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Pesticide Use and Menstrual Cycle Characteristics among Premenopausal Women in the Agricultural Health Study

S. L. Farr[1,2], G. S. Cooper[2], J. Cai[3], D. A. Savitz[1], and D. P. Sandler[2]

[1] Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.
[2] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC.
[3] Department of Biostatistics, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.

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Menstrual cycle characteristics may have implications for women's fecundability and risk of hormonally related diseases. Certain pesticides disrupt the estrous cycle in animals. The authors investigated the cross-sectional association between pesticide use and menstrual function among 3,103 women living on farms in Iowa and North Carolina. Women were aged 21–40 years, premenopausal, not pregnant or breastfeeding, and not taking oral contraceptives. At study enrollment (1993–1997), women completed two self-administered questionnaires on pesticide use and reproductive health. Exposures of interest were lifetime use of any pesticide and hormonally active pesticides. Menstrual cycle characteristics of interest included cycle length, missed periods, and intermenstrual bleeding. The authors used generalized estimating equations to assess the association between pesticide use and menstrual cycle characteristics, controlling for age, body mass index, and current smoking status. Women who used pesticides experienced longer menstrual cycles and increased odds of missed periods (odds ratio = 1.5, 95% confidence interval: 1.2, 1.9) compared with women who never used pesticides. Women who used probable hormonally active pesticides had a 60–100% increased odds of experiencing long cycles, missed periods, and intermenstrual bleeding compared with women who had never used pesticides. Associations remained after control for occupational physical activity.

agriculture; hormone antagonists; hormones; infertility; menstrual cycle; pesticides

Abbreviations: DDT, dichlorodiphenyltrichloroethane; OR, odds ratio.

The menstrual cycle is a hormonally controlled process, although several factors may influence its length and regularity (1). Certain pesticides are known or suspected to have hormonal or ovotoxic properties with consequent adverse reproductive effects on animals and humans (2), but little is known about the effect of pesticides on women's menstrual function. Animals exposed to certain pesticides may experience estrous cycle dysfunction with resultant reduced fecundability, possibly because of endocrine-disruptive effects on reproductive hormones or direct effects on the ovary (2, 3). Menstrual cycle characteristics have implications for women's fecundability (4, 5) and risk of chronic diseases such as osteoporosis and cancers associated with reproductive hormones (1).

Two studies have examined exposure to dichlorodiphenyltrichloroethane (DDT) and menstrual cycle characteristics (6, 7), but, to our knowledge, no studies have examined the association between other pesticides and menstrual cycle characteristics. Women who live and work on farms may be more highly exposed to pesticides than women in the general population. Therefore, we examined the cross-sectional association between currently used pesticides, specifically focusing on probable hormonally active pesticides, and menstrual cycle characteristics among premenopausal women enrolled in the Agricultural Health Study.

MATERIALS AND METHODS

Study population

The Agricultural Health Study is a prospective cohort study of commercial and private (mainly farmer) pesticide applicators and spouses of private applicators (information and questionnaires can be obtained at the following website: www.aghealth.org). Institutional review boards of the

Correspondence to Dr. Sherry L. Farr, 4770 Buford Highway, Mail Stop K-34, Atlanta, GA 30341 (e-mail: sherry@alumni.unc.edu).

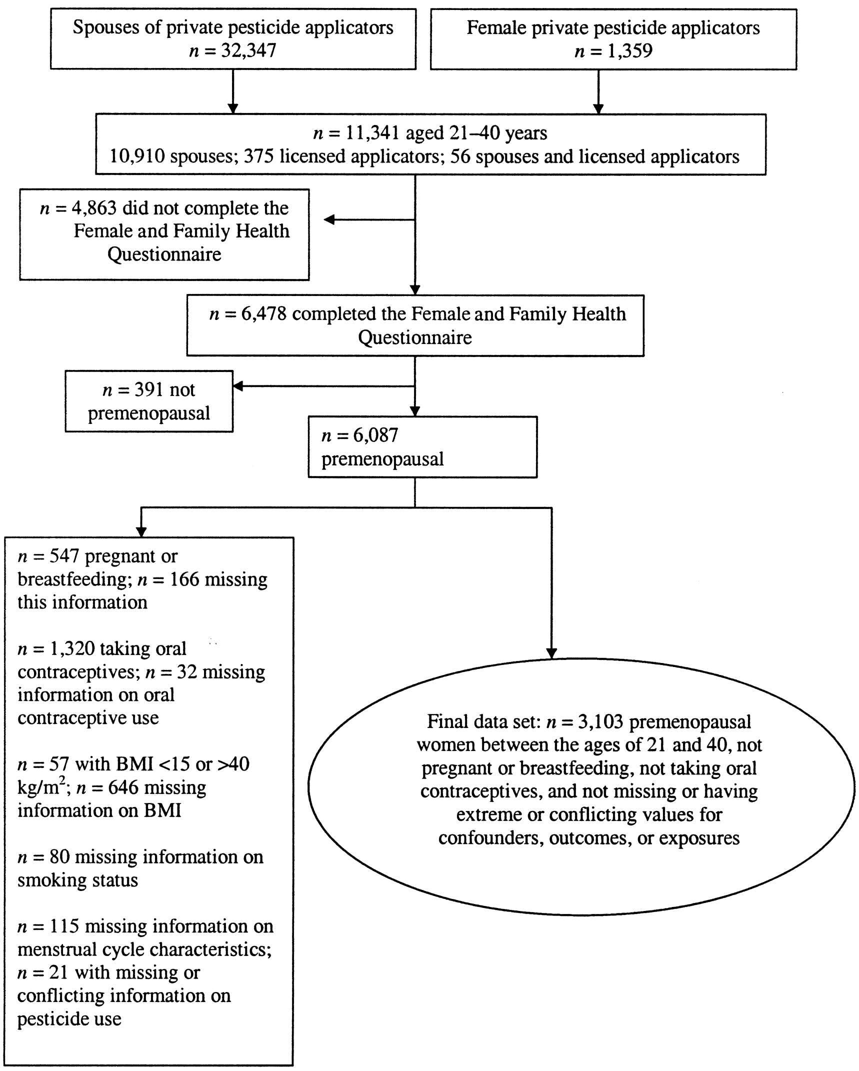

FIGURE 1. Characteristics of the female study population aged 21–40 years from the Agricultural Health Study, Iowa and North Carolina, 1993–1997, analyzed in the current study. BMI, body mass index.

National Cancer Institute and the National Institute of Environmental Health Sciences approved the study. The Agricultural Health Study consists of over 50,000 pesticide applicators from North Carolina and Iowa and more than 32,000 spouses of private applicators (8). Phase I data collection was conducted between 1993 and 1997. Pesticide applicators were recruited at pesticide licensing agencies. Male private applicators who were married were given the Spouse and Female and Family Health Questionnaires to take home to their spouse. Female licensed applicators also received the Female and Family Health Questionnaire. Spouses who did not return their questionnaires by mail were given a subsequent opportunity to enroll by completing the Spouse Questionnaire by telephone.

The Spouse and Applicator Enrollment Questionnaires contained questions on mixing and applying 50 pesticides, farming practices, demographic characteristics, and general health. The Female and Family Health Questionnaire included questions on reproductive health. The current study is based on the responses of female private applicators and female spouses of private applicators who completed the Female and Family Health Questionnaire and the Applicator Enrollment or Spouse Questionnaires, respectively (figure 1).

Seventy-five percent of eligible spouses enrolled in the Agricultural Health Study. Of the enrolled women, 11,341 were between the ages of 21 and 40 years: 10,910 (96.2 percent) were spouses of enrolled farmers, 375 (3.3 percent) were licensed female applicators, and 56 (0.5 percent) were both spouses of enrolled farmers and licensed applicators themselves. Of these enrolled women, 6,478 (57 percent) completed the Female and Family Health Questionnaire; 6,087 (94 percent) of those women were premenopausal by self-report. We excluded 547 women currently pregnant or breastfeeding, 166 women for whom this information was

TABLE 1. Classification of potential endocrine, ovarian, and estrous cycle disruption associated with pesticides in the Agricultural Health Study, Iowa and North Carolina, 1993–1997*

Probable	Possible	Conflicting evidence
	Endocrine disruptors†	
Atrazine	Alachlor	Carbofuran
Lindane	Metribuzin	Benomyl
Mancozeb	Parathion	Dichlorvos
Maneb		Malathion
		Permethrin
		Trifluralin
	Ovarian effects	
Atrazine	Alachlor	Benomyl
Carbaryl	Butylate	Glyphosate
Lindane	Captan	
	Carbofuran	
	Parathion	
	Petroleum oil	
	Trichlorfon	
	Estrous cycle disruptors	
Atrazine	Carbaryl	
Lindane	Carbofuran	
Mancozeb	Cyanazine	
Maneb	Parathion	
	Petroleum oil	

* Limited to pesticides on the market in 1993. The following pesticides showed evidence of no effect or a lack of evidence of an effect on reproductive hormones, the ovary, or the estrous cycle in toxicology studies: 2,4-dichlorophenoxyacetic acid (2,4-D), aldicarb, aluminum phosphide, chlorimuron ethyl, chlorothalonil, chlorpyrifos, coumaphos, diazinon, dicamba, *S*-ethyl dipropylthiocarbamate (EPTC), fonofos, imazethapyr, metalaxyl, methyl bromide, metolachlor, paraquat dichloride, pendimethalin, phorate, terbufos, and ziram.

† The hormones examined were estrogen, androgen, thyroid hormones, progesterone, follicle-stimulating hormone, and luteinizing hormone.

missing, 1,320 women currently taking oral contraceptives, and 32 women for whom information on oral contraceptive use was missing. We also excluded 57 women whose body mass index (weight (kg)/height (m)^2) was extreme (<15.0 or >40.0) and 646 women for whom a value for body mass index was missing. Eighty women were missing information on smoking status, 115 women were missing data on all menstrual cycle characteristics, and 21 women had missing or conflicting values for pesticide use. These exclusions resulted in a final data set of 3,103 premenopausal women aged 21–40 years.

Assessment of menstrual cycle characteristics

We examined the effect of personally mixing or applying pesticides on five menstrual cycle characteristics: short cycles, long cycles, irregular cycles, not experiencing a period for more than 6 weeks in the last 12 months (missed period), and bleeding or spotting between periods in the last 12 months (intermenstrual bleeding). The first three characteristics were based on possible answers to a question about the participant's average menstrual cycle length, with response categories of "24 days or less," "25–30 days," "31–35 days," "36–42 days," "43 days or more," and "too irregular to say." Short periods were defined as 24 days or less. Long periods were defined as more than or equal to 36 days. A woman's period was considered irregular if she chose the answer "too irregular to say." Women were asked about missed periods by the question, "During the past 12 months, did you ever go for 6 weeks or more without a menstrual period? (Do not count times when you were pregnant, breast-feeding, or using birth control pills.)" Intermenstrual bleeding was assessed by the question, "During the past 12 months, did you ever bleed or spot between menstrual periods? (Do not count spotting at the beginning or end of your period.)" The questionnaire did not distinguish between intermenstrual bleeding and spotting at the time of ovulation.

Exposure assessment and assessment of confounding

The pesticide exposure questions for spouses assessed lifetime exposure by asking women whether, in their lifetime, they had ever mixed or applied any of 50 different pesticides, 40 of which were on the market at the time of study enrollment. Using dichotomous variables (yes/no), we examined use of any pesticide in a woman's lifetime as well as ever use of specific functional groups and chemical classes as main exposures in separate analyses. Women were also asked how many days per year, on average, they mixed or applied pesticides, with possible answers of "0 days," "less than 5 days," "5 to 9 days," "10 to 19 days," "20 to 39 days," "40 to 59 days," "60 to 150 days," and "more than 150 days." Based on these subgroups, three categories of women were created: "0 days" (corresponding to the referent group of women who did not use pesticides), "1 to 9 days," and "10 or more days." To examine trends of increased odds of experiencing a menstrual cycle characteristic with increasing days per year of pesticide use, we used an ordinal variable with values equal to the sum of the midpoint of each subgroup weighted by the proportion of subjects in each subgroup. (We used 200 as the midpoint for the subgroup "more than 150 days.") Values for the ordinal variable were 0, 3.9, and 28.8 corresponding to the categories "0 days," "1 to 9 days," and "10 or more days," respectively.

We conducted a literature review by using the National Library of Medicine's PubMed literature database and other toxicology databases to determine which of the 50 pesticides listed in the questionnaires showed evidence of ovarian effects, disruption of estrous cycles in animal models, or evidence of endocrine disruption (estrogen, androgen, progesterone, thyroid, follicle-stimulating hormone, or luteinizing hormone) in in vivo or in vitro tests (table 1) (9). Our aim was to examine effects of recent exposure, so only those pesticides on the market at the time of the questionnaire (1993) were included as exposures in the analyses. We used probable and possible hormonally active or ovotoxic pesticides from table 1 as main exposures in our analyses.

TABLE 2. Number and percentage of women aged 21–40 years with different menstrual cycle lengths reporting missed periods and intermenstrual bleeding,* Agricultural Health Study, Iowa and North Carolina, 1993–1997

Menstrual cycle length†	Missed periods (n = 359)				Intermenstrual bleeding (n = 415)			
	No.	%	r‡	p value	No.	%	r‡	p value
≤24 days (n = 305)	10	3.3	–0.04	0.02	53	17.4	0.05	0.006
25–35 days (n = 2,546)	171	6.7	–0.33	<0.001	303	11.9	–0.09	<0.001
≥36 days (n = 99)	71	71.7	0.43	<0.001	19	19.2	0.04	0.03
Irregular (n = 140)	104	74.3	0.50	<0.001	37	26.4	0.10	<0.001

* Cycle length was defined on the basis of a question about average cycle length, with possible answers of "24 days or less" (short cycles); "25–30 days" or "31–35 days," and "36–42 days" or "43 days or more" (long cycles); and "too irregular to say" (irregular). Information on missed periods was assessed by a question about 6 or more weeks without a menstrual period in the past 12 months. Intermenstrual bleeding was assessed by a question about bleeding or spotting between periods during the past 12 months.

† For 13 women, information on menstrual cycle length was missing.

‡ Pearson correlation coefficient and associated p value.

On the basis of results from a previous analysis of menstrual cycles in the Agricultural Health Study, age, body mass index, education, age at menarche, cigarette smoking, Graves' disease, medically treated depression, and diabetes were identified as possible confounders of an association between pesticides and menstrual function (10). Our base model for all analyses included age as a continuous variable, body mass index as a categorical variable (15.0–<18.5, 18.5–<30.0, and 30.0–40.0 kg/m^2), and a dichotomous variable (smoker/nonsmoker) for smoking status at the time of enrollment. No other variables confounded the association between ever mixing or applying pesticides and menstrual characteristics as assessed by at least a 10 percent change in the odds ratios.

Analysis

Because of the correlated nature of the outcomes (table 2), we used marginal models for simultaneous modeling of the five menstrual cycle characteristics. The generalized estimating equations approach was used to estimate cross-sectional associations. Data were analyzed by using the GENMOD procedure in SAS software (11) to estimate the odds ratios and 95 percent confidence intervals for pesticide use and each menstrual cycle characteristic. We included interaction terms between each confounder and an indicator variable for the menstrual cycle characteristics (short cycles, long cycles, irregular cycles, missed periods, and intermenstrual bleeding) to allow for varying relations across the outcomes. Similarly, we included interaction terms between the exposure of interest and indicator variables for menstrual cycle characteristics to determine the exposure's effect on each characteristic. When a trend toward longer or shorter cycles was seen, we conducted a Wald test for the trend and computed a two-sided p value.

Women whose cycles lasted 25–35 days composed the comparison group for the analyses on short, long, and irregular cycles. The comparison groups for the other outcomes of interest, missed periods and intermenstrual bleeding, included women who did not experience those outcomes. Women who had never used any pesticides were considered the unexposed group for analyses on pesticide exposure, except where otherwise stated in this paper.

Husbands and female licensed applicators were asked whether they had used the specific pesticides in the last 12 months. It is more likely that women whose husbands had used the pesticide in the last 12 months would have used the pesticide themselves in the previous year. In a separate analysis, we limited the "exposed" group to women who reported using the pesticide in their lifetime and they (if licensed applicators) or their husbands reported using the pesticide in the preceding 12 months.

Physical activity may disrupt a woman's menstrual cycle (12–14). Our data on occupational physical activity were limited to days during the last growing season working in the fields (0, 1–10, 11–30, and >30 days). This information was available for spouses but not for licensed applicators, so, in a model limited to spouses, we conducted a subanalysis controlling for days worked in the fields. In separate analyses on probable hormonally active pesticides, we limited our reference group to women who had worked in the fields during the last growing season but who had never used pesticides. We also compared women who had used probable hormonally active pesticides with those who had used pesticides not considered probable or possible hormonally active or ovotoxic, excluding women who had never used pesticides.

RESULTS

The mean age of the women was 35 years, and the mean length of time they had lived or worked on a farm was 21 years (table 3). Over 98 percent of the population was White, and the majority had been educated beyond high school. Approximately 57 percent had ever mixed or applied any pesticide, with the majority of those mixing and applying 1–9 days per year. Thirty-three percent of the women had applied hormonally active or ovotoxic pesticides.

Women who had used any type of pesticide were slightly older and had lived on a farm for more years than women

TABLE 3. Demographic and behavioral characteristics, pesticide use, and menstrual cycle characteristics of 3,103 women aged 21–40 years in the Agricultural Health Study, Iowa and North Carolina, 1993–1997

Characteristic	Total (*n* = 3,103, 100%)*	Used hormonally active or ovotoxic† pesticides (*n* = 1,023, 33.0%)	Used other‡ pesticides (*n* = 731, 23.6%)	Never used pesticides (*n* = 1,349, 43.5%)
	Mean (*standard deviation*)			
Age (years)	34.8 (4.1)	35.3 (3.8)	34.7 (4.2)	34.3 (4.3)
Body mass index (kg/m^2)	24.9 (4.5)	25.3 (4.6)	24.9 (4.4)	24.6 (4.5)
No. of pregnancies	2.9 (1.3)	3.0 (1.4)	2.9 (1.2)	2.8 (1.4)
No. of years living or working on a farm	20.7 (11.9)	23.7 (11.2)	21.7 (11.7)	18.0 (11.9)
	Frequency (*%*)			
Age (years)				
21–25	93 (3.0)	15 (1.5)	24 (3.3)	54 (4.0)
26–30	395 (12.7)	97 (9.5)	93 (12.7)	205 (15.2)
31–35	1,091 (35.2)	355 (34.7)	262 (35.8)	474 (35.1)
36–40	1,524 (49.1)	556 (54.3)	352 (48.2)	616 (45.7)
State				
Iowa	2,332 (75.2)	715 (69.9)	628 (85.9)	989 (73.3)
North Carolina	771 (24.9)	308 (30.1)	103 (14.1)	360 (26.7)
Race				
White	3,061 (98.6)	1,017 (99.4)	725 (99.2)	1,319 (97.8)
Other/multiple	39 (1.3)	6 (0.6)	5 (0.7)	28 (2.1)
Missing	3 (0.1)	0	1 (0.1)	2 (0.1)
Education				
<High school	51 (1.7)	17 (1.7)	3 (0.4)	31 (2.3)
High school/general equivalency diploma	928 (29.9)	285 (27.8)	202 (27.6)	441 (32.7)
>High school	1,863 (60.0)	631 (61.7)	442 (60.5)	790 (58.6)
Missing/multiple	261 (8.4)	90 (8.8)	84 (11.5)	87 (6.4)
Smoking status				
Never smoker	2,209 (71.2)	716 (70.0)	536 (73.3)	957 (70.9)
Former smoker	513 (16.5)	185 (18.1)	106 (14.5)	222 (16.5)
Current smoker	380 (12.2)	122 (11.9)	89 (12.2)	169 (12.5)
Missing§	1 (0.1)	0	0	1 (0.1)

Table continues

who had never used pesticides (table 3). Women who had ever used hormonally active pesticides mixed or applied pesticides more days per year and worked in the fields more days during the last growing season than women who had used other pesticides. Long cycles and missed periods were reported by a slightly larger percentage of women who had used hormonally active pesticides than by women who had never used pesticides. No other major differences existed between groups.

Certain menstrual cycle characteristics were correlated with one another (table 2). Women who reported experiencing short cycles had fewer reports of missed periods and more reports of intermenstrual bleeding than women with cycles 25–35 days in length. Women whose menstrual cycles were long or irregular had more reports of missed periods and intermenstrual bleeding than women with cycles 25–35 days in length.

General pesticide exposures

Increased cycle length was associated with ever mixing or applying any type of pesticide ($p = 0.02$) (table 4). Ever mixing or applying pesticides was also associated with fewer reports of irregular cycles (odds ratio (OR) = 0.55) and increased reports of missed periods (OR = 1.6). There were trends toward increased odds of long cycles ($p = 0.08$) and missed periods ($p < 0.001$) with increasing days of pesticide use.

Among women who had never mixed or applied pesticides, number of days worked in the fields was associated

TABLE 3. Continued

Characteristic	Total (*n* = 3,103, 100%)*	Used hormonally active or ovotoxic† pesticides (*n* = 1,023, 33.0%)	Used other‡ pesticides (*n* = 731, 23.6%)	Never used pesticides (*n* = 1,349, 43.5%)
Pesticide applicator status				
Spouse only	3,035 (97.8)	967 (94.5)	724 (99.0)	1,344 (99.6)
Licensed applicator only	59 (1.9)	50 (4.9)	5 (0.7)	4 (0.3)
Spouse/licensed applicator	9 (0.3)	6 (0.6)	2 (0.3)	1 (0.1)
No. of days per year mixing or applying pesticides				
0	1,349 (43.5)	0	0	1,349 (100)
1–9	873 (28.1)	522 (51.0)	351 (48.0)	0
≥10	345 (11.1)	247 (24.2)	98 (13.4)	0
Missing	536 (17.3)	254 (24.8)	282 (38.6)	0
No. of days worked in the fields during the last growing season¶				
0	1,346 (44.2)	285 (29.3)	277 (38.2)	784 (58.3)
1–10	695 (22.8)	222 (22.8)	211 (29.1)	262 (19.5)
11–30	567 (18.6)	232 (23.8)	144 (19.8)	191 (14.2)
>30	418 (13.7)	226 (23.2)	88 (12.1)	104 (7.7)
Missing	18 (0.6)	8 (0.8)	6 (0.8)	4 (0.3)
Menstrual cycle characteristics#				
Short cycles	305 (9.8)	93 (9.1)	67 (9.2)	145 (10.8)
Long cycles	99 (3.2)	42 (4.1)	21 (2.9)	36 (2.7)
Irregular cycles	140 (4.5)	40 (3.9)	31 (4.2)	69 (5.1)
Missed period	359 (11.6)	128 (12.5)	86 (11.8)	145 (10.8)
Intermenstrual bleeding	414 (13.4)	157 (15.4)	87 (11.9)	171 (12.7)

* The percentages in the headings of the next three columns do not total 100 because of rounding.

† Women who had ever used the following pesticides classified as probable or possible hormonally active or ovotoxic: atrazine, lindane, mancozeb or maneb, carbaryl, alachlor, metribuzin, parathion, butylate, captan, carbofuran, petroleum oil, trichlorfon, or cyanazine; these women may have also used pesticides other than the probable or possible hormonally active or ovotoxic pesticides.

‡ Women who used pesticides categorized as associated with conflicting evidence of hormonal activity or ovotoxicity or that showed no effect or lacked evidence of an effect on reproductive hormones, the ovary, or the estrous cycle.

§ The one woman for whom information on smoking status was missing answered "no" to an additional question on whether she was a current smoker at the time of the questionnaire.

¶ No data were available for women who were licensed applicators only.

Short, long, and irregular cycles were defined on the basis of a question about average cycle length: short = ≤24 days, long = 36–42 days or ≥43 days, irregular = "too irregular to say." Information on missed periods was assessed by a question about going ≥6 weeks without a menstrual period in the past 12 months. Intermenstrual bleeding was assessed by a question about bleeding or spotting between periods during the past 12 months.

with increased odds of missed periods (OR = 1.6, 95 percent confidence interval: 1.1, 2.3 and OR = 1.5, 95 percent confidence interval: 0.79, 2.9 for 1–30 days and >30 days vs. 0 days, respectively). Controlling for days per year worked in the fields by spouses resulted in some changes in the odds of short cycles (OR = 0.81 to OR = 0.71), irregular periods (OR = 0.55 to OR = 0.61), and missed periods (OR = 1.6 to OR = 1.3) when we compared women who had ever used pesticides with those who had never used pesticides. No other associations between pesticide use and menstrual cycle characteristics changed after we controlled for days worked in the fields (data not shown).

Use of carbamate pesticides was associated with increased odds of long cycles (OR = 2.1) and decreased odds of irregular cycles (OR = 0.38) (table 4). Use of herbicides was associated with decreased odds of short cycles (OR = 0.63) and irregular periods (OR = 0.56) and increased odds of missed periods (OR = 1.4). Furthermore, crop insecticides were associated with a shift toward longer cycles (p = 0.04), decreased odds of irregular cycles, and increased odds of missed periods. Use of fumigants was associated with increased odds of short cycles (OR = 6.0) and missed periods (OR = 3.5), although estimates were imprecise. Other associations between chemical classes or functional pesticide groups and menstrual cycle characteristics were weaker.

TABLE 4. Associations between pesticide exposure and menstrual cycle characteristics* among premenopausal women aged 21–40 years in the Agricultural Health Study, Iowa and North Carolina, 1993–1997

Exposure	Total (no.)	Exposed (no.)	Menstrual cycle characteristic: Short		Long		Irregular		Missed period		Intermenstrual bleeding	
			OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Ever mixed or applied pesticides‡	3,103	1,754	0.81	0.63, 1.0	1.4	0.93, 2.1§	0.55	0.41, 0.75	1.6	1.3, 2.0	1.1	0.90, 1.4
No. of days mixing or applying pesticides‡	2,567											
1–9	873		0.62	0.45, 0.84	1.1	0.67, 1.9	0.34	0.21, 0.54	1.4	1.0, 1.8	1.1	0.86, 1.4
≥10	345		1.0	0.69, 1.5	1.7	0.93, 3.2¶	0.84	0.52, 1.4	1.8	1.3, 2.6¶	1.1	0.76, 1.5
Pesticide class#,**												
Anilide	1,509	160	0.84	0.17, 4.2	—††		—		0.81	0.17, 3.8	2.0	0.66, 6.2
Carbamate	2,213	866	0.93	0.62, 1.4	2.1	1.1, 3.7	0.38	0.19, 0.77	1.4	0.94, 2.1	1.2	0.88, 1.8
Dinitroaniline	1,525	176	2.0	0.66, 5.8	—		1.2	0.21, 7.2	0.98	0.29, 3.4	0.60	0.19, 1.9
Organophosphate	2,172	823	0.78	0.48, 1.3	1.3	0.55, 2.9	0.54	0.28, 1.1	1.4	0.93, 2.2	0.96	0.64, 1.4
Triazine	1,518	169	0.89	0.33, 2.4	—		—		1.3	0.40, 4.1	1.0	0.37, 2.9
Functional group#												
Herbicide	2,640	1,291	0.63	0.42, 0.95	0.99	0.50, 2.0	0.56	0.34, 0.94	1.4	1.0, 2.0	1.1	0.79, 1.5
Crop insecticide	2,606	1,259	0.82	0.55, 1.2	1.7	0.96, 3.2§	0.43	0.24, 0.77	1.6	1.2, 2.3	1.2	0.89, 1.7
Livestock insecticide	1,753	404	0.46	0.12, 1.9	1.9	0.39, 9.8	—		1.2	0.45, 3.0	0.66	0.22, 2.0
Fumigant	1,551	202	6.0	1.5, 24.7	—		1.3	0.18, 8.6	3.5	1.0, 12.5	—	
Fungicide	1,628	279	1.8	0.44, 7.5	—		1.0	0.12, 8.6	2.6	0.78, 8.7	0.94	0.24, 3.7

* Short, long, and irregular cycles were defined on the basis of a question about average cycle length: short = ≤24 days, long = 36–42 days or ≥43 days, irregular = "too irregular to say." Information on missed periods was assessed by a question about going ≥6 weeks without a menstrual period in the past 12 months. Intermenstrual bleeding was assessed by a question about bleeding or spotting between periods during the past 12 months. Associations were determined from simultaneous modeling of the five menstrual cycle characteristics by using generalized estimating equations, controlling for age (continuous variable), body mass index (three categories), and current smoking status (yes/no).

† OR, odds ratio; CI, confidence interval.

‡ Comparing women who used any pesticide (hormonally active, ovotoxic, or other) with women who never used any pesticide.

§ Statistically significant shift toward longer menstrual cycles; ever mixed or applied pesticides: $p = 0.02$; crop insecticide: $p = 0.04$.

¶ Trend test using a three-level ordinal variable weighted to the mean number of days of pesticide use per year (0, 3.9, and 28.8 days for the categories of 0, 1–9, and ≥10 days, respectively). Trend p value for long cycles: $p = 0.08$; trend p value for missed periods: $p < 0.001$.

\# Compared with women who never used pesticides.

** Anilides: alachlor, metolachlor; carbamates: aldicarb, benomyl, carbaryl, carbofuran; dinitroanilines: pendimethalin, trifluralin; organophosphates: chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, trichlorfon; triazines: atrazine, cyanazine.

†† Too few women experienced this menstrual cycle characteristic to estimate an effect.

Hormonally active and ovotoxic pesticides

Limiting our analysis of exposed women to those who had ever used probable or possible hormonally active or ovotoxic pesticides only slightly strengthened the associations seen with general pesticide use (table 5). Women who used probable or possible hormonally active or ovotoxic pesticides had fewer reports of irregular menstrual cycles (OR = 0.53) but greater odds of long cycles (OR = 1.6), missed periods (OR = 1.7), and intermenstrual bleeding (OR = 1.3) than women who had never used pesticides. We found trends toward increased odds of long cycles ($p = 0.05$) and missed periods ($p = 0.001$) with increasing days per year of pesticide use among women who used hormonally active pesticides.

Lindane, atrazine, and mancozeb or maneb are probable hormonally active pesticides as well as probable estrous-cycle-disrupting pesticides. Limiting the exposed group to women who had ever used these pesticides further strengthened the associations between pesticide use and menstrual cycle characteristics (table 5). Use of these pesticides was associated with long cycles (OR = 2.7), missed periods (OR = 2.1), and intermenstrual bleeding (OR = 1.6) compared with never use of these pesticides.

We analyzed the probable follicle-stimulating hormone or luteinizing hormone disruptors lindane and atrazine together as a main exposure, excluding women who had also used mancozeb or maneb, a probable thyroid disruptor, to examine the effects of pesticides with differing endocrine profiles. Mancozeb or maneb was also examined after we excluded women who had used lindane or atrazine (table 5). Compared with never mixing or applying pesticides, use of lindane or atrazine was associated with long cycles (OR = 2.7), missed periods (OR = 2.0), and intermenstrual bleeding (OR = 1.7). Use of these pesticides was also associated with decreased odds of irregular cycles (OR = 0.45). Women who had used mancozeb or maneb had four times the odds of experiencing long cycles and two times the odds of experiencing missed periods as women who had never used pesticides. No other outcomes were associated with the use of mancozeb or maneb.

TABLE 5. Associations between hormonal-, ovarian-, or estrous-cycle-disrupting pesticides and menstrual cycle characteristics* among premenopausal women aged 21–40 years in the Agricultural Health Study, Iowa and North Carolina, 1993–1997

Exposure†	Total (no.)	Exposed (no.)	Menstrual cycle characteristic: Short		Long		Irregular		Missed period		Intermenstrual bleeding	
			OR‡	95% CI‡	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any probable or possible hormonally active-, ovarian-, or estrous-cycle-disrupting pesticide§	2,372	1,023	0.82	0.62, 1.1	1.6	1.0, 2.5¶	0.53	0.37, 0.78	1.7	1.3, 2.2	1.3	1.0, 1.6
Probable hormonally active-, ovarian-, or estrous-cycle-disrupting pesticide#	2,283	934	0.81	0.61, 1.1	1.6	1.0, 2.5¶	0.52	0.36, 0.77	1.7	1.3, 2.2	1.2	0.97, 1.6
No. of days mixing or applying pesticides§	2,118											
1–9	522		0.58	0.40, 0.86	1.2	0.66, 2.2	0.31	0.17, 0.57	1.5	1.1, 2.1	1.2	0.89, 1.6
≥10	247		1.2	0.76, 1.8	2.0	1.0, 3.9**	0.81	0.45, 1.4	1.7	1.1, 2.6**	1.2	0.83, 1.8
Probable hormonally active pesticides††	1,561	212	0.86	0.52, 1.4	2.7	1.4, 5.2¶	0.56	0.27, 1.2	2.1	1.4, 3.2	1.6	1.1, 2.4
Lindane, atrazine, excluding mancozeb or maneb	1,510	161	0.92	0.53, 1.6	2.7	1.3, 5.5¶	0.45	0.18, 1.1	2.0	1.3, 3.3	1.7	1.1, 2.7
Mancozeb or maneb excluding lindane and atrazine	1,383	34	1.1	0.34, 3.5	4.7	1.3, 16.6	1.0	0.23, 4.3	2.5	1.0, 5.9	0.95	0.33, 2.8
Pesticide use in the previous 12 months‡‡												
Any possible or probable hormonally active-, ovarian-, or estrous-cycle-disrupting pesticide§	1,586	237	0.99	0.63, 1.6	1.6	0.80, 3.4	0.68	0.37, 1.3	2.3	1.6, 3.4	1.3	0.89, 1.9
Any probable hormonally active pesticide††	1,422	73	0.92	0.42, 2.0	2.4	0.79, 7.1	0.58	0.18, 1.9	2.4	1.3, 4.5	1.4	0.71, 2.6
Any probable hormonally active pesticide												
Controlling for days worked in the field during the last growing season among farmers' wives§§	1,527	186	0.67	0.36, 1.2	2.5	1.2, 5.2¶	0.65	0.27, 1.6	1.6	0.99, 2.6	1.6	1.0, 2.4
Comparison group: women who worked in the fields but never used pesticides	769	212	0.79	0.45, 1.4	2.9	1.4, 6.1¶	0.79	0.35, 1.8	1.6	1.0, 2.6	1.6	1.0, 2.4
Comparison group: women who used "other" pesticides¶¶	943	212	1.1	0.66, 1.9	2.6	1.3, 5.4	1.1	0.49, 2.4	1.6	1.0, 2.5	1.7	1.1, 2.6

* Short, long, and irregular cycles were defined on the basis of a question about average cycle length: short = ≤24 days, long = 36–42 days or ≥43 days, irregular = "too irregular to say." Information on missed periods was assessed by a question about going ≥6 weeks without a menstrual period in the past 12 months. Intermenstrual bleeding was assessed by a question about bleeding or spotting between periods during the past 12 months. Associations were determined from simultaneous modeling of the five menstrual cycle characteristics by using generalized estimating equations, controlling for age (continuous variable), body mass index (three categories), and current smoking status (yes/no).

† All exposures are lifetime exposures, unless otherwise stated.

‡ OR, odds ratio; CI, confidence interval.

§ Comparing women who used lindane, atrazine, mancozeb or maneb, carbaryl, alachlor, parathion, butylate, captan, carbofuran, petroleum oil, trichlorfon, or cyanazine with women who never used any pesticide.

¶ Statistically significant shift toward long menstrual cycles; any probable or possible hormonally active-, ovarian-, or estrous-cycle-disrupting pesticide: $p = 0.008$; probable hormonally active-, ovarian-, or estrous-cycle-disrupting pesticide: $p = 0.01$; probable hormonally active pesticides: $p = 0.007$; lindane, atrazine, excluding mancozeb or maneb: $p = 0.02$; any probable hormonally active pesticide controlling for days worked in the field: $p = 0.006$; any probable hormonally active pesticide (compared with women who worked in the field but never used pesticides): $p = 0.005$.

\# Comparing women who used lindane, atrazine, mancozeb or maneb, or carbaryl with women who never used pesticides.

** Trend test using a three-level ordinal variable weighted to the mean number of days of pesticide use per year (0, 3.9, and 28.8 day, for the categories of 0, 1–9, and ≥10 days, respectively). Trend p value for long cycles: $p = 0.047$; missed periods: $p = 0.001$.

†† Comparing women who used lindane, atrazine, or mancozeb or maneb with women who never used pesticides.

‡‡ Women who used the pesticide in their lifetime and who (if licensed applicators) or whose husband had used the pesticide in the previous 12 months.

§§ Days worked in the field (four categories: 0, 1–10, 11–30, and >30 days).

¶¶ Pesticides not considered probable or possible hormonally active or ovotoxic.

After we excluded from the exposed group female licensed applicators who had not used probable hormonally active pesticides in the last 12 months and spouses whose husbands had not used these pesticides in the last 12 months, the odds of long cycles, missed periods, and intermenstrual bleeding among women exposed to lindane, atrazine, or mancozeb or maneb remained elevated compared with those among unexposed women, but with a greater degree of imprecision (table 5).

We attempted to control for occupational physical activity and the "healthy worker effect" by 1) adjusting for number of days worked in the fields, 2) limiting our reference group to women who had worked out in the fields, and 3) limiting our reference group to women who had applied pesticides other than those considered probable or possible hormonally active or ovotoxic. In all three analyses, the overall pattern for probable hormonally active pesticide use remained, with increased odds of long cycles, missed periods, and intermenstrual bleeding among women mixing or applying probable hormonally active pesticides. However, the odds of short and irregular periods were attenuated in all analyses. Additionally, neither controlling for applicator status nor excluding licensed applicators from our analyses affected associations.

Farm size, types of crops grown, and pesticides used are known to differ among the North Carolina and Iowa participants in the study. However, associations remained similar when analyses were stratified by state (data not shown).

DISCUSSION

To our knowledge, this study is the first to examine the effect of several pesticides on menstrual function in women. Some of the pesticides considered in our analyses affect the ovary or estrous cycle or disrupt certain hormones in animals, and we were able to examine pesticides based on these properties. The population of women was large (n = 3,103), and women who live and work on farms are thought to be among the US female populations most highly exposed to pesticides.

Ever mixing or applying pesticides and using hormonally active pesticides showed trends toward increased menstrual cycle length and increased odds of missed periods. These relations remained after we controlled for occupational physical activity. It is unclear whether the shift toward increased cycle length among pesticide users is due to lengthening of a specific phase of the menstrual cycle or of experiencing missed periods and reporting long cycles. These associations strengthened as we further limited our exposed group to those women who had used the probable hormonally active pesticides shown to affect the estrous cycle in animal studies. The probable hormonally active pesticides also showed a positive association with intermenstrual bleeding.

The three pesticides with the strongest effects on the ovary, the estrous cycle, or reproductive hormones in toxicology studies—lindane, atrazine, and mancozeb or maneb—also seemed to have strong associations in the current study. Lindane has been shown to delay ovulation, reduce the number of corpora lutea, and disrupt the estrous cycle in animals (15–22). Atrazine may alter the estrous cycle and reduce ovarian weight in certain animals (23–30). Both may also disrupt follicle-stimulating hormone or luteinizing hormone in animals or in vitro (16, 18, 31–44). In this study, use of mancozeb or maneb, fungicides shown to affect the thyroid gland in toxicology studies, was associated with increased odds of long cycles and missed periods, although our results were based on a small number of women exposed to these products (n = 34). Conditions that disrupt thyroid hormones in women, such as hypothyroidism and hyperthyroidism, are associated with short and long cycles, amenorrhea, anovulation, and infertility (45, 46). However, self-reported thyroid diseases were not associated with menstrual cycle characteristics in this population of women (10). Exposures to chemicals that affect hormones other than estrogen may be relevant with respect to menstrual cycle function. However, because of the limitations of our data, we are unable to speculate on the mechanisms underlying the association between pesticide use and menstrual cycle characteristics among this population.

Two studies have examined pesticide exposures and menstrual cycle function in human populations (6, 7). Both found associations of serum levels of DDT or dichlorodiphenyldichloroethylene, a breakdown product of DDT, with short cycles (7) and undefined "menstrual disturbances" (6). We were unable to compare our results with these findings because, in 1993, DDT was no longer in use in the United States, only 16 women in our sample had ever used the pesticide, and we did not have biomarkers of exposure. Other environmental and occupational exposures such as polychlorinated biphenyls (47, 48), dioxin (49), and other solvents (50) have been associated with changes in menstrual cycle length and flow. On the basis of toxicology studies, there is speculation that these environmental contaminants may disrupt reproductive hormones or affect the ovary; however, biologic mechanisms for these associations are still unknown.

Long cycles, irregular cycles, missed periods, and intermenstrual bleeding were associated with infertility in this population (10). Other studies have found associations between pesticide exposure and reduced fecundability in women (51–53). However, none of these studies also examined menstrual function.

We restricted our analysis to those women who were between ages 21 and 40 years, had completed two questionnaires from the Agricultural Health Study, and were premenopausal, not pregnant or breastfeeding, and not taking oral contraceptives. Women whose values for body mass index and smoking status were extreme or were missing were also excluded. These exclusion criteria may have introduced bias into our sample. However, demographic characteristics did not differ between women who completed two questionnaires and women who completed only one (10). Additionally, after we controlled for age, we did not find that pregnancy, breastfeeding, and use of oral contraceptives at the time of the questionnaire were associated with ever mixing or applying pesticides. Crude associations between pesticide use and menstrual cycle characteristics did not change after we excluded women whose values for body mass index and smoking status were extreme or missing.

Physical activity may lengthen the menstrual cycle (12–14). After we controlled for occupational physical activity, associations between use of hormonally active pesticides and long cycles, missed periods, and intermenstrual bleeding remained. However, controlling for occupational physical activity attenuated associations between pesticide use and short and irregular periods.

Although this is the first study known to report the impact of specific pesticide use on women living on farms, our pesticide exposure information is limited in detail. Spouses were asked whether they had ever used each of 50 pesticides in their lifetimes. If exposure occurred on a limited basis several years ago and the effect of the pesticide on menstrual function is immediate, labeling these women as "exposed" would dilute an association. It is more likely that women reported pesticides they used most commonly on the farm from one year to the next. Additionally, no substantial changes in odds ratios were found after we restricted the exposed group to women who had used the pesticide in their lifetime and whose husbands had used the pesticide in the last 12 months.

Women classified as "unexposed" may have been exposed to pesticides via work in the fields, contact with their husband, or tracking of pesticides into the home. However, we would expect these scenarios to attenuate our estimate of the odds of menstrual cycle characteristics among exposed women compared with unexposed women.

Recall of menstrual cycle regularity may be unreliable (54–56). Women in this study reported "average" cycle length, and menstrual cycle diaries were not used. However, missed periods and intermenstrual bleeding were inquired about specifically "within the last 12 months," which should lessen the amount of misclassification for these two outcomes. Participants in this study were premenopausal women between the ages of 21 and 40 years. Therefore, it is more likely that these women would report on recent menstrual cycles rather than menstrual cycles from the distant past.

To our knowledge, this study is the first of its kind to examine the effect of hormonally active or ovotoxic pesticides on menstrual function. This type of classification is potentially more informative than groups based on pesticide class or functional group. Our findings, along with results from toxicology studies, suggest that use of certain hormonally active pesticides may affect menstrual cycles. Many studies have examined the risk of infertility or poor semen quality among men exposed to pesticides (57–60); however, few have examined the effect of pesticide exposure on women's reproductive health (6, 7, 51–53). Future research should include detailed menstrual cycle and pesticide exposure data to further elucidate the association between pesticide exposure and menstrual cycle characteristics.

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