Some Epidemiological Principles

4

In studies on the possible relationship between maternal use of a drug and an infant outcome like a congenital malformation, the first epidemiological question to answer is: do maternal use of this drug and the occurrence of the malformation in the infant occur together more often than expected?

4.1 Population Studies

A crucial point is of course to estimate how often the outcome (e.g., a malformation) occurs in the absence of maternal use of the drug. If we have information on drug use by all women and presence of malformations in all infants, this is a rather simple problem, as seen in Fig. 4.1. The population (all pregnant women) is represented by a square and is divided into two vertical areas: one which represents the women who used the drug (exposed) and the other women who did not use the drug. Another division occurs according to the presence of the adverse reproduction outcome (e.g., malformations): one horizontal area with malformations and another without malformations. The striped area represents malformed infants, exposed to the drug, under the assumption that no relationship exists, that is, the expected number of such outcomes. If the rate of malformations is p among all pregnancies and N is the number of exposed pregnancies, the expected number of malformations among the latter will of course be p*N.

Nowadays there are areas or countries where it is possible to study the whole population of pregnant or delivered women by using regional or national health registers. These possibilities are relatively recent, and before that time, other ways to estimate the expected number had to be used, mainly case-control or cohort studies. Both techniques are based on sampling techniques.

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Fig. 4.1 Diagram illustrating exposure and adverse outcome in the population

4.2 Case-Control Studies

A case-control or case-referent study is based on the collection of exposure data for cases (e.g., malformed infants) and controls (e.g., non-malformed infants) and then the exposure rates in the two groups are compared. This is illustrated in Fig. 4.2. Among all non-malformed infants in the population, a group is identified one way or another, and information on maternal drug use among them is obtained. This control group is thus a sample of the non-malformed individuals and, if representative, will give an estimate of exposure rate among mothers of non-malformed infants.

In most instances, information on drug use is obtained from questionnaires or interviews, rarely from medical records produced already during pregnancy. The former exposure information is thus retrospective which carries problems because of recall or interviewer bias. This phenomenon will be discussed later on (Chap. 7).

In some large-scale studies, e.g., those from the US National Birth Defects Prevention Study (Yoon et al. 2001) or the Slone Epidemiology Center Birth Defects Studies (Yao et al. 2013), exposure data were collected by telephone interviews a considerable time after birth which may increase the risk for recall bias. In this situation a further problem exists. One usually has a nonresponse rate of about 30 %. The risk for a selective nonparticipation is large which can give false results. It can be debated if retrospective case-control studies concerning maternal drug use and infant outcome should at all be performed when other and more reliable methodologies exist. The technique may have a place in studies of factors which are more difficult to identify in an objective way, like nutritional factors (e.g., Botto et al. 2015) or the effect of hot water baths – but the same skepticism should be kept in the evaluation of the results.

We can illustrate the problems with these studies with data published on the effect of maternal use of opioid analgesics and infant congenital malformations

Fig. 4.2 Diagram illustrating the principle of a case-control study. The sizes of the two hatched areas are compared

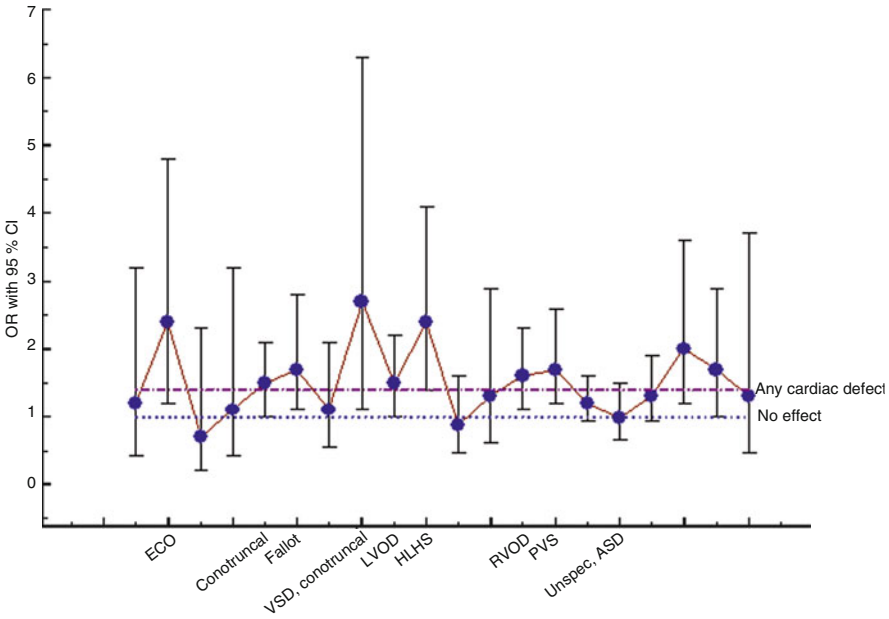

Fig. 4.3 Diagram showing the registered odds ratios (*OR*) with 95 % confidence intervals for 20 different groups of cardiovascular defects according to Broussard et al. (2011). The dashed line gives the average for all these defects and the dotted line the "no effect" line. Cardiovascular types showing significant difference from "no effect" and highlighted in the study are lettered on the X-axis (After Källén and Reis 2016)

(Broussard et al. 2011). These authors worked with data from the National Birth Defects Prevention Study and identified an increased risk for some malformations, including some cardiovascular defects. Figure 4.3 summarizes the odds ratios found for some of the 20 specific cardiac defects studied.

The authors concluded that the nine cardiac types marked were increased in rate after maternal use of opioids. An alternative explanation is that the effect on any cardiac defect of a 40 % increase is due to recall or nonparticipation bias and that the 20 specific types scatter randomly around this value. For one condition (HLHS) the lower confidence limit touches the line for average effect – this is to be expected when 20 comparisons is made.

Various methods have been used to reduce the recall bias phenomenon. One has been to use "sick controls," that is, to make comparisons with another group of malformed infants, e.g., infants with chromosome anomalies or clearly genetic conditions. Parents to such "controls" may, however, have had adequate explanations to the abnormalities and may underreport drug use.

A similar method is to compare different malformations to look for specific associations with drug use. This will probably reduce recall bias but may not eliminate it completely. To be effective the "control" malformations should be of a roughly similar degree of severity as the "case" malformations. Such a technique was early used by Safra and Oakley (1975) in a study of benzodiazepines and orofacial clefts and has been used repeatedly in MADRE (Robert et al. 1994) or SAFE-Med studies (Clementi et al. 2010) from the International Clearinghouse for Birth Defects Surveillance and Research. In the latter studies, data from various congenital malformation registers have been used where exposure information usually had been obtained shortly after the birth of the infants. Also in studies from EUROCAT, a selected malformation has been compared with other malformations with respect to drug exposure, e.g., lamotrigine exposure in infants with orofacial clefts versus infants with other malformations (Dolk et al. 2008).

4.3 Cohort Studies

A second classical epidemiological method is the cohort study (Fig. 4.4). This is based on a group of women with the same exposure, in this case drug use. The rate of outcomes (e.g., malformations in their infants) is compared with the rate of outcomes in a non-exposed cohort. The control cohort is thus a sample of all non-exposed women and will give an idea of the outcome rate (e.g., malformations) among infants of women who were not using the drug in question.

The first problem is usually to identify large enough numbers of exposed women if not information is available for all women in the population (and then a sampling is not needed). We will come back to this problem in Chap. 7. This study design often gives rather small studies with a low power to detect anything but strong effects. A second problem is to identify the outcome under study which sometimes is made by questionnaires or interviews, sometimes from medical documents or registers, e.g., registers of congenital malformations.

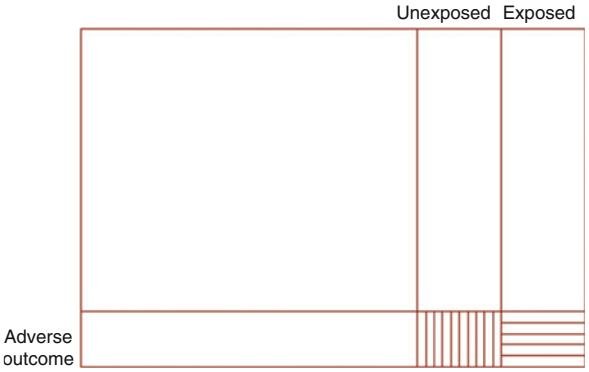

Fig. 4.4 Diagram illustrating the principle of a cohort study. The sizes of the two hatched areas are compared

4.4 Comparison Between Case-Control and Cohort Studies

It is often stated that case-control studies have a higher power to detect associations than cohort studies. This has nothing to do with the type of study but depends on the numbers involved. Generally, the smallest number belongs to the group of exposed outcomes which will therefore contribute most strongly to the uncertainty of the risk estimate. The differences in power between case-control and cohort studies are caused by the difficulties to collect data on large numbers in the latter situation, not on the type of study.

There is a more important difference between case-control and cohort studies. In case-control studies the outcome is decided and it is possible to study many different exposures, e.g., maternal use of different drugs at a certain outcome, e.g., neural tube defects. In cohort studies, the exposure is decided and many different outcomes can be studied, e.g., different malformation types. If the study is restricted to one exposure and one outcome (e.g., use of valproic acid and spina bifida), obviously the two techniques will be equivalent and both are based on sampling from the population in order to get estimates of the expected number of malformed infants after exposure, either estimated from exposure rate in all infants (case-control) or as outcome rate in all infants (cohort). Similarly, expected numbers for the other three groups (unexposed with outcome, exposed, and unexposed without outcome) can be calculated and from these four observed and expected numbers, a chi-square analysis can be made to look for the statistical significance of possible differences in exposure rates between outcome groups or outcome rates between exposure groups (which will be the same). We will come back in greater detail to the evaluation of statistical significances.

4.5 Nested Case-Control Studies

This is illustrated in Fig. 4.5. A crude cohort is first identified where it is likely that the relevant exposure exists. Within that cohort, a case-control study is then performed. Ideally, about half of the crude cohort should be exposed for the factor of interest. This method reduces the number of questionnaires or interviews needed to determine actual exposure – it can be looked upon as a case-control study where exposure rate has been increased by the selection of the crude cohort. Furthermore, the members of the crude cohort may also share common characteristics which otherwise could confound the analysis.

Examples of this type of studies are investigations of infants born after maternal epilepsy, often identified from hospitals specialized in the treatment of epilepsy. With this approach, differential effects of different anticonvulsants can be studied, but no information on the rate in a non-epileptic group of women will exist. In principle this is the background for various registers of anticonvulsants (Russell et al. 2004; Vajda et al. 2004, 2010; Holmes and Wyszynski 2004; Tomson et al. 2004). The crude cohort consists of women with epilepsy and then within that group, risks after exposure to a specific anticonvulsant compared with other anticonvulsants or no anticonvulsants can be made.

4.6 The Sibling Approach

The background to these studies is to compare outcomes in two pregnancies of the same mother, one exposed and the other non-exposed. In this way, the effect of fixed characteristics of the woman can be removed, notably of her genetics. On the other hand, disease status, smoking, body mass index (BMI), and many other things can

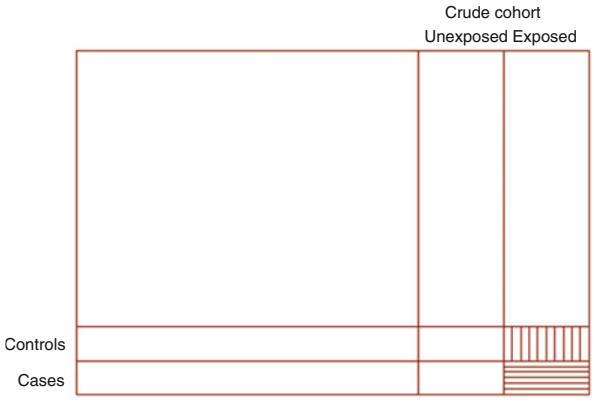

Fig. 4.5 Diagram illustrating the principle of a nested case-control study. Within a crude cohort containing both exposed and non-exposed individuals, a case-control study is performed, comparing the sizes of the hatched areas

have changed between the two pregnancies. Another drawback is that at least two pregnancies are needed for the study and the results may not be applicable for women with only one pregnancy. A great problem is that one not only has to ascertain the drug use in one of the pregnancies but also verify that no drug was used in the other pregnancy. It is definitely a valuable methodology, but one has to be careful in the interpretation of the results.

Most sibling studies on drug use are based on prescription registers. A recent example is the study by Furu et al. (2015) on SSRI drugs and venlafaxine. In this Nordic study, one found an increased risk of a congenital malformation after drug exposure which, however, disappeared in the sibling study – the estimate for any congenital malformation was 1.17 (1.05–1.26) in the covariate-adjusted analysis and 0.92 (0.72–1.17) in the sibling-controlled analysis. Among the 36,772 infants exposed to the drugs in question, only 980 entered the sibling study.

As will be discussed in greater detail later in this book, all information on drug use may have two shortcomings. One is that a woman may have used a drug during pregnancy without this being identified. In interview or questionnaire studies, she may not have told about the drug use and in prescription studies she may have had access to and used drugs which were prescribed much earlier; most drugs have a shelf life of many years. The second problem is that she may not have used a drug which we think she has used. It is rather unlikely that she did not use a drug which she says that she used, but she may have mistaken the time when she used it, notably if data are collected months after delivery. In prescription studies it is a definite risk that she bought the drug but did not use it, especially not during early pregnancy.

Some unpublished data on the effect of antidepressants on preterm birth in singletons will be presented. They are based on data from the Swedish Medical Birth Register for 2005–2013. There were 9595 singleton pregnancies where the mother had reported the use of antidepressants in early pregnancy. Among them 2786 had siblings during the study period; the total number of unexposed siblings was 2922 where the mother had stated the use of any other drug than an antidepressant, including vitamins. The adjusted odds ratio for preterm delivery among the total group was 1.53 (95 % CI 1.42–1.66) while among the antidepressant-exposed infants with siblings, the odds ratio was 1.34 (95 % CI 1.16–1.56). This indicates that the group with siblings is a selected subgroup. The unexposed siblings did not differ from the population: odds ratio = 1.06 (95 % CI 0.93–1.21). Sibling studies may thus give biased data. In this example, however, the study indicates that the effect on preterm birth is at least partly drug induced.

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