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Timing and Patterns of Exposures during Pregnancy and Their Implications for Study Methods

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Patterns of exposure variability across pregnancy were examined for medical, lifestyle, residential, and occupational exposures in a population-based sample of 357 livebirths from 10 rural California counties. A new measure of variability, the ratio of overall prevalence to time-window-specific prevalence, is introduced. The higher the overall : time window (OTW) ratio, the greater the potential for misclassification when using anytime-during-pregnancy prevalence for an agent that exerts its effect in a smaller time window. Exposures to cigarettes, marijuana, saunas/hot tubs, factors related to location of residence, and some workplace substances tended to be of longer duration. Intertrimester concordance was high (κ's > 0.8) for smoking, residential proximity to crops, and use of video display terminals; moderately high (κ's between 0.4 and 0.8) for many occupational exposures; and low (κ's < 0.4) for illnesses, which tended to be of short duration. The lowest OTW ratios were for smoking and some residential exposures (1.1–1.3), while OTW ratios were much higher for paint applications, influenza, vaginal infections, and ultrasound (reaching, e.g., 4–6). Use of anytime-during-pregnancy exposure indices can bias measures of association between risk factors and adverse pregnancy outcomes, particularly if the OTW ratio is high. Misclassification bias occurs if there is a vulnerable time window during which the exposure exerts its effect. The misclassification can be differential when the average length of gestation of cases is shorter than that of controls. For exposures that vary, investigations of pregnancy outcome should collect as much detail as feasible regarding timing. *Am J Epidemiol* 1996;143:597–607.

bias (epidemiology); environmental exposure; epidemiologic methods; fetal death; life style; occupational exposure; pesticides; pregnancy

Although it has been recognized for decades that the impact of exposures incurred during pregnancy frequently depends on the timing of those exposures, epidemiologic studies often collect or report data for exposures occurring at any time during pregnancy or during a relatively wide time interval such as the first half of the pregnancy. With few exceptions (1, 2), little attention has been paid to changes in exposure over the course of pregnancy; virtually no previous work has addressed the implications of such changes for methodology in studies of pregnancy outcomes other than birth defects. Researchers of teratogenesis have been the most cognizant of this issue (1–3).

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Abbreviation: OTW, overall : time window.

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In a case-control study of fetal death, we collected information on several dozen exposures for each month of pregnancy. Although data collected on such a fine scale may be subject to errors of recall, we recognized that such information could easily be grouped later if necessary. On the other hand, this level of detail could provide a gain in the precision of effect measures for exposures whose action is specific to certain time windows. Monthly data also allowed us to evaluate whether the women themselves tended to report exposures at the trimester level (e.g., whether they would tend to give the same response for months 1–3, months 4–6, etc.).

This report focuses on information collected from the controls, who represented a population-based sample of livebirths. The prevalences of a range of medical, lifestyle, residential, and occupational exposures are examined overall and by time period. The patterns of variability in these exposures are described, a new measure of variability is introduced, and concordance within and between trimesters is assessed. We con-

clude with recommendations for improving studies of reproductive outcomes.

MATERIALS AND METHODS

Subject selection

A case-control study of stillbirths and livebirths in 10 agricultural counties in California was initiated to investigate associations with pesticide exposures. A more detailed description of study methods is presented elsewhere (4). Cases were defined as fetal deaths occurring after 20 weeks' gestation and infant deaths occurring within 24 hours of birth. All 642 cases delivered in 1984 were identified from fetal death certificates. Twelve cases were subsequently determined to be ineligible, resulting in 630 cases. Controls were randomly selected using birth certificates from the same year for liveborn infants who survived for more than 24 hours. A total of 642 of these population-based controls were frequency-matched to cases on maternal age and county of maternal residence.

Data sources

Sources of data used in the present report included birth, death, and fetal death certificates and a mailed questionnaire. Data abstracted from birth and fetal death certificates included maternal marital status, age, race/ethnicity, and parity.

An informed consent form and cover letter were mailed to all 1,272 identified women, followed by a self-administered questionnaire which addressed the woman's medical and reproductive history and occupational, residential, medical, and lifestyle exposures. Questionnaires were available in both Spanish and English. A $1.00 bill was included with the questionnaire as an incentive to reply. Nonresponder follow-up was conducted, consisting of a second mailing, a third mailing using registered letters, and phone calls. Incorrect addresses were updated through the California Department of Motor Vehicles and a commercial subject location firm.

Of the 1,272 mothers identified, 74 percent were located (72 percent of cases and 75 percent of controls). Among women who were located, questionnaire response rates were 73 percent for cases and 74 percent for controls, resulting in 332 cases and 357 controls. Results presented here are based on the 357 respondent controls.

The format for questioning the women about month-by-month exposures was as follows. The woman was first asked whether or not she took a specific medication, had a specific disease, used a specific product, etc. The general instructions told the respondent that if she had difficulty remembering any events, she could answer "do not recall." If she responded "yes" to a question on a particular exposure, the questionnaire asked her to circle the months of pregnancy in which the exposure took place, with the digits 1 through 9 printed. Just above the questions that asked about the timing of exposures, the respondent was instructed, "If you cannot recall the exact month, it is better to make your best guess than to leave the question blank." To remind the woman about the dates of her pregnancy and assist her in responding to these timing questions, the dates of her last menstrual period and of delivery, taken from the birth certificate, were provided at the start of the questionnaire. Exposure for each month was entered as a binary variable into the computerized database.

Variables and methods of analysis

Analyses were restricted to those exposures for which there were at least eight controls exposed (2 percent) during pregnancy. The exposures that met this criterion fell into several broad categories, including medications, illnesses and symptoms, medical procedures, home environment exposures, lifestyle factors, and employment-related exposures (specific exposures are listed in tables 2 and 3). Exposures that did not meet our minimum prevalence criterion and that were excluded from this analysis were as follows: medications taken for fatigue, depression, chest pain, epilepsy, acne, a thyroid condition, or an irregular heartbeat; chickenpox and herpes; and a number of employment-related exposures (anesthetic gases, clothing dyes, lead, gasoline, metal dust, fumes, etc.). In addition, for some exposures, timing data were not included in the questionnaire—i.e., physical activity during pregnancy, major life events, residence near a toxic waste site, residence supplied by a well serving 100 or fewer families, etc.

The analyses addressed 1) reporting of exposure prevalences during pregnancy; 2) the adequacy of measuring exposure over the entire pregnancy versus smaller time periods (i.e., by month or by trimester); and 3) patterns of change in exposures during pregnancy.

Among women who reported that they had been exposed, the percentage who provided information on timing was calculated. Prevalences among livebirths for each of these exposures were calculated by month, by trimester, and overall, i.e., at any time during pregnancy.

A new measure of variability, the ratio of overall exposure prevalence to time-window-specific expo-

sure prevalence (hereafter called the overall : time window (OTW) ratio), is introduced here, and this figure was calculated for the exposures of interest in this study. The time-window-specific exposure prevalence was defined as the percentage of women who responded "yes" in that particular time window among all women whose pregnancies lasted to the start of the time window, including all of the unexposed, as well as those who reported exposure and gave details on the months in which they were exposed. That is, we excluded from the denominator of the time-window-specific prevalence 1) those whose pregnancies ended prior to the time window and 2) those who responded "yes" regarding anytime-during-pregnancy exposure but provided no information on timing. For brevity, the trimester served as the time window of interest. A more formal description of this measure of variability is presented below.

Patterns of exposure were examined in greater detail. Duration of exposure was calculated as the average number of months in which the exposure occurred, among exposed women who gave information on timing. In addition, frequencies of episodes of exposure were calculated; two episodes were said to occur if an unexposed month separated them. Inter- and intratrimester concordance were assessed by means of kappa (κ) statistics for all pairwise intertrimester comparisons and for intratrimester comparisons of adjacent and nonadjacent months (e.g., fourth month vs. fifth month and fourth month vs. sixth month, respectively). The kappa statistic indicates the degree of concordance in excess of what would be expected by chance. For calculation of kappas, women who were exposed but gave no information on timing were excluded.

The OTW ratio: a measure of variability across time

The formal definition of the OTW ratio is as follows. Let $p = e/n$, where p = the overall prevalence and e = the number exposed out of n respondents. Let

$$p_i = e_i/(n - d_{i-} - \bar{n}),$$

where e_i is the number who reported being exposed in time interval i, d_{i-} is the number who did not survive to the beginning of interval i, and $\bar{n}$ is the number of respondents who were exposed but gave no information on timing for this exposure. Then OTW = p/p_i.

For example, suppose a study is conducted on 1,000 pregnancies in which 140 women report having been exposed during their pregnancy. Of these women, let us say that 130 specify the months of pregnancy in which they experienced this exposure and 10 do not. Suppose further that months 3 and 4 are relevant for the outcome of interest and that 44 women report having been exposed during these two months. The OTW ratio would then be (140/1,000) (44/990) = 3.15. An OTW ratio this large suggests that substantial misclassification bias would result from using the subjects exposed anytime during pregnancy rather than the 44 women exposed during months 3 and 4.

The higher the OTW ratio, the greater the variability, in terms of different people being exposed, across trimesters. If the OTW ratio is high but does not change across pregnancy, then a similar prevalence is found in each time window, but it is not the same people being exposed at different times. If the OTW ratio changes across pregnancy, the prevalences are changing across time windows. A consistently low OTW ratio implies that the same people are being exposed throughout pregnancy. The OTW ratio, unlike standard measures of concordance, directly relates measures from longer time periods to shorter ones that are included within the longer intervals. Thus, it evaluates how well a crude definition of exposure performs relative to a finer one. The importance of the OTW ratio stems from its relation to the potential for misclassification. The higher the OTW ratio, the more misclassification would be present if the anytime-during-pregnancy measure were used when the etiologically relevant period was the more limited time window. OTW ratios were calculated for exposures of interest in this study.

Continuing the hypothetical example above, suppose the data are distributed among cases and controls as shown in part a of figure 1, using the anytime-during-pregnancy exposure, so that the 140 exposed subjects comprise 120 controls and 20 cases. Part b of the figure represents the two-by-two table in which the exposed group includes only those exposed in the irrelevant time period who were not also exposed in the relevant time period. (Those exposed in the relevant time period are excluded from this table.) To be consistent with the assumption that these exposures are irrelevant, the odds ratio was fixed at 1.0. Part c shows the two-by-two table in which the exposed group correctly includes only those who received their exposure in the relevant time period, regardless of whether they did or did not also receive exposures at other times. In this table, those who were only exposed in the irrelevant time period are in the "unexposed" group. For clarification, figure 2 shows the distribution of exposed subjects by time period: irrelevant period only, relevant period only, and both periods.

Note that the odds ratio based on relevant exposures is 2.85, whereas the odds ratio based on exposures

a: Any exposure

	D	~D	
E	20	120	140
~E	90	770	860
	110	990	1000

OR = 1.43

b: Exposure in irrelevant time period only

	D	~D	
E	9	77	86
~E	90	770	860
	99	847	946

OR = 1.0

c: Exposure in relevant time period

	D	~D	
E	11	33	44
~E	99	847	946
	110	880	990

OR = 2.85

FIGURE 1. Hypothetical example of the use of the overall : time window ratio. Each of the two-by-two tables cross-classifies columns of diseased (D) and nondiseased (~D) persons with rows of exposed (E) and unexposed (~E) members of a cohort of 1,000 pregnant women. *OR, odds ratio.*

In part a, the exposed group includes those who report incurring an exposure at any time during pregnancy. Of the 140 women in the exposed group, information on the timing of the exposure is not available for 10 subjects. These subjects therefore do not appear in either part b or part c of the figure.

In part b, the exposed group includes all persons for whom the exposure took place only during months that are known to be irrelevant to the disease outcome of interest. The unexposed group is the same as in part a—i.e., it includes persons not exposed at all during pregnancy. Persons who had any exposure during the relevant period (n = 44) are omitted from this table, regardless of whether they were also exposed during the irrelevant period.

In part c, the exposed group includes those who were exposed during the relevant period, regardless of any exposures incurred by these same individuals at other time points during pregnancy. Those who were exposed only during irrelevant time periods are included in the unexposed group.

	Exposure in irrelevant time period only	Exposure in relevant time period	
		and in irrelevant time period	but not in irrelevant period
D	9	4	7
~D	77	11	22

FIGURE 2. *Distribution of exposed subjects in the hypothetical* example of figure 1. The numbers of both diseased (D) and nondiseased (~D) persons are shown according to whether exposure occurred during the relevant time period, the irrelevant time period, or both.

incurred at any time during pregnancy is 1.43, having been severely attenuated by the misclassification. Even without data on the distribution of cases and controls, the OTW ratio of 3.15 has predicted a high level of bias.

RESULTS

As table 1 shows, 64 percent of the women in our study who delivered live infants that survived for more than 24 hours were aged 20–29 years; 66 percent were of white, non-Hispanic race/ethnicity; one fourth were Hispanic; and 57 percent were employed during the pregnancy. Three fourths had at least a high school diploma, and 39 percent had been to college. Over 80 percent of the infants were of normal weight, and 85 percent were full-term.

The prevalence of each exposure is shown in table 2 for anytime during pregnancy and for each trimester. Acetaminophen use and ultrasound had the highest exposure prevalences both overall (>50 percent) and by trimester (as high as one third in at least one trimester, for each). Other relatively common exposures (i.e., >10 percent in at least two trimesters) were alcohol consumption, tobacco smoking, insect pesticide applications in the home, living within ¼ mile (0.4 km) of commercially grown crops, living ¼ mile–1 mile (0.4 km–1.6 km) from commercially grown crops, and sauna/hot tub use.

The prevalences of most occupational, residential, and lifestyle exposures did not change much between trimesters, with some exceptions, such as insecticide, pet pesticide, and paint applications, which showed increases between the first and second trimesters. Several other factors also showed a marked second trimester increase, such as urinary tract infections, vaginal infections, ultrasound, acetaminophen use, and influenza. As would be predicted, use of antinausea medication declined over the course of pregnancy, while use of antihypertensive medication increased.

A notable finding is that exposure prevalence in any given trimester is almost always substantially lower than the prevalence for anytime during pregnancy. Thus, even when the prevalence of an exposure remained fairly constant, it was often not the same women who were exposed in the different time periods. For instance, 4–5 percent of women were ex-

TABLE 1. Distribution of maternal characteristics among livebirth controls from 10 counties in California, 1984

	No.	%
Total	357	100
Maternal age (years)		
18–19	24	6.7
20–29	230	64.4
≥30	102	28.6
Unknown	1	0.3
Race/ethnicity		
White non-Hispanic	236	66.1
Hispanic	90	25.2
Black non-Hispanic	14	3.9
Asian	17	4.8
Presumed marital status		
Single	38	10.6
Married	314	88.0
Divorced	1	0.3
Unknown	4	1.1
No. of previous livebirths		
0	126	35.3
1–2	178	49.9
≥3	51	14.3
Unknown	2	0.6
Employed during pregnancy	203	56.9
Education		
0–11 years	65	18.2
High school diploma	130	36.4
More than high school	139	38.9
Unknown	23	6.4
Birth weight (g)		
<2,500	24	6.7
2,500–3,999	290	81.2
≥4,000	43	12.0
Gestational age (weeks)		
26–34	10	2.8
35–37	31	8.7
≥38	305	85.4
Unknown	11	3.1

posed to extreme heat in each trimester, but 9 percent were exposed at some time during pregnancy.

This degree of variation in exposure across pregnancy can be measured as the range of OTW ratios. The higher the OTW ratio, the greater the variability across time windows. In particular, a comparison of tobacco smoking and alcohol consumption is revealing. Both showed similar trimester-specific prevalences—15–20 percent. However, the overall (anytime-during-pregnancy) prevalence of exposure was 31 percent for alcohol but 19 percent for tobacco, reflecting very different patterns of use of these two substances. In other words, women who smoked did so rather consistently across trimesters, while those who drank did so more sporadically. This difference in exposure patterns is well summarized by the OTW ratio, using trimesters as the windows of interest. In smokers, the OTW ratio is consistently 1.1–1.2, whereas for alcohol it ranges from 1.5 to 1.9. From table 2, a substantial amount of variation (across different exposures) in these ratios is evident. For example, residing ¼ mile–1 mile from crops is similar to smoking in that the OTW ratio is low and does not vary much, ranging from 1.1 to 1.3. However, for paint application, the OTW ratio ranges from 2.0 to 5.7; for vaginal infection, from 1.9 to 4.3; and for ultrasound, from 1.6 to 6.1.

As table 3 indicates, the average "duration" of an episode of exposure varied by type of exposure, ranging from 1.1 months to 7.7 months. Illnesses and symptoms tended to be of shorter duration, particularly influenza and fever; whereas smoking, marijuana use, hot tub/sauna use, exposures related to location of residence, and some employment-related exposures tended to be present for the bulk of the pregnancy. The overwhelming majority of exposures were "continuous"—i.e., were reported to occur almost exclusively in adjacent months. In fact, exposures occurred solely in consecutive months for several medications, for many workplaces substances, and for tobacco, marijuana, and cocaine; in other words, no one reported quitting smoking for a full month but then resuming. Between 10 percent and 25 percent of exposed women had at least two episodes for the following exposures: acetaminophen, influenza, vaginal infection, fever, ultrasound, medical x-rays, and alcohol. Only for occupational exposure to pesticides and for garden pesticide applications did more than one fourth of the exposed women have two or more separate episodes of exposure.

Table 3 also displays the percentages of exposed women who gave information on timing. For slightly more than half the exposures analyzed, more than 85 percent of the women specified the months of gestation in which they were exposed. For a small number of exposures, fewer than 75 percent of the women provided information on the specific months of exposure; the lowest percentages were for occupational exposure to pesticides (54 percent), medical x-rays (69 percent), and urinary tract infections (71 percent). (In the case of pesticides, questions on timing of exposure were also asked elsewhere on the questionnaire, which may have led some women to be less meticulous at this point in the questionnaire.) The percentages of women reporting monthly data were not remarkably better or worse in any general category of exposure (e.g., medications, illnesses, occupational exposures, etc.).

TABLE 2. Prevalence (%) of various exposures during pregnancy, by time period of exposure, 10 counties in California, 1984

	Entire pregnancy*	First trimester		Second trimester		Third trimester	
		%†	OTW ratio‡	%†	OTW ratio	%§	OTW ratio
Medicines used							
Antihistamines	10.4	4.0	2.6	6.2	1.7	4.7	2.2
Aspirin	8.4	4.5	1.9	3.7	2.3	2.6	3.2
Acetaminophen	53.8	28.8	1.9	38.0	1.4	31.5	1.7
Prescription pain medication	4.2	1.4	3.0	1.1	3.7	2.3	1.8
Hypertension medication	2.2	0.0	—‖	0.8	2.7	1.7	1.3
Nausea medication	5.9	3.7	1.6	2.5	2.3	0.6	10.1
Illnesses							
Influenza	16.2	4.0	4.1	6.6	2.5	6.2	2.6
Urinary tract infection	7.8	0.6	13.7	4.0	2.0	2.7	2.9
Vaginal infection	17.1	4.0	4.3	8.9	1.9	6.5	2.6
Fever	14.0	4.3	3.3	5.7	2.5	5.6	2.5
Antenatal medical procedures							
Amniocentesis	4.5	1.1	4.0	2.0	2.3	1.5	3.1
Ultrasound	57.7	9.5	6.1	36.2	1.6	23.2	2.5
Radiograph (x-ray)	3.6	0.3	12.8	0.3	12.8	1.8	2.1
Home exposures							
Garden pesticide application	16.0	6.7	2.4	9.4	1.7	8.5	1.9
Insect pesticide application	28.3	9.7	2.9	17.6	1.6	12.6	2.2
Pet pesticide application	12.9	4.0	3.2	7.2	1.8	6.3	2.1
Paint application	19.3	3.4	5.7	9.6	2.0	9.6	2.0
Lacquer/varnish application	4.5	0.6	8.0	0.6	8.0	3.5	1.3
Lived less than 1/4 mile (0.4 km) from crops	21.8	14.7	1.5	16.5	1.3	18.6	1.2
Lived 1/4–1 mile (0.4–1.6 km) from crops	18.5	15.3	1.2	14.8	1.3	16.5	1.1
Lifestyle factors							
Marijuana use	6.4	4.8	1.3	4.8	1.3	8.1	0.8
Sauna/hot tub use (hot or very hot)	18.8	14.2	1.3	14.4	1.3	13.5	1.4
Smoking (any amount)	19.0	17.0	1.1	15.3	1.2	15.9	1.2
Alcohol consumption (any amount)	31.1	16.8	1.9	20.3	1.5	17.7	1.8
Cocaine or "crack" use	2.8	1.7	1.7	0.8	3.3	0.9	3.2
Employment exposures							
Disinfectants	5.0	3.7	1.4	3.7	1.4	3.2	1.6
Extreme heat	9.0	4.0	2.3	4.8	1.9	5.0	1.8
Extreme cold	2.2	1.4	1.6	1.4	1.6	0.9	2.6
Pesticides	3.6	1.1	3.2	1.7	2.1	1.2	3.1
Paint/varnish	4.5	2.8	1.6	2.6	1.7	2.6	1.7
Solvents/degreasers	4.2	2.8	1.5	2.0	2.1	1.2	3.6
Cutting, cooling, or lubricating oils	2.2	2.0	1.1	1.4	1.6	1.2	1.9
Video display terminals	10.4	8.0	1.3	8.8	1.2	7.4	1.4
X-rays	2.8	1.7	1.7	1.1	2.5	0.6	4.8

* Proportions were calculated relative to all 357 controls.

† Proportions were calculated relative to exposed controls who provided any monthly detail plus all nonexposed controls.

‡ OTW, overall:time window prevalence ratio, defined as the exposure prevalence for the entire pregnancy divided by the prevalence for that specific trimester.

§ Proportions were calculated relative to all controls who had a gestation period longer than 6 months, with the exception that controls who reported exposure during pregnancy but provided no monthly detail were excluded from the denominator.

‖ Undefined.

Table 4 gives kappa statistics measuring intra- and intertrimester concordance for selected factors representing a range of types of exposure and variability. Intertrimester concordance was highest for smoking, use of video display terminals, and living less than ¼ mile from crops: Kappas were above 0.8 for all pairwise trimester comparisons. Moderately strong concordance was observed for alcohol, home insecticide application, and acetaminophen use, with all pairwise trimester comparisons showing kappas between 0.4 and 0.8. Other medicines showed lower kappas, and illnesses and sauna/hot tub use showed the lowest. First trimester versus third trimester concordance was not necessarily lower than concordance of adjacent trimesters for illnesses and medications, though it generally was for home, lifestyle, and work exposures.

TABLE 3. Patterns of various exposures during pregnancy among those exposed, 10 counties in California, 1984

	No. exposed at least once	% who reported months of exposure	Average no. of months exposed*	% of exposed women, by no. of episodes of exposure*,†		
				One episode	Two episodes	Three or more episodes
Medicines used						
Antihistamines	37	92	1.5	94	6	0
Aspirin	30	87	3.4	92	4	4
Acetaminophen	192	84	4.3	82	15	3
Prescription pain medication	15	87	2.1	92	8	0
Hypertension medication	8	75	3.2	100	0	0
Nausea medication	21	86	2.2	100	0	0
Illnesses						
Influenza	58	91	1.3	90	8	2
Urinary tract infection	28	71	1.8	95	5	1
Vaginal infection	61	87	1.9	87	11	2
Fever	50	88	1.5	86	11	2
Antenatal medical factors						
Amniocentesis	16	88	1.1	100	0	0
Ultrasound	206	86	1.4	80	15	5
Radiograph (x-ray)	13	69	1.2	89	11	0
Home exposures						
Garden pesticide application	57	75	3.2	72	19	9
Insect pesticide application	101	73	3.6	91	8	1
Pet pesticide application	46	80	3.6	97	3	0
Paint application	69	97	1.8	99	1	0
Lacquer/varnish application	16	94	2.5	93	7	0
Lived less than 1/4 mile (0.4 km) from crops	78	86	7.1	100	0	0
Lived 1/4–1 mile (0.4–1.6 km) from crops	66	92	7.7	98	2	0
Lifestyle factors						
Marijuana use (any amount or frequency)	23	87	6.8	100	0	0
Cocaine or "crack" use	10	80	3.0	100	0	0
Sauna/hot tub use (hot or very hot)	67	85	6.7	98	0	2
Smoking (any amount)	70	91	7.7	100	0	0
Alcohol consumption (any amount)	111	85	4.2	86	11	3
Employment exposures						
Disinfectants	18	72	7.7	100	0	0
Extreme heat	32	91	3.3	97	3	0
Extreme cold	8	75	4.3	100	0	0
Pesticides	13	54	4.0	71	29	0
Paint/varnish	16	100	3.9	100	0	0
Solvents/degreasers	15	80	5.2	100	0	0
Cutting, cooling, or lubricating oils	8	88	6.3	100	0	0
Video display terminals	37	86	6.6	97	3	0
X-rays	10	80	3.4	100	0	0

* Based upon data from women who reported exposure by month.
† Exposures occurring in adjacent months constituted one episode; two episodes were considered to have occurred if one or more unexposed months separated them.

Intratrimester concordance was not necessarily greater than intertrimester concordance, and in some cases it was lower. The intratrimester data also indicate that women do not tend to recall their exposures in trimester blocks. If they did, intratrimester kappas would be universally high. On the contrary, these women, who represented a population-based sample of women who delivered a liveborn infant, frequently reported exposures for only part of a trimester.

In general, the same factors that displayed strong intertrimester concordance tended to have strong intratrimester concordance as well, and factors with moderate concordance showed a similar pattern. However, there were two exceptions: Sauna/hot tub use showed substantially higher concordance within trimesters than between trimesters, and alcohol consumption had somewhat lower kappas within trimesters. As expected, adjacent months showed somewhat stronger concordance than nonadjacent ones within a trimester. The largest kappas were usually between months 1 and 2.

DISCUSSION

Although few researchers would argue against the principle that timing of exposures is important, in

TABLE 4. Kappa coefficients for the prevalence of selected exposures during pregnancy, by pairs of time periods, 10 counties in California, 1984

	Intertrimester comparisons			Intratrimester comparisons								
				First trimester			Second trimester			Third trimester		
	First trimester vs. second trimester	Second trimester vs. third trimester	First trimester vs. third trimester	Month 1 vs. month 3	Month 1 vs. month 2	Month 2 vs. month 3	Month 4 vs. month 6	Month 4 vs. month 5	Month 5 vs. month 6	Month 7 vs. month 9	Month 7 vs. month 8	Month 8 vs. month 9
Medicines used												
Antihistamines	0.47	0.33	0.51	0.67	0.87	0.79	0.49	0.24	0.59	0.47	0.52	0.80
Aspirin	0.39	0.38	0.21	0.13	0.68	0.39	0.40	0.40	0.61	0.33	0.44	0.57
Acetaminophen	0.49	0.54	0.51	0.53	0.75	0.62	0.34	0.45	0.54	0.60	0.63	0.78
Illnesses												
Influenza	0.12	0.08	0.13	0.03	0.24	0.06	−0.22	−0.15	0.08	−0.16	−0.16	0.34
Vaginal infection	0.13	0.25	0.12	0.12	0.25	0.06	0.23	0.26	0.20	0.17	0.52	0.61
Fever	0.06	0.26	0.07	0.04	0.07	0.19	−0.10	−0.15	0.11	−0.21	−0.07	0.42
Home exposures												
Insect pesticide application	0.54	0.52	0.50	0.60	0.80	0.66	0.16	0.46	0.35	0.56	0.75	0.69
Paint application	0.18	0.12	0.04	0.48	0.72	0.63	0.05	0.26	0.34	−0.01	0.11	0.40
Lived less than 1/4 mile (0.4 km) from crops	0.89	0.89	0.84	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Lifestyle factors												
Sauna/hot tub use (hot or very hot)	0.24	0.30	−0.10	0.73	0.79	0.86	0.62	0.67	0.78	0.84	0.84	0.81
Smoking (any amount)	0.92	0.96	0.88	0.95	0.98	0.97	0.97	1.00	0.97	0.90	0.98	0.92
Alcohol consumption (any amount)	0.58	0.72	0.49	0.80	0.85	0.86	0.72	0.74	0.84	0.76	0.83	0.88
Employment exposures												
Extreme heat	0.43	0.63	0.23	0.48	0.71	0.78	0.21	0.71	0.50	0.19	0.53	0.55
Video display terminals	0.91	0.88	0.82	0.87	1.00	0.87	0.62	0.35	0.45	0.55	0.69	0.71

practice, the literature on pregnancy outcome largely ignores this issue, seemingly in the belief that collecting accurate data for short time windows is not feasible. Indeed, when we initiated this study, many prominent epidemiologists advised us not to try to collect month-by-month information, and some did not believe that women could recall information about trimesters of exposure.

The high proportion of women who reported month-by-month exposure information suggests that pregnancy may be a time of heightened awareness of the timing of events, and that epidemiologic studies can take advantage of this phenomenon. Nevertheless, there is some loss of exposure information when up to 46 percent of women do not provide timing information for a given exposure. Thus, the advantage of using time-window-specific information must be weighed against the loss due to missing information for the particular exposure of interest. When the proportion missing is high, the important issue is whether these occur at random.

Another consideration is that errors of recall are possible, and some women may incorrectly believe that their exposures were incurred in certain months when in fact they were not. Although no attempt was made in this study to validate self-reported exposures, several characteristics of these data suggest internal consistency and validity. First, work histories were generally continuous until the third trimester. Second, exposures related to residential location were of longer duration than others, as would be expected. Third, only a small proportion of those who reported smoking reported later months of no smoking, suggesting not only that most women did not quit smoking during pregnancy but also that these women were fairly honest in answering the questions. Fourth, illegal behaviors such as marijuana and cocaine use were reported, again supporting the validity of the information. Fifth, exposures likely to be of shorter duration, such as influenza or fever, were reported to have occurred primarily in one month and only occasionally in more than one month. Sixth, consistent with known biologic phenomena, use of hypertension medication was reported predominantly toward the end of pregnancy, while the reported use of nausea medication was highest in the first trimester and progressively declined throughout pregnancy.

Data from this investigation show substantial variability in exposure prevalence across different time periods of pregnancy. Of the factors studied, the highest overall prevalences were for acetaminophen use, ultrasound, alcohol, and insect pesticide applications. Exposures showing the greatest variability across trimesters, with at least one OTW greater than 6, were

urinary tract infections, medical x-rays, nausea medication, lacquer/varnish applications, and ultrasound. Factors for which all OTW ratios were greater than 2 were influenza, urinary tract infection, fever, amniocentesis, medical x-rays, paint application, and occupational exposure to pesticides. Concordance between trimesters was generally moderate or low: Kappas were usually less than 0.5, with a few exceptions. For instance, high concordance ($\kappa > 0.8$) was found for residential exposures and for some lifestyle (smoking) and occupational (video display terminals) exposures. Many factors also showed low intratrimester concordance. Pesticide exposures, both at work and in home gardens, were more likely than other exposures to occur in separate episodes (months separated by at least one unexposed month). Illnesses and medical procedures were most likely to be of short duration, while residential exposures were of the longest duration.

The crucial role of the timing of exposures during pregnancy, combined with this strong evidence of variability, indicates that misclassification can be a substantial problem in studies that use a single exposure measure for the entire pregnancy. Our data showed a substantially lower prevalence for many exposures when trimester-specific figures were used as opposed to the single anytime-during-pregnancy prevalence. Additionally, the intratrimester kappa coefficients indicate variability within trimesters for many exposures.

Reproductive toxins work by a variety of mechanisms, and the timing of exposures during pregnancy is critical to their effects (5). Consider morphologic development: While some structures form within 1 or 2 weeks of conception (6), some portions of the central nervous system continue to develop throughout the entire pregnancy (7). Functional, as opposed to structural, deficits from nervous system insults have also been traced to specific periods of exposure (8). For instance, a variety of agents have been shown to cause hypoactivity, reflex delays, and locomotor abnormalities in rats when administered to the dam on either gestational day 12 or day 19, but hyperactivity when administered on days 14–18 (9).

In humans, time-window-specific effects have been demonstrated for thalidomide (10), radiation (11, 12), maternal rubella (13), smoking (14, 15), and alcohol (16, 17). In infants who are born alive after early embryonic intrauterine radiation exposure, congenital abnormalities are not observed. Infants exposed to radiation in gestational weeks 4–11 exhibit a high incidence of severe mental retardation in association with reduced skeletal growth that includes microcephaly (12). Exposure during weeks 12–20 produces less severe mental retardation, and beyond 20 weeks, no effect is seen. Similarly, Lieberman et al. (14) and others (15, 18, 19) have shown that the impact of smoking on the incidence of low birth weight is considerably reduced among women who quit smoking during pregnancy. Lieberman et al. (14) found that women who stopped smoking by the third trimester had no elevated risk for a small-for-gestational age birth in comparison with nonsmokers.

In short, timing is critical to the nature and magnitude of reproductive toxic response for a diverse range of pathways/outcomes, including structural malformations, behavioral teratogenicity, and fetal growth. Accurate assessment of exposure requires examination of the appropriate time window. Nevertheless, most epidemiologic studies on pregnancy outcomes other than congenital malformations, as well as some studies of malformations, collect exposure data that is far less specific than is desirable.

A major finding of our investigation is that time-window-specific exposures often have a lower prevalence than the single anytime-during-pregnancy exposure measure. A similar finding was previously reported by Heinonen et al. (1) and by Nelson and Forfar (2). Both of these previous studies addressed drug exposures only. Our results extend those findings to many other exposures. Secondly, we found that the ratio of overall prevalence to trimester-specific prevalence varies considerably, from about 1.1 to >5. This variability provides a good index of the potential for misclassification of an exposure which exerts its effect in a limited time period.

For many exposures, there is a strong potential for misclassification in studies that collect data on only one measure for the entire pregnancy; and for some outcomes, even collection of trimester-specific data will entail substantial error. If the time window needed for a particular exposure to exert a specific effect is narrow, substantial misclassification becomes even more likely. Furthermore, misclassification could be differential in many studies. Consider a scenario where an exposure early in pregnancy is potentially causal. In this situation, a longer gestation period will mean a higher probability of exposure at some irrelevant time points (later in pregnancy). Additionally, length of gestation is almost always related to (or is even used to define) the adverse outcome of pregnancy. Thus, cases will have less opportunity (due to a shorter pregnancy) to incur an irrelevant exposure and hence be misclassified than controls, particularly if the relevant time window is early in pregnancy. This problem would occur in both case-control and cohort studies that use exposure anytime during pregnancy. With differential misclassification, the direction of

bias can be either toward or away from the null (20). However, when the differential is known, the direction of the bias can be predicted; e.g., where controls are more likely to be erroneously classified as exposed, the bias will be toward the null.

Where variability in exposure is low—i.e., when the ratio of overall prevalence to time-window-specific prevalence is close to 1.0—crude (single) measures of exposure will imply low misclassification rates. Although in some circumstances these could still induce considerable bias, one can generally place more confidence in studies using anytime-during-pregnancy exposure when the OTW ratio is near 1. In addition, for exposures with OTW ratios near 1, measuring exposure during one period may not be problematic even if that were not the relevant period. We caution the reader that the variability in prevalences of exposure found in our study, as measured by kappa statistics and by the ratios of overall prevalence to trimester-specific prevalence, may not generalize to other studies. Some populations may exhibit less residential mobility or higher rates of quitting smoking, and these factors may themselves change over calendar time. The numerical results are best viewed as exemplary of the potential ranges of variability in exposures over the course of pregnancy. Nevertheless, some general patterns may apply to other populations, such as the shorter durations of illness exposures and the longer durations of residential exposures.

On the basis of this investigation, we offer the following recommendations for studies of pregnancy outcome. First, in general, measures that assume constant exposure throughout pregnancy without data to support this assumption should not be used, since they may introduce substantial misclassification whenever some time periods are relevant and others are not. For studying outcomes in which the relevant time window is short or unknown and the exposures are likely to vary, recording information on a month-by-month basis is to be preferred, if feasible. Other than smoking and factors associated with residential location, many exposures examined in this investigation varied markedly, even from month to month. At a minimum, trimester-specific data should be collected whenever possible.

When collection of exposure data for only the relevant time period is infeasible (e.g., when there is a long period of recall or when existing records that do not contain detailed data on timing are used), researchers should carefully consider the concomitant biases that could result from the use of such data. These concerns should be recognized both when planning studies and when interpreting findings.

Second, misclassification resulting from use of an exposure time window that is too wide will, in most pregnancy outcome studies, be differential. Like stillbirths, most adverse pregnancy outcomes involve or are related to lower gestational age at termination (e.g., spontaneous abortion, low birth weight), and most malformations occur either exclusively or more frequently at earlier gestational ages of delivery. If preterm delivery is the outcome, then, by definition, cases will have shorter periods of gestation. That is, for almost any adverse outcome of pregnancy, cases will a priori be less likely than controls to experience exposure. As a result, whenever some time periods are more critical than others, a measure of exposure based on prevalence at any time during pregnancy will be more likely to misclassify controls than cases, particularly if the relevant time period is early in pregnancy. Hence, not only is misclassification likely, in many instances it will be differential, and the direction of the induced bias can be predicted.

Third, once the appropriate time-specific data are collected, this information must be taken into account in the analyses. The best available biologic information should be used to determine the relevant time period. Analyses focusing on this period will be the least biased.

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