Identification of Maternal Use of Drugs

7

Different methods have been used to identify women who have used drugs or specific drugs during pregnancy.

7.1 Questionnaires or Interviews in a Case-Control Setting

In many registers of congenital malformations, women who had a malformed infant are interviewed soon after birth about factors which could have caused the malformation like drug usage. In some, interviews are also made of normal controls, often next baby born with the same sex as the malformed infant. This is made in order to get a control material which is matched to the cases with respect to place, time of birth, and infant sex. As will be discussed later, infant sex can obviously affect malformation risk but in most cases not drug use during pregnancy. An advantage is that interviews are made a short time after delivery, but in spite of this a risk for recall bias exists.

In other studies, women are interviewed some time (sometimes a long time) after the delivery with similar interviews of controls. The largest such study is the US National Birth Defects Prevention Study (Yoon et al. 2001) from which numerous publications have appeared during the last decades. Exposure information is obtained from telephone interviews months after delivery. The nonresponse rate is high, about 30 %, which can also easily cause bias.

This type of data collection may be the only available in some settings like studies in developing countries, but results should always be looked upon with suspicion because of the risks of bias. In developed countries, other methods are preferable.

B. Källén, *Drugs During Pregnancy*, DOI 10.1007/978-3-319-40697-8_7

7.2 Prospective Randomized Studies

The gold standard in medical research is the prospective randomized study. Such studies are rare in the field of drug teratogenesis for obvious ethical reasons. To this is added that such a study would with necessity be too small for an evaluation of rare outcomes like malformations. In one recent study, the authors performed a randomized study of the adverse drug reactions when doxylamine was used for nausea and vomiting in pregnancy (Koren et al. 2015). The study went on for 2 weeks, and 131 women got the drug and 125 got a placebo. The presence of congenital malformations in the infants was not studied, and it had been rather impossible to do so due to the low numbers. In this situation the condition which was treated was not very serious, and a placebo could be accepted.

A randomized study comparing two different but from the point of view equally effective drugs could be ethically acceptable. An example is a study on the suggested risk of paroxetine versus citalopram on cardiovascular defects. A paired analysis, supposing an 1 % cardiovascular disease rate in the total material, would need nearly 2300 pairs in order to demonstrate a doubling of the risk (alpha = 0.05, beta = 0.80). Even so, women may object to getting paroxetine as there is at least a suspicion that it may increase the risk for some cardiac defects.

From a practical point of view, a randomized study on teratogenicity of drugs is no reasonable option.

7.3 Teratology Information Services (TIS)

In many countries there exist TIS organizations. Doctors and sometimes patients can call the TIS and get information on possible risks associated with drug use during pregnancy. In most circumstances, the woman has already used the drug and wants information if the risk is so large that the pregnancy should be interrupted and perhaps also if she can continue using the drug during the rest of the pregnancy. This gives a perfect possibility to prospectively identify drug use, and at the conversation with the woman details like dose and timing of the use can be obtained and also information on other factors of interest, including other drug use than that which her concerns refers to.

There are two main problems with this approach. One is that it is difficult to get together large enough numbers in order to study malformation risks. The second problem concerns the follow-up procedure. This is usually made by contacts after the estimated time of delivery, either with the woman or with her doctor. The quality of this information can be debated, and one can notice that the reported malformation rates in controls are often quite low. A third problem is the obvious selection bias which is obtained as only data for women who are concerned about the drug use are included.

Controls are often women who have contacted the TIS with questions about exposures which are regarded as harmless, a procedure which is somewhat subjective.

One of the most active TIS organizations in the world is probably the Canadian Motherisk. A very large number of original papers have been published from this organization. Most are based on small materials. We can as an example take a relative recent study on gabapentin use which was based on 223 pregnancies exposed to gabapentin and 223 unexposed pregnancies, that is, the woman had asked for advice after an exposure which was judged non-teratogenic (Fuji et al. 2013). In the abstract it is said that the rates of major malformations were similar in the two groups ($p = 0.845$) and that the drug does not seem to increase the risk for a major malformation. This conclusion is based on 7 malformed infants among 170 live born infants after gabapentin and 5 among 201 live born infants in the control group. If these two rates are compared with Fisher exact test, the p-value is 0.40 (2 sided), and the odds ratio estimate is 1.68 (95 % confidence interval 0.45–6.85). Thus, the conclusion should be that the study is too small to exclude a nearly seven times increased risk, and the risk estimate shows a nearly 70 % increased risk. This is a typical situation when data are presented from one single TIS. The highest value of such a small study is that it can exclude a really strong teratogenic effect of the magnitude which was seen after thalidomide where about 20 % of exposed infants had severe malformations and these were of a similar type.

By adding data from different TIS, it has been possible to increase numbers (e.g., McElhatton et al. 1996). Such a combined material runs a risk of heterogeneity both in the identification of the drug use and in the method and completeness of the follow-up of the pregnancies, and this complication has to be taken into consideration when data are analyzed. It is also important that women acting as controls are selected proportionally between the involved systems so exposed cases from different countries are not compared with a control material from one country.

Sometimes no control material is presented, but the recorded rate of malformed infants is compared with a general figure of "1–3 %." It should be remembered that controls are needed not so much in order to estimate the true rate of malformed infants in the population studied but more importantly to evaluate how complete ascertainment has been. Ascertainment rates probably vary more than actual rates.

7.4 Prospective Studies of Pregnant Populations

In an ideal world, there would exist recorded exposure data for all pregnancies in a population. One way to obtain that is to start a research project when all pregnant women are questioned early in pregnancy (in order to avoid recall bias) about drug use since she became pregnant. Questions on other variables, e.g., pregnancy history, smoking, and BMI, could also be included. Then all pregnancies should be followed until delivery, and the infants born should be examined for morbidity, including congenital malformations. Such studies have usually been made as time-limited research project. One of the earliest such study was the Collaborative Perinatal Project which was first mounted in the 1950s (thus before thalidomide) and collected data from 14 university-connected hospitals in USA (Heinonen et al. 1977). This study covered over 50,000 pregnancies and gave important

information on drugs used at that time (1958–1965). The authors stressed in their analysis that some malformations have roughly the same rate in the participating hospitals, while other malformations vary strongly in rate. They also distinguished between major and minor malformations and made numerous detailed tabulations of rates of groups of malformations, mainly divided after organ systems. This study is still an important source of information, but naturally modern drugs were not included.

After the thalidomide tragedy, a number of smaller prospective studies were carried out. One of these was made at the Malmö hospital in Sweden in 1963–1964. All pregnant women who attended prenatal care and the only hospital in the city were interviewed repeatedly during pregnancy, among other things concerning drug use and smoking. It was a small study of only 6,300 pregnancies, and numbers were too small to investigate congenital malformations in detail. One report from the study concerned maternal smoking (Kullander and Källén 1971), and further reports described some common drug groups (Kullander and Källén 1976).

More recently prospective studies have been performed in Denmark and in Norway. The Norwegian study (MoBa) is based on questionnaires sent to the mothers in connection with their attendance to ultrasound investigations around week 15 (Magnus et al. 2006). The study was made during 1999–2005. The participation rate is only about 43 %, but the study contains detailed information on more than 64,000 pregnancies. The study has been used for many different studies including some on drug use during pregnancy. The Danish National Birth Cohort study was performed in 1996–2002 and referred to more than 100,000 births, approximately 30 % of the women who gave birth (Olsen 2001; Liew et al. 2014). Information on drug use in pregnancy was obtained by telephone interviews at gestational weeks 12 and 30.

7.5 Pregnancy Registers

This term is often used for registers of pregnancies exposed for specific drugs and have usually been organized by the drug industry. An example is the GlaxoSmithKline Lamotrigine Pregnancy Registry. This register "is intended to provide an early signal of potential risks in advance from formal epidemiological studies" (Foreword to Interim Report from Lamotrigine Pregnancy Registry, 2004). Prospective data on drug exposure were collected from a number of countries around the world. No control material was available, but the observed rates of congenital malformations were compared with data in the literature.

The register also collected retrospective data, after the outcome of the pregnancy was known. Such data are probably biased but can give information on an aggregation of a specific type of malformations.

The register closed down after 18 years (Cunnington et al. 2011) and had then collected 1558 first trimester monotherapies, reported prospectively without finding any signs of an increased risk for any specific congenital malformation (based on 35 malformed infants).

Another example on a register which is specifically built for the study of one group of drugs is the Massachusetts General Hospital National Pregnancy Register for Atypical Antipsychotics (Cohen et al. 2015). It consists of a prospective recording of women using such drugs in pregnancy and controls, mainly women with psychiatric conditions but using other drugs. The register is still small: 353 women using such antipsychotics and 134 controls and the power to study congenital malformations is low, to which is added that the ascertainment of malformations appears low, less than 2 %.

7.6 The Swedish Medical Birth Register

In the Nordic countries, there are medical birth registers which contain data on (nearly) all deliveries in the countries. The Swedish register was started in 1973, and information on drug use was added in 1994. Since 1982, the register is based on copies of the medical documents at the prenatal care (which practically all pregnant women attend and which is free of charge), delivery, and the pediatric examination of the newborn. Identical medical forms are used in all Swedish hospitals since 1982. This form contains space for the recording of drugs used as reported by the woman at the first prenatal care visit, usually in week 10–12. Later drug use as initiated by the prenatal care is also recorded. This system has formed a large data base with drug exposure information obtained in early pregnancy, at present containing data for 1.7 million deliveries. It has been used in numerous studies on the effect of maternal drug use on infant outcome. The drug information is stored as Anatomic, Therapeutic, Chemical (ATC) codes. There are some information on dosage and timing, but these are incomplete and cannot be used in most instances (Källén and Otterblad 2001).

In practice this is equivalent with an ongoing prospective study even though it is less detailed than most prospective studies of drug use during pregnancy.

The information on drug use is thus based on what the woman tells the interviewing midwife. She may have forgotten about temporarily used drugs or may avoid telling about the use of some "sensitive" drugs, for instance, use of recreational drugs. Furthermore, the midwife may miss to record the reported drug or may do it in a way which makes it difficult or impossible to interpret the recording. Drug names are recorded in clear text and then centrally transferred into ATC codes, a partly rather tedious work, notably when drug names are wrongly spelt or written down in a hard way to read. For these reasons, some drug exposures will be missed. It is also possible that the woman mentioned drugs which were used outside the period of pregnancy – an example is that some women report drugs used for ovulation stimulation in spite of the fact that they were used before pregnancy. If the woman's first visit to prenatal care is early, e.g., in weeks 6–7, she may have used drugs later during the first trimester which were not recorded. An effort to compare prescription data with data from the Swedish Medical Birth Register indicated a good agreement for chronically used drugs, less good for drugs used temporarily

(Stephansson et al. 2011). We will come back to the significance of missing data and inclusion of invalid data.

The system thus has some disadvantages but also advantages: the data base is growing, and newly introduced drugs will find their way into it while most prospective research studies are time limited. Information on drug use is retrieved in early pregnancy, and a recall bias is unlikely even though one cannot exclude the possibility that, for instance, a bleeding in early pregnancy may affect the information given.

7.7 Prescription Registers

During the last decades, prescription registers have appeared in some countries including the Nordic ones. These registers are formed from the computerization of prescriptions at the drug stores when a patient fills a prescription. Thanks to the use of personal identification numbers such information can be linked to registers over pregnancy outcome. This gives a relatively simple access to information on which drugs the woman has been prescribed just before or during pregnancy. As pointed out above, the registers can also be used to identify diseases in the child in long-term follow-up studies.

There are some drawbacks of such systems. One is that drugs given in association with hospitalizations will not be included; neither is over the counter drugs. A more serious problem is that it is not known if the woman actually used the drug after buying it. Especially if she gets a prescription when she is early pregnant – or even only suspects she is pregnant – she may be unwilling to take the drug or postpones treatment until later when she has passed the most dangerous period, the first trimester. This will include unexposed pregnancies in the group thought to be exposed. On the other hand, she may well have used drugs which she got on prescription even years before the pregnancy – most drugs have a long shelf-life. She may also have used drugs which she had obtained in other ways, from partner, friends, or bought via the Internet. Data from prescription registers will therefore have uncertainties both by including or excluding actual exposures.

Relatively few studies have been made on the validity of such data. The problem with drugs used during hospital care was illustrated in studies from Sweden (Linder et al. 2015) and from Denmark (Haerskjold et al. 2015), both studying palivizumab use as prophylaxis for RSV in high-risk children.

One study in Norway used the prescription register as the gold standard and studied drug information in the Medical Birth Register (Espnes et al. 2011). For most drug categories, the latter data were much less complete than the prescription data. So, for example, there were a total of 701 instances recorded with diazepam, 612 of them only in the prescription data. This probably shows a low registration in the birth register but a noncompliance can also explain the discrepancy. Among the 89 such cases which were reported in the birth register, 26 (29 %) were not identified from the prescription register. For anticonvulsants, the birth register identified

497 exposures, 51 of which (10 %) were not found in the prescription register – and 290 were only identified in the latter register.

A comparison has been published of data on antidepressant use from a prescription register and interview data from the Swedish Medical Birth Register (Källén et al. 2011). The results indicated that for studies of exposures during early pregnancy, interview data gave a more complete and correct picture than prescription data – if the latter should be used, they should be limited to prescriptions given during pregnancy or possibly include prescriptions given within 1 month before pregnancy. If we accept that exposure actually occurred if the woman had reported so or if she had got a prescription in months 2–3 of pregnancy ($n = 5750$), 78 % were identified from the interview studies and only 55 % from prescriptions.

During the second to third trimester, no interview data were available, only information from the prenatal care medical records that the woman had been instructed to take an antidepressant – she may or may not have got a prescription from the prenatal care or from another source or could already have access to the drugs. In this situation, data from prescriptions were more complete as judged from the effect on neonatal complications. This indicates that women who had been recommended to take antidepressants to a large extent did not follow the advice or she used medicines she already possessed. Against the latter possibility speaks the fact the women who got no prescription but had been recommended by the prenatal care to take the medicine had no increased risk of complications (OR = 0.85).

This exercise demonstrates some problems to use prescription registers in order to identify drug use among pregnant women.

7.8 The Effect of Errors in Drug Exposure Ascertainment

As mentioned above in this chapter, some methods of drug ascertainment may error by including non-exposed cases as exposed. Non-exposure may be the result of the use of prescription registers as source of ascertainment or be due to misinformation in interviews. It may also be due to the use of drugs outside the sensitive period for the malformation studied. An effect of this error will be a bias of risk estimates toward null, and it cannot result in too high-risk estimates. It may give a false impression of harmlessness of a drug if the risk estimate is too low and may therefore not reach statistical significance.

If a woman had used a drug and this was not registered, it hardly affects risk estimates but will of course reduce the power of the study. It will mean that among the women regarded as unexposed some were actually exposed, but they will be few compared with the truly unexposed women and therefore hardly affect the risk estimate for the unexposed women.

Let us take a hypothetical situation where in a population of 100,000 women, 1000 had used a drug with a three times increased risk for a congenital malformation and the background rate of malformations in the unexposed women was 3 %.

If all 1000 exposed women were identified, we would have found 90 infants with malformations, a risk ratio of 3.0, 95 % CI 2.4–3.6.

If instead we had a group of 1000 women, only half of which were actually exposed, the number of malformed infants would be 60 (45 + 15, 6 %)and among the remaining 99,000 unexposed women, of course the risk would still be 3 % and the risk ratio would be 2.0, 95 % CI 1.5–2.5.

If only half of the 1000 exposed women (500) were identified, we would have 45 malformed infants, and among the apparently unexposed 99,500 women, there would be 3015 malformed infants (2970 + 45), a risk ratio of 2.97, 95 % CI 2.2–3.9: a very slight decrease of the risk ratio estimate but a wider confidence interval.

The most common way to get a falsely high-risk estimate is to rely on retrospectively ascertained exposure information. Irrespectively of how trained the interviewer is or how well formulated the questionnaire is, it is difficult to avoid the fact that a woman who has had a malformed child is more likely to remember – or even falsely recall – the use of drugs than a woman who has a normal child. This is one of the two main drawbacks of retrospective case-control studies using healthy controls. The second is the sometimes high rate of nonresponders (often about 30 %) which can give strongly biased results. It is sometimes argued that the fact that statistically significant results are sometimes obtained for some drugs but not for others argues for a true effect. A likely interpretation, however, is that for all studied malformations, the risk estimates scatter around a common increased estimate, which likely is due to recall and/or nonparticipation bias.

7.9 Information on Dosage of Drugs Used

Obviously the amount of the drug used is of interest but perhaps not so much as is often stated. There are situations when a dose dependency has been described, e.g., for anticonvulsants (Tomson et al. 2011) and paroxetine (Bérard et al. 2007). Quite often the information on dosage is obtained from prescription information, and it is far from certain that the prescribed dose is identical with that taken. Furthermore, the value of interest is hardly the dose taken by the woman but the amount which reaches the embryo. Different metabolisms in different women may result in different concentrations reaching the embryo after the same amount of drug taken. Up to 25 % of commonly prescribed drugs are metabolized by a highly polymorphic hepatic enzyme CYP2D6. Given the same dosage, phenotypic slow metabolizers of CYP2D6, that is, 7–10 % of a Caucasian population (Bertilsson et al. 2002), may show a higher serum concentration than extensive metabolizers, and this may increase the risk for malformations.

When only single tablets have been taken, the risk for damage is obviously lower than when a drug has been used for a longer period. This will mean that inclusion of cases who took only a few tablets in the overall risk estimate may bias it toward null in a similar way as inclusion of cases with exposures outside the sensitive embryonic period.

References

Bérard A, Ramos É, Rey E, Blais L, St-André M, Oraichi D (2007) First trimester exposure to paroxetine and risk of cardiac malformations in infants. The importance of dosage. Birth Def Res (Part B) 80:18–27

Bertilsson L, Dahl ML, Dalén P, Al-Shurbaji A (2002) Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 53:111–122

Cohen LS, Viguera AC, McInerney KA, Freeman MP, Sosinsky AZ, Moustafa D et al (2015) Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Register for atypical antipsychotics. Am J Psychiat. doi:10.1176/appl.ajp.2015.150400506

Cunnington MC, Well JG, Messerheimer JA, Ferber S, Yerby M, Tennis P (2011) Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology 76:1817–1823

Espnes MG, Bjørge T, Engeland A (2011) Comparison of recorded medication use in the Medical Birth Registry of Norway with prescribed medicines registered in the Norwegian Prescription Database. Parmacoepidemiol Drug Saf 20:243–248

Fuji H, Goel A, Bernard N, Pistelli A, Yates LM, Stephens S et al (2013) Pregnancy outcomes following gabapentin use. Neurology 80:1565–1570

Haerskjold A, Henriksen L, Way S, Malham M, Hallas J, Pedersen L et al (2015) The Danish National Prescription Registry in studies of a biological pharmaceutical: palivizumab – validation against two external data sources. Clin Epidemiol 7:305–312

Heinonen OP, Slone D, Shapiro S (1977) Birth defects and drugs in pregnancy. Publishing Sciences Group, Inc., Littleton

Källén B, Nilsson E, Otterblad OP (2011) Antidepressant use during pregnancy: comparison of data obtained from a prescription register and from antenatal care records. Eur J Clin Pharmacol 67:839–845

Källén B, Otterblad OP (2001) Monitoring of maternal drug use and infant congenital malformations. Does loratadine cause hypospadias? Int J Risk Safety Med 14:115–119

Koren G, Clark S, Hankins GD, Caritis SN, Umans JG, Miodovnik M et al (2015) Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting in pregnancy; a randomized placebo controlled trial. Pregnancy Childbirth 15:59. doi:10.1186/s12884-015-0488-1

Kullander S, Källén B (1971) A prospective study of smoking and pregnancy. Acta Obst Gynecol Scand 50:83–94

Kullander S, Källén B (1976) A prospective study of drugs and pregnancy. 1. Psychopharmaca. Acta Obst Gynecol Scand 55: 25–33; 2. Anti-emetic drugs. Acta Obst Gynecol Scand 55: 105–11; 3. Hormones. Acta Obst Gynecol Scand 55: 221–4; 4. Miscellaneous drugs. Acta Obst Gynecol Scand 55:287–295

Liew Z, Ritz B, Rebordosa C, Lee P-C, Olsen J (2014) Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 168:313–320

Linder M, Byström C, Keiler H, Bergman G, Haerskjold A (2015) Use of palivizumab is underestimated in the Swedish Prescribed Drug Register – implications for register-based drug studies. Clin Epidemiol 7:45–51

Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C, and the MoBa Study Group (2006) Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 35:1146–1150

McElhatton PR, Garbis HM, Eléfant E, Vial T, Bellemin B, Mastroiacovo P et al (1996) The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants. A collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 10:285–294

Olsen J (2001) The Danish National Birth Cohort – its background, structure and aim. Scand J Publ Health 29:300–307

Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H (2011) Drug use during pregnancy in Sweden – assessed by the Prescribed Drug Register and the Medical Birth Register. Clin Epidemiol 3:43–50

Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A et al for the EURAP study group (2011) Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy register. Lancet Neurol 10:609–617

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SJ et al (2001) The national birth defects prevention study. Public Health Rep 116(Suppl):32–40