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ORIGINAL REPORT

Drug certainty-response in interview-based studies

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ABSTRACT

Purpose Imperfect recall of exposure timing challenges the ascertainment of medications in interview-based studies.
Methods We propose an algorithm to classify medication exposure, taking into account recall certainty. The availability of medication use details, including duration of use, start and stop dates, and maternal estimates of how certain they were about these dates, allowed classification of subjects as either likely or possibly exposed in the first trimester of pregnancy. We applied the algorithm to study an association between prenatal tetracycline exposure and risk of congenital heart defects previously reported by the National Birth Defects Prevention Study, using 1993–2008 data from 11 517 subjects in the Slone Epidemiology Center Birth Defects Study.
Results Among women exposed to tetracyclines during pregnancy ($n = 58$), 50% and 19% were likely and possibly exposed, respectively, in the first trimester, and 31% were exposed outside the first trimester. Compared with non-use during pregnancy, the crude OR for exposure outside the first trimester was 1.0 (95%CI 0.4–2.5), and that for exposed (likely or possibly, combined) in the first trimester was 1.7 (95%CI 0.9–3.2); however, the ORs based on the algorithms were 0.9 (95%CI 0.3–3.0) for possibly exposed and 2.2 (95%CI 1.0–4.6) for likely exposed.
Conclusions A "certainty-response" (stronger association with higher level of certainty) was found within exposures in the window of etiological interest. Algorithms for exposure classification that incorporate recall certainty may be useful in interview-based studies.

KEY WORDS—algorithms; epidemiologic methods; interviews as topic; maternal exposure; questionnaires; uncertainty

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INTRODUCTION

In pharmacoepidemiology, interview data provide a valuable source of exposure information for studies that are focused on actual use of medications (rather than on evidence of prescription or dispensing). However, given that exposure information often is obtained retrospectively in interview-based studies, the precise ascertainment and classification of medication use may be limited by imperfect recall of exposure timing. Although some subjects may be able to recall exact start and stop dates, others may only be able to recall a more imprecise time frame (e.g., sometime in particular month(s)). This is an important consideration in studies where accurate timing of exposure is critical, such as etiologic studies of birth defects, where gestational timing of exposure is crucial. Consider two scenarios: Ms Smith and Ms Jones have the same dates for their first trimesters, from mid-February to mid-May 2010. Ms Smith is able to specifically recall her medication use of 7 days starting on May 1 and stopping on May 7. We can be relatively confident that, based on this report, Ms Smith was exposed in the first trimester. Alternatively, Ms Jones is not able to recall the exact dates of exposure but only that she took the medication for 7 days, starting and stopping sometime in May 2010. We can only say that Ms Jones is possibly exposed in the first trimester.

In most etiologic studies, study subjects are usually dichotomized into exposed or unexposed for the period of interest. However, questionnaires may collect exposure details including the dates when exposure began

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and ended, the interviewee's estimates of the certainty of recall of each of these dates (e.g., exact date or more imprecise time frame), and the duration of exposure; such information can allow drug exposure to be classified according to certainty of use during a given time window. This more detailed classification allows evaluation of "certainty responses" (stronger association with higher level of certainty), which, like dose-responses[1] would, if demonstrated, support a true association between the exposure and outcome under study.

Using an interview-based pregnancy study with prenatal medication use details collected retrospectively, we developed an algorithm to classify exposure, taking into account the subject's recall certainty in reported timing of medication use. We assessed the applicability of the algorithm by applying it to study a previously reported association from a case–control analysis of data from the National Birth Defects Prevention Study that observed a 2.2-fold increased risk of congenital heart defects (CHDs) following periconceptional exposure to tetracyclines.[2]

METHODS

Data source

We used data from the Slone Epidemiology Center Birth Defects Study (BDS), an ongoing case–control surveillance program on birth defects in relation to environmental exposures (primarily medications) in North America. The BDS has, since 1976, interviewed mothers of infants with and without birth defects from various centers in North America. For the period of our study, 1993–2008, subjects were recruited from the greater metropolitan areas of Boston, Philadelphia, Toronto, San Diego County, and Michigan, as well as from birth defects registries in Massachusetts and New York State. Eligible subjects were identified in various ways, including review of admissions and discharges at major pediatric referral hospitals and clinics and through regular contact with newborn nurseries in community hospitals (to identify infants born with defects who might not have been referred to major centers). Non-malformed control infants have been identified at participating birth hospitals since 1993. In addition, beginning in 1998 and 2004, mothers of malformed and non-malformed subjects were identified through established state-based birth defects registries in Massachusetts and New York, respectively. Finally, in 1998, recruitment expanded to include a population-based sample of non-malformed infants throughout Massachusetts identified from vital records information provided by the Massachusetts Department of Public Health. Institutional review board approval was obtained where appropriate. The study is fully compliant with requirements of the Health Insurance Portability and Accountability Act.

Mothers of identified infants provide informed consent for interview and are asked to also provide a release for their infant's medical record. Using highly structured interview procedures and questionnaires, trained study nurses interview mothers within 6 months of delivery either in person (1976 to mid-1998) or by telephone (mid-1998 to present). Information is sought about demographic characteristics; reproductive, medical, and lifestyle (e.g., cigarette smoking, consumption of alcohol and caffeine) factors; and diet. Also collected are details of all medications used (prescription and over-the-counter, including vitamins, minerals, and herbal products) at any time from 2 months before the last menstrual period (LMP) date through the end of the pregnancy. Mothers and study nurses are all unaware of the various hypotheses under consideration at the time of interview.

To maximize recall of medication exposures and minimize the likelihood of errors in exposure assessment, questionnaires have been highly structured as a series of increasingly detailed questions to elicit medication exposure information from several lines of inquiry.[3] Interviewers first ask questions about the occurrence of any of a list of illnesses (e.g., infections, asthma) during pregnancy and the medications taken for those illnesses, then about the use of categories of medications (e.g., antibiotics, inhalers), and finally about use of specific products, including brand and generic names and dosage forms. Mothers who report taking a particular medication are further asked to identify, as accurately as possible, the dates when use began and ended. Recall of the timing of medication use is enhanced by the use of a calendar that highlights the mother's reported LMP date, her delivery date, and other significant events (e.g., Christmas). We considered exposure timing to be uncertain if mothers could only recall the month and year but not the day(s) of exposure (i.e., they report exposure as being sometime in a particular month); exposure timing was considered unknown if mothers could not recall the month of exposure. Mothers also are asked details about their pattern of use of each reported medication, including duration (days of treatment) and frequency of use (e.g., days per week or month). Mothers who cannot recall the pattern of use are considered to have unknown duration or frequency of use.

Algorithm to classify timing of exposure

Using data from the BDS, we developed an exposure classification algorithm, taking into account recall

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certainty in reported timing of medication exposure. For the timing of pregnancy periods, the LMP date was determined by early ultrasound examination or maternal recall. We defined the estimated date of conception as 14 days after the LMP date and the first trimester of pregnancy as 90 days following the estimated date of conception (encompassing the etiologically important period of structural development for most organ systems). In this analysis, the exposure window of interest is the first trimester.

We considered exposure in the first trimester to include maternal use of medication on at least 1 day during that period. Based on the precision of the start and stop dates reported by the subjects and duration of use, we classified drug exposure into four categories: (i) completely unexposed (i.e., not exposed at any time from 2 months before the LMP date through the end of pregnancy); (ii) likely exposed in the first trimester of pregnancy; (iii) possibly exposed in the first trimester; and (iv) exposed outside the first trimester. For uncertain start/stop dates reported as being sometime in a particular month, we considered the possible exposure period to be the widest interval consistent with her report (e.g., if a mother reported medication use starting and stopping in May, we assigned May 1 as her start date and May 31 as her stop date). We classified a mother as being *likely* exposed in the first trimester if her medication use, given her duration of use but independent of date certainty, had to at least partially include the first trimester. She was classified as *possibly* exposed if the use, given the reported duration but based on uncertain dates, could fall within the first trimester or completely outside of it. Figure 1 depicts all possible exposure scenarios in relation to the window of interest and provides the drug exposure classification, as well as some case examples, for each scenario.

We estimated the number of exposed days in the first trimester using the following equation:

Number of exposed days in window of interest = *Duration* × *Frequency of use* × *Proportion of exposure period that overlapped window of interest*

where duration is the number of days of use, and frequency is the density of exposure (e.g., daily, twice a week, and once a month). For example, if a mother with her first trimester beginning 8 May 2010 reported antibiotic use daily during 2 weeks starting on 1 May 2010 and stopping on 14 May 2010, her number of exposed days in the first trimester is estimated as 7 days (i.e., $14 \times 7/7 \times 7/14$). Whereas, if she reported analgesic use twice a week over this 2-week period, her number of exposed days in the first trimester is estimated as 2 days (i.e., $14 \times 2/7 \times 7/14$).

Application of exposure classification algorithm

To study a previously reported association between periconceptional exposure to tetracyclines and the risk of CHDs,[2] we applied the exposure classification algorithm to data obtained from mothers of 4543 cases and 6974 non-malformed controls interviewed by the BDS between 1993 (when non-malformed infants were first enrolled) and 2008. We excluded infants with chromosomal defects; known Mendelian inherited disorders; syndromes; DiGeorge sequence (associated with 22q deletion); amniotic bands; and peripheral/branch pulmonary artery stenosis, as well as premature infants with only patent foramen ovale, secundum atrial septal defect, atrial septal defect not otherwise specified, and patent ductus arteriosus.

Using our exposure classification algorithm, we classified all subjects who reported systemic tetracycline exposure into "completely unexposed at any time from 2 months before the LMP date through the end of pregnancy" (reference category for all analyses), "likely exposed in the first trimester," "possibly exposed in the first trimester," or "exposed outside the first trimester." To assess the impact of incorporating a measure of certainty relative to the traditional "any exposure" classification, we also created the "any exposure" category by combining likely and possibly exposed into a single category of "potentially exposed."

We calculated crude ORs and 95%CIs for tetracycline exposure and CHDs for each exposure category. Among infants who were likely exposed in the first trimester, we further assessed the strength of the association between those exposed for less than 12 days (the average duration of treatment) and those exposed for 12 days or more in the window of interest. As the aim of this study was not to test the hypothesis of a possible causal relationship between prenatal tetracycline exposure and CHDs but rather to evaluate an algorithm designed to classify exposure, taking into account recall certainty in reported exposure timing, only crude results were presented. Nonetheless, crude OR estimates were not attenuated when geographic region, interview year, maternal race/ethnicity, age, education, diabetes, urinary tract infection, and number of fetuses (multiple versus single) were taken into account.

RESULTS

The distributions of selected maternal characteristics among mothers of cases ($n = 4543$) and non-malformed controls ($n = 6974$) included in the analysis are presented in Table 1. Of these total of 11 517

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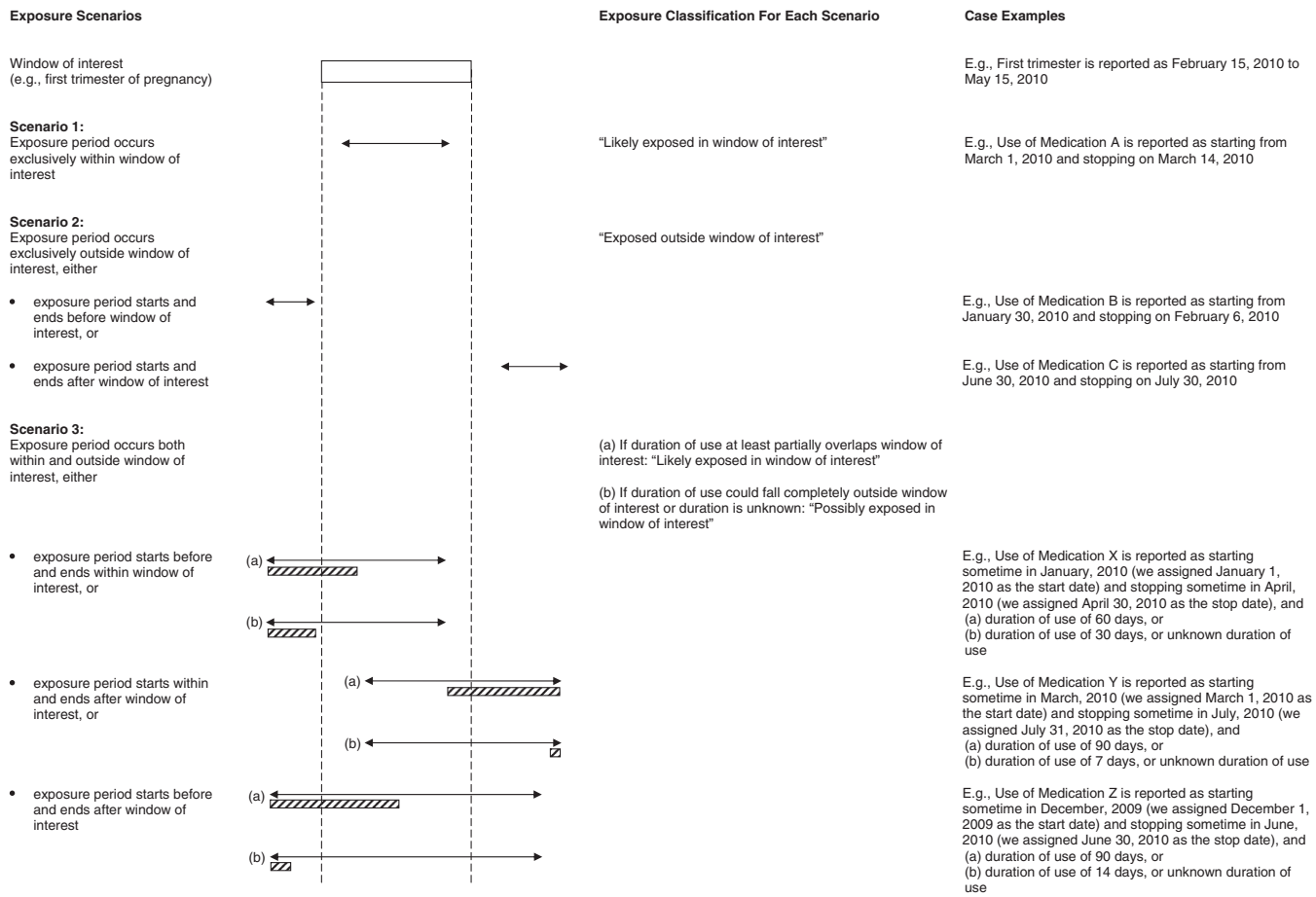

Figure 1. All possible exposure scenarios in relation to the window of interest and the respective exposure classification for each scenario. The white rectangle depicts the window of interest, with the boundaries denoting the start and stop dates, respectively, that define an exposure within that window. The horizontal arrows identify the possible exposure period, with the left and right arrow heads denoting the start and stop dates of exposure, respectively. The shaded bars depict the duration of exposure.

mothers, 58 (0.5%) were exposed to tetracyclines (tetracycline, doxycycline, and minocycline) from 2 months before the LMP date through the end of pregnancy. Based on the algorithm, 29 (50.0%) and 11 (19.0%) were considered likely and possibly exposed, respectively, in the first trimester; 18 (31.0%) were considered exposed outside the first trimester (specifically, 14 (24.1%) before the estimated date of conception and four (6.9%) after the first trimester).

As shown in Table 2, compared with non-use of tetracyclines in the period from 2 months before the LMP date through the end of pregnancy, the crude OR of CHDs for women potentially exposed (likely or possibly exposed, combined) to tetracyclines in the first trimester was 1.7 (95%CI 0.9–3.2). Through the more detailed classification of first-trimester exposures derived from the algorithm, the crude ORs were 0.9 (95%CI 0.3–3.0) for possibly exposed and 2.2 (95%CI 1.0–4.6) for likely exposed. Among infants who were likely exposed, the strength of the association increased with increasing number of days exposed in the first trimester: the crude OR for those exposed for fewer than 12 days was 2.1 (95%CI 0.7–5.9), whereas that for those exposed for 12 days or more was 3.1 (95%CI 0.9–10.2). These estimates were based on small numbers.

To assess whether there is differential recall of certainty of timing between cases and controls, we considered whether the observed association changed when we used an alternative control group—composed of infants with malformations other than CHDs; results did not change appreciably (Table 2). Furthermore, we considered whether another exposure (amoxicillin) also might be associated with CHDs when non-malformed infants were the comparison group; we did not find increased risks (Table 3).

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Table 1. Selected maternal characteristics among mothers of cases (infants with congenital heart defects overall) and non-malformed controls: Slone Epidemiology Center Birth Defects Study, 1993–2008

Characteristic*	Cases ($n = 4543$)		Non-malformed controls ($n = 6974$)	
	No.	(%)	No.	(%)
Maternal race/ethnicity				
Non-Hispanic White	3223	(70.9)	5163	(74.0)
Hispanic	630	(13.9)	845	(12.1)
Non-Hispanic Black	328	(7.2)	491	(7.0)
Non-Hispanic Asian, Pacific islander	219	(4.8)	336	(4.8)
Others	143	(3.1)	139	(2.0)
Maternal age (years)				
< 25	1025	(22.6)	1380	(19.8)
25–29	1239	(27.3)	1820	(26.1)
30–33	1222	(26.9)	2004	(28.7)
≥ 34	1056	(23.2)	1752	(25.1)
Maternal pre-pregnancy weight (kg)				
< 55	1063	(23.4)	1726	(24.7)
55–60	1080	(23.8)	1757	(25.2)
61–69	1004	(22.1)	1658	(23.8)
≥ 70	1358	(29.9)	1769	(25.4)
Maternal education (years)				
< 13	1538	(33.9)	1892	(27.1)
13–15	1135	(25.0)	1703	(24.4)
≥ 16	1865	(41.1)	3376	(48.4)
Maternal smoking				
Never	2609	(57.4)	4049	(58.1)
Before pregnancy only	1012	(22.3)	1717	(24.6)
During pregnancy	922	(20.3)	1206	(17.3)
Maternal alcohol consumption				
Never	1815	(40.0)	2551	(36.6)
Before pregnancy only	755	(16.6)	1237	(17.7)
During pregnancy†	1973	(43.4)	3186	(45.7)
Maternal conditions and medications				
Pre-existing diabetes mellitus	120	(2.6)	39	(0.6)
Pre-existing hypertension	64	(1.4)	83	(1.2)
Infection in first trimester	2211	(48.7)	3245	(46.5)
Respiratory infection	1479	(32.6)	2197	(31.5)
Urinary tract infection	302	(6.6)	385	(5.5)
Other infections	915	(20.1)	1371	(19.7)
Fever in first trimester	557	(12.3)	800	(11.5)
Periconceptional use of folic acid	2776	(61.1)	4588	(65.8)
With family history of congenital heart defects	463	(10.2)	421	(6.0)
Multiple pregnancy (more than one fetus)	251	(5.5)	203	(2.9)

*Numbers do not add up to the total because of missing data.
†Includes women with infrequent alcohol intake (less than once per month anytime during pregnancy).

DISCUSSION

Using detailed prenatal medication exposure information collected retrospectively through maternal interviews as part of the BDS study, we developed and evaluated the applicability of an algorithm to classify the timing of medication exposure, taking into account recall certainty in reported exposure dates. When we applied the algorithm to study the reported risk of CHDs with prenatal tetracycline exposure, a "certainty-response" (stronger association with higher level of certainty) was found with our classification of exposure into "possibly exposed" and "likely exposed" in the window of etiological interest, which, in this case, was the first trimester. These findings suggest that an algorithm based on "certainty-responses" may have value in increasing the accuracy of exposure classification.

This approach of "certainty-response" algorithms can be extrapolated to other epidemiologic studies where accurate timing of exposure is crucial and where data sources have available detailed exposure information that facilitates consideration of the certainty of exposure timing. The use of "certainty-responses" may provide more valid risk estimates for the exposure–disease relation and thereby enhance the identification of true associations.

It should be recognized that the "certainty-response" algorithm may be biased in the presence of differential recall of certainty of timing between mothers of cases and controls. Among all "potentially (likely or possibly, combined) exposed" subjects, if cases were more certain of their exposure timing than the controls, there would be more cases than controls in the "likely exposed" category and less cases than controls in the "possibly exposed" category. This would overestimate the OR for the "likely exposed" group and underestimate the OR for the "possibly exposed" group. The reverse would occur if controls were more certain of their exposure timing than cases. However, there was no evidence for such bias in the alternative analyses we conducted.

Although we focused on medication use as our exposure, the algorithm can be applied to classify any exposure (e.g., cigarette smoking, alcohol consumption, and infection), and where numbers are sufficient, it may be applied to narrow windows of exposure. The algorithm may have its greatest value for exposures with short durations relative to the window of interest (including exposures at irregular intervals such as medications used on an "as needed" basis), where uncertainty in exposure timing may be more of an issue. This was the case in our example of antibiotics, with an average duration of 12 days and an exposure window of one trimester. Clearly, the shorter the duration of exposure and the narrower the critical window, the more challenging it will be to classify timing of exposure accurately. For exposures with long durations (e.g., chronically taken medications like anti-hypertensives and anti-diabetics), uncertainty in exposure timing would be of less concern, and the algorithm would have little added value.

Analyses involving duration or cumulative days of exposure can be incorporated into the algorithm. For specific studies with larger samples, it might be appropriate to further restrict "likely exposed" to subjects with more than a few days of exposure during the

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Table 2. Prenatal use of systemic tetracyclines among mothers of cases (infants with congenital heart defects overall) and non-malformed, as well as malformed, controls according to exposure categories: Slone Epidemiology Center Birth Defects Study, 1993–2008

Exposure category	Cases ($n = 4543$)		Non-malformed controls ($n = 6974$)		Crude OR (95% CI)	Malformed controls ($n = 7485$)		Crude OR (95% CI)
	No.	(%)	No.	(%)		No.	(%)	
Completely unexposed*,†	4515	(99.4)	6944	(99.6)	1.0	7450	(99.5)	1.0
Only exposed outside the first trimester‡	7	(0.2)	11	(0.2)	1.0 (0.4–2.5)	13	(0.2)	0.9 (0.4–2.2)
Potentially (likely or possibly, combined) exposed in the first trimester	21	(0.5)	19	(0.3)	1.7 (0.9–3.2)	22	(0.3)	1.6 (0.9–2.9)
Possibly exposed in the first trimester	4	(0.1)	7	(0.1)	0.9 (0.3–3.0)	7	(0.1)	0.9 (0.3–3.2)
Likely exposed in the first trimester	17	(0.4)	12	(0.2)	2.2 (1.0–4.6)	15	(0.2)	1.9 (0.9–3.7)

*Reference category.
†Not exposed to tetracyclines at any time from 2 months before the last menstrual period date through the end of pregnancy.
‡Exposed to systemic tetracyclines any time in the periods either 2 months before the last menstrual period date through the estimated date of conception or after the first trimester through the end of pregnancy.

Table 3. Prenatal use of amoxicillin among mothers of cases (infants with congenital heart defects overall) and non-malformed controls according to exposure categories: Slone Epidemiology Center Birth Defects Study, 1993–2008

Exposure category	Cases ($n = 4543$)		Non-malformed controls ($n = 6974$)		Crude OR (95% CI)
	No.	(%)	No.	(%)	
Completely unexposed*,†	4169	(91.8)	6396	(91.7)	1.0
Only exposed outside the first trimester‡	200	(4.4)	331	(4.7)	0.9 (0.8–1.1)
Potentially (likely or possibly, combined) exposed in the first trimester	173	(3.8)	247	(3.5)	1.1 (0.9–1.3)
Possibly exposed in the first trimester	36	(0.8)	70	(1.0)	0.8 (0.5–1.2)
Likely exposed in the first trimester	137	(3.0)	177	(2.5)	1.2 (0.9–1.5)

*Reference category.
†Not exposed to amoxicillin at any time from 2 months before the last menstrual period date through the end of pregnancy.
‡Exposed to amoxicillin any time in the periods either 2 months before the last menstrual period date through the estimated date of conception or after the first trimester through the end of pregnancy.

period of interest. In the current study, further stratification of those "likely exposed" according to the number of days exposed suggested, based on very small numbers, a potential dose-response (stronger association with more days exposed). The algorithm could be adapted to specific scenarios. For example, for drugs with long half-life or sustained biologic effects, investigators might want to consider a subject exposed for months after a single dose.

In conclusion, algorithms for exposure classification that incorporate the subject's self-reported certainty regarding exposure dates may be useful in interview-based drug safety studies, particularly for exposures of short duration.

CONFLICT OF INTEREST

Martha M. Werler is a paid advisor to studies of rheumatoid arthritis drugs that are sponsored by drug companies that may or may not make tetracyclines. Dr. Werler does not know the product lines.

KEY POINTS
- Imperfect recall of exposure timing is a challenge for ascertainment of medications in interview-based studies, particularly in the area of birth defects, where timing is critical.
- In this article, we developed and evaluated the applicability of an algorithm to classify medication exposure, taking into account maternal recall certainty in reported exposure dates in interview-based studies.
- Our findings suggest that an algorithm based on "certainty responses" (stronger association with higher level of certainty) may have value in increasing the accuracy of exposure classification.

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