filing cabinets at U.C. Davis, separate from identifying information.

Data Entry and Editing

Data were keypunched twice, once for data entry and once for verification, and stored on magnetic tape as ASCII files. Data were read into SAS datafiles (Statistical Analysis System, SAS Institute, Cary, NC) and run through a series of range-check programs to ensure that each value fell within the expected range or corresponded to a codebook entry. Logic-check programs also were run to ensure that all expected data were present and that skip patterns were followed correctly.

Data Analyses

Menstrual cycle characteristics were obtained in baseline interviews and from daily diaries. Baseline interview provided information on the woman's usual ability to predict within 4 days (irrespective of symptoms) when her next menstrual period would begin ("Generally speaking, in the past year, has the length of your cycles, that is, the length of time from the beginning of bleeding for one menstrual period to the beginning of bleeding for the next, usually varied by less than four days? That is, are your menstrual periods fairly regular [within 4 days] so that you usually know when your next menstrual period will start [without using any symptoms you may have to predict this]?"), her usual cycle length ("In the past year, what was the usual length of your menstrual cycles? That is, how many days were there from the first day of one menstrual period to the first day of the next one?"), and age at menarche ("How old were you when you had your first menstrual period?"). Daily diaries provided prospective follow-up data on menstrual bleeding, making it possible to compute mean cycle length (MCL) per woman, standard deviation (SD) of MCL per woman, mean days of bleeding per menstrual period, and probability of extreme (<24- or >35-day) cycle lengths.

Because the distribution of the SD in cycle lengths per woman was skewed to the right, per-woman standard deviations were transformed with natural logarithms (ln) to compute the ln of SD in cycle lengths (LSDCL). For any woman with a SD of zero, a value of 0.25 day was used to take the natural logarithm, since the lowest nonzero value for SD was 0.56. This 0.25 day was subtracted following exponentiation of the mean for each group of the natural logarithm SD. Cycles were excluded from all analyses if laboratory assays of urinary hormones [Lasley et al., 1995] indicated a definite or possible conception, if information on menstrual bleeding was missing, or if the daily diary indicated steroid hormones were used during that cycle.

RESULTS

Of the 3,915 fab and nonfab women selected for participation, 435 left their companies before they could be contacted. The number of women selected in each plant ranged from 181 to 1,252. Of the 3,480 women selected and still at their companies at the time of the group meetings, 2,147 (62%) attended group meetings. Some women who did not attend group meetings did complete the screening procedure. Participation rates in the screening largely did not differ by age, ethnicity, or fab work status (Table I).

Although data on ethnicity and fab status from screening questionnaires were not completely compatible with data provided by companies for sample selection, a total of 2,639 women (75.8%) completed the screening questionnaire (Table II).

TABLE I. Prospective Component Participation Rates in Screening and Follow-Up (Among Eligibles) by Age, Ethnicity, and Fabrication (Fab) or NonFabrication (Nonfab) Status

	Sample[a]		Screened[b,c]		Eligible[b]		Interviewed in follow-up[b]	
	n	% of total	n	% of selected	n	% of screened	n	% of eligible
Age (years)								
<29	811	20.7	539	66.5	161	29.9	114	70.8
30–34	1,077	27.5	755	70.1	254	33.6	169	66.5
35–39	1,084	27.7	712	65.7	204	28.6	139	66.7
≥40	886	22.6	596	67.3	111	18.6	62	55.9
Missing[d]	57	1.5	37	64.9	2	5.4	0	—
Totals	3,915	100.0	2,639	67.4	739	28.0	481	65.1
Ethnicity								
White, non-Hispanic	1,894	48.4	1,295	68.4	292	22.6	216	74.0
Hispanic	675	17.2	442	65.5	102	23.1	65	63.7
Black	153	3.9	99	64.7	31	31.3	22	71.0
Asian	1,128	28.8	727	64.4	275	37.8	140	50.9
Other	20	0.5	49[c]	—	39	78.6	38	97.4
Missing[c]	45	1.1	27	60.0	0	—	0	—
Totals	3,915	100.0	2,639	67.4	739	28.0	481	65.1
Work status								
Nonfab	2,006	51.2	1,416	70.6	413	29.2	265	64.2
Fab	1,860	47.5	1,223	65.7	326	26.7	216	66.3
Missing[d]	49	1.2	0[c]	—	0	—	0	—
Totals	3,915	100.0	2,639	67.4	739	28.0	481	65.1

[a]Age, ethnicity, and fab-nonfab status are based on company assessment.
[b]Age, ethnicity, and fab-nonfab status are based on questionnaire data.
[c]Among the 3,915 women in the sample, 435 no longer worked at the company at the time of screening; their age, ethnicity, and fab status were unknown, so they could not be subtracted from these categories. Therefore, the total participation rate in the screening was 75.8%, somewhat higher than shown.
[d]After women were screened, most missing values became known, resulting in fewer women in the missing category among screened, eligible, and interviewed women.

There were 629 women who had not responded after three attempted contacts; they were sent screening questionnaires by mail (including 204 women who were also mailed a $3 check with the questionnaire to encourage completion); the 114 (18.1%) who returned them were included in the 2,639 total. Of the 2,639 women who completed the screening questionnaire, 739 (28.0%) were eligible for the follow-up (Table II), including 20 of the 114 who responded by mail, and 1,868 were ineligible for various reasons (Table III). Of the 739 eligible women, 481 (65%) completed the baseline interview, including 9 of the 114 who responded by mail (Table II). Participation rates for the follow-up largely did not differ by age, ethnicity, or fab work status (Table I). More than half the enrolled women completed five or more menstrual cycles of diary data (Table IV). A total of 402 women contributed at least one complete cycle of urine samples, and even though about one third of cycles had at least one missing sample, only 9.8% of all possible urine samples were missing.

The first observation of methodological interest was the distribution of usual cycle lengths recalled at baseline compared with MCLs observed from daily diaries. Although MCLs were more dispersed than usual cycle lengths, the central tendency for both measures was similar (Fig. 4). When cumulative distribution of usual cycle length at baseline was compared with MCL from the diaries, differences in the two

TABLE II. Recruitment and Participation of Fabrication (Fab) and Nonfabrication (Nonfab) Women for the Prospective Component

	Fab n (%)	Nonfab n (%)
Sample selected	1,860	2,006
Women screened	1,223 (66)	1,416 (71)
Women eligible	326 (27)	413 (29)
Women interviewed	216 (66)	265 (65)
Women completing ≥1 menstrual cycle	152 (70)	250 (94)
Total cycles completed	752	1,210

TABLE III. Reasons for Ineligibility to Participate in Prospective Follow-up, by Fabrication (Fab) or Nonfabrication (Nonfab) Work Status and by Plant Location[a]

	Work status				Plant location					
	Fab (n = 900)[b]		Nonfab (n = 968)[b]		California (n = 1,400)		Utah (n = 500)		All sites (n = 1,900)	
Major disqualifying criteria	n	%	n	%	n	%	n	%	n	%
Female sterilized	367	40.8	311	32.1	484	34.6	194	38.8	678	35.7
Pregnant	46	5.1	65	6.7	78	5.6	33	6.6	111	5.8
Oral contraceptives or steroids	172	19.1	251	25.9	328	23.4	95	19.0	423	22.3
IUD	18	2.0	21	2.2	29	2.1	10	2.0	39	2.1
Male partner sterilized	77	8.6	65	6.7	90	6.4	52	10.4	142	7.5
No sexual intercourse	176	19.6	223	23.0	311	22.2	88	17.6	399	21.0
No menstrual period	24	2.7	16	1.7	24	1.7	16	3.2	40	2.1
Other[c]	20	2.2	16	1.7	56	4.0	12	2.4	68	3.6

[a]Each category excluded all participants counted in previous categories.
[b]The 32 women with unknown fab-nonfab status were excluded.
[c]Categories included: plans to leave company soon, no freezer, language difficulty, not employed full time, and refused to answer questions used to determine eligibility.

measures were small. Medians were essentially the same, but diary MCLs were somewhat longer, and the cycle length reported on the baseline indicated a preference for the accepted normal cycle length of 28 days. Ten percent of women were excluded from these calculations because their cycles were too irregular for them to provide a usual cycle length at baseline.

The cumulative distribution of MCLs from the diaries was compared for women reporting regular and irregular cycles at baseline. Longer cycles were more common among women who reported irregular cycles at baseline (Fig. 5). The median MCL observed from the diaries was 34 days for women reporting irregular cycles and 28 days for women reporting regular cycles. Self-reports of irregular cycles distinguished women with greater variability in cycle lengths computed from the diary data (Fig. 6). Women reporting irregular cycles at baseline had a median LSDCL of 7.5 days, compared with about 2.5 days for women reporting regular cycles (Fig. 7). In addition, women who reported irregular cycles at baseline were significantly more likely to have MCLs longer than 35 days and standard deviation of cycle lengths longer than 7 days (Table V).

TABLE IV. Distribution of Total Menstrual Cycles Contributed by Fabrication (Fab) and Nonfabrication (Nonfab) Women in Prospective Component

	Fab		Nonfab	
Total cycles contributed	N	%	N	%
1	15	9.9	25	10.0
2	14	9.2	27	10.8
3	11	7.2	19	7.6
4	22	14.5	30	12.0
5	14	9.2	28	11.2
6	29	19.1	57	22.8
7	35	23.0	44	17.6
≥8	12	7.9	20	8.0
Total cycles	752		1,210	

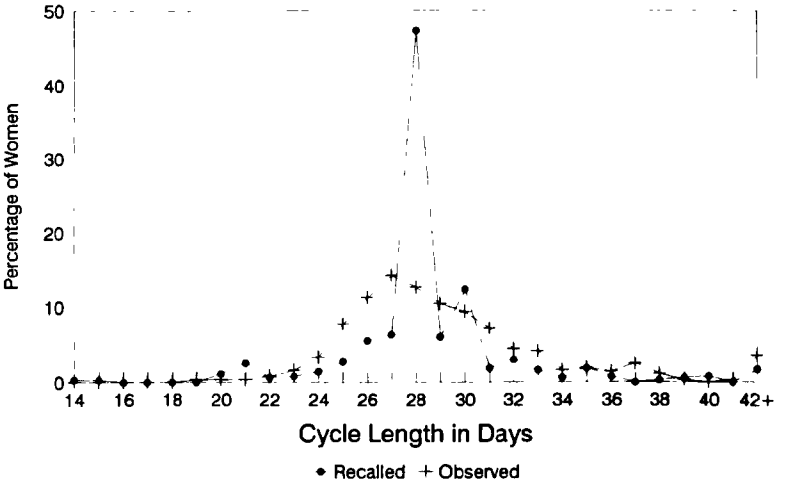

Fig. 4. Usual cycle length recalled at baseline vs. mean cycle length recorded in daily diaries.

DISCUSSION

This paper reports the methods, methodologies, and findings of a unique prospective study of reproductive health in working women. It is one of the first studies to employ daily diaries and urinary measures in a multiethnic group of working women. The participation and compliance demonstrate the feasibility of this approach in such a study population, and the accumulated data and stored urine samples provide the opportunity for additional work to assess ovarian function and markers of exposure in this population.

Three quarters of women selected for screening in the prospective component completed the screening questionnaire. Participation was higher among women employed in Utah (vs. California) and among white women, but participation largely did not differ between fab and nonfab workers or by age or ethnicity. Eligible women differed from all screened women primarily with regard to factors related to the likelihood of pregnancy (e.g., currently attempting or planning pregnancy, history of

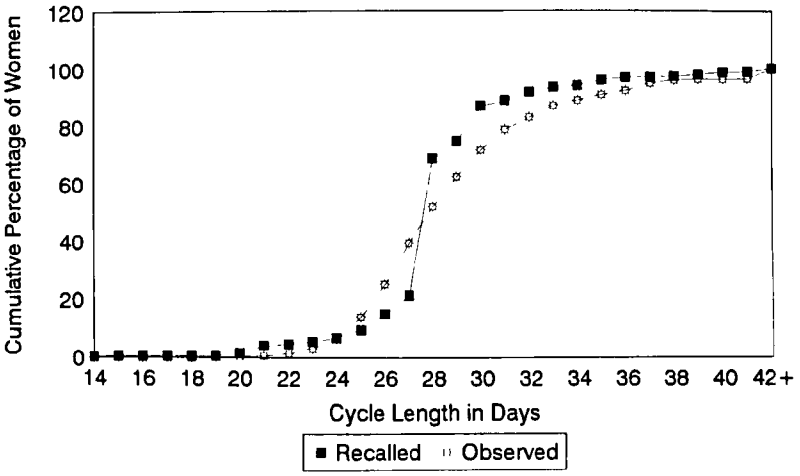

Fig. 5. Cumulative distributions of usual cycle length recalled at baseline and of mean cycle length observed from daily diaries.

TABLE V. Observed Mean Cycle Length and Mean of the ln Standard Deviation in Cycle Length by Self-Report of Regular vs. Irregular Cycles

	Self-reported			
	Regular		Irregular	
Observed	n	%	n	%
Mean cycle length[a]				
<24 days	13	3.5	2	5.9
24–35 days	321	87.5	19	55.9
>35 days	33	9.0	13	38.2
	$x^2 = 27.3$, df = 2, $p \leq 0.001$			
Standard deviation in cycle length[b]				
≤7 days	292	87.7	16	59.3
>7 days	41	12.3	11	40.7
	$x^2 = 16.3$, df = 1, $p \leq 0.001$			

[a]One woman excluded for whom self-report information on regularity was unavailable.
[b]Includes only women with >1 completed cycle observed.

infertility, and marital status) but did not differ greatly on most other factors, such as age, ethnicity, education, smoking, household income, work shift, and gravidity. Because eligibility criteria were established to identify women at risk of pregnancy, differences related to pregnancy plans, past infertility, and marital status were expected.

Among women eligible for follow-up, two thirds enrolled, and 20% did not complete at least one cycle because they dropped out or became ineligible (e.g., started oral contraceptives, had a tubal ligation, or were laid off, on medical leave, or pregnant at baseline). Only 9.8% of urine samples were missing. The high cooperation and compliance with follow-up procedures were particularly notable in light of industry downsizing at that time. These workforce reductions caused worker con-

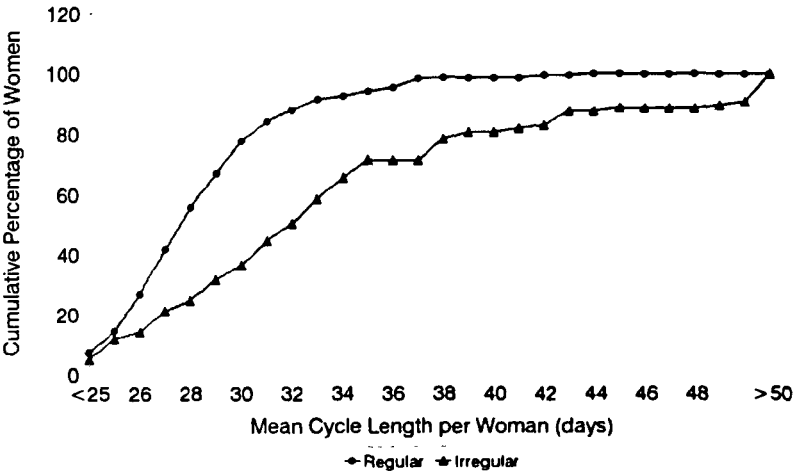

Fig. 6. Cumulative distributions of mean cycle lengths in regular vs. irregular women.

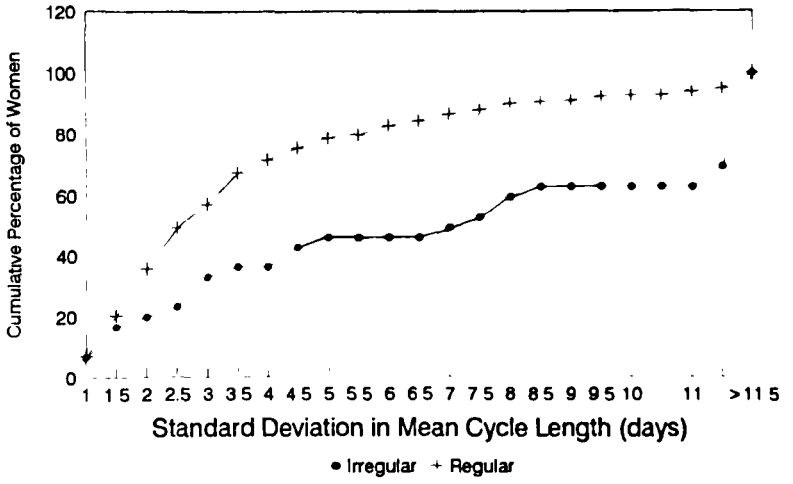

Fig. 7. Logarithm of standard deviation in mean cycle lengths among women reporting irregular vs. regular cycles at baseline. Computation only includes women with >1 complete cycle.

cerns about job security that could have compromised cooperation. While downsizing reduced overall sample size in the prospective component, it did not appear to diminish cooperation or compliance. Fab and nonfab participants did not differ greatly in number of cycles of urine collection and diaries completed; most completed five or more cycles.

Characterizing ovarian dysfunction requires direct evidence, such as analyses of urinary reproductive hormones. This prospective approach requires appropriate follow-up, laboratory assays, and statistical analysis, which are all costly and labor intensive but less subject to potential bias [Snowden, 1977]. These methods require more participation and involvement from study participants, but some studies show

that non–clinic-based, working women recognize the importance of studies of occupational effects on reproduction and can be willing and compliant participants [Wright et al., 1992]. Menstrual calendars or diaries have been used in several classic [Vollman, 1956; Treloar et al., 1967; Chiazze et al., 1968] and recent [Harlow and Matanoski, 1991; Wilcox et al., 1988] studies of the menstrual cycle. On the other hand, surveys produce a large amount of data in a relatively short time [Snowden, 1977].

The findings of the present investigation suggest that self-reporting of irregular cycles provides useful information when prospective studies are not practical or feasible. The present prospective study is among the first to undertake intensive follow-up with daily diaries and urine collection in a large, non–clinic-based population of women who were not attempting pregnancy. The investigators succeeded in obtaining good participation and compliance in a relatively demanding study of participants not necessarily motivated by desire for pregnancy.

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REFERENCES

Chiazze L, Brayer FT, Mascico JJ, Parker MP, Duffy BJ (1968): The length and variability of the human menstrual cycle. JAMA 203:377–380.

Harlow SD, Matanoski GM (1991): The association between weight, physical activity and stress and variation in the length of the menstrual cycle. Am J Epidemiol 133:38–49.

Lasley BL, Lohstroh P, Kuo A, Gold EB, Eskenazi B, Samuels SJ, Overstreet JW (1995): Laboratory methods for evaluating early pregnancy loss in an industry-based population. Am J Ind Med, 28:771–781.

Saiki CL, Green RS, Gold EB, Schenker MB (1995): Communication issues in a multicomponent study of semiconductor employees. Am J Ind Med, 28:883–911.

Snowden R (1977): The statistical analysis of menstrual bleeding patterns. J Biosoc Sci 9:107–120.

Treloar AE, Boynton RE, Behn BG, Brown BW (1967): Variation of the human menstrual cycle through reproductive life. Int J Fertil 12:77–126.

Vollman RF (1956): The degree of variability of the length of the menstrual cycle in correlation with age of the woman. Gynaecologia 142:310–314.

Wilcox AJ, O'Connor JF, Schlatterer JP, Armstrong EG (1988): Incidence of early loss of pregnancy. N Engl J Med 319:189–194.

Wright DM, Kesner JS, Schrader SM, Chin NOW, Wells VE, Krieg EF Jr (1992): Methods of monitoring menstrual function in field studies: Attitudes of working women. Reprod Toxicol 6:401–409.