DDE and Shortened Duration of Lactation in a Northern Mexican Town

Beth C. Gladen, PhD, and Walter J. Rogan, MD

ABSTRACT

Objectives. Worldwide declines in the duration of lactation are cause for public health concern. Higher levels of dichlorodiphenyl dichloroethene (DDE) have been associated with shorter durations of lactation in the United States. This study examined whether this relationship would hold in an agricultural town in northern Mexico.

Methods. Two hundred twenty-nine women were followed every 2 months from childbirth until weaning or until the child reached 18 months of age. DDE was measured in breast milk samples taken at birth, and women were followed to see how long they lactated.

Results. Median duration was 7.5 months in the lowest DDE group and 3 months in the highest. The effect was confined to those who had lactated previously, and it persisted after statistical adjustment for other factors. These results are not due to overtly sick children being weaned earlier. Previous lactation lowers DDE levels, which produces an artifactual association, but simulations using best estimates show that an effect as large as that found here would arise through this mechanism only 6% of the time.

Conclusions. DDE may affect women's ability to lactate. This exposure may be contributing to lactation failure throughout the world. (*Am J Public Health.* 1995;85:504–508)

Introduction

Declines in both the initiation and the duration of lactation have been reported from around the world.[1] This is of serious public health concern because of the associated increased morbidity and mortality, which are most striking in developing countries but are also detectable in developed countries.[2,3] The declines have mostly been attributed to social factors such as lack of education, "modernization," household structure, attitudes, and medical practices.[4,5] A few xenobiotics are also known to affect lactation; examples are hormonal contraceptives[6,7] and smoking.[8,9] In addition, higher maternal levels of DDE (dichlorodiphenyl dichloroethene, the most stable derivative of the pesticide DDT) have been associated with shortened duration of lactation in the general population in North Carolina.[10]

Mexico has relatively high DDE levels,[11] and the Comarca Lagunera, a cotton-growing region in the north where DDE was used heavily, has especially high levels.[12,13] To see whether the previous results could be replicated, we undertook a study of maternal DDE and duration of lactation in this region.

Methods

The study took place in Tlahualilo, a town in the state of Durango. Tlahualilo is in the Comarca Lagunera region and thus can be expected to have high DDE levels. It is an agricultural town and relatively culturally homogeneous, potentially eliminating some extraneous variability in lactation patterns. Finally, the town is of appropriate size to provide an adequate sample size in a reasonable time frame.

We enrolled pregnant women after informed consent was obtained and followed them to determine how long they lactated. Enrollment occurred between September 1988 and October 1989. To be eligible, the women had to be willing to participate; had to speak Spanish; had to have lived in the area for 3 years; had to have no plans to move away or to be away for 2 months in the next 2 years; had to be 16 or older; had to have a live birth; had to have no more than five other children; had to be planning to breast-feed; and had to have no anticipated deadline that would determine the length of lactation, such as returning to work. The current child had to be a singleton, could not be premature (under 2 kg or 36 weeks), and had to be free of major birth defects or illnesses.

A questionnaire was administered shortly after the child's birth; it included demographic and socioeconomic items, medical history of the mother, reproductive history of the mother, mother's attitudes toward child feeding, and information about the pregnancy and delivery. Each woman was visited every 2 months until her child was weaned or was 18 months old. Questionnaires were administered at each visit; they included information about the feeding of the child, any illnesses of the child or the mother, and growth of the child.

Milk samples were collected by manual expression near birth and at 6

Beth C. Gladen is with the Statistics and Biomathematics Branch and Walter J. Rogan is with the Office of the Scientific Director, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Requests for reprints should be sent to Beth C. Gladen, PhD, Statistics and Biomathematics Branch, Mail Drop A3-03, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709.

This paper was accepted September 22, 1994.

months. The milk was analyzed for p,p'-DDE and p,p'-DDT by capillary gas chromatography with electron capture detection.[14] Since DDE and DDT partition into fat and the fat content of milk samples varies, fat content was measured and the results expressed as grams of DDE or DDT per grams of milk fat.

Time until weaning was analyzed by methods for censored data. We constructed Kaplan-Meier curves and assessed differences between them by use of Wilcoxon tests. We also fit proportional hazards models, where DDE was included as a categorical predictor. These are models in which the hazard (the instantaneous probability of weaning, given that weaning has not yet occurred) for a woman in one DDE group is a constant ratio of the hazard for the baseline group. Whether the DDE groups differed was assessed by Wald tests; these provide simultaneous tests of whether the DDE parameters are all equal to zero. Analysis was done with the computer package SAS (SAS Institute, Cary, NC).

The reasons for weaning a child are quite variable. Some are relevant to the hypothesis under study and some are not. For lactations observed in full, we separated reasons into those in which external factors intruded on the lactation process and those where the lactation process may have failed. Reasons indicating external factors were illness of mother (20 cases), breast problems (4), separation of mother and child (10), pregnancy (11), use of oral or injectable contraceptives (14), and mother's perception that the child was old enough to be weaned (14). Reasons indicating possible failure were insufficient milk (61 cases), child's refusal of the breast (42), both these reasons (9), and child's adverse reaction to milk or failure to thrive (10). We repeated the analyses, considering a lactation that ended owing to external factors to have been censored at that point.

Hormones influence the lactation process.[6,7] Once a woman becomes pregnant or takes contraceptives or other hormonal medications, her risk of weaning may be different from what it was before. We repeated the analyses, excluding all data after pregnancy or hormonal medication began, considering this as additional censoring.

Proportional hazards models were adjusted for the factors shown in Table 1, which have been shown to be related to duration of lactation.[4,5,15–25] The categories shown in the table were used in the analyses.

TABLE 1—Description of the Sample: 229 Lactating Women, Tlahuallio, Mexico

	%
Maternal age, y	
16–19	24
20–24	33
25–29	31
≥30	12
Paternal age, y	
16–19	12
20–24	31
25–29	30
≥30	27
Maternal education, y	
0–4	29
5–9	50
10–13	22
Paternal education, y	
0–4	29
5–9	42
10–13	29
Mother employed before pregnancy	
Yes	9
No	91
Father's job	
Farm or farm-related	63
White collar	13
Blue collar	20
Other	4
Family income, thousand pesos per month	
<100	35
100–200	31
>200	35
Father living with mother	
Yes	90
No	11
No. of children	
1	31
2	28
3+	41
Maternal body mass index (kg/m^2)	
<22.5	31
22.5–27.5	42
≥27.5	27
Maternal tricep skinfold thickness, mm	
14–19	12
20–29	62
30–35	25
Maternal health during pregnancy	
Good	59
Fair	35
Poor	7
Mother received instructions on feeding at prenatal care	
Yes	10
No	90
Where child was born	
Hospital or clinic	94
Home or midwife	6
Hours until child was first fed	
0–19	17
24	45
≥25	37
Feeding pattern in hospital	
Demand	63
Schedule	37
Child given milk in a bottle in hospital	
Yes	85
No	15
Child's sex	
Male	54
Female	46
Birthweight, kg	
<3	31
3–3.5	36
≥3.5	34
Formula present in the house at birth	
Yes	66
No	35
Age when mother thinks weaning should begin, mo (asked at admission)	
1–2	14
3	49
4–5	18
≥6	18

Several other factors were not included. Only four mothers smoked, and the maximum smoked was three cigarettes per day. At admission, only seven women were unaware of brand names of formulas and where formulas could be purchased; all but one of those women could name brands by the next visit. Time of introduction of alternate foods is predictive of duration; however, since failure of lactation would cause early introduction, this factor was not included.

One of the strongest predictors of duration of lactation is duration of previous lactations. Since any previous lactation would also have been influenced by the mother's DDE, this factor was not adjusted for; inclusion of a second outcome correlated with the outcome of interest as a predictor is not appropriate when assessing causal relationships. However, the correlation among successive lactations may cause an additional problem in interpretation. A relationship between DDE and duration can arise simply because women who have previously lactated for long periods will be more likely to do so again and will have reduced their body burden of DDE by

TABLE 2—Relationship between DDE Levels and Duration of Lactation, 229 Mexican Women and 722 US Women

p,p'-DDE, ppm, fat basis	Mexico[a]		United States[b]	
	% of Women	Median Duration, mo	% of Women	Median Duration, mo
0–2.5	13	7.5	51	7.8
2.5–5.0	26	5.0	39	6.1
5.0–7.5	29	3.0	6	3.5
7.5–10.0	14	3.5	} 4	...
10.0–12.5	9	4.0		3.8
≥12.5	9	3.0		...

Note. DDE levels are from the breast milk sample collected at birth.
[a]Data from the present study.
[b]Data from study described in Rogan et al.[10]

excreting it in the milk. We assessed whether a relationship occurred for causal reasons or for artifactual reasons by methods described below and in the Appendix.

Results

We screened 398 women; nearly all pregnant women in the area during the enrollment period were screened. Of these, we enrolled 239; 8 were not willing to participate and 151 were ineligible for reasons listed in the methods section. Of the 239, 7 moved away immediately, 1 refused further participation, and 2 had no DDE measurements because of interference or lack of phase separation during extraction. The remaining 229 women are the subject of this report: 195 were followed until they weaned their children, 13 dropped out while still lactating, and 21 were still lactating at 18 months. Descriptive statistics are presented in Table 1.

The median duration of lactation, as calculated from a Kaplan-Meier curve, was 4 months. Thirty-eight percent of the women were lactating at 6 months, 24% at 12 months, and 11% at 18 months. These durations are shorter than national rates in Mexico, where 50% of mothers are breast-feeding at 6 to 7 months.[26]

Table 2 shows the distribution of DDE levels seen in the samples collected at birth. Eighty-nine percent of the DDT measurements at birth were below detection limits, so DDT was not considered further.

Women with higher DDE levels lactated for shorter periods, with median duration, as calculated from Kaplan-Meier curves, declining from 7.5 to 3.0 months (Table 2); the curves differ significantly ($P = .04$). Analogous data from the US study[10] are shown for comparison; the results are similar, although the numbers at high levels are small.

To incorporate covariates, we needed to use semiparametric models. Using a proportional hazards model, we first calculated unadjusted hazard ratios. They are shown in the first line of Table 3; they differ significantly ($P = .04$, $df = 5$). We did another analysis in which we considered a lactation that ended owing to external factors (as defined in the Methods section) to have been censored at that point. The resulting hazard ratios are shown in the second line of Table 3; they differ significantly ($P = .04$, $df = 5$). We did another analysis in which we excluded all data after pregnancy or hormonal medication began, considering this as additional censoring; 71 women were affected by this change. The resulting hazard ratios are shown in the third line of Table 3; they do not differ significantly ($P = .28$, $df = 5$), although the estimates are similar to the previous two sets.

Various other factors have been shown to be related to lactation. We repeated the three analyses above, adjusting for the factors listed in Table 1. The results are shown in the last three lines of Table 3; they differ significantly in all three cases ($P = .01$, $P < .01$, $P = .02$, respectively; dfs = 5).

A relationship between DDE and duration can arise simply because a woman who previously lactated for long periods will be more likely to do so again and will have reduced her body burden of DDE by excreting it in the milk. We separated the 71 women having their first child and 24 others who had not previously lactated from those who had lactated previously (Table 4); the median durations are from Kaplan-Meier curves. There is little evidence of an effect of DDE in first lactations, and adjustments as above do not change this finding. Thus we considered whether the effect seen in later lactations might be wholly due to this artifact. The two things driving the artifact are the correlation of successive lactations and the drop in DDE levels over lactation. The correlation between the duration of the study lactation and that of the immediately preceding one was .27; the correlation with the average of all past durations was .34. Eighty women had both birth and 6-month DDE levels available. The median ratio of the 6-month sample to the birth sample was 0.56. Using these values and others specified in the Appendix, we did a simulation to determine whether the effect seen in the total population could be explained by this artifact. Only 6% of the time did the simulated data produce an effect as large as or larger than that seen in the actual data. The median simulated effect was about half the size of the observed effect.

DDE might directly interfere with the lactation process. It might also affect lactation indirectly, if DDE is toxic to the child and a change in feeding method is made in an attempt to improve the child's health. At each visit, we asked the mother whether the child's health since the last visit had been good, fair, or poor. There was a slight (not statistically significant) tendency for mothers who reported fair or poor health to have weaned their children; for example, at the first visit, 26% of those reporting good health and 32% of those reporting fair or poor health had weaned their children. However, there was no tendency for mothers with higher DDE levels to report worse health; for example, at the first visit, 50% of those in the lowest DDE group and 57% of those in the highest reported good health. Similarly, there was no tendency for DDE to be associated with specific illnesses or with slower growth.

Discussion

Our results provide further evidence that DDE interferes with lactation. Although the magnitude of the effect is not as big as it first appears, owing to an artifactual explanation, simulations using best estimates show that an effect as large as that we found would be produced by this artifact alone only 6% of the time. The lack of any detectable effect on children's health makes it likely that DDE is directly affecting the lactation process.

TABLE 3—Hazard Ratios for Weaning Associated with Differing DDE Levels

Type of Analysis	DDE at Birth, ppm, fat basis (95% CI)					
	0–2.5	2.5–5.0	5.0–7.5	7.5–10.0	10.0–12.5	≥ 12.5
Crude	1.0	1.3 (0.8, 2.2)	1.6 (0.9, 2.6)	2.0 (1.1, 3.5)	1.8 (1.0, 3.4)	2.4 (1.3, 4.5)
Crude, censored for external reasons for weaning	1.0	1.0 (0.5, 2.0)	1.9 (1.0, 3.6)	1.9 (0.9, 3.9)	1.7 (0.8, 3.8)	2.3 (1.0, 5.1)
Crude, censored for external reasons for weaning and use of hormones	1.0	1.2 (0.5, 2.9)	2.1 (0.9, 4.6)	1.7 (0.7, 4.3)	2.1 (0.8, 5.4)	2.4 (0.9, 6.4)
Adjusted	1.0	0.7 (0.4, 1.5)	1.3 (0.6, 2.6)	1.3 (0.6, 2.5)	1.3 (0.6, 3.0)	2.6 (1.1, 5.9)
Adjusted, censored for external reasons for weaning	1.0	0.5 (0.2, 1.3)	1.5 (0.6, 3.9)	1.1 (0.4, 2.9)	1.2 (0.4, 3.6)	2.8 (0.9, 8.6)
Adjusted, censored for external reasons for weaning and use of hormones	1.0	0.5 (0.1, 2.0)	1.8 (0.5, 7.4)	1.1 (0.3, 4.4)	1.6 (0.3, 7.8)	3.1 (0.7, 13.7)

Note. Entries are estimated ratios of hazard of weaning, relative to the 0–2.5 group. CI = confidence interval.

Overall, the magnitude of the effect seen here is quite similar to that seen previously in a US study[10] (see Table 2). However, in the US study, there was an effect in women who had not previously lactated.

The most plausible explanation of a relationship between DDE and duration of lactation is estrogenicity. O,p-DDE is a weak but persistent estrogen.[27] Although we measured p,p′-DDE, the isomer with the highest concentration, we expect that women with higher p,p′-DDE will have higher o,p-DDE. P,p′-DDE, the nonestrogenic form, does not inhibit lactation in rats[28]; o,p-DDE has not been tested. DDE has been associated in some studies with increased risk of breast cancer, and this effect, if it exists, may be related to estrogenicity.[29,30]

The high levels of estrogen in pregnancy inhibit the onset of full lactation, and it is the fall in estrogen at term that, in part, allows the onset of lactation.[31] The immediate postpartum period is a nadir in the production of endogenous estrogen; estrogen inhibits the activity of prolactin on the breast. Estrogen as DES was used to suppress lactation, and contraceptive estrogens decrease milk volume.[32] Thus, it is plausible that a persistent exogenous estrogen-like compound could decrease the quantity of milk, leading to early weaning. The most common reason women gave for weaning was insufficient milk.

Exposure to DDE is universal, and there is no obvious way to prevent exposure now that DDT has been banned in most countries. Many of the other persistent pesticides also have some estrogenic activity. It is possible that at least some of the lactation failure seen in the developing world is due to the exposure of women to DDE or to other environmental estrogens. If this is true, it has serious implications for infant mortality. Further research on the effects of environmental influences on lactation and on possible mechanisms for such effects is warranted. □

TABLE 4—Relationship between DDE and Duration of Lactation

p,p′-DDE, ppm, fat basis	First Lactation		Later Lactations	
	% of Women (n = 95)	Median Duration, mo	% of Women (n = 134)	Median Duration, mo
0–5.0	32	3.0	43	8.8
5.0–7.5	36	2.5	24	4.1
7.5–10.0	14	1.5	15	5.0
≥ 10.0	19	4.0	18	2.8

Acknowledgments

We thank Dr Margarett Davis and Dr Roberto Rivera for help in planning the study; Dr Carlos Ortega, Dr Amali Muñiz Torres, and Ms Elizabeth Gutierrez for supervision of the field work; Ms Izaura Meraz-Rodriguez and Ms Ana-Elizabeth Garcia-Valdez for conduct of the field work; Dr Linda Sheldon for chemical analyses, and Ms N. Beth Ragan and Ms Joanna Smith for data management.

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APPENDIX—Details of Simulation

All parameters were chosen to provide as close a fit as possible to the actual data. We generated two simulated lactations per woman, with associated durations and DDE levels. We used the values from the second lactation to fit a proportional hazards model relating the hazard of weaning linearly to DDE. In the observed data for lactations excluding the first, the coefficient from such a model is .076, adjusted for the covariates mentioned in the main text. Note that in the main text, DDE is always treated categorically.

Log-normal durations of lactation were generated by exponentiating bivariate normals. The first simulated duration was truncated at 24 months, since feeding beyond that point would have very little effect on subsequent DDE. The second duration was censored at 18 months to mimic the study design. The simulated durations had median 4.2, shape parameter 1.3, and correlation .30. Recall that the correlation between the duration of the study lactation and that of the immediately preceding one was .27; the correlation with the average of all past durations was .34.

The first DDE was also a log-normal variate, with median 5.94 (the observed median) and shape parameter 0.6. Recall that the median ratio of the 6-month sample to the birth sample was 0.56. The second simulated DDE was generated from the first by multiplying by exp(−0.097 [first duration]) to account for this decline and then multiplying by a normal deviate with mean 1 and standard deviation 0.233 to introduce variability comparable to that seen in the actual data.

We generated 229 such women per experiment and 1000 experiments. Only 6% of the simulated DDE coefficients were equal to or greater than the observed value of .076. The median coefficient was .042.

To assess the sensitivity of the results to the estimated parameters, we did 100 simulations each with different values. Changing the duration parameters to a median of 4 and a shape of 1.2 yielded an empirical P value of 6%. Changing instead the correlation of durations to .25 yielded $P = .055$; changing it to .34 yielded $P = .10$. Changing the standard deviation of the DDE ratio to 0.283 yielded $P = .07$; changing it to 0.183 yielded $P = .15$. Changing the rate of decline of DDE to 0.077 yielded $P = .05$; changing it to 0.117 yielded $P = .135$.