COLLECTION AND ANALYSIS OF DRUG SAFETY DATA IN PREGNANCY

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Much of what I will touch on will be taken from the perspective of Motherisk,[1] where we as service providers speak to patients and practitioners on a day to day basis.

Why do we want to collect and analyze drug safety data in pregnancy? The most important reason is to discover possible adverse pregnancy outcomes associated with drugs and other exposures during pregnancy. We also want to be able to identify signals and establish risks early in the life span of a drug release; and finally, to disseminate this information back to patients and health care providers so that rational choices about disease management in pregnancy can be made. We therefore need to collect the information, analyze it, and report it back in a way that is scientifically valid but also makes sense to the clinician and patient who needs the information.

Generally this type of research is done in the post-marketing phase because drugs are RARELY evaluated in human pregnancy prior to market release; pregnant women are actively excluded from drug trials. Despite this lack of information, some 50% of women will take at least one drug in pregnancy, and if we add to that the prescriptions drugs used to treat pain at delivery, we have over 98% of women exposed to drugs during pregnancy.[2] Most importantly, many patients may require continued pharmacotherapy in pregnancy, particularly those with chronic diseases.

Where are we now? Currently in Canada there are no regulated, standardized methods of collecting or reporting drug safety data in pregnancy; most reporting is voluntary. Worldwide methods for data collection vary, but can include: manufacturer registries, observational studies from research facilities (prospective, retrospective, or case control studies), and database linkage studies (often governmental or third party insurers), which work well in countries where pharmacotherapy is paid for by a centralized agency. Why is this such a complex issue?

In the normal population, adverse events are normally seen shortly after exposure, however, in pregnancy events can occur long after exposure (at least the duration of a pregnancy, and sometimes many years later). Therefore any process for collecting and analyzing data regarding drugs in pregnancy is a long term endeavour. In addition, adverse outcomes, particularly teratogenic outcomes, are rare. Most drugs that cause malformations do so in a small percentage of exposures, so you need to collect data on large groups of patients in order to begin to see these adverse events. Furthermore, the physiological changes in pregnancy and concomitant exposures and medical conditions that can confound the outcomes, makes evaluating the data complex.

I will discuss some of the strategies for collecting data and describe some of the pros and cons of these strategies.

The voluntary registry is a program usually initiated by manufacturers[3], although there are now third party companies offering this as a service. Information is generally obtained by spontaneous reporting. Most data are retrospective, which is associated with a reporting bias, where negative outcomes are more likely to be reported. Registries tend to have variable data quality, often relying on second and third hand sources which may not have all of the relevant patient data. There can be duplication of results since different individuals may report the same case. There is no consistent methodology across registries and across different companies or organizations.

As was discussed earlier, the US FDA/CDER has issued a guidance document.[4] It is a very comprehensive document outlining; when, where and, how to maintain a registry, strategies for

active recruitment, sources of follow-up data and describes how to select comparison groups. Details about data collection and minimum data sets (i.e., required variables and categories in which they should be collected) are also discussed, as well as sample size. It leads industry into all the items they need to consider to establish a registry.

In the four years since the guidance document was issued, there have been very few new voluntary registries created. Most of the companies that had registries before the guidance document was published are still maintaining them. Some companies have initiated registries for new agents because they are required to do so, e.g., some newer antirheumatic drugs.

Unfortunately, most manufacturer registries still do not generate, collect or report comparator groups and there is very little data analysis or interpretation of findings. Analysis is generally limited to summary reports and tables of case counts. Data from these registries are rarely published in peer reviewed literature, and so are not readily accessible by clinicians.

One of the other strategies is database linkage.[5,6] Large amounts of patient data can be collected from populations where health care and medications are paid for by some form of insurance, either governmental or third party. Some of the issues with these data are the possibility of duplication occurring if there are errors in linkage process or inconsistencies in variable coding. This is important for rare events and verification is warranted. Cases can be unlinked if patients move in or out of a region during the study interval. Since these studies rely on prescription records errors can occur if exposure data is not verified (i.e., prescription records do not necessarily indicate that the medication was consumed). Very large data sets can be accumulated with this methodology. There is good data interpretation and the data are accessible and peer reviewed.

The third strategy to be discussed is the observational study. This is the typical research we do at Motherisk.[7] It is commonly spearheaded by research groups or industry and is characterized as a cohort or case control study (prospective or retrospective). When research is kept within a single centre, there is good data quality. Collaboration across different research centres can provide some standardization of processes and data types. Without electronic management, data collection can be arduous and cumbersome. Everything from locating the data, following cases and maintaining the associated documentation can become very labour intensive. What results are sample sizes smaller than one would see in a database linkage study. There has been good interpretation of this type of data. It has been well published in peer reviewed journals, e.g., by our group and others, and therefore is accessible and can be transferred back to the clinician.

What I would like to propose is that we need a conglomeration of all these strategies to optimize the data that we have and we need to use the right scientists to interpret the outcomes. That is, let's work with existing infrastructure. We have a number of centres (research, pharma and government) that have the capability to provide the expertise to achieve this goal. Teratogen Information Services and large obstetrical units are ideally situated to collect patient data as they encounter the patients within their day-to-day operations. In order to move forward and collaborate amongst sites and even across countries, we need a tool that can be streamlined across all sites and assist with standardizing the data collected. More and more health care in all disciplines is moving towards the electronic health record. Computer use is common in the general population and there is increasing reliance on automation. We are storing and capturing more information and can use technology to assist in analysis. But the caveat is that we need to do it right; make sure it's working; ensure the system is secure, validated, tested. We need funding for creation and maintenance.

The existing FDA document and currently published studies suggest good clear guidelines for a minimum data set. Patients can be good reporters of their own health information. Using defined standards will assist in ensuring uniform data is collected electronically. The appropriate tool and minimum data requirements would standardize the type of data the individual sites are allowed to collect and define the way the variables are to be collected. In this way electronic data can more easily be linked to existing databases (prescription, Medicare).The bottom line is that the situation is complex. Data that may be

convincing or adequate to one person is unconvincing to another. For example, the kinds of risks that patients are willing to accept may be quite different from what we believe they will accept. Standardization and defined data sets will promote good data collection. Good electronic capture software can be implemented across various sites, thus increasing sample size and standardize output. The key is to link human expertise to interpret data (statisticians, clinicians, epidemiologists, teratologists, geneticists) and to express the meaning of findings back to patients and practitioners in a practical and useful way.

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