# THE SEMICONDUCTOR HEALTH STUDY: METHODS FOR PROSPECTIVELY ASSESSING REPRODUCTIVE FUNCTION IN WAFER FABRICATION EMPLOYEES

E.B. Gold,[1] B. Eskenazi,[2] B. Lasley,[1] S. Samuels,[1] J. Overstreet,[1] S.K. Hammond,[3] M. O'Neill Rasor,[1] C. Hines,[2,4] M.B. Schenker[1]

[1]Divisions of Occupational/Environmental Medicine and Epidemiology and of Reproductive Biology, University of California at Davis, ITEH, Davis, California 95616; [2]University of California at Berkeley, Berkeley, California; [3]University of Massachusetts Medical Center; [4]Currently at the National Institute for Occupational Safety and Health (NIOSH), Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, Ohio 45226

Over the past 30 years, increasing numbers of women have entered the workforce, so that now upwards of 70% of women in the United States work outside the home. Thus, many women have occupations that place them in environments that are potentially hazardous to their reproductive health in terms of physical, chemical and psychological stressors or exposures. Often standards for workplace exposures are based on levels that cause acute effects. It is possible that the reproductive system may be compromised at lower levels than these standards. Thus, adverse reproductive health effects may be a sensitive indicator of occupational exposures. In addition, the emotional impact of infertility, adverse pregnancy outcomes, and menstrual cycle disruptions and the prevalence of these conditions make them a source of concern for a large segment of the working population. For all these reasons, in recent years, some investigators in occupational epidemiology have increasingly turned their attention to potential adverse effects of occupational exposures on reproductive health.

One issue arises very early in undertaking such studies: what is the optimal design for conducting an investigation of the effects of workplace exposures on adverse reproductive health outcomes? Case-control studies are generally less labor-intensive and less expensive but raise legitimate concerns about recall bias and validation of past exposures. Historical cohort designs generally

address recall bias and exposure assessment somewhat better but have difficulties with identifying former workers, tracing subjects, and validating outcomes. Prospective designs generally attain more accurate exposure assessment and ascertainment of outcomes but are more labor-intensive and costly and have the potential problems of subject recruitment, compliance, and drop-out.

This paper will describe the design and methodologic issues that arose in a prospective study of potential adverse reproductive health effects in women working in the semiconductor industry. This prospective study was conducted as one component of a larger study which also had historical cohort, cross-sectional and industrial hygiene/exposure assessment components. It is hoped that some of the methodologic results will provide insights into the relative merits of recalled versus prospectively collected information on reproductive health indicators.

This study was originally proposed because of a report by Pastides and coworkers (1), showing an increased risk of spontaneous abortions (SABs) in women working in the photolithography and diffusion areas of the fabrication rooms in one semiconductor company. Because of some concerns about the design of the study, the industry funded a Scientific Advisory Panel of well-known, academic and government researchers in the areas of occupational epidemiology, industrial hygiene, endocrinology and statistics to write a request for proposals and to provide peer review of the proposals. The Scientific Advisory Panel also was advisory during the conduct of the study. Following this peer review, the UC Davis proposal, which included investigators from UC Berkeley and the University of Massachusetts Medical Center, was approved and funded.

The study was designed to examine adverse reproductive health risks in workers who fabricate silicon wafers. A number of potential workplace exposures were of concern in this industry. First, particular interest focused on glycol ethers and other solvents, based on the prevalence of their use and animal and human literature showing adverse reproductive effects (2). In addition, a number of dopants (such as arsenic), which alter conductive properties of the wafers, have also been implicated, largely in the animal literature, as being associated with adverse reproductive outcomes. Finally, the

environment and physical and ergonomic aspects of the workplace were also of concern.

The primary objective of the prospective component of this study was to compare rates of pregnancy and pregnancy loss as well as menstrual cycle function in women currently working in silicon wafer fabrication (fab) and non-fabrication (nonfab) using prospectively collected daily diaries and urine samples.

Since most of the study's recruitment and data collection activities were conducted on company time for the convenience of subjects, much coordination of scheduling took place with supervisors or managers, as well as with the women. Contact with supervisors and women was preceded by putting up posters around the company site, including women's rest rooms. The study sample consisted of all women aged 18-44 years working in fabrication and a sample of women working in nonfab jobs who were frequency matched on age and ethnicity. These women were invited to attend a group meeting on company time conducted by Dr. Gold or Dr. Eskenazi. Over 200 group meetings were held and involved a slide presentation about the study and a question-and-answer period, and accommodated women's work schedules, including night and swing shifts. Subsequently, women were administered a screening questionnaire for eligibility in the follow-up study. This was self-completed in a private room at the company on company time. Over 2600 women were screened. The eligibility criteria are described below. Eligible women were then approached and recruited for follow-up, the details of which are also provided below.

The primary goal was to recruit women at increased likelihood of becoming pregnant. Thus, eligibility was not restricted to women attempting pregnancy. The eligibility criteria were: (a) age 18 through 44 years; (b) not currently pregnant; (c) menstruated within previous two months; (d) had sexual intercourse within previous two months; (d) not sterilized and partner not sterilized; (e) not using oral contraceptives, steroid hormones, or an intrauterine device; (f) had a working freezer; (g) not planning to leave the company within the next three months; and (h) ability to speak English, Tagalog, Spanish, or Vietnamese.

At baseline, following informed consent, eligible women who were willing to participate in the follow-up portion of the study were administered a detailed in-person interview in a private room at the company on company time. Less than half of the follow-up population was white. Approximately 30% were Asian, most of whom were Filipino, and 14% were Hispanic. In anticipation of a diverse population, all of our questionnaires, diaries and advertising pamphlets were translated into Spanish and Tagalog and most into Vietnamese as well. A number of bicultural interviewers who were bilingual in English and Spanish or Tagalog were hired. The baseline interview data included demographic, lifestyle and medical factors, and a detailed reproductive history, as well as questions about workplace activities, which were developed by our industrial hygiene study component. The baseline interview was completed by 481 women.

During follow-up women were asked to complete a daily diary that contained questions about urine collection, menstrual flow, premenstrual symptoms, intercourse, birth control, illness, medications, smoking, caffeine and alcohol consumption, and exercise on a daily basis. In addition, they answered work-related questions about hours worked, lifting, standing, use of video display terminals and other equipment, evacuations, and spills on a daily basis. The daily diary was designed as an outer envelope on card stock which contained the questions and an insert that had each day of the month identified at the top of a column in which the women filled in the answers each day.

Women also collected first morning urine every day for six months or six menstrual cycles. The urine was collected in a beaker and then poured into a 5-ml vial that was labelled with a bar code, the woman's human subject number, and the day and date. The vials were kept in a plain cardboard box that had a calendar in the bottom to ensure that the vial was put in the right place, and the box containing filled vials was stored in the freezer. The women were also provided with a soft-sided cooler and blue ice to transport the frozen urine samples. Once a month they were called and given a brief questionnaire about changes in work or pregnancy status. Kit exchange days were held at the company, and women were informed during the monthly interview when and where these would be held. At the kit exchange each woman would turn in her frozen urine

samples and completed diary insert for the month and would receive a clean urine collection kit and diary insert for the next month and would be paid $35.

The urine samples were screened for the 10 days prior to and 5 days following each onset of menses using an immunoenzymometric assay to detect human chorionic gonadotropin (hCG) (3). All cycles found positive for HCG by this screen were confirmed by an immunoradiometric assay for hCG and urinary steroid metabolites, which provided an objective indicator of conception and early fetal loss (EFL). More than half of the women enrolled completed 5 or more cycles of follow-up.

In addition to assessing conceptions and EFLs, it was possible to examine a number of menstrual cycle characteristics, based on the diary data. Cycles in which a conception occurred were excluded from all menstrual cycle analyses. Mean cycle length/woman (MCL) was used as an indicator of central tendency of cycle length, since comparison of means of all cycles in each group (fab and nonfab) might result in over-representation of women with short cycles. Standard deviation in cycle length/woman (SDCL) provided a measure of variability in cycle length and took into account the number of cycles a woman contributed. Mean days of bleeding and probability of long ($>35$ days) or short ($<24$ days) cycles were also examined, the latter two to provide measures of extreme cycle lengths. Most of the small amount of available literature indicates that cycles shorter than 24 days or longer than 35 days would be in the extreme 10% of cycles (4, 5, 6).

One observation of methodologic interest was the difference in the usual cycle length women recalled at baseline compared to their MCL observed using the daily diaries. The latter showed more dispersion than the former. A comparison of the cumulative distribution of usual cycle length reported on the baseline interview with the MCL observed on follow-up by diary also showed that, while the differences in the two measures were small and the medians were essentially the same, longer MCLs were observed during follow-up.

Furthermore, a comparison of the MCL observed during follow-up in women reporting at baseline having regular vs. irregular cycles

revealed a marked shift toward longer cycles for the women who reported at baseline having irregular cycles in the past year. The median of the MCL from the diary follow-up was 34 days in those reporting irregular cycles compared to 28 days in those reporting regular cycles. In addition, self-report of irregular cycles distinguished women with greater variability in cycle lengths as measured by the SDCL observed during follow-up. Women reporting at baseline that they usually had irregular cycles had a median SDCL of 7.5 days, compared to about 2.5 days in women who reported usually having regular cycles.

There is some literature to suggest that long cycles are indicative of delay of ovulation (7), perhaps due to an environmental insult early in the cycle, and that short cycles may be indicative of anovulation (8), which might also be affected by environmental stresses. Thus, both of these measures of extremes in cycle lengths are potentially important indicators and relatively easily obtained in occupational epidemiologic studies and may be indicators of reduced fertility. However, at the moment, the only way to be sure that disruption of ovulation has occurred is to analyze daily urine samples for steroid hormone metabolites, which requires expensive follow-up, laboratory assay and statistical analysis procedures. While the prospective approach is a more costly and labor-intensive method than cross-sectional or historical designs to obtain information about MCL, variability in MCL and extreme cycle lengths, it presumably does provide more accurate measures. If resources are limited, however, these findings suggest that self report of irregular cycles does provide some discrimination of disruption of the cycle, although there was not complete agreement with the data obtained during follow-up. Thus, while a balancing of the need for accuracy vs. available resources must be considered, these findings support both the feasibility of the prospective approach as well as the utility of recalled information when a prospective study is not practical.

**References**

1. Pastides H, Calabrese EJ, Hosmer DW Jr, Harris DR (1988): Spontaneous abortion and general illness symptoms among semiconductor manufacturers. J Occup Med 30:543-51.

2. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Division of

Standards Development and Technology Transfer. Criteria for a Recommended Standard: Occupational Exposure to Ethylene Glycol Monomethyl Ether, Ethylene Glycol Monoethyl Ether, and Their Acetates. September 1991.

3. Taylor CA, Overstreet JW, Samuels SJ, Boyers SP, Canfield RE, O'Connor JF, Lasley BL (1992): Prospective assessment of early fetal loss using an immunoenzymometric screening assay for detection of urinary human chorionic gonadotropin. Fert Steril 57:1220-4.

4. Vollman RF (1956): The degree of variability of the length of the menstrual cycle in correlation with age of woman. Gynaecologia 142:310-4.

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

6. Chiazze L, Brayer FT, Macisco JJ, Parker MP, Duffy BJ (1968): The length and variability of the human menstrual cycle. JAMA 203:377-80.

7. Aksel S. (1981): Hormonal characteristics of long cycles in fertile women. Fert Steril 36:521-3.

8. Matsumoto S, Tamada T, Konuma S. (1979): Endocrinological analysis of environmental menstrual disorders. Int J Fert 24:233-9.

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