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COMMENTARY

Setting Standards for Pregnancy Registries

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In this issue of *Drug Safety*, Bird et al. [1] describe the enrollment and retention of enrollees in 34 pregnancy registries in USA. When introducing the topic, the authors noted the limited sources of information available on the safety of medical products used in pregnant women: [1] passive data collection through either spontaneous reports to the manufacturer of the product or the US Food and Drug Administration's Adverse Event Reporting System; and [2] the active data collection through pregnancy registries.

How good are these sources? To my knowledge, the accuracy of neither of these two systems has been assessed systematically. For example, it could be helpful to compare the findings in the manufacturer's spontaneous reports with the findings for the same product in a pregnancy registry conducted in the same geographic region. This comparison would make it possible to assess the accuracy of the different sources of information used, such as the mother's verbal reports, the findings in copies of the pediatrician's examination findings, any *International Classification of Diseases*, Ninth or Tenth Revision codes used, and any other sources used.

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1 Pregnancy Registries

How about the accuracy of pregnancy registries? My perspective reflects my experiences and observations in directing the North American AED (antiepileptic) Pregnancy Registry, since it began enrolling in 1997 over 10,000 eligible pregnant women. During this time, concerns about the reliability and accuracy of pregnancy registries have been raised in the medical literature. In response to these concerns, I have developed these suggestions for maximizing the quality of the information developed from a pregnancy registry:

1. Provide a definition of each outcome to be tabulated. In the case of malformations, develop, in advance, a list of inclusion and exclusion criteria to be followed.
2. Establish the 'time window' for identifying an abnormality. Is it determined 'at birth', or 'first week of life' or 'birth to the time of the postpartum interview' or 'from birth to 1 year of age?'
3. Effective recruitment of eligible women is crucial. Adjust recruitment strategies to reflect effective new methods, such as using social media [2].
4. Recruit an unexposed comparison group, so that the comparison uses data obtained in the same manner by the same staff and protocols for contacts with all enrollees.
5. Interview the mother. With her written permission, obtain copies of the pediatricians' descriptions of findings and those of relevant consultants.
6. Include in the staff evaluating the potential malformations reported physicians who have had personal experience with the common major and minor abnormalities being described.

7. Continue the pregnancy registry for a specific medication long enough to develop sample sizes large enough to determine whether the exposure of concern causes an increase in the rate of occurrence of common malformations, such as cleft lip and palate or myelomeningocele, each of which has a frequency of about 1 in 2000 in Boston [3].

There are essential details to be developed in following these guidelines; here are four we have found to be very important:

(1) What is the prevalence of malformations identified in the 'time window' used in a pregnancy registry? Published guidelines have used rates at birth of 2–4% or 3–5%. These rates are not realistic. The upper limits are too high.
The findings in two malformations surveillance programs, one in the state of Utah [4] and another in Boston [3, 5] have shown significantly lower rates. A population-based survey of 270,878 births in Utah (2005–2009) showed that 2.03% of the infants had major birth defects. After subtracting the birth defects associated with chromosome abnormalities or Mendelian disorders, the prevalence rate was 1.7%. The hospital-based surveillance in Boston of 289,365 infants (including livebirths, stillbirths, and elective terminations for abnormalities identified in prenatal testing) showed that 2.4% had malformations. The rate was 2.0% after subtracting those due to chromosome abnormalities and mendelizing phenotypes. These findings in two large studies show that a statement about the expected prevalence rate at birth should be in the range of 1.7–2.0%.

(2) Is it acceptable for a pregnancy registry to not recruit an unexposed comparison group and, instead, to use the prevalence rates established by the Metropolitan Atlanta Congenital Defects Program [6]? The director of this program has stressed in public presentations that this is NOT an appropriate comparison group for a pregnancy registry. She noted that ascertainment of infants with malformations in the Metropolitan Atlanta Congenital Defects Program is through multiple sources and is quite different from the methods used by pregnancy registries.
However, it is notable that the prevalence rate for the Metropolitan Atlanta Congenital Defects Program between birth and 7 days of age was 2.09% of livebirths over a 25-year period (1968–2003) without subtracting the abnormalities attributed to chromosome abnormalities or Mendelian disorders.

(3) Should the pregnancy registry include, as an abnormal outcome, a structural abnormality identified by prenatal ultrasound screening? We exclude these findings unless they are identified at birth by the examining pediatrician. If the pediatrician does not detect an abnormality in her/his exam, the finding is excluded as 'ultrasound only'. In our experience, in many instances, the diagnosis 'hydronephrosis' is not confirmed in postnatal studies. In addition, a uniform system of prenatal screening of all enrolled pregnant women is not possible.
If a pregnancy registry includes these 'ultrasound only' findings, it is essential that this registry applies the same inclusion criteria to its unexposed comparison group. Our analysis of the findings in 1000 consecutive infants born at BWH showed that the prevalence rate of all malformations would be increased by 2%, when these findings are included [7]. This would double the background prevalence rate for malformations in the unexposed population.

(4) 'Mild' heart defects, specifically atrial septal defects, ventricular septal defects, and pulmonary valve stenosis, are very common. In a study of the malformations identified between birth and 1 year of age, these 'mild' heart defects are the most common findings, many of which were identified after the first 5 days of life [8].
The pregnancy registry needs a strategy to evaluate these findings. Ideally, the pregnancy registry will have the mother's assistance so that the reports from subsequent evaluations by cardiologists and echocardiography can be obtained. Criteria have been published for classifying atrial septal defects as not significant and significant [9]. Excluding some of the infants with small atrial septal defects as not having a malformation could affect significantly the findings in the exposed population.

Those who conduct pregnancy registries will not all agree with these suggestions. Publishing the findings from other approaches will facilitate a comparison of the value of different approaches. The Teratology Society has developed a workshop on pregnancy registries at its annual meetings. This is a setting in which the staff from different registries can discuss ideas about the methodology and compare findings.

Ultimately, the development of pregnancy registries would be more effective if there were a national center for pregnancy registries. This center could provide advice and data on the experiences of different models of pregnancy registries.

Compliance with Ethical Standards

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